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Purine *N*-Oxides. XLIII. 9-Hydroxy-8-methylhypoxanthine, -xanthine, and -guanine[1]

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A total synthesis of 9-hydroxy-8-methylpurine derivatives by way of an imidazole *N*-oxide derivative is described. Closures of 5-amino-1-benzyloxy-2-methylimidazole-4-carboxamide with formate or carbonate esters yielded the hypoxanthine and xanthine analogs and through a guanidino derivative yielded the guanine analog. Triethyl orthoacetate was used in an improved preparation of the acetimidate from aminocyanoacetamide.

While 3-hydroxyxanthine and 3-hydroxyguanine are oncogens comparable in potency to the oncogenic arylamines or hydrocarbons, the isomeric 1-hydroxyxanthine induces inflammations and granulomas which rarely develop into tumors.[2-4] The distinct differences in the biological responses to the 1- and 3-hydroxyxanthine suggest that it would be desirable to investigate the 7 and 9 isomers. The latter bear the oxygen on an imidazole rather than on a pyrimidine nitrogen and no examples of N oxidation of the imidazole portion of a purine have been observed. Numerous 1 or 3 derivatives have been obtained by peroxy acid oxidations of purines or pyrimidines,[5-11] and several pyrimidine *N*-oxides have been obtained by total syntheses.[2,12,13] N oxidation of guanine yields 3-hydroxyguanine[2,14,15] and its hydrolysis yields 3-hydroxyxanthine.[6,14] 3-Hydroxyxanthine has also been obtained by total synthesis from 1-benzyloxy-6-aminouracil.[13] 1-Hydroxyxanthine has been synthesized[16] from an imidazole derivative obtained from adenine 1-oxide.[5]

There have been two reported syntheses of purines with an oxygen on an imidazole nitrogen. Goldner and Deitz[17] obtained 7-hydroxytheophylline (1,3-dimethyl-7-hydroxyxanthine), and they and Taylor and Garcia[18] obtained similar 8-alkyl or aryl derivatives, by ring closures of 1,3-dimethyl-5-nitroso-6-amino- or alkylaminouracils. Timmis reported[19] the synthesis of 8-phenyl-7-hydroxy-2,6-diaminopurine from the adduct of benzaldehyde anil with 2,4,6-triamino-5-nitropyrimidine. An approach to unsubstituted 7-hydroxyxanthine is being described.[20]

Attempts to prepare 9-hydroxypurine derivatives by a classical Traube-type synthesis *via* 4-alkoxyamino-5-aminopyrimidines failed because the reduction of a 5-nitro or 5-phenylazo group was accompanied by reduction of the 4-alkoxyamino group. An alternative approach by the synthetic route elaborated for purines by Shaw[21] has been successful. His studies included 9-alkylpurines from 1-alkyl-5-aminoimidazole-4-carboxamide, and a 9-benzyloxy group has now been incorporated instead of the 9-alkyl group. In this initial study ethyl acetimidate HCl was utilized because of its stability, and also because studies of the mechanism of reactions[22] and the metabolic fates[23] of the 3-hydroxypurines suggest that the 8-methyl-9-hydroxy-

(1) This investigation was supported in part by funds from the National Cancer Institute (Grant No. CA 08748).

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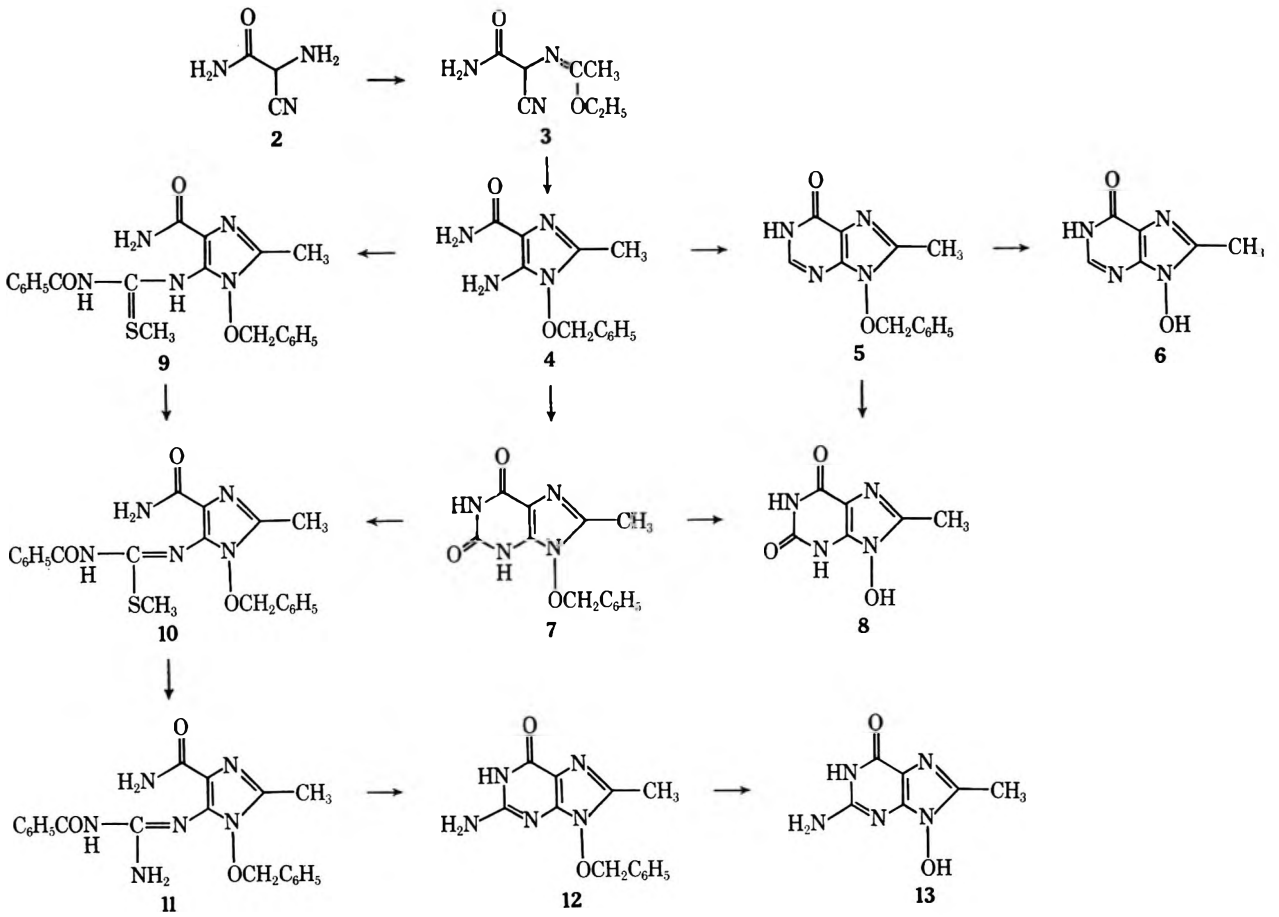
SCHEME I



purines will eventually be desired. Direct repetition of the present sequence of reactions with ethyl orthoformate or ethyl formimidate HCl have failed to yield 9-hydroxypurines without the 8 substituent, but a modification of the Shaw-type synthesis is proving satisfactory.[24]

Results

Ethyl-*N*-[(carbamoylcyano)methyl]acetimidate (**3**) (Scheme I) was prepared by mixing in aqueous solution at room temperature ethyl acetimidate hydrochloride and 2-amino-2-cyanoacetamide (**2**) prepared[21] from cyanoacetamide (**1**). Subsequently better yields of this imino ether were obtained from 2-amino-2-cyanoacetamide and triethyl orthoacetate. The imino ether **3** reacted with benzyloxyamine in methanol to give 5-amino-1-benzyloxy-2-methylimidazole-4-carboxamide (**4**). A comparison of the ir, uv, and nmr spectra with those of 5-amino-1-cyclohexyl-2-methylimidazole-4-carboxamide prepared according to Shaw[21] permitted assignment of the structure **4**.

Several studies in this laboratory have shown that *N*-benzyloxy derivatives may be hydrolyzed to NOH or may lose the complete benzyloxy group on heating at high temperatures in acid media. Procedures involving acid for the closure of the imidazole derivatives to purines were therefore avoided. Yamazaki, Kumashiro, and Takenishi have developed[25] a useful method for the ring closure of ribosylaminoimidazole carboxamide (ribosyl-AICA) to inosine and xanthosine, and it was found to be most applicable for ring closure of 1-benzyloxy-2-methyl-AICA (**4**). This was refluxed in ethanol with ethyl formate in the presence of excess sodium ethoxide to give 9-benzyloxy-8-methylhypoxanthine (**5**) in 78% yield. A similar reaction of **4** with diethyl carbonate gave 9-benzyloxy-8-methylxanthine (**7**) in 20% yield.

Klötzer has shown[15] that debenzylation of *N*-benzyloxypyrimidines to the pyrimidine *N*-oxides can be accomplished in high yields with 32% HBr in glacial acetic acid, thus avoiding the use of hydrogen and metal catalysts, which in many cases give the parent pyrimidines instead of the *N*-oxides. This debenzylating agent was found to yield pure samples of the hydrobromides of both 9-hydroxy-8-methylhypoxanthine (**6**) and -xanthine (**8**), from which the free bases could be obtained.

For cyclization of **4** to a guanine derivative the several methods used by Yamazaki, *et al.*,[26,27] for the preparation of guanosine were investigated. With **4** the optimum conditions involved treatment with benzoyl isothiocyanate[28] in refluxing acetone. This resulted in 5-(*N'*-benzoylthiocarbamoyl)amino-1-benzyloxy-2-methylimidazole-4-carboxamide (**9**) in 88% yield. Methyl iodide and **9** in aqueous sodium hydroxide at room temperature yielded 5-(*N'*-benzoylmethylmercaptocarbamoyl)amino-1-benzyloxy-2-methylimidazole-4-carboxamide (**10**) in 76% yield. In ethanol containing 2% ammonia at 100°, **10** gave 5-*N'*-benzoyl-

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(25) A. Yamazaki, I. Kumashiro, and T. Takenishi, *J. Org. Chem.*, **32**, 3258 (1967).
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(28) R. L. Frank and P. V. Smith, *Org. Syn.*, **28**, 89 (1948).

guamidino-1-benzyloxy-2-methylimidazole-4-carboxamide (**11**). This was not isolated, but after removal of ethanol the residue was heated in 1 *N* sodium hydroxide, cooled, and acidified to yield a mixture of 9-benzyloxy-8-methylguanine (**12**) and benzoic acid. The benzoic acid was removed by extraction with hot ethyl ether and **12** was crystallized from ethanol. Debenzylation of this compound with 32% HBr in acetic acid resulted in 9-hydroxy-8-methylguanine HBr, from which the free base **13** was obtained. The intermediates **9**, **10**, and **11** do not give distinctive ultraviolet spectra, but nmr spectra and analysis of **9** and **10** confirmed the assigned structures. The final products, **6**, **8**, and **13**, are not sufficiently soluble in DMSO for nmr measurements. Reductions of each in hot HI yielded the corresponding parent purines, which were identified chromatographically.

The ultraviolet spectra (Table I) of the anions of

TABLE I

UV SPECTRA AND pK_a'S OF 9-HYDROXYPURINES

pH	Species	λ_{max}, nm ($\epsilon \times 10^{-3}$)			pK_a
		9-Hydroxy-8-methylhypoxanthine			
0.0	+1			252 (11.4)	
					1.73 ± 0.04
3.5	0	221 sh (9.5)	235 (12.3)	252 (11.5)	
					5.73 ± 0.06[a]
8.0	−1		238 (29.3)	265 sh (7.5)	
13.0	−2		232 (24.2)	251 (9.3)	10.75 ± 0.07
		9-Hydroxy-8-methylguanine			
−0.6	+1	212 (15.3)	254 (9.7)	277 sh (6.4)	
					2.65 ± 0.07
4.5	0	236 (13.8)	257 sh (7.1)	275 (6.6)	
					6.53 ± 0.08[a]
9.0	−1	238 (22.3)	278 (7.7)		
					11.07 ± 0.07
13.0	−2	231 (18.6)	275 (8.9)		
		9-Hydroxy-8-methylxanthine			
−0.6	+1	237 (6.3)	262 (10.1)		
					1.51 ± 0.05
3.0	0	235 (6.2)	266 (10.3)		
					5.14 ± 0.07[a]
6.5	−1	223 (15.8)	275 (11.5)		
					8.14 ± 0.05
13.0	−2	230 (25.6)	280 (8.8)		

[a] Potentiometric titration; others determined by optical methods.

the three 9-hydroxypurines have a strong absorption in the 225–235-nm range—three to four times that of the maxima of their longer wavelength bands. With purines bearing the *N*-oxide group in the pyrimidine ring it was deduced[14] that an $\geqslant N \rightarrow O$ or an enol anion, $-OC^- = N \rightarrow O-$, is associated with strong absorption in the 225–235-nm region. The present spectra extend the evidence, initially made on 7-hydroxytheophylline,[17] that similar interpretations are valid for imidazole *N*-oxide derivatives. In Table I the compounds are designated as *N*-hydroxy derivatives, since that appears to be the predominant tautomer in the neutral species, while the *N*-oxide form predominates in the anions.

The absorptions of the neutral species of 9-hydroxy-8-methylhypoxanthine, ϵ 12.3 × 10^3 at 235 nm, and of 9-hydroxy-8-methylguanine, ϵ 13.8 × 10^3 at 236 nm, compared to the values of ϵ 29.3 and 22.3 × 10^3 at 238 nm, respectively, for the monoanions, indicates that the neutral species of each does have a considerable proportion of the *N*-oxide tautomer with a proton on N-7. With 9-hydroxy-8-methylxanthine the maximum absorption of ϵ 25.6 × 10^3 at 230 nm is fully reached only in the dianion. The lower absorption, ϵ 15.8 × 10^3 at 223 nm at pH 6.5, suggests that the xanthine derivative yields a mixture of monoanions, which must include *N*-hydroxy and *N*-oxide tautomers. The similarity of the neutral and protonated species shows that the neutral species is almost exclusively the *N*-hydroxy form.

The 9-hydroxy-8-methylxanthine and guanine do not show the second absorption band above 300 nm which is observed with the enolate anions of a series of 3-hydroxyxanthines and guanines.[14]

Experimental Section

The uv spectra were determined with a Unicam SP800 spectrometer, and the p*K*'s were determined by methods described[29] at 23 ± 1°, spectrophotometrically with 0.01 *M* buffers[30] with the use of a Beckman DU spectrophotometer. Nmr spectra were determined with a Varian A-60 spectrometer in DMSO-d_6, or in $CDCl_3$ as specified. Analyses were performed by Spang Laboratories, Ann Arbor, Mich.

Ethyl *N*-[(Carbamoylcyano)methyl]acetimidate (3).—A suspension of 2-amino-2-cyanoacetamide[31] (9.9 g, 0.1 mol) in triethyl orthoacetate (100 ml) was heated on a steam bath (with occasional shaking) until all the starting material had gone into solution. A rapidly moving non-uv-absorbing spot began to appear on a thin layer chromatography plate (tlc) run in 9:1 chloroform–ethanol and developed with iodine, and which had the same R_f value as that of the acetimidate prepared by Shaw's method.[21] The heating was continued for about 2 hr, when tlc indicated that all the starting material had reacted. The hot, pale yellow liquid was decanted from a small quantity of brown gum (*i.e.*, decomposed starting material) and cooled at −10° until crystallization was complete. The product **3** was collected and washed with petroleum ether (bp 30–60°). It was crystallized from ethyl acetate–petroleum ether as plates: mp 105° (lit.[21] mp 105°); yield 13 g (77%); nmr δ 7.5 (s, 2, $CONH_2$), 5.3 (s, 1, CHN), 4.2 (q, 2, OCH_2CH_3), 2.2 (s, CCH_3), 1.25 (t, 3, CH_2CH_3).

5-Amino-1-benzyloxy-2-methylimidazole-4-carboxamide (4).—The acetimidate **3** (8.45 g, 0.05 mol) and benzyloxyamine (9.2 g, 0.075 mol) in methanol (20 ml) were heated on a steam bath for about 30 min or until tlc of the solution indicated the absence of the imino ether and a new uv-absorbing spot appeared. This was eluted with ethanol and its uv spectrum, λ_{max} 267 nm, corresponded to that of the known cyclohexyl derivative prepared by Shaw's method.[21] The dark red solution was evaporated to dryness *in vacuo*, and the syrupy residue was chromatographed on a silica gel column (4 × 30 cm) which was eluted with chloroform (which removed the unreacted benzyloxyamine) and then with 9:1 $CHCl_3$–EtOH until the eluent, monitored by tlc, indicated the absence of the required imidazole. The fractions containing the product were evaporated, and the solid residue was triturated with ether and collected. Recrystallization from ethanol gave plates of **4**: mp 208–209° dec; yield 5.04 g (41%); uv λ_{max}^{EtOH} 267 nm (ϵ 13.6 × 10^3), sh 214 (ϵ 12.5 × 10^3); nmr δ 7.5 (s, 5, C_6H_5), 6.67 (s, 2, $CONH_2$), 5.83 (s, 2, NH_2), 5.2 (s, 2, $-OCH_2C_6H_5$), 2.0 (s, 3, CCH_3).

Anal. Calcd for $C_{12}H_{14}N_4O_2$: C, 58.56; H, 5.73; N, 22.77. Found: C, 58.60; H, 5.75; N, 22.87.

9-Benzyloxy-8-methylhypoxanthine (5).—The imidazole **4** (492 mg, 0.002 mol) was dissolved in ethanol (40 ml) containing sodium (460 mg, 0.02 mol); to this was added 1.3 ml (0.016 mol) of ethyl formate. The mixture was heated on a steam bath for 3 hr, during which time a precipitate formed. The dark brown reaction mixture was cooled, and water (50 ml) was added to dissolve the precipitate. Upon acidification with glacial acetic acid the product precipitated and was collected and washed with water. Recrystallization from ethanol with charcoal treatment afforded white plates of the hypoxanthine **5**: yield 403 mg (78%); mp 256° dec; uv $\lambda_{max}^{pH\ 1}$ 251 nm (ϵ 12.9 × 10^3), $\lambda_{max}^{pH\ 13}$ 255 nm (ϵ 14.2 × 10^3); nmr δ 8.00 (s, 1, CH=N), 7.48 (s, 5, C_6H_5), 5.35 (s, 2, $OCH_2C_6H_5$), 2.2 (s, 3, CCH_3), 11.9 (br, 1, NH).

(29) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962.

(30) D. D. Perrin, *Aust. J. Chem.*, **16**, 572 (1963).

(31) L. H. Smith, Jr., and P. Yates, *J. Amer. Chem. Soc.*, **76**, 6080 (1954).

Anal. Calcd for $C_{13}H_{12}N_4O_2$: C, 60.94; H, 4.69; N, 21.86. Found: C, 61.03; H, 4.77; N, 21.77.

8-Methyl-9-hydroxyhypoxanthine (6).—9-Benzyloxy-8-methylhypoxanthine (5) (256 mg, 0.001 mol) was dissolved in 5 ml of warm glacial acetic acid, and 5 ml of 32% HBr in glacial acetic acid was added. The mixture was heated on a steam bath for 3.5 hr, during which time a precipitate formed. The reaction mixture was then cooled and the HBr salt was collected and washed thoroughly with ether. The product was dissolved in hot water containing a few drops of concentrated ammonia, treated with charcoal, and precipitated with glacial acetic acid. The 9-hydroxy-8-methylhypoxanthine was collected, washed with water, ethanol, and ether, and dried *in vacuo* at 78° over P_2O_5, yield 130 mg (78%).

Anal. Calcd for $C_6H_6N_4O_2$: C, 43.37; H, 3.64; N, 33.72. Found: C, 43.29; H, 3.66; N, 33.55.

9-Benzyloxy-8-methylxanthine (7).—A solution of the imidazole 4 (492 mg, 0.002 mol), diethyl carbonate (2 ml, 0.016 mol), and metallic sodium (460 mg, 0.02 g-atom) in ethanol was refluxed for 6 hr. The dark brown reaction mixture was cooled, and water (50 ml) was added to dissolve the precipitate. After acidifying with concentrated hydrochloric acid, the reaction mixture was concentrated *in vacuo* to precipitate **7**, which was collected and washed with water, ethanol, and ether: yield 115 mg (21%); uv $\lambda_{max}^{pH\ 1}$ 242, 263 nm; $\lambda_{max}^{pH\ 13}$ 250, 278 nm; nmr δ 7.45 (s, 5, C_6H_5), 5.26 (s, 2, $OCH_2C_6H_5$), 2.3 (s, 3, CCH_3), 10.70 (1, N^1H), 12.3 (br, 1, N^3H).

8-Methyl-9-hydroxyxanthine (8).—The debenzylation of **7** (82 mg, 0.003 mol) was carried out as above and the free base **8** was obtained from the hydrobromide salt by dissolving in hot dilute ammonia, treatment with charcoal, and precipitating by addition of glacial acetic acid. The white crystals were collected, washed with water, ethanol, and ether, and dried *in vacuo* over P_2O_5 at 78°, yield 44 mg (80%).

Anal. Calcd for $C_6H_6N_4O_2$: C, 39.56; H, 3.32; N, 30.76. Found: C, 39.39; H, 3.40; N, 30.80.

5-(*N'*-Benzoylthiocarbamoyl)amino-1-benzyloxy-2-methylimidazole-4-carboxamide (9).—The imidazole **4** (4.92 g, 0.02 mol) was dissolved in hot acetone (110 ml) and to this was added a 100-ml acetone solution containing 1.1 equiv of benzoyl isothiocyanate.[28] The mixture was refluxed for approximately 2 hr, or until tlc of the solution showed that all the 1-benzyloxyimidiazole (**4**) had reacted. The yellow precipitate that formed during the reaction was collected and washed with acetone. Recrystallization from chloroform–ethanol, after charcoal treatment, afforded the benzoyl thiocarbamoylaminoimidazole derivative (**9**) as pale yellow needles: yield 7.23 g (88%); mp 195–196° dec; λ_{max}^{EtOH} 242, sh 285 nm; nmr δ 8.1 (m, 2, COC_6H_5), 7.7 (m, 3, COC_6H_5), 7.49 (s, 5, $-CH_2C_6H_5$), 5.3 (s, 2, $OCH_2C_6H_5$), 2.18 (s, 3, CCH_3), 7.2 (br, 2, $CONH_2$), 11.93 (s, 2, $-NHCSNH-$).

Anal. Calcd for $C_{20}H_{19}N_5O_3S$: C, 58.67; H, 4.67; N, 17.10; S, 7.83. Found: C, 58.71; H, 4.85; N, 16.78; S, 7.80.

5-(*N'*-Benzoyl-*S*-methylisothiocarbamoyl)amino-1-benzyloxy-2-methylimidazole-4-carboxamide (10).—**9** (4.09 g, 0.01 mol) dissolved in 0.1 *N* sodium hydroxide (200 ml) was treated with 1 ml of methyl iodide at room temperature. After being stirred for several hours the solution was adjusted to pH 6 with glacial acetic acid, and then extracted several times with chloroform (100 ml). The combined chloroform extracts were dried (Na_2SO_4), concentrated to a small volume, and chromatographed over a column of silica gel with $CHCl_3$–EtOH (9:1). The eluent was monitored by tlc. Concentration of the appropriate fractions afforded **10**, which was recrystallized from ethanol: yield 3.23 g (76%); mp 165–167° dec; uv λ_{max}^{EtOH} 237 nm; nmr δ 8.80 (m, 2, COC_6H_5), 7.56 (m, 3, COC_6H_5), 7.41 (s, 5, $CH_2C_6H_5$), 7.30 (s, 2, $CONH_2$), 5.29 (s, 2, $OCH_2C_6H_5$), 2.62 (s, 3, SCH_3), 2.04 (s, 3, CCH_3).

Anal. Calcd for $C_{20}H_{21}N_5O_3S$: C, 59.57; H, 4.99; N, 16.54; S, 7.57. Found: C, 59.38; H, 4.99; N, 16.44; S, 7.67.

5-*N'*-Benzoylguanidino-1-benzyloxy-2-methylimidazole-4-carboxamide (11).—**10** (2.12 g, 0.005 mol) was treated with 50 ml of 2% NH_3–ethanol at 100° in a steel bomb for 3 hr. At the end of the reaction the odor of methylmercaptan could be recognized. The solvent was removed *in vacuo* to give **11**, which was pure enough for use in the ring closure step, as indicated by its uv and nmr spectra: uv $\lambda_{max}^{pH\ 1}$ 243 nm, $\lambda_{max}^{pH\ 13}$ 260 nm; nmr ($CDCl_3$) 7.9 (m, 2, COC_6H_5), 7.5 (m, 3, COC_6H_5), 7.3 (s, 5, $CH_2C_6H_5$), 5.12 (s, 2, $OCH_2C_6H_5$), 1.98 (s, 3, CCH_3), 7.2 (br, 2, $CONH_2$), 6.3 (br, 2, CNH_2).

9-Benzyloxy-8-methylguanine (12).—To the solid residue of **11** was added 200 ml of 0.5 *N* sodium hydroxide and the solution was warmed on a steam bath for 3 hr. The reaction mixture was then cooled and acidified with glacial acetic acid. The concurrent white precipitates of benzoic acid and the 9-benzyloxyguanine were collected and washed with water. The benzoic acid was removed by several extractions, or continuous extraction, with hot ethyl ether (200 ml). The residue remaining was crystallized from ethanol, after charcoal treatment, to afford **12** as white needles: yield 813 mg (60%); uv $\lambda_{max}^{pH\ 1}$ 256 nm (ϵ 13.8 × 10^3), sh 277 (9.29 × 10^3); $\lambda_{max}^{pH\ 12}$ 259 nm sh (ϵ 12.0 × 10^3), 267.5 (12.7 × 10^3); nmr δ 7.5 (s, 5, C_6H_5), 7.05 (s, 2, NH_2), 5.33 (s, 2, $OCH_2C_6H_5$), 2.4 (s, 3, CCH_3).

Anal. Calcd for $C_{13}H_{13}N_5O_2$: C, 57.43; H, 4.83; N, 25.77. Found: C, 57.23; H, 4.80; N, 25.93.

8-Methyl-9-hydroxyguanine (13).—The debenzylation of **12** (542 mg, 0.002 mol) was carried out as above. The free base **13** was obtained from the hydrobromide salt by dissolving in hot dilute ammonia, treatment with charcoal, and precipitating by addition of glacial acetic acid. The white crystals were collected, washed with water, ethanol, and ether, and dried *in vacuo* over P_2O_5 at 78°, yield 279 mg (77%).

Anal. Calcd for $C_6H_7N_5O_2$: C, 39.69; H, 3.98; N, 38.57. Found: C, 39.84; H, 3.87; N, 38.25.

Registry No.—**3**, 34407-35-7; **4**, 34407-36-8; **5**, 34407-37-9; **6**, 34407-38-0; **7**, 34407-39-1; **8**, 34407-40-4; **9**, 34417-80-6; **10**, 34417-81-7; **11**, 34407-41-5; **12**, 34407-42-6; **13**, 34407-43-7.

Acknowledgment.—We express appreciation to Mr. Gerald Reiser for assistance with the p*K* determinations, to Mr. Marvin J. Olsen for nmr spectra, and to Dr. J. C. Parham for helpful discussions.

Purine N-Oxides. XLIV. The Cyclization of 6-Amino-5-nitrosouracil with Formaldehyde. Preparation and Properties of 7-Hydroxyxanthine[1]

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7-Hydroxyxanthine has been obtained from the reaction of one of the tautomeric forms of 6-amino-5-nitrosouracil and formaldehyde. Its 7-acetoxy derivative reacts rapidly with nucleophiles in neutral aqueous solutions to yield 8-substituted xanthines. Similar facile nucleophilic substitutions at position 8 are observed with 3-acetoxyxanthine, and an analogous mechanism *via* a common intermediate is proposed.

The xanthine *N*-oxide which is derived from the peroxy acid oxidation product of guanine was first designated xanthine-x-*N*-oxide,[3] and later 7-hydroxyxanthine.[4] It was proven to be 3-hydroxyxanthine[5] by both degradation and by total synthesis. The ability of 3-hydroxyxanthine to induce tumors[6] and its chemical properties, including the facile reaction of its 3-*O*-acyl derivative[7] with nucleophiles to yield 8-substituted xanthines,[8,9] have been studied in some detail. 1-Acetoxyxanthine fails to undergo such a reaction,[8] and 1-hydroxyxanthine is very weakly oncogenic.[6] The behaviors of the 7- and 9-hydroxyxanthine derivatives are of particular interest, and syntheses of 9-hydroxy derivatives are in process.[10]

Several synthetic routes to 7-hydroxyxanthine have been explored in this laboratory without success. While 7-hydroxytheophylline and its 8-alkyl derivatives are known,[11,12] the syntheses which led to them have not been successful without blocking groups in the 1 and 3 positions.

We now report the isolation of 7-hydroxyxanthine (**7**) from the mixture resulting from the reaction of 6-amino-5-nitrosouracil (**2**) with aqueous formaldehyde.[13] The yield of pure 7-hydroxyxanthine is low, but the few steps involved make the synthesis of preparative value.

It has been shown that 6-amino-5-nitrosouracil exists in three tautomeric forms (**2a**, **2b**, and **2c**, Scheme I) which differ in their color.[15] The tautomer which is thought to be the nitrosoamino species, **2a**, is apparently the only proper one for this preparation. Samples of 6-amino-5-nitrosouracil (**2**) obtained by a brief nitrosation of 6-aminouracil with $NaNO_2$ in HCl proved satisfactory in the condensation. Recrystallization, or prolonged stirring of 6-amino-5-nitrosouracil in the mother liquor, gave a product which failed to give a satisfactory yield of 7-hydroxyxanthine. The cyclization proceeds at 100° and a pH of 2.5–3.5. Higher pH's prevent the reaction. At lower pH's there is increased hydrolysis of **2** to 5-nitrosobarbituric acid (**1**, violuric acid). A few other solvent systems have been tried: in boiling 4:1 dioxane–H_2O there was formation of a large amount of 6-aminouracil;[16] in 50% ethanol there was negligible reaction.

A major product is uric acid, and, if the reaction is prolonged, little or no 7-hydroxyxanthine (**7**) and much more uric acid (**8**) are obtained. The ability of 7-hydroxyxanthine to rearrange to uric acid in the reaction mixture was demonstrated by boiling **7** in aqueous formaldehyde.

The products are all solubilized in the reaction mixture, presumably as their *N*-hydroxymethyl derivatives. Although most of the *N*-hydroxymethyl groups are lost upon treatment with ammonia, their continued presence complicates the isolation procedures. 1-Hydroxymethyl-7-hydroxyxanthine (**6**) was also isolated and characterized. It is stable at room temperature, but in hot water or hot NH_4OH it is hydrolyzed to **7**.

The separation of the reaction products was carried out by ion-exchange chromatography over Dowex-50, $-H^+$. A fraction containing primarily 7-hydroxyxanthine could be eluted with H_2O and recognized by its characteristic uv absorption, including the appearance of a maximum at 225 nm upon addition of alkali. Two additional fractions which have this spectral characteristic were eluted prior to 7-hydroxyxanthine. One of them contained a methylol derivative isomeric with **6**.

Several possible intermediates are shown in Scheme I. They are probably all hydroxymethylated on some of their nitrogens. It is probable that such hydroxymethyl groups influence the reaction in the same manner as 1- and 3-alkyl groups appear to have influenced previous syntheses of 7-hydroxytheophylline derivatives. It is of interest to consider the mechanisms proposed for similar reactions, although none consider the apparent need of blocking the 1 and 3 nitrogens. Probably the most logical intermediate is **3**, which could yield **7** by a mechanism proposed by Goldner.

(1) This work was supported in part by funds from the National Cancer Institute (Grant No. CA 08748).

(2) David A. Gimbel Memorial Fellow.

(3) G. B. Brown, K. Sugiura, and R. M. Cresswell, *Cancer Res.*, **25**, 986 (1965).

(4) T. J. Delia and G. B. Brown, *J. Org. Chem.*, **31**, 178 (1966).

(5) U. Wölcke and G. B. Brown, *ibid.*, **34**, 378 (1969).

(6) K. Sugiura, M. N. Teller, J. C. Parham, and G. B. Brown, *Cancer Res.*, **30**, 184 (1970).

(7) N. J. M. Birdsall, T. C. Lee, and U. Wölcke, *Tetrahedron*, **27**, 5961 (1971).

(8) N. J. M. Birdsall, U. Wölcke, T. C. Lee, and G. B. Brown, *ibid.*, **27**, 5969 (1971).

(9) N. J. M. Birdsall, U. Wölcke, J. C. Parham, and G. B. Brown, *ibid.*, **28**, 3 (1972).

(10) A. A. Watson and G. B. Brown, *J. Org. Chem.*, **37**, 1867 (1972); A. A. Watson, unpublished work.

(11) (a) H. Goldner, G. Dietz, and E. Carstens, *Justus Liebigs Ann. Chem.*, **691**, 142 (1966); (b) *ibid.*, **693**, 233 (1966).

(12) E. C. Taylor and E. E. Garcia, *J. Amer. Chem. Soc.*, **86**, 4721 (1964).

(13) Taylor and Garcia[12] carried out a condensation of 1,3-dimethyl-4-amino-5-nitrosouracil with benzaldehyde in DMF, and report 8-phenyl-7-hydroxytheophylline as an intermediate in the formation of 8-phenyltheophylline. In other reports[11a,12] benzanil was used as a source for benzaldehyde for formation of an 8-phenylpurine 7-oxide, including one from a 5-nitro pyrimidine.[14]

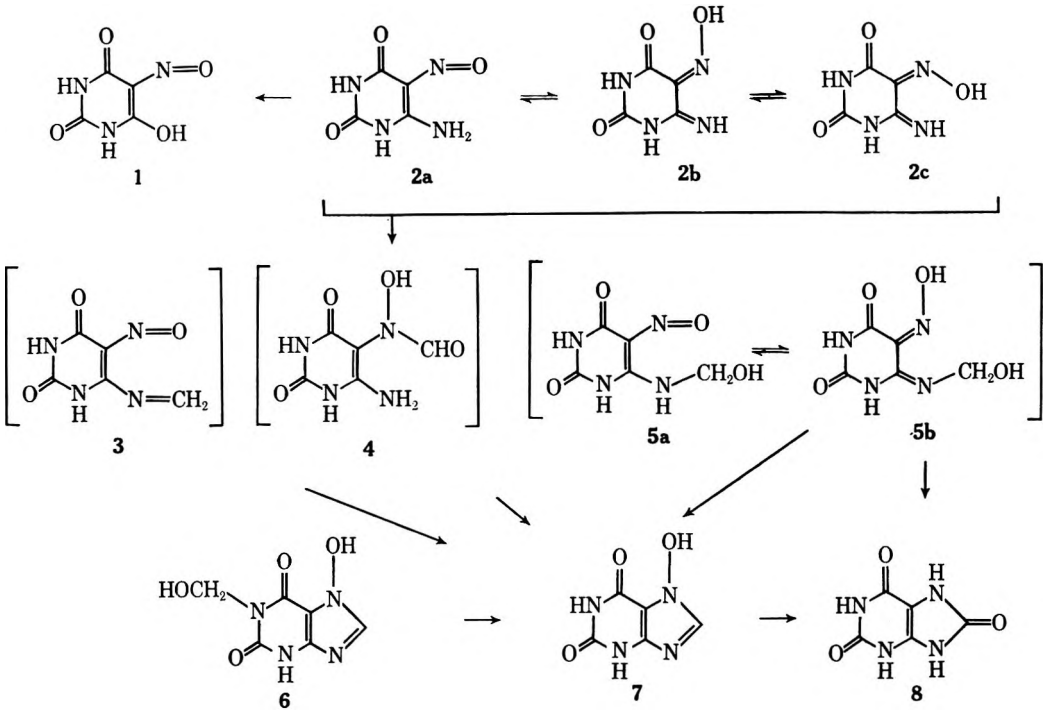
(14) G. M. Timmis, I. Cooke, and R. G. W. Spickett in G. E. W. Wolstenholme and C. M. O'Connor, Ed., "Chemistry and Biology of Purines," J. and A. Churchill, London, 1957, p 134.

(15) I. Lifschitz and L. Kritzman, *Chem. Ber.*, **50**, 1719 (1917).

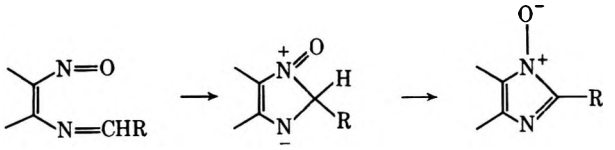
(16) An apparent hydrolytic loss of a 5-nitroso group from a 1,3-disubstituted **2** has previously been noted.[17]

(17) A. D. McNaught and G. B. Brown, *J. Org. Chem.*, **32**, 3689 (1967).

SCHEME I

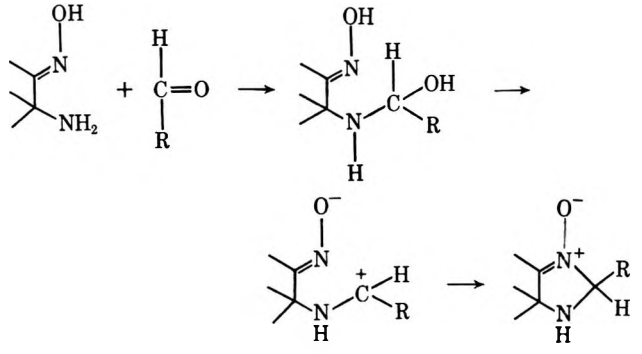


et al.,[11b] and by Taylor and Garcia[12] for similar condensations to 8-methyl- or phenyl-7-hydroxytheophyllines.

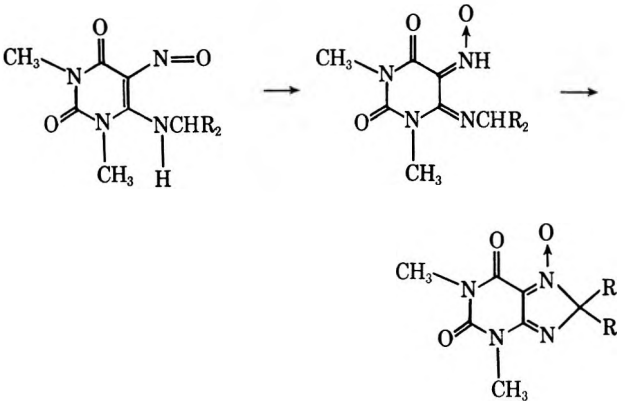


A hydrazone of a structure similar to **4**, the formation of which must involve an oxidation and reduction, was proposed[18] in the cyclization of 1,3-dialkyl-6-amino-5-nitrosouracil with aldehyde hydrazones. If formed, **4** would lead to a classical Traube approach to **7**.

Intermediate **5** could also yield either a uric acid (**8**) or a xanthine derivative (**7**) by loss of one molecule of water, as was proposed by Gnichtel[19] in the case of the formation of imidazoline *N*-oxides from anti-α-amino-oximes and aldehydes. **5a** could also lead to **3** by loss of water.



The formation of the products which are thought to be hydroxymethyl derivatives of 7-hydroxyuric acid and of 8-amino-7-hydroxyxanthine could be explained only by a reaction involving removal of hydrogens from intermediate **5**. An analogous dehydrogenation reaction is known to be involved in the formation of 8,8-dialkyl derivatives of 7-hydroxy-8-*H*-theophyllines, for which Goldner, *et al.*,[20] propose the following.



We have not isolated an intermediate pyrimidine derivative, but intermediates which are apparently basic remain on the Dowex-50 [H^+] during elution by H_2O. After thorough elution of the column with H_2O, elution with HCl yields additional quantities of uric acid, 7-hydroxyxanthine, and also some 8-aminoxanthine. The latter may be the result of ammonia used in the work-up. This suggests that further ring closure may occur during the elution by acid.

When the red-violet tautomer of 6-amino-5-nitrosouracil is used, a yellow product was obtained which does not yield **7**. Its elemental analysis and nmr spectrum suggest a polyhydroxymethyl derivative which is not an *N*-oxide derivative.

A concerted study of the nitroso tautomers, and derivatives of them, will be needed to clarify the mechanism involved, and to improve the yield.

Pure 7-hydroxyxanthine is obtained upon rechroma-

(18) F. Yoneda, K. Ogiwara, M. Kanahori, and S. Nishigaki, *J. Chem. Soc. D*, 1068 (1970).

(19) H. Gnichtel, *Chem. Ber.*, **103**, 2411 (1970).

(20) (a) H. Goldner, G. Dietz, and E. Carstens, *Justus Liebigs Ann. Chem.*, **692**, 134 (1966); (b) **698**, 145 (1966); (c) **699**, 145 (1966).

TABLE I

pK_a'S AND UV SPECTRA OF 7-HYDROXYXANTHINE AND DERIVATIVES

pH	Species	λ_{max}, mm ($\epsilon \times 10^{-3}$)	λ_{min}, mm ($\epsilon \times 10^{-3}$)	pK_a
		7-Hydroxyxanthine		
−2.4	+1	231 (5.7), 262 (8.1)	226 (5.6), 243 (4.5)	−0.25 (±0.08)
2.0	0	201 (22.2), 268 (8.22)	241 (2.77)	5.04[c] (±0.04)
7.3	−1	223 (14.4), 256 (7.11), 276[a] (4.82)	245 (6.41)	9.64[c] (±0.05)
13	−2	227 (19.3), 245, 296 (6.16)	267 (2.96)	
		7-Hydroxy-1-hydroxymethylxanthine		
−2	[+1]	232 (6.40), 262 (9.67)	223 (5.93), 243 (5.37)	−0.1[b]
2	0	201 (26), 268 (10.3)	242 (3.57)	5.0[b]
7	−1	203 (11), 223 (17.1), 256 (8.57), 277[a] (6.0)	245 (7.74)	9.5[b]
12	−2	228 (23.0), 246,[a] 297 (7.4)	212 (11.1), 267 (3.3)	
		7-Hydroxytheophylline[d]		
3	0	208 (23), 230[a] (6.7), 273 (9.1)	247 (3.5)	5.14[c] (±0.05)
8–13	−1	226 (17.2), 257 (7.4), 282 (5.9)	216 (15.5), 248 (7.1) 273 (5.8)	
		7-Hydroxy-8-methyltheophylline[e]		
3	0	208 (24), 230–235[a] (6.7), 275 (10.5)	247 (3.7)	5.59[c] (±0.05)
8–13	−1	228 (17), 250–257[a] (7.8), 280 (6.5)	216 (14.1), 273 (6.4)	

[a] Shoulder. [b] Estimated from isosbestic spectra. [c] Electrometic determination. [d] Reference 11b. [e] Reference 11a.

tography of the main fraction. It can be reduced to xanthine with Raney nickel. The nmr spectrum shows a sharp peak of the imidazole aromatic hydrogen with a chemical shift of δ 7.97 and distinctive peaks for the hydrogens at positions 1 and 3, at δ 10.75 and 11.45, respectively.[21] In the nmr spectrum of compound **6**, the N-1 hydrogen was replaced by the hydroxymethyl group. The uv spectra of the neutral species and of the monoanion of 7-hydroxyxanthine are almost identical with those of the corresponding species of 7-hydroxytheophylline (Table I). The first ionization involves the *N*-hydroxyl group, since it is accompanied by the appearance of the characteristic absorption at 223 nm which is attributed to an N→O group.[22] At a higher pH a dianion is formed from 7-hydroxyxanthine, and this ionization probably involves the proton at N-3; it is accompanied by a shift of the maxima to higher wavelengths. The absence of the absorption at 223 nm in the neutral species provides evidence that the major tautomer in that species is the 7-hydroxy rather than the 7-*N*-oxide structure. The pK_a of protonation of −0.25 compared to that of 3-hydroxyxanthine of 0.35 is in accord with a protonation at N-9, in the same ring with the *N*-OH.

7-Hydroxyxanthine could be converted to uric acid in aqueous thioacetic acid. After gentle treatment with acetic anhydride in acetic acid, 7-acetoxyxanthine (**10**, Scheme II) could be isolated. It is unstable in H_2O, in which it undergoes rearrangement to uric acid. It is also unstable in DMSO, but more stable in dry dioxane.

The reactivities of 7-acetoxyxanthine are remarkably similar to those of 3-acetoxyxanthine, **11**. In aqueous solutions at room temperature in the presence of nucleophiles, it yields a series of 8-substitution products (Scheme II) identical with those obtained from 3-acetoxyxanthine under similar conditions.[8] Thus, it yields 8-chloro-, 8-nitro-, 8-pyridinium, 8-methylmercapto-, and 8-ethoxyxanthines upon treatment with aqueous NaCl, $NaNO_2$, pyridine, methionine, and ethanol, respectively. These reactions involving substitutions by nucleophiles are obviously intermolecular. The products have been characterized after overnight reaction periods, but the early development of color in the reaction with pyridine suggests that the times required may be much less.

At pH's above 4 **10** yields some xanthine in addition to 8-substitution products. With sodium iodide it yields only xanthine, and no 8-substitution product. At pH's between 4.5 and 7.4 it also yields an H_2O-insoluble blue product. This behavior is again directly analogous to that of 3-acetoxyxanthine.[8]

The similarity of the products from 7-acetoxyxanthine and from 3-acetoxyxanthine (**11**) in H_2O suggest that the 8-substitution reactions of each may well proceed *via* the same intermediates. For the facile 3-acyloxypurine 8-substitution reaction,[8] which occurs with increasing rapidity between pH 3 and 7, the anion **12**, dehydroxanthine (**14**), and the carbonium ion **15** were proposed as intermediates.[9] Ionization of **10** to the anion **13** and departure of the 7-acetoxy group would also yield dehydroxanthine (**14**) and thence the carbonium ion **15**.

In further analogy to the deductions made regarding the origin of xanthine from 3-acetoxyxanthine, the reduction of **10** to xanthine could likewise occur through a radical anion arising from homolytic cleavage of the anion **13**.

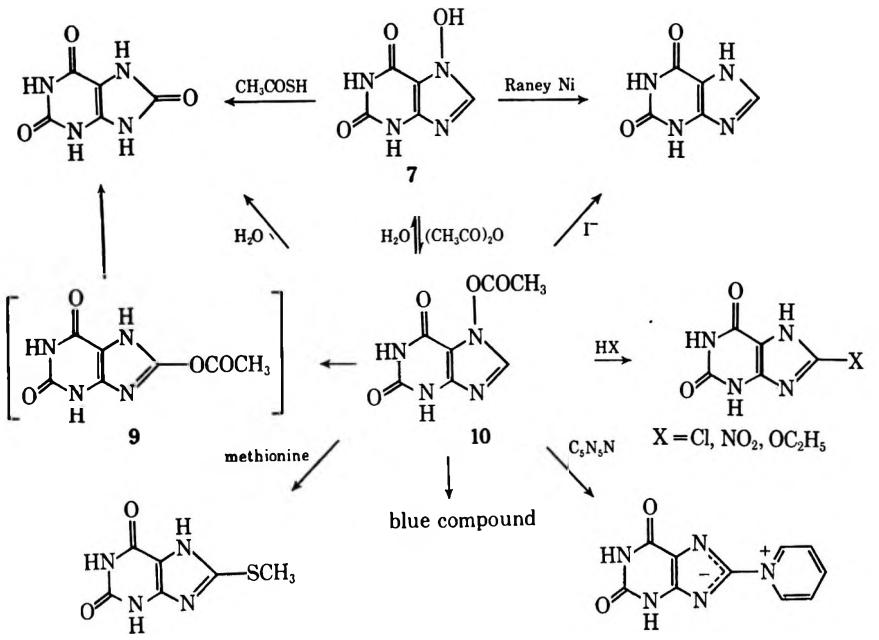
The rearrangement of 7-acetoxyxanthine (**10**) to uric acid involves only a shift to the adjacent atom and could well occur through an intramolecular reaction within a solvent cage, to yield **9** (Scheme II) and thence uric acid. Ir evidence suggested that intermediate **9** was obtained, but it is apparently less stable than the 8-acetoxytheophylline obtained from 7-hydroxytheophylline.[11b]

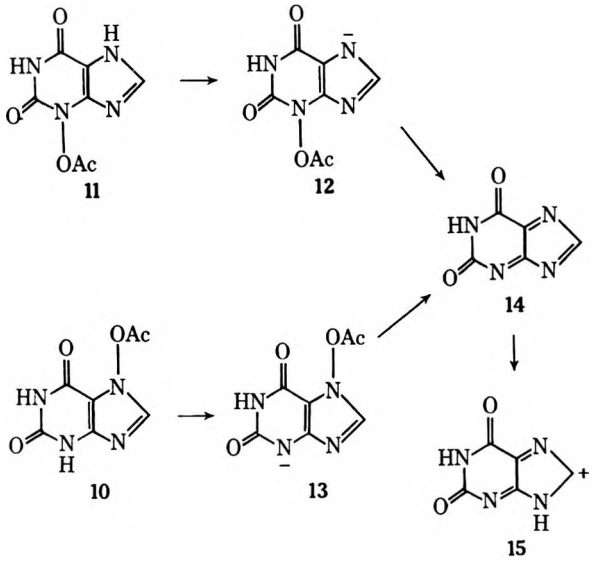
At pH 4.75 the reaction of **10** to yield uric acid, and some xanthine, proceeds about 2.5-fold faster than does that of 3-acetoxyxanthine. This could be due to either the possible intramolecular character of the present reaction, or, if uric acid formation is also an intermolecular reaction, to a pK_a of the ionization of **10** to **13** which is somewhat lower than that of **11** to **12**.

(21) The hydrogen at the 1 position in xanthine has always a lower chemical shift than that in the 3 position: N. J. M. Birdsall, unpublished work.

(22) J. C. Parham, T. G. Winn, and G. B. Brown, *J. Org. Chem.*, **36**, 2639 (1971).

SCHEME II





From the similarities of the reactivities of 7-acetoxyxanthine to those of 3-acetoxyxanthine, it is possible that 7-hydroxyxanthine will, like a 3-hydroxyxanthine, be a potent chemical oncogen. That and further comparisons of the chemical behaviors of the two isomers require study.

In a preliminary experiment 2,4-diamino-6-hydroxy-5-nitrosopyrimidine was condensed with formaldehyde, and 8-hydroxyguanine was obtained. For that reaction it may be possible to obtain the presumed intermediate, 7-hydroxyguanine, for comparison with the behavior of 3-hydroxyguanine.

Experimental Section

The uv spectra were determined with a Unicam SP800A recording spectrophotometer, the ir spectra (KBr or Nujol) with a Perkin-Elmer Model 221 spectrophotometer, and the nmr data with a Varian A-60 spectrometer with DMSO-d_6 as a solvent and TMS as an internal standard. The pK_a's were determined electrometrically or spectrophotometrically by the methods of Albert and Serjeant[23] with a Beckman DU spectrophotometer and buffers of 0.001 M ionic strength.[24] Below pH 2 and above pH 12 pH's were adjusted with KOH and HCl (or H_2SO_4) to give the calculated $H°$ values; pH's 1–13 were measured on a Beckman Research pH meter. For ϵ values a Cary Model 15 spectrophotometer was used. Dowex-50 columns were prepared from BioRad AG-50W-X8, 200–400 mesh, and washed with 3 N HCl before loading. The elution of columns was monitored with an ISCO Model UA-2 uv analyzer.

On a standardized analytical Dowex-50 column similar to that of Uziel and Cohn,[25] 9 × 150 mm, 200–400 mesh, eluted with 1 N HCl at 60 ml/hr and monitored at 240, 260, and 290 nm, these 8-substituted xanthines show the following retention volumes, in milliliters: 8-nitro-, 14; 8-chloro-, 14; 8-ethoxy-, 35; 8-methylmercapto-, 75; 8-amino-, 114; 8-pyridinium-, 205. Uric acid appears at 13, 7-hydroxyxanthine at 35, and xanthine at 67.

From the same column eluted with 0.05 N HCl, uric acid appears at 14, 7-hydroxyxanthine at 48, 3-hydroxyxanthine at 84, 1-hydroxyxanthine at 185, and xanthine at 375 unless the latter is eluted earlier with 1 N HCl.

6-Amino-5-nitrosouracil (2a).—6-Aminouracil (6.35 g) was stirred in H_2O (350 ml) and a solution of $NaNO_2$ (3.85 g) at room temperature in H_2O (50 ml) was added, followed by 1 N HCl (120 ml). After 4–5 min the solid became blue-violet and was quickly collected by filtration (6.8 g). This solid, which can be stored dry for at least a few weeks, was used without further purification.

Anal. Calcd for $C_4H_4N_4O_3$: C, 30.78; H, 2.58; N, 35.89. Found: C, 30.72; H, 2.57; N, 35.98.

The same tautomer could also be prepared by boiling the orange tautomer (0.5 g)[15] in H_2O (50 ml) for 2 min and filtering immediately. The red-purple (**2b**) and the orange (**2c**) tautomers were prepared as described previously.[15] The ir spectrum of the orange tautomer differs considerably from those of the other two. There are smaller differences between the blue-violet and red-purple tautomers. The differences are in the NH(OH) region (3000–3200 cm^{-1}), the C=O region (1600–1800 cm^{-1}), and at 1325, 1275, and 870 cm^{-1}.

7-Hydroxyxanthine (7).—H_2O (400 ml) was brought to the boiling point, formalin solution (55 ml) was added, and the solution was heated again to boiling. 6-Amino-5-nitrosouracil (3.9 g) was added to the boiling solution in small portions, with stirring, during a 10-min period. The stirring and boiling were continued for an additional 20 min, or until the uv maximum, at first near 260 nm, shifted to 273 nm. This was monitored by diluting 0.1-ml aliquots to 25 ml with 0.01 N HCl and recording the spectra. The pH of the mixture, measured at 100°, was an apparent 2.5. When the maximum reached 273 nm, the

(23) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962.

(24) D. D. Perrin, *Aust. J. Chem.*, **16**, 572 (1963).

(25) M. Uziel, C. K. Koh, and W. E. Cohn, *Anal. Biochem.*, **25**, 77 (1968).

reaction was stopped by cooling the flask to room temperature. The relative intensity of the 273 band to one at 317 nm (the nitroso compound) was then about 3:1. The solution was then concentrated under vacuum below 45° to 50 ml, 1 *N* HCl (25 ml) was added, and the solution was concentrated again to a volume of 25 ml. The pink solution was loaded on a Dowex-50 column (43 × 200 mm) and eluted with 850 ml of H_2O. The first 150 ml, containing violuric acid (1) and uric acid, were neutralized with NH_4OH, concentrated, and separated by chromatography on a smaller column (10 × 150 mm). On paper chromatography with 3% NH_4HCO_3, they had R_f values of 0.7 and 0.4, respectively. The next 700 ml, which had an absorption maximum at 270 nm, were concentrated in vacuum to 25 ml, concentrated NH_4OH (25 ml) was added, and the solution was stirred for 2 hr at room temperature. It was then concentrated under vacuum to 25 ml, a little 1 *N* HCl was added to dissolve any precipitate, and the solution was loaded onto another Dowex-50 column (20 × 290 mm). The column was eluted with H_2O (700 ml), followed by 1 *N* HCl (600 ml). The first fractions, 80–180 ml, contained additional 1 and 8. The next fraction, 180–260 ml, had a uv spectrum similar to that of 7-hydroxyxanthine, but was unstable on further work-up. The next 260–340 ml yielded, upon evaporation, a hydroxymethyl derivative of **7**, which is apparently a less stable isomer than the one, **6**, described below. It gave an elementary analysis similar to that of **6** but its uv maxima were at about 3–4 nm longer wavelengths. It yielded some 7-hydroxyxanthine upon rechromatography. The next fraction, 340–500 ml, was essentially pure 7-hydroxyxanthine (**7**). Upon evaporation of the solvent and recrystallization twice from H_2O, with charcoal if needed, it yielded 0.5–0.6 g (8–10%) of white crystals. This eluted as a single sharp band at 48 ml from the analytical column. When dried at room temperature under vacuum it gave elementary analyses for a hemihydrate.

Anal. Calcd for $C_5H_4N_4O_3 \cdot {}^1/_2H_2O$: C, 33.89; H, 2.82; N, 31.70. Found: C, 33.89; H, 2.82; N, 31.81.

The anhydrous 7-hydroxyxanthine was obtained on drying over P_2O_5 at 100° under vacuum: nmr (DMSO-d_6) δ 7.97 (8-CH), 10.75 (1-NH), 11.45 (3-NH), 12.2 (7-OH, br); ir (Nujol) 3400 (OH), 3200 (NH), 1680 cm^{-1} (C=O). The uv spectral data and pK_a's are given in Table I.

Anal. Calcd for $C_5H_4N_4O_3$: C, 35.72; H, 2.40; N, 33.33. Found: C, 35.83; H, 2.41; N, 33.19.

Although other fractions contain 7-hydroxyxanthine or derivatives which yield it, this one fraction represents the practical yield.

Nothing was eluted by an additional 200 ml of water. Elution with 1 *N* HCl was then started and the eluate again contained uric acid and **7** in the initial 20–100 ml, and 8-aminoxanthine appeared from 120 to 250 ml. The latter was isolated upon evaporation and was identified by elementary analysis and uv spectrum.[26]

7-Hydroxy-1-hydroxymethylxanthine (**6**).—6-Amino-5-nitrosouracil (**2a**) (0.5 g) was added to a boiling solution of formalin (6 ml) and H_2O (40 ml) as described above. Instead of concentrating and treating with HCl, the reaction mixture was stirred for 4 hr with 1.0 g of Dowex-50 and filtered, and the resin was washed with 100 ml of water. The solution and washings were evaporated to 20 ml under vacuum and loaded on a Dowex-50 column (20 × 290 mm). The column was eluted with 500 ml of H_2O. The fraction from 100 to 300 ml showed an unsymmetrical trailing peak with an absorption maximum near 270 mm. It was concentrated under vacuum to 10 ml and again put on a Dowex-50 column (20 × 290 mm) and eluted with H_2O. The 270-nm absorbing material was largely eluted as a nearly symmetrical peak from 280 to 400 ml. It was evaporated under vacuum and **6** was obtained by crystallization from water (0.05 g). Dried at room temperature, it gave an analysis for a monohydrate.

Anal. Calcd for $C_6H_6N_4O_4 \cdot H_2O$: C, 33.34; H, 3.73; N, 25.92. Found: C, 33.43; H, 3.67; N, 26.03.

The anhydrous product was obtained on drying at 100°: nmr (DMSO-d_6) δ 5.23 (CH_2), 6.0 (COH, broad), 8.01 (8-CH), 11.73 (3-NH), 12.3 (7-OH, broad); ir (Nujol) 3350 (OH), 1680 (C=O), 1640 cm^{-1} (C=O, a band absent in **2**).

Anal. Calcd for $C_6H_6N_4O_4$: C, 36.37; H, 3.05; N, 28.28. Found: C, 36.17; H, 3.10; N, 28.33.

8-Amino-7-hydroxy-x-hydroxymethylxanthine.—A product, which analyses and spectra suggest to be the title compound, was obtained in an attempt to isolate a basic intermediate from the reaction of 6-amino-5-nitrosouracil with formaldehyde. 6-Amino-5-nitrosouracil (0.4 g) was added to a boiling solution of formalin (6 ml) and H_2O (40 ml), and the reaction was followed as described above. After stopping the reaction and concentrating the solution to 10 ml, it was loaded on a Dowex-50 column (20 × 290 mm). After elution of acidic products with H_2O (900 ml), the column was eluted with 0.4 *N* HCl (200 ml). The eluate was concentrated under vacuum to 20 ml, and concentrated NH_4OH (8 ml) was added with cooling. Upon keeping overnight at room temperature the product precipitated. Recrystallized from H_2O it was still brown (0.05 g). It was dried at 100°: uv, pH 2, λ_{max} 206, 275, λ_{min} 245 nm; pH 7, λ_{max} 226, 257, 287, λ_{min} 272 nm; pH 12, λ_{max} 226, 292, λ_{min} 273 nm.

Anal. Calcd for $C_6H_7N_5O_4$: C, 33.80; H, 3.31; N, 32.85. Found: C, 33.86; N, 3.42; C, 32.88.

Reaction of Other Tautomers of 2 with Formaldehyde.—By the procedure described for 7-hydroxyxanthine, the orange tautomer gave a very low yield of **7** and a larger amount of uric acid.

With the red-purple tautomer a trailing peak of a yellow product was obtained from the column. After concentration and treatment with 1 *N* NH_4OH, followed by evaporation to dryness and crystallization from water, it gave an unidentified yellow product. The elementary analyses and nmr spectrum suggest the presence of methylene or hydroxymethyl groups: nmr (DMSO-d_6) δ 4.83 (CH_2, broad peak), 5.24 (CH_2).

Anal. Calcd for $C_7H_8N_4O_4$: C, 39.63; H, 3.80; N, 26.41. Found: C, 39.58; H, 3.81; N, 26.29.

Hydrogenation of 7-Hydroxyxanthine to Xanthine.—7-Hydroxyxanthine (**7**) (24 mg) was dissolved in hot H_2O (5 ml), Raney nickel (150 mg) was added, and the solution was boiled for 30 min and filtered hot The filtrate was left at room temperature and xanthine, identified through its ir and uv spectra, crystallized (20 mg) (90%).

Reaction of 7-Hydroxyxanthine with Thioacetic Acid.—7-Hydroxyxanthine (**7**) (10 mg) was stirred for 1 week with CH_3COSH (10 mg) in H_2O (2 ml). The solution was loaded on a Dowex-50 column (1 × 10 cm) and eluted with water. The first fraction was evaporated and the residue was crystallized from H_2O. The product was identified as uric acid by its uv and ir spectra.

Acetylation of 7-Hydroxyxanthine. A. 7-Acetoxyxanthine.—Dry 7-hydroxyxanthine (**7**) (0.15 g) was stirred with glacial acetic acid (4.5 ml) and acetic anhydride (4.5 ml) at room temperature until the solution was clear (2–3 hr). Dry ether (150 ml) was added and the solution was kept for 96 hr in the freezer. The product which crystallized was collected by filtration, washed with dry ether, and dried under vacuum overnight at room temperature (0.15 g). The product melts at 155° (with decomposition) when heated rapidly, but does not melt when heated slowly, suggesting the formation of uric acid during slow heating. The elementary analysis corresponded to a hemiacetate of **10**. Drying at elevated temperatures or for a longer period resulted in loss of acetic acid and was accompanied by decomposition.

Anal. Calcd for $C_7H_6N_4O_4$: C, 40.01; H, 3.36; N, 23.33. Found: C, 40.02; H, 3.30; N, 23.35.

When the nmr was taken in DMSO-d_6, a rapid decomposition could be observed. The band of the proton from position 8 (δ 8.21) disappears while at the same time CH_3 protons of the acetoxy group change their chemical shift from δ 2.40 to 2.35 and finally to 1.92, the last corresponding to that of acetic acid.

Ir (KBr) follows: 3200 (NH), 2800 (NH with hydrogen bond), 1800 (C=O, of acetoxy group), 1670 cm^{-1} (C=O).

B. Acetylation under the Conditions for the Preparation of 3-Acetoxyxanthine.—With acetic anhydride and acetic acid at room temperature for 5 days,[7] uric acid and an unstable intermediate, possibly **9**, precipitated. More material could be precipitated by the addition of ether. The ir band at 1820 cm^{-1}, attributed to an *N*-acetoxy group, is weaker and an ester carbonyl absorption at 1750 cm^{-1} is present. This is apparently a mixture containing 8-acetoxyxanthine and 7-acetoxyxanthine. Upon drying most was converted to uric acid. Low nitrogen analyses from the crude product suggest the presence of more than one acetyl group.

Reduction of 7-Acetoxyxanthine with KI.—The acetoxyxanthine (**10**) (6 mg) was stirred for 1 hr with 10% aqueous KI (0.25 ml). The solution turned red and gave a positive starch test for iodine. Only xanthine was detected upon chromatog-

(26) L. F. Cavalieri and A. Bendich, *J. Amer. Chem. Soc.*, **72**, 2587 (1950).

raphy over Dowex-50 with 0.05 *N* HCl. Its identity was verified by its uv spectrum.

Reactions of 7-Acetoxyxanthine with Nucleophiles.—7-Acetoxyxanthine (**10**) was treated overnight with ethanol or with aqueous solutions of methionine, NaCl, $NaNO_2$, or pyridine as described for 3-acetoxyxanthine.[3] The formation of 8-ethoxy, 8-methylmercapto, 8-chloro, 8-nitro, and 8-pyridinium xanthines, respectively, was accompanied by some formation of uric acid and xanthine. The products were isolated by chromatography and identified by their uv spectra.

The rate of reaction of **10** in acetate buffer at pH 4.75 was compared with that of 3-acetoxyxanthine by repeated scans of the changing spectra at intervals. The half-times for completion of the reactions were approximately 10 and 25 min, respectively.

Blue Compound.—Upon stirring 7-acetoxyxanthine in cold 0.1 *N* phosphate buffer at pH 7, the solution turns purple followed by precipitation of a blue compound. A similar product is obtained by adding a few drops of 0.01 *N* NaOH to a cold H_2O solution. Like the blue compound obtained from 3-acetoxyxanthine[3] it is insoluble in H_2O and most organic solvents, and is decomposed in base or acid and by heating in H_2O.

Registry No.—**2a**, 34407-58-4; **6**, 34407-59-5; **7**, 16870-90-9; **10**, 34407-61-9; **11a**, 883-16-9; **11b**, 1012-82-4.

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Synthesis of 3′ and 5′ Nucleotides Derived from 2′-Amino-2′-deoxyuridine

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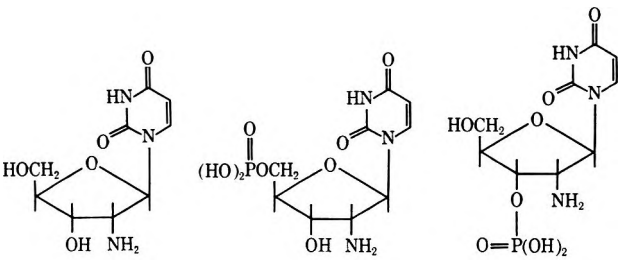
The previously described 2′-azido-2′-deoxyuridine has been converted into 2′-azido-2′-deoxy-5′-*O*-trityluridine (**5**) and thence to 3′-*O*-acetyl-2′-azido-2′-deoxyuridine (**7**). Phosphorylation of the latter compounds gave, after removal of protecting groups, 2′-azido-2′-deoxyuridine 3′-phosphate (**8**) and 2′-azido-2′-deoxyuridine 5′-phosphate (**9**) which are suitable intermediates for the preparation of 2′-amino-2′-deoxyuridine containing oligonucleotides, etc., for biochemical study. Catalytic reduction of the azido function of **8** and **9** gave 2′-amino-2′-deoxyuridine 3′-phosphate (**3**) and 2′-amino-2′-deoxyuridine 5′-phosphate (**2**) in crystalline form.

Recently we have described the synthesis of 2′-amino-2′-deoxyuridine (**1**) and its conversion into 2′-amino-2′-deoxycytidine.[2] Since these compounds contain free 3′- and 5′-hydroxyl groups, it should be possible to convert them chemically into short oligonucleotides containing amino groups in place of the normal 2′-hydroxyl functions. These compounds would be of interest in order to study the effect of an adjacent amino group on the stability of the phospho diester linkage and also to show whether such compounds would function as messengers in a protein-synthesizing system.[3] Along similar lines, Glinski, *et al.*,[4] have recently described the preparation of phosphate esters derived from 3′-amino-3′-deoxythymidine and 5′-amino-5′-deoxythymidine, while Letsinger and Mungall[5] have prepared short oligonucleotides containing phosphoramidate linkages derived from the latter compounds. These compounds, being derived from 2′-deoxy nucleosides, do not, however, permit one to examine the questions posed above. In this paper we describe the preparation of both 2′-amino-2′-deoxyuridine 5′-phosphate (**2**) and of its isomer 2′-amino-2′-deoxyuridine 3′-phosphate (**3**).

Rather than devising a suitable protecting group for the 2′-amino function of **1**, we have preferred to do the appropriate transformations using, as the starting material, 2′-azido-2′-deoxyuridine (**4**), the immediate precursor of **1**. Thus the selective protection of the 5′-hydroxy group was readily achieved *via* formation of the trityl ether **5**, which was obtained in 86% yield.



1 **2** **3**

Compound **5** could be crystallized only with difficulty, but its homogeneity and structure was readily apparent from its nmr spectrum, which showed, *inter alia*, the presence of a free 3′-hydroxy group at 5.97 ppm. The latter signal was coupled to $C_{3'}H$ which appeared as a pseudoquartet at 4.44 ppm collapsing to a pseudotriplet upon addition of D_2O. Acetylation of **5** gave amorphous, but analytically pure, 3′-*O*-acetyl-2′-azido-2′-deoxy-5′-*O*-trityluridine (**6**) in quantitative yield. Removal of the trityl ether from **6** was achieved by treatment with 80% acetic acid, giving crystalline 3′-*O*-acetyl-2′-azido-2′-deoxyuridine (**7**) in 88% yield.

Phosphorylation of both **5** and **7** was accomplished by reaction with 2-cyanoethyl phosphate and dicyclohexylcarbodiimide (DCC) in pyridine.[6] Following removal of protecting groups by treatment with alkali (and acid in the case of **5**) the corresponding phosphate esters 2′-azido-2′-deoxyuridine 3′-phosphate (**8**) and 2′-azido-2′-deoxyuridine 5′-phosphate (**9**) were isolated by ion exchange chromatography in yields of 60 and 69% respectively.

Catalytic hydrogenation of the free acid forms of **8** and **9** rapidly converts the azido function to the corresponding amines, the reduction being readily followed by paper electrophoresis in 1 *M* acetic acid. Under

(1) Syntex Postdoctoral Fellow, 1968–1970.

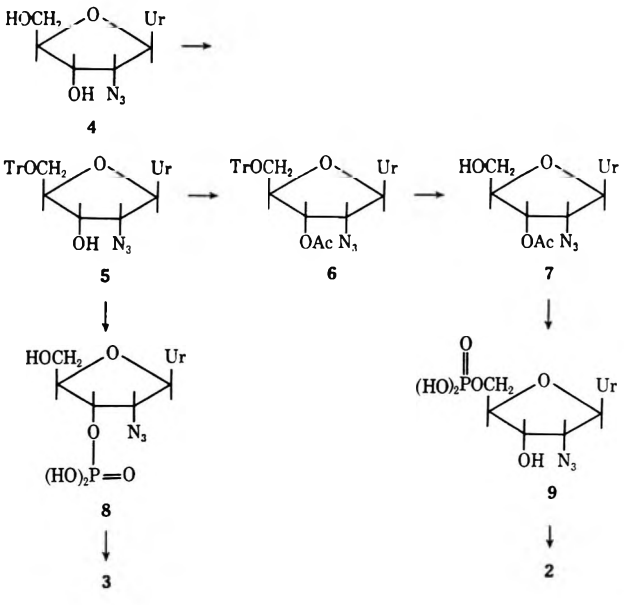
(2) D. Wagner, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, **36**, 250 (1971).

(3) See, *e.g.*, M. W. Moon, S. Nishimura, and H. G. Khorana, *Biochemistry*, **5**, 937 (1966), for a related study involving 2′-deoxy nucleosides.

(4) R. P. Glinski, M. S. Khan, R. L. Kalamas, and C. L. Stevens, *Chem. Commun.*, 915 (1970).

(5) R. L. Letsinger and W. S. Mungall, *J. Org. Chem.*, **35**, 3800 (1970).

(6) G. M. Tener, *J. Amer. Chem. Soc.*, **83**, 159 (1961).



these conditions, the starting materials (**8** and **9**) move as monoanions while the products are zwitterions with no net charge and give positive tests for amino groups with ninhydrin. Following removal of the catalyst, the amino phosphates (**2** and **3**) were obtained in crystalline form in yields of 88 and 70%, respectively. The 2′-amino 3′-phosphate (**3**) could also be obtained in an overall yield of 60% from **5** without purification of any intermediates.

The selective phosphorylation of the 5′-hydroxy group of **4** could also be achieved using phosphorus oxychloride in trimethyl phosphate.[7] Following charcoal absorption and ion exchange chromatography, crude **9** was obtained in about 50% yield and appeared to be fairly pure by paper chromatography and enzymatic degradation (see below). Upon catalytic hydrogenation, however, several minor by-products were produced in addition to **2** and crystallization of the pure product was difficult. Because of the ease of preparation of the pure product *via* the blocked intermediate **7**, this route was explored no further.

While the azido phosphates **8** and **9** were difficult to distinguish by paper chromatography in many solvent systems, the amino phosphates **2** and **3** were analytically separable in several solvents (see Experimental Section). A clear distinction between the 3′- and 5′-phosphate isomers could, however, be made by enzymatic means. Thus incubation of the 5′-phosphate derivatives **2** and **9** with unfractionated *Crotalus adamanteus* venom led to complete dephosphorylation to the parent nucleosides **1** and **4** within 2–3 hr under standard conditions. The 3′-phosphate isomers (**3** and **8**), on the other hand, remained completely unchanged for at least 48 hr under the same conditions. Since sugar-modified nucleotides such as 2′-*O*-methyl nucleoside 5′-phosphates are known to be resistant towards the action of the 5′-nucleotidase present in certain snake venoms,[8] it is interesting that both the 2′-amino and 2′-azidouridine 5′-phosphates are substrates. Since there was no observable dephosphorylation of either **3** or **8** after 48 hr of incubation, the very low levels of nonspecific phosphomonoesterase known to be present in *Crotalus adamanteus* venom do not lead to any spurious results.[9]

The azido phosphates **8** and **9** are clearly suitable starting materials for the preparation of 2′-amino-2′-deoxyuridine containing oligonucleotides, nucleoside polyphosphates, etc., for biochemical studies. Further work in these directions will be reported at a later date.

Experimental Section

General Methods.—Thin layer chromatography (tlc) was carried out on 0.25-mm layers of Merck silica gel GF and products were detected by examination under ultraviolet light or by spraying with a 5% solution of ammonium molybdate in 10% sulfuric acid followed by brief heating at 150°. Preparative tlc was done on 20 × 100 cm glass plates coated with a 1.3-mm layer of Merck silica gel HF and column chromatography on Merck silica with 0.05–0.20 mm particles. Paper chromatography was carried out on Whatman No. 40 paper using the following systems: I, 1-propanol–concentrated NH_4OH–H_2O (6:3:1); II, 2-propanol–concentrated NH_4OH–H_2O (7:1:2); III, 1-butanol–acetic acid–H_2O (5:2:3); IV, isobutyric acid–1 *N* NH_4OH–0.1 *M* disodium ethylenediamine tetraacetic acid (100:60:1.6); V, ethanol–1 *M* ammonium acetate, pH 7.5 (5:2).

Nuclear magnetic resonance spectra were recorded using a Varian HA-100 spectrometer and are reported in parts per million downfield of an internal standard of tetramethylsilane. The assignments of sugar protons were confirmed by spin decoupling studies. We are particularly thankful to Dr. M. L. Maddox and Mrs. J. Nelson for their help with nmr studies. Other instrumental analyses were obtained by the staff of the Analytical Laboratories of Syntex Research. Some elemental analyses were obtained by Dr. A. Bernhardt, Mulheim, Germany.

2′-Azido-2′-deoxy-5′-*O*-trityluridine (5).—A solution of 2′-azido-2′-deoxyuridine (**4**, 1.35 g, 5 mmol)[2] and chlorotriphenylmethane (1.53 g, 5.5 mmol) in anhydrous pyridine (25 ml) was heated at 100° for 2 hr and then cooled and poured into ice-water. The resulting syrup was dissolved in chloroform, washed with water, and applied to a column containing 150 g of silicic acid. Elution with chloroform removed excess tritanol and colored impurities, while elution with chloroform–ethyl acetate (1:1) gave 2.19 g (86%) of **5** as a homogeneous dry foam that can be used directly in the next step. An analytical sample could be crystallized from chloroform–hexane: mp 168–170°; λ_{max}^{MeOH} 261 nm (ε 9700); ν_{max} (KBr) 2110, 1695 cm^{-1}; ORD positive Cotton effect $[\Phi]_{284\ nm}^{pk}$ 8100°, $[\Phi]_{272\ nm}$ 0°, $[\Phi]_{252\ nm}^{tr}$ −14,300°; nmr (DMSO-d_6) 3.32 (s, 2, $C_{5'}H_2$), 3.99 (m, 1, $C_{4'}H$), 4.26 (dd, 1, $J_{1',2'}$ = 4 Hz, $J_{2',3'}$ = 6 Hz, $C_{2'}H$), 4.44 (ddd, 1, $J_{2',3'} = J_{3',4'} = J_{3',OH}$ = 6 Hz, collapsing to an apparent triplet with D_2O, $C_{3'}H$), 5.36 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.75 (d, 1, $J_{1',2'}$ = 4 Hz, $C_{2'}H$), 5.97 (d, 1, $J_{3',OH}$ = 6 Hz, $C_{3'}OH$), 7.25–7.45 (m, 15, Ar), 7.70 ppm (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Anal. Calcd for $C_{28}H_{25}N_5O_5$ (511.52): C, 65.74; H, 4.93; N, 13.69. Found: C, 65.71; H, 4.92; N, 13.42.

3′-*O*-Acetyl-2′-azido-2-deoxy-5′-*O*-trityluridine (6).—A solution of **5** (1.53 g, 3 mmol) and acetic anhydride (4 ml) in pyridine (15 ml) was kept overnight at room temperature and then evaporated to dryness. The residue was dissolved in ethyl acetate, washed three times with water, dried ($MgSO_4$), and evaporated, leaving 1.7 g (100%) of **6** as a chromatographically homogeneous foam: λ_{max}^{MeOH} 260 nm (ε 9100); ν_{max} (KBr) 2115, 1745 cm^{-1}; nmr ($CDCl_3$) 2.11 (s, 3, OAc), 3.44 (dd, 1, J_{gem} = 11 Hz, $J_{4',5'a}$ = 2 Hz, $C_{5'a}H$), 3.62 (dd, 1, J_{gem} = 11 Hz, $J_{4',5'b}$ = 3 Hz, $C_{5'b}H$), 4.2 (m, 1, $C_{4'}H$), 4.30 (dd, 1, $J_{1',2'} = J_{2',3'}$ = 5 Hz, $C_{2'}H$), 5.34 (dd, 1, $J_{2',3'} = J_{3',4'}$ = 5 Hz, $C_{3'}H$), 5.41 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.04 (d, 1, $J_{1',2'}$ = 5 Hz, $C_{1'}H$), 7.25–7.45 (m, 15, Ar), 7.78 ppm (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Anal. Calcd for $C_{30}H_{27}N_5O_6$ (553.56): C, 65.09; H, 4.92; N, 12.65. Found: C, 64.78; H, 5.21; N, 12.56.

3′-*O*-Acetyl-2′-azido-2′-deoxyuridine (7).—A solution of **6** (1.53 g, 2.77 mmol) in 80% acetic acid (25 ml) was heated at

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(8) M. Honjo, Y. Kanai, Y. Furukawa, Y. Mizuno, and Y. Sanno, *Biochem. Biophys. Acta*, **87**, 698 (1964).

(9) E. Sulkowski, W. Björk, and M. Laskowski, *J. Biol. Chem.*, **238**, 2477 (1963).

100° for 10 min. After addition to water (100 ml), the mixture was filtered and the filtrate was evaporated to dryness. The residue was coevaporated several times with methanol and then crystallized from ethanol, giving 760 mg (88%) of **7**: mp 196–198° with prior gas evolution and darkening above 180°; λ_{max}^{MeOH} 259 nm (ϵ 9700); nmr (pyridine-d_5) 2.08 (s, 3, OAc), 4.03 (dd, 1, J_{gem} = 12 Hz, $J_{4',5'a}$ = 2.5 Hz, $C_{5'a}H$), 4.18 (dd, 1, J_{gem} = 12 Hz, $J_{4',5'b}$ = 2.5 Hz, $C_{5'b}H$), 4.45 (m, 1, $C_{4'}H$), 4.91 (dd, 1, $J_{1',2'}$ = 7 Hz, $J_{2',3'}$ = 6 Hz, $C_{2'}H$), 5.80 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.89 (dd, 1, $J_{2',3'}$ = 6 Hz, $J_{3',4'}$ = 3 Hz, $C_{3'}H$), 6.70 (d, 1, $J_{1',2'}$ = 7 Hz, $C_{1'}H$), 8.35 ppm (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Anal. Calcd for $C_{11}H_{13}N_3O_6$ (311.25): C, 42.44; H, 4.21; N, 22.50. Found: C, 42.76; H, 4.39; N, 22.27.

2'-Azido-2'-deoxyuridine 5'-Phosphate (9).—Dicyclohexylcarbodiimide (824 mg, 4 mmol) was added to an anhydrous pyridine solution (5 ml) of **7** (311 mg, 1.0 mmol) and pyridinium 2-cyanoethyl phosphate (2 mmol).[6] After 24 hr at 23° paper electrophoresis (pH 7.5) of an aliquot indicated essentially complete conversion to a monoanion. Water (1 ml) was added and the mixture was kept overnight prior to dilution with water and filtration. The filtrate was evaporated to dryness, coevaporated with ethanol, and partitioned between water and ether. The aqueous phase (30 ml) was made 0.2 *N* in sodium hydroxide and heated at 100° for 30 min. The solution was passed through 20 ml of Dowex 50 (H^+) resin, adjusted to pH 8 with ammonia, and applied to a 2 × 40 cm column of DEAE Sephadex (HCO_3^-). Elution with a linear gradient of triethylammonium bicarbonate (4 l., 0.005–0.25 *M*) gave a major peak containing 8200 optical density units at 262 nm (82%). The pooled peak was evaporated *in vacuo* and repeatedly coevaporated with methanol. An aqueous solution of the final residue was passed through a 1 × 10 cm column of Dowex 50 (H^+) resin and the effluent was evaporated *in vacuo* to one half its volume. It was then neutralized to pH 8.5 with barium hydroxide, filtered, and precipitated by addition of two volumes of ethanol. After reprecipitation, the material was washed with ethanol, acetone, and ether and then dried *in vacuo*, giving 384 mg (69%) of the barium salt of **9** as the tetrahydrate.

This material was free of ultraviolet-absorbing or phosphorus-containing impurities as judged by paper chromatography in solvents I, II, III, IV, and V (R_f's 0.34, 0.50, 0.36, 0.42, 0.67), $\lambda_{max}^{pH\ 1}$ 260 nm (ϵ 10,500).

Anal. Calcd for $C_9H_{10}N_5O_8PBa \cdot 4H_2O$ (556.6): N, 12.58; P, 5.56. Found: N, 12.29; P, 5.84.

2'-Amino-2'-deoxyuridine 5'-Phosphate (2).—A solution of the barium salt of **9** (0.52 mmol) was passed through 10 ml of Dowex 50 (H^+) resin, and the acidic solution (30 ml) was stirred in an atmosphere of hydrogen in the presence of 100 mg of 5% palladium on barium sulfate catalyst.[10] After 40 min, paper electrophoresis in 1 *M* acetic acid showed reduction to be complete and the mixture was filtered through Celite. Evaporation of the filtrate left 180 mg of a white residue that was crystallized from water (2 ml) by slow addition of ethanol, giving 148 mg (88%) of **2** as needles which darken above 265° and decompose at 272–274°. This product was chromatographically homogeneous on paper in solvents I, II, III, IV, and V with R_f's of 0.21, 0.37, 0.12, 0.34, and 0.56; $\lambda_{max}^{pH\ 1}$ 260 nm (ϵ 9400).

Anal. Calcd for $C_9H_{14}N_3O_8P$ (323.2): C, 33.44; H, 4.36; N, 13.00. Found: C, 33.36; H, 4.46; N, 12.70.

2'-Azido-2'-deoxyuridine 3'-Phosphate (8).—A solution of pyridinium 2-cyanoethyl phosphate (2 mmol)[6] was rendered anhydrous by several evaporations with pyridine and to it was added 2'-azido-2'-deoxy-5'-*O*-trityluridine (**5**, 511 mg, 1 mmol). After one further evaporation, the mixture was dissolved in pyridine (10 ml), DCC (824 mg, 4 mmol) was added, and the solution was stirred at room temperature for 3 days. Water (2 ml) was added and the mixture was stirred overnight. It was then diluted with water (10 ml) and filtered, and the residue was washed with water. The filtrates were evaporated to dryness, coevaporated several times with ethanol to remove pyridine, and partitioned between water and ether. The aqueous solution was evaporated, dissolved in 80% acetic acid, and heated at 100° for 10 min. The solvent was evaporated *in vacuo* and residual acetic acid was carefully removed by coevaporation with ethanol. The residue was partitioned between water and ether and the aqueous solution was concentrated to 25 ml. This solution was made 0.2 *M* in sodium hydroxide and heated at 100° for 30 min. It was then passed through a column (1 × 15 cm) of Dowex 50 (H^+) resin and the effluent was adjusted to pH 8 with ammonia prior to application to a 2 × 30 cm column of DEAE Sephadex (HCO_3^-). The column was washed with water and eluted with a linear gradient (4 l.) of triethylammonium bicarbonate (0.005–0.25 *M*). A single major ultraviolet-absorbing peak (7000 optical density units at 262 nm, 70%) was obtained, pooled, and evaporated to dryness. After careful removal of residual bicarbonate by repeated coevaporation with methanol, the residue was dissolved in water and passed through a 1 × 10 cm column of Dowex 50 (H^+) resin. The acidic effluent was concentrated *in vacuo* to one-half its volume and adjusted to pH 8.7 with aqueous barium hydroxide. The solution was filtered and two volumes of ethanol were added. The resulting white precipitate was washed with ethanol, acetone, and ether and dried *in vacuo*, giving 333 mg (60%) of the barium salt of **8** as its tetrahydrate. It gave a single ultraviolet-absorbing and phosphorus-containing spot (R_f's 0.32, 0.48, 0.34, 0.47, 0.61) on paper chromatography using solvents I, II, III, IV, and V and on paper electrophoresis at pH 7.5, $\lambda_{max}^{pH\ 1}$ 260 nm (ϵ 10,800).

Anal. Calcd for $C_9H_{10}N_5O_8PBa \cdot 4H_2O$ (556.6): N, 12.58; P, 5.56. Found: N, 12.36; P, 5.58.

2'-Amino-2'-deoxyuridine 3'-Phosphate (3). A. From 8.—An aqueous solution of the barium salt of **8** (0.47 mmol) was passed through a column containing 5 ml of Dowex 50 (H^+) resin. The acidic effluent (25 ml) was vigorously stirred in a hydrogen atmosphere with 200 mg of a 5% palladium on barium sulfate catalyst for 80 min, at which time paper electrophoresis in 1 *M* acetic acid showed complete reduction giving a neutral, ninhydrin-positive spot. The mixture was filtered and evaporated to dryness, giving a white residue that was crystallized twice from hot aqueous ethanol, giving 112 mg (70%) of **3** as its monohydrate that darkens above 250° and has not melted at 280°: $\lambda_{max}^{pH\ 2}$ 258 nm (ϵ 9900); R_f's in solvents I, II, III, IV, and V 0.24, 0.37, 0.18, 0.42, and 0.56.

Anal. Calcd for $C_9H_{14}N_3O_8P \cdot H_2O$ (341.2): C, 31.68; H, 4.72; N, 12.31; P, 9.07. Found: C, 31.51; H, 4.78; N, 12.48; P, 8.93.

B.—Without Isolation of Intermediates.—An anhydrous pyridine (25 ml) solution of 2-cyanoethyl phosphate (4 mmol) and **5** (1.8 mmol) was mixed with DCC (1.65 g, 8 mmol) and stirred at room temperature for 3 days, at which point tlc (ethyl acetate–chloroform, 1:1) showed no further **5** to be present. After addition of water (5 ml) and storage for 1 hr, the mixture was evaporated to dryness and the residue was treated with 80% acetic acid (50 ml) at 100° for 30 min. The mixture was diluted with water (30 ml), filtered, and evaporated to dryness. After several coevaporations with water, the residue was dissolved in 1 *N* lithium hydroxide (10 ml) and heated at 100° for 30 min. The solution was passed through a column containing 25 ml of Dowex 50 (H^+) resin and the acidic effluent (50 ml) was stirred in a hydrogen atmosphere with 700 mg of 5% palladium on barium sulfate catalyst for 2 hr. After filtration of the catalyst, the solution was evaporated to dryness and the residue was crystallized from hot aqueous ethanol, giving 365 mg (60%) of **3** identical with that from A above.

Action of *Crotalus adamanteus* Venom on 2, 3, 8, and 9.—The enzyme used was a solution of 10 mg of crude *Crotalus adamanteus* venom in 1 ml of 0.1 *M* tris buffer at pH 8.0. The above enzyme solution (20 μl) was added separately to solutions containing 1 μmol of the free acids **2** and **3** and the ammonium salts of **8** and **9** in 0.05 ml of 0.1 *M* tris buffer pH 8 and incubated at 37°. Complete dephosphorylation of **2** and **9** to the parent nucleosides (**1** and **4**) was achieved within 2–3 hr, while **3** and **8** remained completely unchanged after 24 and 48 hr as shown by paper chromatography in solvent I.

Registry No.—**2**, 34407-64-2; **3**, 34407-65-3; **5**, 34407-66-4; **6**, 34407-67-5; **7**, 34407-68-6; **8** Ba salt, 34417-82-8; **9** Ba salt, 34407-69-7.

(10) Engelhard Industries, Newark, N. J.

Conversion of (−)-β-Hydrastine into (−)-Bicuculline and Related Phthalideisoquinolines

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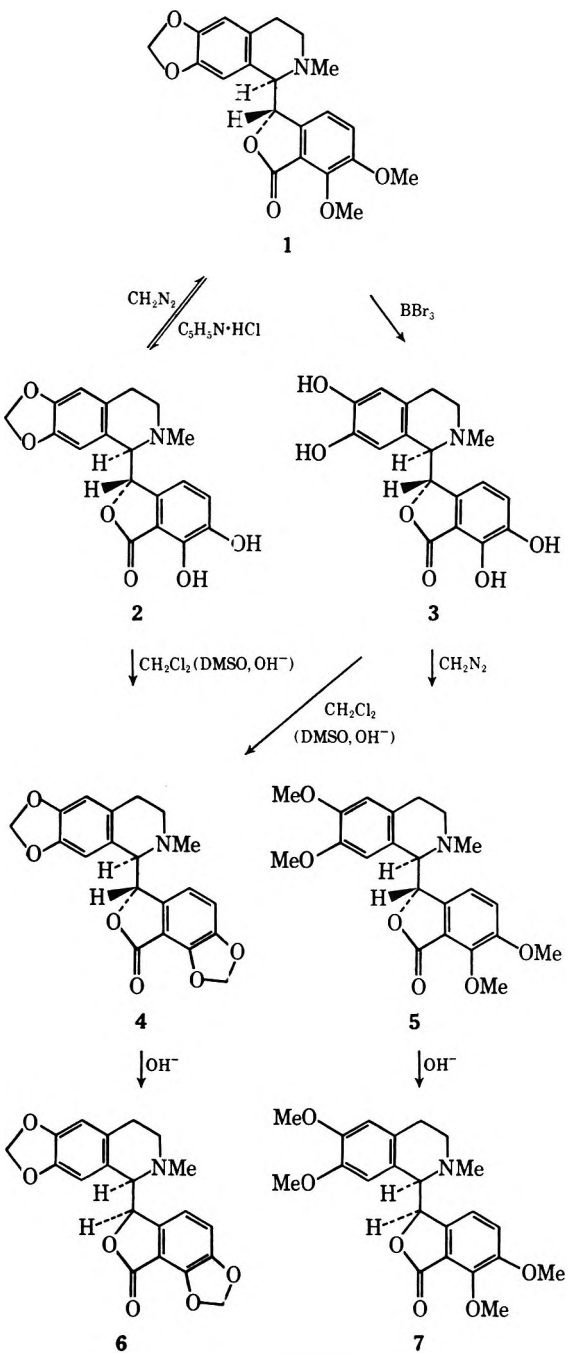
Commercially available (−)-β-hydrastine (1) was O-demethylated to the tetraphenol **3** followed by bis-O-methylenation or complete O-methylation to afford the rare phthalide alkaloid (−)-bicuculline (**4**) and the new phthalideisoquinoline (−)-cordrastine II (**5**), respectively. Alkaline isomerization provided the corresponding C-9 epimers capnoidine (**6**) and (−)-cordrastine I (**7**). An X-ray analysis of **4** HBr confirmed the assignments of absolute configuration.

In connection with our studies on the total synthesis of the benzazepine alkaloid rhoeadine,[1] a bismethylenedioxy-substituted phthalideisoquinoline was required as starting material. While the known[2] phthalide alkaloids (−)-bicuculline (**4**) and its epimer capnoidine (**6**) as well as the corresponding antipodes (+)-bicuculline and adlumidine contain such a substitution pattern, they are neither commercially available nor is their isomeric mixture, previously obtained by a multistep synthesis as *x*-bicuculline,[3] readily accessible. In contrast, we now report a facile and novel synthesis of the heretofore rare alkaloid (−)-bicuculline (**4**) based on O-dealkylation of commercially available (−)-β-hydrastine (**1**) followed by O-methylenation. Utilizing this approach, the tetramethoxy-substituted phthalideisoquinoline **5** was also prepared and the method was extended by isomerization of **4** and **5** to provide the C-9 epimers capnoidine (**6**) and **7**, respectively.

Treatment of (−)-β-hydrastine (**1**) with pyridine hydrochloride or boron tribromide in methylene chloride effected O-demethylation or complete deetherification to afford 30% of the diphenol **2** or 90% of the tetraphenol **3**, respectively. While diazomethane reconverted **2** into the starting material **1**, reaction of **2** or **3** in dimethyl sulfoxide with methylene chloride and 1 equiv of sodium hydroxide[4] provided in approximately 30% yield the same bismethylenedioxy-substituted phthalide **4**, identical in all respects with natural (−)-bicuculline.[2] Thus, the stereochemical assignment for the phenolic intermediates was secured.

As an extension of the utility of this approach, complete O-methylation of the tetraphenol **3** with diazomethane afforded the corresponding tetramethoxy-substituted phthalideisoquinoline **5**. In addition, treatment of **4** and **5** with alcoholic potassium hydroxide effected epimerization at the C-9 position to form the alkaloid capnoidine (**6**) and the related tetramethoxy derivative **7**, respectively.[4a] While the isomeric phthalides **5** and **7** are new, one of the racemates has been isolated as the alkaloid cordrastine[5] and the racemic diasteromers cordrastine I and cordrastine II have been obtained by synthesis.[6] By nmr and tlc comparison with the synthetic racemates,[7] **5** and **7** could be assigned as (−)-cordrastine II and (−)-cordrastine I, respectively.



(1) W. Klötzer, S. Teitel, and A. Brossi, *Helv. Chim. Acta*, **54**, 2057 (1971).

(2) For leading references, see F. Šantavý in "The Alkaloids," Vol. XII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1970, p 396.

(3) P. W. G. Groenewoud and R. Robinson, *J. Chem. Soc.*, 199 (1936).

(4) W. Bonthrone and J. W. Cornforth, *J. Chem. Soc. C*, 1202 (1969).

(4a) NOTE ADDED IN PROOF.—Recently G. Gáal, P. Kerekes and B. Bognár, *J. Prakt. Chem.*, **313**, 935 (1971), reported the epimerization of (−)-α-narcotine at the C-1 position by successive treatment with cyanogen bromide and mineral acid. It should therefore be possible to prepare all four isomers of **4** and **5**.

(5) R. H. F. Manske, *Can. J. Res.*, **B16**, 81 (1938).

(6) R. D. Haworth and A. R. Pinder, *J. Chem. Soc.*, 1776 (1950).

(7) We are grateful to Professor R. D. Haworth, Sheffield University, England, for providing us with samples of racemic cordrastine I and cordrastine II.

Based on comparison of the nmr, ORD, and CD spectral data, (−)-β-hydrastine (**1**), (−)-bicuculline (**4**), and (−)-cordrastine II (**5**) all possess the 1*R*,9*S* configuration, while the epimers capnoidine (**6**) and (−)-cordrastine I (**7**) belong to the 1*R*,9*R* series. Unequivocal confirmation of the absolute configuration of these interrelated phthalides, previously assigned by other methods,[2] was obtained by an X-ray crystallographic analysis[8] of (−)-bicuculline hydrobromide (**4** HBr).

Experimental Section[9]

(+)-1-(*R*)-[6,7-Dihydroxy-3-(*S*)-phthalidyl]-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (2).—A mixture of 5 g (12 mmol) of (−)-β-hydrastine hydrochloride (1 HCl) and 15 g of pyridine hydrochloride was heated at 190° in a N_2 atmosphere for 30 min. The resulting solution was cooled to room temperature and partitioned between 150 ml of a 1:1 mixture of EtOAc and saturated $NaHCO_3$. The aqueous phase was separated and extracted with two 75-ml portions of EtOAc, and the combined organic extracts were evaporated. The residue (2 g) was crystallized from 50 ml of CH_2Cl_2 to give 1.5 g (35%) of **2**: mp 210–211°; R_f (system A) 0.29; $[\alpha]_D$ +140° (*c* 1, 1 *N* HCl); nmr δ 2.43 (s, 3, NCH_3), 2.1–2.9 (m, 4, CH_2CH_2), 3.96, 5.55 (2 d, 2, *J* = 4 Hz, 2 CH), 5.68 (s, 2, 2 OH), 5.92 (d, 2, OCH_2O), 6.50, 6.62 (2 s, 2, 2 aromatic), 6.83, 6.93 (2 d, 2, *J* = 8 Hz, 2 aromatic); uv max 296 nm (ε 6250), 318 (4900), 220 (3050) (infl), 240 (11,000); ORD (*c* 0.138, MeOH) $[\phi]_{600}$ −10°, $[\phi]_{589}$ −15°, $[\phi]_{340}$ −5850° (tr), $[\phi]_{303}$ +12,870° (pk), $[\phi]_{282}$ +4180° (tr), $[\phi]_{248}$ +18,000° (pk), $[\phi]_{239}$ +14,780° (tr), $[\phi]_{234}$ +16,710° (pk), $[\phi]_{210}$ −179,400° (tr); CD (*c* 0.0036 *M*, MeOH) $[\theta]_{380}$ 0, $[\theta]_{317}$ −12,170; $[\theta]_{293}$ +2070, $[\theta]_{284}$ 0, $[\theta]_{261}$ +8020, $[\theta]_{252}$ 0, $[\theta]_{223}$ +110,600, $[\theta]_{212}$ 0, $[\theta]_{204}$ −249,000.

Anal. Calcd for $C_{19}H_{17}NO_6$: C, 64.22; H, 4.82; N, 3.94. Found: C, 64.55; H, 5.03; N, 3.78.

Reconversion of Diphenol 2 into (−)-β-Hydrastine (1).—A mixture of 500 mg (1.4 mmol) of **2** in 30 ml of MeOH containing an excess of CH_2N_2 in Et_2O was stored at 4° for 2 hr and then at 25° for 18 hr. The solution was evaporated in a stream of N_2, and the residue was suspended in H_2O and extracted with CH_2Cl_2. The extract was acidified with ethanolic HCl and evaporated, and the residue was crystallized from a mixture of EtOH and Et_2O to give 400 mg (69%) of 1 HCl, mp 116–117°, $[\alpha]_D$ +121° (*c* 4, 1 *N* HCl), identical in mixture melting point, tlc, and optical rotation with authentic (−)-β-hydrastine hydrochloride.

(+)-1-(*R*)-[6,7-Dihydroxy-3-(*S*)-phthalidyl]-6,7-dihydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (3 HCl).—To a solution of 20 g (48 mmol) of (−)-β-hydrastine hydrochloride (1 HCl) in 300 ml of CH_2Cl_2 at −70° was added over 20 min a solution of 31 g (124 mmol) of BBr_3 in 250 ml of CH_2Cl_2. After stirring at room temperature for 17 hr, the reaction mixture was cooled to 4°, 300 ml of MeOH was added over 20 min, and then the mixture was evaporated. The residue was dissolved in 300 ml of H_2O and rendered neutral with saturated $NaHCO_3$, and the resulting precipitate was collected and dissolved in ethanolic HCl. The solution was evaporated and the residue was crystallized from a mixture of EtOH and Et_2O to give 16 g (90%) of **3** HCl: mp 205–206°; R_f (system A) 0.08; $[\alpha]_D$ +176.6° (*c* 1, MeOH); nmr δ 2.73 (s, 3, NCH_3), 2.6–4.0 (m, 4, CH_2CH_2), 4.96, 5.55 (2 s, 2, 2 CH), 6.27, 6.57 (2 s, 2, 2 aromatic), 7.08, 7.25 (2 d, 2, *J* = 8 Hz, 2 aromatic), 8.63, 9.04, 9.68, 9.98 (4 br, 4, 4 OH); uv max 292 nm (ε 4500), 321 (4500), 220 (27,500) (infl), 240 (10,000); ORD (*c* 0.344, MeOH) $[\phi]_{600}$ +470°, $[\phi]_{589}$ +500°, $[\phi]_{349}$ +1690° (tr), $[\phi]_{298}$ +18,780° (pk), $[\phi]_{281}$ +12,150° (tr), $[\phi]_{242}$ +55,240° (pk), $[\phi]_{210}$ −403,220° (tr); CD (*c* 0.0091 *M*, MeOH) $[\theta]_{370}$ 0, $[\theta]_{319}$ −5300, $[\theta]_{301}$ 0, $[\theta]_{290}$ +6960, $[\theta]_{271}$ +2100, $[\theta]_{226}$ +165,700, $[\theta]_{214}$ 0, $[\theta]_{207}$ −353,500.

Anal. Calcd for $C_{18}H_{17}NO_6 \cdot HCl$: C, 56.92; H, 4.78; N, 3.69. Found: C, 56.69; H, 5.13; N, 3.50.

(−)-2-Methyl-6,7-methylenedioxy-1-(*R*)-[6,7-methylenedioxy-3-(*S*)-phthalidyl]-1,2,3,4-tetrahydroisoquinoline [(−)-Bicuculline] (4). A. From 3.—A mixture of 10.4 g (27.4 mmol) of **3** HCl and 5.6 g (140 mmol) of powdered NaOH in 40 ml of CH_2Cl_2 and 140 ml of DMSO was stirred at 120° under a N_2 atmosphere for 1 hr, cooled, adjusted to pH 2 with 3 *N* HCl, and evaporated under reduced pressure. The residue was triturated with two 200-ml portions of CH_2Cl_2 and filtered, and the combined organic extracts were washed with 100-ml portions of saturated $NaHCO_3$ and evaporated. The residue (7 g) was dissolved in 100 ml of benzene and chromatographed over 35 g of silica gel. Elution with 500 ml of a 2:3 mixture of EtOAc and benzene followed by evaporation and crystallization from EtOH gave 3.4 g (34%) of **4**: mp 193–194°; $[\alpha]_D$ −120° (*c* 1, $CHCl_3$); $[\alpha]^{33}D$ −128° (*c* 0.27, $CHCl_3$) [lit.[10] mp 193–195°, $[\alpha]^{33}D$ −110° (c 0.27, $CHCl_3$); R_f (system B) 0.4; nmr ($CDCl_3$) δ 2.60 (s, 3, NCH_3), 2.0–3.0 (m, 4, CH_2CH_2), 4.09, 5.63 (2 d, 2, *J* = 4 Hz, 2 CH), 5.97, 6.20 (2, 2, 4, 2 OCH_2O), 6.25, 6.95 (2 d, 2, *J* = 8 Hz, 2 aromatic), 6.50, 6.64 (2 s, 2, 2 aromatic); uv max 220 nm (ε 29,300), 235 (11,700) (infl), 296 (6500), 320 (5500); ORD (*c* 0.184, 0.1 *N* HCl) $[\phi]_{650}$ +260°, $[\phi]_{589}$ +320°, $[\phi]_{348}$ +200° (tr), $[\phi]_{301}$ +9900° (pk), $[\phi]_{284}$ +4860° (tr), $[\phi]_{248}$ +26,500° (pk), $[\phi]_{242}$ +25,500° (tr), $[\phi]_{236}$ +29.500° (pk), $[\phi]_{209}$ −280,000° (tr); CD (*c* 0.005 *M*, 0.1 *N* HCl) $[\theta]_{365}$ 0, $[\theta]_{324}$ −3200, $[\theta]_{303}$ 0, $[\theta]_{294}$ +4600, $[\theta]_{273}$ +400, $[\theta]_{228}$ +106,000, $[\theta]_{213}$ 0, $[\theta]_{204}$ −332,000. ORD and CD mirror images of natural (+)-bicuculline[11] (antipode of **4**) were within experimental error.

Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.51; H, 4.87; N, 3.80.

An aliquot of **4** was converted into the hydrobromide with ethanolic HBr and crystallized from EtOH: mp 257–258°; $[\alpha]_D$ +96.9° (*c* 1, MeOH); nmr δ 2.97 (s, 3, NCH_3), 2.8–3.7 (m, 4, CH_2CH_2), 5.31, 5.70 (2 s, 2, 2 CH), 5.91, 5.98 (s, 2, OCH_2O), 6.25, 6.29 (s, 2, OCH_2O), 6.33, 6.84 (2 s, 2, 2 aromatic), 7.42 (s, 2, aromatic); uv max 222 nm (ε 27,600), 235 (11,900) (infl), 295 (6120), 322 (5540); ORD (*c* 0.448, MeOH) $[\phi]_{600}$ +390°, $[\phi]_{589}$ +409°, $[\phi]_{340}$ −1000° (tr), $[\phi]_{302}$ +13,500° (pk), $[\phi]_{281}$ +2750° (tr), $[\phi]_{244}$ +37,500° (pk), $[\phi]_{237}$ +35,000° (tr), $[\phi]_{233}$ +38,750° (pk), $[\phi]_{211}$ −269,960° (tr); CD (*c* 0.01 *M*, MeOH) $[\theta]_{380}$ 0, $[\theta]_{320}$ −5200, $[\theta]_{303}$ 0, $[\theta]_{294}$ +6300, $[\theta]_{275}$ 0, $[\theta]_{268}$ −1000, $[\theta]_{261}$ −200, $[\theta]_{255}$ −1100, $[\theta]_{252}$ 0, $[\theta]_{226}$ +136,000, $[\theta]_{214}$ 0; X-ray[8] orthorhombic, space group $P2_12_12_1$, a = 8.720, b = 8.882, c = 25.645 Å, Z = 4, d_{obsd} = 1.48 g cm^{-3}, μ (Cu Kα) = 34.4 cm^{-1}, R = 3.7% (all atoms except hydrogens anisotropic).

Anal. Calcd for $C_{20}H_{17}NO_6 \cdot HBr$: C, 53.59; H, 4.05; N, 3.13. Found: C, 53.62; H, 4.14; N, 3.05.

B. From 2.—A mixture of 3.5 g (20 mmol) of **2** and 0.9 g (42 mmol) of powdered NaOH in 10 ml of CH_2Cl_2 and 30 ml of DMSO was heated at 120° under N_2 for 1 hr and worked up by the procedure given above to yield 1.1 g (30%) of **4**, identical in mixture melting point, tlc, and optical rotation with **4** prepared *via* **A**.

(−)-2-Methyl-6,7-dimethoxy-1-(*R*)-[6,7-dimethoxy-3-(*S*)-phthalidyl]-1,2,3,4-tetrahydroisoquinoline [(−)-Cordrastine II] (5).—A mixture of 7 g (18.5 mmol) of **3** HCl in 50 ml of MeOH containing an excess of CH_2N_2 in Et_2O was stored at 4° for 4 hr and then at room temperature for 48 hr. The solution was evaporated at 40° in a stream of N_2, the residue was suspended in water and extracted with EtOAc, and the extract was chromatographed over 30 g of silica gel. Elution with 300 ml of EtOAc followed by evaporation gave 5.5 g of a residue which was dissolved in ethanolic HBr, evaporated, and crystallized from

(8) We are indebted to our colleague Dr. J. F. Blount for the X-ray analysis; details will be published independently.

(9) Melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. Thin layer chromatography employed silica gel G plates developed for 10 cm with either solvent system A (80 CH_3CN:20 NH_4OH), system B (1 EtOAc:1 benzene), or system C (EtOAc) and visualized with modified Dragendorff's reagent. Nmr spectra were obtained in DMSO-d_6, unless otherwise noted, on a Varian HA-100 instrument. Uv spectra were measured in 2-propanol with a Cary recording spectrophotometer, Model 14M. Optical rotations were measured with a Perkin-Elmer model at 25° unless otherwise indicated. Rotatory dispersion curves were determined at 23° with a Durrum-Jasco spectrophotometer, Model 5, using 1-cm, 0.1-cm, or 0.1-mm cells. Circular dichroism curves were measured on the same instrument and are expressed in molecular ellipticity units [θ]. Extracts of products were washed with water and dried over anhydrous sodium sulfate prior to evaporation. Reported yields are of isolated products homogeneous to tlc.

(10) M. S. Yunusov and S. Yu. Yunusov, *Chem. Natur. Compounds*, **4**, 54 (1968); *Chem. Abstr.*, **69**, 684a (1968).

(11) G. Snatzke, W. Wollenberg, J. Hrbek, Jr., F. Šantavý, K. Bláha, W. Klyne, and R. J. Swan, *Tetrahedron*, **25**, 5059 (1969).

EtOH to yield 5.2 g (59%) of **5** HBr: mp 212–213°; $[\alpha]_D$ +188° (*c* 1, MeOH); nmr δ 3.05 (s, 3, NCH_3), 2.8–3.8 (m, 4, CH_2CH_2), 2.68 (s, 3, OCH_3), 3.71 (s, 6, 2 OCH_3), 3.87 (s, 3, OCH_3), 5.32, 5.40 (2 s, 2, 2 CH), 6.39, 6.84 (2 s, 2, 2 arom), 7.66, 7.81 (2 d, 2, J = 8 Hz, 2 aromatic); uv max 220 nm (ϵ 31,500) (infl), 235 (17,900) (infl), 289 (4550), 311 (3950).

Anal. Calcd for $C_{22}H_{25}NO_6 \cdot HBr$: C, 55.01; H, 5.46; N, 2.92. Found: C, 54.69; H, 6.01; N, 2.56.

Neutralization of the above hydrobromide and crystallization of the resulting free base from a mixture of ether and petroleum ether (bp 30–60°) afforded **5**: mp 90°; $[\alpha]_D$ −10° (*c* 1, $CHCl_3$); R_f (system C) 0.09; nmr δ 2.47 (s, 3, NCH_3), 2.1–2.9 (m, 4, CH_2CH_2), 3.46, 3.69 (2 s, 6, 2 OCH_3), 3.79 (s, 6, 2 OCH_3), 4.04, 5.75 (2 d, 2, J = 3.5 Hz, 2 CH), 6.31 (s, 1, aromatic), 6.59 (d, 1, J = 8 Hz, aromatic), 6.65, 7.30 (2 s, 2 2 aromatic); uv max 220 nm (ϵ 22,600) (infl), 235 (11,850) (infl), 290 (4170), 310 (3380); ORD (*c* 0.415, MeOH) $[\phi]_{700}$ +209°, $[\phi]_{589}$ +740°, $[\phi]_{334}$ −910° (tr), $[\phi]_{296}$ +11,060° (pk), $[\phi]_{285}$ +9370° (tr), $[\phi]_{245}$ +49,610° (pk), $[\phi]_{209}$ −245,660° (tr); CD (*c* 0.01 *M*, MeOH) $[\theta]_{360}$ 0, $[\theta]_{360}$ 0, $[\theta]_{317}$ −7400, $[\theta]_{292}$ 0, $[\theta]_{289}$ +480, $[\theta]_{285}$ 0, $[\theta]_{272}$ −2500, $[\theta]_{261}$ 0, $[\theta]_{222}$ +94,200, $[\theta]_{210}$ 0, $[\theta]_{203}$ −168,270; identical within experimental error in tlc and nmr which we obtained with racemic cordrastine II[7] (racemate of **5**).

Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.14; H, 6.23; N, 3.45.

(−)-2-Methyl-6,7-methylenedioxy-1-(*R*)-[6,7-methylenedioxy-3-(*R*)-phthalidyl]-1,2,3,4-tetrahydroisoquinoline (Capnoidine) (6).—A solution of 3 g (0.82 mmol) of **4** and 3 g (54 mmol) of KOH in 50 ml of MeOH was refluxed for 72 hr, acidified with 6 *N* HCl, and evaporated. The residue was dissolved in 5% $NaHCO_3$ and extracted with Me_2Cl_2, and the extract was evaporated. The residue was crystallized from 50 ml of a 9:1 mixture of benzene and EtOAc to give 2 g (66%) of **6**: mp 239–240° (lit.[12] mp 236°); $[\alpha]_D$ −114° (*c* 1, $CHCl_3$) [lit.[13] $[\alpha]_D$ −113.2° (*c* 2, $CHCl_3$)]; R_f (system B) 0.78; nmr ($CDCl_3$) δ 2.49 (s, 3, NCH_3), 2.3–3.2 (m, 4, CH_2CH_2), 3.93, 5.60, (2 d, 2, J = 3.5 Hz, 2 CH), 5.82, 6.17 (2 s, 4, 2 OCH_2O), 6.37, 6.64 (2 s, 2, 2 aromatic), 6.89, 7.11 (AB, 2, J = 8 Hz, aromatic); uv max 221 nm (*c* 28,100), 235 (12,200) (infl), 2.96 (6050), 322 (5300); ORD (*c* 0.177, 0.1 *N* HCl) $[\phi]_{600}$ −55°, $[\phi]_{589}$ −57°, $[\phi]_{348}$ +2755° (pk), $[\phi]_{300}$ −5510° (tr), $[\phi]_{287}$ −4580° (pk), $[\phi]_{275}$ −4990° (tr), $[\phi]_{260}$ −3220° (pk), $[\phi]_{233}$ −72,780° (tr), $[\phi]_{213}$ +127,400° (pk); CD (*c* 0.001 *M*, 0.1 *N* HCl) $[\theta]_{400}$ 0, $[\theta]_{324}$ +6146, $[\theta]_{293}$ +1560, $[\theta]_{250}$ +19,380, $[\theta]_{241}$ 0, $[\theta]_{224}$ −120,800, $[\theta]_{213}$ 0, $[\theta]_{206}$ +106,250; identical within experimental error in ORD and CD with natural capnoidine.[11]

Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.59; H, 4.82; N, 3.77.

Evaporation of the mother liquors followed by crystallization from 20 ml of ethanol afforded 1 g (33%) of unreacted **4**. Treatment of **6** with KOH in MeOH effected epimerization to give a 9:1 mixture of **6** and **4** as visualized by tlc.

(−)-2-Methyl-6,7-dimethoxy-1-(*R*)-[6,7,dimethoxy-3-(*R*)-phthalidyl]-1,2,3,4-tetrahydroisoquinoline [(−)-Cordrastine I] (7).—A solution of 6 g (12.5 mmol) of **5** HBr and 6 g (107 mmol) of KOH in 120 ml of MeOH was refluxed for 72 hr and worked up by the procedure in the preceding example to yield a reaction product which upon crystallization from EtOH afforded 3 g (60%) of **7**: mp 189–190°; R_f (system C) 0.58; $[\alpha]_D$ −99° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 2.61 (s, 3, NCH_3), 2.2–3.2 (n, 4, CH_2-CH_2), 3.69 (s, 3, OCH_3), 3.77 (s, 6, 2 OCH_3), 3.86 (s, 3, OCH_3), 4.02, 5.57 (2 d, 2, J = 3.5 Hz, 2 CH), 6.33, 6.66 (2 s, 2, 2 aromatic), 6.97, 7.28 (2 d, 2, J = 8 Hz, 2 aromatic); uv max 220 nm (ϵ 32,000) (infl), 290 (4800), 310 (3720); ORD (*c* 0.367, 0.1 *N* HCl) $[\phi]_{700}$ −72°, $[\phi]_{589}$ −86°, $[\phi]_{328}$ +4620° (pk), $[\phi]_{292}$ −9800° (tr), $[\phi]_{264}$ −3670° (pk), $[\phi]_{251}$ −6670° (tr), $[\phi]_{245}$ −5170° (pk); $[\phi]_{227}$ −99,300° (tr); CD (*c* 0.009 *M*, 0.1 *N*HCl) $[\theta]_{260}$ 0, $[\theta]_{310}$ +11,300, $[\theta]_{284}$ +870, $[\theta]_{238}$ +39,130, $[\theta]_{231}$ 0, $[\theta]_{216}$ −160,870, $[\theta]_{208}$ 0; identical within experimental error in tlc and nmr which we obtained with racemic cordrastine I[7] (racemate of **7**).

Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.18; H, 6.30; N, 3.51.

The above mother liquors were adjusted to pH 2 with ethanolic HBr and evaporated, and the residue was crystallized from EtOH to yield 1.7 g (28% of unreacted **5** HBr.

(12) R. H. F. Manske, *Can. J. Res.*, **14B**, 347 (1936).
(13) R. H. F. Manske, *J. Amer. Chem. Soc.*, **72**, 3207 (1950).

Registry No.—**1** HCl, 5936-28-7; **2**, 34408-04-3; **3** HCl, 34408-05-4; **4**, 19730-80-4; **4** HBr, 34408-06-5; **5**, 34408-07-6; **5** HBr, 34417-89-5; **6**, 25344-52-9; **7**, 34408-08-7.

Acknowledgment.—We wish to thank the following members of our Physical Chemistry Department (Director, Dr. R. P. W. Scott): Dr. F. Scheidl for the microanalyses, Dr. T. Williams for the nmr spectra, Dr. V. Toome for the uv, ORD, and CD spectra, and Dr. J. F. Blount for the X-ray crystallography.

Opium Alkaloids. XIII.[1,2a] Isolation of 16-Hydroxythebaine

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Received November 11, 1971

A new hydrophenanthrene alkaloid has been isolated from opium and characterized as 16-hydroxythebaine by means of uv, ir, nmr, and mass spectrometry.

The hydrophenanthrene alkaloids of opium have been studied extensively, and their biosynthesis in the living plant has been established in considerable detail. Investigation of the minor alkaloid constituents of opium has led to the isolation of a new alkaloid of this group. It was isolated from the nonphenolic alkaloid fraction of opium and purified by preparative thin-layer chromatography (tlc) on silica gel and by column chromatography on neutral aluminum oxide.

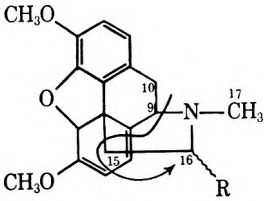
(1) See E. Brochmann-Hanssen, *J. Pharm. Sci.*, in press, for paper XII in this series.

(2) (a) Supported by Research Grant No. MH-03487 from the National Institute of Mental Health, Bethesda, Md. (b) To whom inquiries should be directed.

Structural Studies. Gas Chromatography.—When subjected to gas chromatographic analysis (glc), the new alkaloid had the same retention time as thebaine on a nonpolar column (2% silicone rubber, SE-30, 200°, 8 min). However, treatment with bistrimethylsilylacetamide (BSA) resulted in a slight but noticeable shortening of the retention time indicating the presence of an active hydrogen. On a polar cyanosilicone column (2% XE-60, 210°) the effect of silylation was more pronounced, the retention time shifting from 22 to 10 min while that of thebaine remained unchanged.

Mass Spectrometry.—The mass spectrum displayed a molecular ion peak at *m/e* 327 shown by accurate

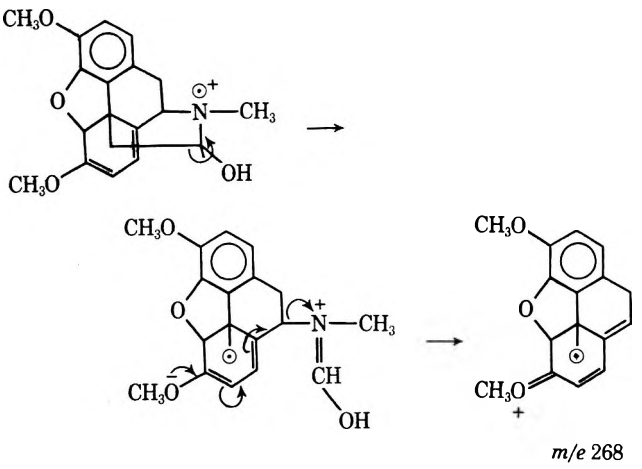
mass measurements[3,4] to correspond to $[C_{19}H_{21}NO_4]^+$. The fragmentation pattern was very similar to that reported for thebaine[5] which has the empirical formula $C_{19}H_{21}NO_3$. This strongly suggested that the new compound might be an oxygenated thebaine derivative. The nature of the oxygen function as a free hydroxyl group was indicated by a peak at *m/e* 309 corresponding to $C_{19}H_{19}NO_3$ (M − H_2O). This was further substantiated by an increase in the molecular ion of one mass unit on deuteration with CH_3OD while the *m/e* 309 fragment remained unchanged (M − HOD). Silylation gave a mono-TMS derivative (M^+ = 399, corresponding to $C_{22}H_{29}NO_4Si$) in which the actual silylation of the hydroxyl function can be deduced from the observation of an abundant M − Me_3SiOH fragment at *m/e* 309 of proper composition. The most prominent fragment of the spectrum (*m/e* 254) has the composition $C_{16}H_{11}O_3$, reflecting the loss of a C_3H_7NO moiety comprising the hydroxyl substituent. This may also be concluded from the fact that the peak at *m/e* 254 remained unshifted in the spectrum of the deuterated compound. The positions of attachment of the hydroxyl group, therefore, appeared to be limited to C-15, C-16, and C-17 (I). Comparable elimination of a C_3/N unit under loss, gain, or retention of hydrogen (M − C_3H_6N, M − C_3H_8N, and M − C_3H_7N, in decreasing importance) is highly characteristic of the fragmentation behavior of thebaine and represents the most prominent feature of the upper mass range of its spectrum.



I

Analysis of the less abundant fragments M − C_2/N and C_2/N under high resolution conditions permitted distinction between the two likely sites of attachment, C-15 and C-16, in favor of the latter. Attachment to C-17 (=N-$^{17}CH_2OH$) could largely be disregarded on grounds of chemical instability. While thebaine displays an appreciable peak at *m/e* 268 which consists, contrary to earlier observations, of the two components M − C_2H_5N and M − C_2H_3O in a ratio of approximately 2:1, hydroxythebaine formed a corresponding M − C_2H_5NO species of even higher abundance. This demonstrated loss of the nitrogen atom together with the hydroxyl group and the two α-carbon atoms, C-16 and C-17, and established the former as the most likely site of attachment. In thebaine, generation of an unstabilized primary radical (C-15) makes initial α cleavage of the C-15/C-16 bond less favorable in comparison to 9,10 cleavage, but should gain additional driving force upon donor substitution at C-16

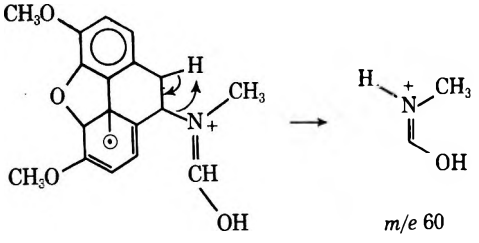
SCHEME I



(Scheme I). This type of cleavage generates a suitable leaving group for subsequent heterolytic dissociation of an allylic immonium ion, shown recently to represent a favorable mode of fragmentation in comparable benzylic heterolysis.[6]

Inspection of the C_2/N ions gave additional support for the presence of a hydroxyl group at the 16 position. The *m/e* 44 fragment (C_2H_6N) of thebaine has its analog in a less abundant, but nevertheless highly characteristic C_2H_6NO fragment at *m/e* 60 (Scheme II).

SCHEME II



The fragmentation of the 16-TMSO derivative exhibited similar features, *e.g.*, loss of a $C_2H_4NOSiMe_3$ moiety from the molecular ion (*m/e* 399 → *m/e* 268) and formation of a $C_2H_5NOSiMe_3$ species (*m/e* 132). This is in perfect analogy to loss of C_2H_5NO and formation of a C_2H_6NO fragment in the case of 16-hydroxythebaine.

Uv, Ir, and Nmr Spectroscopy.—The uv spectrum of the isolated substance in ethanol gave maxima at 225 and 285 mμ and was very similar to the spectrum of thebaine.[7] Similarity with thebaine is also apparent in the ir spectra of the compound taken under various conditions.[8] Characteristic differences are mainly observed in the carbonyl region, *i.e.*, in a band at 1735 cm^{-1}, absent in thebaine[9] and strongly dependent in its intensity on the pH of the medium. It is of low intensity in liquid films deposited on KBr and in $CHCl_3$ solution, however, very intense after addition of traces of NaOH to the latter. This band is likely to be due to the carbonyl function of an "open" amino aldehyde tautomer which exists in equilibrium with the cyclic α-

(3) Complete real-time high-resolution spectra were obtained at a resolving power of approximately 20,000 by scanning an MS-902 mass spectrometer on line with an SDS Sigma computer.

(4) The authors wish to thank Dr. A. L. Burlingame of the Space Sciences Laboratory of the University of California, Berkeley, for access to his high-resolution mass spectrometry facilities, and Mr. B. R. Simoneit of the same laboratory for assistance in the precise mass measurements.

(5) D. M. S. Wheeler, T. H. Kinstle, and K. L. Rinehart, Jr., *J. Amer. Chem. Soc.*, **89**, 4494 (1967).

(6) W. J. Richter and W. Vetter, *Org. Mass Spectrom.*, **2**, 781 (1969).

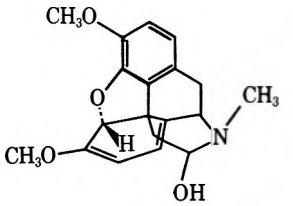
(7) A. W. Sangster and K. L. Stuart, *Chem. Rev.*, **65**, 69 (1965).

(8) The authors are indebted for these measurements to Mr. K. O. Alt, Ciba-Geiby AG, CH-4002 Basle, Switzerland.

(9) Sadtler Standard Spectra, Midget Edition, Spectrum Number 4104, edited by Sadtler Research Laboratories, Inc., Philadelphia, Pa. 19104.

hydroxyamine form. The nmr spectrum[10] in deuteriochloroform with internal TMS standard also showed distinct similarities to that of thebaine: two methoxyl singlets at 3.86 and 3.62 (thebaine, 3.84 and 3.59) and a *N*-methyl group at 3.40 ppm (thebaine, 2.46). The spectrum further showed a one-proton singlet (C-5) at 5.41 (thebaine, 5.29) and two doublets (J = 6–7 cps) representing the C-7 and C-8 protons, resonating at 5.82 and 5.11 (thebaine, 5.54 and 5.02), and two aromatic protons in an AB quartet at 6.65 and 6.68 ppm (thebaine, 6.61 and 6.64). The strong downfield shift of the *N*-methyl protons indicated the presence of an electron-withdrawing group on an adjacent carbon atom.

It seems reasonable that the 16-hydroxy function may exist in solution in both epimeric forms interconvertible *via* the amino aldehyde.[11] However, the axial orientation of the hydroxy group in a half-chair conformation of the piperidine ring (II) may be considered the most prominent molecular species based on the downfield shift of the protons at C-5, C-7, and C-8.



II

Alkaloids which contain a hydroxyl group in the α position to the heterocyclic nitrogen are not uncommon, but have not been found previously among the hydrophenanthrenes. Thebaine is a very reactive molecule, and one cannot exclude the possibility that 16-hydroxythebaine may be an artifact produced during the drying or storage of opium or during the isolation and purification of the alkaloids. So far, extensive studies of the chemical reactions of thebaine have not revealed a product of this nature. *In vitro* oxidation of codeine introduces a hydroxyl function in the 10 position.[12] On the other hand, the biosynthesis postulated for several opium alkaloids involve oxidation at a carbon atom adjacent to the nitrogen, *e.g.*, biosynthesis of chelidonine, narcotine, porphyroxine, or protopine. It is, therefore, conceivable that the hydroxyl group is introduced at the reticuline stage and that 3-hydroxyreticuline may undergo biotransformation in the normal way to 16-hydroxythebaine. This view gains support from the fact that (+)-reticuline produced in the biosynthetic sequence is racemized in the opium poppy by an oxidation–reduction system.[13]

(10) Japan Electronic Optics Laboratory Model JNM 4H-100.

(11) R. W. King, C. F. Murphy, and W. C. Wildman, *J. Amer. Chem. Soc.*, **87**, 4912 (1965).

(12) H. Rapoport and G. W. Stevenson, *ibid.*, **76**, 1796 (1954).

(13) A. R. Battersby, D. M. Foulkes, and R. Binks, *J. Chem. Soc.*, 3323 (1965).

(14) E. Brochmann-Hanssen, B. Nielsen, and K. Hirai, *J. Pharm. Sci.*, **56**, 754 (1967).

(15) E. Brochmann-Hanssen, A. Y. Leung, K. Hirai, and G. Zanati, *Planta Med.*, **18**, 366 (9970).

Experimental Section

Isolation.—Four pounds of powdered opium of Indian origin were extracted and a preliminary separation of alkaloid groups was carried out as described in a previous communication.[14] A chloroform solution of the nonphenolic fraction was concentrated under reduced pressure. Addition of methanol gave a heavy precipitate containing mainly codeine and cryptopine. The filtrate was evaporated to dryness and the residue was extracted with ether. The ether solution was concentrated and subjected to preparative tlc on silica gel with chloroform–methanol (9:1) (double development). The alkaloid band having the lowest R_f value (*ca.* 0.05) was scraped off and extracted with methanol. The methanol solution, which contained several alkaloids as indicated by glc and analytical tlc, was concentrated and chromatographed on a column of neutral alumina (Woelm, activity IV) with benzene and ethanol. The polarity of the eluent was increased gradually during the elution by increasing the concentration of ethanol from 0 to 50%. The progress of the elution was monitored by glc and micro tlc. After the elution of 13-oxycryptopine[15] a new alkaloid appeared in the eluate. The fractions containing this alkaloid were combined and evaporated to dryness under reduced pressure. The yellowish-brown residue (29 mg) was crystallized from a mixture of acetone and petroleum ether (bp 30–60°), yielding pale yellow crystalline prisms which melted at 126–128° (capillary) and 118–119° (micro mp, K.). The crystalline compound exhibited single, well-defined spots in three different tlc systems, *e.g.*, silica gel with chloroform–methanol (9:1) and benzene–ethanol (4:1), alumina with benzene–ethanol (4:1).

Registry No.—II, 34388-67-5.

The Hydroboration of Dihydrothujopsene

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Received December 7, 1971

The hydroboration of dihydrothujopsene (2) at room temperature affords as the major component the abnormal hydroboration addition product, tertiary alcohol **7**, and a minor product, diol 8, derived from the normal hydroboration addition orientation.

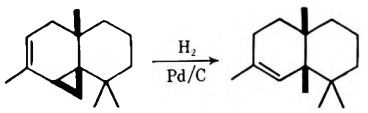
Although a number[1] of recent publications have dealt with the intriguing chemistry of the sesquiterpene hydrocarbon (−)-thujopsene (1) there has appeared no chemistry pertaining to dihydrothujopsene[2] (2), derived from 1 by catalytic 1,4 reduction.

During the course of some systematic investigations on the chemistry of thujopsene-derived hydrocarbons, we examined the hydroboration of dihydrothujopsene (2), expecting to obtain the secondary alcohol mixture **3** and **4** for eventual oxidation to the corresponding ketones. Although two products in a 77:23 ratio were indeed isolated in an overall yield of 84%, neither of these afforded the spectral or chemical characteristics compatible with secondary alcohols **3** and **4**.

The major component of the hydroboration reaction

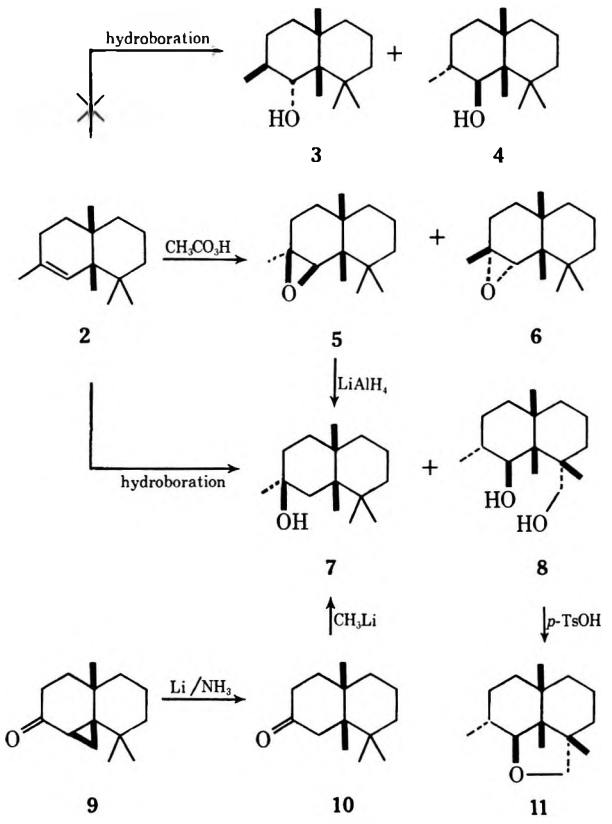
(1) See H. U. Daeniker, A. R. Hochstetler, K. Kaiser, and G. C. Kitchens, *J. Org. Chem.*, **37**, 1 (1972), and references cited therein.

(2) T. Norin, *Acta Chem. Scand.*, **15**, 1676 (1961).

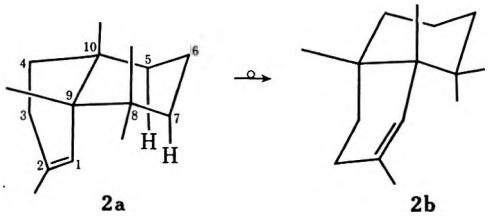


1 2

clearly was a tertiary alcohol, as evidenced by five methyl singlets in the nmr spectrum and by its inertness toward standard Jones reagent. Furthermore, this alcohol **7** was found to be identical with the tertiary alcohol obtained by reduction of epoxide **5** and with the tertiary alcohol derived from ketone **10** by treatment with methyllithium. The structure of ketone **10** is well established, since it is easily obtained *via* Birch reduction of the known ketone dihydromayurone (**9**).[3]



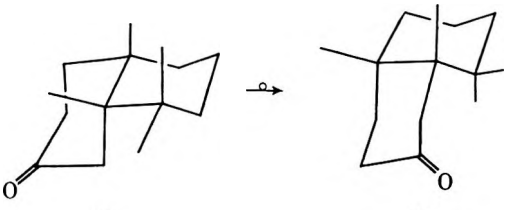
The conversion of epoxide **5** to tertiary alcohol **7** shows that both epoxidation and hydroboration occur predominantly from the same face of the precursor dihydrothujopsene molecule. Although the cis ring fusion in **2** forces us to consider both steroid (**2a**) and nonsteroid (**2b**) cis decalin forms, conformational



2a 2b

analysis indicates that the steroid form **2a** should be favored. Attack of an external reagent on the least hindered β face of the double bond (the α face is badly hindered by the axial hydrogens at C-5 and C-7) affords the stereochemistry indicated for the major epoxide **5** and the major hydroboration product **7**. The same conclusion, β-face attack for hydroboration, has been published for the structurally and conformationally closely related (−)-thujopsene (**1**) molecule,[4] and for the epoxidation of 5β-Δ^3-cholestene, reported[5] to favor β-face over α-face attack by a 9:1 ratio.

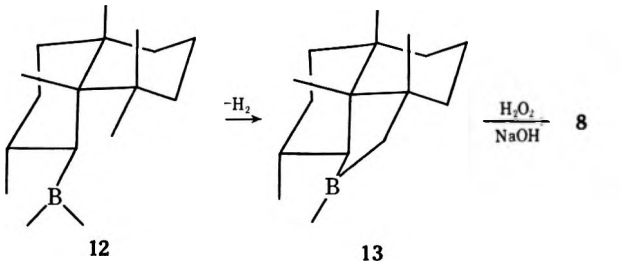
Additional proof for the stereochemical assignment is afforded by the conversion of ketone **10** to tertiary alcohol **7**. Steroid conformation **10a**, again the most



10a 10b

favored, predicts attack from the less hindered α face to afford alcohol **7**, as found, whereas the less favored conformation **10b** predicts β-face attack with formation of the epimeric tertiary alcohol. Previous reports in 3-keto steroids with a cis A–B ring fusion, where the steroid conformation for rings A and B must hold due to the trans B-C ring fusion, show that the major alcohol product from Grignard reactions is indeed that obtained *via* attack from the α face.[6]

The minor hydroboration product showed a one-proton doublet at δ 3.64 and a two-proton AB pattern centered at δ 2.30 consistent with diol structure **8**. Treatment of diol **8** with *p*-toluenesulfonic acid in benzene afforded a quantitative conversion into the corresponding cyclic ether **11**. Diol **8** must arise in the hydroboration reaction from the internal dialkylborane intermediate **13** derived from the initial monoalkylborane **12** by loss of the elements of hydrogen.[7]



12 13

Molecular models clearly indicate the close proximity of the hydrogens on the α methyl at C-8 with the β-alkylborane substituent at C-1 obtained from β-face attack with the expected orientation of the borane addition. Unfortunately, the same arguments can be advanced from α-face attack of the borane followed by ring inversions and loss of the elements of hydrogen from the β methyl at C-8. Both diol **14** and subsequent ether product **15** would exhibit nmr spectra virtually identical with those of diol **8** and ether **11**, respectively.

Regarding the stereochemistry of diol **8**, we must compare the 92:8 ratio of epoxides **5** and **6** to the 77:23 ratio of hydroboration products **7** and **8**. We have earlier proved that both epoxide **5** and alcohol **7** derive

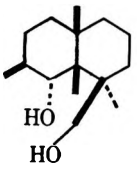
(3) (a) T. Nozoe, H. Takeshita, S. Ito, T. Ozeki, and S. Seto, *Chem. Pharm. Bull.*, **8**, 936 (1960); (b) W. G. Dauben and A. C. Ashcraft, *J. Amer. Chem. Soc.*, **85**, 3673 (1963).

(4) S. P. Acharya and H. C. Brown, *J. Org. Chem.*, **35**, 3874 (1970).

(5) V. Sanda and J. Fajkos, *Collect. Czech. Chem. Commun.*, **32**, 3726 (1967).

(6) R. J. Gritter and R. J. Albers, *J. Org. Chem.*, **29**, 728 (1964).

(7) H. C. Brown, K. J. Murray, H. Müller, and G. Zweifel, *J. Amer. Chem. Soc.*, **88**, 1443 (1966).



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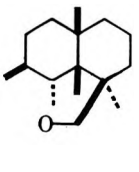

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from β-face attack on 2. Since only two epoxides are possible from 2, the minor epoxide must possess structure 6 derived from α-face attack. If the steric requirements in the transition state for hydroboration are similar to or greater than that for epoxidation, one would then expect that β-face attack indeed holds for the minor hydroboration product and structure 8 is correct. Conversely, if the steric requirements for hydroboration are less than that for epoxidation, one might expect α-face attack to afford structure 14 for the diol product.

Previous studies[8] on selected substituted cyclohexene derivatives have indicated only very slight differences in the stereochemical outcome of epoxidation as compared to hydroboration on the same molecule. Although the generality of this conclusion has not been rigorously established, in view of the threefold difference in the amount formed of epoxide 6 *vs.* diol 8, we feel that β-face attack indeed holds for both hydroboration products and that the diol therefore possesses structure 8 rather than 14.

This hydroboration reaction is unique in two interesting aspects. The major product, tertiary alcohol 7, corresponds to Markovnikov hydration of the double bond, whereas in all known examples to date the anti-Markovnikov product always predominates. For example, 1,1-dimethyl-*tert*-butylethylene affords 98% of the secondary alcohol and only 2% of the tertiary alcohol.[9] Styrene affords 80% of the expected primary alcohol and 20% of the secondary alcohol due to electronic effects of the aromatic ring.[9] In our case, trisubstituted olefin 2, no such electronic effects can be invoked to explain the dramatic reversal of the hydroboration orientation. The steric effects of the C-8 *gem*-dimethyl group and the angular methyl group at C-9 in 2 must be so overwhelming that this consideration governs the attack of the borane rather than the usual electronic directing effects.

The second aspect of this reaction involves the facile formation of the dialkylborane intermediate 13 from the monoalkylborane 12. Conversions of this type are well known[7] but usually occur only at elevated temperatures such as refluxing diglyme (160°). Logan and Flautt have previously[10] shown that *trans*-1,2-di-*tert*-butylethylene readily formed an internal dialkylborane upon heating with borane in refluxing diglyme, but could isolate the expected secondary alcohol product if the reaction was performed at 30°. In our case no evidence for a secondary alcohol product could be obtained at 25°, even this temperature being sufficient to form dialkylborane 13, the precursor of diol 8.

Experimental Section

Materials and Equipment.—(−)-Thujopsene (1) was readily obtained in 99% purity by careful fractional distillation of Hibawood oil through a 2-ft Goodloe column, bp 67–68° (0.5 mm), $n^{20}D$ 1.5050, $[\alpha]^{25}D$ −92.5° (neat).

Spectra were recorded using a Perkin-Elmer 457 grating ir spectrophotometer and a Varian A-60A nmr spectrometer. Gas chromatography was performed on an F & M 720 instrument employing a 2 m × 0.25 in. copper column packed with 20% Carbowax on Chromosorb G. Combustion analyses were determined by Schwartzkopf Microanalytical Laboratory, Woodside, N. Y.

Dihydrothujopsene (2).—A 250-g (1.21 mol) sample of (−)-thujopsene (1) was hydrogenated with 5 g of 5% palladium on carbon catalyst at 30° in a Parr shaker. The reaction was stopped when 1 molar equiv of hydrogen had been absorbed. The mixture was filtered and the filtrate was distilled, affording 238 g (94%) of colorless liquid: bp 67° (0.3 mm); $n^{20}D$ 1.5042 (lit.[3] $n^{20}D$ 1.5100); $[\alpha]^{25}D$ −49° (neat) (lit.[3] $[\alpha]D$ + 24°); ir (neat) 1675, 1090, 1061, 1022, 969, 858 cm^{-1} (lit.[3] 1675 cm^{-1}); nmr ($CDCl_3$) δ 0.92, 0.96 (s, 6 H each), 1.66 (s, 3 H), 5.30 (s, 1 H, $W_{1/2}$ = 4 Hz). Analysis by gas chromatography showed no unreacted thujopsene and a purity of 95% for the product, olefin 2.

1α,2α-Epoxy-2β,8,8,9β,10β-pentamethyldecalin (6).—To a vigorously stirred mixture of 206 g (1 mol) of dihydrothujopsene (2), 400 ml of hexane, and 75 g of anhydrous sodium acetate was added 270 g (1.42 mol) of 40% peracetic acid over 1 hr. After heating at 40° for 18 hr, an additional 100 g of 40% peracetic acid was added and allowed to agitate for an additional 24 hr. Water (400 ml) was added and the mixture was extracted with hexane. The combined organic phases were washed basic with 10% sodium carbonate solution and once with aqueous sodium thiosulfate solution. Gas chromatography showed three components, unreacted 2 (1.5%), epoxide 6 (8.0%), and epoxide 5 (90.5%). Distillation through a 37-cm column packed with glass helices afforded 208 g (94%) of the epoxide mixture 5 and 6, bp 78–82° (0.5 mm). Spinning band redistillation of this material afforded in the early fractions a pure sample of the minor epoxide 6 which exhibited the following characteristics: bp 72° (0.4 mm); $n^{20}D$ 1.4945; ir (neat) 1245, 1210, 1110, 1020, 918, 885, 815, 583 cm^{-1}; nmr ($CDCl_3$) δ 0.91, 0.98, 1.26 (s, 3 H each), 1.04 (s, 6 H), 2.67 (s, 1 H); $[\alpha]^{25}D$ +41° (neat).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.83; H, 11.76.

Identical epoxide product ratios were obtained when the epoxidation was performed employing tetrahydrofuran as the solvent.

1β,2β-Epoxy-2α,8,8,9β,10β-pentamethyldecalin (5).—Continued spinning band distillation from the preceding experiment afforded pure major epoxide 5 which exhibited the following characteristics: bp 75° (0.4 mm); $n^{20}D$ 1.4958; $[\alpha]^{25}D$ +19° (neat); ir (neat) 1079, 1037, 1008, 948, 862, 820 cm^{-1}; nmr ($CDCl_3$) δ 0.97, 1.06 (s, 6 H each), 1.29 (s, 3 H), 2.84 (s, 1 H).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.21; H, 11.74.

2α,8,8,9β,10β-Pentamethyl-2β-decalol (7). A. From the Hydroboration of Dihydrothujopsene (2).—A solution (125 ml, 0.125 mol) of 1 *M* borane in tetrahydrofuran was placed under nitrogen and cooled to 5°. Dihydrothujopsene (2) (25 g, 0.121 mol) was added and the mixture was stirred at 25° for 18 hr. The solution was cooled to 0° and water (10 ml) was carefully added, followed by 10% aqueous sodium hydroxide (100 ml) and 30% hydrogen peroxide (100 ml). After stirring at 40° for 3 hr, hexane (100 ml) was added and the layers were separated after filtration from an insoluble precipitate. The aqueous phase was extracted with hexane. The combined organic extracts were washed with 10% sodium thiosulfate solution and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, affording 27 g of a viscous oil. Hexane (25 ml) was added and the solution was refrigerated overnight. Filtration afforded 7.4 g of crystalline alcohol 7: mp 93–94°; $[\alpha]^{25}D$ +34° (c 20%, $CHCl_3$); ir (KBr) 3430, 1291, 1211, 1182, 1162, 1115, 1080, 925, 908, 881 cm^{-1}; nmr ($CDCl_3$) δ 0.78, 1.03, 1.06, 1.12, 1.19 (s, 3 H each).

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.31; H, 12.65.

The mother liquors from the above crystallization were chromatographed on 250 g of silica gel. Elution with hexane gave 0.8 g (3%) of unreacted dihydrothujopsene (2). Further elution with 5% ether in hexane afforded 10.8 g of additional crystalline alcohol 7 (total isolated yield 18.2 g, 67%).

B. From Reduction of Epoxide 6.—A sample of epoxide 6 (5.0 g, 22.5 mmol) and lithium aluminum hydride (4.5 g, 115

(8) D. J. Pasto and F. M. Klein, *J. Org. Chem.*, **33**, 1468 (1968).
(9) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **82**, 4708 (1960).
(10) T. J. Logan and T. J. Flautt, *ibid.*, **82**, 3446 (1960).

mmol) in anhydrous dimethoxyethane (60 ml) was allowed to reflux for 72 hr. The mixture was cooled, and water (9 ml) was added followed by 10% aqueous sodium hydroxide (7.5 ml). After stirring at room temperature for 5 hr, the mixture was filtered and the solvent was removed at reduced pressure, affording 5.0 g of viscous oil. Analysis by gas chromatography showed three components, which were identified as dihydrothujopsene (16%), unreacted epoxide **6** (47%), and tertiary alcohol **7** (37%) on the basis of vpc retention times and by comparison of the ir and nmr spectra of the isolated components with those of authentic samples.

C. From Ketone 10.—To a sample of ketone **10** (800 mg, 3.8 mmol) dissolved in ether (12 ml) was added over 20 min a solution of 2.3 *M* methyllithium in ether (10 ml, 23 mmol). After stirring at 30° for 0.5 hr, the mixture was cooled and water (10 ml) was carefully added. The mixture was extracted with ether and the organic extracts were dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure, affording 900 mg of crude solid material. Analysis by gas chromatography gave two peaks with retention times of tertiary alcohol **7** (56%) and starting ketone **10** (44%). Separation of the two peaks by preparative gas chromatography afforded a pure sample of tertiary alcohol **7**, mp 93–94°, with an ir and nmr spectra identical with those obtained from part A above.

8α-Hydroxymethyl-2α,8β,9β,10β-tetramethyl-1β-decalol (8).—Continued elution of the chromatography column employed in the separation of the hydroboration products of dihydrothujopsene (see part A above) with 25% ether in hexane afforded 4.2 g (17%) of crystalline diol **8**, mp 104–106°. Crystallization from ether at −15° afforded the analytical sample: mp 115–116°; $[\alpha]^{25}D$ −24° (*c* 15%, $CHCl_3$); ir (KBr) 3200 (OH), 1182, 1049, 1025, 1001, 918 cm^{-1}; nmr ($CDCl_3$) δ 0.97, 1.04, 1.07 (s, 3 H each), 1.02 (d, 3 H, J = 5.5 Hz), 3.28, 3.32 (2 H AB pattern, J_{AB} = 6 Hz), 3.64 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.17; H, 11.53.

8,8,9β,10β-Tetramethyl-2-decalone (10). To a mixture of freshly distilled ammonia (100 ml), anhydrous ether (40 ml), and ketone **9**[3a] (4.0 g, 19.5 mmol) was added lithium wire (300 mg, 43.5 mmol) in 50-mg portions over 15 min. The resulting deep blue mixture was stirred for 1.0 hr; then a 1:1 ethanol–ether mixture (10 ml) was added. The ammonia was allowed to evaporate and the residue was extracted with ether. The ether extracts were washed with brine and dried over magnesium sulfate. The solvent was removed at reduced pressure and the residue was crystallized from hexane (20 ml) affording 3.4 g (84%) of ketone **10**: mp 150–151°; $[\alpha]^{25}D$ +10° (*c* 15, $CHCl_3$); ir (KBr) 1700 (C=O), 1296, 1270, 1111, 1018 cm^{-1}; nmr ($CDCl_3$) δ 0.81; 0.88, 1.05, 1.10 (s, 3 H each).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.60; H, 11.47.

2aβ,5aβ,8α,8bβ-Tetramethyldecahydronaphtho[1,8-*bc*]furan (11).—A solution containing diol **8** (1.5 g, 6.25 mmol) and *p*-toluenesulfonic acid (100 mg) in benzene (25 ml) was heated to reflux with a water separator for 1.5 hr. The solution was cooled and washed with sodium bicarbonate solution, and the solvent was removed at reduced pressure. Distillation of the residual oil afforded 1.34 g (97%) of ether **11**: bp 100° (bath temperature) (0.5 mm); $n^{20}D$ 1.5042; $[\alpha]^{25}D$ +1° (neat); ir (neat) 1075, 1026, 1000, 975 cm^{-1}; nmr ($CDCl_3$) δ 0.84, 0.97, 1.05 (s, 3 H each), 0.95 (d, 3 H, J = 5.5 Hz), 3.46, 3.49 (2 H, AB pattern, J_{AB} = 8 Hz), 3.85 (d, 1 H, J = 10.5 Hz).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.17; H, 11.76.

Attempted Oxidation of Alcohol 7.—A sample of alcohol **7** (200 mg, 0.9 mmol) was dissolved in acetone (5 ml) and cooled to 5°. Standard Jones reagent (0.25 ml, 1.1 molar equiv) was added dropwise at 5°. The mixture was stirred at 5° for 10 min and at 20° for 10 min. Isopropyl alcohol (1 ml) was then added, followed by 10 ml of water. The mixture was well extracted with hexane. The orgaic extracts were washed with water and sodium bicarbonate solution, and the solvent was removed at reduced pressure. The ir and nmr spectra of the crude crystalline residue (200 mg) were identical with those of the starting alcohol **7**.

Determination of the Product Ratios from the Hydroboration of Dihydrothujopsene (2).—The hydroboration procedure as described above was repeated employing olefin **2** (1.5 g, 7.5 mmol) and 1 *M* borane in tetrahydrofuran solution (8.5 ml) for 18 hr at 25°. The same oxidative work-up procedure afforded 1.6 g of viscous oil. This oil was treated with *p*-toluenesulfonic acid (100 mg) in benzene (20 ml) at reflux with a water separator for 2 hr. The mixture was cooled and washed with sodium bicarbonate solution and the solvent was removed under reduced pressure. The residue was distilled on a microstill head, affording 1.30 g of mobile oil, bp 80–100° (bath temperature) (0.5 mm). This mixture showed three peaks by vpc analysis identified as dihydrothujopsene (**2**, 35%), the corresponding 2,3 double bond isomer (42%), and ether **11** (23%).

Ether **11** arises solely from dehydration of diol **8** and the two olefins from dehydration of tertiary alcohol **11**. The ratio of the two hydroboration products **7** and **8** is thus shown to be 77:23, respectively.

Registry No.—**2**, 34407-70-0; **5**, 34407-71-1; **6**, 34417-83-9; **7**, 34407-72-2; **8**, 34407-73-3; **10**, 34407-74-4; **11**, 34407-75-5.

Acknowledgment.—The author wishes to thank Dr. Garry Kitchens and Dr. Gary Shaffer for their helpful discussions during the course of the above investigation.

Symmetry Considerations and the Mechanism of the Hydroboration Reaction. The Nature of π Complexes

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Consideration of the orbital symmetry of the species involved in the hydroboration of olefins shows that the four-center transition states usually proposed have significant symmetry barriers. An alternate pathway involving a complex between the olefin and the borane is discussed in terms of the three-center electron-deficient bonds implied by the π-complex formalism. It is concluded on the basis of the symmetry of these three-center molecular orbitals that the conversion of such π complexes to products can be a concerted process which does not involve significant charge separation or rearrangement to a σ complex.

Despite the great synthetic utility of the hydroboration reaction, there is surprisingly little known about its mechanism. This is certainly due in part to the great complexity of the hydroboration reaction mixtures and the concomitant difficulty of quantitative kinetic measurements in such systems. In our studies of the hydroboration of methylchlorosilylalkenes[1] we found that a consideration of the orbital symmetry of the reactants and products provides a useful insight into the

(1) P. R. Jones, J. K. Myers, and R. C. Rains, *J. Organometal. Chem.*, **34**, C9 (1972); 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, Abstract INOR 126.

pathway of the reaction and prediction of products. The path which results from these considerations involves a π complex intermediate, a species of the type often postulated in reaction mechanisms. The symmetry and nature of the three-center molecular orbitals implied by the π complex formalism and their implications with respect to reaction paths have not heretofore been discussed.

Any mechanism for the reaction between a borane and an olefin must account for several well-known facts.

(i) The reaction results in cis,anti-Markovnikov addition of the elements B–H to an olefinic double bond.[2]

(ii) The direction of addition is strongly influenced by steric effects, giving boron substitution on the least hindered carbon of the olefin.[2] However, electronic effects can occasionally overcome the steric requirements of the addition with electron-withdrawing groups on the olefin favoring substitution α to the electronegative substituent.[1-5]

(iii) The hydroboration reaction is very facile, addition usually being complete within a few minutes.[1-4] The activation energy for the reaction of BH_3 with ethylene in the gas phase has been estimated to be 2 kcal/mol.[6] However, the rate of the reaction is solvent dependent, and its half-life increases significantly in solvents with strong Lewis base character.[7] A hydrogen–deuterium kinetic isotope effect has been reported for the reaction of chloroboranes with olefins.[8,9] Pasto and coworkers have recently observed that the hydroboration of tetramethylethylene with borane in tetrahydrofuran exhibits both a hydrogen–deuterium and a boron(10)–boron(11) kinetic isotope effect.[10]

The pathways which have been proposed for the hydroboration reaction involve species ranging from the traditional four-centered transition state[2,7] between the olefin and a dissociated molecule of borane, **1**, or between the olefin and one of the bridged B–H bonds of a dimeric borane, **2**,[11] to a triangular π complex, **3**. The π complex intermediate has been proposed[12,13] in analogy to the mechanism suggested for the addition of aluminum alkyls to olefins,[14] to explain the stereochemistry of the 1-butanol-*1-d* produced by the asymmetric hydroboration of *cis*-1-butene-*d* with diisopinocamphenylborane.[13] Although arguments against intermediate **3** have been made on the basis of other stereochemical results[15] and the kinetic isotope effects which have been observed, a consideration of the molecular orbitals implied by **3** reveals it to be a highly probable intermediate for the hydroboration reaction which satisfactorily accounts for all the known facts.

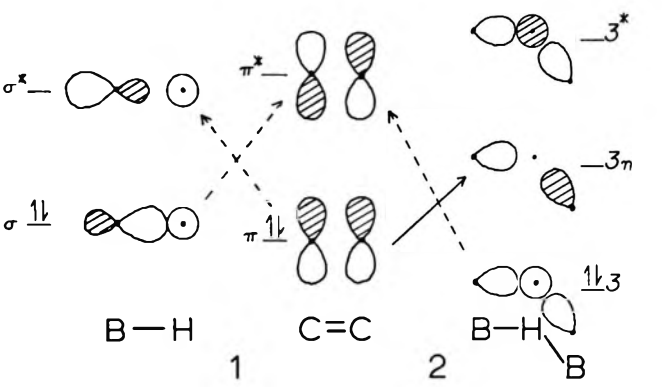
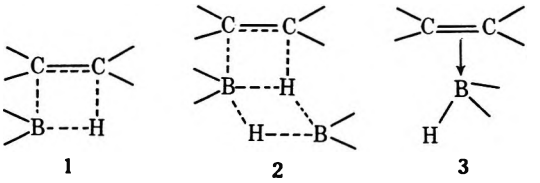


Figure 1.—Symmetry of the orbitals involved in the concerted four-center reaction of an olefin with a monomeric borane, **1**, and a bridged borane, **2**: ----, symmetry-forbidden processes; ——, symmetry-allowed process.



Both transition states **1** and **2** have significant symmetry barriers which make them unlikely candidates for the extremely rapid hydroboration reaction. As is illustrated in Figure 1, transition state **1** requires concerted electron flow from the π orbital of the olefin to the σ^* orbital of the B–H bond, and from the σ B–H orbital to the π^* orbital of the olefin. The net overlap between these pairs of orbitals should be very small indeed, resulting in a symmetry restriction typical of concerted four-center additions to olefins.[16]

Similarly, transition state **2**, illustrated on the right side of Figure 1, is symmetry forbidden. It requires interaction of the three-center bonding orbital of a B–H–B bridge (**3**) with the π^* orbital of the olefin. There can be no net overlap of these orbitals and the concerted transition state **2** is thus ruled out.

It is useful to consider the B–H–B bridge illustrated in Figure 1 as a typical example of the molecular orbitals involved in a three-center electron-deficient bonding system. The lowest lying molecular orbital, **3**, is a bonding orbital which has no nodes between the atoms and is the only occupied orbital. The 3n orbital is a nonbonding orbital with high density at the terminal atoms of the three-center system and a node at the central atom, and it is unoccupied. The highest energy orbital, 3*, is antibonding with nodes between each of the atoms, and is generally not involved in the reactions of systems containing such three-center molecular orbitals.

Nucleophilic attack on an electron-deficient three-

(2) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962. It should be pointed out that if the polarization of the boron–hydrogen bond, $B^{\delta+}$–$H^{\delta-}$, is considered the addition is better termed Markovnikov.

(3) H. C. Brown and K. A. Keblys, *J. Amer. Chem. Soc.*, **86**, 1791 (1964); H. C. Brown and O. J. Cope, *ibid.*, **86**, 1801 (1964); H. C. Brown and R. M. Gallivan, Jr., *ibid.*, **90**, 2906 (1968); H. C. Brown and R. L. Sharp, *ibid.*, **90**, 2915 (1968).

(4) D. J. Pasto and Sr. R. Snyder, O. S. F., *J. Org. Chem.*, **31**, 2773, 2777 (1966); D. J. Pasto and J. Hickman, *J. Amer. Chem. Soc.*, **89**, 4445, 5608 (1967).

(5) D. Seyferth, *J. Amer. Chem. Soc.*, **81**, 1844 (1959); D. Seyferth, H. Yamazaki, and Y. Sato, *Inorg. Chem.*, **2**, 734 (1963); M. Kumada, N. Imaki, and K. Yamamoto, *J. Organometal. Chem.*, **6**, 490 (1966).

(6) T. P. Fehlner, *J. Amer. Chem. Soc.*, **93**, 6366 (1971).

(7) R. Koster, G. Griasnow, W. Larbig, and P. Binger, *Justus Liebigs Ann. Chem.*, **672**, 1 (1964).

(8) D. J. Pasto and S. Z. Kang, *J. Amer. Chem. Soc.*, **90**, 3797 (1968).

(9) G. Zweifel, *J. Organometal. Chem.*, **9**, 215 (1967).

(10) D. J. Pasto, B. Lepeska, and T. C. Cheng, *J. Amer. Chem. Soc.*, in press. Professor Pasto informed us of these very significant kinetic studies prior to the submission of his manuscript. We are indebted to him for his permission to discuss the results in this paper and for his helpful comments in this area.

(11) H. C. Brown and A. W. Moerikofer, *J. Amer. Chem. Soc.*, **83**, 3417 (1961).

(12) D. Seyferth in "Progress in Inorganic Chemistry," Vol. III, F. A. Cotton, Ed., Wiley-Interscience, New York, N. Y., 1962, p 210.

(13) A. Streitwieser, Jr., L. Verbit, and R. Bittman, *J. Org. Chem.*, **32**, 1530 (1967).

(14) R. Robinson, *Chem. Age (London)*, **74**, 977 (1956).

(15) D. J. Pasto and F. M. Klein, *J. Org. Chem.*, **33**, 1468 (1968).

(16) R. G. Pearson, *Accounts Chem. Res.*, **4**, 152 (1971); *Chem. Eng. News*, **48**, 66 (1970).

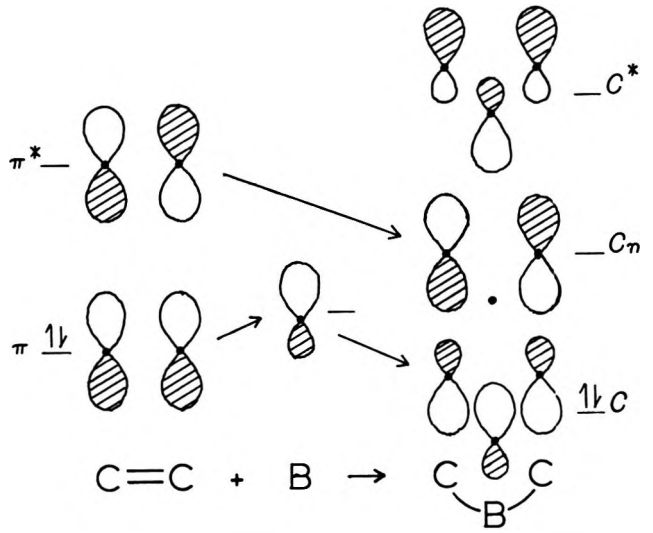
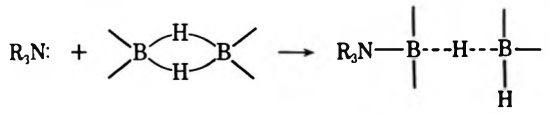
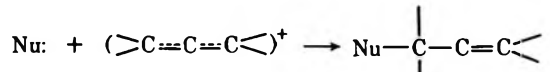


Figure 2.—Symmetry of the orbitals involved in the reaction of an olefin with a borane to form a π complex containing a C–B–C three-center bond.

center system is analagous to the process which occurs when ammonia or an amine reacts with diborane.[17] The 3n orbital is occupied by a pair of electrons from



the nucleophile, becoming a σ bond between the nucleophile and one of the terminal atoms. Orthonormalization prohibits interaction of the orbital on the attacked atom with the three-center molecular orbital. This leaves the two remaining atomic orbitals and a pair of electrons as a two-center, σ bond between the bridging atom and the other member of the three-center system. A similar description applies to nucleophilic attack on allyl cations except that in this case the three-center bond becomes a π bond between the two atoms removed from the point of attack.



For the hydroboration reaction, the symmetry of the orbitals involved in intermediate **3** is illustrated in Figure 2. The formation of this π complex may be regarded as the interaction of the olefin's π electrons with a vacant boron orbital, as is probably the case in the gas-phase reaction of borane with ethylene.[6] In solution a more reasonable path is the displacement of a solvent molecule from boron's coordination sphere by the olefin. Less likely, though possible, is a nucleophilic attack on a B–H–B bridge by the olefin similar to the process discussed above and indicated by the solid arrow in Figure 1. All of these processes are symmetry allowed. Regardless of which occurs, the result is a three-atom, two-electron bond, which is best described in terms of three-center molecular orbitals, using one p orbital from each of the carbons of the olefin and an orbital of p symmetry on boron. It is important to note that this bonding description requires *no* rehybridization of the carbon atoms of the double

(17) R. W. Parry and S. G. Shore, *J. Amer. Chem. Soc.*, **80**, 15 (1958).

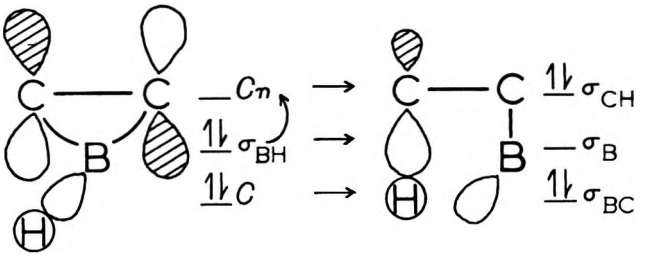
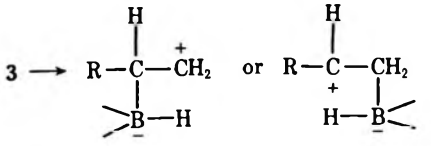


Figure 3.—Orbital symmetry and electron flow for the conversion of a C–B–C three-center system to two σ bonds.

bond, as was suggested by Pasto's stereochemical results.[15] The lowest bonding molecular orbital (Figure 2, C) is occupied and has the same symmetry as the original π orbital of the olefin. The lowest vacant orbital of the complex, and most important in our consideration (Figure 2, Cn), has the same symmetry as the original π* orbital of the olefin, is nonbonding, and may be regarded as a "virtual" π* orbital.

The major arguments against the π complex intermediate, **3**, are based on the assumption that such π



complexes must rearrange to σ complexes in subsequent steps of the reaction. Such a rearrangement appears unlikely in view of the nearly identical internal and terminal kinetic isotope effects observed for the addition of monochloroborane to substituted styrenes;[8] the hydrogen–deuterium and boron(10)–boron(11) kinetic isotope effects;[10] and the similarity of Hammett ρ values for internal and terminal addition to styrenes.[18] Further, any significant buildup of hydridic character on the boron hydrogens would be expected to lead to reduction of groups such as chlorosilanes present in the reaction mixture. Because we observed no reduction of the silicon–chlorine bonds during the addition of borane in tetrahydrofuran to methylchlorosilylalkenes,[1] we were forced to look for a path for the hydroboration reaction consistent with the known facts about the reaction and our results.

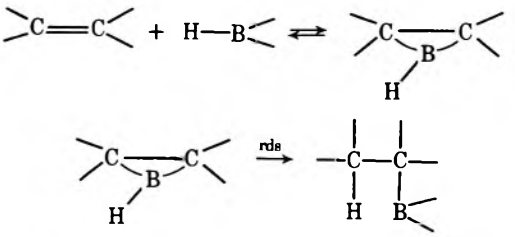
A point which is overlooked by most chemists, but which becomes apparent when the symmetry of the orbitals involved in π complexes is considered, is that such complexes can convert to products in a symmetry-allowed *concerted* process, illustrated in Figure 3. The conversion amounts to a flow of electrons from the σ system of the moiety involved in the π complex (boron in this case) to the Cn three-center molecular orbital. As the Cn orbital is occupied and becomes a σ bond between carbon and hydrogen, the C three-center bonding orbital of the complex becomes a boron–carbon σ bond.

The concept of a three-center molecular orbital description of the bonding in a π complex applied to the hydroboration reaction accounts well for the details of this reaction. The steric requirements of the reaction are easily understood, since the complex should form

(18) J. Klein, E. Dunkelblum, and M. A. Wolff, *J. Organometal. Chem.*, **7**, 377 (1967). However, see ref 10 for a discussion of apparent discrepancies in the Hammett correlations.

on the least hindered side of the olefin. The direction of addition depends on two factors: the orientation of the remaining hydrogens on boron in the complex, and the electronic effect of other substituents on the olefin. With bulky groups on the olefin or boron one would expect the hydrogen on boron to be juxtaposed with the internal lobe of the Cn orbital of the π complex. The conversion of this intermediate to products would result in boron substitution on the least hindered carbon of the olefin. With strongly electron-withdrawing substituents on the olefin, the collapse of the complex to product should be influenced by the tendency of the electron pair in the preformed three-center bond to move toward the more electron-deficient carbon, giving boron substitution α to the electronegative group when the steric factors of the reaction permit.

In summary, we consider the hydroboration reaction as a two-step process, the first step an equilibrium resulting in the production of three-center, two-electron π complex intermediate (eq 1); the second step a rate-determining *concerted* conversion of the intermediate to products (eq 2). This mechanism satisfies the requirements of the hydroboration reaction while not involving the buildup of any significant hydridic character on the boron hydrogens. More important, the fact that olefin π complexes can convert to products by a concerted, symmetry-allowed process not involving significant charge separation in the transition state should be useful in the consideration of other reactions which involve such intermediates.



(1)

(2)

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A New Synthesis of Coenzyme Q_1

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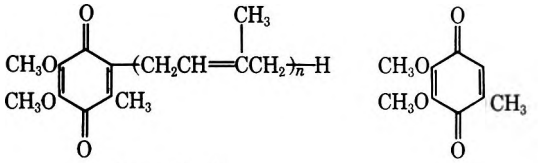
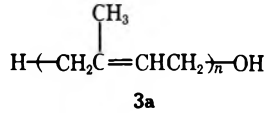
A new synthesis of coenzyme Q_1 is reported. 2,3-Dimethoxy-5-methylbenzoquinone (2) is converted to 6-bromo-2,3-dimethoxy-5-methylhydroquinone bis(methoxymethyl) ether (18), which is condensed with 1,1-dimethyl-π-allylnickel bromide (9) in hexamethylphosphoramide to afford 2,3-dimethoxy-5-methyl-6-(3-methyl-2-butenyl)hydroquinone bis(methoxymethyl) ether (19) in good yield. The hydrolysis of the condensation product 19 followed by oxidation gives coenzyme Q_1. The reaction of 9 with several other aryl halides is also reported.

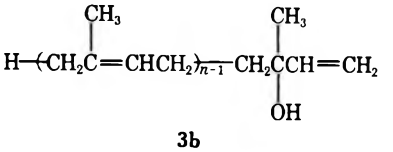
Coenzyme Q_n (1), ubiquinone 5*n*, functions in electron transfer and oxidative phosphorylation. The ten known ubiquinones, coenzyme Q_1–Q_{10}, are named according to the number of isoprene units in the side chain. Coenzymes Q_6–Q_{10} were isolated by Lester[1,2] and their structures were determined as **1**[3-5] (n = 6–10). These compounds were synthesized by Folkers, *et al.*,[3] and also by Isler and coworkers.[4,5]



1, n = 1–10 **2**



3a



3b

In the synthesis of coenzyme Q_n there are three key steps, which include (i) a synthesis of 2,3-dimethoxy-5-methylbenzoquinone (2), (ii) a stereospecific synthesis of the polyprenyl alcohols **3a** or **3b**, (iii) a condensation of the aromatic nucleus 2 with the alcohols **3a** or **3b**.

All of the coenzyme Q_n synthesis reported involved the condensation of 2,3-dimethoxy-5-methylhydroquinone (4) with **3a** or **3b** using acid catalysts. Such condensation reactions suffer from the disadvantage that cyclization to chromanol and a cyclization of the unsaturated isoprenoid side chain often results. In order to minimize these side reactions, many kinds of catalysts ($SnCl_2$, K_2SO_4, oxalic acid, BF_3, etc.) have been used.[6] Unfortunately, these methods generally give low yields and, in addition, much labor is needed to isolate the condensation product from the complex reaction mixture. Reported here is a new method for the

(1) F. L. Crane, Y. Hatefi, R. L. Lester, and C. Widmer, *Biochim. Biophys. Acta*, **25**, 220 (1957).

(2) R. L. Lester, F. L. Crane, and Y. Hatefi, *J. Amer. Chem. Soc.*, **80**, 4751 (1958).

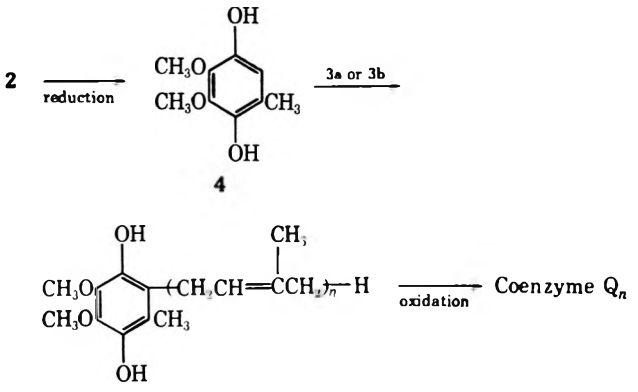
(3) D. E. Wolf, C. H. Hoffman, N. R. Trenner, B. H. Arison, C. H. Shunk, B. O. Linn, J. F. McPherson, and K. Folkers, *ibid.*, **80**, 4752 (1958).

(4) R. A. Morton, U. Gloor, O. Schindler, W. M. Wilson, L. H. Chopard-dit-Jean, F. W. Hemming, O. Isler, W. M. F. Leat, J. F. Pennock, R. Rüegg, U. Schwieter, and O. Wiss, *Helv. Chim. Acta*, **41**, 2343 (1958).

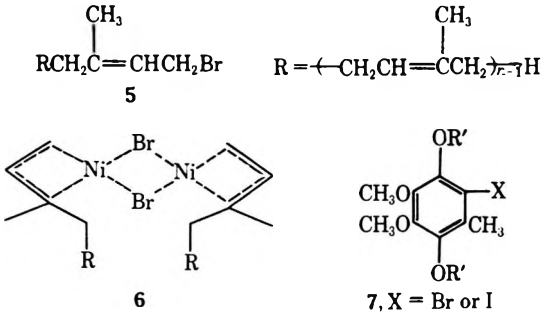
(5) U. Gloor, O. Isler, R. A. Morton, R. Rüegg, and O. Wiss, *ibid.*, **41**, 2357 (1958).

(6) Merck Co., British Patent 921,538, 928,161 (1963); *Chem. Abstr.*, **59**, 6316, 14032 (1963).

synthesis of coenzyme Q which does not suffer from the above drawbacks.

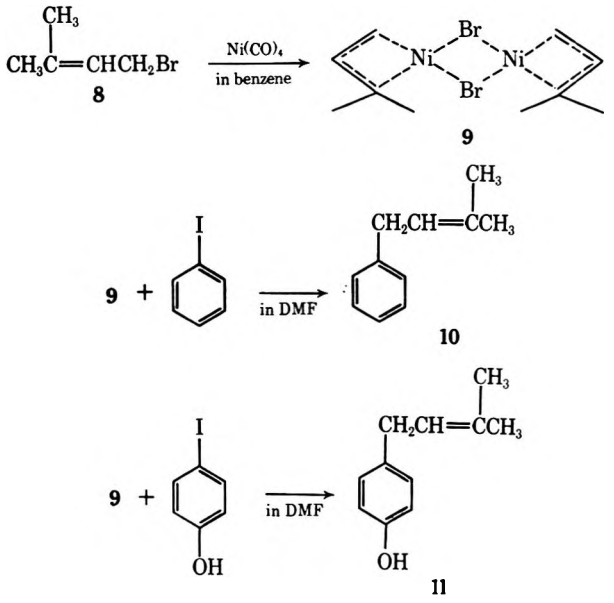


Recently a number of organometallic complexes have been used for syntheses which proceed under mild conditions and in good yields. Corey and Semmelhack reported that π-allylic nickel complexes react with aliphatic or aromatic halides under a mild condition to afford the corresponding allylic derivatives in good yields and in high selectivity.[7] We, therefore, thought that the reaction of the π-allylic nickel complexes **6** prepared from polyprenyl bromide (**5**) with the halogenated derivative **7** of 2,3-dimethoxy-5-methylbenzoquinone (**2**) would give coenzyme Q_1. Indeed, such a transformation did take place.

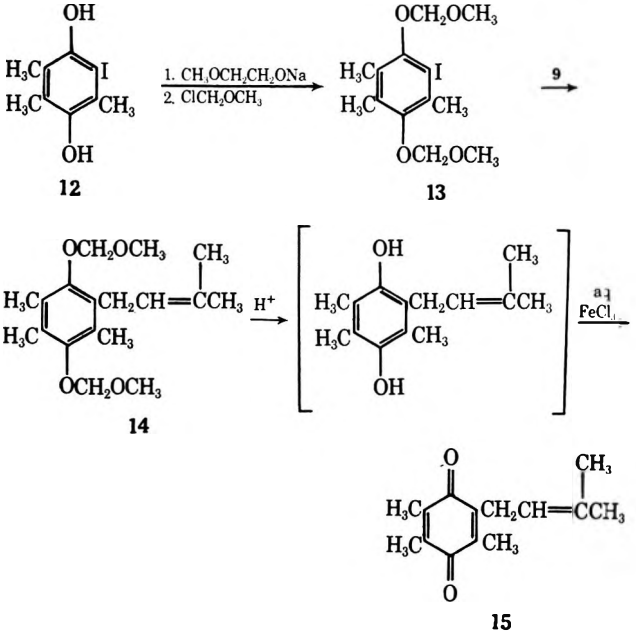


The reaction of 1-bromo-3-methyl-2-butene (**8**) with nickel carbonyl in benzene at 50° under a stream of nitrogen gave 1,1-dimethyl-π-allylnickel bromide (**9**), which corresponds to the side chain of coenzyme Q_1. After removal of benzene under vacuum this compound was reacted with iodobenzene at 20° in dimethylformamide (DMF) to give (3-methyl-2-butenyl)benzene (**10**) in good yield, showing high reactivity and high selectivity to the aromatic halide. Since there has been no report on the reaction of π-allylic nickel complexes with aromatic halides having a hydroxyl substituent,[7] the influence of a phenolic hydroxyl substituent was investigated using *p*-iodophenol. *p*-Iodophenol reacted with 1,1-dimethyl-π-allylnickel bromide (**9**) in DMF at 20° to give *p*-(3-methyl-2-butenyl)phenol (**11**) in 38% yield. This result shows that a hydroxyl group does not prevent the condensation reaction, although the yield is lower.

Reaction of a π-allylic nickel complex with halogenated hydroquinones was attempted next. Treatment of 1,1-dimethyl-π-allylnickel bromide (**9**) with iodotrimethylhydroquinone (**12**) gave trimethylhydroquinone in 25% yield, while reaction with iodotrimethylbenzoquinone gave **12** in 60% yield. It is concluded from the above results that the oxidizable and reducible functional groups must be protected.



Since it has been reported that the methoxymethyl group is easily removed under very mild conditions,[8] this was thought to be a suitable protecting group for hydroquinone derivatives which are very sensitive to an acid and base. Iodotrimethylhydroquinone bis(methoxymethyl) ether (**13**) was prepared from **12** and chloromethyl methyl ether. The reaction of **13** with **9** in DMF at 50° for 10 hr gave the condensation product **14** in good yield. The structure of **14** was assigned on the basis of the nmr spectrum (see Experimental Section). Removal of the methoxymethyl groups in **14** by methanolic HCl, followed by oxidation with aqueous ferric chloride, afforded (3-methyl-2-butenyl)trimethylbenzoquinone (**15**).

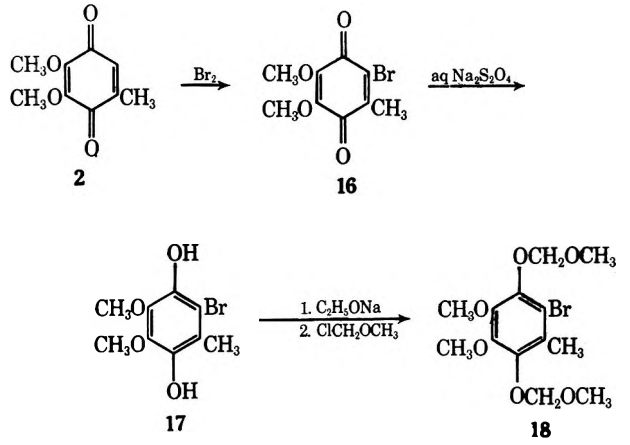


The above result suggested a new synthesis of coenzyme Q_1 by application of the same reaction sequence to the halogenated derivative of 2,3-dimethoxy-5-methylbenzoquinone (**2**). Bromination of **2** gave

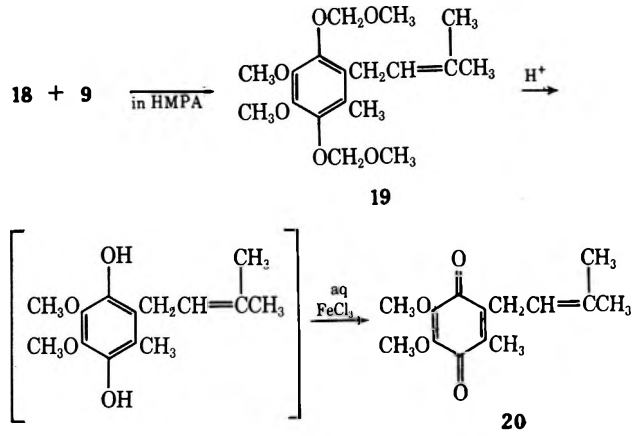
(7) E. J. Corey and M. F. Semmelhack, *J. Amer. Chem. Soc.*, **89**, 2755 (1967).

(8) R. Stern, J. English, Jr., and H. G. Cassidy, *ibid.*, **79**, 5792 (1957).

6-bromo-2,3-dimethoxy-5-methylbenzoquinone (**16**), which was reduced and methoxymethylated to give 6-bromo-2,3-dimethoxy-5-methylhydroquinone bis-(methoxymethyl) ether (**18**).



The reaction of **18** with **9** in DMF at 50° did not proceed. Even at 75° only a trace of the condensation product **19** was detected. Since it has been thought that a coordinating solvent, *e.g.*, DMF, coordinates with π-allylic nickel complexes and activates them,[7] hexamethylphosphoramide (HMPA) was substituted as solvent because it coordinates with metal complexes more strongly than DMF.[9] When **18** was treated with **9** in HMPA at 60°, **19** was obtained in 57% yield. Hydrolysis and oxidation of **19** was followed by purification by column chromatography to give 2,3-dimethoxy-5-methyl-6-(3-methyl-2-butenyl)benzoquinone, coenzyme Q_1 (**20**).



This new synthesis of coenzyme Q_1 should provide a general method for synthesizing higher homologs. Further work in this area is in progress.

Experimental Section

General.—Boiling points and melting points are uncorrected. Infrared (ir) spectra were recorded on a Hitachi Model 215 spectrophotometer. Ultraviolet (uv) spectra were recorded on a Hitachi Model EPS-3T spectrophotometer. Nuclear magnetic resonance (nmr) spectra were obtained on JEOL Model C-60 spectrometer. Reactions involving π-allylnickel complexes were carried out under a stream of nitrogen.

(3-Methyl-2-butenyl)benzene (10).—To a stirred solution of 10.3 g (0.06 mol) of nickel carbonyl in 58 g of dry benzene was added dropwise 6.0 g (0.04 mol) of 1-bromo-3-methyl-2-butene[10] (**8**) in 36 g of dry benzene at 50° for 1.5 hr under a stream of nitrogen. The reaction mixture was allowed to stand at 50° for 2 hr and cooled. Benzene was removed under reduced pressure and 42 ml of DMF was added to the dark red residue. To this solution was added 6.4 g (0.03 mol) of iodobenzene[11] in 20 ml of DMF at 20° for 1.5 hr. The reaction mixture was stirred for 3 hr and, after treatment with water containing a small quantity of hydrochloric acid, extracted with petroleum ether (bp 30–50°). The extract was washed with water, dried with magnesium sulfate, and freed of solvent. The residual liquid was distilled to give 3.3 g (75%) of **19**: bp 74–77° (8 mm); $n^{20}D$ 1.5165 [lit.[12] bp 81.2–81.6° (11 mm); $n^{20}D$ 1.5136]; ir (neat) 2925, 1670, 1600, 1450, 735, 695 cm^{-1}; nmr (CCl_4) δ 1.71 (s, 6, 2 CH_3), 3.29 (d, 2, J = 7 Hz, CH_2), 5.29 (t, 1, J = 7.5 Hz, =CH), 7.10 (s, 5, C_6H_5).

p-(3-Methyl-2-butenyl)phenol (11).—1,1-Dimethyl-π-allylnickel bromide (**9**) was prepared from 6.0 g (0.04 mol) of **8** and 10.3 g (0.06 mol) of nickel carbonyl by the same method described above. To the solution of **9** in 40 ml of DMF was added dropwise 5.0 g (0.023 mol) of *p*-iodophenol[13] in 15 ml of DMF at 20°. The reaction mixture was stirred for 3 hr and, after treatment with water containing a small quantity of hydrochloric acid, extracted with petroleum ether. The extract was washed with water, dried with magnesium sulfate, and freed of solvent, and the residual oil was chromatographed on silica gel. Elution with 50% benzene in petroleum ether gave 1.4 g (38%) of **11**: $n^{20}D$ 1.5429 (lit.[14] $n^{20}D$ 1.5400); ir (neat) 3320, 2920, 1614, 1514, 1234, 818 cm^{-1}; nmr (CCl_4) δ 1.67 (s, 6, 2 CH_3), 3.17 (d, 2, J = 7.5 Hz, CH_2), 5.21 (t, 1, J = 7.5 Hz, =CH), 5.52 (s, 1, OH), 6.78 (q, 4, C_6H_4).

Iodotrimethylhydroquinone Bis(methoxymethyl) Ether (13).—To a stirred solution of 11.2 g (0.04 mol) of iodotrimethylhydroquinone (**12**)[15] in 80 ml of ethylene glycol monomethyl ether were added dropwise a quater portion of the solution prepared by dissolving 3.7 g (0.16 mol) of sodium in 48 ml of ethylene glycol monomethyl ether and then 3.2 g (0.04 mol) of chloromethyl methyl ether, with the temperature of the reaction mixture being maintained at −10 to 0° under dry nitrogen. The remaining alcoholate solution was dropped in three equal portions, each addition being followed by dropwise addition of 3.2-g portions of chloromethyl methyl ether. After all addition were complete, the reaction mixture was stirred for 1 hr at −10 to 0° and treated with water. Collection of the precipitates by suction and recrystallization from petroleum ether gave 12.1 g (82.9%) of **13**: mp 85–86°; ir (KBr) 2900, 2830, 1460, 1380, 1165, 1065, 970, 930 cm^{-1}; nmr ($CDCl_3$) δ 2.18, 2.26, and 2.42 (3 s, 9, 3CH_3), 3.61 and 3.69 (2 s, 6, 2 OCH_3), 4.89 and 4.99 (2 s, 4, 2 OCH_2O).

Anal. Calcd for $C_{13}H_{19}O_4I$: C, 42.64; H, 5.23. Found: C, 42.44; H, 5.18.

(3-Methyl-2-butenyl)trimethylbenzoquinone (15).—**9** was prepared from 6.4 g (0.04 mol) of **8** and 10.3 g (0.06 mol) of nickel carbonyl by the same method described above. To the solution of **9** in 40 ml of DMF was added dropwise 5.5 g (0.015 mol) of **13** in 45 ml of DMF at 50° over 1 hr. The reaction mixture was stirred at 50° for 9 hr and, after treatment with water containing a small quantity of ammonia and ammonium chloride and filtration, extracted with chloroform. The extract was washed with water, dried with magnesium sulfate, and freed of solvent. The residual liquid (4.2 g) consisted of **13** (10%) and **14** (90%) by nmr assay,[16] but **14** could not be isolated by column chromatography on silica gel. A portion of the residue (2.0 g) was dissolved in 35 ml of methanol containing a drop of hydrochloric acid. The solution was refluxed for 1 hr, cooled, neutralized with alcoholic potassium hydroxide, and freed of solvent. The residue (1.3 g) was dissolved in 30 ml of ether, oxidized with aqueous ferric chloride, and extracted with ether. The extract was washed with water, dried with magnesium sulfate, and freed of solvent to give a reddish oil, which was chromatographed on silica gel. Elution with 5% isopropyl

(9) H. Normant, *Angew. Chem., Int. Ed. Engl.*, **6**, 1046 (1967).

(10) J. Tanaka, T. Katagiri, and S. Yamada, *Nippon Kagaku Zasshi*, **87**, 877 (1966).

(11) H. J. Lucas and E. R. Kennedt, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 351.

(12) L. Bateman and J. I. Cunneen, *J. Chem. Soc.*, 2283 (1956).

(13) F. B. Dains and F. Eberly, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 355.

(14) E. A. Vdovtsova, *Zh. Org. Khim.*, **1** (12), 2192 (1965).

(15) H. W. J. Cressman and J. R. Thirtle, *J. Org. Chem.*, **31**, 1279 (1966).

(16) As a result of comparison with the nmr spectrum of **13**, chemical shifts of protons in **14** are as follows: δ ($CDCl_3$) 1.72 and 1.80 [2 s, =C-(CH_3)$_2$], 2.21 (s, 3 CH_3), 3.43 (d, CH_2), 3.63 (s, 2 OCH_3), 4.92 (s, 2 OCH_2O), 5.10 (m, =CH).

ether in *n*-hexane afforded 1.1 g of **15**. The estimated yield of **15** from **13** was 67%: ir (neat) 2970, 2930, 1640, 1440, 1375, 1300, 1260, 840, 710 cm^{-1}; uv max (95% EtOH) 260 mμ (ε 18,900) and 267 (19,100) [lit.[17] uv max (95% EtOH) 259 mμ (ε 17,200) and 266 (17,200)]; nmr (CCl_4) δ 1.65 and 1.71 [2 s, 6, $=C(CH_3)_2$], 1.93 (s, 9, 3 CH_3), 3.10 (d, 2, J = 7.5 Hz, CH_2), 4.89 (t, 1, J = 7.5 Hz, CH=).

Anal. Calcd for $C_{14}H_{18}O$: C, 77.03; H, 8.31. Found: C, 76.83; H, 8.51.

6-Bromo-2,3-dimethoxy-5-methylbenzoquinone (16).—To a stirred solution of 10.6 g (0.058 mol) of **2**[18] in 120 ml of carbon tetrachloride was added dropwise 10.5 g (0.068 mol) of bromine at room temperature. The reaction mixture was stirred for 2 hr, treated with water, dried with magnesium sulfate, and evaporated. The dark residue was washed with a very small quantity of ethanol until the color of crystals turned to red and recrystallized from petroleum ether to afford 11.2 g (74%) of **16**: mp 73–74°; ir (KBr) 2850, 1650, 1600, 1280 cm^{-1}.

Anal. Calcd for $C_9H_9O_4Br$: C, 41.41; H, 3.47. Found: C, 41.26; H, 3.62.

6-Bromo-2,3-dimethoxy-5-methylhydroquinone (17).—The quinone **16** (5.0 g) was dissolved in warm methanol and to this solution was added warm aqueous sodium hydrosulfite until the red color of the solution disappeared. Removal of methanol under reduced pressure in a stream of nitrogen afforded 4.3 g (83%) of **17**: mp 73–74°; ir (KBr) 3300, 2880, 1450, 1420, 1280, 1105, 1070, 1000, 910 cm^{-1}; nmr (CCl_4) δ 2.21 (s, 3, CH_3), 3.84 and 3.88 (2 s, 6, 2 OCH_3), 5.14 and 5.27 (2 s, 2, 2 OH).

Anal. Calcd for $C_9H_{11}O_4Br$: C, 41.09; H, 4.21. Found: C, 40.81; H, 4.43.

6-Bromo-2,3-dimethoxy-5-methylhydroquinone Bis(methoxymethyl) Ether (18).—To a stirred solution of 6.0 g (0.023 mol) of **17** in 150 ml of absolute ethanol was added dropwise 0.6 g (0.025 mol) of sodium in 13 ml of absolute ethanol and then 2.0 g (0.025 mol) of chloromethyl methyl ether at −10 to 0° under a stream of nitrogen, and then 1.8 g of sodium in 39 ml of absolute ethanol and 6.0 g of chloromethyl methyl ether were added by the same method described in the preparation of **13**. The reaction mixture was stirred for 3 hr at −10 to 0°, filtered, and concentrated under reduced pressure in a stream of nitrogen. The concentrated solution was washed with dilute aqueous potassium hydroxide and water and extracted with ether. The extract was dried with magnesium sulfate, freed of solvent, and chromatographed on silica gel. Elution with 30% isopropyl ether in *n*-hexane afforded 6.7 g (83.2%) of **18**: $n^{20}D$ 1.5282; ir (neat) 2800, 1460, 1405, 1380, 1160, 1000, 965 cm^{-1}; nmr (CCl_4) δ 2.29 (s, 3, CH_3), 3.48 and 3.56 (2 s, 6, 2 OCH_2OCH_3), 3.79 (s, 6, 2 OCH_3), 4.93 and 4.98 (2 s, 4, 2 OCH_2O).

Anal. Calcd for $C_{13}H_{19}O_6Br$: C, 44.33; H, 5.72. Found: C, 44.52; H, 5.53.

2,3-Dimethoxy-5-methyl-6-(3-methyl-2-butenyl)benzoquinone (Coenzyme Q_1) (20).—**9** was prepared from 4.5 g (0.03 mol) of **8** and 8.7 g (0.05 mol) of nickel carbonyl by the same method described above. To the solution of **9** in 36 ml of HMPA was added 5.4 g (0.015 mol) of **18** in 20 ml of HMPA at room temperature. The reaction mixture was warmed to 60° and stirred for 12 hr. The solution was treated with water containing a small quantity of ammonia and ammonium chloride, filtered, and extracted with petroleum ether. The extract was washed with water, dried with magnesium sulfate, and freed of solvent, affording a residual liquid (4.9 g) which consisted of **18** (43%) and **19** (57%) by nmr assay.[19] This liquid was chromatographed, but **19** could not be isolated. A 3-g portion of the liquid was dissolved in 50 ml of methanol containing a drop of hydrochloric acid. The solution was refluxed for 1 hr, cooled, neutralized with alcoholic potassium hydroxide, and freed of solvent. The residue was dissolved in 15 ml of ether, oxidized with aqueous ferric chloride, and extracted with ether. The extract was washed with water, dried with magnesium sulfate, and freed of solvent to afford a reddish oil, which was chromatographed on silica gel. Elution with 20% isopropyl ether in *n*-hexane afforded 0.89 g of **20**. The estimated yield of **20** from **18** was 40%: ir (neat) 2950, 1650, 1460, 1270, 1100, 1020 cm^{-1}; uv max (*n*-hexane) 270 mμ (ε 15,100); nmr (CCl_4) δ 1.65 and 1.73 [2 s, 6, $=C(CH_3)_2$], 1.94 (s, 3, CH_3), 3.08 (d, 2, J = 7.5 Hz, CH_2), 3.89 (s, 6, 2 OCH_3), 4.82 (t, 1, J = 7.5 Hz, CH=).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.28; H, 7.39.

Registry No.—**10**, 4489-84-3; **11**, 1200-09-5; **13**, 34417-76-0; **15**, 2134-78-3; **16**, 30685-17-7; **17**, 34417-79-3; **18**, 34407-31-3; **20**, 727-81-1.

(17) P. Mamont, P. Cohen, and R. Azerad, *Bull. Soc. Chim. Fr.*, 1485 (1967).

(18) W. K. Anslow, J. N. Ashley, and H. Raistrick, *J. Chem. Soc.*, 439 (1938).

(19) As a result of comparison with the nmr spectrum of **18**, chemical shifts of protons in **19** are as follows: δ (CCl_4) 1.67 and 1.73 [2 s, $=C(CH_3)_2$], 2.09 (s, CH_3), 3.28 (d, CH_2), 3.47 (s, 2 OCH_2OCH_3), 3.67 (s, 2 OCH_3), 4.90 (s, 2 OCH_2O), 5.09 (m, =CH).

Synthesis of Steroidal Aziridines

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Desmostanyl 3α-acetate (**5**) was synthesized from litocholic acid and converted into the aziridine **8**, the essential steps being addition of iodine isocyanate to **5** which was converted to the corresponding carbamate **7**. Treatment of **7** with alcoholic base formed the aziridine **8**. Analogous sequence of reactions led to the formation of aziridine **9** from stigmasteryl acetate.

It has been reported recently that the aziridine functional grouping shows favorable carcinostatic activity in a number of tumor systems.[1] Most of the compounds reported to date have had the nitrogen mustard group attached to certain positions on the nucleus of the steroid. In connection with our work on the utilization of natural sterols and their derivatives by insects,[2] it was of interest to synthesize some steroidal aziridines having the nitrogen function in the side chain of the steroid.[3]

In the present communication we report the synthesis of 5,6-dihydro-24,25-iminodesmostanyl acetate (**8**) and 22,23-iminostigmasteryl acetate (**9**). Desmostanyl 3α-acetate (**5**) was readily obtained by the photochemical Wolff rearrangement in a THF–methanol solution of diazo ketone **2**[4] to give the methyl ester **3**. Grignard reaction of **3** with methylmagnesium iodide and subsequent dehydration[5] yielded **5**. Addition of iodine isocyanate[6] to **5** gave the adduct **6**,[7]

(1) S. A. Dyogtera, *Angew. Chem., Int. Ed. Engl.*, **1**, 600 (1962).

(2) R. Ikan, A. Markus, P. Klein, Z. Levinson, and E. D. Bergmann, *J. Insect Physiol.*, submitted for publication.

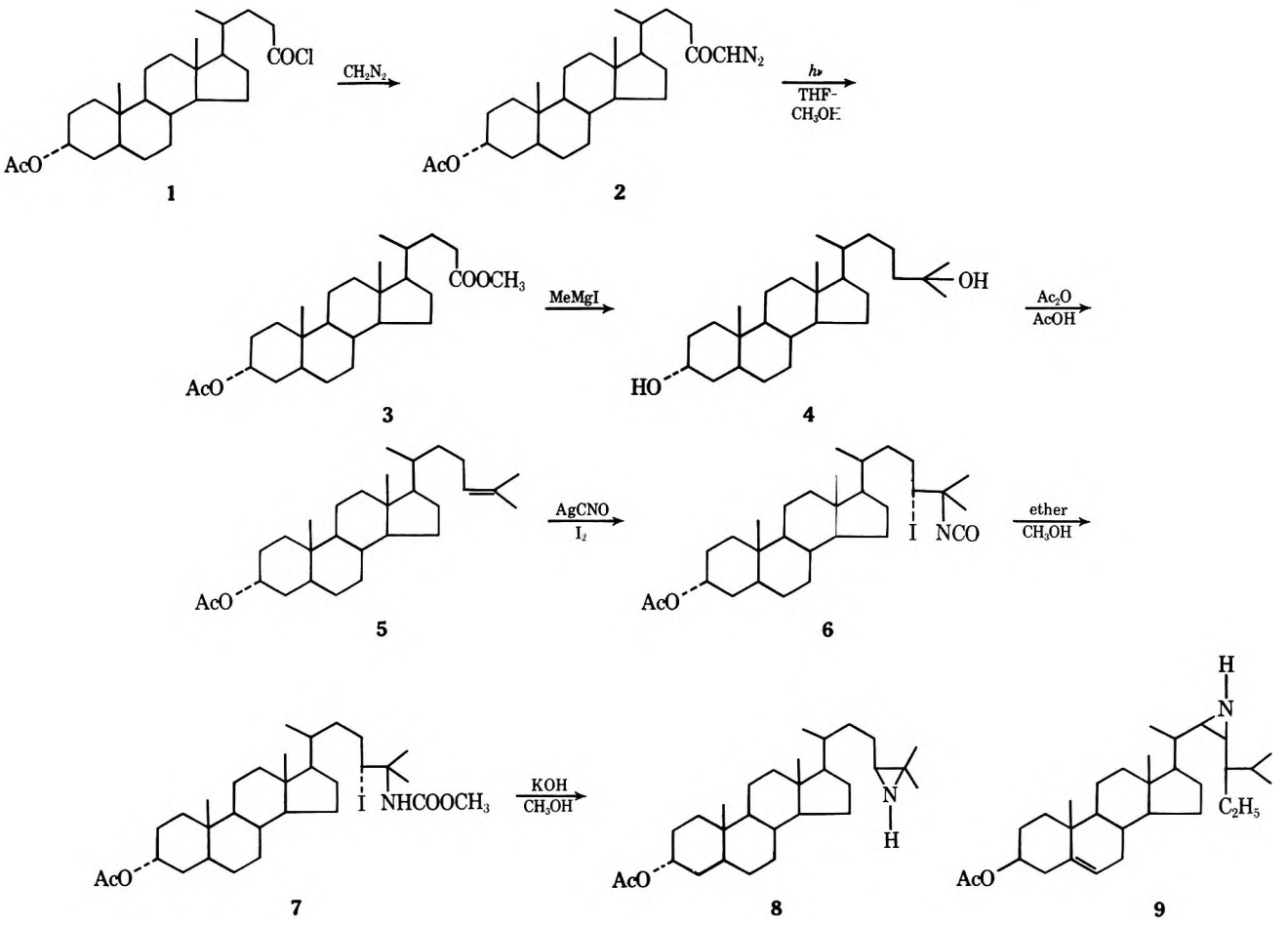
(3) Preliminary tests have indicated that the new aziridines caused total mortality of the larvae of *Dermestes maculatus*.

(4) A. S. Kende and Z. Goldschmidt, *Org. Photochem. Syn.*, **1**, 92 (1971).

(5) G. Habermehl and G. Volkwein, *ibid.*, **742**, 145 (1970).

(6) A. Hassner, M. E. Lorber, and C. Heathcock, *J. Org. Chem.*, **32**, 540 (1967).

(7) Structure **6** was tentatively assigned on the basis of the previous studies of INCO addition to olefins.[6]



which was converted with methanol to the corresponding methyl iodocarbamate **7**. Treatment of **7** with ethanolic potassium hydroxide readily effected the ring closure to form the expected aziridine **8**. The parallel synthesis using stigmasteryl acetate and iodine isocyanate yielded the aziridine **9**.

Experimental Section[8]

Methyl Homolitocholate 3α-Acetate. (3).—To a solution of 10 g of litocholic acid 3α-acetate in 100 ml of dry benzene, 3.5 g of oxalyl chloride was added dropwise. The mixture was refluxed for 3 hr, benzene was removed under reduced pressure, and the residue was triturated with dry petroleum ether (bp 30–60°), leaving 9 g of solid residue of litocholyl chloride 3α-acetate (**1**), which was dissolved in 100 ml of benzene and added dropwise at 5° to a dry ethereal solution of diazomethane (prepared from 40 g of nitrosomethylurea). The mixture was left overnight at room temperature and the ether was evaporated, leaving the diazo ketone **2** as yellowish crystals (9 g): ν_{max} 2100 (–$COCHN_2$), 1725 cm^{-1} (–$COOCH_3$); λ_{max} 253 mμ (ε 20,000) and 310 (9000). Diazo ketone **2** (9 g) was dissolved in 160 ml of tetrahydrofuran and 40 ml of methanol, and the solution was irradiated in a Pyrex vessel, using a Hanovia Q-81 high-pressure burner immersion lamp until no nitrogen was evolved. The solution was concentrated *in vacuo*, and the residue was chromatographed on a Florisil (200 g) column. The products were eluted with 100 ml each of solutions of benzene in hexane with concentrations of 10, 20, 40, and 50% (v/v), followed by solutions of chloroform in benzene, 10, 20, 40, and 50% (v/v), and finally with chloroform. Fractions which contained the desired product (as detected by tlc) were pooled, concentrated, and recrystallized from methanol: mp 69–70°; yield 6.3 g (71%); $[\alpha]^{20}D$ +46.9° (*c* 1.0); ν_{max} 1725 cm^{-1}.

Anal. Calcd for $C_{28}H_{46}O_4$: C, 75.3; H, 10.3. Found: C, 75.4; H, 10.4.

25-Hydroxycholestan-3α-ol (4).—To the Grignard reagent prepared from 3 g of magnesium and 19.2 g of methyl iodide in 50 ml of ether, 8 g of **3** in 50 ml of dry benzene was added dropwise and the mixture was refluxed for 1 hr. Ether was distilled off and then the mixture was refluxed for a further 4 hr and allowed to stand overnight at room temperature. Hydrochloric acid (5%) was added and the product was extracted with benzene. Distillation of benzene and recrystallization of the residue from methanol yielded 5.2 g (70%) of the product melting at 130–132°, ν_{max} 3350 cm^{-1} (–OH), $[\alpha]^{25}D$ +30.2° (*c* 1.0).

Anal. Calcd for $C_{27}H_{48}O_2$: C, 80.6; H, 11.4. Found: C, 80.4; H, 11.5.

5,6-Dihydrodesmostanyl 3α-Acetate (5).—25-Hydroxycholestan-3α-ol (5.7 g), 270 ml of acetic acid, and 27 ml of acetic anhydride were refluxed for 20 hr.[5] The cooled solution was concentrated *in vacuo* and the residue was treated with 500 ml of water. The oily product was extracted with benzene and chromatographed on a Florisil (100 g) column. The product was recrystallized from acetone: mp 93°; yield 4.1 g (70%); $[\alpha]^{25}D$ +47.5°; ν_{max} 1720 cm^{-1}; nmr δ 2.0 (–$COOCH_3$ s), 5.2 (–HC=C<, m).

Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.3; H, 11.2. Found, C, 81.6; H, 11.4.

24,25-Iminodesmostanyl Acetate (8).—5,6-Dihydrodesmostanyl 3α-acetate (1.5 g) was dissolved in 20 ml of anhydrous ether, and 1.8 g of silver cyanate was added.[9] The suspension was cooled in an ice–salt bath while being stirred magnetically. When the slurry had cooled to −15°, 1 g of solid iodine was added and the stirring was continued for 2 hr in the cold and then for 6 hr at room temperature. At the end of the reaction, the slurry had a bright canary yellow color. The ether solution was filtered through Celite to remove the yellow inorganic salts, then evaporated in the cold. There was obtained 1.7 g (80%) of light tan solid, mp 125°, ν_{max} 2260 (–N=C=O), 1720 cm^{-1}

(8) Melting points were determined on a Thomas-Hoover apparatus. Optical rotations were measured in chloroform. Nmr spectra were recorded for deuteriochloroform solutions using a Varian HA-100 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 137 spectrometer using Nujol oil, and ultraviolet spectra were recorded on a Unicam SP-800 spectrophotometer using ethanol.

(9) A. Hassner and C. Heathcock, *J. Org. Chem.*, **30**, 1748 (1965).

(-$COOCH_3$), which was dissolved in 50 ml of 1:1 ether–methanol and refluxed for 4 hr. The solvent was distilled off and the residue was recrystallized from methanol to give 1.5 g (80%) of **7**: mp 96–97°; ν_{max} 3430, 1740, 1725, 1520, 1225, 775, 648 cm^{-1}; λ_{max} 265 mμ (ε 480); nmr δ 4.8–5.2, 3.6 (-OCH_3).

A solution of 1.5 g of the carbamate **7** and 5 g of potassium hydroxide in 50 ml of ethanol and 5 ml of water was refluxed for 30 min.[10] The solution was cooled to room temperature and poured into water. The turbid solution was extracted with benzene, washed thoroughly with water, dried over magnesium sulfate, and filtered and the solvent was evaporated. The residue crystallized upon standing: mp 88–89°; yield 0.8 g (70%); $[\alpha]^{25}D$ +21°; ν_{max} 1730 cm^{-1}; molecular ion *m/e* 383 (calcd, 383).

Anal. Calcd for $C_{29}H_{49}NO_2$: N, 3.1. Found: N, 2.9.

22,23-Iminostigmasteryl Acetate (9).—The reactions were carried out analogously to the preparation of **8**. Thus addition of INCO to stigmasteryl acetate in dry THF gave a 79% yield of an adduct (ν_{max} 2260 and 1725 cm^{-1}). Treatment of the adduct with methanol gave a 90% yield of the iodo carbamate: mp 128°; ν_{max} 3430, 1740, 1725, 1520, 1227, 775, 648 cm^{-1}; λ_{max} 265 mμ (ε 450); nmr δ 5.6 (H, broad doublet), 5.0 (NH), 4.8 (CHI), multiplet), 4.2 ($CHNHCOOCH_3$, multiplet). The aziridine **9** was obtained in 90% yield: mp 88–89°; $[\alpha]^{25}D$ −24.5°; ν_{max} 3270 cm^{-1} (-NH); molecular ion *m/e* 409 (calcd, 409).

Anal. Calcd for $C_{31}H_{51}NO_2$: N, 3.2. Found: N, 3.1.

Registry No.—**3**, 34389-06-5; **4**, 34389-07-6; **5**, 34389-08-7; **6**, 34389-09-8; **7**, 34389-10-1; **8**, 34388-68-6; **9**, 34388-69-7.

Acknowledgment.—The authors wish to thank Mr. G. Grossman for the biological tests and Mrs. V. Filer, Bar-Ilan University, Ramat Gar, for mass spectroscopic measurements.

(10) A. Hassner and C. Heathcock, *Tetrahedron*, **20**, 1037 (1964).

The Stereochemistry of Azetidine Deaminations. On the Nature of the Trimethylene Intermediate

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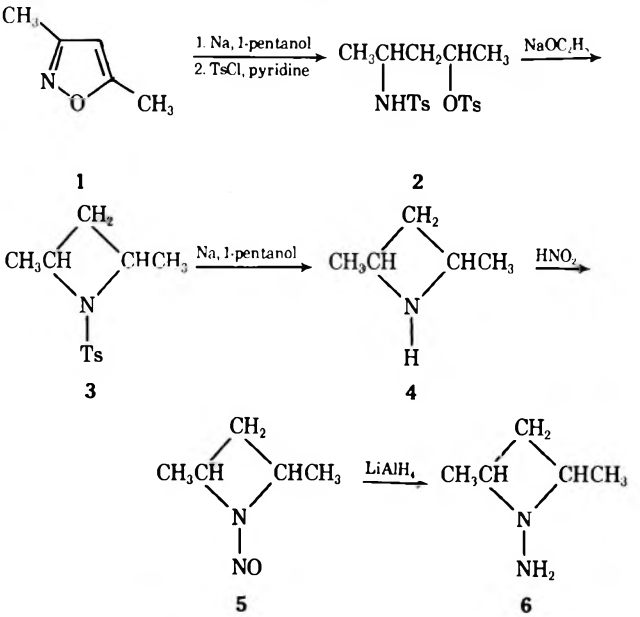
Pure stereoisomers of 2,4-dimethylazetidine (**4**), *N*-nitroso-2,4-dimethylazetidine (**5**), and *N*-amino-2,4-dimethylazetidine (**6**) were prepared. Reaction of *cis*-**4** with difluoramine, of *cis*-**5** with sodium dithionite, and of *cis*-**6** with mercuric oxide produced virtually identical mixtures of *cis*- and *trans*-1,2-dimethylcyclopropanes (**7**), in which *trans*-**7** predominated, thus indicating that these deaminations proceed through a common diazene intermediate. Analogous reactions of *trans*-**5** and *trans*-**6** yielded *cis*-**7** and *trans*-**7** in the ratio of 68:32. It is proposed that a mechanism involving a planar trimethylene intermediate could account for the stereochemical crossover and for the differences in the product distribution between azetidine deaminations and 1-pyrazoline pyrolyses, but that a superposition of "quasi-concerted" processes may offer a more attractive rationalization.

The trimethylene diradical has frequently been invoked[3] as an intermediate in the isomerization of cyclopropanes[3–6] and in the decomposition of 1-pyrazolines.[3,7,8] Since trimethylenediazene is known[12] to afford cyclopropane and nitrogen under very mild conditions and since the electronic structure of trimethylene is thought[10] to depend critically on the CCC angle, we considered it worthwhile to investigate the stereochemistry of azetidine deaminations.

The synthesis of the starting materials **4**, **5**, and **6** is outlined in Chart I. A crystalline diastereomer of mp 120–120.5° could be obtained from the oily mixture of ditosylates **2** by fractional recrystallizations from methanol. By implication, this must be *threo*-**2**, since it yields pure *cis*-**3** on treatment with sodium ethoxide in ethanol. The stereochemistry of *cis*-**3** is rigorously

CHART I



established by its nmr spectrum, which exhibits three complex groups of signals for the ring protons, centered at about δ 1.3 (1 H), 2.1 (1 H), and 3.65 (2 H). The stereochemical purity of *cis*-**3** follows from its conversion to *cis*-**4** and *cis*-**5**, the latter containing less than 0.3% *trans*-**5** as shown by vpc analysis.

The mother liquors of **2**, enriched in the erythro diastereomer, were subjected to an analogous reaction sequence and afforded a mixture consisting approxi-

(1) This work is based on a dissertation submitted by D. G. P. in partial fulfillment of the requirements for the Ph.D. degree at the University of Notre Dame.

(2) Alfred P. Sloan Research Fellow.

(3) For the extensive earlier literature on this problem and for the intriguing history of the ideas consult the bibliography in ref 4–11.

(4) J. A. Berson and J. M. Balquist, *J. Amer. Chem. Soc.*, **90**, 7343 (1968).

(5) W. L. Carter and R. G. Bergman, *ibid.*, **90**, 7344 (1968); R. G. Bergman and W. L. Carter, *ibid.*, **91**, 7411 (1969).

(6) M. R. Willcott, III, and V. H. Cargle, *ibid.*, **91**, 4310 (1969).

(7) M. P. Schneider and R. J. Crawford, *Can. J. Chem.*, **48**, 628 (1970), and earlier papers in this series.

(8) D. E. McGreer and J. W. McKinley, *ibid.*, **49**, 105 (1971), and earlier papers in this series.

(9) D. M. Lemal in "Nitrenes," W. Lwowski, Ed., Interscience, New York, N. Y., 1970, p 345.

(10) R. Hoffmann, *J. Amer. Chem. Soc.*, **90**, 1475 (1968).

(11) L. M. Stephenson and J. I. Brauman, *ibid.*, **93**, 1988 (1971).

(12) C. L. Bumgardner, K. J. Martin, and J. P. Freeman, *ibid.*, **85**, 97 (1963).

TABLE I

PRODUCTS OF AZETIDINE DEAMINATIONS AND 1-PYRAZOLINE PYROLYSES[a]

Reaction	Number of runs	Solvent	Temp, °C	Total yields of hydrocarbons, %	Relative yields, %[b] cis-7	trans-7	Olefins
cis-4 + HNF_2	1	Neat	0	65	16.8	83.2	<0.3
cis-5 + $Na_2S_2O_4$	2	25% Aqueous ethanol	40	67[c]	15.6	84.4	<0.3
trans-5 + $Na_2S_2O_4$	3	25% Aqueous ethanol	40	67[c]	68.5	31.5	<0.3
cis-6 + HgO	2	Ethanol	40	71[c]	15.5	84.5	<0.3
cis-6 + HgO	1	1-Pentanol	140	*d*	18.7	81.3	<0.3
trans-6 + HgO	2	Ethanol	40	71[c]	67.7	32.3	<0.3
cis-9[e] pyrolysis	6	Gas phase	200	98	33.2	66.1	0.7
trans-9[e] pyrolysis	6	Gas phase	200	98	72.6	25.4	2.0

[a] R. J. Crawford and A. Mishra, *J. Amer. Chem. Soc.*, **87**, 3768 (1965); **88**, 3963 (1966). [b] In those cases where more than one run was made, the numbers were reproducible within about ±0.5%, except for the reaction of *trans*-5 + $Na_2S_2O_4$, for which the experimental scatter amounted to ±1.5%. [c] Determined using a mixture of stereoisomeric starting materials. [d] Not determined. [e] 3,5-Dimethyl-1-pyrazoline = 9.

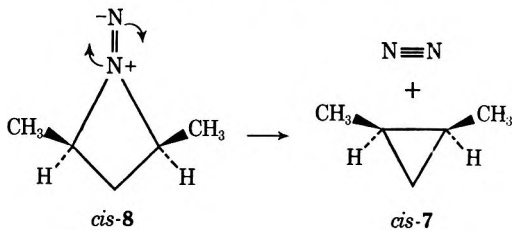
mately of 30% *cis*-5 and 70% *trans*-5. Separation on a preparative vpc column yielded *trans*-5 in greater than 99.7% purity. Its stereochemistry is proved by the isochronism of the ring methylene protons, which give rise to a triplet at δ 2.14 (2 H).

The reagents used for the deaminations of **4**, **5**, and **6** and the reaction conditions are summarized in Table I. The low-boiling products were collected in traps and analyzed by vpc and nmr. The *cis*- and *trans*-1,2-dimethylcyclopropanes (**7**) needed for comparison were prepared from the authentic 1,1-dibromo-2,3-dimethylcyclopropanes[13] by reduction with sodium in 1-pentanol.

Discussion

On the basis of the results in Table I we draw the following conclusions. (1) The three different deamination reactions proceed through a common intermediate, the diazene **8**. (2) In analogy to the stereospecific deaminations of *cis*- and *trans*-2,3-butenimines[14] one might have expected that the diazenes **8** could produce the dimethylcyclopropanes **7** stereospecifically under retention of configuration (*cis*-**8** → *cis*-**7**; *trans*-**8** → *trans*-**7**) in a concerted cheletropic reaction characterized by a nonlinear departure of the nitrogen molecule (Chart II). This possibility, tentatively

CHART II



cis-8 *cis*-7

favored by Lemal[9] on general grounds, can at best only partially account for the results. Since the formation of a cyclopropane bond under inversion of configuration at one of the α carbons concerted with a linear nitrogen extrusion does not seem possible sterically, we conclude that at least a major fraction of the deaminations involve additional intermediates. (3) The observed partial crossover in stereochemistry is reminiscent of the analogous phenomenon detected in the pyrolyses of 3,5-dimethyl-1-pyrazolines[15] (**9**), the results of which are included in Table I. The most economical explanation of the observations therefore appears to consist in the hypothesis of a concerted linear expulsion of nitrogen from **8** concomitant with disrotation to a planar trimethylene diradical of the type **10a** (Chart III) (the 0,0 species in Hoffmann's[10] terminology), which subsequently undergoes preferential controtatory ring closure.[10,15]

CHART III

0,0 0,90 90,90

10a **10b** **10c**

The obvious difficulty with this explanation stems from the quantitative differences in the isomer distribution observed for the azetidine deaminations and pyrazoline pyrolyses and from the fact that no olefins could be detected in the former reactions. As the data in Table I show, this discrepancy is not easily disposed of by blaming it on spurious effects such as temperature and reaction conditions. A similar insensitivity of the product composition in the pyrazoline thermolyses to changes in temperature has also been noticed by Crawford.[15] McGreer's[16] data suggest a general decrease in the degree of stereochemical crossover in going from the gas phase to the solution phase, whereas the deamination of *cis*-2,4-dimethylazetidine yields more *trans*-**7** than the pyrolysis of *cis*-**9**. Nitrogen-containing intermediates do not seem to provide an escape hatch either. Crawford[7,15] has presented experimental evidence supporting[17] a concerted fission of both carbon–nitrogen bonds in 1-pyrazolines. If a nitrogen-containing intermediate with a lifetime sufficient for rotation and back-side displacement[17] were

(13) P. S. Skell and A. Y. Gardner, *J. Amer. Chem. Soc.*, **78**, 3409 (1956).
(14) J. P. Freeman and W. H. Graham, *ibid.*, **89**, 1761 (1967).
(15) R. J. Crawford and A. Mishra, *ibid.*, **87**, 3768 (1965); **88**, 3963 (1966).
(16) D. E. McGreer, N. W. F. Chiu, M. G. Vinje, and K. C. K. Wong, *Can. J. Chem.*, **43**, 1407 (1965).
(17) For a dissenting view, see P. B. Condit and R. G. Bergman, *Chem. Commun.*, 4 (1971).

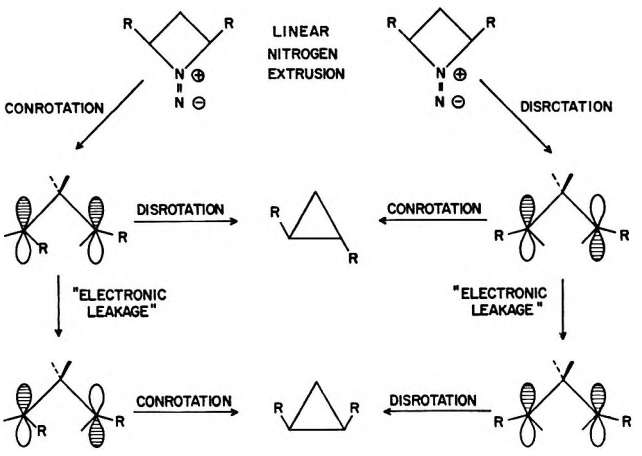


Figure 1.—Possible azetidine deamination pathways.

involved in the decomposition of **8**, it would be surprising if it could not also close the ring to form the 1-pyrazoline, which is thermally stable at that temperature, in analogy to the diradical rearrangement mechanism frequently observed for open-chain ylides.[18] No such reaction was observed for the deaminations of Table I; control experiments established that 0.2% of pyrazolines could easily have been detected.

Beyond this point we can only speculate. If one postulates a competing conrotatory pathway from **8** to **10a** one arrives at the scheme shown in Figure 1. It should be noted that such a competing conrotatory pathway does *not* require a nonlinear cheletropic extrusion of nitrogen. Hoffmann[10] predicted a crossover of π levels in **10a** at a CCC angle of about 100°. A 0,0 species with a CCC angle smaller than 100° could thus be produced initially by conrotation and linear departure of nitrogen from **8** in a concerted fashion, and this species could become a doubly excited electronic configuration of **10a** within one period of a CCC bending vibration. "Electronic leakage" (see Figure 1) could then produce an electronic configuration in which two electrons occupy the MO of opposite symmetry. In this scheme the observed stereochemical crossover emerges as a consequence of faster ring closure as compared to the rate of electronic leakage along *both* pathways, and the differences in the product distributions between the azetidine deaminations and 1-pyrazoline pyrolyses can be accounted for by suitable choices of the various rate constant ratios.[19]

In the light of recent theoretical work[20,21] there can be no question that the scheme of Figure 1 is grossly oversimplified. A single-configuration description of the diradical singlet state of **10a** is clearly inadequate; according to Salem's calculations[20] the two single-determinant singlet wave functions obtained by placing two electrons into the MO's of either symmetry mix almost equally at the equilibrium geometry of **10a**. The process termed "electronic leakage" in Figure 1 therefore only amounts to a small change in the mixing

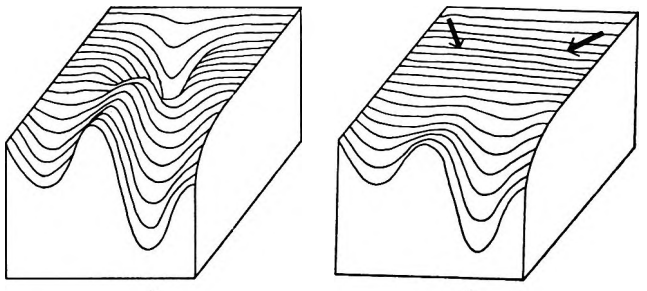


Figure 2.—Schematic potential hypersurfaces: (a) for a reaction proceeding through a genuine intermediate; (b) for a reaction proceeding through a twixtyl.

coefficients as a function of the CCC angle. Of perhaps even more serious consequence is the assumption, implicit in the scheme of Figure 1, that **10a** represents a genuine intermediate residing in a subsidiary energy minimum and capable of discriminating between two or more competing rate processes. Salem's work[20] casts serious doubt on the validity of such an assumption and suggests that this "species" rather represents a more or less flat plateau (with respect to certain internal coordinates) in the potential hypersurface, a situation for which Hoffmann, *et al.*,[22] have recently introduced the term "twixtyl." Finally, the scheme of Figure 1 does not readily explain the relative rates of diastereomerizations and enantiomerizations in the pyrolysis of cyclopropanes,[4,5] for which intermediates of a different structure have been invoked.[4,5] It seems desirable, therefore, to seek a modification of the scheme in Figure 1 that can simultaneously accommodate the results of the nitrogen elimination reactions[23] and the cyclopropane isomerizations. We should like to suggest that such a modification might be found along the following lines.[25]

It has traditionally been supposed[26] that a reliable criterion for the intervention of a high-energy intermediate in a chemical reaction is the possibility of "branching" after the rate-determining step and that the product ratios are controlled by the relative heights of the potential troughs leading out of a subsidiary energy minimum (Figure 2a), independent of how the intermediate itself had been generated. In a genuinely concerted reaction, on the other hand, the structural characteristics of the rate-determining transition state are thought to be sufficient to seal the further fate of the reaction. If Salem's[20] *ab initio* calculations, which yielded species closely resembling **10b** and **10c** with energies virtually equal to that of **10a**, should prove to be sufficiently reliable, we may be dealing with an intermediate situation of a "quasi-concerted" reaction, indicated schematically in Figure 2b. In such a quasi-concerted reaction there is no "resting point" along the reaction coordinate, but the structural characteristics of the "transition state" do *not* completely deter-

(18) J. E. Baldwin, J. E. Brown, and G. Höfle, *J. Amer. Chem. Soc.*, **93**, 788 (1971), and earlier papers in this series.

(19) Alternatively, the partial randomization of stereochemistry may be attributed to competitive bond rotation in the intermediate **10a** instead of electronic leakage, an interpretation corresponding more closely to that preferred by previous workers.[3]

(20) L. Salem, *Bull. Soc. Chim. Fr.*, 3161 (1970); Y. Jean and L. Salem, *Chem. Commun.*, 382 (1971).

(21) L. Salem and C. Rowland, *Angew. Chem.*, **84**, 86 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 92 (1972).

(22) R. Hoffmann, S. Swaminathan, B. G. Odell, and R. Gleiter, *J. Amer. Chem. Soc.*, **92**, 7091 (1970).

(23) There exists the possibility that some related elimination reactions[24] leading to cyclopropanes also fall into this category.

(24) B. M. Trost, W. L. Schinski, and I. B. Mantz, *J. Amer. Chem. Soc.*, **91**, 4320 (1969); P. S. Skell, K. J. Klabunde, and J. H. Plonka, *Chem. Commun.*, 1109 (1970); H. A. J. Carless and E. K. C. Lee, *J. Amer. Chem. Soc.*, **92**, 6683 (1970).

(25) This suggestion is closely akin to the conclusions reached by Salem.[20,21]

(26) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **9**, 751 (1970).

mine the final outcome of the reaction. Conventional activated-complex theory is ill suited for describing such a situation and one should therefore explicitly consider individual trajectories.[27] The product distribution then emerges as the result of a superposition of individual quasi-concerted trajectories, ensemble averaged over the "momentum" distribution at the point of entry into the plateau (indicated schematically by arrows in Figure 2b), and would be expected to depend on subtle details of that "momentum" distribution, in contrast to genuinely concerted reactions.[28,30]

The preceding analysis should not be construed to mean that there are no energetic preferences on the potential hypersurface, but only that they may not be exclusively controlling the course of a quasi-concerted reaction. If this proposal should turn out not to be totally unreasonable, there would no longer be any need for invoking a different type of intermediate in the cyclopropane isomerizations.[4,5] By the same token, the difficulty of having to require[4] that the cyclopropane ring opening could not be the microscopically reverse process of the ring closure from Crawford's[15] intermediate would be eliminated, provided only that the principle of microscopic reversibility is applied correctly, as recently shown by Kinsey.[32]

The experimental evidence now available, including that presented in this paper, can at best only furnish a hint that a description in terms of an ensemble average of quasi-concerted trajectories may sometimes provide an attractive alternative to the usual picture of a diradical intermediate whose fate is determined by a competition between ring closure, bond rotation, hydrogen migration, etc. It would be a pointless alternative, however, if a twixtyl really were operationally indistinguishable from a true intermediate.[22] It seems to us that this can only be part of the whole story. In particular we wish to point out that the analysis presented here leads to two novel conclusions, each of which is, in principle, amenable to experimental test. (1) The fate of a twixtyl, as reflected in its product distribution, should depend on the nature of its chemical precursor. (2) A twixtyl emanating from one and the same chemical precursor should still show different chemistry if one succeeds in controlling its mode of generation selectively by external means.

(27) This has already been pointed out by Hoffmann, *et al.*,[22] for the closely related case of the tetramethylene diradical twixtyl.

(28) It is important to realize that there is an essential difference between this hypothetical situation and that of "hot-molecule" reactions[29] of the conventional type. The possibility that activated species are involved in certain photochemical reactions purportedly proceeding through diradical intermediates has recently been discussed by Stephenson and Brauman.[31] In the thermal reactions considered here the initial distribution of the energy over translational, rotational, and vibrational states need not deviate from a normal Boltzmann distribution. Rather, the difference between genuinely concerted and quasi-concerted reactions has to be attributed to the following two features. (i) Every individual transition state (there may of course be more than one) leads to just one single product (or its enantiomer) in a concerted reaction, but to more than one product in a quasi-concerted reaction. (ii) Since there is, by hypothesis, no resting point along the reaction coordinate in a quasi-concerted reaction, differences in the "momentum" distribution at the point of entry into the plateau, which are to be expected if the "same" twixtyl is generated from different precursors, should stand a much higher chance not to become completely equilibrated before the system reaches one of the exit valleys leading to product than in the case of ordinary "hot" molecules. In other words, "reactive relaxation" may effectively compete with nonreactive relaxation, even in solution and for large molecules. The product ratios are expected to be a sensitive function of this distribution, whereas in a concerted reaction such differences, if not too drastic, would only change the macroscopic rate of the reaction but not the product.

(29) For a review see B. S. Rabinovitch and M. C. Flowers, *Quart. Rev., Chem. Soc.*, **18**, 122 (1964).

(30) There is a close relationship to the previously proposed "recoil" effect in the pyrolysis of bicyclic azo compounds.[31]

(31) E. L. Allred and R. L. Smith, *J. Amer. Chem. Soc.*, **89**, 7133 (1967); W. R. Roth and M. Martin, *Justus Liebigs Ann. Chem.*, **702**, 1 (1967).

(32) J. L. Kinsey, *J. Chem. Phys.*, **54**, 1206 (1971).

Experimental Section

4-Aminopentan-2-ol (Threo–Erythro Mixture.)—The following procedure proved to be superior to that described in the literature.[33] To a refluxing solution of 10.0 g (103 mmol) of 3,5-dimethylisoxazole (**1**) in 250 ml of 1-pentanol was added 24 g of sodium in 1-g pieces over a period of 6 hr. Water (150 ml) was added to the cold solution, the layers were separated, and the aqueous phase was extracted with four 15-ml portions of chloroform. The chloroform solution was concentrated and the residue was added to the alcoholic layer. The product was extracted from the alcohol with 75 ml of 6 *N* hydrochloric acid, and the acidic solution was washed twice with 10-ml portions of ether and made strongly alkaline with potassium hydroxide pellets. Extraction with ten 10-ml portions of chloroform and work-up by distillation afforded 4.2 g (41 mmol, 40%) of the amino alcohol mixture, bp 72–75° (20–25 mm) [lit.[33] bp 72–77° (20 mm)]. The *threo-p*-nitrobenzamide derivative melted at 129–130° (lit.[33] mp 131–132°).

4-(*p*-Toluenesulfonamido)-2-pentyl *p*-Toluenesulfonate (2).—*p*-Toluenesulfonyl chloride (18.5 g, 97 mmol) was added to a cold (−3°) solution of 5.0 g (48.5 mmol) of the 4-aminopentan-2-ol diastereomer mixture in 100 ml of dry pyridine and the solution was kept at −15° for 4 days, during which time pyridine hydrochloride precipitated. The mixture was poured onto 400 g of ice, and the red oil was washed with cold, dilute hydrochloric acid, dissolved in chloroform, dried (Na_2SO_4), and treated with Norit. Addition of petroleum ether (bp 35–60°) to the filtrate gave 12.5 g (30.5 mmol, 63%) of the ditosylate mixture **2** as a tan oil which slowly solidified, mp 55–90°.

When a solution of 140 g of the diastereomer mixture **2** in 300 ml of methanol was refrigerated at −20° for 20 hr, 62 g of crude crystalline material was obtained, which yielded 33.5 g of pure *threo*-**2** upon three additional recrystallizations from methanol: mp 120–120.5°; $\delta_{TMS}^{CDCl_3}$ 7.5 (m, 8), 4.8 (m, 2), 3.4 (m, 1), 2.43 (s, 6), 1.72 (t, 2), 1.16 (d, 3), 0.98 (d, 3).

Anal. Calcd for $C_{19}H_{25}NO_5S_2$: C, 55.45; H, 6.12; N, 3.40. Found: C, 55.55; H, 6.15; N, 3.16.

The erythro isomer of **2** was not obtained in pure form, but only as enriched material from the mother liquors.

***cis*-2,4-Dimethyl-*p*-toluenesulfonazetidide (*cis*-3).**—To a refluxing solution of 2.5 g (37 mmol) of sodium ethoxide in 500 ml of absolute ethanol was added a solution of 11.5 g (37 mmol) of *threo*-**2** in 300 ml of absolute ethanol over a period of 40 hr. The solution was heated for an additional 10 hr, concentrated to a volume of 200 ml, and poured onto 600 g of ice to yield 5.0 g (28 mmol, 75%) of *cis*-**3** as a precipitate: mp 141.5–142°; $\delta_{TMS}^{CDCl_3}$ 7.52 (AB pattern, 4), 3.65 (m, 2), 2.42 (s, 3), 2.1 (m, 1), 1.36 (d, 6), 1.3 (m, 1).

Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found: C, 60.28; H, 7.06; N, 5.69.

***cis*-2,4-Dimethylazetidine (*cis*-4).**—To a refluxing solution of 10.4 g (43 mmol) of *cis*-**3** in 300 ml of 1-pentanol was added 23 g of sodium in 1-g pieces over a period of 6 hr. Water (150 ml) was added to the cold solution, the layers were separated, and the aqueous phase was subjected to distillation, which was discontinued when the temperature of the vapors reached 100°. The distillate was combined with the alcoholic phase and the amine was extracted with dilute hydrochloric acid. The acidic solution was washed with ether, made strongly basic, and partially distilled. Upon addition of potassium hydroxide pellets to the first 20 ml of distillate, 3.6 g of an oil separated, which on distillation afforded 3.2 g (38 mmol, 89%) of *cis*-**4** as a hygroscopic oil: bp 84–86° (750 mm); δ_{TMS}^{neat} 3.7 (multiplet overlapping a broad singlet, total intensity approximately 4.5), 2.3 (m, 1), 1.4 (m, 1), 1.13 (d, 6). The *p*-bromobenzenesulfonyl derivative melted at 131°.

Anal. Calcd for $C_{11}H_{14}NO_2SBr$: C, 43.42; H, 4.64; N, 4.60. Found: C, 43.15; H, 4.75; N, 4.54.

***N*-Nitroso-*cis*-2,4-dimethylazetidine (*cis*-5).**—A solution of 1.0

(33) J. Sicher, M. Pankova, J. Jonas, and M. Svoboda, *Collect. Czech. Chem. Commun.*, **24**, 2727 (1959).

g (12 mmol) of *cis*-4 in 30 ml of 50% aqueous acetic acid was heated with 2.0 g of sodium nitrite to 80° for 3 hr. The oil precipitated with potassium hydroxide was chromatographed on a neutral silica gel column. Elution with chloroform afforded 1.1 g (10 mmol, 85%) of *cis*-5: bp 55° (2.5 mm); δ_{TMS}^{neat} 5.0 (m, 1), 4.2 (m, 1), 2.7 (m, 1), 1.63 (d, 3), 1.38 (d, 3), 1.5 (m, 1). Its mass spectrum (70 eV) showed prominent peaks at *m/e* 114, 84, 70, 42, 41, and 30. Its stereochemical purity was checked on two vpc columns[34,35] and found to be greater than 99.7%.

N-**Nitroso-*trans*-2,4-dimethylazetidine** (*trans*-5).—The solid material isolated from the mother liquors remaining after crystallization of pure *threo*-2 was subjected to procedures identical with those described above. The product thus obtained was shown by vpc[35] to consist of 30% *cis*-5 and 70% *trans*-5. Preparative separation on a 15 ft × 0.5 in. 20% Carbowax 20M on Chromosorb G column, using an Aerograph Autoprep Model A-700 gas chromatograph, yielded pure (>99.7%[34,35]) *trans*-5: bp 40° (0.9 mm); $\delta_{TMS}^{CDCl_3}$ 5.2 (m, 1), 4.7 (m, 1), 2.14 (t, 2), 1.67 (d, 3), 1.40 (d, 3). Its mass spectrum was identical with that of *cis*-5.

N-**Amino-*cis*-2,4-dimethylazetidine** (*cis*-6).—A solution of 1.5 g (13 mmol) of *cis*-5 in 10 ml of dry ether was added dropwise to a slurry of 2.0 g of lithium aluminum hydride in 20 ml of dry ether under stirring and the mixture was heated under reflux for an additional 12 hr. Water (2.0 ml) was then added dropwise under cooling, followed by gradual addition of 2.0 ml of 10% sodium hydroxide and an additional 4.0 ml of water. The mixture was filtered and the ether solution was extracted with dilute hydrochloric acid. The residual ether was removed from the aqueous solution by an air stream, and the solution was made strongly alkaline and partially distilled. Addition of potassium hydroxide pellets to the first 15 ml of the distillate precipitated 1.2 g (12 mmol, 92%) of *cis*-6 as a yellow oil: δ_{TMS}^{neat} 4.4 (broad singlet), 2.9 (m, 2), 2.1 (m, 1), 1.16 (d, 6), 1.1 (m, 1). Its mass spectrum (70 eV) showed a parent peak at *m/e* 100. Vpc analysis[34] demonstrated a stereochemical purity of >99.7%.

In a preliminary experiment a *p*-nitrobenzaldehyde derivative of mp 74–76° was prepared from a 2:3 mixture of *cis*-6 and *trans*-6.

Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.52; H, 6.32; N, 17.94.

N-**Amino-*trans*-2,4-dimethylazetidine** (*trans*-6).—When a procedure identical with that used for the preparation of *cis*-6 was applied to *trans*-5, *trans*-6 was obtained in greater than 99.7% stereochemical purity: δ_{TMS}^{neat} 4.4 (broad singlet), 3.52 (sextet, 2), 1.62 (t, 2), 1.19 (d, 6).

1,2-Dimethylcyclopropanes (*cis*-7 **and** *trans*-7).—To a solution of 8.3 g (36 mmol) of *cis*- or *trans*-1,1-dibromo-2,3-dimethylcyclopropane, prepared according to the procedure of Skell and Gardner,[13] in 300 ml of 1-pentanol was added with stirring 3.3 g of sodium in small pieces over a period of 3 hr. After the reaction had subsided, the mixture was warmed to 45° and the cyclopropane was distilled into a Dry Ice trap under a slow stream of nitrogen. The nmr spectra of the products are very complex, but sufficiently different to permit approximate analysis of mixtures.[36] Injection of the pure isomers and of mixtures into two different vpc columns[34,37] showed that *trans*-7 was the faster eluting isomer in both cases.

Reaction of 5 with Sodium Dithionite.—To a slurry of 6.0 g (33 mmol) of sodium dithionite in 25 ml of 20% sodium hydroxide was added a solution of 1.0 g (8.8 mmol) of a mixture consisting of 30% *cis*-5 and 70% *trans*-5 in 9 ml of ethanol. The mixture was stirred at 40° and the low-boiling products were swept out by a slow stream of nitrogen. After 4 hr 0.28 g of a colorless liquid had been collected in a Dry Ice trap, shown by nmr (CCl_4) to be a mixture of *cis*-7 and *trans*-7. The liquid was further analyzed by vpc[34,37] and found to consist of 39% *cis*-7 and 61% *trans*-7 as the only detectable products. Addition of *cis*- and *trans*-2-pentene to the product mixture gave two additional peaks in the gas chromatogram;[38] a control experiment established that 0.3% of 2-pentenes could be detected. The dithionite reaction mixture was extracted with ether to give 0.3 g of starting material, for an overall yield of isolated cyclopropanes of 67%.

The stereochemically pure isomers of 5 were subjected to identical reaction conditions and the product compositions were determined by vpc analysis.[34,37] Reisolated unreacted starting materials were in both cases shown by vpc[35] to be identical with the original, uncontaminated by the other isomer or by detectable side products.

In a further control experiment a trace of *trans*-3,5-dimethyl-1-pyrazoline[39] was added to the 30:70 mixture of *cis*- and *trans*-5, which was then subjected to the above reaction conditions. Vpc analysis[35] of the recovered starting material showed three additional unidentified components.

Reaction of 6 with Mercuric Oxide.—A solution of 0.85 g (8.5 mmol) of a 29:71 mixture of *cis*- and *trans*-6 in 4 ml of absolute ethanol was added to 6.3 g (30 mmol) of yellow mercuric oxide in 20 ml of absolute ethanol and the mixture was stirred for 3 hr at 40° under a slow stream of nitrogen. The material (0.42 g, 71%) collected in a Dry Ice trap was found by vpc[34,37] to consist exclusively of dimethylcyclopropanes. The individual isomers were subjected to an identical procedure; *cis*-6 was also deaminated at 140° using refluxing 1-pentanol as a solvent.

Reaction of *cis*-4 with Difluoramine.—The procedure previously described[12] was followed using 20 mmol of *cis*-2,4-dimethylazetidine and 5 mmol of difluoramine (generated by the hydrolysis of triphenylmethyldifluoramine[40]). A total of 3.3 mmol (65%) of a mixture of 1,3-dimethylcyclopropanes (Table I) was collected in a methylcyclohexane slush bath and analyzed by gas chromatography. The other gaseous product, nitrogen (67%), was identified by its mass spectrum.

Registry No.—*threo*-2, 34414-32-9; *erythro*-2, 34414-33-0; *cis*-3, 34414-34-1; *cis*-4, 34414-35-2; *cis*-4 *p*-bromobenzenesulfonyl derivative, 34414-36-3; *cis*-5, 34414-37-4; *trans*-5, 34414-38-5; *cis*-6, 34414-39-6; *trans*-6, 34414-40-9; 6 *p*-nitrobenzaldehyde derivative, 34414-41-0.

Acknowledgments.—We are grateful to Professor C. L. Bumgardner for carrying out the difluoramine experiment and to numerous colleagues for commenting on a preliminary version of the manuscript, especially to Professor R. G. Bergman, whose spirited objections provided a source of great stimulation. This research was supported by Grant No. 3428-A1 from the Petroleum Research Fund.

(34) 6 ft × 0.12 in. 10% UCW 98 Chromosorb W.

(35) 10 ft × 0.25 in. 20% Carbowax 20M on Chromosorb G.

(36) The cis isomer displays an isolated group of signals around 458 Hz upfield from internal $CHCl_3$ at 60 MHz, which is absent in the trans isomer.

(37) 20 ft × 0.25 in. 20% SE-30 on Chromosorb W.

(38) The order of elution was *trans*-7, *trans*-2-pentene, *cis*-2-pentene, *cis*-7.

(39) R. J. Crawford, A. Mishra, and R. J. Dummel, *J. Amer. Chem. Soc.*, **88**, 3959 (1966).

(40) W. H. Graham and C. O. Parker, *J. Org. Chem.*, **28**, 850 (1963).

Stereochemistry of Opening of Cyclopropanols. *trans*-2,3-Di-*tert*-butylcyclopropanone Hemiketals

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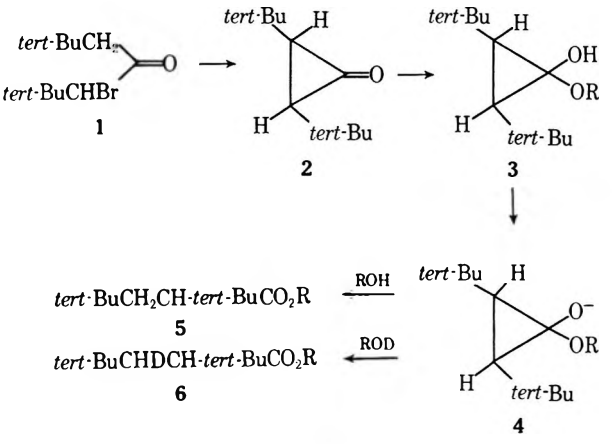
trans-2,3-Di-*tert*-butylcyclopropanone was converted by methyl alcohol–sodium methoxide and ethylene glycol with its sodium salt to the corresponding 2-*tert*-butyl-4,4-dimethylpentanoate esters, *tert*-$BuCH_2CH$-*tert*-$BuCO_2R$. The stereochemistry of proton substitution at C 3 was determined to be no less than 97 and 93% retention by use of the combination of deuterium-labeled solvents and nmr analysis of the diastereomeric deuterium-labeled products. Because similar but more general systems have previously yielded substantial amounts of inversion with these dissociating solvents, the results indicate the operation of a very strong factor favoring retention, and an explanation is advanced in terms of the specific and unusual geometry of the system studied.

Various results have been reported for the stereochemistry of the electrophilic substitution involved in base-catalyzed ring opening of cyclopropanols.[1] Almost complete inversion (with respect to carbon as the leaving group) was found in the opening of *trans*-2-phenyl-1-methylcyclopropanol[2] with sodium hydroxide in dioxane–water, the only solvent system used. Opening of *trans*-2,3-dibutyl-2,3-dimethylcyclopropanol,[3] *endo*- and *exo*-7-hydroxy-1,6-dimethyl[4.1.0]bicycloheptanes,[4] and tricyclo[4.4.1.$0^{1,6}$]undecan-11-ol[3] proceeded with almost complete retention with potassium *tert*-butoxide in *tert*-butyl alcohol, but considerable amounts of inversion were observed with ethylene glycol and its sodium salt. In all these results the influence of a previously recognized solvent influence is discernible: low dielectric, nondissociating solvents, like *tert*-butyl alcohol, favoring retention and high dielectric, dissociating solvents, like water and ethylene glycol, affording substantial amounts of inversion.[5] However, it should not be surprising to find cyclopropanols possessing unusual features which do not conform to such behavior, and indeed 1-hydroxynortricyclene[6] opens with almost complete inversion in *tert*-butyl alcohol (as well as in methyl alcohol). The present study counterbalances this example with the *trans*-2,3-di-*tert*-butylcyclopropanone hemiketals (**3**), representing another unusual system which also fails to conform, but, in the opposite sense, affording almost complete retention in methyl alcohol and ethylene glycol. The hemiketals were not isolated as such but were formed *in situ* by mixing *trans*-2,3-di-*tert*-butylcyclopropanone (**2**) with the appropriate alcohol.[7] In the presence of alkoxide and excess alcohol, the conjugate bases of the hemiketals (**4**) suffer ring opening to 2-*tert*-butyl-4,4-dimethylpentanoate esters (**5**); this conversion constitutes the second half of the normal Favorskii reaction[8] which occurs upon base treatment of an α-halo ketone, in the present case α-bromodineopentyl ketone (**1**).



Although obtention of unlabeled ester **5** cannot reveal the stereochemistry of electrophilic substitution, the diastereotopic nature of the geminal protons on C 3 does allow this determination, in principle, by generation, in deuterated solvents, of the two diastereomeric monodeuterated esters represented by **6**, one corresponding to retention and the other to inversion.

Analysis and Results.—In practice the determination of stereochemistry of hemiketal opening by using deuterated solvents was considered to be applicable providing that (a) nmr spectroscopy provided a viable analysis of the diastereomers represented by **6** and (b) randomizing exchange did not obscure the anticipated stereochemical differentiation, most obviously by enolization of the product esters; both conditions were met.[9]

The all-proton ester **5**, R = CH_3, was prepared by the Favorskii reaction on α-bromo ketone **1**, best by using a sample of commercial potassium *tert*-butoxide in *tert*-butyl alcohol, which yielded directly, not the *tert*-butyl ester, but the corresponding acid, presumably from the action of adventitious hydroxide in the *tert*-butoxide. Diazomethane treatment afforded the methyl ester.

The 100-MHz spectrum of the methyl ester was somewhat clearer than the 60-MHz spectrum, displaying the expected ABC pattern in almost AMX form, with chemical shifts and coupling constants readily assigned to the individual protons of **5** in a conformation essentially frozen about the C 2,3 bond with the

(1) Earlier results with discussion are presented by C. H. DePuy, *Accounts Chem. Res.*, **1**, 33 (1968), and T. D. Hoffman and D. J. Cram, *J. Amer. Chem. Soc.*, **91**, 1009 (1969).

(2) C. H. DePuy, F. W. Breitbeil, and K. R. DeBruin, *ibid.*, **88**, 3347 (1966).

(3) A. R. Fritzberg, Ph.D. Thesis, Wesleyan University, 1971.

(4) P. S. Wharton and T. I. Bair, *J. Org. Chem.*, **31**, 2480 (1966).

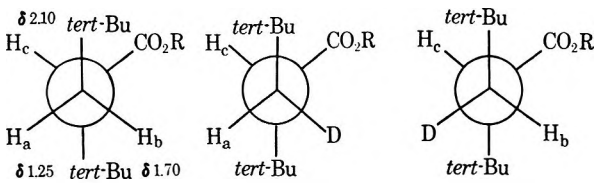
(5) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, Chapters 3 and 4. A useful summary is presented on pp 153–155.

(6) A. Nickon, J. L. Lambert, S. J. Lambert, R. O. Williams, and N. H. Werstiuck, *J. Amer. Chem. Soc.*, **88**, 3354 (1966).

(7) J. F. Pazos and F. D. Greene, *ibid.*, **89**, 1030 (1967).

(8) A. S. Kende, *Org. React.* **11**, 261 (1960).

(9) This was not found to be the case in the base-catalyzed opening of *trans*-2,3-di-*tert*-butylcyclopropanol, which was simply prepared by lithium aluminum hydride reduction of **2**; the 2-*tert*-butyl-4,4-dimethylpentanal generated in deuterated solvents was found to have completely exchanged the α hydrogen for deuterium.[3]

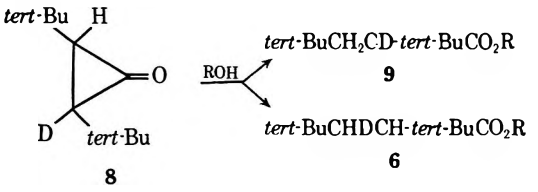


tert-butyl groups trans related (see **7**):[10] δ 1.25 (H_a), 1.70 (H_b, deshielded relative to H_a by the proximate ester function) and 2.10 ppm (H_c) with J_{ab} = 14.0, J_{ac} = 1.2, and J_{bc} = 10.7 Hz (corresponding to geminal, vicinal-gauche, and vicinal-trans relations, respectively). Negligible exchange of the acidic hydrogen of the ester (H_c) occurred when it was treated with base in deuterated solvent under conditions which generated the ester from the cyclopropanone. Thus, on opening the cyclopropanone in methyl alcohol-*O*-*d* with sodium methoxide, both *threo*- and *erythro*-**6**, R = CH_3, could be formed by electrophilic substitution, with each diastereomer exhibiting its own distinct nmr spectrum.

The spectrum of the ester experimentally obtained[11] consisted most obviously of two large and approximately equal peaks, each with a small coupling of *ca.* 1 Hz centered at δ 1.25 and 2.10 ppm corresponding to H_a and H_c of *threo*-**6**, R = CH_3 (and a retention mechanism). From integrations of the regions of absorption corresponding to the BC pattern of *erythro*-**6**, R = CH_3, an upper limit of 3% was placed on this species, showing that the stereochemistry of proton addition had occurred with no less than 97% retention of stereochemistry.[12]

Opening of the cyclopropanone in ethylene glycol-*O*-d_2 in the presence of its sodium salt yielded **6**, R = CH_2CH_2OH, with a spectrum for the a, b, and c hydrogens which similarly revealed that no less than 93% of proton addition had occurred with retention of stereochemistry.

One other slightly unusual inverse labeling experiment yielded stereochemical results. Dineopentyl ketone was repeatedly dissolved in methyl alcohol-*O*-*d* containing sodium methoxide until 98% of the four α hydrogens had been exchanged for deuterium. By treatment with cupric bromide in chloroform–ethyl acetate[13] the ketone was converted to α-bromo ketone **1** containing 95% of deuterium in the three α positions. However, the Favorskii reaction on the deuterated bromo ketone, carried out with the same sample of commercial potassium *tert*-butoxide in *tert*-butyl alcohol, as described for the all-proton compound, afforded, after esterification, a methyl ester in which only one deuterium atom per molecule remained. The nmr spectrum suggested the sequence of events which had taken place, starting with exchange of the deuterium atom on the methine carbon prior to closure to the cyclopropanone.[14] The cyclopropanone thus became effectively monolabeled (**8**), with one hydrogen and one deuterium atom attached to the ring, and subsequent opening, with an almost equal probability of breaking the two possible ring bonds, yielded a mixture of **9** and **6**.



Although there is no stereochemical consequence observable from the formation of **9**, there is in the formation of **6**, with the difference that *threo*-**6** now corresponds to inversion and *erythro*-**6** to retention.

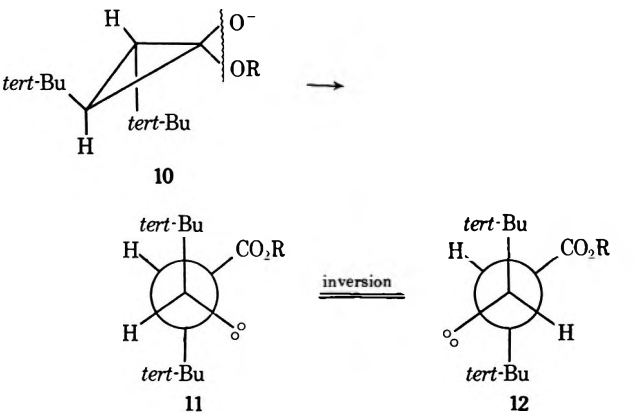
Experimentally, the nmr spectrum of the methyl ester obtained consisted most obviously of almost equal intensity AB and BC patterns arising from **9** and *erythro*-**6** (retention), and, by integrating over the region of absorption of the a and c protons corresponding to *threo*-**6** (inversion), it was concluded that no less than 95% retention had occurred.

Discussion

In the opening of cyclopropanone **2** under Favorskii conditions in *tert*-butyl alcohol with (presumably) hydroxide ion, the observed retention result does not require a special explanation, and the operation of any special effect is masked by the nondissociating character of the solvent which alone could be responsible for the stereochemical result.[5]

However, the stereochemical result of retention in methyl alcohol and ethylene glycol indicates the operation of a strong effect opposing the natural dissociative forces of the solvents, and an explanation can be sought for in the unusual and specific geometry of the system.

Considering the substitution to be of the SEl category, opening of the hemiketal **10** presumably occurs with rotation of the carbanion terminus of the breaking bond such that the most stable, all-staggered conformation **11** is reached directly (rotation in the opposite sense yields a conformation in which the *tert*-butyl groups are gauche-related), assuming a pyramidal configuration for the carbanion. The most stable con-



figuration of the inverted carbanion is similarly likely to be **12** and, although there is no formidable or lopsided torsional barrier apparent in the simplest inversion process which converts **11** to **12** by sweeping a

(10) Diagrams indicate the absolute stereochemistry of only one of the two enantiomeric sets of racemic systems.

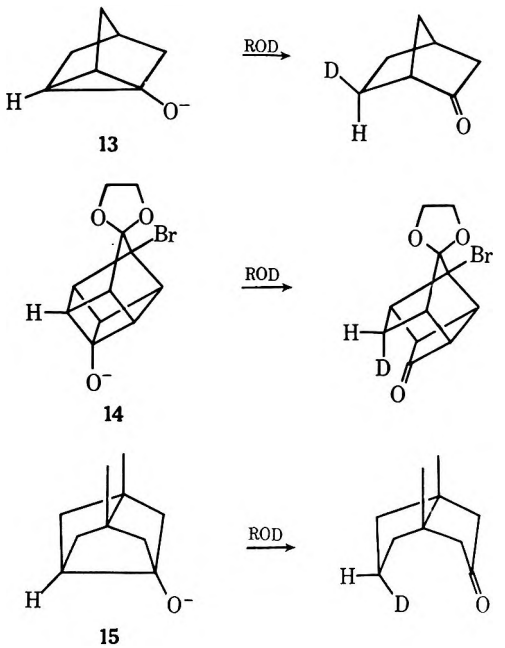
(11) All spectra were subjected to deuterium decoupling.

(12) No lower limit can usefully be attributed to inversion product because of the difficulty of separating any real signals from noise and adventitious or satellite peaks.

(13) L. C. King and G. K. Ostrum, *J. Org. Chem.*, **29**, 3459 (1964).

(14) For examples of exchange in the Favorskii reaction see F. G. Bordwell, R. R. Frame, R. G. Scamehorn, J. G. Strong, and S. Meyerson, *J. Amer. Chem. Soc.*, **89**, 6704 (1967).

hydrogen atom across the vicinal *tert*-butyl group as the carbanion hybridization changes, the two configurations, in conformations **11** and **12**, must be considerably different in energy because of differential solvation. Carbanion **11** is effectively solvated by the gauche ester function and its accompanying solvent shell, whereas carbanion **12** is surrounded by a relatively hydrophobic region which is intensified by the bulk of the *tert*-butyl groups.[15] The stereochemical consequence of these relationships is clearly retention: uninverted carbanion is more stable than inverted carbanion, and it is surrounded by favorably disposed solvent molecules on its open face. In general, it may be anticipated that a system with an intrinsic and extreme molecular asymmetry[16] will open with a strong stereochemical preference. The recent literature provides other examples in this category, and rationalization of the results presents an interesting exercise: cyclopropoxide **13**[6] opens with inversion whereas caged cyclobutoxide **14**[17] and strained cyclopentoxide **15**[18] open with retention.



Experimental Section

Physical Data.—Melting and boiling points are uncorrected. The spinning band distillation was carried out on a Nester-Faust 24-in. Teflon column, NFT-50, fitted with an automatic reflux ratio control. Gas–liquid phase chromatography was performed on a Varian Aerograph unit, Model A-90-P, using two 5 ft × 0.25 in. stainless steel columns packed with 60/80 firebrick coated with (1) 20% Apiezon L and (2) 20% SF-96. Infrared spectra were recorded using a Perkin-Elmer 137 infrared spectrometer.

Nmr spectra were recorded using a Varian A-60A spectrometer except for one 100-MHz spectrum of methyl 2-*tert*-butyl-4,4-dimethylpentanoate which was generously run on a Varian HA-100 unit at Yale University. Chemical shifts are reported with reference to an internal tetramethylsilane standard. Deuterium decoupling was performed with a Nuclear Magnetic Resonance Specialties Heteronuclear Spin Decoupler, Model HD-60, and multiscan averaging was carried out with the assistance of a Varian 620i computer. Analyses of small concentrations of protons were made by comparing integrations of their signal intensities with those of appropriate ^{13}C satellite signals.

α-Bromodineopentyl Ketone (3-Bromo-2,2,6,6-tetramethyl-4-heptanone) (1).—Bromination of dineopentyl ketone was carried out by following the procedure of King and Ostrum.[13] To a three-necked flask equipped with a paddle-stirrer, reflux condenser attached to a gas trap, and dropping funnel were added 73.2 g (0.328 mol) of cupric bromide and 160 ml of ethyl acetate. To the ethyl acetate, heated to reflux, was added dropwise, over a 30-min period, a solution of 30.0 g (0.176 mol) of dineopentyl ketone in 165 ml of chloroform. The reaction mixture was stirred and maintained at reflux for an additional 6 hr. At that time essentially all of the solid dark green cupric bromide had been replaced by solid white cuprous bromide, although the green color of the solution persisted. The reaction mixture was filtered, washed several times with water, and dried. Solvent was removed by evaporation and the residue was subjected to a spinning band distillation, with monitoring of the distillate by glpc on column 1 at 150° (retention times of 5.1 and 17.8 min were observed for dineopentyl ketone and the α-bromo ketone, respectively.) Complete separation from starting material gave 30.4 g (69%) of a colorless liquid: bp 66–67° (2.5 mm); ir (film) 5.82 μ; nmr (CCl_4) δ 4.11 (s, 1), 2.50 (s, 2), 1.13 (s, 9), and 1.03 ppm (s, 9).

Favorskii Reaction of α-Bromodineopentyl Ketone. Methyl 2-*tert*-Butyl-4,4-dimethylpentanoate (5 = 7).—To a solution of 300 mg of α-bromo ketone in 1.0 ml of *tert*-butyl alcohol was added 400 mg of potassium *tert*-butoxide (MSA Research). The mixture was stirred at 40° for 12 hr. Work-up afforded 40 mg of a neutral oil and 195 mg (87%) of a white solid acid which could be crystallized from methanol–water: mp 69.5–71.5°; ir (CCl_4) 5.80 μ; nmr (CCl_4) δ 12.28 (s, 1), 2.25–1.17 (ABC pattern, 3), 0.98 (s, 9), and 0.90 ppm (s, 9).

Treatment of the carboxylic acid with diazomethane yielded, after work-up, an oil which was purified by preparative glpc on column 2 at 135°: ir (film) 5.76 μ; nmr (CCl_4) δ 3.58 (s, 3), 2.10, 1.70, 1.25 (H_c, H_b, and H_a of ABC pattern, J_{ab} = 14.0, J_{ac} = 1.2, J_{bc} = 10.7 Hz), 0.89 (s, 9), and 0.84 ppm (s, 9).

Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.89; H, 12.13. Found: C, 72.02; H, 12.24.

Favorskii Reaction of α-Bromodineopentyl Ketone-α,α',α'-d_3.—To 25 ml of methanol-*O*-*d* (99% d_1) in which 200 mg of sodium had been dissolved was added 10.0 g of dineopentyl ketone. The solution was maintained at 45° for 20 hr and then cooled and quenched by the rapid addition, with stirring, of 20 ml of 15% aqueous acetic acid. Work-up afforded ketone with 73% α-d_4 deuterium incorporation (theoretical, 75%). Three repetitions of this treatment afforded 8.24 g of ketone with 98% α-d_4 deuterium incorporation.

α-Bromodineopentyl ketone-α,α',α'-d_3, with 95% α-deuterium incorporation, was prepared from the tetradeuterated ketone by the procedure already described for the undeuterated compound, with, however, precaution to remove traces of protonic contaminants in the solvents: ethyl acetate was distilled from phosphorus pentoxide and chloroform was filtered through active alumina and then distilled. To a solution of 130 mg of deuterated α-bromo ketone in 1.0 ml of *tert*-butyl alcohol was added 135 mg of potassium *tert*-butoxide (MSA Research). The reaction mixture was stirred at room temperature for 4 hr. Work-up afforded 20 mg of a neutral oil and 68 mg (71%) of a white solid acid. Esterification of 65 mg of the acid with diazomethane afforded 55 mg of a neutral oil which was purified by preparative glpc on column 2 at 135°. The nmr spectrum of the methyl 2-*tert*-butyl-4,4-dimethylpentanoate so obtained is described in the text.

Opening of *trans*-2,3-Di-*tert*-butylcyclopropanone. A.—Into an nmr tube were placed 80 mg (0.48 mmol) of di-*tert*-butylcyclopropanone[7] and 0.80 ml of methanol-*O*-*d* (99% d_1), in which had been dissolved 10 mg (0.48 mmol) of sodium, and the sealed tube was placed in a bath maintained at 61° for 13 hr. The reaction mixture was then diluted with 10 ml of pentane, washed with water, and dried. Removal of solvent gave 75 mg of an oil whose nmr spectrum corresponded to that of undeuterated methyl 2-*tert*-butyl-4,4-dimethylpentanoate except for the region δ 2.7–1.1 ppm, which contained two major broad signals at

(15) The other conformations available to inverted carbanion are comparable to **11** with respect to solvation but are disfavored by a gauche interaction of the *tert*-butyl groups.

(16) Intrinsic asymmetry of the type under discussion can be defined with respect to the formation of diastereomeric products upon protonation as distinct from intrinsic symmetry which yields enantiomeric products. Other unsymmetrical carbanion systems are discussed in ref 5.

(17) A. J. Klunder and B. Zwanenburg, *Tetrahedron Lett.*, 1721 (1971).

(18) W. T. Borden, V. V. M. Cabell, and T. Ravindranathan, *J. Amer. Chem. Soc.*, **93**, 3800 (1971).

δ 2.10 and 1.25 ppm which sharpened to doublets ($J \cong 1$ Hz) upon deuterium decoupling. The ester was purified by preparative glpc and its nmr spectrum was then multiscanned through the region δ 2.7–1.1 ppm with deuterium decoupling to determine the relative amounts of diastereoisomers **8** and **9** present, with results as discussed in the text.

B.—Into an nmr tube were placed 80 mg (0.48 mmol) of di-*tert*-butylcyclopropanone and 1.20 ml of ethylene glycol-*O*-d_2[19] in which 5.0 mg (0.25 mmol) of sodium had been dissolved. Some solid material separated after a few minutes and the mixture was periodically agitated during immersion of the tube for 14 hr in an oil bath maintained at 61°. The reaction mixture was transferred to a separatory funnel with 15 ml of pentane and the pentane solution was washed with water and then dried. Removal of solvent and preparative glpc of the residue on column 2 at 172° gave a colorless liquid with a retention time of 13 min: ir (CCl_4) 2.79, 2.89, and 5.75 μ; nmr (CCl_4) δ 4.2–3.6 (A_2B_2 pattern, 4), 2.14 (broad, 1, changed to a doublet, $J \cong 1$ Hz, upon deuterium decoupling), 1.80 (broad, 1, changed to a doublet, $J \cong 1$ Hz, upon deuterium decoupling), 0.92 (s, 9), and 0.86 ppm (s, 9). The spectrum was then multiscanned through the region δ 2.7–1.1 ppm with deuterium decoupling to determine the relative amounts of diastereoisomers **8** and **9** present, with results as discussed in the text.

(19) D. J. Cram and B. Rickborn, *J. Amer. Chem. Soc.*, **83**, 2178 (1961).

Registry No.—**1**, 33712-48-0; **2**, 14743-58-9; **5**, 33712-50-4; α-bromodineopentyl ketone-α,α′,α′-d_3, 33712-51-5.

Stereospecific Rearrangement during the Piperidine-Catalyzed Condensation of Benzaldehyde and Bis(ethylsulfonyl)methane. An Abnormal Knoevenagel Condensation

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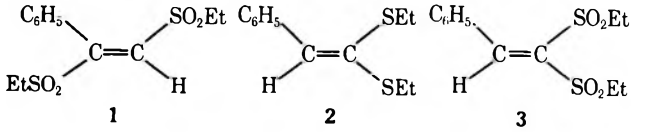
The piperidine-catalyzed Knoevenagel condensation between benzaldehyde and bis(ethylsulfonyl)methane gives not the reported β,β-bis(ethylsulfonyl)styrene (**3**) but stereospecifically rearranged (*E*)-α,β-bis(ethylsulfonyl)styrene (**1**). An independent synthesis of **1** and its stereostructurally related isomer (*Z*)-α,β-bis(ethylsulfonyl)styrene (**7**) is presented. When the condensation is carried out with excess piperidine, α-(ethylsulfonyl)-β-piperidinostyrene (**10**) is isolated in good yield.

During the course of another study, we were interested in preparing the previously reported β,β-bis(ethylsulfonyl)styrene (**3**).[1-3] Two sets of workers, Leonard[1] and Oftedahl, *et al.*,[2] reported a synthesis of **3** by a Knoevenagel-type condensation between benzaldehyde and bis(ethylsulfonyl)methane catalyzed by piperidine and piperidine acetate, respectively. Earlier, Rinzema, *et al.*,[3] had reported the synthesis of **3** by the perphthalic acid oxidation of β,β-bis(ethylthio)styrene (**2**). Although the melting points reported for **3** are coincidentally close,[4] our investigation of the reaction reported by Leonard and by Oftedahl showed that the compound reported by them as **3** is actually (*E*)-α,β-bis(ethylsulfonyl)styrene (**1**).



A mechanism with its stereochemical implications is presented for the formation of **1** and other products observed during this reaction. An independent synthesis of **1** and its stereostructurally related isomer (*Z*)-α,β-bis(ethylsulfonyl)styrene (**7**) is also presented.

Results and Discussion

When either the synthesis reported by Leonard or by Oftedahl was repeated, we obtained a 33–37% yield of **1**. Although **1** has the approximate melting point (94–96°)[3] reported for **3**, it lacks the strong ir band near 1620 cm^{-1} reported by Rinzema.[5] A sample of **3** was prepared by the method of Rinzema, *et al.*,[3] and was found to be different from the Leonard–Oftedahl product **1**. As reported by Rinzema, *et al.*, **3** reacts rapidly and exothermically with phenylhydrazine, generating benzaldehyde phenylhydrazone and bis(ethylsulfonyl)methane. Under the same conditions, **1** remains unchanged.

Independent Synthesis and Stereochemistry of 1.—An independent synthesis of **1** was desired. The base-catalyzed addition of mercaptans to acetylenic compounds in general, and acetylenic sulfones specifically, has been studied by several workers. Among them, Truce[6] and Stirling[7] have shown the additions to be stereospecifically trans. The addition of ethyl mercaptan to ethyl phenylethynyl sulfone (**5**)[8] was expected to give (*Z*)-β-(ethylsulfonyl)-α-(ethylthio)styrene (**6**), which could subsequently be oxidized to (*Z*)-α,β-bis(ethylsulfonyl)styrene (**7**), the stereoisomer of **1**.

Treatment of **5** with sodium ethanethiolate in ethanol at 5° gave **6** (23%) and (*E*)-α-(ethylthio)-β-(ethylsulfonyl)styrene (**8**) (2%). Surprisingly, the major product (42% yield) was β-(ethylsulfonyl)-β-(ethylthio)styrene (**4**).

The structure of **4** was assigned from its perphthalic acid oxidation to **3**. Oxidation of the major β-(ethyl-

(1) E. C. Leonard, *J. Org. Chem.*, **30**, 3258 (1965).

(2) M. L. Oftedahl, J. W. Baker, and M. W. Dietrich, *ibid.*, **30**, 296 (1965).

(3) L. C. Rinzema, J. Stoffelsma, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **78**, 359 (1959).

(4) Melting points reported for **1**: Leonard, 93–95°; Oftedahl, 96–97°; Rinzema, *et al.*, 92–93°.

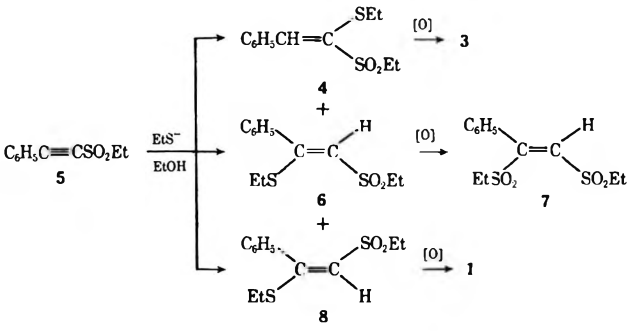
(5) Neither Leonard's nor Oftedahl's paper presented ir data. However, the ir spectrum of the compound Oftedahl reported as **3** can be found in "Sadtler's Standard Spectra," Sadtler Research Laboratories, Philadelphia, Pa., 1966, ir spectrum no. 28346.

(6) W. E. Truce and J. A. Simms, *J. Amer. Chem. Soc.*, **78**, 2756 (1956).

(7) J. M. Stirling, *J. Chem. Soc.*, 5856 (1964).

(8) (a) Prepared by the *m*-chloroperbenzoic acid oxidation of the previously reported ethyl phenylethynyl sulfide.[8b] (b) L. Brandsma, H. E. Wijers, and C. Jonkers, *Recl. Trav. Chim. Pays-Bas*, **83**, 208 (1964). (c) Compound **5** has recently been synthesized by an alternate procedure: W. E. Truce and G. C. Wolf, *J. Org. Chem.*, **36**, 1727 (1971).

sulfonyl)-α-(ethylthio)styrene (6) [assigned the *Z* stereostructure by the rule of trans addition] yielded 7. Oxidation of 8 gave the desired 1.



The stereostructures assigned to 7 and 1 are also supported by the following interpretation of nmr data. In styrene itself, the order of chemical shifts for the vinyl protons (in order of decreasing δ) is gem > cis > trans.[9] This order is in large part due to the anisotropy effect of the aromatic ring, largely coplanar with the double bond. However, in 2,6-dimethylstyrene,[10] where for steric reasons the aromatic ring and the double bond are twisted out of coplanarity, the order becomes gem > trans > cis.[11] Steric interaction between the bulky α-(ethylsulfonyl) group and the aromatic ring in both 1 and 7 causes the phenyl and vinyl group to twist away from coplanarity. Anisotropy effects of the aromatic ring in conjunction with the twisted conformations of 1 and 7 cause the greater shielding of the phenyl–vinyl cis proton,[12] resulting in an upfield shift in 7 (δ 6.9) relative to 1 (δ 7.4).

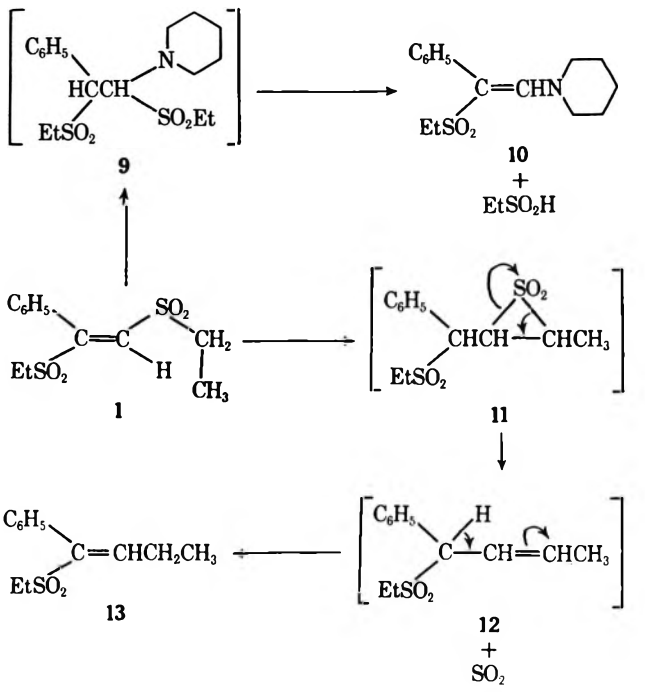
Further evidence in support of these stereochemical assignments is obtained from comparison of the vinyl proton chemical shifts of 7 and 1 to those reported for (*Z*)- and (*E*)-α,β-bis(*p*-tolylsulfonyl)styrene.[13]

Further Rearrangements.—In addition to the 33–37% yield of 1 which we obtained from the Leonard–Oftedahl reaction, we also isolated 30–40% of β-ethyl-α-(ethylsulfonyl)styrene (13), which was not reported by either Leonard or Oftedahl. The substitution pattern for 13 was assigned on the basis of the 7-Hz coupling between the vinyl proton and the methylene protons of the vinylic ethyl group;[14] however, the stereostructure of 13 remains unassigned.

Treatment of 1 in refluxing benzene with excess piperidine gave two products, 13 and 10. The minor product of this reaction, 13, can arise through intermediates 11 and 12 as depicted in Scheme I.

Intermediate 11, formed by internal addition to the α,β-unsaturated sulfone 1, could be expected to decompose with loss of sulfur dioxide as shown, since episulfones are intermediates in the Ramberg–Bäcklund reaction.[15]

SCHEME I



The major product isolated from this reaction was α-(ethylsulfonyl)-β-piperidinostyrene (10). Although 10 can be formed from 1, it can be prepared directly in good yield by the reaction of benzaldehyde, bis(ethylsulfonyl)methane, and excess piperidine. The substitution pattern of 10 (vinyl proton α to the piperidino group) was assigned from the vinyl hydrogen nmr chemical shift (δ 7.15). This is similar to the chemical shift of the vinyl protons of α-(methylsulfonyl)-β-pyrolidinostyrene (δ 7.42), reported by Wells and Abbott.[16] The chemical shifts of vinyl protons β to the amino function in β-sulfonyl enamines are found in the region δ 4.5–5.5.[17]

The condensation of benzaldehyde with two other bis(alkylsulfonyl)methanes was investigated. The piperidine-catalyzed condensation (~10 mol %) of benzaldehyde with bis(methylsulfonyl)methane leads to the rearranged α,β-bis(methylsulfonyl)styrene (14). Although 14 was not synthesized independently, the rearranged structure was assigned, since 14 failed to exhibit an ir band in the 1600-cm^{-1} region and, in addition, its five aromatic protons appear as an nmr singlet, as is the case with 1, 7, and the other α-alkylsulfonyl styrenes examined. The *E* configuration is assigned to 14 by analogy to 1. When the condensation is carried out with 2 equiv of piperidine, the product isolated is α-(methylsulfonyl)-β-piperidinostyrene (15), identical with the minor product obtained (4% yield) from the reaction of methanesulfonyl chloride and β-piperidinostyrene (17). Wells and Abbott[16] isolated 2-phenyl-3-piperidinothietane 1,1-dioxide (19) from this reaction but did not report the isolation of 15. However, from the reaction of β-pyrrolidinostyrene (18) and methanesulfonyl chloride, these workers

(9) "Sadtler's Standard Spectra," Sadtler Research Laboratories, Philadephia, Pa., 1969, nmr spectrum no. 6408M.

(10) Reference 9, 1966, nmr spectrum no. 1689M.

(11) The assignments for the cis and trans vinyl protons are reversed in Sadtler, but can be correctly assigned by consideration of the magnitude of the gem-cis and gem-trans coupling constants.

(12) A contour diagram of the anisotropy effects of an aromatic ring can be found in L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 95.

(13) (*Z*) δ 6.9, (*E*) δ 7.8: V. Calo, G. Modena, and G. Scorrano, *J. Chem. Soc. C*, 1344 (1968).

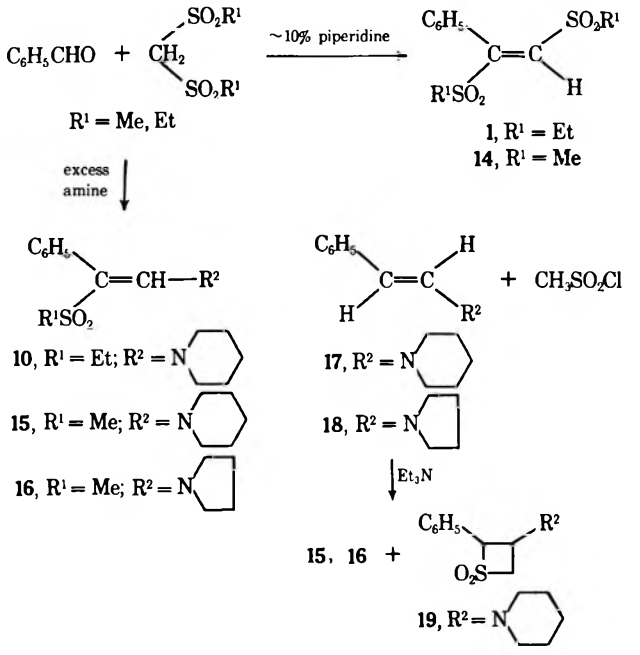
(14) Coupling constants for systems $-CH_2CH{=}C<$ are 5–10 Hz, whereas systems $HC{\equiv}C{-}CH_2-$ have J = 0–2 Hz: R. J. Abraham in "Nuclear Magnetic Resonance for Organic Chemists," D. W. Mathieson, Ed., Academic Press, New York, N. Y., 1967, p 132.

(15) F. G. Bordwell and N. P. Neurieter, *J. Amer. Chem. Soc.*, **85**, 1209 (1963).

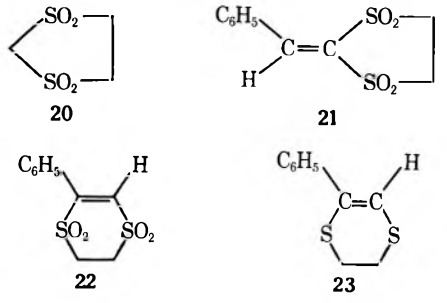
(16) J. N. Wells and F. S. Abbott, *J. Med. Chem.*, **9**, 489 (1966).

(17) W. E. Truce and D. G. Brady, *J. Org. Chem.*, **31**, 3543 (1966).

did isolate a low yield of α-(methylsulfonyl)-β-pyrrolidinostyrene (16). The physical data (ir, nmr, melting point) for 16 reported by these workers are all in agreement with those for the 16 which we obtained by the reaction of benzaldehyde, bis(methylsulfonyl)-methane, and 2 equiv of pyrrolidine.[18]



When the piperidine-catalyzed condensation of benzaldehyde and 1,3-dithiolane 1,1,3,3-tetroxide (20) was carried out, the unrearranged condensation product, 2-benzylidine-1,3-dithiolane-1,1,3,3-tetroxide (21) was obtained, and not 2,3-dihydro-5-phenyl-*p*-dithiin 1,1,4,4-tetroxide (22). The synthesis of 22 was accomplished by perphthalic acid oxidation of 2,3-dihydro-5-phenyl-*p*-dithiin (23).[19]



Mechanism.—Scheme II fits the observed facts and products of the rearrangement.

Formation of the intermediate 24 could arise by either of the two paths pictured, since treatment of α,α-dipiperidinotoluene (26) with bis(ethylsulfonyl)methane in refluxing benzene also results in formation of 10. In this case, 2 equiv of piperidine are available and the reaction is driven to 10. Additionally, treatment of 3 in refluxing benzene with a catalytic amount of piperidine gives 1. The involvement of a secondary amine in the formation of 24 and subsequent rearrangement to 1 as depicted is supported by the fact that the Knoevenagel condensation catalyzed by a tertiary amine (triethylamine) which cannot, therefore, lead to an aziridinium ion, gives the unrearranged 3. The formation of 13 may occur by several paths, since, in addition to its formation during the Leonard–Oftedahl reaction, 13 is also generated by treatment of 1 with triethylamine in refluxing toluene.

Stereochemical Implications of the Mechanism.—The Leonard–Oftedahl reaction yields 1 with no 7 observed among the products. The intermediacy of 7 in the formation of 1 is ruled out, since treatment of 7 with a catalytic amount of piperidine in refluxing benzene does not give 1. This reaction results in a small yield of 10; however, the bulk of the 7 is recovered unchanged and no 1 can be detected in the reaction mixture. The stereospecific formation of 1 is explained by stereoelectronic factors (Scheme III).

Intermediate 24 is shown in the most favorable conformation (largest groups farthest apart). Back-side displacement of the sulfinate anion by nitrogen gives the aziridinium intermediate 25. Reopening of the aziridinium salt by backside attack of sulfinate gives conformation 9a. Rotation to conformation 9b and subsequent trans elimination of piperidine yields 1.

The explanation of the failure of 21 or its related intermediates to yield the rearranged 22 is speculative. First, in carbocyclic systems at least, cyclization to five-membered rings is favored over cyclization to six-membered rings.[20] Thus it may be that the equilibrium in this heterocyclic case favors 27 over 29. Secondly, granted that 29 is formed appreciably (Scheme IV), trans elimination of piperidine is precluded. Formation of 22 would then have to take place by an energetically less favorable cis elimination.

Experimental Section

All melting points were obtained on a Thomas-Hoover melting point apparatus and are corrected. Infrared spectra were obtained with a Perkin-Elmer Model 137 infrared spectrometer and nmr data were obtained using a Varian A-60A instrument.

Piperidine-Catalyzed Condensation of Benzaldehyde and Bis(ethylsulfonyl)methane.—A mixture of benzaldehyde (7.95 g, 0.075 mol), bis(ethylsulfonyl)methane[21] (10.0 g, 0.05 mol), piperidine (0.75 ml), and benzene (50 ml) was heated under reflux while water was removed with the aid of a Dean–Stark trap. After 3 days the theoretical amount of water had been collected and the reaction mixture was cooled to room temperature. The benzene was removed under reduced pressure and the residue was steam distilled to remove excess benzaldehyde. The nonsteam volatile portion was extracted into methylene chloride, dried, and concentrated. The residue was chromatographed over silica gel. Elution with 6:1 benzene–ethyl acetate gave 4.8 g (42%) of 13 which was recrystallized from ether–hexane: mp 45–46°; nmr ($CDCl_3$) δ 7.35 (s, 5, ArH), 7.00 (t, 1, J = 7 Hz, vinyl H), 2.75 (q, 2, J = 7 Hz, CH_2SO_2), 2.01 (quintet, 2, J = 7 Hz, CH_3CH_2CH=), 1.23 (t, 3, J = 7 Hz, CH_3), 1.07 (t, 3, J = 7.5 Hz, CH_3).

Anal. Calcd for $C_{12}H_{16}O_2S$: C, 64.30; H, 7.14; S, 14.29. Found: C, 64.15; H, 7.28; S, 14.10.

Further elution gave 5.2 g (37%) of 1 which was recrystallized from 95% ethanol: mp 94–96°; ir (Nujol mull) ~ 1600 cm^{-1} (no band); nmr ($CDCl_3$) δ 7.40 (s, 6, 5 ArH + 1 vinyl H), 2.83 (q, 2, CH_2), 2.81 (q, 2, CH_2), 1.25 (t, 3, $-CH_3$), 1.23 (t, 3, $-CH_3$).

Anal. Calcd for $C_{12}H_{16}O_4S_2$: C, 50.00; H, 5.56. Found: C, 49.81; H, 5.43.

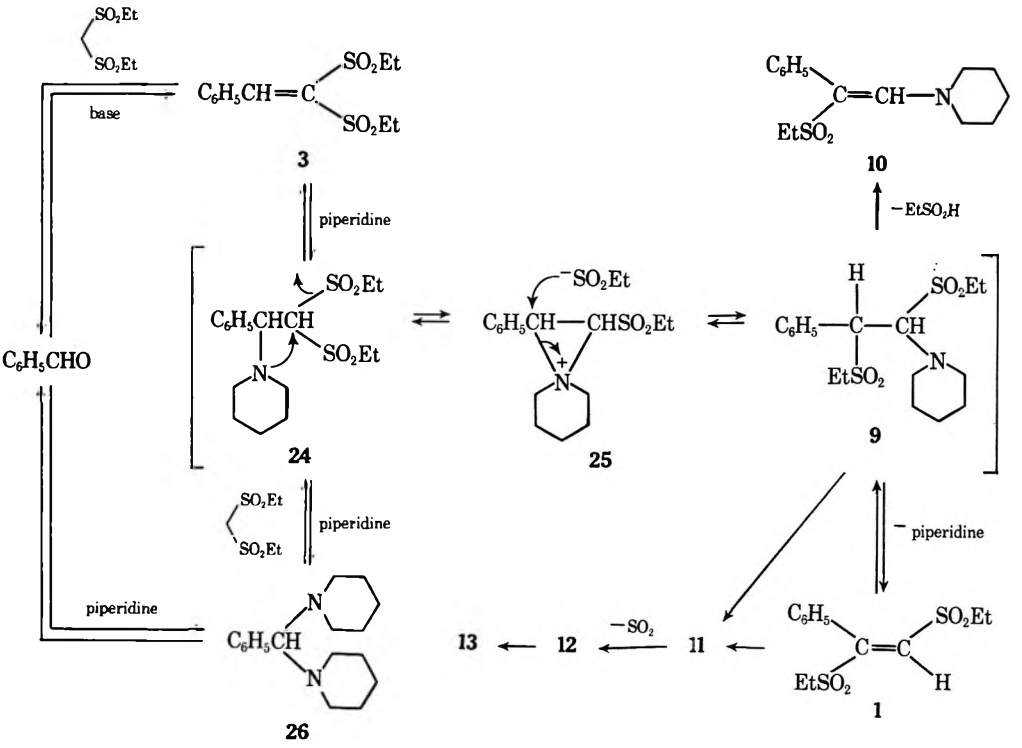
(18) We also isolated a substantial amount of benzyl methyl sulfone[19] from this reaction.

(19) (a) The 23 was kindly supplied by Dr. Girts Kaugars of these laboratories, who prepared it from phenacyl bromide and ethanedithiol by a method[19b] similar to that reported for the preparation of 2,3-dihydro-5,6-diphenyl-*p*-dithiin. (b) H. Rubinstein and M. Wuerthele, *J. Org. Chem.*, **34**, 2762 (1969).

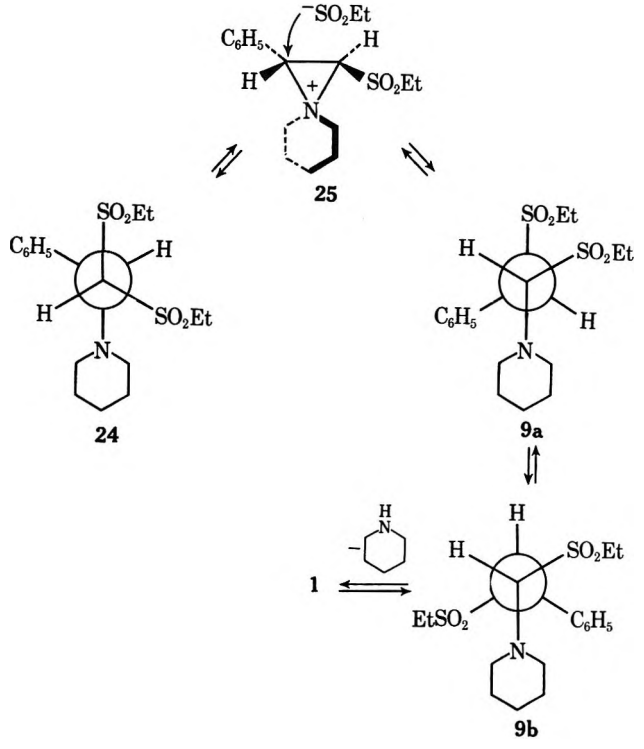
(20) E. L. Eliel in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, pp 115, 116.

(21) M. W. Cronyn, *J. Amer. Chem. Soc.*, **74**, 1225 (1952).

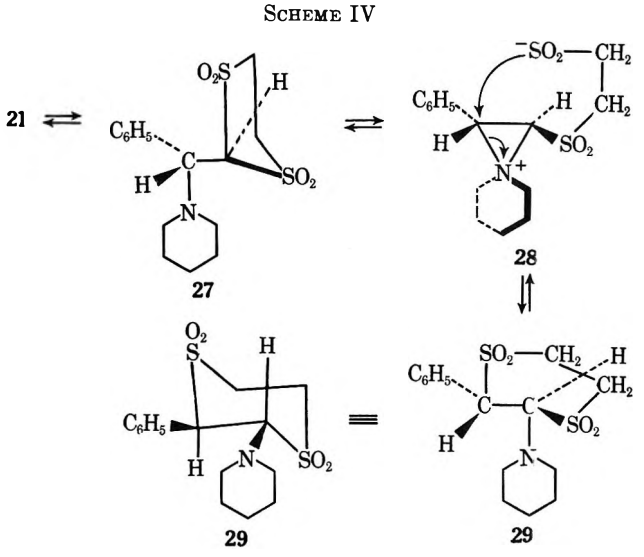
SCHEME II



SCHEME III



SCHEME IV



Ethyl Phenylethynyl Sulfone.—A solution of ethyl phenylethynyl sulfide[8b] (16.2 g, 0.10 mol) in chloroform (150 ml) was maintained at 5° while *m*-chloroperbenzoic acid (40.7 g of 85% material, 0.20 mol) in chloroform (400 ml) was added over a period of 90 min. The reaction was warmed to 25°. After 18 hr the reaction was filtered to remove precipitated *m*-chlorobenzoic acid. The chloroform layer was washed with 5% sodium bicarbonate solution containing a small amount of sodium bisulfite, washed with brine, and then dried ($MgSO_4$). Concentration under reduced pressure at 30° gave ethyl phenylethynyl sulfone (5) as an oil (19.4 g, 100% yield). Distillation of a small sample of 5 under reduced pressure led to partial decomposition with loss of sulfur dioxide. An analytical sample of 5 was obtained by chromatography over silica gel with elution by 6:1 benzene–ethyl acetate.

Anal. Calcd for $C_{10}H_{10}O_2S$: C, 61.83; H, 5.19. Found: C, 61.43; H, 5.49.

The nmr spectrum ($CDCl_3$) [δ 7.75–7.20 (m, 5, ArH), 3.34 (q, 2, J = 7 Hz, CH_2), 1.55 (t, 3, J = 7 Hz, CH_3)] and ir spectrum (neat) [2160 (C≡C) and 1320 and 1140 cm^{-1} (SO_2)] are in agreement with the acetylenic sulfone structure.

Addition of Sodium Ethanethiolate to Ethyl Phenylethynyl Sulfone.—Ethyl phenylethynyl sulfone (0.97 g, 0.005 mol) dissolved in absolute ethanol (2.0 ml) was added to a solution of sodium ethanethiolate (0.005 mol) in ethanol (5.0 ml) at 5°. The reaction was warmed to 25° and after standing for 3 hr was poured onto ice water (50 ml) containing ammonium chloride (0.50 g). The mixture was extracted with methylene chloride (2 × 25 ml), dried ($MgSO_4$), and concentrated under reduced pressure to give a light yellow oil (1.30 g). This was chromatographed over silica gel (130 g) and eluted with a 1:2 mixture of ethyl acetate–hexane. Fractions (10 ml) were collected and β-(ethylthio)-β-(ethylsulfonyl)styrene (4) was eluted in fractions 13–20. Removal of the solvent under reduced pressure gave 4 as an oil (0.54 g, 42%): ir (neat) 1580, 1300, 1130 cm^{-1}; nmr ($CDCl_3$) δ 8.15 (s, 1, vinyl H), 8.10–7.85 (m, 2, ortho ArH), 7.60–

7.40 (m, 3, ArH), 3.33 (q, 2, J = 7 Hz, SO_2CH_2), 3.05 (q, 2, J = 7 Hz, $-SCH_2$), 1.30 (t, 3, J = 7 Hz), 1.23 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{12}H_{16}O_2S_2$: C, 56.21; H, 6.29. Found: C, 56.08; H, 6.49.

Further elution (fractions 41–49) gave (*Z*)-α-(ethylthio)-β-(ethylsulfonyl)styrene (**6**) (0.30 g, 23%) as an oil: ir (neat) 1540, 1300, 1120 cm^{-1}; nmr ($CDCl_3$) δ 7.45 (s, 5, ArH), 6.35 (s, 1, vinyl H), 3.42 (q, 2, J = 7 Hz, SO_2CH_2), 2.52 (q, 2, J = 7 Hz, SCH_2), 1.47 (t, 3, J = 7 Hz), 1.12 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{12}H_{16}O_2S_2$: C, 56.21; H, 6.29. Found: C, 56.00; H, 6.69.

Fractions 58–64 were concentrated to yield 0.023 g (2%) of (*E*)-α-(ethylthio)-β-(ethylsulfonyl)styrene (**8**): mp 60–62°; ir (Nujol) 1600, 1550, 1300, 1125 cm^{-1}; nmr ($CDCl_3$) δ 7.42 (s, 5, ArH), 6.15 (s, 1, vinyl H), 2.83 (q, 2, J = 7 Hz), 2.70 (q, 2, J = 7 Hz), 1.35 (t, 3, J = 7 Hz), 1.23 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{12}H_{16}O_2S_2$: C, 56.21; H, 6.29. Found: C, 56.64; H, 6.36.

Perphthalic Acid Oxidation of β-(Ethylthio)-β-(ethylsulfonyl)-styrene (4).—A solution of **4** (0.50 g, 0.00196 mol) in chloroform (15 ml) was cooled to 5° and a solution of monoperphthalic acid (0.0043 mol) in ether (12 ml) was added. The reaction was warmed to 25° and after standing for 72 hr the reaction mixture was treated with saturated sodium bicarbonate solution (50 ml) containing sodium bisulfite (0.10 g). The organic layer was separated and the aqueous layer was extracted with chloroform (25 ml). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give, after crystallization from benzene–hexane, 0.27 g (48%) of β,β-bis(ethylsulfonyl)-styrene (**3**). Recrystallization from absolute ethanol gave an analytical sample: mp 97.5–98.5°; ir (Nujol) 1590 cm^{-1}; nmr ($CDCl_3$) δ 8.43 (s, 1, vinyl H), 7.85–7.15 (m, 5, ArH), 3.50 (q, 2, J = 7 Hz, CH_2), 3.35 (q, 2, J = 7 Hz, CH_2), 1.35 (t, 3, J = 7 Hz, CH_3), 1.30 (t, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{12}H_{16}O_4S_2$: C, 50.00; H, 5.56. Found: C, 50.07; H, 5.75.

Perphthalic Acid Oxidation of (*Z*)-α-(Ethylthio)-β-(ethylsulfonyl)styrene (6).—A solution of **6** (0.085 g, 0.31 mmol) in chloroform (3 ml) was treated with monoperphthalic acid (0.70 mmol) in ether (2.5 ml). After standing at 25° for 24 hr the reaction mixture was treated with saturated sodium bicarbonate solution (10 ml) containing a small amount of sodium bisulfite. The organic layer was separated and the aqueous layer was extracted with chloroform (10 ml). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give 0.089 g (98%) of (*Z*)-α,β-bis(ethylsulfonyl)styrene (**7**) as a pale yellow oil which crystallized upon standing. An analytical sample was recrystallized from benzene–hexane: mp 83.5–85°; ir (Nujol) 1560, 1300, 1130 cm^{-1}; nmr ($CDCl_3$) δ 7.50 (s, 5, ArH), 6.90 (s, 1, vinyl H), 3.62 (q, 2, J = 7 Hz), 3.33 (q, 2, J = 7 Hz), 1.45 (t, 3, J = 7 Hz), 1.33 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{12}H_{16}O_4S_2$: C, 50.00; H, 5.56; S, 22.20. Found: C, 50.15; H, 5.75; S, 22.37.

Perphthalic Acid Oxidation of (*E*)-α-(Ethylthio)-β-(ethylsulfonyl)styrene (8).—A solution of **8** (0.052 g, 0.20 mmol) in chloroform (3 ml) was treated with a solution of monoperphthalic acid (0.42 mmol) in ether (3 ml). After standing at 25° for 24 hr the reaction mixture was washed with saturated sodium bicarbonate solution (10 ml) containing a small amount of sodium bisulfite. The phases were separated and the aqueous phase was extracted with chloroform (15 ml). The organic phases were combined, dried ($MgSO_4$), and concentrated to give crystalline (*E*)-α,β-bis(ethylsulfonyl)styrene (**1**) (0.056 g, 96%).

Conversion of (*E*)-α,β-Bis(ethylsulfonyl)styrene (1) to α-(Ethylsulfonyl)-β-piperidinostyrene (10) and β-Ethyl-α-(ethylsulfonyl)styrene (13).—A solution of **1** (144 mg, 0.50 mmol) and piperidine (50 mg, 0.55 mmol) in benzene (10 ml) was heated under reflux for 17 hr. The solution was cooled to room temperature and concentrated under reduced pressure. The resulting oil was chromatographed on a preparative silica gel tlc plate using 1:1 ether–hexane as the developing solvent. Elution of the appropriate bands gave **10** (51 mg, 36%) and **13** (8 mg, 7%). An analytical sample of **10** was recrystallized from ethanol–water: mp 84–86°; ir (Nujol) 1620 cm^{-1} (very strong); nmr ($CDCl_3$) δ 7.28 (s, 5, ArH), 7.15 (s, 1, vinyl H), 3.10–2.78 (m, 4, $-CH_2N$), 2.68 (q, 2, J = 7 Hz, CH_2CH_3), 1.43 [narrow m, 6, $-(CH_2)_3-$], 1.20 (t, 3, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; S, 11.48. Found: C, 64.40; H, 7.85; S, 11.54.

α-(Ethylsulfonyl)-β-piperidinostyrene (10).—Benzaldehyde (11.4 g, 0.11 mol), bis(ethylsulfonyl)methane (10.0 g, 0.050 mol), and piperidine (9.4 g, 0.11 mol) were refluxed in benzene (100 ml) for 48 hr with azeotropic removal of water. The reaction mixture was cooled to room temperature and the benzene solution was washed with cold 1 *N* hydrochloric acid and brine and then dried ($MgSO_4$). The solution was concentrated under reduced pressure and chromatographed on silica gel. Elution with 1:1 hexane–ethyl acetate gave 10.1 g (75%) of crystalline **10**.

(*E*)-α,β-Bis(methylsulfonyl)styrene (14).—Benzaldehyde (6.36 g, 0.060 mol), bis(methylsulfonyl)methane[22] (10.0 g, 0.058 mol), and piperidine (0.85 g) were heated under reflux in toluene (100 ml) with azeotropic removal of water. After 18 hr 1.1 ml of water had been collected and the reaction mixture was cooled and concentrated under reduced pressure. The mass of crystals which was obtained was recrystallized from 2-propanol to give 7.34 g (49%) of **14**. A second crystallization from 2-propanol gave an analytical sample: mp 156–158°; ir (Nujol) ~1600 cm^{-1} (no band); nmr [$(CD_3)_2SO$] δ 7.93 (s, 1, vinyl H), 7.60 (s, 5, ArH), 3.15 (s, 3, CH_3), 3.06 (s, 3, CH_3).

Anal. Calcd for $C_{10}H_{12}O_4S_2$: C, 46.20; H, 4.62; S, 24.60. Found: C, 46.23; H, 4.55; S, 24.55.

α-(Methylsulfonyl)-β-piperidinostyrene (15).—Benzaldehyde (10.6 g, 0.10 mol), bis(methylsulfonyl)methane (17.2 g, 0.10 mol), and piperidine (17.0 g, 0.20 mol) were heated to reflux in toluene with azeotropic removal of water. After 16 hr the theoretical amount of water had been collected and the solution was cooled to room temperature, washed with water, and dried ($MgSO_4$). Removal of the toluene at reduced pressure gave a crystalline mass which was recrystallized from ethanol–water to give 16.0 g (60%) of **15**. A second crystallization from ethanol–water gave an analytical sample: mp 105–106.5°; ir ($CHCl_3$) 1620 cm^{-1} (strong); nmr ($CDCl_3$) δ 7.52 (s, 5, ArH), 7.45 (s, 1, vinyl H), 3.25–2.85 (m, 4, NCH_2), 2.75 (s, 3, CH_3), 1.75–1.25 [m, 6 $(-CH_2)_3$].

Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28; S, 12.08. Found: C, 63.14; H, 7.39; N, 5.37; S, 11.99.

Reaction of β-Piperidinostyrene and Methanesulfonyl Chloride.—β-Piperidinostyrene[23] (18.7 g, 0.10 mol) was dissolved in benzene (100 ml), and triethylamine (10.1 g, 0.10 mol) was added. A solution of methanesulfonyl chloride (11.4 g, 0.10 mol) in benzene (50 ml) was added slowly, keeping the reaction temperature at 25°. After 18 hr the precipitated triethylamine hydrochloride was removed by filtration. The filtrate was extracted with cold 1 *N* hydrochloric acid (2 × 100 ml) to remove **19**. The organic phase was washed with water and dried ($MgSO_4$). Removal of benzene under reduced pressure gave 2.8 g of an oil which was further purified by chromatography over silica gel. Elution with 2:1 benzene–ethyl acetate gave 1.1 g (4.2%) of **15**.

Reaction of Benzaldehyde and Bis(methylsulfonyl)methane with Excess Pyrrolidine.—Benzaldehyde (10.6 g, 0.10 mol), bis(methylsulfonyl)methane (17.2 g, 0.10 mol), and pyrrolidine (14.2 g, 0.20 mol) in toluene (200 ml) were heated under reflux with azeotropic removal of water. After 16 hr the solution was cooled to room temperature and water (100 ml) was added. A crystalline precipitate formed and was removed by filtration to give 5.0 g of benzyl methyl sulfone,[16] mp 125–127° (lit. mp 126–127°).

The organic and aqueous phases were separated and the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure, yielding 11.5 g of an orange-brown oil. Chromatography over silica gel and elution with 2:1 benzene–ethyl acetate gave 3.5 g (14%) of crystalline α-(methylsulfonyl)-β-pyrrolidinostyrene[16] (**16**). An analytical sample was recrystallized from ethanol–water, mp 143–144.5° (lit. mp 145°). The nmr and ir spectra conform to those reported in the literature.

Anal. Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57; S, 12.76. Found: C, 62.63; H, 6.94; N, 5.76; S, 12.51.

2-Benzylidine-1,3-dithiolane 1,1,3,3-Tetroxide (21).—Benzaldehyde (10.6 g, 0.10 mol), 1,3-dithiolane 1,1,3,3-tetroxide[24] (17.0 g, 0.10 mol), and piperidine (1.0 g) were heated under re-

(22) D. T. Gibson, *J. Chem. Soc.*, 2637 (1931).

(23) C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1936).

(24) (a) W. Baumann, *ibid.*, **26**, 1129 (1893). (b) A more convenient synthesis of 1,3-dithiolane 1,1,3,3-tetroxide was achieved by oxidation (hydrogen peroxide in aqueous acetic acid) of 1,3 dithiolane[24c] (90% yield) obtained from the boron trifluoride catalyzed reaction between ethanedithiol and dimethoxymethane.[24d] (c) D. J. Martin, *J. Org. Chem.* **34**, 473 (1969). (d) This type of exchange reaction was used by Corey and Seebach for the preparation of 1,3-dithiane: E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075 (1965).

flux in toluene (250 ml). Water was removed azeotropically and after 23 hr the theoretical amount had been collected. The reaction was cooled to room temperature and the crystalline precipitate of **21** (18.0 g) was removed by filtration. Additional **21** (6.9 g) was obtained by concentration of the filtrate. An analytical sample was obtained by recrystallization from acetone–water and then from ethyl acetate: mp 192–194°; ir (Nujol) 1600 cm^{-1} (strong); nmr [$(CD_3)_2SO$] δ 8.10 (s, 1, vinyl H), 8.15–7.85 (m, 2, ortho ArH), 7.75–7.45 (m, 3, ArH), 4.28–4.05 (narrow m, 4, $-CH_2CH_2-$).

Anal. Calcd for $C_{10}H_{10}O_4S_2$: C, 46.50; H, 3.91. Found: C, 46.43; H, 3.87.

2,3-Dihydro-5-phenyl-*p*-dithiin 1,1,4,4-Tetroxide (22).—2,3-Dihydro-5-phenyl-*p*-dithiin[19] (1.80 g, 0.0093 mol) was dissolved in ethyl acetate (50 ml) and the solution was cooled to 5°. Monoperphthalic acid (0.041 mol) in ether (120 ml) was added and the reaction mixture was warmed to room temperature and allowed to react for 22 hr. The solvent was removed under reduced pressure and the solid residue was washed with 5% sodium bicarbonate solution (3 × 50 ml) and then water. The residue was chromatographed on silica gel. Elution with ethyl acetate gave 0.80 g (33%) of **22**. Recrystallization from propanol gave an analytical sample: mp 205–206°; nmr [$(CD_3)_2SO$] δ 7.70–7.40 (narrow m, 6, 5 ArH, vinyl H), 4.42 (s, 4, $-CH_2CH_2-$).

Anal. Calcd for $C_{10}H_{10}O_4S_2$: C, 46.50; H, 3.91; S, 24.83. Found: C, 46.70; H, 3.78; S, 24.56.

Reaction of α,α-Dipiperidinotoluene with Bis(ethylsulfonyl)methane.—α,α-Dipiperidinotoluene[25] (6.45 g, 0.025 mol), bis(ethylsulfonyl)methane (5.0 g, 0.025 mol), and glacial acetic acid (0.1 ml) in benzene (100 ml) was heated under reflux for 40 hr. The mixture was cooled to room temperature, washed with water (125 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was crystallized from ether–hexane to give 3.68 g (53%) of α-(ethylsulfonyl)-β-piperidinostyrene (**10**).

Piperidine-Catalyzed Conversion of β,β-Bis(ethylsulfonyl)styrene (3) to (*E*)-α,β-Bis(ethylsulfonyl)styrene (1).—A solution of **3** (144 mg) and piperidine (15 mg) in benzene (10 ml) was heated under reflux for 48 hr. Thin layer chromatography on silica gel with development by 6:1 benzene–ethyl acetate showed **1** to be the major product.

Triethylamine-Catalyzed Condensation of Benzaldehyde and Bis(ethylsulfonyl)methane.—A mixture of benzaldehyde (5.3 g, 0.05 mol), bis(ethylsulfonyl)methane (5.0 g, 0.025 mol), triethylamine (0.5 ml), and benzene (35 ml) was heated at reflux for 16 hr. During this time water (0.42 ml) was removed with the aid of a Dean–Stark trap. The reaction mixture was cooled to room temperature and the benzene was removed under reduced pressure. Trituration of the residue with hexane gave a mass of crystals which were purified by chromatography over silica gel and elution with 2:1 benzene–ethyl acetate, yielding 1.47 g (21%) of **3**.

Triethylamine-Catalyzed Conversion of (*E*)-α,β-Bis(ethylsulfonyl)styrene (1) to β-Ethyl-α-(ethylsulfonyl)styrene (13).—A solution of **1** (1.44 g) and triethylamine (0.60 g) in toluene (20 ml) was heated under reflux for 30 hr. The solution was cooled, concentrated under reduced pressure, and chromatographed over silica gel. Elution with 6:1 benzene–ethyl acetate gave **13** (180 mg, 16%).

Attempted Conversion of 7 to 1.—A solution of **7** (25 mg, 0.087 mmol) and piperidine (0.74 mg, 0.0087 mmol) was heated under mild reflux for 48 hr. Tlc and nmr analysis of the product mixture indicated the presence of a minor amount of **10**. However, the bulk of the product was unchanged **7**. No **1** was observed.

(25) E. Staple and E. C. Wagner, *J. Org. Chem.*, **14**, 559 (1949).

Registry No.—**1**, 34407-76-6; **3**, 3363-77-7; **4**, 34407-78-8; **5**, 33987-87-0; **6**, 34407-80-2; **7**, 34417-84-0; **8**, 34407-81-3; **10**, 34407-82-4; **13**, 34407-83-5; **14**, 34407-84-6; **15**, 34407-85-7; **21**, 34407-86-8; **22**, 34407-87-9; piperidine, 110-89-4; benzaldehyde, 100-52-7; bis(ethylsulfonyl)methane, 1070-92-4.

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Metalated Carboxylic Acids. IV. Reactions of Metalated Carboxylic Acids with Epoxides. Substituted Steroidal Spiro γ-Lactones from Spiro β-Epoxides[1]

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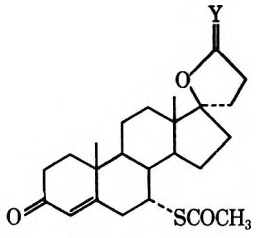
Attempts to convert spiro β-epoxide **2** to **5d** as a model for the preparation of substituted spiro lactones **5a–c** resulted in the observation that acetic acid can be metalated under mild conditions when treated with lithium diisopropylamide. Treatment of **2** with **6a** ($M^+ = Li^+$) successfully concluded the intended transformation. Extensions to homologous and functionally substituted examples established that the metalation of aliphatic carboxylic acids is a general phenomenon and use of these reagents permitted the preparation of **5a–c, f, g** in useful yields. The poor solubility and incomplete metalation of acetic acid were avoided by use of simple acetic acid derivatives in the same sequence. Some of these examples gave improved yields of epoxide cleavage products, **14a–c**. The reaction of metalated carboxylic acids with model epoxides served to illustrate an attractive route to γ-lactones, especially where the introduction of sterically bulky or geminal substituents is desired. When steroidal epoxides are treated with metalated carboxylic acids bearing bulky substituents, unequal amounts of C-21 substituted spiro lactones are obtained. The major isomers are assigned 21*S* stereochemistry which are related to the high field C-18 nmr absorption based on epimerization studies.

Large numbers of structurally diverse steroids have been studied with respect to their potential as aldosterone inhibitors.[2,3] Of those reported, **1a–c** have emerged as some of the more effective examples[3] capable of eliciting this type of biological response. These examples share as their most distinctive structural feature a five-membered spiro ring attached to C-17 of the steroid nucleus and it is this structural unit which provides the greatest synthetic challenge and the greatest biological interest. Correlations of biological activity with variations in the structure of the spiro ring indicate that the oxygen atom, if present, should be β oriented, that the oxidation state of the lactone carbonyl carbon of **1a** is not critical,[3b] and that substituent rings with more than five members

(1) Portions of this report have appeared in the following patents: (a) P. L. Creger, U. S. Patent 3,320,242 (1967); (b) U. S. Patent 3,413,288 (1968); (c) U. S. Patent 3,506,652 (1970).

(2) G. DeStevens, "Diuretic Chemistry and Pharmacology," Academic Press, New York, N. Y., 1963, Chapter 7.

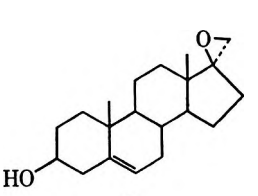
(3) (a) R. C. Tweit, E. A. Brown, S. Kraychy, S. Mizuba, R. D. Muir, and R. T. Nicholson, *Chem. Pharm. Bull.*, **12**, 859 (1964), and earlier papers in this series; (b) G. E. Arth, H. Schwam, L. H. Sarett, and M. Glitzer, *J. Med. Chem.*, **6**, 617 (1963); (c) W. F. Johns and E. A. Brown, *J. Org. Chem.*, **31**, 2099 (1966); D. Bertin and J. Perronnet, *Bull. Soc. Chim. Fr.*, 564 (1964).



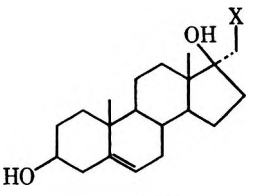
1a, Y = O
b, Y = H_2
c, Y = H, OH

display decreased activity.[3a,b] At the time the present study was initiated,[4] structures containing a spiro ring at C-17 with a β-oriented oxygen atom and fewer than five members were not known, although structures containing a spiro oxetane unit[5] have been described more recently.

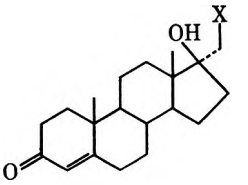
A logical approach to the synthesis of steroids containing spiro three-membered rings with a β-oriented oxygen atom (β-epoxides, *e.g.*, **2**) was made available when reactions of carbonyl compounds with sulfur ylides were described.[6] These reagents offered the attractive advantages of permitting use of available precursors and allowing construction of the spiro ring with stereochemistry which was not conveniently accessible by previous methods. Subsequently, reactions of these reagents with steroidal ketones were actively explored by several groups.[1b,7] Thus the preparation of **2** was established as the most immediate synthetic objective in the present work, and, depending on its success and stereospecificity, it could be carried on in a sequence of reactions as a logical precursor to substituted spiro lactones, **5**. Finally, standard procedures could be employed to manipulate the functionality in the A and B rings to produce **8–10** for biological evaluation. Attempts to convert **2** to **5** resulted in the observation that the metalation of carboxylic acids is a general phenomenon[8] and it was the use of these reagents with **2** that permitted construction of the spiro lactone rings. Later studies demonstrated the utility of metalated carboxylic acids for the preparation of trialkylacetic acids,[9a] dialkylacetic acids,[9b] alkylbenzoic acids,[9c] and β-hydroxy acids.[9d] The present report considers reactions of metalated carboxylic acids with epoxides, particularly **2**.



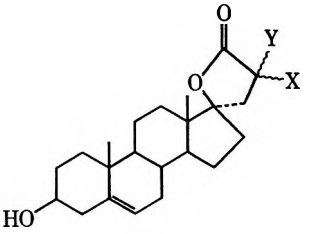
2



3a, X = OCH_3
b, X = N_3

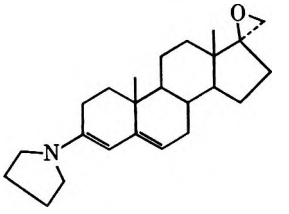


4a, X = OCH_3
b, X = N_3

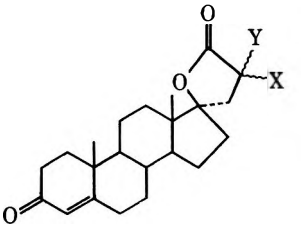


5a, X = CH_3; Y = H
b, X = C_2H_5; Y = H
c, X = CH_3; Y = CH_3
d, X = H; Y = H
e, X = CN; Y = H
f, X = C_4H_9; Y = H
g, X = C_6H_5; Y = H
h, X = OCH_3; Y = H

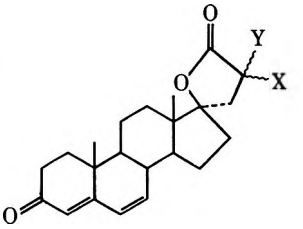
$[CR_2CO_2]^{2-}Li^+M^+$
6a, R = H
b, R = CH_3



7



8a, X = CH_3; Y = H
b, X = C_2H_5; Y = H
c, X = CH_3; Y = CH_3
d, X = H; Y = H
e, X = C_4H_9; Y = H
f, X = C_6H_5; Y = H



9a, X = CH_3; Y = H
b, X = C_2H_5; Y = H
c, X = CH_3; Y = CH_3

Results

Steroidal Epoxides.—The treatment of 3β-hydroxyandrost-5-en-17-one (acetate) with excess dimethylsulfonium methylide resulted in the formation of (17*S*)-spiro[androst-5-ene-17,2′-oxiran]-3β-ol (**2**) as the exclusive functional product[1a,10] isolated in 75–90% yields. The availability of **2** permitted consideration of the second objective, the preparation of **5**, but before proceeding, attempts were made to evaluate the reactivity of the relatively hindered epoxide ring toward simple nucleophiles. To illustrate ring cleavage, treatment of **2** with sodium methoxide in methanol or with methanolic sodium hydroxide yielded 17-(methoxymethyl)-androst-5-ene-3β,17β-diol[11] (**3a**), from which **4a** could be obtained by Oppenauer oxidation. Similarly, reaction of **2** with sodium azide gave 17-(azidomethyl)androst-5-

(4) Except for a few isolated experiments, the present work was completed in 1964–1965.

(5) E. A. Brown, *J. Med. Chem.*, **10**, 546 (1967); B. Singh and R. G. Christiansen, *J. Pharm. Sci.*, **60**, 491 (1971).

(6) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, Chapter 9, reviews the earlier literature.

(7) (a) G. Drefahl, K. Ponsold, and H. Schick, *Chem. Ber.*, **65**, 3529 (1964); (b) C. E. Cook, R. C. Corley, and M. E. Wall, *J. Org. Chem.*, **33**, 2789 (1968); (c) D. Bertin and L. Nedelec, *Bull. Soc. Chim. Fr.*, 2140 (1964); (d) K. G. Holden, U. S. Patent 3,300,489 (1967). a–d describe examples using 17-keto steroids.

(8) Reactions of more than 50 carboxylic acids with various electrophiles have been studied.

(9) (a) P. L. Creger, *J. Amer. Chem. Soc.*, **89**, 2500 (1967); *Org. Syn.*, **50**, 58 (1970); (b) *J. Amer. Chem. Soc.*, **92**, 1397 (1970); (c) *ibid.*, **92**, 1396 (1970); (d) G. W. Moersch and A. W. Burkett, *J. Org. Chem.*, **36**, 1149 (1971).

(10) 10–15% of **2** acetate was also isolated. None of the isomeric (17*R*)-spiro[androst-5-ene-17,2′-oxiran]-3β-ol was detected by nmr analysis. The ir spectra revealed no unreacted ketonic contaminants.

(11) G. Muller and M. Stefanovic, U. S. Patent 3,022,324 (1962); K. G. Holden, U. S. Patent 3,375,280 (1968).

ene-3β,17β-diol (**3b**), sequentially converted to **4b**. In contrast to the high yields experienced with simple azide and methoxide anions, diethyl sodiomalonate in tetrahydrofuran (THF) or dimethoxyethane failed to produce products expected from attack of the carbanion on the epoxide ring, although the latter transformation has been reported[7d] using different reaction conditions. The less hindered anion from ethyl cyanoacetate in the same solvent (THF) gave **5e** in low yield. In an effort to minimize steric hindrance in the carbanionic reagent and to reduce delocalization of the charge, carbanions with a single activating substituent were considered for use in the reaction. Sodium sodioacetate[12] seemed ideally suited for this purpose, but, on reaction with **2** in refluxing THF, no **5d** could be detected. In retrospect, the known properties[12,13] of sodium sodioacetate made it a poor choice for reaction with **2** because of its low solubility, high association, and extreme stability. Despite initial failures, the simplicity of the intended transformation demanded that it be given further serious consideration.

The relatively high acidity of acetate ion[14,15] ($pK_a \sim 24$) suggested that a variety of bases should be effective for removing a proton from the α carbon of a carboxylate salt and that the vigorous conditions used for the formation of sodium sodioacetate[12] were unnecessary. Further, no necessary relationship could be presumed to exist between the solubility of the metalated species and the solubility of the corresponding carboxylate salts, which made it possible to consider polar, aprotic, organic solvents for use as the reaction medium. Lithium diisopropylamide was ultimately selected as base because its steric bulk would minimize competitive side reactions between the amine, diisopropylamine, and an added electrophile. Additionally, the reagent was soluble in and did not react readily with coordinative, aprotic organic solvents and, like other metal amides, lithium diisopropylamide should be a more effective metalating agent[16] in proton transfer reactions than conventional organometallic agents, RM, many of which are capable of reacting with the carboxylate function. Finally, as cation, lithium should be more tightly associated with the anion[17] because it is a "harder" acid than sodium[18] and it could be expected to coordinate with the amine, diisopropylamine, with a presumed beneficial effect on the solubility of the complex in THF, which was chosen as solvent.

When acetic acid was added to 2 equiv of lithium diisopropylamide in THF, a colorless suspension of **6a** and unmetalated lithium acetate was produced. Following addition of **2**, the mixture was heated to reflux and **5d** was isolated in 55% yield. Repetitions which also used an excess of **6a** gave 50–60% of **5b** and the remainder of **2** was recovered. In these initial experiments, neither the product yields nor the homogeneity of the reaction mixture were consistently improved by use of hexamethylphosphoramide (HMP) as cosolvent[1b] and difficult removal from the steroid products discouraged its extensive use.

Spiro lactone **2** was easily isolated and identified. Addition of water afforded convenient separation of the intermediate carboxylate salt from unreacted **2**, and subsequent acidification of the aqueous extracts resulted in closure of the lactone ring. The nmr spectrum of **5d** revealed that reaction had occurred at the epoxide function by the absence of the well-defined AB quartet in **2** (ν_A δ 2.90, ν_B δ 2.61, J_{AB} = 5.5 Hz). The ir spectrum displayed ν(C=O) absorption at 1764 cm^{-1} suitable for a γ-lactone and the elemental analysis and other physical properties compared favorably with known values.[19] Similarly, treatment of **7**[1b] with **6a** ($M^+ = Li^+$) produced **8d** in 45% yield after hydrolysis of the enamine blocking group. Lower yields were experienced when metalated acetic acid was treated with other electrophiles. For example, reaction of **6a** ($M^+ = Li^+$) with benzophenone either in THF or THF–HMP mixtures (3:1 v/v) gave only 19% of 3,3-diphenylhydracyclic acid, and treatment with heptyl bromide gave only 12% of nonanoic acid.

The relatively mild conditions used with lithium diisopropylamide for the metalation of acetic acid indicated that other carboxylic acids should behave similarly. Ultimately, the addition of **2** to mixtures containing excess metalated propionic, butyric, hexanoic, phenylacetic, and isobutyric acids provided **5a–c, f, g** in yields ranging from 70 to 87%. The crude products consisted of mixtures of C-21 isomers which could not be separated easily by thin layer chromatography or by recrystallization. As an exception, recrystallization of **8f** allowed separation of the less soluble isomer, which was present in major amount. The minor isomer was not obtained pure. The major isomer was assigned a 21*R* configuration[20] based on its proportion in the reaction mixture, comparison of the C-18 chemical shifts in the nmr spectra,[21] and epimerization studies with related examples reserved for later discussion.

Alkylated spiro lactones **5a–c** were oxidized under Oppenauer conditions[22] to give **8a–c**. Further oxidation with chloranil in *tert*-butyl alcohol and later in toluene–acetic acid[23] gave **9a–c** in yields of 60–85% after chromatography. Finally, treatment of **9a–c** with thiolacetic acid[24] gave **10a–c** in 60–65% yields.

Metalation of methoxyacetic acid resulted in the formation of functionally substituted spiro lactone **5h** on reaction with **2**, but only in 19% yield. The low yield could be attributed to incomplete metalation of

(12) D. O. DePree and R. D. Closson, *J. Amer. Chem. Soc.*, **80**, 2311 (1958).

(13) H. Hopff and H. Diethelm, *Justus Liebigs Ann. Chem.*, **691**, 61 (1966).

(14) R. G. Pearson and R. L. Dillon, *J. Amer. Chem. Soc.*, **75**, 2439 (1953).

(15) D. J. Cram, *Chem. Eng. News*, 92 (1963); D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, Chapter 1; H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, Chapter 7. These present convenient comparative tables of pK_a values for a variety of carbon acids.

(16) R. Huisgen and J. Sauer, *Chem. Ber.*, **92**, 192 (1959); T. Cuvigny and H. Normant, *Bull. Soc. Chim. Fr.*, 2000 (1964).

(17) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90**, 4462, 4464 (1968).

(18) R. G. Pearson, *ibid.*, **85**, 3533 (1963); see B. Saville, *Angew. Chem., Int. Ed. Engl.*, **6**, 928 (1967), for a review.

(19) J. A. Cella, E. A. Brown and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959).

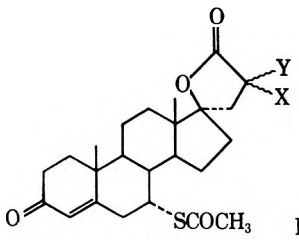
(20) R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, **5**, 385 (1966).

(21) (a) N. S. Bhacca and D. A. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, Chapter 2; (b) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, London, 1969, p 241 ff.

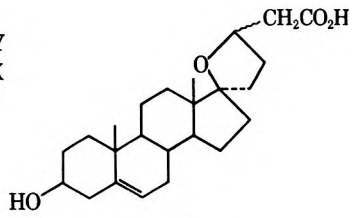
(22) C. Djerassi, *Org. React.*, **6**, 207 (1951).

(23) H. Specht, H. Jahn, and A. Stackowiak, East German Patent 41,938 (1965); *Chem. Abstr.*, **64**, 14245g (1966).

(24) R. M. Dodson and R. C. Tweit, *J. Amer. Chem. Soc.*, **81**, 1224 (1959); J. H. Cella and R. C. Tweit, *J. Org. Chem.*, **24**, 1109 (1959).



10a, X = CH_3; Y = H
b, X = C_2H_5; Y = H
c, X = CH_3; Y = CH_3



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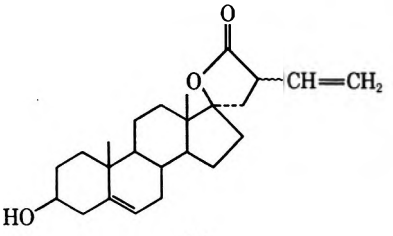

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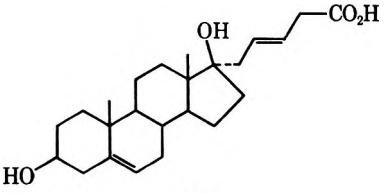

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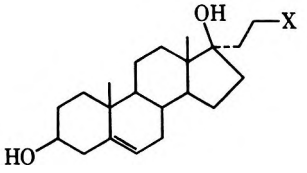
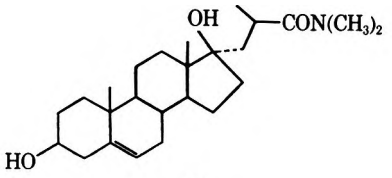


14a, X = CN
b, X = $CON(CH_3)_2$
c, X = $CON(CH_3)CH_2CH_2N(CH_3)_2$



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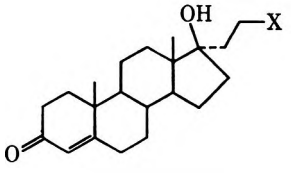
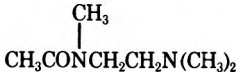


16a, X = $CON(CH_3)_2$
b, X = $CONHCH_3$



17

the carboxylate salt owing to poor solubility of the metalated intermediate or to the deactivating influence of the methoxy substituent,[25] which inhibited proton abstraction. Lower than average yields were also experienced in reactions of alkyl halides with other oxygenated acetic acids, such as phenoxyacetic acid[9b] and ethoxyacetic acid.[26]

(25) J. Hine, L. G. Mahone, and C. L. Liotta, *J. Amer. Chem. Soc.*, **89**, 5911 (1967).
(26) Unpublished results.

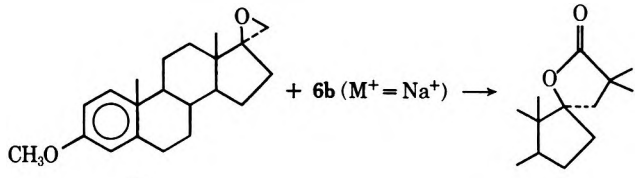
Anions generated from crotonic acid,[27] crotonic acid esters,[28] 3-butenoic acid,[29] or alkylidenemalonic acid esters[30] react almost exclusively at the carbon atom α to the carboxyl(ate) function(s) when treated with simple, unhindered alkyl halides. In contrast, if **2** is used as alkylating agent for metalated crotonic acid steric hindrance to approach at the α carbon of the crotonic acid dianion should make reaction at the terminal carbon more favorable. Terminal alkylation was observed, but the desired product, **11**, was not detected; instead, a mixture of **12** and **13** was obtained in addition to unreacted **2**. Lactone **12** was easily identified as a mixture of epimers. The ν(C=O) absorption (1757 cm^{-1}) established the presence of the lactone ring, and C-18 methyl absorption at δ 0.94 and 1.00 in the nmr spectrum provided evidence for epimeric vinyl substituents. Vinylic multiplets were centered at δ 5.05, 5.15, and 5.90. Carboxylic acid **13** displayed ν(C=O) and ν(C=C) absorptions at 1704 and 1655 cm^{-1}, respectively. The nmr spectrum displayed multiplets at δ 5.92 and 5.67 for vinyl protons and a multiplet at δ 3.63, which is appropriate for the methylene substituent adjacent to the carboxyl group and flanked by a vinyl substituent.

The relatively low yields experienced in the reaction of **2** with metalated acetic acid prompted use of simple acetic acid derivatives in the same sequence in order to overcome incomplete metalation and poor solubility of the carbanionic intermediate. The addition of acetonitrile at -60 or 0° to a THF solution containing 1 equiv of lithium diisopropylamide gave a homogeneous solution from which the carbanionic product soon precipitated.[1c,31] Addition of a THF solution of **2** gave 92% of nitrile **14a**. Similarly, after treatment with lithium diisopropylamide at 0°, *N*,*N*-dimethylacetamide gave 87% of **14b**, and treatment of **7**[1a-c] with *N*-methylacetamide gave 51% of **16b** following hydrolysis of the enamine blocking group. The reaction of acetamide with 2 equiv of lithium diisopropylamide at 40° resulted in its dehydration, a result not observed for simple carboxamides with unsubstituted alkali amides.[32] The acetonitrile which resulted was metalated and, on reaction with **2**, 65% of **14a** was produced when an excess of the reagents was used. To obtain a more soluble variant of the acyclic product, use of *N*-[2-(dimethylamino)ethyl]-*N*-methylacetamide (**17**) gave **14c** (70%) after acidification. In a similar manner, incomplete metalation of propionic acid was overcome by treating **2** with metalated *N*,*N*-dimethylpropionamide, which gave a higher (98%) yield of epoxide cleavage product (**15**) than was obtained using propionic acid.

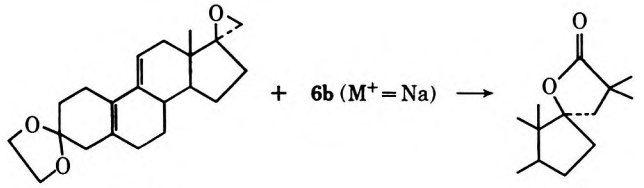
(27) A. J. Birch, *J. Chem. Soc.*, 1551 (1950).
(28) K. Sisido, K. Sie, and H. Nozaki, *J. Org. Chem.*, **27**, 2681 (1962); as an exception, C. R. Hauser and W. H. Puterbaugh, *J. Amer. Chem. Soc.*, **75**, 1068 (1953), report that *tert*-butyl crotonate condenses at the γ carbon with acetophenone.
(29) F. F. Blicke and H. Zinnes, *J. Amer. Chem. Soc.*, **77**, 4849, 6247 (1955), report that vinylacetic acid condenses at the γ carbon with cyclohexanone.
(30) A. C. Cope, H. L. Holmes, and H. O. House, *Org. React.*, **9**, 107 (1957).
(31) K. Ziegler and H. Ohlinger, *Justus Liebigs Ann. Chem.*, **495**, 84 (1932); D. N. Crouse and D. Seebach, *Chem. Ber.*, **101**, 3113 (1968); E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **33**, 3402 (1968).
(32) E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **31**, 3317 (1966); E. M. Kaiser, R. L. Vaulx, and C. R. Hauser, *ibid.*, **32**, 3640 (1967); E. M. Kaiser, D. M. von Schriltz, and C. R. Hauser, *ibid.*, **33**, 4275 (1968).

The reaction of metalated acetic acid esters[33] with 2 promised to provide another alternative for the introduction of a two-carbon fragment. The principal attraction again was the improved solubility to be expected for the carbanionic intermediate as compared to metalated acetic acid, but the possibility of condensation reactions of the intermediate suggested use of a sterically hindered ester.[34] When *tert*-butyl acetate was treated with lithium diisopropylamide followed by 2 at ambient temperature, no epoxide cleavage products could be identified. In addition to unchanged 2, the acetate of 2, (17*S*)-spiro[androst-5-ene-17,2′-oxiran]-3β-ol acetate, was obtained in 19–42% yields depending on the length of the reaction period.

The generality of the reaction of metalated carboxylic acids with steroidal spiro epoxides was extended by treatment of 3-methoxy-(17*S*)-spiro[estra-1,3,5(10)-triene-17,2′-oxirane][26,35] (**18**) with metalated isobutyric acid (**6b**, $M^+ = Na^+$) to produce **19** (82%). In like manner, (17′*S*)-dispiro[1,3-dioxolane-2,3′-estra-5′(10′),-



18 **19**

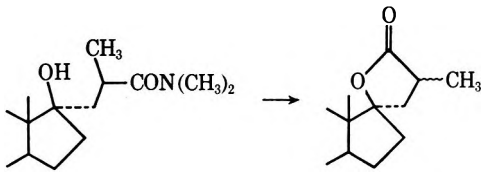


20 **21**

9′(11′)-diene-17′,2″-oxirane][26] (**20**) gave **21** as a noncrystalline solid (73%) which was identified from its spectra, but attempted acid hydrolysis of the ketal gave a mixture of noncrystalline double bond isomers which could not be separated and characterized. Finally, treatment of **18** with metalated *N*,*N*-dimethylpropionamide as an alternative to metalated propionic acid gave **22** (75%) and a substantial amount (25%) of **18** was recovered from a single trial.

Hydrolysis of the various amide or nitrile derivatives produced the desired lactones. For example,

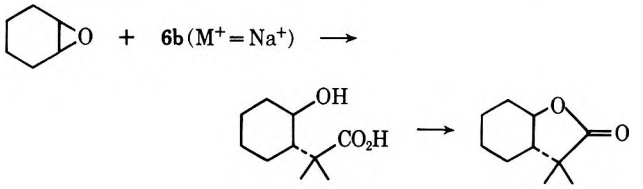
18 + $[CH_3CHCON(CH_3)_2]^-Li^+$ ⟶



22 **23**

base hydrolysis of **14a** gave **5d** (75%) on acidification and similar treatment of **15** and **22** produced **5a** (70%) and **23** (99%), respectively. The reaction of C-17 steroidal spiro epoxides with anions generated from amide or nitrile derivatives of acetic or propionic acids followed by hydrolysis of the amide or nitrile products affords a satisfactory synthetic alternative to the use of metalated acetic and propionic acids by producing the desired lactones in higher overall yields.[1c]

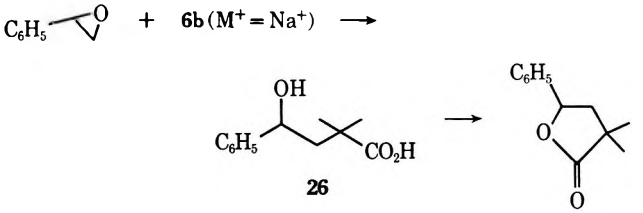
Model Epoxides.—Reactions of metalated carboxylic acids with epoxides of varying structure can be studied most easily by use of model compounds. As an example of a nonterminal epoxide, treatment of cyclohexene oxide with metalated isobutyric acid, **6b** ($M^+ = Na^+$), at 40° gave **24** (91%). The ir spectrum of the crude product failed to reveal evidence of spontaneous ring closure after acidification of the reaction mixture.



24 **25**

Cyclization was effected by heating a toluene suspension of the crude product with azeotropic water removal to give **25**. In contrast, cyclooctene oxide failed to react with **6b** ($M^+ = Na^+$) in THF either at 35° or at reflux. Similarly, metalated 3,3-dimethylbutyric acid failed to react with cyclohexene oxide at 50°. In each case, the epoxide and the carboxylic acid were recovered in high yield after the usual aqueous work-up. Likewise, metalation of methacrylic acid by either of the general procedures A or B (see Experimental Section) gave homogeneous solutions, but no epoxide cleavage products could be detected on treatment with cyclohexene oxide.

Styrene oxide reacted with **6b** ($M^+ = Na^+$) at the terminal, β carbon to give a hydroxy acid which could be isolated if sufficient care were exercised and for which structure **26** was proposed. Cyclization in refluxing benzene gave a lactone which was assigned



26 **27**

structure **27**. Styrene oxide is known to be subject to attack by anions at either carbon of the epoxide function, although sterically bulky anions can be expected to react at the terminal carbon.[36] Attack at the terminal carbon was concluded from the nmr spectrum. Hand calculations[37] of the well-defined ABX spin coupling pattern produced the following values: ν_A, δ

(33) (a) C. R. Hauser and W. H. Puterbaugh, *J. Amer. Chem. Soc.*, **73**, 2972 (1951); C. R. Hauser and W. H. Puterbaugh, *ibid.*, **75**, 1068 (1953); (b) K. Sisido, H. Nozaki, and O. Kurihara, *ibid.*, **74**, 6254 (1952); K. Sisido, Y. Kazama, H. Kodama, and H. Nozaki, *ibid.*, **81**, 5817 (1959); (c) M. W. Rathke, *ibid.*, **92**, 3222 (1970); M. W. Rathke and A. Lindert, *ibid.*, **93**, 2318 (1971); Y-N. Kuo, F. Chen, C. Ainsworth, and J. J. Bloomfield, *Chem. Commun.*, 136 (1971).

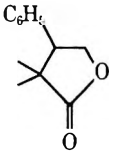
(34) Self-condensation may not be so serious as originally surmised.[33c]

(35) C. E. Cook, R. C. Corley, and M. E. Wall, *J. Org. Chem.*, **33**, 2789 (1968).

(36) A. Rosowsky in "Hetercyclic Compounds with Three- and Four-membered Rings, Part One," A. Weissberger, Ed., Interscience, New York, N. Y., 1964, Chapter 1.

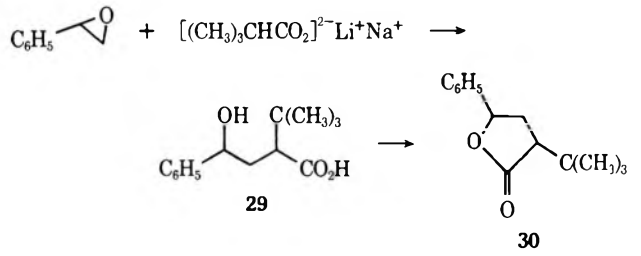
(37) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, London, 1965, pp 357 ff; D. W. Mathieson, "Nuclear Magnetic Resonance for Organic Chemists," Academic Press, New York, N. Y., 1967, p 85 ff.

2.44; ν_B, δ 1.98; ν_X, δ 5.43; $J_{AB} = -13.1$ Hz; $J_{AX} = 10.1$ Hz; $J_{BX} = 6.3$ Hz. The geminal coupling constant, J_{AB}, was assumed to be negative by analogy,[38] and line frequency and intensity calculations[37] indicated that J_{AX} and J_{BX} had identical although undefined signs. The chemical shift for the X proton at C-5 of structure **27** corresponds well with published examples,[39] and the geminal coupling constant, J_{AB}, closely corresponds to values reported[40] for geminal protons at C-4 of model γ-lactones. The alternative structure, **28**, would be expected[40] to display $J_{AB} \cong 9$–10 Hz, and, in addition, it should display considerably different chemical shifts for the A, B, and X protons.



28

Treatment of styrene oxide with metalated 3,3-dimethylbutyric acid gave a relatively stable hydroxy acid, **29**, whose structure was assigned by analogy with



29 **30**

26. Cyclization in refluxing toluene gave lactone **30** as a mixture of cis and trans isomers as determined from the doublets obtained for the *tert*-butyl (δ 1.05, 1.08) and phenyl (δ 7.35, 7.38) substituents in its nmr spectrum and the broad ν(C=O) band (1758 cm^{-1}) in its ir spectrum.

Discussion

Formation of Metalated Carboxylic Acids.—Inorganic carboxylate salts react with organometallic reagents with an outcome which is dependent both upon the structure of the carboxylic acid and upon the constitution of the organometallic agent. Simple organolithium reagents react cleanly with lithium carboxylates to produce ketones by a highly useful synthetic process.[41] The reaction proceeds without disturbing the stereochemical integrity of the α carbon of the lithium carboxylate when simple organolithium reagents are used, but examples with more reactive organolithium reagents are lacking.[41] An intermediate position between proton abstraction at the α carbon and nucleophilic addition at the carboxylate function is occupied by Grignard reagents.[42] Carboxylic acids with activating aryl or olefinic substituents attached to the α carbon display predominant proton abstraction and they produce highly useful Ivanov reagents.[43] Aliphatic carboxylic acids suffer varying degrees of nucleophilic addition. Similar results have been reported for alkali metal amides in ammonia, which react with olefinic[27] and aryl-[44] acetic acids by proton abstraction. Under more severe conditions, sodium amide,[12,45] sodium metal, and/or sodium hydride[46] react in the absence of solvent by proton abstraction with various sodium carboxylates including aliphatic examples to produce dianions with apparent limited synthetic utility.[13] Likewise, carboxylate salts of aliphatic carboxylic acids undergo proton abstraction in modest to satisfactory yields at the α carbon when treated with relatively ionic organosodium reagents[47] or with alkali metal radical anions.[48] Thus what is one of the first examples[47a] of an aliphatic metalated carboxylic acid resulted from carbonation studies of pentylsodium by Morton and coworkers. Extensions to other examples,[47b] clarification of the mechanism of the carbonation reaction,[49] and inclusion of a long-chain example[50] in addition to deuteration studies[51] indicated the existence of aliphatic carboxylic acid dianions. The low and variable yields observed for the formation of the dianions restricted synthetic applications. Use of sodium amide at high temperatures indicated that high yields of dianions were possible in selected cases, but documented results reveal poor reactivity toward added electrophiles.[12,13,45,46]

The use of lithium diisopropylamide as proton transfer agent in the present work or related lithium amides[26] permitted both formation of high yields of metalated carboxylic acids and suitable reactivity toward epoxides as electrophiles. Examples **5a–h**, **12**, and **13** suggest that formation of metalated carboxylic acids is reasonably general and that routine laboratory procedures may be used. The high yields enjoyed in these examples suggest further that lithium diisopropylamide is a base strong enough to abstract α protons from di- and monoalkylacetic acids, which by analogy with esters[14,52] should be considerably less acidic than acetate ion. Proton abstraction by a highly hindered base such as lithium diisopropylamide can be expected to proceed without initial addition to the carboxylate function, as was suggested for sodium amide.[12]

(38) Reference 21b, p 270.

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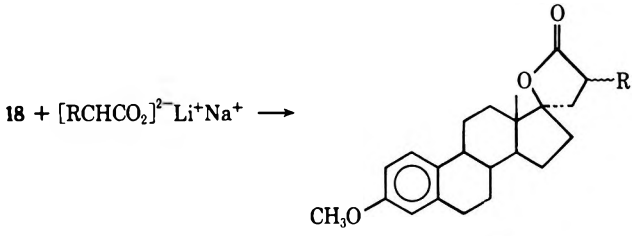
Stereochemistry and Steric Hindrance.—The failure of cyclooctene oxide to react with metalated isobutyric acid and the failure of metalated 3,3-dimethylbutyric acid to react with cyclohexene oxide can be attributed to steric hindrance in each of the reactants. Forcing conditions above the reflux temperature of THF were not attempted. Under the conditions employed, recovered yields of the carboxylic acid and epoxide were high. Likewise, styrene oxide showed a preference for attack at the less hindered, terminal carbon with sterically hindered metalated carboxylic acids, as demonstrated by **27** and **30**. Steric effects also assume an important role in determining stereochemistry at C-21 in reactions of metalated carboxylic acids with steroid epoxide **2**.

Lactones **5** were obtained as inseparable mixtures of C-21 isomers. Oppenauer oxidation of **5g** gave **8f**. The predominant, less soluble isomer so formed was easily separated by crystallization. Nmr spectra of **5g** showed absorption at 59 Hz for the C-18 methyl resonance of one isomer of the mixture and superposition of the same resonance of the second isomer on C-19 at 62 Hz. Oxidation product **8f** revealed absorption at 65 (major) and 61 Hz (minor) for C-18 of the two isomers. Attempts to assign structure based on the shielding effect[53] resulting from the ring current of the C-21 phenyl substituent, however, proved to be inconclusive.

Attack of the metalated carboxylic acid at the steroidal epoxide can be rationalized in favor of preferential formation of either the 21*R* or 21*S* phenyl isomer. The more hindered 21*S* isomer should be capable of isomerization on base treatment, while the 21*R* isomer should be conformationally stable in the presence of a strong base. Conformational stability, or lack of it, permits correlations of structure with C-18 peak positions in the nmr spectra. A more suitable model was required because of the base sensitivity of the Δ^4-3-ketone functional combination present in the A ring of **8f**. Consequently, **31a**, which resulted from treatment

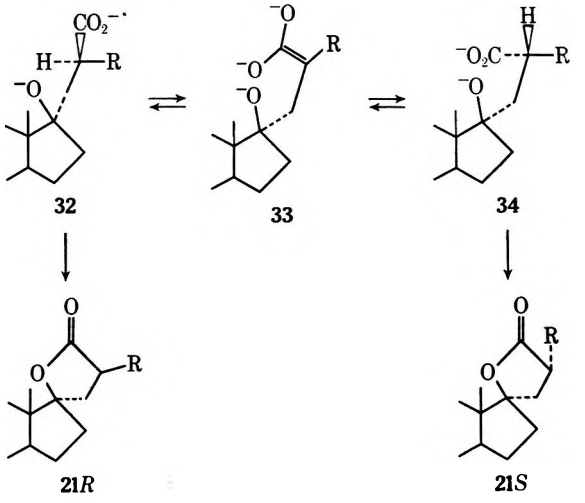


31a, R = C_6H_5
b, R = C_6H_{11}

of **18** with metalated phenylacetic acid, was used for this purpose. The ratio of the peak heights for C-18 methyl absorptions of the isomers of **31a** at 61 (major) and 65 Hz (minor) was 3.1:1. Treatment with *tert*-BuOK reversed peak intensities with C-18 absorptions at 61 Hz (minor) and 65 Hz (major) in the ratio 1:2.4. The logical conclusion may then be drawn that the high-field C-18 absorption is due to the 21*S* isomer and the low-field absorption is due to the 21*R* isomer. Structural similarities at C-18 in **5g** and **8f** allows an analogous conclusion—high field C-18 absorption relates to the 21*S* isomer. Finally, Oppenauer oxidation of **5g** in toluene caused isomerization at C-21 and the pure isomer of **8f** which was isolated can be characterized with 21*R* stereochemistry (C-18, 65 Hz).

Similar results were obtained when **18** was treated with metalated cyclohexylacetic acid. The isomeric mixture of **33b** obtained in 89% yield displayed two C-18 methyl absorptions in the nmr spectrum at 55 (major) and 59 Hz (minor) with peak intensities in the ratio 3.1:1. Since the cyclohexyl substituent approximates the steric bulk of phenyl, treatment with *tert*-BuOK could be expected to give a similar reversal of peak intensities, and this result was observed. The shift differences for the C-18 methyl absorptions in **33a** cannot then be attributed to differing influences of the ring current in the 21*S* isomer *vs.* the 21*R* isomer.

Stereochemistry and Anion–Dianion Equilibria.—Alkylation of metalated carboxylic acids with epoxides proceeds by monosubstitution. The ability of alkyl- or arylacetic acids to undergo twofold reaction with electrophiles depends upon the formation of the dianion of once-alkylated carboxylate anion. Treatment of **18** with 3 equiv of metalated phenyl- or cyclohexylacetic acids for 18 hr gave 21*S*-substituted spiro lactones, **31a,b**, on acidification as the predominant products. Attack by the metalated carboxylic acid from the least sterically hindered conformation of the reactants and accompanied by inversion at C-20 would produce **32**. If the reasonable assumption is made that the acidity of alkylated carboxylate anion differs



by only 1–2 pK_a units[14,52,54] from the parent carboxylate anion (phenyl or cyclohexyl acetate), then the excess metalated species could produce **33** as a long-lived,[55] delocalized[26] dianionic carboxylic acid. Long-lived carbanions can be expected to display a relatively small k_e/k_α value,[55] so that, if formed, **33** should invert given the favorable stereochemistry of the present system. On acidification, **34** would produce the 21*S* spiro lactones observed.

The observation that 21*S* spiro lactones **31a,b** are major products requires that inversion occur at C-21, and, hence, that formation of **33** is a significant process in the overall reaction. Formation of high yields of monosubstituted products and without detectable disubstitution can be accommodated by assuming steric

(53) Reference 21b, p 94 ff.

(54) W. L. Rellahan, W. L. Gumbry, and H. D. Zook, *J. Org. Chem.*, **24**, 709 (1959).

(55) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 92.

hindrance to the second alkylation step. This assumption draws support from the previous discussion, which cited the failure of metalated 3,3-dimethylbutyric acid to react with cyclohexene oxide and of the failure of metalated isobutyric acid to react with cyclooctene oxide. Thus, **33** is formed under the reaction conditions, but it fails to react further.

Experimental Section[56]

General Methods for the Preparation of Metalated Carboxylic Acids. Procedure A.—To a solution of 10.1 g (100 mmol) of diisopropylamine in 100–200 ml of anhydrous THF was added, by injection, 63 ml of a standard solution of *n*-butyllithium in heptane or hexane (1.60 *M*, 100 mmol) at a temperature below 10°. After 10 min at 0°, 50 mmol of the appropriate carboxylic acid in a small volume of anhydrous THF was added, and the mixture was warmed to 30–35° for 30 min to complete the metalation.

Procedure B.—A detailed procedure for the preparation of metalated carboxylic acids from preformed sodium carboxylates has been published.[9a] The procedure used with steroidal epoxides differed only by prior removal of the mineral oil from the sodium hydride by washing with heptane on a tared, sintered funnel.

Less reactive lithium hydride may be substituted for sodium hydride, but longer reaction periods are required for complete conversion of the acid to lithium carboxylate. In some cases, metalated intermediates prepared from lithium carboxylates are more soluble. Carbanionic intermediates prepared from alkylacetic acids *generally* produce heterogeneous mixtures in THF and those prepared from dialkylacetic acids are *generally* homogeneous.

I. Steroidal Epoxides. A. Exploratory Reactions of 2 with Simple Nucleophiles. 1. 17-(Methoxymethyl)androst-5-ene-3β,17β-diol (3a).—To a solution of 1.2 g (50 mg-atoms) of sodium in 100 ml of methanol was added 3.0 g (10 mmol) of **2**. After heating to reflux for 18 hr, the solution was acidified with excess acetic acid and the solvent was evaporated. The residue was taken up in chloroform–ether, the resulting solution was washed with water, then dried ($MgSO_4$) and evaporated, and the product was recrystallized from methanol, yielding a total of 2.80 g (85%) of **3a** in two crops: mp 160–163°; $[\alpha]^{24}D$ −97°; ir ($CHCl_3$) 3625 and 3575 cm^{-1}; nmr δ 0.90 (s, C-18), 1.03 (s, C-19), 3.38 (s, OCH_3).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.46; H, 10.15.

Oppenauer oxidation[22,57] of crude **3a** obtained from a repetition of the above procedure on a 7.5-mmol scale yielded 1.15 g (46%) of **4a** after chromatography and recrystallization from 50% ethanol: mp 118–119.5°; $[\alpha]^{24}D$ +66.6°; ir (KBr) 3500, 1685, and 1620 cm^{-1}; uv 241 nm (E_1^1 479); nmr δ 0.92 (s, C-18), 1.18 (s, C-19), 3.35 (s, OCH_3).

2. 17-(Azidomethyl)androst-5-ene-3β,17β-diol (3b).—A mixture of 3.0 g (10 mmol) of **2** in 50 ml of dioxane and 3.3 g (50 mmol) of sodium azide in 25 ml of water was stirred at reflux for 20 hr. The cooled mixture was diluted with 200 ml of ether and the aqueous layer was discarded. After washing with water, the solution was dried ($MgSO_4$) and evaporated. The crude product, 3.3 g (97%), mp 145–150°, displayed a single tlc spot on silica gel. Recrystallization from acetonitrile produced a sample for analysis: mp 149–152°; $[\alpha]^{24}D$ −88°; ir (KBr) 3400 and 2100 cm^{-1}; nmr δ 0.88 (s, C-18), 1.01 (s, C-19), 3.38 (q, J = 12 Hz, $-CH_2N_3$).

Anal. Calcd for $C_{20}H_{31}N_3O_2$: C, 69.52; H, 9.05; N, 12.17. Found: C, 69.42; H, 8.86; N, 12.37.

Oppenauer oxidation[22,57] of **3b** on a 10-mmol scale gave 3.00 g (91%) of crude **4b** and 1.75 g (52%) after column chromatography on alumina and recrystallization from 50% ethanol: mp 153–155°; $[\alpha]^{24}D$ +57.1°; uv 241 nm (E_1^1 444); ir 3430, 2100, 1654, and 1610 cm^{-1}; nmr δ 0.93 (s, C-18), 1.18 (s, C-19), 3.38 (q, J = 12 Hz, $-CH_2N_3$).

Anal. Calcd for $C_{20}H_{29}N_3O_2$: C, 69.94; H, 8.51; N, 12.24. Found: C, 69.87; H, 8.41; N, 12.37.

3. 4′,5′-Dihydro-3β-hydroxy-5′-oxo-(17*R*)-spiro[androst-5-ene-17,2′(3′*H*)-furan]-4′-carbonitrile (5e).—A solution of 5.7 g (50 mmol) of ethyl cyanoacetate in 10 ml of THF was added to 50 mmol of lithium diisopropylamide in 200 ml of THF. After 5 min at ambient temperature, 3.0 g (10 mmol) of **2** in 50 ml of THF was added and the mixture was stirred at reflux for 18 hr. The cooled mixture was treated with 6.0 g (100 mmol) of acetic acid and 100 ml of water. The organic layer was dried and evaporated and the residue was chromatographed, yielding 0.80 g (27%) of **2**, mp 165–175°. Further elution with benzene and benzene plus 20% ethyl acetate gave 0.50 g (14%) of **5e**, mp 200–215°. A sample for analysis was prepared by recrystallization from 50% ethanol, mp 212–223°, ir (KBr) 2260 and 1770 cm^{-1}.

Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46. Found: C, 74.31; H, 8.51.

B. Metalation and Reactions of Acetic Acid. 1. 4′,5′-Dihydro-3β-hydroxy-(17*R*)-spiro[androst-5-ene-17,2′(3′*H*)-furan]-5′-one (5d).—Metalated acetic acid was prepared on a 50-mmol scale in 200 ml of THF according to procedure A. A solution of 3.0 g (10 mmol) of **2**[1a] in 50 ml of THF was added and the stirred mixture was heated to reflux for 18 hr. Water (100 ml) and ethanol were added to the cooled mixture; then it was acidified with excess 3 *N* hydrochloric acid. After stirring at ambient temperature for 0.5 hr, the phases were separated and the solvents were evaporated. The residue was taken up in chloroform–ether and the solution was washed with 2 *N* sodium hydroxide and brine, dried ($MgSO_4$), and evaporated. Chromatography gave 1.85 g (55%) of **5d**, mp 175–186°, on elution with benzene plus 20% ethyl acetate. Recrystallization from 40% ethanol showed mp 180–187°. The ir spectrum was identical with that of the same material obtained from base hydrolysis of **14a,b** (procedure I.D.2,3).

Repetitions of this procedure on a 20-mmol scale using 150 mmol of lithium diisopropylamide in 75 ml of hexamethylphosphoramide and 150 ml of THF gave a homogeneous mixture of **6a** (M^+ = Li^+) initially, but a precipitate soon formed. Crystallization of the product and chromatography of the residue gave 3.2–3.3 g (48%) of **5b**, mp 182–190°.

2. 4′,5′-Dihydro-(17*R*)-spiro[androst-4-ene-17,2′(3′*H*)-furan]-3,5′-dione (8d).—Metalated acetic acid was prepared on a 50-mmol scale in 200 ml of THF according to procedure A. A solution of 2.90 g (8.2 mmol) of **7**[1a–c] in 25 ml of THF was added and the mixture was stirred at reflux for 18 hr.

At the conclusion of the reaction period, 100 ml of water was added and the mixture was stirred at reflux for 2 hr. Another 100-ml portion of water was added to the cooled mixture and the aqueous layer was back-extracted with 100 ml of ether. Ethanol (100 ml) was added and the warm (50°) aqueous alcoholic solution was acidified to congo red with excess 6 *N* hydrochloric acid. Following 2 hr of stirring, the acidic mixture was extracted with chloroform and the extracts were combined, washed with water, dried, and evaporated. The crude **8d** amounted to 1.25 g (45%), mp 140–146°. Benzene elution of an alumina column containing the crude product gave several crystalline fractions. The homogeneity of each fraction was determined by tlc. The crystalline fractions were pooled and recrystallized from 50% ethanol to produce a sample for analysis: mp 166–167° (lit.[19] mp 163–165°); $[\alpha]^{25}D$ +81.5°; ir (KBr) 1778, 1675, and 1620 cm^{-1}; uv 240 nm (E_1^1 496); nmr δ 0.97 (s, C-18), 1.21 (s, C-19).

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.28; H, 8.83.

3. 3,3-Diphenylhydracrylic Acid.—Procedure A was operated at 30° with 50 mmol of acetic acid in a solvent mixture consisting of 150 ml of THF and 50 ml of hexamethylphosphoramide. Benzophenone (9.1 g, 50 mmol) in 50 ml of THF was added and the homogeneous mixture was stirred at 20°. After 2 hr, the mixture was acidified with excess 2 *N* hydrochloric acid. The organic phase was separated, washed with water, dried ($MgSO_4$), and evaporated. When diluted with hexane, the residue deposited 2.3 g (19%) of product: mp 222–223° dec; nmr (pyridine) δ 3.65 (s, 2, $-CH_2-$); ir (KBr) 3480 and 1690 cm^{-1}.

(56) Melting points were determined on a Thomas-Hoover apparatus and are corrected. Boiling points are uncorrected. The nmr spectra were determined on a Varian A-60 spectrometer in deuteriochloroform solutions unless otherwise specified. Infrared spectra were obtained on Beckmann IR-7 and IR-9 spectrometers, and ultraviolet spectra were measured as methanol solutions on a Cary Model 11 instrument. Optical rotations were determined as 1.00% solutions in chloroform. Anhydrous tetrahydrofuran was obtained by passing commercial material through a column of basic alumina (Woelm, activity grade I). Diisopropylamine was stirred with and then distilled from calcium hydride. Column chromatography used neutral alumina (Woelm, activity grade III).

(57) J. F. Eastham and R. Teranishi, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 192.

TABLE I

Compd	Yield, %	Mp, °C	Nmr, δ C-18	Nmr, δ C-19	Ir ν(C=O), cm⁻¹	Uv λmax, nm (E_1^1)	[α]²⁵D, degree	Calcd, % C	Calcd, % H	Found, % C	Found, % H
5a[a]	70	214–220	0.92 0.98	1.02	1762		−103	77.05	9.56	77.04	9.39
5b	87	231–236	0.93 0.99	1.03	1753		−101	77.38	9.74	77.37	9.80
5f	76	215–218	0.92 0.99	1.02	1758		−98.4	77.95	10.06	77.50	10.08
5g	75	256–261	0.98	1.05	1750		−112	79.96	8.61	79.98	8.58
5h	19	177–181	0.92 0.97	1.03	1780		−103	73.76	9.15	73.69	9.12
8a	90	182–185	0.98 1.04	1.22	1770 1672	240.5 (464)	+66	77.50	9.05	77.40	9.17
8b	84	160–163	0.96	1.21	1760 1678	240 (448)	+63	77.80	9.25	77.72	9.10
8e	35	153–156	0.93 1.01	1.19	1776 1680	240 (422)	+52	78.35	9.61	78.36	9.64
8f	71	250–253	1.07	1.20	1778 1678	240 (370)	+53	80.35	8.19	80.16	8.18
9a	85	214–222	1.02 1.09	1.16	1770 1660	283 (730)	+1.7	77.92	8.53	77.89	8.49
9b	82	107–110	1.00 1.07	1.13	1766 1660	282 (714)	−12.8	78.22	8.75	78.00	8.57
9c	61	202–204	1.07	1.13	1768 1666	283 (741)	−23.8	78.22	8.76	78.12	8.84
10a[b]	64	138–140	0.98 1.05	1.26	1768 1690	238 (444)	−30.4	69.73	7.96	69.23	8.04
10b[c]	64	236–237	0.97	1.25	1768 1686	238 (432)	−10	70.23	8.16	69.98	8.17
10c[d]	61	242–244	1.00	1.22	1762 1680	239 (440)	−30	70.23	8.16	69.84	7.88

[a] $[\alpha]^{26}D$ −103° (c 0.32, $CHCl_3$). [b] S, 7.65; found, 7.68. [c] S, 7.22; found, 7.46. [d] S, 7.22; found, 7.67.

4. **Nonanoic Acid.**—Metalated acetic acid was prepared according to procedure A on a 200-mmol scale in 300 ml of methylal. Addition of 35.8 g (200 mmol) of 1-bromoheptane yielded, after stirring at 30° for 18 hr, 3.9 g (12%) of crude nonanoic acid. Distillation provided material of analytical quality,[58] bp 118–119° (5.0 mm), $n^{24}D$ 1.4312,

C. Metalation and Reactions of Substituted Acetic Acids.

1. **4′,5′-Dihydro-3β-hydroxy-4′,4′-dimethyl-(17*R*)-spiro[androst-5-ene-17,2′(3′*H*)-furan]-5′-one (5c).**—Isobutyric acid (50 mmol) was metalated according to procedure A in 200 ml of THF, yielding a homogeneous solution of **6b** ($M^+ = Li^+$). A solution of 3.0 g (10 mmol) of **2**[1a] in 50 ml of THF was added and the mixture was heated to reflux for 18 hr. After heating for a few minutes, the salt of the epoxide cleavage product began to separate.

At the conclusion of the reaction period, 250 ml of water was added to the cooled mixture. The organic layer was separated and washed with 50 ml of water. The aqueous layers were combined and back-extracted with 100 ml of ether. Ethanol (100 ml) was added and the warm (50°) solution was acidified to congo red with excess 6 *N* hydrochloric acid. After stirring for 3 hr, the spiro lactone was isolated by extraction with three 75-ml portions of chloroform. The chloroform extracts were freed of excess isobutyric acid by washing with two 50-ml portions of 2 *N* sodium hydroxide and brine, after which they were dried ($MgSO_4$) and evaporated, yielding 3.00 g (81%) of **5c**. Recrystallization from 80% ethanol produced a sample for analysis: mp 184–185.5°; $[\alpha]^{25}D$ −103°; ir (KBr) 1770 and 1742 cm^{-1}; nmr δ 0.99 (s, C-18), 1.03 (s, C-19), 1.27, 1.35 (s, C-21).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.18; H, 9.73.

The same procedure was used for several other examples, which are collected in Table I. Monosubstituted acetic acids produced heterogeneous mixtures of the metalated intermediate when either procedure A or B was used.

2. **4′,5′-Dihydro-4′,4′-dimethyl-(17*R*)-spiro[androst-4-ene-17,2′(3′*H*)-furan]-3,5′-dione (8c).**—Oppenauer oxidation[57] of **5c** in toluene on a 5.1-mmol scale yielded 1.45 g (77%) of **8c** in two crops on recrystallization from 40% ethanol, mp 204–208°. Further recrystallization from ethyl acetate–hexane produced a sample for analysis: mp 209–211°; $[\alpha]^{23}D$ +51.5°; uv 240 nm (E_1^1 450); ir (KBr) 1758 and 1678 cm^{-1}; nmr δ 1.00 (s, C-18), 1.20 (s, C-19), 1.25, 1.35 (s, C-21).

Anal. Calcd for $C_{24}H_{36}O$: C, 77.80; H, 9.25. Found: C, 77.56; H, 9.12.

The products, **8a,b**, which resulted from the use of **5a,b** in the same procedure are listed in Table I.

3. **4′,5′-Dihydro-4′-methyl-(17*R*)-spiro[androsta-4,6-diene-17,2′(3′*H*)-furan]-3,5′-dione (9a).**—A mixture of 4.70 g (13.1 mmol) of **8a** and 3.40 g (13.8 mmol) of chloranil and 47 ml [10:1 solvent (ml):steroid (g)] of a solvent mixture consisting of 8:2 toluene–acetic acic (v/v) was heated to reflux for 45 min. The dark, homogeneous solution was cooled and diluted with 100 ml of benzene. The precipitate of tetrachlorohydroquinone was removed; then it was washed with benzene, and the filtrates were washed with five 100-ml portions of 1 *N* sodium hydroxide and water. After drying ($MgSO_4$) the solvents were removed, leaving a brown, crystalline residue. Elution of an alumina column containing the product with benzene and benzene plus 10% ethyl acetate gave 3.95 g (85%) of **9a** in several fractions. Recrystallization from benzene–isopropyl ether produced a sample for analysis: mp 214–222°; $[\alpha]^{25}D$ +1.7°; uv 283 nm (E_1^1 730); ir (KBr) 1770, 1660, 1612, and 1582 cm^{-1}; nmr δ 1.02, 1.09 (d, C-18), 1.16 (s, C-19), 1.22, 1.34 (d, C-21).

Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.92; H, 8.53. Found: C, 77.89; H, 8.49.

The solvent system employed in this procedure[23] gave superior yields with **8a,b** than with use of more conventional[59] *tert*-butyl alcohol with **8c**. Data for **9b,c** are listed in Table I. The 7α-thioacetyl derivatives, **10a–c**, were prepared as described in existing procedures[24] and they are listed in Table I.

4. **4′,5′-Dihydro-3β-hydroxy-4′-vinyl-(17*R*)-spiro[androst-5-ene-17,2′-(3′*H*)-furan]-5′-one (12).**—A solution of 100 mmol of lithium diisopropylamide in 200 ml of THF was prepared according to procedure A. A benzene solution containing 4.3 g (50 mmol) of crotonic acid was dried by azeotropic distillation

(58) Analytical and spectral data were obtained for this product.

(59) R. Owyang in "Steroid Reactions," C. Djerassi, Ed., Holden-Day, San Francisco, Calif., 1963, Chapter 5.

and concentrated to 75 ml before it was added at 0–10° to the lithium diisopropylamide. The resulting solution was stirred at 30° for 0.5 hr; then 3.0 g (10 mmol) of **2**[1a] in 50 ml of THF was added and the final solution was stirred at 40° for 18 hr.

Water (100 ml) and chloroform–ether (100 ml) were added to the cooled mixture. The organic layer was separated and washed with 50 ml of water. The aqueous layers were combined and back-extracted with 100 ml of ether, and the ether layer was combined with the original organic layer.

Ethanol (100 ml) was added to the aqueous solution and, after warming (50°), it was acidified to congo red with excess 6 *N* hydrochloric acid. After stirring for 3 hr, the acidic products were isolated with three 75-ml portions of chloroform. The chloroform extracts were freed of acidic products by washing with two 50-ml portions of 1 *N* potassium hydroxide. Finally, the chloroform solution was washed with brine, dried ($MgSO_4$), and evaporated. Crude **12** so obtained amounted to 1.10 g (28%). Recrystallization from 50% ethanol produced a sample for analysis: mp 228–235°; $[\alpha]^{25}D$ −125°; ir (KBr) 3515 and 1752 cm^{-1}; nmr δ 0.94, 1.00 (d, C-18), 1.03 (s, C-19), 5.65–6.28 (m, $-CH{=}CH_2$).

Anal. Calcd for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: 77.39; H, 9.16.

Acidification of the potassium hydroxide extracts with excess 6 *N* hydrochloric acid and extraction with three 75-ml portions of chloroform permitted isolation of **13** contaminated with excess crotonic acid. Trituration with acetone–hexane produced 0.20 g of solid which was recrystallized from 50% ethanol: mp 214–218°; $[\alpha]^{27}D$ −63° (c 1.01, dioxane); ir (KBr) 3420, 1704, 1655, and 960 cm^{-1}; nmr (DMSO) δ 0.80 (s, C-18), 0.98 (s, C-19), 3.63 (m, $C{=}CCH_2CO_2H$).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.20; H, 9.34. Found: C 73.96; H, 9.31.

The spectral data support **13** as the structure for this product. The nmr absorption at δ 3.63 corresponds to similar absorption at δ 3.08 (m, $=CCH_2CO_2H$) determined for vinylacetic acid for comparison. Assignment of the weak ir absorption at 960 cm^{-1} to a π (=CH) vibration for a trans-disubstituted carbon–carbon double bond is considered tenuous.

Evaporation of the washed and dried organic layer from the original reaction yielded 2.00 g (67%) of crude **2**, identified by tlc and ir comparison.

D. Metalation and Reactions of Acetic Acid Derivatives.

1. 3β,17-Dihydroxy-17α-pregn-5-ene-21-carbonitrile (14a).—To a stirred solution containing 50 mmol of lithium diisopropylamide in 200 ml of THF was added 2.05 g (50 mmol) of acetonitrile in 10 ml of THF at 0°. After 5–10 min the carbanionic species began to separate. A solution of 3.0 g (10 mmol) of **2**[1a] in 50 ml of THF was added and the mixture was stirred at ambient temperature for 18 hr. At the conclusion of the reaction period, 200 ml of water and 200 ml of ether were added. The organic layer was separated and washed successively with two 50-ml portions of 2 *N* hydrochloric acid and 50 ml of water. After being dried ($MgSO_4$) the solvents were removed, leaving 3.15 g (92%) of crude **14a**. Recrystallization from 80% ethanol yielded white crystals: mp 240–245°; $[\alpha]^{24}D$ −71° (c 1.02, dioxane); ir (KBr) 2260 cm^{-1}; nmr (pyridine) δ 1.03, 1.05 (C-18, C-19).

Anal. Calcd for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.69; N, 4.07. Found: C, 76.87; H, 9.76; N, 4.07.

When acetamide was added to 2 equiv of lithium diisopropylamide and treated with **2**,[1a] **14a** (65%) was obtained, mp 238–239° after recrystallization. Spectra (ir and nmr) were identical with those determined for **14a** prepared from metalated acetonitrile.

2. 4′,5′-Dihydro-3β-hydroxy-(17*R*)-spiro[androst-5-ene-17,-2′(3′*H*)-furan]-5′-one (5d) by Hydrolysis of 14a.—A mixture of 6.86 g (20 mmol) of **14a**, 5.6 g (100 mmol) of potassium hydroxide, and 50 ml of ethylene glycol was heated to reflux for 6 hr. The condenser was set down and the ethylene glycol was distilled at aspirator pressure. After cooling, 200 ml of water was added and the mixture was warmed until the solid dissolved, and then it was poured into 200 mequiv of dilute hydrochloric acid. The crude hydroxy acid was taken up in 200 ml of 80% ethanol and the solution was acidified with an arbitrary small volume of 6 *N* hydrochloric acid. After the warm solution was stirred for 1 hr, the ethanol was evaporated and the residue was taken up in chloroform. The chloroform solution was washed with water, dried ($MgSO_4$), and evaporated, yielding 6.8 g (99%) of crude **5d**, mp 173–181°. Elution of an alumina column with benzene–20% ethyl acetate gave 5.2 g (75%), mp 188–192°, in several fractions. Recrystallization from 60% ethanol gave white crystals: mp 191–194°; $[\alpha]^{25}D$ −98°; ir (KBr) 1766 cm^{-1}; nmr δ 0.95 (s, C-18), 1.03 (s, C-19).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.37. Found: C, 76.66; H, 9.47.

A similar hydrolysis with sodium hydroxide in aqueous ethanol for 6 hr gave 67% of **5d** after alumina chromatography, mp 190–192°, $[\alpha]^{25}D$ −96°.

3. 3β,17-Dihydroxy-*N*,*N*-dimethyl-17α-pregn-5-ene-21-carboxamide (14b).—The carbanion of *N*,*N*-dimethylacetamide was prepared on a 50-mmol scale by the procedure described for metalated acetonitrile (I.D.1). A solution of 3.0 g (10 mmol) of **2**[1a] in 50 ml of THF was added and the homogeneous solution was heated to reflux for 18 hr. After 20 min, the product began to separate.

At the conclusion of the reaction period, 100 ml of 1 *N* hydrochloric acid and 50 ml of chloroform were added at a temperature below 10°. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated, yielding 3.4 g (87%) of crude **14b**, mp 205–212° dec. Recrystallization from acetonitrile raised the melting point to 217–220° dec: $[\alpha]^{24}D$ −96.3°; ir (KBr) 1626 and 1598 cm^{-1}; nmr (CF_3CO_2H) δ 1.05 (s, C-18), 1.12 (s, C-19), 3.33, 3.40 [d, $N(CH_3)_2$].

Anal. Calcd for $C_{24}H_{39}NO_3$: C, 73.99; H, 10.09; N, 3.60. Found: C, 74.17; H, 10.07; N, 3.64.

4. 3β,17-Dihydroxy-*N*,*N*,21-trimethyl-17α-pregn-5-ene-21-carboxamide (15).—A solution containing 100 mmol of the carbanion of *N*,*N*-dimethylpropionamide in 300 ml of THF was prepared at 0° according to the procedure described for acetonitrile (I.D.1). A solution of 6.0 g (100 mmol) of **2**[1a] in 100 ml of THF was added and the homogeneous solution was stirred at 60° for 18 hr.

Work-up as described for **14b** (I.D.3) gave 7.8 g (98%) of crude **15**, mp 205–213° dec. Recrystallization of a portion of the crude product from acetonitrile produced a sample for analysis: mp 217–220° dec; $[\alpha]^{25}D$ −106°; ir (KBr) 1624 and 1592 cm^{-1}; nmr δ 0.83 (s, C-18), 1.02 (s, C-19), 1.06, 1.18 (d, C-21), 2.92, 3.11 [d, $N(CH_3)_2$].

Anal. Calcd for $C_{25}H_{41}NO_3$: C, 74.39; H, 10.24; N, 3.47. Found: C, 74.31; H, 10.18; N, 3.37.

Hydrolysis of **15** with sodium hydroxide in aqueous ethanol for 6 hr gave 68% of **5a** after alumina chromatography. The melting point and ir spectrum were identical with those of the same product prepared by treating **2** with metalated propionic acid (Table I).

5. *N*-[2-(Dimethylamino)ethyl]-3β,17-dihydroxy-*N*-methyl-17α-pregn-5-ene-21-carboxamide (14c).—A mixture of 24.7 g (242 mmol) of *N*,*N*,*N*′-trimethylethylenediamine and 50 g (500 mmol) of acetic anhydride was stirred at ambient temperature for 18 hr. The mixture was poured into excess, dilute potassium hydroxide and the product was extracted with chloroform. Distillation of the residue remaining from the dried and evaporated extracts yielded 23.3 g (67%) of **17**: bp 91–92° (5.0 mm); $n^{25}D$ 1.4560; ir (film) 1644 cm^{-1}; nmr δ 1.93 (s, CH_3CO).

Anal. Calcd for $C_7H_{16}N_2O$: C, 58.30; H, 11.18; N, 19.43. Found: C, 58.47; H, 11.09; N, 19.37.

A solution containing 50 mmol of the carbanion of **17** in 300 ml of THF was prepared at 0° according to the procedure described for acetonitrile (I.D.1). A solution of 6.0 g (20 mmol) of **2**[1a] in 100 ml of THF was added and the homogeneous solution was stirred at 60° for 18 hr.

At the conclusion of the reaction period, 3.0 g (50 mmol) of acetic acid and 200 ml of water were added. The organic layer was separated; then it was washed with water and finally dried ($MgSO_4$) and evaporated. Recrystallization from ethyl acetate gave 5.9 g of **14c** and alumina chromatography of the filtrate residue gave 0.3 g of **14c** for a combined yield of 6.2 g (70%), mp 115–116.5°. Recrystallization from ethyl acetate produced a sample for analysis: mp 117–118°; $[\alpha]^{25}D$ −80°; ir 1620 cm^{-1}; nmr δ 0.98 (s, C-18), 1.01 (s, C-19), 2.25 [s, $N(CH_3)_2$].

Anal. Calcd for $C_{27}H_{46}NO_3$: C, 72.60; H, 10.38; N, 6.27. Found: C, 71.92; H, 10.22; N, 5.98.

6. 17-Hydroxy-*N*,*N*-dimethyl-3-oxo-17α-pregn-4-ene-21-carboxamide (16a).—A solution containing 50 mmol of metalated dimethylacetamide in 200 ml of THF was prepared as described in procedure I.D.3. A solution of 2.70 g (7.7 mmol) of **7**[1a-c] in 50 ml of THF was added and the mixture was stirred at reflux for 18 hr. After cooling slightly, 12.0 g (200 mmol) of acetic acid and 30 ml of water were added, and the mixture was stirred for 3 hr without further heating. The solution was diluted with

ether (200 ml) and the organic layer was washed with 2 *N* hydrochloric acid, dried ($MgSO_4$), and evaporated. Recrystallization from 40% ethanol yielded 1.50 g (50%) of **16a** in two crops, mp 202–205° dec. Further crystallization from the same solvent gave a sample for analysis: mp 216–218° dec; $[\alpha]^{24}D$ +32°; uv 241 nm (E_1^1 414); ir 1680 and 1618 cm^{-1}; nmr δ 0.92 (s, C-18), 1.18 (s, C-19).

Anal. Calcd for $C_{24}H_{37}NO_3$: C, 74.38; H, 9.62; N, 3.62. Found: C, 74.29; H, 9.55; N, 3.58.

7. 17-Hydroxy-*N*-methyl-3-oxo-17α-pregn-4-ene-21-carboxamide (16b).—Substitution of *N*-methylacetamide for *N*,*N*-dimethylacetamide in the preceding experiment and use of 2 equiv of lithium diisopropylamide gave a heterogeneous mixture of the carbanionic intermediate. Recrystallization of the crude product from 50% ethanol gave 1.55 g (51%) of **16b** in two crops, mp 164–168° dec. Chloroform elution of an alumina column and crystallization from 50% ethanol produced an analytical sample: mp 208–210° dec; $[\alpha]^{25}D$ +46°; uv 241 nm (E_1^1 434); ir (KBr) 1675 and 1650 cm^{-1}; nmr (pyridine) δ 1.07 (s, C-18), 1.09 (s, C-19), 2.87, 2.94 (d, $NHCH_3$).

Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 73.40; H, 9.35; N, 3.80.

8. 17-Hydroxy-3-methoxy-*N*,*N*,21-trimethyl-19-nor-17α-pregna-1,3,5(10)-triene-21-carboxamide (22).—Substitution of $18^{26,35}$ for 2^{1a} in procedure I.D.7, but on a 30-mmol scale, gave 8.95 g (75%) of **22** after crystallization and alumina chromatography of the filtrate residue: mp 140–142°; $[\alpha]^{25}D$ +1.8°; ir (KBr) 1634 and 1617 cm^{-1}; nmr δ 0.88 (s, C-18), 1.12, 1.22 (d, C-21), 2.98, 3.14 [d, $N(CH_3)_2$].

Anal. Calcd for $C_{25}H_{37}NO_3$: C, 75.14; H, 9.33; N, 3.51. Found: C, 75.18; H, 9.42; N, 3.71.

9. 4′,5′-Dihydro-3-methoxy-4′-methyl-(17*R*)-spiro[estra-1,3,5(10)-triene-17,2′(3′*H*)-furan]-5′-one (23).—Hydrolysis of **22** on a 14.2-mmol scale with potassium hydroxide in ethylene glycol following procedure I.D.2 gave 5.0 g (99%) of **23**. Recrystallization from acetonitrile gave white needles: mp 155–157°; $[\alpha]^{25}D$ +4.1°; ir (KBr) 1776 cm^{-1}; nmr δ 0.93, 1.00 (d, C-18), 1.22, 1.33 (d, C-21), 3.76 (s, OCH_3).

Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 78.13; H, 8.57.

10. (17*S*)-Spiro[androst-5-ene-17,2′-oxiran]-3β-ol Acetate.—To a solution of 50 mmol of lithium diisopropylamide in 200 ml of THF prepared according to general procedure A was added 5.8 g (50 mmol) of *tert*-butyl acetate at 0°. After stirring for 15 min, a solution of 3.0 g (10 mmol) of **2** in 50 ml of THF was added and the solution was stirred for 60 hr. During the reaction period the temperature gradually reached ambient temperature.

At the conclusion of the reaction period, 100 ml of water was added and the organic layer was washed with 2 *N* hydrochloric acid and 10% sodium carbonate. The residue recovered from the dried organic layer was chromatographed on alumina. Elution with benzene–hexane, benzene, and benzene plus 20% ethyl acetate yielded 1.60 g (53%) of **2** and 1.45 g (42%) of **2** acetate, mp 96–97°, identified by ir comparison. A shorter, 24-hr reaction period gave 19% of **2** acetate.

II. Model Epoxides. 1. *trans*-2-Hydroxy-α,α-dimethylcyclohexaneacetic Acid (24).—A solution of **6b** ($M^+ = Na^+$) was prepared in 200 ml of THF on a 300-mmol scale according to general procedure B. The solution was cooled to 0° and 29.4 g (300 mmol) of cyclohexene oxide was added over 10 min. The ice bath was retained for 1 hr, then the mixture was warmed to 40° for 18 hr.

At the conclusion of the reaction period, 400 ml of water was added at a temperature below 15°. The aqueous layer was separated and the reaction flask and the organic layer were washed with a mixture of 100 ml of water and 150 ml of ether. The aqueous layers were combined; then they were back-extracted with 100 ml of ether and acidified to congo red at a temperature below 10°. The crude product was taken up in chloroform, and the chloroform solution was washed with water, dried ($MgSO_4$), and evaporated to yield 51 g (91%) of **24**, mp 113–115°. Recrystallization of a 5-g sample from acetonitrile gave white needles: mp 126–127°; ir (KBr) 3530 and 1695 cm^{-1}; nmr (DMSO-d_6) δ 0.98, 1.07 (*gem* CH_3), 3.17 (>CHO).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.48; H, 9.74. Found: C, 64.63; H, 9.83.

2. *trans*-Hexahydro-3,3-dimethyl-2(3*H*)-benzofuranone (25).—The remaining 46 g (247 mmol) of **24** obtained in the preceding experiment was suspended in 300 ml of toluene and the mixture was stirred at reflux beneath a phase-separating head for 18 hr. The cooled solution was diluted with ether and washed successively with two 75-ml portions of 2 *N* sodium hydroxide and 100 ml of brine; then it was dried ($MgSO_4$) and evaporated, leaving 34.5 g (83%) of crude **25**. Recrystallization from 125 ml of hexane gave 25.9 g (62%) of white needles on refrigeration: mp 57–59°; ir (KBr) 1775 cm^{-1}; nmr (CCl_4) δ 1.00, 1.13 (gem CH_3), 3.78 (>CHO).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58. Found: C, 71.14; H, 9.64.

3. 4-Hydroxy-2,2-dimethyl-4-phenylbutyric Acid (26).—Styrene oxide was substituted for cyclohexene oxide in procedure II.1. Crude **26** obtained from the acidified aqueous layers was collected, suspended in water for washing, and dried at 40° in a vacuum oven, yielding 43.6 g (70%) of crude **26**, mp 75–90°. The crude hydroxy acid was dissolved in 0.5 *N* sodium hydroxide and the solution was extracted with ether to remove contaminating lactone **27**. After charcoal treatment, the aqueous solution was cooled to 10°, and then it was acidified with 6 *N* hydrochloric acid and the solid was collected, washed with water, and dried at 30° in a vacuum oven: mp 107–108°; ir (KBr) 3360, 1705, and 1774 cm^{-1} (trace).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.71. Found: C, 69.03; H, 7.64.

4. Dihydro-3,3-dimethyl-5-phenyl-2(3*H*)-furanone (27).—Crude **26** obtained from repetition of procedure II.3 was dissolved in 200 ml of hot acetonitrile and cooled. In addition to 8.0 g (13%) of **26** which crystallized from the solution, evaporation of the filtrate gave 48 g (84%) of **27**. Distillation, bp 114–116° (20 μ), followed by recrystallization from hexane produced a sample: mp 45–46°; ir (KBr) 1773 cm^{-1}; nmr (CCl_4) 1.20, 1.27 (s, 3 each, *gem*-CH_3), 2.20 (m, 2, CH_2), 5.33 (m, 1, >CHO).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 76.02; H, 7.59.

5. 2-(β-Hydroxyphenethyl)-3,3-dimethylbutyric Acid (29).—A heterogeneous mixture containing 200 mmol of metalated 3,3-dimethylbutyric acid in 300 ml of THF was prepared according to general procedure B. To the cooled mixture was added 24.0 g (200 mmol) of styrene oxide over 5 min and the final suspension was warmed to 40° for 18 hr. After a brief period at 40°, a homogeneous solution was obtained.

At the conclusion of the reaction period, a total of 400 ml of water was added in two portions at a temperature below 15°. The aqueous layers were separated, combined, and back-extracted with ether and residual ether was removed on a rotary evaporator before charcoal treatment. The resulting solution was acidified to congo red with a small excess of 6 *N* hydrochloric acid at a temperature below 15° and the precipitated product was collected, suspended in ice water, and dried at 40° in a vacuum oven. There was obtained 34.4 g (73%) of **29**: mp 129–137°; ir (KBr) 3450, 1709, 1274, and 900 cm^{-1}; nmr (DMSO-d_6) δ 4.38 (m, 1, ArCHOH), 7.32 (s, 5, ArH). Two *t*-Bu absorption peaks at δ 0.82 and 0.92 indicated partial cyclization in the DMSO solution.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.44; H, 8.55.

6. 3-*tert*-Butyldihydro-5-phenyl-2(3*H*)-furanone (30).—A total of 22.9 g (97 mmol) of **29** was suspended in 200 ml of benzene and the stirred mixture was heated to reflux beneath a phase-separating head until water evolution was complete. Removal of the solvent on a rotary evaporator gave 21.8 g (100%) of **30**, mp 43–48°. Two recrystallizations from 100 ml of hexane gave white leaflets: mp 48–54°; ir (KBr) 1758 cm^{-1}; nmr δ 1.08 [s, 9, $C(CH_3)_3$], 1.6–2.8 (m, 3, $>CHCH_2-$), 5.1–5.6 (m, 1, ArOCHC), 7.35, 7.40 (d, 5, ArH).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.14; H, 8.29.

III. Stereochemistry. 1. 4′,5′-Dihydro-3-methoxy-4′-phenyl-(17*R*)-spiro[estra-1,3,5(10)-triene-17,2′(3′*H*)-furan]-5′-one (31a).—Metalated phenylacetic acid was prepared on a 60-mmol scale as a heterogeneous mixture in 150 ml of THF following general procedure B. A solution of 6.0 g (20 mmol) of $18^{26,35}$ in 50 ml of THF was added and the temperature of the stirred mixture was adjusted to 35° for 18 hr.

At the conclusion of the reaction period, 150 ml of water and 100 ml of ether were added at a temperature below 15°. The aqueous phase was separated and the reaction flask and the organic layers were washed with a mixture of 100 ml of water and 100 ml of ether. The aqueous layers were combined, back-extracted with 100 ml of ether, and then acidified with excess

6 *N* hydrochloric acid. Methanol (200 ml) was added and the mixture was stirred at 50° for 2 hr. The solid remaining after evaporation of the methanol was taken up in chloroform–ether and the solution was washed with two 50-ml portions of 2 *N* sodium hydroxide and brine. Crude **31a** obtained by evaporating the dried ($MgSO_4$) solution amounted to 9.1 g (>100%). Recrystallization from 70 ml of acetonitrile yielded 5.25 g (63%) of white needles: mp 180–188°; $[\alpha]^{25}D$ −52.5°; ir (KBr) 1774 cm^{-1}; nmr δ 1.00, 1.07 (d, C-18). C-18 peak heights appeared in the ratio 3.1:1.

Anal. Calcd for $C_{28}H_{32}O_3$: C, 80.74; H, 7.74. Found: C, 80.97; H, 7.86.

A second crop of **31a** was obtained from 150 ml of ethanol amounting to 1.80 g (22%), mp 160–164°, with C-18 peak heights at δ 1.00 and 1.07 in the ratio 1:1.7. The combined yield amounted to 7.05 g (85%).

2. Isomerization of 31a with Potassium *tert*-Butoxide.—To a solution of 0.70 g (5 × 3.6 mg-atoms) of potassium in 50 ml of *tert*-butyl alcohol was added 1.50 g (3.6 mmol) of **31a** with C-18 nmr peaks at 60 and 64 Hz in the ratio 3.1:1. After heating to reflux under nitrogen for 16 hr, the cooled mixture was acidified with 2.1 g (10 × 3.6 mmol) of acetic acid and the solvent was evaporated. The residue was stirred with chloroform and water, and the dried chloroform solution was evaporated. Trituration with 15 ml of ethanol yielded 1.10 g (73%) of isomerized **31a**, mp 153–155°, with C-18 nmr peaks at 61 and 65 Hz in the ratio 1:2.4.

3. 4′-Cyclohexyl-4′,5′-dihydro-3-methoxy-(17*R*)-spiro[estra-1,3,5(10)-triene-17,2′(3′*H*)-furan]-5′-one (31b).—Metalated cyclohexylacetic acid was prepared on a 60-mmol scale as a heterogeneous mixture in 150 ml of THF following general procedure B. A solution of 6.0 g (20 mmol) of **18** in 25 ml of THF was added and the stirred mixture was warmed to 45–50° for 18 hr.

At the conclusion of the reaction period, 150 ml of water and 100 ml of hexane were added to the homogeneous solution. The aqueous layer was separated and the reaction flask and organic layer were washed with a mixture of 100 ml of water and 100 ml of ether. The aqueous layers were combined, back-extracted with 100 ml of ether, and acidified with excess 6 *N* hydrochloric acid. Methanol (200 ml) was added and the warm (50°) mixture was stirred for 2 hr. The solids remaining after removal of the methanol were taken up in chloroform–ether and the solution was washed with two 50-ml portions of 2 *N* sodium hydroxide and brine. Crude **31b** obtained by evaporating the dried ($MgSO_4$) solution amounted to 7.5 g (89%). Recrystallization from ethanol gave white needles: mp 143–146°; $[\alpha]^{25}n$ −16.3°; ir (KBr) 1768 cm^{-1}; nmr δ 0.92, 0.98 (d, C-18). The peak heights appeared in the ratio 3.1:1.

Anal. Calcd for $C_{28}H_{38}O_3$: C, 79.58; H, 9.07. Found: C, 79.60; H, 8.80.

4. Isomerization of 31b with Potassium *tert*-Butoxide.—To a solution of 1.0 g (5 × 5 mg-atoms) of potassium in 50 ml of *tert*-butyl alcohol was added 2.1 g (5 mmol) of **31b** with C-18 nmr peaks at 55 and 59 Hz in the ratio 3.1:1. After heating to reflux under nitrogen for 18 hr, the cooled solution was acidified with 3.0 g (50 mmol) of acetic acid and the solvent was evaporated. The residue was stirred with chloroform and water, and the dried chloroform solution was evaporated. The pooled crystalline fractions obtained by eluting an alumina column with hexane–benzene amounted to 2.0 g (95%). The pooled material showed C-18 nmr peaks at 55 and 59 Hz in the ratio 1:4.3. The sample displayed mp 143–147° after recrystallization from 90% acetic acid: $[\alpha]^{25}D$ −14.7°; ir (KBr) 1770 cm^{-1}; nmr δ 1.08, 1.15 (d, C-18); peak height ratio, 1:9.4.

Anal. Calcd for $C_{28}H_{38}O_3$: C, 79.58; H, 9.07. Found: C, 79.58; H, 8.90.

Registry No.—**2**, 847-75-6; **2** acetate, 34414-55-6; **3a**, 19605-33-5; **3b**, 31552-58-6; **4a**, 19605-34-6; **4b**, 34414-59-0; **5a**, 34414-60-3; **5b**, 34414-61-4; **5c**, 16387-03-4; **5d**, 13934-61-7; **5e**, 34414-64-7; **5f**, 34414-65-8; **5g**, 34414-66-9; **5h**, 34414-67-0; **6a** (M^+ = Li^+), 31509-80-5; **8a**, 34414-69-2; **8b**, 34414-70-5; **8c**, 34414-71-6; **8d**, 976-70-5; **8e**, 34414-73-8; **8f**, 34440-55-6; **9a**, 34440-56-7; **9b**, 34440-57-8; **9c**, 34440-58-9; **10a**, 34440-59-0; **10b**, 34440-60-3; **10c**, 34440-61-4; **12**, 34440-62-5; **13**, 34440-63-6; **14a**, 34440-64-7; **14b**, 18290-18-1; **14c**, 34440-66-9; **15**, 34440-67-0; **16a**, 18290-22-7; **16b**, 34427-52-6; **17**, 20929-21-9; **22**, 34440-70-5; **23**, 34440-71-6; **24**, 34440-72-7; **25**, 34440-73-8; **26**, 34440-74-9; **27**, 20215-55-8; **29**, 34440-76-1; **30**, 34440-77-2; 21*R*-**3a**, 34440-78-3; 21*S*-**31a**, 34440-79-4; 21*R*-**31b**, 34440-80-7; 21*S*-**31b**, 34440-81-8; acetic acid, 64-19-7; lithium diisopropylamide, 34440-82-9.

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Stereoselective Alkylation Reactions. I. Organomagnesium and Organoaluminum Addition to 4-*tert*-Butylcyclohexanone. Unusual Stereoselectivity Involving Trimethylaluminum Alkylation in Benzene

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The stereochemistry of addition of methylmagnesium and methylaluminum compounds to 4-*tert*-butylcyclohexanone in several solvents has been studied. Specifically methylmagnesium fluoride, chloride, bromide, and iodide, dimethylmagnesium, and trimethylaluminum were allowed to react with 4-*tert*-butylcyclohexanone in hexane, benzene, diethyl ether, tetrahydrofuran, diphenyl ether, and triethylamine. Reactions involving organomagnesium compounds and trimethylaluminum in diethyl ether and tetrahydrofuran results in predominant equatorial attack to form the axial alcohol product (~73%) regardless of the halide and the mode of addition. In reactions involving trimethylaluminum in hydrocarbon solvent where the $(CH_3)_3Al$:ketone ratio is 1:1, similar results are observed. However, when the ratio is 2:1 or greater a drastic reversal of the stereochemistry is observed resulting in predominant axial attack to form the equatorial alcohol (~90%). The mechanism and stereochemistry of these reactions are discussed.

The steric course of organometallic alkylation and metal hydride reduction reactions involving cyclic ketones is a very fundamental problem in organic chemistry which does not seem to be well understood. It was originally proposed by Dauben and coworkers[1] that the course of hydride reduction reactions is de-

(1) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, **78**, 2579 (1956).

termined primarily by the relative stabilities of the two isomeric products in the absence of significant steric influence involving the attacking reagent on the substrate. However, when steric influences are sufficiently large, the reaction path can change from axial attack to equatorial attack, producing the less stable isomer. These reaction paths are termed "product development control" and "steric approach control," respectively. As shown in Table I, for addition reactions involving

TABLE I

ADDITION REACTIONS TO 4-*tert*-BUTYLCYCLOHEXANONE[a]

Reagent	*A*[b]	Axial alcohol, %
$LiAlH_4$	0	8[c]
$LiAlH[OC(CH_3)_3]_3$	0	10[d]
HCN	0.17	10[e]
HC≡CH	0.18	11[f]
CH_2=$CHCH_2MgBr$		48[g]
CH_3MgBr	1.70	60[h]
C_2H_5MgBr	1.75	69[i]
n-C_3H_7MgBr		74[g]
$(CH_3)_2CHMgBr$	2.15	82[i]
$(CH_3)_3CMgCl$	>4.2	100[i]

[a] In $(C_2H_5)_2O$ except for $LiAlH[OC(CH_3)_3]_3$, HCN, and HC≡CH. [b] See ref 2. [c] See ref 3. [d] See ref 4. [e] See ref 5. [f] See ref 6. [g] See ref 7. [h] See ref 8a. [i] See ref 8b.

4-*tert*-butylcyclohexanone the relative amount of the trans alcohol obtained from equatorial attack increases as the size of the entering groups increases.[2-8]

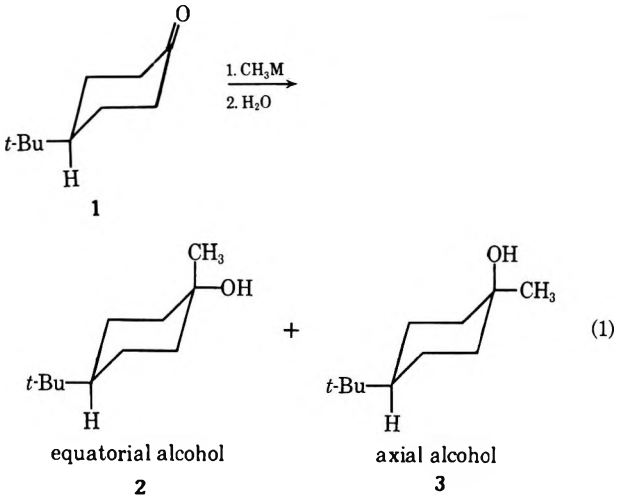
An alternate explanation based on pure steric approach has been suggested.[4] For a small entering group which does not interfere with the 3,5 axial substituents, the reaction will be directed exclusively by the 2,6 axial substituents, which hinder equatorial attack. However, as the size of the entering group becomes larger, the interactions with 3,5 axial substituents increase and the reaction proceeds in favor of equatorial attack. This proposal was later supported and advanced by a consideration of the transition-state geometry.[9] The relative magnitudes of the interaction of 3,5 and 2,6 axial substituents with the entering group is purely based on the transition-state bond lengths; *i.e.*, the extent of axial attack will increase as the bond distance decreases. Therefore, the greater domination by the 3,5 axial substituents in the case of Grignard alkylation reactions can be rationalized on the basis that the transition state for the addition of a Grignard reagent occurs at a greater distance from the carbonyl carbon than the analogous addition of the hydride.

Later, the relative magnitudes of "torsional strain" with respect to equatorial attack and of "steric strain" with 3,5 axial substituents with respect to axial attack in the reactantlike transition state were claimed to be the major factors controlling the stereochemistry of hydride reduction and alkylation reactions.[7] In the reactions between hydrides and unhindered cyclohexanones, the "steric strain" in axial attack is expected to be smaller than the "torsional strain" in equatorial attack; therefore the predominant alcohol is the equatorial one from axial attack. However, as the "effective bulk" of the entering groups or the 3,5 axial substituents become larger, the situation is reversed. It has also been pointed out that the "effective bulk" of the entering reagent depends not only on the "intrinsic bulk" but also on solvation, the bond distance in the transition state, and the mechanism of the reaction.

Although organometallic alkylation reactions have found extensive applications in synthesis, this type of reaction has attracted much less attention in comparison with metal hydride reduction reactions with respect to stereochemical studies. In view of the recent better understanding of both the composition of organometallic compounds in solution and the mechanisms of organometallic alkylation reactions, we feel that a better understanding of the stereochemistry of such reactions is now possible.

An ideal system for investigating the stereochemistry of organometallic alkylation reactions involves the reaction of 4-*tert*-butylcyclohexanone (1) with trimethylaluminum and methyl Grignard reagents. Studies involving Grignard reagents are desirable because of the wide scope and versatility of these reagents, and studies involving trimethylaluminum are desirable since this reagent is soluble in both ether and hydrocarbon solvents and thus solvent effects can be evaluated.

As shown in eq 1, the reaction gives a mixture of the



equatorial and axial alcohols. Since alkylation reactions involving trimethylaluminum can give no reduction product and involve reaction of only one of the methyl groups,[10,11] results involving this compound should provide the least complicated data. Furthermore, the mechanisms of trimethylaluminum addition to ketones are well understood both in benzene[10] and in diethyl ether.[11] This reaction is known to proceed *via* two distinct mechanistic paths depending on the ratio of $(CH_3)_3Al$ to ketone. At 1:1 ratio the reaction is first order in $(CH_3)_3Al$ and is presumed to proceed *via* a four-center transition state, whereas at 2:1 ratio (or greater) the reaction is second order in $(CH_3)_3Al$ and is presumed to proceed *via* a six-center transition state.

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(11) E. C. Ashby and J. Laemmle, *J. Org. Chem.*, **33**, 3389 (1968).

TABLE II
REACTIONS OF 4-*tert*-BUTYLCYCLOHEXANONE WITH TRIMETHYLALUMINUM

Solvent	Expt	$(CH_3)_3Al$/ketone	Concn of $(CH_3)_3Al$, *M*	Time	Recovery of ketone, %	Total yield of alcohol products, %	Yield of axial alcohol, %[a]
Benzene	1	3.00	0.475	1.0 hr	0	89	12[d]
Benzene	2	3.00	0.475	2.0 hr	0	87	17
Benzene	3	2.00	0.448	2.0 hr	0		17
Benzene	4	1.50	0.405	2.0 hr	34		53
Benzene	5	1.00	0.369	2.0 hr	48		73
Benzene	6	1.00	0.0224	2.0 hr	58		74
Benzene	7	1.00	1.205	2.0 hr	44		56
Benzene	8	0.50	0.278	2.5 hr	75		80
Hexane	9	4.50	0.54	2.0 hr	0	90	9
$(C_6H_5)_2O$[c]	10	3.08	0.329	6 days	0	99	15
$(C_6H_5)_2O$	11	1.54	0.269	5 days	3	70	26
$(C_6H_5)_2O$	12	1.03	0.228	6 days	23	56	53
$(C_6H_5)_2O$	13	0.79	0.176	4 min	49	39	72
				5 days	33	37	72
$(C_6H_5)_2O$	14	0.49	0.116	6 days	21	30	72
THF	15	3.02	0.211	3 days	53	12	74
				38 days	20	16	73
THF	16	2.94	0.308	3 days	55	15	74[c]
THF	17	1.03	0.164	3 days	55	10	72[c]
THF	18	1.00	0.176	3 days	53	8	73
THF	19	0.50	0.042	16 days	35	5	73
				38 days	26	7	73
$(C_2H_5)_2O$[c]	20	3.01	0.329	4 days	38	40	75
$(C_2H_5)_2O$	21	0.51	0.141	4 days	20	23	74
$(C_2H_5)_3N$[c]	22	3.08	0.329	6 days	31	0	*b*
$(C_2H_5)_3N$	23	1.03	0.228	6 days	19	0	*b*
$(C_2H_5)_3N$	24	0.49	0.116	6 days	21	0	*b*

[a] Normalized per cent: per cent trans + per cent cis = 100. [b] No measurement was made. [c] The reactions were carried out using benzene solutions of $(CH_3)_3Al$ and ketone containing the polar solvent. [d] Ketone added to $(CH_3)_3Al$.

In addition, numerous stereochemical addition studies[8,12] have already been carried out using ketone **1**, which should make the present studies easier to interpret. Although the importance of the solvent involved in these reactions is well recognized, it is surprising that systematic studies of the solvent effect on stereochemical addition are very limited. Therefore, the reaction of trimethylaluminum and ketone **1** in several selected solvents was undertaken. Since methylmagnesium fluoride has recently been prepared in this laboratory in tetrahydrofuran and shows unique properties,[13] it was decided to investigate the behavior of this particular reagent and other Grignard reagents toward 4-*tert*-butylcyclohexanone under the same conditions involving alkylation with trimethylaluminum. Since trimethylaluminum is known to react with ketones by two different mechanistic paths in benzene solvent, the determination and comparison of equatorial to axial alcohol ratios obtained *via* each mechanistic path and further comparison with ratios found for Grignard reagent alkylation was considered to be most important.

Experimental Section

Materials.—Trimethylaluminum was obtained from Texas Alkyls, Inc., and was purified by distillation under vacuum through a 1-ft packed column, taking the center cut for the present studies. 4-*tert*-Butylcyclohexanone (Frinton) was distilled under vacuum and its purity was estimated by glpc to be at least 99.9%. Tetradecane (99.9% pure, Chemical Samples Co.) was used as an internal standard in the glpc analyses. Methylmagnesium fluoride was prepared as described previously.[13a] Clear and colorless solutions of methylmagnesium chloride and bromide were prepared by reaction of methyl halides with magnesium turnings (doubly sublimed, Dow Chemical Co.) in tetrahydrofuran. Dimethylmagnesium was prepared from the corresponding mercury compound by reaction with magnesium metal.[14] Benzene, hexane, diethyl ether, tetrahydrofuran (THF), diphenyl ether, and triethylamine were distilled from lithium or sodium aluminum hydride prior to use.

Analyses.—The concentrations of trimethylaluminum solutions were determined by hydrolysis of an aliquot followed by aluminum analysis. Aluminum analysis was carried out by EDTA–zinc acetate titration at pH 4 using dithizone as an indicator. The concentrations of Grignard reagent solutions were determined by hydrolysis of an aliquot followed by magnesium analysis. Magnesium analysis was carried out by EDTA titration at pH 10 using Eriochrome Black T as an indicator.

Glpc analyses were performed using 6-ft matched columns of 10% FFAP on 80–100 mesh Diatoport S. The identity of the peaks was determined by comparison of the hydrolyzed products formed on reaction of ketone **1** with methyllithium and methylmagnesium bromide.[12d] Under the conditions of rate 55 ml/min, injection temperature 200°, and detector temperature 310°, the retention times for tetradecane, cis alcohol, ketone, and trans alcohol are 12, 28, 31, and 36 min at a column temperature of 80°. The two alcohols are known to have the same response ratio.[15] In no case was the presence of 1-methyl-4-*tert*-butylcyclohexanone (from the dehydration of the alcohols) detected.[12d] The amount of the recovered ketone was calculated from the area ratio of ketone to internal standard before and after the reaction.

Reactions.—All the reactions were carried out under a nitrogen atmosphere and the glassware was flash flamed and flushed with nitrogen prior to use. The standard solutions of trimethylaluminum and 4-*tert*-butylcyclohexanone in benzene and in THF

(12) (a) W. J. Houlihan, *J. Org. Chem.*, **27**, 3860 (1962); (b) ref 8a; (c) J. L. Namy, E. Henry-Basch, and P. Freon, *C. R. Acad. Sci., Ser. C*, **268**, 1607 (1969); (d) P. R. Jones, E. J. Goller, and W. J. Kauffman, *J. Org. Chem.*, **34**, 3566 (1969); (e) P. R. Jones, W. J. Kauffman, and E. J. Goller, *ibid.*, **36**, 186 (1971).

(13) (a) E. C. Ashby and S. H. Yu, *J. Org. Chem.*, **36**, 2123 (1971); (b) E. C. Ashby and S. H. Yu, *J. Organometal. Chem.*, **29**, 339 (1971).

(14) E. C. Ashby and R. C. Arnott, *J. Organometal. Chem.*, **14**, 1(1968).

(15) J. J. Uebel and H. W. Goodwin, *J. Org. Chem.*, **33**, 3317 (1968).

TABLE III
REACTIONS OF 4-*tert*-BUTYLCYCLOHEXANONE WITH METHYLMAGNESIUM COMPOUNDS

Reagent	Expt	Solvent	CH_3MgX/ ketone	Concn of CH_3MgX, *M*	Time, hr	Recovery of ketone, %	Total yield of alcohol products, %	Yield of axial alcohol, %[a]
$(CH_3)_2Mg$	25	THF	3.04	0.25	20	2	98	74
$(CH_3)_2Mg$	26	THF	3.04	0.25	20	2	85	75[b]
$(CH_3)_2Mg$	27	THF	0.52	0.06	0.2	75	19	74
					20	53	18	74
$(CH_3)_2Mg$	28	$(C_2H_5)_3N$	1.49	0.10	8	20	56	76
$(CH_3)_2Mg$	29	$(C_2H_5)_3N$	0.55	0.08	1	34	39	76
					8	23	40	77
$(CH_3)_2Mg$	30	Benzene	3.50	0.96	0.5	27	52	72
			0.47	0.15	0.5	48	32	68
CH_3MgF	31	THF	3.2	0.61	20	1	92	73
	32	THF	0.53	0.17	20	55	29	74
CH_3MgBr	33	THF	2.8	0.37	20	0	97	70
	34	THF	0.47	0.10	20	42	26	72
CH_3MgCl	35	THF	3.0	0.49	20	1	100	71
	36	THF	0.52	0.23	20	29	37	71

[a] Normalized per cent: per cent trans + per cent cis = 100. [b] With the addition of 5% of $CoCl_2$.

were stored in a heavy-walled glass bulb sealed with a three-way Teflon stopcock. The reactions were carried out in 15-ml bottles fitted with a rubber septum cap.

The following standard procedure will serve to illustrate the reactions in benzene. A 1.6-ml standard benzene solution of trimethylaluminum (0.985 *M*, 1.58 mmol) was added *via* a syringe into a bottle containing 3 ml of benzene and 1 ml of standard benzene solution of ketone 1 (0.479 *M*, 0.479 mmol) with internal standard at 25°. After the reaction was completed, the solution was cooled in an ice bath and slowly hydrolyzed with 2 ml of saturated ammonium chloride solution. Analysis was carried out by glpc as previously described. The reactions of methylmagnesium compounds were carried out in a similar fashion.

Results

The results of the reactions of 4-*tert*-butylcyclohexanone with trimethylaluminum and methylmagnesium compounds are summarized in Tables II and III. The following observations can be noted by examination of the tables.

1. The stereochemical results of the reactions of trimethylaluminum in benzene and in diphenyl ether are dependent on the ratio of trimethylaluminum to ketone. The amount of axial alcohol decreases from 80% to 12% in benzene and from 72% to 15% in diphenyl ether as the $(CH_3)_3Al$ to ketone ratio increases. On the other hand, the stereochemical results in diethyl ether and tetrahydrofuran are independent of the $(CH_3)_3Al$ to ketone ratio and give a 72–74% yield of axial alcohol in both solvents. The reactions of $(CH_3)_3Al$ and ketone in triethylamine give no addition product.

2. The presence of a weakly coordinating solvent, such as benzene (runs 16 and 17), in the reaction of $(CH_3)_3Al\cdot THF$ with ketone, or addition of a free radical promoter, $CoCl_2$ (run 26), in the reaction of $(CH_3)_2Mg\cdot THF$ with ketone has no effect on the stereochemical results.

3. The stereochemical results of the reactions of methylmagnesium compounds in THF were also independent of the ratio of reactants and the yield of axial alcohol (71–75%) was essentially independent of the particular methylmagnesium compound used. Reaction of dimethylmagnesium with ketone in triethylamine gave results similar to those observed in THF.

4. The isomeric ratios in all reactions studied are independent of reaction time. Consequently, isomer equilibration is not a factor under the conditions of these reactions.

5. The reactions with excess methyl metallic compounds yield predominantly the alcohols with little enolization. However, the reactions with excess ketone and of trimethylaluminum in the more basic solvents appear to produce a considerable amount of higher molecular weight products from aldol condensation.[12b]

Discussion

The results of the present and previous studies concerning the stereochemistry of methyl metallic compound addition to 4-*tert*-butylcyclohexanone are summarized in Table IV. If a true understanding of these stereochemical results is to be forthcoming, one should consider in detail the mechanism of the alkylation reactions involved and the nature of the organometallic species present in solution.

Association of the Organometallic Alkylation Agent. — The composition of methyl metallic compounds in both hydrocarbon and ether solvents is reasonably well understood at the present time. Methyllithium is tetrameric in diethyl ether.[16] Methylmagnesium compounds are best represented by an equilibrium-type association (eq 2) in diethyl ether,[17] except methyl-

$$\text{trimer} \rightleftharpoons \text{dimer} \rightleftharpoons 2RMgX \rightleftharpoons R_2Mg + MgX_2 \rightleftharpoons \text{dimer} \rightleftharpoons \text{trimer} \quad (2)$$

magnesium fluoride[13b] and $CH_3MgOC(C_2H_5)_2CH_3$,[18] which are dimeric. All methylmagnesium halides and dimethylmagnesium are monomeric in tetrahydrofuran[17c] and triethylamine,[19] except methylmagnesium fluoride, which is dimeric in tetrahydrofuran.[13b] Trimethylaluminum is dimeric in benzene[20] and diphenyl ether,[21] is monomeric in diethyl ether,[22] and is

(16) P. West and R. Waack, *J. Amer. Chem. Soc.*, **89**, 4395 (1967).
(17) F. Walker and E. C. Ashby, *ibid.*, **91**, 3845 (1969).
(18) G. E. Coates, J. A. Heslop, M. E. Redwood, and D. Redley, *J. Chem. Soc. A*, 1118 (1968).
(19) E. C. Ashby and W. E. Becker, *J. Amer. Chem. Soc.*, **85**, 118 (1963).
(20) (a) N. Muller and P. E. Pritchard, *ibid.*, **82**, 248 (1960); (b) K. C. Williams and T. L. Brown, *ibid*, **88**, 5460 (1966).
(21) K. Hatada and H. Yuki *Tetrahedron Letters*, 213 (1968).
(22) E. C. Ashby, J. Carter, and J. R. Sanders, unpublished results.

TABLE IV

REACTIONS OF 4-*tert*-BUTYLCYCLOHEXANONE WITH METHYL METALLIC COMPOUNDS

Reagent	Registry no.	$(C_2H_5)_2O$ Association	$(C_2H_5)_2O$ Axial alcohol, %	THF Association	THF Axial alcohol, %
CH_3Li	917-54-4	4	64[a]		
$(CH_3)_2Mg$	2999-74-8	1–2[b]	65[c]	1	74
CH_3MgF	420-09-7			2	74
CH_3MgCl	676-58-4	2	59[d]	1	71
CH_3MgBr	75-16-1	1–2[b]	61[a,c]	1	71
CH_3MgBr		1–2[b]			
CH_3MgBr		1[e]	68[a]		
CH_3MgI	917-64-6	1–2[b]	54[a]		
CH_3MgI		1[e]	62[a]		
$CH_3MgOCCH_3(C_2H_5)_2$	13132-19-9	2	74[c]		
$(CH_3)_3Al$	75-24-1	1	75[f]	1	73
$(CH_3)_2Zn$	544-97-8	1	38–46[a]		
$(CH_3)_2Cd$	506-82-1	1	41–54[a]		

[a] See ref 12d. [b] Monomer ⇄ dimer equilibrium at the concentrations employed. [c] See ref 12b. [d] See ref 12a. [e] Monomeric at 0.1 *M*. [f] Namy, *et al.*,[12c] report 75% at 35°.

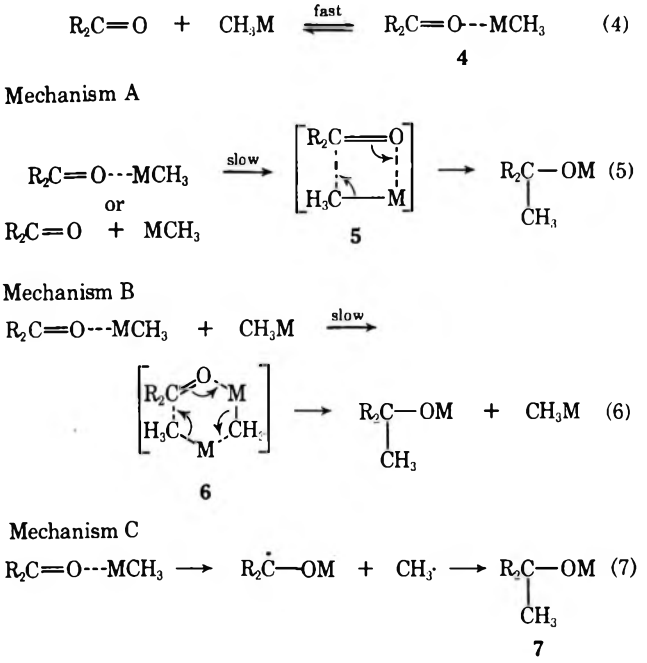
expected to be monomeric in tetrahydrofuran and triethylamine. Dimethylzinc and dimethylcadmium are monomeric in diethyl ether.[23]

Importance of the Alkylation Mechanism.—Three mechanisms of addition reactions of organometallic compounds with ketones have been proposed from kinetic studies. In spite of the fact that most organometallic compounds are associated in solution, it is believed that it is the monomeric species (eq 3) that

$$(CH_3M)_n \rightleftharpoons nCH_3M \qquad (3)$$

reacts with the ketone to form a complex **4** in a fast equilibrium step (eq 4).[10,24] The product is then formed either by a relatively slow intramolecular rearrangement of the complex or by a bimolecular attack,[25] both presumably *via* a cyclic four-center transition state **5** (mechanism A), by a relatively slow attack on the complex by a second molecule of monomeric organometallic species, presumably *via* a cyclic six-center transition state **6** (mechanism B), or by a single electron transfer mechanism involving free radical intermediates (mechanism C).

Compared to most organometallic alkylation reactions the mechanism of aluminum alkyl addition to ketones seems to be well understood. The reaction path in benzene is dependent on the ratio of reactants. The reaction proceeds entirely *via* mechanism A when the aluminum alkyl to ketone ratio is 1:1 or less and entirely *via* mechanism B when the aluminum alkyl to ketone ratio is 2:1 or greater.[10] However, the same reaction in diethyl ether proceeds *via* mechanism A independent of the ratio of reactants.[11] Since the reaction of organomagnesium compounds with ketones has proven to be very complex kinetically for a number of reasons, the mechanism has been the subject of considerable controversy for a number of years. Only recently have we determined unequivocally that this reaction is first order in the organomagnesium species.[26]



Thus, this reaction does not proceed by mechanism B as originally thought.[27] The existence of mechanism C as a major pathway has been overruled at least in the cases where methyl Grignard reagents prepared from ultrapure magnesium metal[28] are allowed to react with excess benzophenone[26] in diethyl ether. Presumably when Grignard reagents prepared from triply sublimed magnesium or Grignard grade turnings,[28] ketones of low reduction potential,[29] or Grignard reagents capable of easy electron transfer, *e.g.*, *tert*-BuMgBr,[30] are used in the reaction, mechanism C can participate to a significant degree. Since mechanism C presumably represents a side reaction and not a major reaction pathway under the conditions of our studies, only

(23) K. S. Rao, B. P. Stoicheff, and R. Turner, *Can. J. Phys.*, **38**, 1516 (1960).

(24) R. Waack and M. A. Doran, *J. Amer. Chem. Soc.*, **91**, 2456 (1969).

(25) Kinetically it is impossible to distinguish between the reaction as proceeding *via* rearrangement of the complex (1) or by bimolecular attack (2): (1) K + G ⇌ C → P or (2) P ← K + G ⇌ C.

(26) E. C. Ashby, J. Laemmle, and H. M. Neumann, *J. Amer. Chem. Soc.*, **93**, 4601 (1971).

(27) (a) A. Tuulmets, *Reakts. Sposobnost Org. Soedin.*, **6**, 854 (1969); (b) J. Koppel, L. Margus, and A. Tuulmets, *ibid.*, **5**, 1041 (1968); (c) E. C. Ashby, R. Duke and H. M. Neumann, *J. Amer. Chem. Soc.*, **89**, 1964 (1967).

(28) E. C. Ashby, F. W. Walker, and H. M. Neumann, *J. Chem. Soc. D*, 330 (1970).

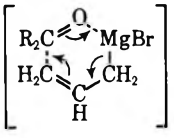
(29) J. F. Fauvarque and E. Rouget, *C. R. Acad. Sci., Ser. C*, 1355 (1971).

(30) T. Holm and I. Crossland, *Acta Chem. Scand.*, **25**, 59 (1971).

mechanism A[26,31] will be considered in discussions of reactions involving methyl Grignard compounds. Since the reactions of organolithium compounds with ketones are extremely fast, there are few reports concerning detailed mechanistic studies of this reaction and thus the mechanism still remains in doubt.

The results of this investigation are represented by the data in Table II. The reactions of $(CH_3)_3Al$ with ketone **1** in diethyl ether and THF give ~73% of the axial alcohol (equatorial attack) regardless of the ratio of alkylating agent to ketone. When the $(CH_3)_3Al$ to ketone ratio in benzene or diphenyl ether was 1:1 or less, similar results were observed (~80% axial alcohol). Likewise the reactions of $(CH_3)_2Mg$, CH_3MgF, CH_3MgCl, and CH_3MgBr in THF give similar results (~73% axial alcohol). On the other hand, the reaction of $(CH_3)_3Al$ in benzene or diphenyl ether with ketone **1** gives substantially different results (~88% equatorial alcohol or 88% axial attack) when the $(CH_3)_3Al$ to ketone ratio is 2:1 or greater.

The unusual stereochemical results found for the reaction of trimethylaluminum with 4-*tert*-butylcyclohexanone in benzene can be explained on the basis that the reaction had previously been shown to proceed by two distinct paths depending on the $(CH_3)_3Al$ to ketone ratio: *via* mechanism A under conditions of excess ketone and *via* mechanism B under conditions of excess aluminum alkyl. Thus, the two different mechanistic paths produce substantially different stereochemical results, namely 88% axial attack when the $(CH_3)_3Al$ to ketone ratio is 2:1 or greater (mechanism B) and 80% equatorial attack when the ratio is 1:1 or less (mechanism A). A previous report[7] concerning the stereochemistry of reactions of ketone **1** with similar "intrinsic bulk" reagents, allyl- and *n*-propylmagnesium bromide, showed that allylmagnesium bromide exhibited considerably more axial attack than the *n*-propyl compound, presumably because of the cyclic six-centered transition state **7**[32] possible in the



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reaction of the allylic Grignard compound. In this reaction 52% of the equatorial attack (axial attack) is formed using allylmagnesium bromide whereas 26% is formed using *n*-propylmagnesium bromide (Table I). The actual reasons for the unusual stereochemical results obtained from the reactions *via* a six-centered transition state are subtle. However, one of the possible reasons involves the flexibility of the resulting six-centered transition state (**6** and **7**) resulting in a minimization of steric interactions. Thus, axial attack *via* **6** should be a lower energy pathway than that experienced *via* **5**, which is presumably the transition state involved in the reactions involving *n*-propylmagnesium bromide. Clarification of this latter point revolves about the following argument. The results obtained from the reactions of trimethylaluminum and methylmagnesium compounds in diethyl ether and tetrahydrofuran are independent of the ratio of reactants. Therefore, these reactions presumably proceed *via* only one mechanism. Furthermore, since the amount of trans alcohol obtained from these reactions is close to the 75% observed in the reaction of trimethylaluminum in diethyl ether, the present data indicate that the reaction of ketones with Grignard reagents proceeds *via* mechanism A in spite of the controversial results obtained from previous kinetic studies.[26,31]

The answer to the question as to why the six-centered transition produces substantially different stereochemical results than the four-centered transition can also be explained by a mechanism involving a transition state in which the cyclohexane ring is in the boat form. In the boat form, attack should take place preferentially at the position opposite to the flagpole hydrogen. When the ring flips back to the chair form, the alkyl group is in the axial position and the bulky $OAL(CH_3)_2$ group is in the more favorable equatorial position. We have recently determined E_a for the reaction of $(CH_3)_3Al$ with benzophenone in benzene in 1:1 ratio to be 19.2 kcal and in 2:1 ratio to be 10.9 kcal.[33] Assuming that the boat conformation in a cyclohexanone derivative is of somewhat lower energy (3–5 kcal) than a cyclohexane derivative (6 kcal) owing to the absence of 1–4 flagpole interactions, the proposal of a boat conformation is well within the existing energy considerations. There seems to be no preference at this time for either the chair or boat mechanism. It is believed that similar stereochemical studies using *cis*-3-methyl-4-*tert*-butylcyclohexanone should resolve this problem. With an axial 3-methyl group in the 4-*tert*-butylcyclohexanone system, axial attack should be deterred if the reaction proceeds through the chair conformation and should be relatively undisturbed if the reaction proceeds through the boat conformation. Work is in progress to distinguish between these two possibilities.

Importance of Solvent.—Before discussion of the importance of the solvent in determining the stereochemistry of organometallic alkylation reactions, the number of solvent molecules coordinated to the organometallic compound must be considered. Trialkylaluminum compounds have been investigated by nmr and found to coordinate to only 1 mol of solvent [THF, $(C_2H_5)_2O$, and $(C_2H_5)_3N$].[34] A sharp break in the curve produced on plotting chemical shift *vs.* mole fraction at 1:1 ratio in toluene was observed. Furthermore, the monoetherates of trimethylaluminum and diethyl ether or tetrahydrofuran are distillable under vacuum.[22] Organomagnesium compounds are normally coordinated with 2 mol of solvent, as reported by analysis, molecular weights,[35] and nmr[36] studies.

Unfortunately, the role of solvent in the addition reaction is usually neglected in the proposed mechanisms for the sake of simplicity. Recently, however, the importance of solvent in Grignard alkylation reactions has been discussed.[31d] Scheme I, using trimethylaluminum as the alkylating agent and S as the solvent

(31) (a) T. Holm, *ibid.*, **23**, 579 (1969); (b) J. Billet and S. G. Smith, *Tetrahedron Lett.*, 4467 (1969); (c) J. Billet and S. G. Smith, *J. Amer. Chem. Soc.*, **90**, 4108 (1968); (d) H. O. House and J. E. Oliver, *J. Org. Chem.*, **33**, 929 (1968); (e) S. G. Smith and J. Billet, *J. Amer. Chem. Soc.*, **89**, 6948 (1967).

(32) H. Felkin and G. Roussi, *Tetrahedron Lett.*, 4153 (1965).

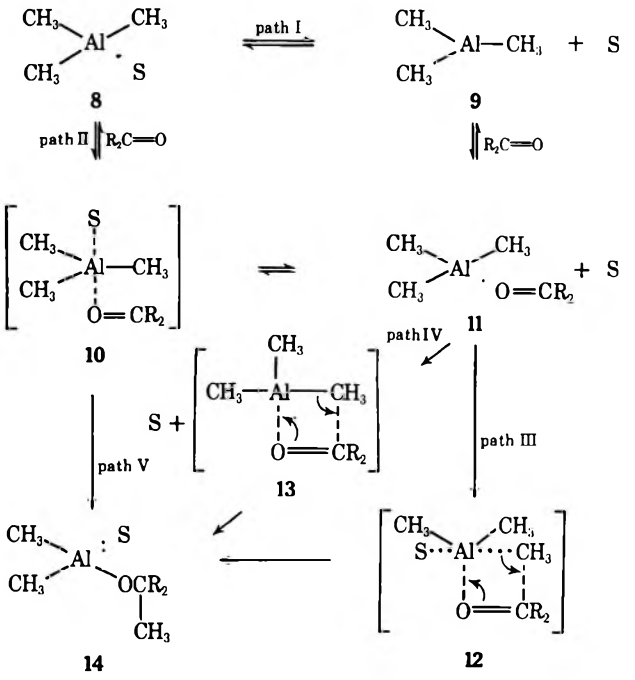
(33) E. C. Ashby and J. Laemmle, work in progress.

(34) Y. Takshi, *Bull. Chem. Soc. Jap.*, **40**, 612 (1967).

(35) G. E. Coates and J. A. Heslop, *J. Chem. Soc. A*, **26** (1966).

(36) J. Ducom, *C. R. Acad. Sci., Ser. C*, **268**, 1259 (1968).

SCHEME I

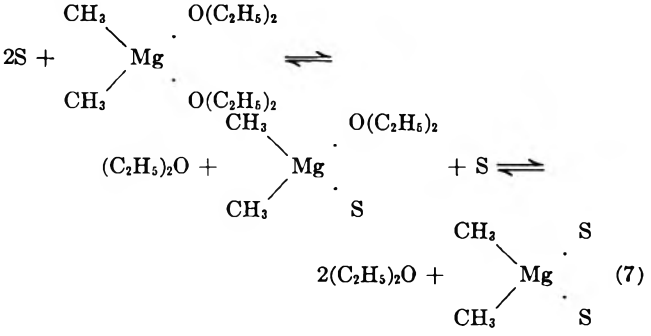


molecule, represents the possible reaction pathways involving alkylation reactions.

The solvent ligand can either be dissociated to form the tricoordinate intermediate **9**[37] (path I) or be displaced by the ketone *via* a pentacoordinate transition state **10** (path II) prior to the formation of the tetracoordinate complex **11**. The product **14** can be formed either with or without the presence of solvent in complex **11** by (1) rearrangement of the methyl group *via* a four-centered transition state involving pentacoordinate aluminum **12**[38] (path III) or (2) tetracoordinate aluminum **13** (path IV).

It appears reasonable to expect that the reaction path which requires the dissociation (path I) or the displacement (path II) of the ligand prior to formation of the complex will be retarded by the presence of a good donor solvent. Actually the decrease in reaction rate as the solvent basicity increases has been observed in the addition reagents of Grignard reagents to nitriles[39] and aluminum alkyls to ketones,[10,11] reduction of ketones with Grignard reagents,[40] abstraction of the acidic hydrogen atom from terminal acetylenes by Grignard reagents,[41] and exchange of alkyl groups between two different metal alkyls.[42]

The effect of solvent on the rate-determining product formation step *via* path III should be considered in some detail. For example, a strong donor solvent may accelerate the rate of alkyl transfer by assisting the dissociation of the carbon–metal bond in transition state **12**. However, in view of the rate retardation observed, if path III is followed, it is more likely that the nature of the ketone, the metal, and the alkyl group have a greater effect on the reaction rate than the solvent. However, the alternative possibility involving formation of a pentacoordinate transition state **10** without dissociation or displacement of the initial solvating ligand (path V) has been recently proposed from kinetic studies involving the reaction of benzophenone and dimethylmagnesium.[14e] Because the addition of monodentate ligands had little effect on reaction rate except on addition of a large excess of ligand and the addition of the bidentate ligands had a substantial effect either to accelerate or to retard the rate of addition reaction in diethyl ether, it was suggested that only the steric bulk properties of the ligand affects the reaction rate *via* transition state **10**. However, the same results can also be rationalized by mechanisms involving the loss of the initial solvating ligand. Equation 7 shows the exchange of ligands in a diethyl ether solution of dimethylmagnesium.



(7)

Since diethyl ether itself is a good donor ligand, the addition of a 1- to 2-fold excess of tetrahydrofuran (a better ligand) cannot shift the equilibrium completely to the right. However, since the equilibrium is expected to be very rapid, the reaction probably will proceed *via* the more active diethyl etherate species. Therefore, the significant retardation is only observed with a large excess of tetrahydrofuran. On the contrary, the bidentate ligands form a stable chelate. The addition of a small amount of these ligands can shift the equilibrium completely to the right and thus show a significant change in the reaction rate. The reasons for the different rates of the reaction with the addition of the bidentate ligands does not seem to be well understood. It is possible that the solvent effect on the product formation step (**10**, **12**) becomes important in the presence of the bidentate ligands. Thus, it appears that the relative magnitude of the solvent effects on the complex and product formation steps determines the acceleration or retardation of the reaction.

The stereochemical results obtained in diphenyl ether are similar to the results obtained in benzene. Initially this result might seem strange; however, it is known that trimethylaluminum and diphenyl ether form a weak solvate.[21] Thus, although free trimethylaluminum is present in low concentration (eq 8), the

$$(CH_3)_3Al \cdot O(C_6H_5)_2 \rightleftharpoons (CH_3)_3Al + O(C_6H_5)_2 \qquad (8)$$

unsolvated organometallic is so much more reactive than the solvated form that the entire reaction proceeds

(37) R. A. Kovar and G. L. Morgan [*J. Amer. Chem. Soc.*, **91**, 7269 (1969)] have presented evidence through nmr studies for the existence of a monosolvated–disolvated equilibrium in dimethylberyllium dimethyl sulfide. Furthermore, typical magnesium compounds are isolated as monoetherates from solution by vacuum drying at room temperature.

(38) Both pentacoordinate transition states **10** and **12** are assumed to be similar to the transition state in an S_N2 reaction; however, the leaving and attacking position of the solvent ligand are different in the two transition states.

(39) (a) H. Edelstein and E. I. Becker, *J. Org. Chem.*, **31**, 3375 (1966); (b) A. A. Scala and E. I. Becker, *ibid.*, **30**, 3491 (1965).

(40) S. V. Vitt, E. I. Khristove, and V. B. Bondorev, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, **8**, 1780 (1969).

(41) J. H. Wotiz and G. L. Proffitt, *J. Org. Chem.*, **30**, 1240 (1965).

(42) N. S. Ham and T. Mole, *Progr. Nucl. Magn. Resonance Spectrosc.*, **4**, 91 (1969).

through the unsolvated form. Such is not the case with other ethers such as diethyl ether. The diethyl etherate of trimethylaluminum is so stable that it can be distilled undissociated.

The amount of axial alcohol obtained from the reactions of trimethylaluminum in diethyl ether and tetrahydrofuran is independent of the ratio of reactants (Table II). Therefore, the reactions in tetrahydrofuran are expected to proceed only *via* mechanism A as in diethyl ether. It is interesting to note that the amount of axial alcohol obtained from the reaction with excess ketone in diphenyl ether is the same as in diethyl ether and tetrahydrofuran. The fact that the stereochemistry *via* mechanism A is independent of the nature of the solvent is compatable with the mechanism involving displacement or dissociation of the solvent prior to formation of the product. Without the loss of the solvent (path V), the amount of axial alcohol would be expected to increase as a function of the bulk property of the solvent from tetrahydrofuran to diethyl ether to diphenyl ether. The similar stereochemical results obtained from the reaction of $(CH_3)_3Al$ with excess ketone **1** in benzene (80%) as compared to the reactions in diethyl ether or THF (73%) indicate once again the absence of the solvent ligand in the transition state **13**.

The participation of at least one ether ligand in the transition state involving organomagnesium compounds has been indicated by asymmetric induction studies involving the reaction of dimethylmagnesium and benzaldehyde in the presence of an optically active ether.[43] Therefore, after one of the ligands is displaced, the remaining solvating ligand may affect the stereochemistry of addition in the case of organomagnesium compounds. However, the stereochemistry of the addition reactions of 3-*tert*-butylcyclopentanone with methyl-, ethyl-, and isopropylmagnesium compounds was found to be independent of the solvent [THF, $(C_2H_5)_2O$, and anisole].[44] In the present studies only small differences in stereochemistry are observed in the reactions of methylmagnesium compounds in diethyl ether and in tetrahydrofuran and dimethylmagnesium in triethylamine. These results indicate once again that solvent attachment to the metal in the transition state is not important.

The reaction rate and the product ratio of addition to reduction was found to decrease as the electropositivity of the metal in the organometallic compound varies from lithium to magnesium to aluminum and the halide in the Grignard compound varies from chloride to bromide to iodide. It is surprising to find out that the identity of the halide except iodide and the metal except aluminum in diethyl ether has little effect on the stereochemistry of the addition reaction in both tetrahydrofuran and diethyl ether (Table IV). It is most likely that the stereochemistry of alkylation is dependent on pure steric factors and the electronic factor plays only a minor role. Hence, the same stereochemical results do not imply the nature of the actual reacting species involved as suggested in a previous report.[12b]

Methylmagnesium alkoxide addition to 4-*tert*-butylcyclohexanone has been reported to give a higher axial alcohol yield than the corresponding methylmagnesium halides and the reaction was suggested to involve a different reaction species.[12b] Indeed, recent kinetic studies from this laboratory concerning the reaction of excess benzophenone with dimethylmagnesium show that the alkoxide $[CH_3MgOC(CH_3)(C_6H_5)_2]$ is an intermediate reacting species and it reacts as a dimer.[24a] This result is compatible with the prediction that the bulkier dimer should result in more equatorial attack.

A recent report suggested that the stereochemistry of addition is a function of the association of the reacting species.[12d] According to this suggestion the reactions of methylmagnesium bromide and iodide at 0.1 and 0.8 *M* concentration in diethyl ether should lead to less axial alcohol at the lower concentration, which is exactly the reverse of the observed results (Table IV). Previous studies from this laboratory indicate that the monomer is the reaction species regardless of the degree of association. If the monomer is the reactive species, regardless of the concentration, then the amount of axial product should increase with a decrease in concentration owing to the increased selectivity expected at the lower concentrations. If the dimeric species were to react, it would be expected to do so *via* a six-centered transition state to give predominantly equatorial alcohol; however, the axial alcohol is produced in 68% yield.

Registry No.—**1**, 98-53-3.

Acknowledgment.—We are indebted to Dr. Paul R. Jones, University of New Hampshire, for valuable information concerning glpc analysis and the National Science Foundation (Grant No. GP-14795) for partial support of this work.

(43) W. French and G. F. Wright, *Can. J. Chem.*, **42**, 2474 (1964).
(44) J. C. Richer and P. Belanger, *ibid.*, **44**, 2067 (1966).

Silicon-Containing Carbanions. II. Ketene Thioacetal Synthesis *via* 2-Lithio-2-trimethylsilyl-1,3-dithiane

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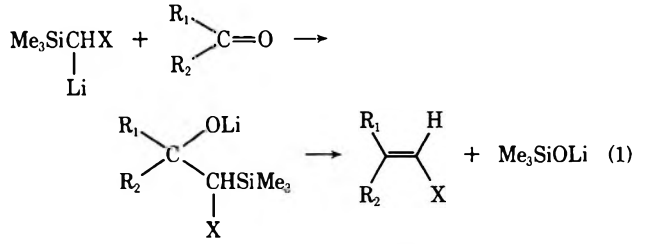
2-Lithio-2-trimethylsilyl-1,3-dithiane (1) reacts with aldehydes and ketones to afford ketene thioacetals (2) directly in good yields. The carbonyl compounds employed included aromatic ketones, hindered, enolizable aldehydes and ketones, and α,β-unsaturated aldehydes and ketones. The latter underwent exclusive 1,2 addition to the carbonyl group. Several of the ketene thioacetals were reduced to thioacetals by a protonation–hydride transfer sequence using trifluoroacetic acid and triethylsilane in methylene chloride to illustrate the usefulness of the reaction as a synthetic method for accomplishing the conversion of R_1R_2CO to R_1R_2CHCHO. Evidence is presented to indicate that the stabilization of an adjacent carbonium ion by electron release from sulfur is appreciable.

Organolithium reagents which bear a trimethylsilyl substituent at the carbanionic center react smoothly with aldehydes and ketones according to eq 1.[1-3] In



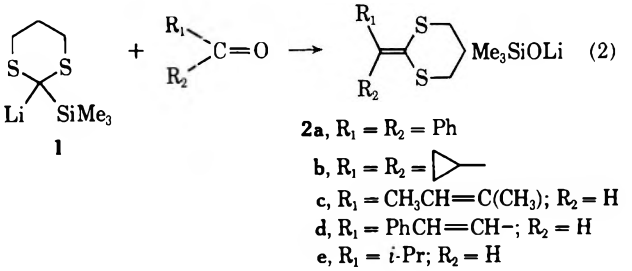
X = SMe, $P(S)Ph_2$, PPh_2 (ref 1)
X = SPh, $P(O)(OEt)_2$ (ref 2)
X = Ph, H (ref 3)

most cases, the decomposition of the presumed intermediate is spontaneous and the olefin products are obtained directly and in good yield.

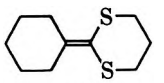
This modification of the Wittig–Horner olefin synthesis holds great promise for organic transformations, particularly in the preparation of heteroatom-substituted olefins. Described here is an extension of this method to the synthesis of ketene thioacetals (2) by the reaction of aldehydes and ketones with 2-lithio-2-trimethylsilyl-1,3-dithiane (1) (eq 2).[3a]

In addition to possessing an interesting π system, ketene thioacetals are proving to be useful synthetic intermediates.[4] Thus, 2 can be converted to a carboxylic acid by hydrolysis, the overall reaction sequence being one which converts R_1R_2CO to $R_1R_2CHCO_2H$.[5,6] The conversion of R_1R_2CO to R_1R_2CHCHO *via* 2 can also be accomplished, since reduction of the double bond of 2 leads to the thioacetal **3** of R_1R_2CHCHO. This reduction is readily carried out by the protonation–hydride transfer sequence shown in eq 3.[7]

Corey and Seebach have described the metalation of 2-substituted 1,3-dithianes (**3**) and shown how the resulting organolithium reagents function as nucleophilic carbonyl equivalents.[5,8] Therefore, conversion



2a, $R_1 = R_2 = Ph$
b, $R_1 = R_2 =$
c, $R_1 = CH_3CH{=}C(CH_3)$; $R_2 = H$
d, $R_1 = PhCH{=}CH{-}$; $R_2 = H$
e, $R_1 = i\text{-Pr}$; $R_2 = H$



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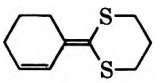
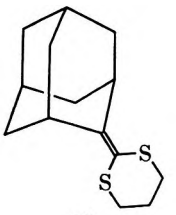
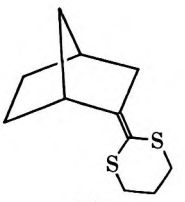


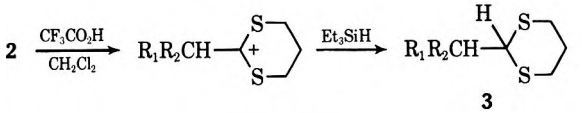
2g



2h

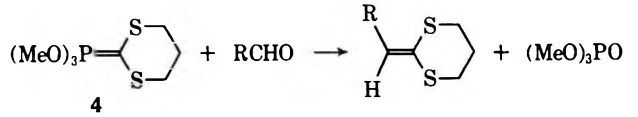


2i



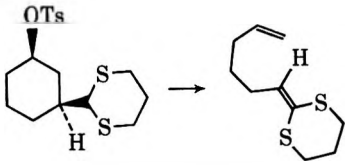
of R_1R_2CO to $R_1R_2CHCOR_3$ by reaction of the anion of **3** with alkyl halides followed by hydrolysis[9] is a practical process.

Existing methods for the synthesis of ketene thioacetals suffer from a lack of generality. Most procedures involve alkylation of the intermediates resulting from reaction of carbanions with carbon disulfide and are limited to substrates such as diethyl malonate and nitromethane which form stable carbanions. Corey and Märkl[10] have developed a highly selective ketene thioacetal synthesis employing ylide **4** which reacts with aldehydes but not ketones.



A novel fragmentation leading to ketene thioacetals has been reported by Marshall,[6] *e.g.*

(1) D. J. Peterson, *J. Org. Chem.*, **33**, 780 (1968).
(2) F. A. Carey and A. S. Court, *J. Org. Chem.*, **37**, 939 (1972).
(3) T. H. Chan, E. Chang, and E. Vinokur, *Tetrahedron Lett.*, 1137 (1970).
(3a) NOTE ADDED IN PROOF.—Professor Dieter Seebach (Giessen) has independently developed a similar ketene thioacetal synthesis based on **1** which will be described in a forthcoming publication.
(4) R. M. Carlson and P. M. Helquist, *ibid.*, 173 (1969).
(5) D. Seebach, *Synthesis*, 17 (1969).
(6) J. A. Marshall and J. L. Belletire, *Tetrahedron Lett.*, 871 (1971).
(7) F. A. Carey and J. R. Neergaard, *J. Org. Chem.*, **36**, 2731 (1971).
(8) E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075 (1965).
(9) (a) E. J. Corey and B. W. Erickson, *J. Org. Chem.*, **36**, 3553 (1971); (b) E. Vedejs and P. L. Fuchs, *ibid.*, **36**, 366 (1971).
(10) E. J. Corey and G. Märkl, *Tetrahedron Lett.*, 3201 (1967).



Addition of the anion of 1,3-dithiane to aldehydes and ketones yields alcohols which can be converted to ketene thioacetals by subsequent acid-catalyzed dehydration or by dehydrohalogenation of the derived chloride.[5,8]

Results and Discussion

Synthesis of Ketene Thioacetals.—Metalation of 2-trimethylsilyl-1,3-dithiane by *n*-butyllithium in tetrahydrofuran to afford **1** has been described by Corey[11] and by Brook[12] who used this reagent for the synthesis of α-silyl ketones. Reaction of **1** with aldehydes and ketones is rapid and efficient and produces ketene thioacetals **2** as the first isolable product. The results of a number of reactions summarized in Table I and eq 2

TABLE I

REACTIONS OF 1 WITH ALDEHYDES AND KETONES

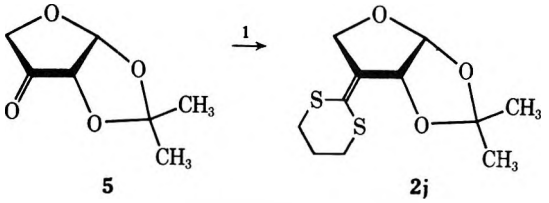
Carbonyl compd	Product	Yield, %[a]
Benzophenone	**2a**	78
Dicyclopropyl ketone	**2b**	68
Tiglaldehyde	**2c**	80
Cinnamaldehyde	**2d**	70
Isobutyraldehyde	**2e**	44
Cyclohexanone	**2f**	62
Cyclohexenone	**2g**	40
Adamantanone	**2h**	95
2-Norbornanone	**2i**	64
1,2-*O*-Isopropylidene-D-*glycero*-tetros-3-ulose	**2j**	25

[a] The yields are based on isolated amount of purified product and are not corrected for recovered starting material.

serve to indicate the varied types of ketene thioacetals which can be prepared by this method. The carbonyl compounds employed include aromatic and aliphatic ketones, enolizable aldehydes and ketones, α,β-unsaturated aldehydes and ketones, and sterically hindered ketones. Evidence in support of the ketene thioacetal structures was obtained by conventional analytical and spectroscopic means and is presented in the Experimental Section along with pertinent physical constants. Reagent **1** reacts well with unhindered or nonenolizable ketones but is less effective toward addition to hindered, enolizable substrates such as isobutyraldehyde. No ketene thioacetal was obtained when **1** was allowed to react with pinacolone. The keto sugar 1,2-*O*-isopropylidene-D-*glycero*-tetros-3-ulose (**5**)[13] also gave low yields of **2j**.

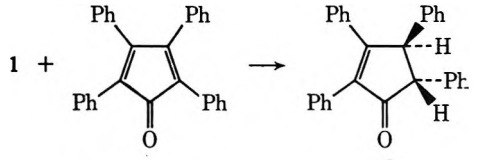
Only 1,2 addition was observed with α,β-unsaturated aldehydes and ketones to produce the unsaturate ketene thioacetals.

Reaction of **1** with tetraphenylcyclopentadienone did not lead to the formation of the expected carbonyl



5 **2j**

addition product **8** but instead gave the products of electron transfer, tetraphenylcyclopentenone (**6**) and the dimer **7**.[14]



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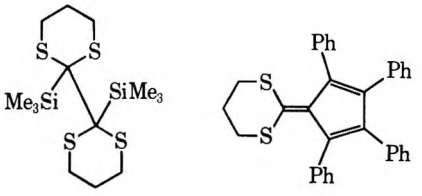
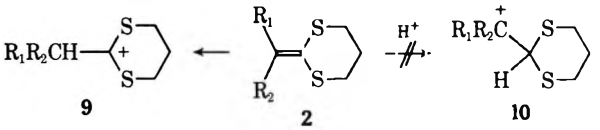


7 **8**

Conversion of Ketene Thioacetals to 3.—Several of the ketene thioacetals prepared by the above procedure were converted to the corresponding aldehydes to illustrate the use of these intermediates in synthetic problems. Benzophenone was converted to diphenylacetaldehyde by way of reduction of **2a** to **3** (R_1 = R_2 = Ph) followed by oxidative hydrolysis of **3** to Ph_2CHCHO. The reduction step was accomplished in 87% yield with triethylsilane and trifluoroacetic acid in methylene chloride (eq 3) and the hydrolysis step in 70% yield using *N*-bromosuccinimide in acetonitrile–water.[5a]

In similar fashion **2f** was prepared from cyclohexanone and reduced to 2-cyclohexyl-1,3-dithiane [**3**, $R_1 + R_2 = -(CH_2)_{-5}$] in 63% yield, which was then hydrolyzed to cyclohexanecarboxyaldehyde in 93% yield.

The diphenyl and dicyclopropyl ketene thioacetals (**2a** and **2b**) proved very useful in determining the site of protonation of the double bond in ketene thioacetals. Evidence was provided previously that the site of protonation of the ferrocene-derived ketene thioacetal **2k** is the carbon atom adjacent to the ferrocene to give the sulfur-stabilized carbonium ion **9** rather than at the dithiane ring position to give the ferrocenylmethyl cation **10**. This implies a high de-



9 **2** **10**

a, $R_1 = R_2$ = Ph
b, $R_1 = R_2$ = cyclopropyl
k, R_1 = ferrocenyl; R_2 = H

gree of stabilization by sulfur, presumably by electron donation using the lone pairs, of an adjacent carbonium ion since it is well established that ferrocenylmethyl cations are very stable ions.[15] We have examined this

(11) E. J. Corey, D. Seebach, and R. Freedman, *J. Amer. Chem. Soc.*, **89**, 434 (1967).

(12) A. G. Brook, J. M. Duff, P. F. Jones, and N. R. Davis, *ibid.*, **89**, 431 (1967).

(13) F. A. Carey, D. H. Ball, and L. Long, Jr., *Carbohyd. Res.*, **3**, 205 (1966); D. H. Ball, F. A. Carey, I. L. Klundt, and L. Long, Jr., *ibid.*, **10**, 121 (1969).

(14) Oxidative dimerization of anions of 1,3-dithiane has been observed; see ref 5 and 8.

(15) E. A. Hill and R. Wiesner, *J. Amer. Chem. Soc.*, **91**, 509 (1969); J. Feinberg and M. Rosenblum, *ibid.*, **91**, 4324 (1969).

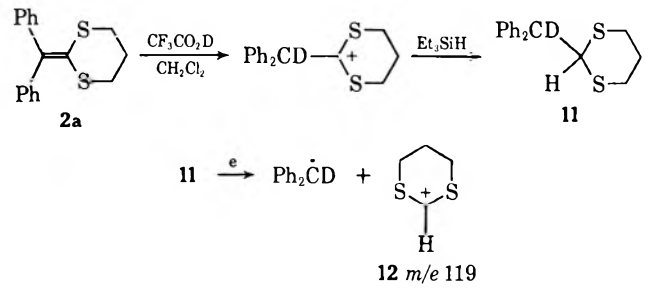
question in more detail and confirm our original conclusions regarding the stabilization by sulfur.

Ketene thioacetal **2b** was prepared and the site of protonation was studied by nmr. Regioselective protonation of the double bond was observed to produce the sulfur-stabilized carbonium ion **9b** in preference to the cyclopropyl-stabilized ion **10b**.[16] Addition of trifluoroacetic acid to a solution of **2b** in deuteriochloroform in an nmr tube led to the appearance of a new species characterized by a one-proton triplet of δ_{TMS} 2.8 assigned to the methine proton in ion **9**. The signals assigned to the $-SCH_2-$ protons in **2b** undergo a downfield shift of 0.7 ppm on protonation consistent with development of positive charge in the dithiane ring. Moreover, in contrast to the behavior observed with cyclopropylmethyl cations generated under similar conditions, the cyclopropyl rings remain intact as shown by the signals at δ 0.2–0.8 and 1–1.3. From previous observations with cyclopropylmethyl cations, we would expect that, if protonation had occurred to give a cyclopropyl-stabilized carbonium ion, ring-opening to yield a 3-butenyl trifluoroacetate would have been rapid.[17]

The diphenyl ketene thioacetal **2a** was also shown to produce a sulfur-stabilized carbonium ion (**9a**) on protonation by a labeling experiment in which **2a** was converted to **11** with trifluoroacetic acid-*d* and triethylsilane. Under these conditions the monodeuterated thioacetal was obtained, as evidenced by nmr and mass spectrometry.

Undeuterated **11** exhibits an AB quartet (J = 10 Hz) in which the center of gravity of the doublet at lower field is 4.79 ppm from internal TMS and the doublet at higher field is at 4.15 ppm. The spectrum of deuterated material has a single peak at 4.79 ppm corresponding to addition of a single deuterium to the double bond. The mass spectrum was also in accord with monodeuteration, as evidenced by the fragment at *m/e* 287 for the molecular ion. The position of deuteration was determined from the mass spectrum to be at the carbon atom bearing the two phenyls. The base peak in the spectrum of **11** is at *m/e* 119 and corresponds to fragment ion **12**. Since this is also the base peak in deuterated product it follows that Scheme I correctly describes the reaction path.

SCHEME I



These observations that carbonium ions at the 2 position of a 1,3-dithiane are formed preferentially to diphenylmethyl cations, dicyclopropylmethyl cations, and ferrocenylmethyl cations lead to the conclusion that stabilization by electron release from sulfur is appreciable and that sulfur is at least as stabilizing a substituent as cyclopropyl.[18]

(16) For an exhaustive list of references on cyclopropylmethyl cations see P. v. R. Schleyer and V. Buss, *J. Amer. Chem. Soc.*, **91**, 5880 (1969).

(17) F. A. Carey and H. S. Tremper, *ibid.*, **91**, 2969 (1969).

Experimental Section

Nmr spectra were recorded on a Hitachi Perkin-Elmer R-20 spectrometer in $CDCl_3$ and chemical shifts are reported in parts per million (δ) from internal tetramethylsilane. Infrared spectra were measured on a Perkin-Elmer 337 grating instrument as KBr disks for solids and pressed films for liquids. Melting points are corrected and were determined on a Thomas-Hoover apparatus. Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-6E spectrometer at an ionizing potential of 70 eV.

Microanalyses were performed by Alfred Bernhardt, Engelskirchen, West Germany.

All reactions involving organolithium reagents were carried out in an atmosphere of dry nitrogen. Tetrahydrofuran was distilled from lithium aluminum hydride. *n*-Butyllithium in hexane was purchased from Alfa Inorganics.

General Procedure for Synthesis of Ketene Thioacetals.—To a solution of 1.92 g (10 mmol) of 2-trimethylsilyl-1,3-dithiane in 10 ml of dry tetrahydrofuran was added 4.5 ml (10 mmol) of a solution of *n*-butyllithium in *n*-hexane. After stirring for 15 min at 0° a solution of 10 mmol of the aldehyde or ketone in 5 ml of tetrahydrofuran was added and the reaction mixture was maintained at 0° for 15 min, then 15 min at 25°. Brine (15 ml) was added and the product was extracted with two 10-ml portions of ether, dried ($MgSO_4$), filtered, and evaporated to yield the crude product.

2-Diphenylmethylene-1,3-dithiane (2a).—Recrystallization of the crude product from reaction of benzophenone with **1** from ethanol gave 2.20 g (78%) of **2a**, mp 133.5–135.5° (reported[5,8] mp 134.5–135°).

2-(1,1-Dicyclopropyl)methylene-1,3-dithiane (2b).—Evaporative distillation of the crude product from reaction of dicyclopropyl ketone with **1** at 125° (0.1 mm) afforded 1.44 g (68%) of **2b** as a clear liquid: nmr ($CDCl_3$) δ 0.6–0.8 (m, 8, cyclopropyl CH_2), 1.2–1.6 (m, 2, cyclopropyl CH), 2.1 (q, 2, CCH_2C), 2.9 (t, 4, $-SCH_2$).

The analytical sample was obtained by preparative tlc on silica gel using cyclohexane as the solvent.

Anal. Calcd for $C_{11}H_{16}S_2$: C, 62.20; H, 7.59. Found: C, 62.10; H, 7.42.

2-(2-Methyl-2-butenylidene)-1,3-dithiane (2c).—Tiglaldehyde (25 mmol) in 10 ml of tetrahydrofuran was added to a solution of 25 mmol of **1** in 10 ml of tetrahydrofuran and worked up as described above to afford 4.3 g of crude product. Distillation afforded 3.7 g (80%) of **2c**: bp 97–98° (0.35 mm); nmr ($CDCl_3$) δ 1.7 (d, 3, J = 7 Hz, $CH_3CH=$), 1.82 (s, 3, $CH_3C=$), 2–2.3 (m, 2, $SCHCH_2$), 2.7–3 (m, 4, SCH_2), 5.5 (q, 1, J = 7 Hz, $CH_3-CH=$), 6.3 (s, 1, HC=C). Distillation apparently resulted in cis–trans isomerization of the double bond (acid-catalyzed?), since the purified product showed an additional vinyl H singlet at δ 6.42 and an additional $CH_3CH=$ quartet centered at δ 5.3.

Anal. Calcd for $C_9H_{14}S_2$: C, 58.01; H, 7.57. Found: C, 57.90; H, 7.41.

2(3-Phenyl-2-propenylidene)-1,3-dithiane (2d).—From 25 mmol of **1** and 25 mmol of *trans*-cinnamaldehyde in tetrahydrofuran was obtained 6.28 g of crude product which deposited 4.0 g of **2d** as yellow crystals from hexane–ether, mp 84° (reported[10] mp 86–87°). The nmr spectrum was identical with that of authentic material prepared as described in ref 10: nmr ($CDCl_3$) δ 2.0–2.4 (m, 2, SCH_2CH_2), 2.8–3.1 (m, 4, SCH_2), 6.58 (d, 1, J = 15 Hz), 6.63 (d, 1, J = 10 Hz), 7–7.6 (m, 6, aromatic + vinyl).

2(2-Methylpropylidene)-1,3-dithiane (2e).—Distillation of the crude product from 25 mmol of isobutyraldehyde and **1** gave 3.4 g of material, bp 84–89° (1.5 mm), contaminated with 2-trimethylsilyl-1,3-dithiane. A 400-mg portion was purified by preparative tlc to give 223 mg of **2e** as a colorless liquid corresponding to a net yield of 44%.

2-Cyclohexylidene-1,3-dithiane (2f).—The condensation of cyclohexanone with **1** was performed on a 25-mmol scale and the

(18) G. A. Russell and L. A. Ochrymowycz, *J. Org. Chem.*, **35**, 764 (1969), have suggested on the basis of hydrolysis experiments that the ion $Ph_2CCH(SCH_3)_2^+$ is more stable than $Ph_2CHC(SCH_3)_2^+$. The reaction on which this comparison was based is a complicated one which may involve episulfonium ion intermediates and, therefore, is subject to some uncertainty.

crude product was recrystallized from ethanol to yield 3.09 g (62%) of **2f**, mp 91.5–93.5° (reported[5] mp 93.6–94°).

3-[2-(1,3-dithianylidene)]cyclohexene (2g).—Cyclohexenone (25 mmol) on reaction with 25 mmol of **1** afforded, after recrystallization of the crude product from ethanol, 2.0 g of **2i** as white crystals: mp 59°; nmr ($CDCl_3$) δ 1.7 (q, 2, CH_2 at C-5 of cyclohexenyl), 2–2.3 (m, 4, CH_2 at C-6 of cyclohexenyl and SCH_2CH_2), 2.5 (t, 2, CH_2 at C-4 of cyclohexenyl), 2.9 (m, 4, SCH_2), 5.8 (d of t, 1, H at C-1 of cyclohexenyl, $J_{1,2} = 10$, $J_{1,5} = 3$ Hz), 6.7 (d of t, 1, H at C-2 of cyclohexenyl, $J_{2,6} \cong 1$ Hz).

Anal. Calcd for $C_{10}H_{14}S_2$: C, 60.55; H, 7.11. Found: C, 60.29; H, 7.11.

2[2-(1,3-dithianylidene)]adamantane (2h).—Adamantanone (10 mmol) and **1** reacted to afford a clear sirup which was chromatographed on 60 g of Woelm silica gel and eluted with methylene chloride to yield 2.41 g (95%) of **2h** as a sirup which deposited 1.44 g (57%) of pure product on crystallization from ethanol: mp 45–46°; nmr ($CDCl_3$) δ 1.5–2.3 (broad envelope, 14, CH_2 and CH), 2.8 (m, 4, $-SCH_2$), 3.3 (broad s, 2, allylic CH).

Anal. Calcd for $C_{14}H_{20}S_2$: C, 66.62; H, 7.98. Found: C, 66.50; H, 7.74.

2-[2-(1,3-dithianylidene)]norbornane (2i).—Reaction of **1** with 2-norbornanone was done on a 25-mmol scale. The crude product was stripped of volatile impurities at 0.1 mm to leave 3.2 g (64%) of product which crystallized on cooling: nmr ($CDCl_3$) δ 1–1.8 (m, 6, CH_2 at C-5, -6, and -7 of norbornyl), 2–2.6 (m, 5, CH_2 at C-5 of dithiane plus CH_2 at C-3 and C-H at C-4 of norbornyl), 2.5–3 (m, 4, $-SCH_2$), 3.3 (broad s, 1, CH at C-1 of norbornyl).

The analytical sample was obtained by recrystallization from ethanol, mp 37–38°.

Anal. Calcd for $C_{11}H_{16}S_2$: C, 62.20; H, 7.59. Found: C, 62.09; H, 7.42.

1,2-*O*-Isopropylidene-3-[2-(1,3-dithianylidene]-D-*glycero*-tetrose (2j).—From 3.8 mmol of 1,2-*O*-isopropylidene-D-*glycero*-tetros-3-ulose and 4 mmol of **1** was obtained 1.06 g of crude product which was stripped of volatile impurities at 0.1 mm. Preparative tlc on silica gel gave 230 mg (24%) of **2j** as a clear sirup which crystallized on standing: nmr ($CDCl_3$) δ 1.39 and 1.45 (two s, 6, isopropylidene CH_3), 2–2.4 (m, 2, $SCHCH_2$), 2.8–3 (m, 4, SCH_2), 4.53 (s, 2, CH_2 at C-4), 5.16 (d, 1, $J_{1,2} = 4$ Hz, CH at C-2), 5.82 (d, 1, $J_{1,2} = 4$ Hz, anomeric CH).

The analytical sample was obtained by recrystallization from cyclohexane, mp 75°.

Anal. Calcd for $C_{11}H_{16}O_3S_2$: C, 50.74; H, 6.19; S, 24.63. Found: C, 50.54; H, 6.33; S, 24.75.

Reaction of 1 with Tetraphenylcyclopentadienone.—This reaction was carried out on a 5.2-mmol scale and the crude product (3.1 g) was purified by preparative tlc on silica gel using cyclohexane as the solvent. From 310 mg of crude product was eluted first 50 mg (50%) of 2-trimethylsilyl-2-(2-trimethylsilyl-1,3-dithianyl)-1,3-dithiane (**7**): mp 122°; nmr ($CDCl_3$) δ 0.38 (s, 18, $SiMe_3$), 1.8–2.5 (m, 4, $-SCH_2CH_2$), 3.4–3.8 (m, 8, $-SCH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 382 (2), 193 (26), 192 (29), 191 (100), 149 (20), 73 (55).

Anal. Calcd for $C_{14}H_{30}S_4Si_2$: C, 43.92; H, 7.90; S, 33.51. Found: C, 44.07; H, 7.68; S, 33.41.

The second product eluted was tetraphenylcyclopentadienone (50 mg, 25%), mp 160–162° (reported[19] mp 162–163°). The most polar product, a yellow oil identified as 1-*n*-butyl-2,3,4,5-tetraphenylcyclopentadienol[20] from its ir, nmr, and mass spectrum, was isolated in 45% yield.

Reduction of 2a by Hydride Transfer.—To a solution containing 284 mg (1 mmol) of **2a** and 0.2 ml of triethylsilane in 5.0 ml of methylene chloride was added 0.5 ml of trifluoroacetic acid. The resulting red solution was allowed to stand for 24 hr. Saturated sodium bicarbonate solution was added and the layers were separated. The aqueous phase was extracted with 10 ml of methylene chloride and the combined organic extracts were dried over magnesium sulfate and evaporated. Recrystallization of the resulting product from ethanol gave 250 mg (87%) of 2-diphenylmethyl-1,3-dithiane as white crystals, mp 115–117°, which were identical with authentic material.

Authentic material was prepared by reaction of diphenylacetaldehyde with 1,3-propanedithiol in boron trifluoride etherate. The analytical sample was obtained as white needles by recrystallization from ethanol: mp 119–120°; nmr ($CDCl_3$) δ 1.9–2.2 (m, 2, SCH_2CH_2), 2.7–2.9 (m, 4, SCH_2), 4.15 (d, 1, $J = 10$ Hz, $HCPh_2$), 4.79 (d, 1, $J = 10$ Hz, HCS_2), 7.3 (s, 10, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 286 (4), 167 (10), 166 (6), 165 (18), 121 (11), 120 (6), 119 (100).

Anal. Calcd for $C_{17}H_{18}S_2$: C, 71.28; H, 6.34; S, 22.38. Found: C, 70.92; H, 6.27; S, 22.58.

Reduction of 2a with Triethylsilane–CF_3CO_2D.—A solution of trifluoroacetic acid-*d* in 10 ml of methylene chloride was prepared from 1 ml (1.49 g, 7 mmol) of trifluoroacetic anhydride and 0.14 ml (154 mg, 7.7 mmol) of D_2O. A 5-ml portion of this solution was added to 284 mg (1 mmol) of **2a** and 0.2 ml of triethylsilane and the reaction mixture was worked up as in the preceding experiment to afford 205 mg (72%) of deuterated **11**, mp 117–120°. The nmr spectrum was identical with that of authentic material except for the disappearance of the doublet at δ 4.15 and the collapse of the doublet at δ 4.79 to a broadened singlet; mass spectrum (70 eV) *m/e* (rel intensity) 287 (3), 284 (6), 168 (6), 167 (3), 166 (9), 165 (5), 121 (12), 120 (7), 119 (100).

Hydrolysis of 2-Diphenylmethyl-1,3-dithiane.—A solution containing 2.0 g (7 mmol) of the 2-substituted dithiane in 12 ml of acetonitrile was added to a solution of 7.4 g (42.0 mmol) of *N*-bromosuccinimide in 60 ml of 4:1 acetonitrile–water and stirred for 5 min at 0°. The solution was added to 200 ml of saturated sodium sulfite solution and extracted with 400 ml of 1:1 hexane–methylene chloride. The organic phase was washed with 200 ml of 1 *M* sodium bicarbonate, 200 ml of water, and 200 ml of brine and dried over magnesium sulfate. Evaporation of the solvent at 25° gave 950 mg (70%) of pure product, the ir spectrum of which was identical with that of authentic diphenylacetaldehyde;[21a] nmr ($CDCl_3$) δ 4.79 (d, 1, $J = 2$ Hz, Ph_2CH), 7.2 (s, 10, aromatic), 9.80 (d, 1, $J = 2$ Hz, aldehyde CH).

Conversion of 2f to Cyclohexanecarboxaldehyde.—A solution containing 400 mg (2.0 mmol) of **2f**, 1.0 ml of trifluoroacetic acid, and 0.4 ml of triethylsilane in 10 ml of methylene chloride was allowed to stand for 20 hr and then poured into 30 ml of saturated sodium bicarbonate. The layers were separated, the aqueous phase was extracted with a further 10-ml portion of methylene chloride, and the combined organic extracts were dried over magnesium sulfate. Evaporation of the methylene chloride left a sirup which crystallized. Recrystallization from ethanol–water afforded 254 mg (63%) of 2-cyclohexyl-1,3-dithiane, mp 51.5–52.5° (reported[5] mp 51.6–52.4°).

Hydrolysis of 450 mg (2.22 mmol) of this material was accomplished by adding a solution of it in 3.0 ml of acetonitrile to 2.37 g (13.3 mmol) of *N*-bromosuccinimide in 15 ml of 4:1 acetonitrile–water and stirring for 5 min. The work-up was on one-fourth the scale of the preceding experiment and yielded 243 mg (93%) of cyclohexanecarboxaldehyde which was identical in respect to ir spectrum with that reported.[21b]

Registry No.—**1**, 34410-04-3; **2b**, 34399-58-1; **2c**, 34399-59-2; **2g**, 34399-60-5; **2h**, 34399-61-6; **2i**, 34399-62-7; **2j**, 34399-63-8; **7**, 34399-64-9; **11**, 34399-65-0; 2-diphenylmethyl-1,3-dithiane, 34399-66-1; diphenylacetaldehyde, 947-91-1.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

(19) (a) N. O. V. Sonntag, S. Linder, E. I. Becker, and P. E. Spoerri, *J. Amer. Chem. Soc.*, **75**, 2283 (1953); (b) J. A. Ciabattoni and G. A. Berchtold, *J. Org. Chem.*, **31**, 1336 (1966).

(20) A. G. Bonagura, M. B. Meyers, S. J. Storfer, and E. I. Becker, *ibid.*, **76**, 6122 (1954).

(21) C. J. Pouchert, "The Aldrich Library of Infrared Spectra," Aldrich Chemical Co., 1970: (a) Spectrum 674C; (b) Spectrum 217E.

Photoinduced Formation of Vinylcyclohexatriene-Iron Carbonyl Complexes from Substituted Vinylbenzenes. Localization of Electrons in Aromatic Substrates *via* π Coordination to Metal[1]

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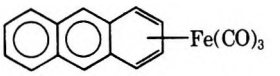
The irradiation of styrene and other vinylbenzene substrates **7** with $Fe(CO)_5$ at room temperature affords complexes of metal π coordination to two, four, and eight electrons of the eight π-electron system: 1′,2′-*dihapto*-tetracarbonyliron–styrenes (**8**) (styrene–tetracarbonyliron), 1′,2′,1,2-*tetrahapto*tricarbonyliron–styrenes (**9**) (styrene–tricarbonyliron), and 1′,2′,1,2-*tetrahapto*-3,4,5,6-*tetrahapto*bistricarbonyliron–styrenes (**10**) (styrene–bistricarbonyliron). Both chemical and spectral evidence indicates that complexed units of **9** and **10** are well represented by the classical diene–tricarbonyliron model and that aromatic character of the original substrate is no longer present in these complexes. The reaction is general for substitution (Alk, Ar, Hal, OCH_3) at the 1′, 2′, 3, and 4 positions of the styrene skeleton. From reactions of meta-substituted styrenes, positional isomers of bistricarbonyliron complexes corresponding to the two trapped Kekulé structures are isolated. Only one such isomer is isolated from ortho-substituted styrenes and none from substrate with both ortho positions substituted. α,β-Unsaturated rings fused to benzene have not afforded complexes similar to **9** or **10**. Experimental evidence shows that the reaction sequence is **7** → **8** → **9** → **10**, and though steps **7** → **8** and **9** → **10** can be effected with $Fe_2(CO)_9$ in the dark, the step **8** → **9** has been induced only in the presence of a light source.

We discuss in this paper synthesis of stable neutral tricarbonyliron complexes which originate from the contribution of aromatic electrons to coordination. Experimental evidence shows that formation of diene-type tricarbonyliron complexes from aromatic substrates can occur in systems of the following type: (a) those containing vinyl substituent(s) on benzene which provide a more reactive center for initial complexation and a more stable intermediate (vinyl–tetracarbonyliron) prior to diene–tricarbonyliron formation, and (b) those of condensed aromatic rings in which the delocalization energy lost on coordination of one of the condensed rings is relatively small. Application of the second route led to the isolation of stable tricarbonyliron complexes on a terminal ring of anthracene (**1**),[2] benzanthracene, and related heterocycles.[3] The success of the first route seems to be very dependent both on the particular substrate and the reaction conditions. Prior to our work, styrene failed to produce stable diene–tricarbonyliron complexes when treated with $Fe_2(CO)_9$,[4] $Fe_3(CO)_{12}$,[5] or $Fe(CO)_5$,[6] or when irradiated in a benzene solution of $Fe(CO)_5$.[4] However, α- and β-vinylnaphthalenes did yield monotricarbonyliron complexes which involve two vinylic and two aromatic π electrons in coordination, yet retain an aromatic benzene ring (**2**, **3**).[2,8] Introduction of a second vinyl group to styrene strongly enhances the tendency to form diene–iron complexes, for example, the isomeric complexes **4** and **5**.[5] Results of X-ray structural studies of **2**–**5** have demonstrated the occurrence of bond fixation in these tricarbonyliron complexes.[8] Similar conclusions were drawn from an nmr study of anthracene–tricarbonyliron (**1**).[9]



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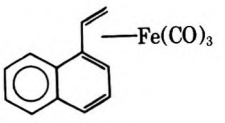
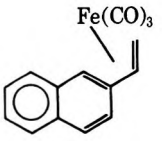


2



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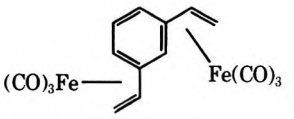

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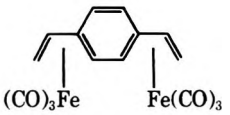
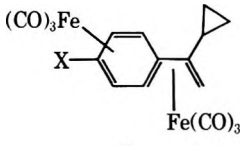


5

Some time ago we found that 1-substituted 1-cyclopropylethylenes react photochemically with $Fe(CO)_5$ to give as major products substances derived from reaction at the vinyl–cyclopropane portion of the molecule.[1b] When the substituent was an aromatic moiety, it was possible to isolate, in addition, a small amount of a stable carbonyliron complex which on degradative oxidation reverted to the original substrate. Further analysis revealed that the structure was consistent with a bistricarbonyliron complex in which coordination involved all of the eight π electrons of the vinyl–arene portion, and the cyclopropane ring remained intact. From our evidence we assigned this material the structure depicted by **6**.[1b,c] We would like to report now the results of our continued studies of iron carbonyls in reactions with the eight π-electron systems of styrene and its derivatives.



6

(1) Parts of this work have been the subject of preliminary communications: (a) R. Ben-Shoshan, R. Victor, and S. Sarel, Abstracts, 40th Conference of the Israel Chemical Society, Haifa, Oct 1970; *Israel J. Chem.*, **8** (Supplement), 9p (1970); (b) R. Victor, R. Ben-Shoshan, and S. Sarel, *Tetrahedron Lett.*, 4253 (1970); (c) *ibid.*, 4257 (1970); (d) *Chem. Commun.*, 1680 (1970).

(2) T. A. Manuel, *Inorg. Chem.*, **3**, 1794 (1964).

(3) R. A. Bauer, E. O. Fischer, and C. G. Kreiter, *J. Organometal. Chem.*, **24**, 737 (1970).

(4) E. Koerner von Gustorf, M. C. Henry, and C. DiPietro, *Z. Naturforsch. B*, **21**, 42 (1966).

(5) T. A. Manuel, S. L. Stafford, and F. G. A. Stone, *J. Amer. Chem. Soc.*, **83**, 3597 (1961).

(6) G. F. Emerson, private communication cited in ref 7.

(7) B. J. Nicholson, *J. Amer. Chem. Soc.*, **88**, 5157 (1966).

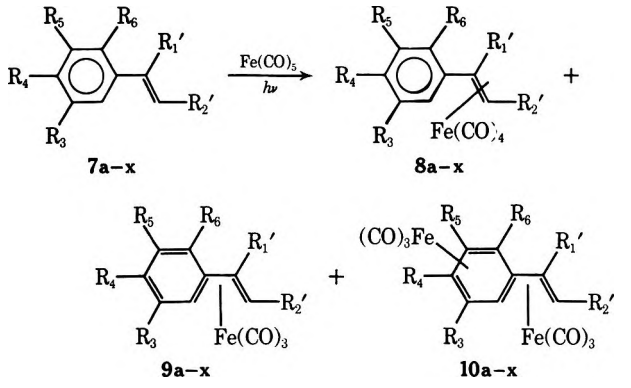
(8) R. E. Davis and R. Pettit, *ibid.*, **92**, 716 (1970).

(9) H. Günther, R. Wenzl, and H. Klose, *Chem. Commun.*, 605 (1970).

Results

We have found that the formation of the bistricarbonyliron complexes **10** of styrene systems **7** was general for large variation in the substitution when equimolar quantities of **7** and $Fe(CO)_5$ were irradiated at room temperature (see Table III for listings of R).[10] In some cases it was possible to isolate complexes derived from tetracarbonyliron coordination of the vinyl electrons (**8**) and from tricarbonyliron coordination of the vinyl electrons and two of the six aromatic electrons (**9**) (Scheme I). Complexes of type **8** find precedent

SCHEME I



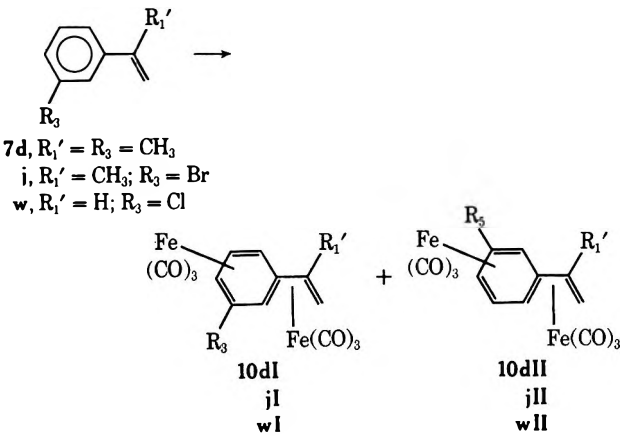
in the literature,[4] while complexes of types **9** and **10** were isolated and characterized first in this study. Monitoring of the reaction by ir analysis showed the appearance of products in the order **8**, **9**, **10**.

Relative Reactivity of Substrates.—Reactions of substrates substituted at the 2′ position were slower in production of the complex of type **8**. Irradiation of β-bromostyrene and of indene produced only a small amount of the tetracarbonyliron complex, and, during the usual reaction time and under standard conditions, no other organoiron materials were detected. Under similar conditions, phenanthrene was inert.

Substitution at the ortho position decreased the rate of formation of complexes of type **9**, as observed by ir monitoring, and the only complexes of type **10** isolated in these cases were those in which the original ortho substituent (CH_3, F, Cl, Br[12]) was a part of the ring complex unit; the alternative compels the substituent into a position endo to the metal of the external complex unit. Irradiation of 2,6-dimethylstyrene produced the tetracarbonyliron complex rapidly, but neither of the tricarbonyliron species of types **9** or **10** was observed.

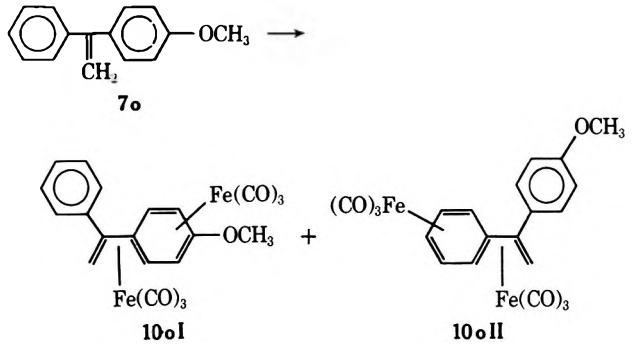
Formation and Isolation of Isomers.—When meta-substituted styrenes were irradiated with $Fe(CO)_5$, both possible bistricarbonyliron isomers were isolated (Scheme II).[1c] Similarly, when another aromatic unit

SCHEME II



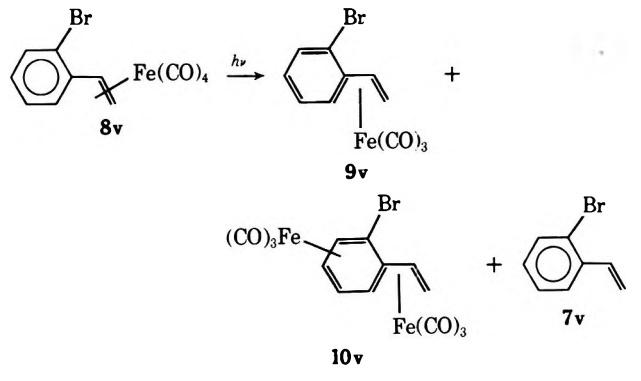
was substituted at a vinylic position of styrene, the bistricarbonyliron complexes derived from coordination to each aromatic system were obtained (Scheme III).

SCHEME III

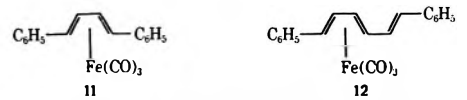


Variations from the Standard Reaction.—Irradiation of **7** with $Fe(CO)_5$ at elevated temperatures did not afford **8**, **9**, or **10**. When **7** was treated with $Fe_2(CO)_9$ at room temperature in the dark, only complex **8** was obtained. Irradiation of **8**, however, gave rapid production of **9**, and continued irradiation yielded **10** which could be isolated with the uncoordinated substrate **7** (Scheme IV). Similar production of **7** and

SCHEME IV

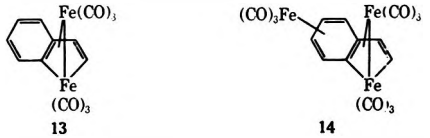


(10) Under similar conditions 1-vinylnaphthalene, 1,3-divinylbenzene, 1,4-diphenylbutadiene, and 1,6-diphenyl-1,3,5-hexatriene (in CH_2Cl_2) underwent reaction to give the known coordinated compounds **2**,[2] **4**,[5] **11**,[5] and **12**.[11]



(11) H. W. Whitlock, Jr., and Y. N. Chuah, *Inorg. Chem.*, **4**, 424 (1965).

(12) In addition to **8v** and **10v**, which were obtained from the reaction of 2-bromostyrene (**7v**), two complexes derived from dehydrobromination were also isolated: 1,1,1-tricarbonylferraindene-π-tricarbonyliron (**13**) and 1,1,1-tricarbonylferraindene-π-bistricarbonyliron (**14**). Their formation and their properties are the subjects of a separate communication.[13]



(13) R. Victor, R. Ben-Shoshan, and S. Sarel, *Chem. Commun.*, 1241 (1971).

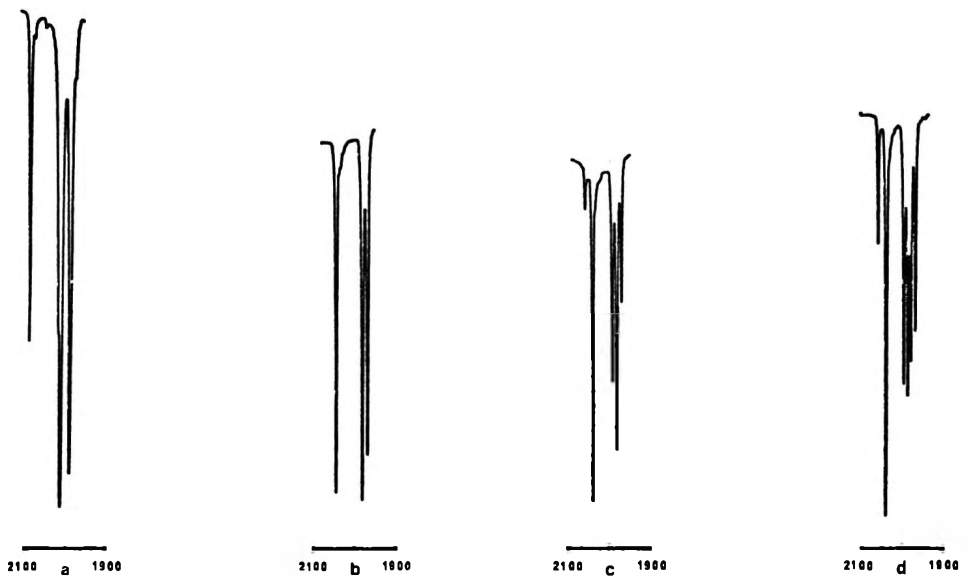
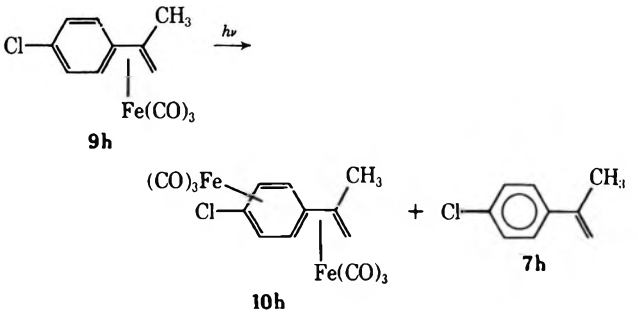


Figure 1.—Characteristic infrared metal carbonyl absorptions (hexane solution): (a) Styrene–tetracarbonyliron complex (**8**); (b) styrene–tricarbonyliron complexes (**9**), (c and d) styrene–bistricarbonyliron complexes (**10**).

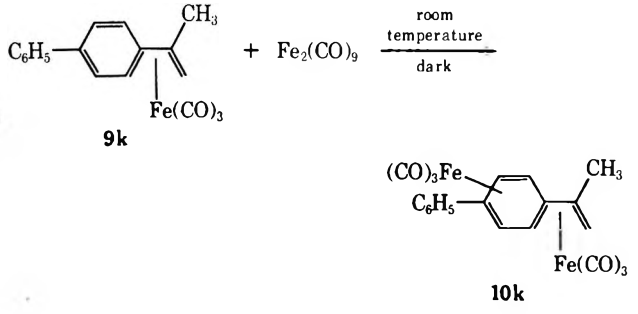
10 was observed in the irradiation of a complex **9** (Scheme V), though formation of **10** was considerably

SCHEME V



faster when $Fe(CO)_5$ was added to the irradiation solution. Production of the diiron complex **10** from the monoiron complex **9** was also observed when a complex **9** was treated with $Fe_2(CO)_9$ in the dark (Scheme VI).

SCHEME VI



Spectral and Physical Properties. Mass Spectra.—Spectra were taken of all isolated complexes of **8**, **9**, and **10**. The fragmentation pattern common to all of them was successive loss of carbonyl and iron units to the fragment in which one iron remained on the original styrene. Further fragmentation varied with the nature of the substituents on the ligand. A more intensive treatment of the mass spectra of these complexes will be given in a separate paper.

Tetracarbonyliron Complexes 8.—Only derivatives unsubstituted at the 1′ and 2′ positions were isolated: **8a**, liquid; **8t**, mp 62°; **8u**, mp ~30°; **8v**, mp 57°; **8w**, liquid.

A. Infrared.—There are four bands in the metal carbonyl region (see Figure 1a and Table I), and full spectra show loss of the original vinyl bands from ~1630 and ~900 cm^{-1}.

TABLE I
CHARACTERISTIC INFRARED ABSORPTIONS OF COMPLEXES 8, 9, AND 10

Complex	ν_{CO} (hexane), cm^{-1}	$\nu_{C=C}$ (KBr), cm^{-1}
8[a]	~2080, 2015 (sh), 2005, 1985 (±5)	[b]
9[a]	~2044, 1980, 1968 (±5)	
9b		751
9h		803
9i		804
9k		813, 708, 772[c]
10g–i, 10jII, 10t–v, 10wII, 10x	~2060, 2044, 2000, 1990, 1983, 1972 (±5)	
10c	2055, 2040, 1987, 1983, 1973, 1970	
10a, 10b, 10d–f, 10k–s	~2055, 2040, 1990, 1980,[d] 1967 (±5)	
10jI, 10wI	2058, 2042, 2000, 1986,[d] 1969	
10k, 10n, 10oI, 10oII, 10s		[e]

[a] General for all isolated compounds. [b] Bands of aromatic unsaturation are present and shifted only slightly from the corresponding substrate **7**. [c] Uncomplexed phenyl group. [d] Overlap of two absorptions. [e] The uncomplexed aryl groups give characteristic absorptions.

B. Nuclear Magnetic Resonance.—Spectra are characterized by a general upfield shift of the original vinylic protons (Δ ~2.5 ppm) and by a decrease in coupling between protons at C-2′ and C-1′ when compared to values in the uncomplexed ligand **7**.[14] The effect of the complexed moiety on the adjacent aromatic proton(s) is also one of shielding by at least 0.3 ppm.

Tricarbonyliron Complexes 9.—Melting points of isolated complexes are given in Table IV (Experimental Section).

(14) *Cf.* E. Weiss, K. Stark, J. E. Lancaster, and H. D. Murdoch, *Helv. Chim. Acta*, **46**, 288 (1963).

TABLE II

NMR SPECTRAL PARAMETERS[a] OF TRICARBONYLIRON–STYRENE COMPLEXES 9 AND COMPARATIVE SPECTRAL DATA

Complex		Chemical shifts, τ: 2′a (2″a)	2′b (2″b)	1′ (1″)	2 (2‴)	Others
9b[b]	$R_{1'}=CH_3$	9.78 d	8.19 d	7.42 (3) s	7.09 d	H_3–H_6: 2.39 (1), ~2.95 (3)
9h[b]	$R_{1'}=CH_3, R_4=Cl$	9.84 d	8.21 d	7.43 (3) s	7.27 d	H_3, H_5, H_6: 2.36 (1), ~3.07 (2)
9i[b]	$R_{1'}=CH_3, R_4=Br$	9.84 d	8.23 d	7.48 (3) s	7.40 d	H_3, H_5, H_6: 2.58 (1), ~2.99 (2)
9k[b]	$R_{1'}=CH_3, R_4=C_6H_5$	9.72 d	8.18 d	7.40 (3) s	6.99 d	H_3, H_5, H_6: 2.27 (1), ~2.70 (2), ϕ ~2.58
4[c]		9.65 dd 9.72 dd	8.20 dd 8.23 dd	4.30 t 4.46 t	7.48 s[d] 7.88 d[e]	H_3: 3.65 dd; H_4: 3.25 dd
3[f,g]		9.70 dd	8.13 dd	3.55 t	7.39 d	H_3: 3.24 dd; H_4: 2.87 d; H_5–H_8: 1.71 (1); 2.54 (3)

[a] Solutions in $CDCl_3$, TMS internal standard. [b] J (Hz): $H_{2'a}H_{2'b} \simeq 2.4$–2.6; $H_2H_3 \simeq 6.0$. [c] J (Hz): $H_{2'a}H_{2'b} \simeq H_{2''a}H_{2''b} \simeq 2.7$; $H_{2'a}H_{1'} \simeq H_{2''a}H_{1''} \simeq 9.0$; $H_{2'b}H_1 \simeq H_{2''b}H_{1''} \simeq 7.0$; $H_2H_3 = 5.3$; $H_3H_4 = 9.2$. [d] $H_{2'''}$. [e] H_2. [f] J (Hz): $H_{2'a}H_{2'b} = 2.6$; $H_{2'a}H_{1'} = 9.0$; $H_{2'b}H_{1'} = 7.2$; $H_2H_3 = 5.7$; $H_3H_4 = 9.1$. [g] Some of the nmr data of this compound have been reported in ref 2.

A. Infrared.—There are three strong bands of metal carbonyl absorption[15] (see Figure 1b and Table I), and full spectra show loss of aromatic absorption though retention of carbon–carbon unsaturation.

B. Nuclear Magnetic Resonance.—Chemical shift assignments of protons involved in the complexed moiety ($H_{2'a}$, $H_{2'b}$, H_2) were based on splitting patterns and on qualitative literature values which place the proton endo to iron ($H_{2'a}$) at higher field than the exo proton ($H_{2'b}$).[16,17] Spectra are characterized by high-field appearance of the original vinyl protons and one of the ring protons (H_2) (see Figure 2a and Table II). Chemical shifts and coupling constants of these protons are comparable to those of related complexes from 1-vinylnaphthalene (**2**) and *m*-divinylbenzene (**4**), also appearing in Table II.

Bistricarbonyliron Complexes (10).—Melting points are listed in Table IV (Experimental Section).

A. Infrared.—There are five to six bands of metal carbonyl absorption (see Figures 1c and 1d and Table I). Those exhibiting six bands were generally substituted on the ring by halogen and those with five bands were generally nonhalogen compounds. Full spectra corroborate complete loss of carbon–carbon unsaturation by the disappearance of strong bands from ~1600–1500 and ~900–700 cm^{-1}, excepting those compounds which contain an additional aromatic group not involved in coordination.

B. Nuclear Magnetic Resonance.—See Figures 2b, 2c, and 2d, and Table III. Chemical shift assignments were made from double irradiation experiments on styrene–bistricarbonyliron (**10a**), spin–spin coupling patterns, and coupling constants. Protons involved in the external complex unit appear at higher field than in the analogous complexes **9**, while coupling constants $J_{2'a2'b}$ are of similar value (Tables II and III). Methyl protons at C-1′ also appear at higher field (Δ ~0.5 ppm) than in the **9** analogs. Protons on the ring complex unit (H_3–H_6) appear downfield of corresponding protons in the external diene complex unit by ~1.5–2.0 ppm, and this deshielding is greater at positions 5 and 6 than at 3 and 4. Of the terminal protons H_6 appears downfield of H_3 by ~0.25 ppm, and of the central protons H_5 appears downfield of H_4 by ~0.35 ppm when effects of substituents are discounted. Methyl protons at positions 3 and 6 and 4 and 5 are shifted in the same manner. The direction of deshielding is viewed as a result of unequal anisotropic effects of the external complex on the ring positions.[18]

Discussion

Studies of reactions of styrene derivatives **7** and of isolated complexes **8** and **9** indicate that the sequence of product formation is that outlined in Scheme VII. Both the initial coordination of the vinylic π electrons (**7** → **8**) and coordination of the ring diene electrons

(15) Both the shape and the relative positions of these bands are common to other diene–tricarbonyliron complexes; *e.g.*, **2**, $\nu_{CO} \simeq 2043$, 1980, 1970 cm^{-1}; **11**, $\nu_{CO} \simeq 2058$, 1996, 1987 cm^{-1}; **12**, $\nu_{CO} \simeq 2045$, 1986, 1975 cm^{-1}.

(16) G. F. Emerson, J. E. Mahler, R. Kochhar, and R. Pettit, *J. Org. Chem.*, **29**, 3620 (1964).

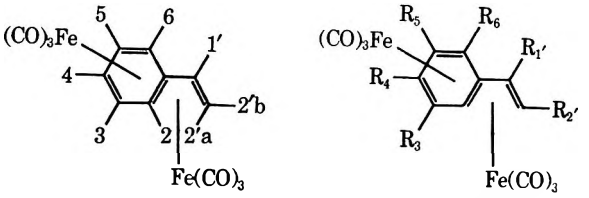
(17) Such assignments are also borne out in complexes **10** from coupling values $J_{2'a1'}$ and $J_{2'b1'}$, Table III.

(18) In diene–tricarbonyliron derivatives protons on the central carbons and protons of methyl groups at these positions are deshielded relative to those associated with the terminal carbons.[16,19] By extension, protons at positions 5 and 6 would fall under such an influence by closer association to the central carbon (C-1) of the external unit complex than protons at positions 3 and 4 which are more closely associated to the terminal carbon (C-2).

(19) A. J. Birch, P. E. Cross, J. Lewis, D. A. White, and S. B. Wild, *J. Chem. Soc. A*, 332 (1968).

TABLE III

NMR SPECTRAL PARAMETERS[a,b] OF BISTRICARBONYLIRON–STYRENE COMPLEXES 10



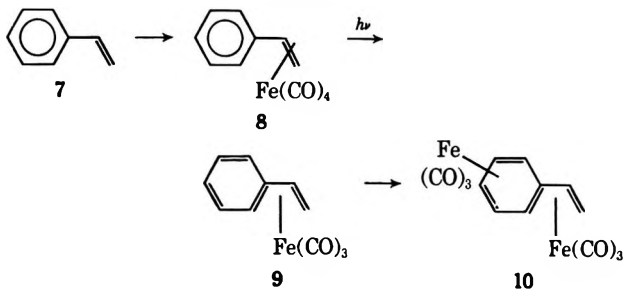
10	R	Chemical shift, τ 2'a	2'b	1'	2	3	4	5	6
a	all R = H	9.93 dd	8.51 dd	5.02 dd	7.90 d[c]	6.59 t[c]	3.86 m	3.50 m	6.41 d[c]
b	$R_{1'}$ = CH_3	9.80 d	8.45 d	7.95 (3) s	8.14 d[c]	6.59 t[c]	3.92 m	3.55 m	6.30 d[c]
c	$R_{1'}$ = R_6 = CH_3	9.74 d	8.43 d	7.84 (3) s	8.11 d[c]	6.78 m	3.98 m	3.61 dd	8.04 (3) s
dI	$R_{1'}$ = R_3 = CH_3	9.68 d	8.36 d	7.93 (3) s	8.28 s[c]	8.43 (3) s	4.03 d[c]	3.55 dd	6.35 d[c]
dII	$R_{1'}$ = R_5 = CH_3	9.79 d	8.43 d	7.90 (3) s	8.11 d[c]	6.70 t[c]	3.95 d[c]	7.42 (3) s	6.30 s[c]
e	$R_{1'}$ = R_4 = CH_3	9.79 d	8.42 d	7.91 (3) s	8.08 d[c]	6.57 dd	7.63 (3) s	3.57 dd	6.33 dd
f	$R_{1'}$ = CH_3; R_4 = OCH_3	9.85 d	8.45 d	7.89 (3) s	8.15 d[c]	6.40 dd	6.16 (3)s	3.78 dd	6.72 dd
g	$R_{1'}$ = CH_3; R_4 = F	9.83 d	8.37 d	7.90 (3) s	8.34 m	6.26 m		3.36 m	6.71 m
h	$R_{1'}$ = CH_3; R_4 = Cl	9.87 d	8.44 d	7.95 (3) s	8.26 dd[c]	6.33 dd		3.36 dd	6.53 dd
i	$R_{1'}$ = CH_3; R_4 = Br	9.83 d	8.40 d	7.91 (3) s	8.22 d[c]	6.25 dd		3.28 dd	6.42 dd
jI	$R_{1'}$ = CH_3; R_3 = Br	9.72 d	8.36 d	7.94 (s) s	~7.94[d]		~3.63[e]	~3.74[e]	6.36 d[c]
jII	$R_{1'}$ = CH_3; R_5 = Br	9.84 d	8.36 d	7.87 (3) s	8.30 d[c]	6.64 m	3.67 d[c]		5.97 s[c]
k	$R_{1'}$ = CH_3; R_4 = C_6H_5	9.74 d	8.39 d	7.87 (3) s	7.94 d[c]	6.02 dd	*f*	3.12 dd	6.25 dd
l	$R_{1'}$ = CH_3; R_4 = $CH(CH_3)_2$	9.76 d	8.41 d	7.95 (3) s	8.05 d[c]	6.52 dd	*g*	3.53 dd	6.41 dd
m	$R_{1'}$ = CH_3; R_4 = $C(CH_3)_3$	9.72 d	8.37 d	7.93 (3) s	8.00 d[c]	~6.39[e]	8.63 (9) s	3.49 dd	~6.39[e]
n	$R_{1'}$ = C_6H_5	9.59 d	8.11 d	2.59 (5) m	7.95 d[c]	6.55 t[c]	3.82 m	3.42 m	6.36 d[c]
oI	$R_{1'}$ = C_6H_5; R_4 = OCH_3	9.69 d	8.19 d	2.66 (5) m	8.06 dd	6.43 dd	6.18 (3) s	3.75 dd	6.83 dd
oII	$R_{1'}$ = *p*-$CH_3OC_6H_4$	9.58 d	8.09 d	*h*	7.94 d[c]	6.52 t[c]	3.81 m	3.42 m	6.35 d[c]
p	$R_{1'}$ = Δ; R_4 = OCH_3	10.24 d	8.60 d	*i*	8.20 dd	6.44[e]	6.22 (3) s	3.75 dd	6.49[e]
q	$R_{2'}$ = CH_3	9.07 m	8.68 (3) d[j]	5.16 d	7.93 d[c]	6.61 t[c]	3.89 m	3.55 m	6.41 d[c]
r	$R_{2'}$ = CH_3; R_4 = OCH_3	9.15 m	8.68 (3) d[k]	5.06 d	7.97 d[c]	6.44 dd	6.16 (3) s	3.78 dd	6.83 dd
s	$R_{2'}$ = C_6H_5	8.18 d	2.89 (5) s	4.49 d	7.58 d[c]	6.53 t[c]	3.81 m	3.49 m	6.31 d[c]
t	R_6 = F	9.88 dd	8.37 dd	4.58 t[c]	7.93 m	6.65 m	4.15 m	3.42 m	
u	R_6 = Cl	9.90 dd	8.38 dd	4.53 dd	8.03 d[c]	6.58 t[c]	4.02 m	3.26 dd	
v	R_6 = Br	9.92 dd	8.38 dd	4.56 t[c]	8.06 d[c]	6.55 t[c]	4.03 m	3.16 dd	
wI	R_3 = Cl	9.85 dd	8.43 dd	4.98 t[c]	7.89 s[c]		~3.77[e]	~3.77[e]	6.47 d[c]
wII	R_5 = Cl	9.95 dd	8.52 dd	4.96 t[c]	8.15 d[c]	6.81 t[c]	3.75 d[c]		6.17 s[c]
x	R_4 = Cl	9.98 dd	8.47 dd	4.91 t[c]	8.00 d[c]	6.30 dd		3.27 dd	6.56 dd

[a] Solutions in $CDCl_3$, TMS internal standard. [b] *J* taken for all compounds (Hz): $H_{2'a}H_{2'b}$ = 2.2–2.7; $H_{2'a}H_{1'}$ = 7.8–9.0; $H_{2'b}H_{1'}$ = 6.7–7.2; H_3H_4 = 5.0–5.7; H_3H_6 = 1.5–1.9; H_4H_5 = 6.0–6.3; H_4H_6 = 1.5–2.7; H_5H_6 = 4.5. [c] Peaks broad due to further coupling. [d] Hidden under methyl peak. [e] Chemical shifts overlapped. [f] τ 2.33 (m, 2), 2.63 (m, 3). [g] τ 7.49 (m, 1), 8.56 (d, 3), 8.62 (d, 3, *J* = 6.3 Hz). [h] τ 2.58 (d, 2), 3.15 (d, 2, *J* = 8.7 Hz), 6.18 (s, 3). [i] τ 8.23 (m, 1), 8.93–9.51 (m, 4). [j] $J_{H_{2'a}CH_3}$ = 6.0 Hz. [k] $J_{H_{2'a}CH_3}$ = 6.6 Hz.

(**9** → **10**) could be effected with $Fe_2(CO)_9$ in the absence of light. The transition involving coordination of two of the ring electrons (**8** → **9**) could not be effected without photoactivation. Both the requirement of an energy source for this step and the observed instability of **9** relative to **10** would be predicted from considerations of the energy needs for loss of aromaticity (**8** → **9**) and the energy compensation in the formation of the second diene–tricarbonyliron unit (**9** → **10**).

Loss of aromatic character in complexes **9** is observed by the high-field appearance (~τ 7.0) of one of the ring protons (H_2) in the nmr spectra, by the disappearance of aromatic bands in the ir spectra, and in the ability of those complexes to undergo further reaction with iron carbonyl under mild conditions to give complexes **10**. The representation of the complexed units of **9** and **10** as classical diene–tricarbonyliron units is also indicated from spectral data in the characteristic metal carbonyl absorption in the ir, and in the nmr chemical shift separation of central and terminal protons of each unit. It can be demonstrated further that nmr chemical shift contributions of substituents within a complex on the

SCHEME VII

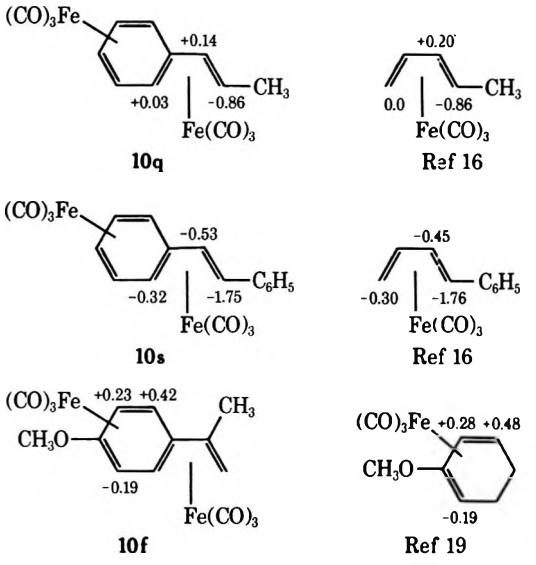


7 8 9 10

protons of the same unit are of the same order as those observed for butadiene- and cyclohexadiene–tricarbonyliron derivatives. This is illustrated in Scheme VIII. The values given represent the chemical shift

SCHEME VIII

A COMPARISON OF STYRENE–BISTRICARBONYLIRON COMPLEXES (10) WITH SUBSTITUTED DIENE–TRICARBONYLIRON MODELS, BY SUBSTITUENT CHEMICAL SHIFT CONTRIBUTIONS



differences when the substituent (CH_3, C_6H_5, or CH_3O) replaces a proton, and comparison is made between complex units of **10** and those of diene complexes from the literature.

It follows from the spectral data that similarity between complexed units of **9** and **10** with diene–tricarbonyliron models can be drawn both to the nature of π coordination between metal and organic ligand and to bonding within the ligand. Thus, all of the eight π electrons of the original system would be localized within the individual diene units (four and four), and freedom of rotation at the bond between the original vinyl and aromatic groups will be lost on the formation of **9** and **10**. Both characteristics are dramatized by the isolation of positional isomers of originally meta-substituted styrenes, **10dI** and **dII**, **10jI** and **jII**, and **10wI** and **wII**. Within isomer pairs the original six π electrons of the aromatic system have been trapped in both Kekulé-type structures, represented by **15** and **16**,

15 16

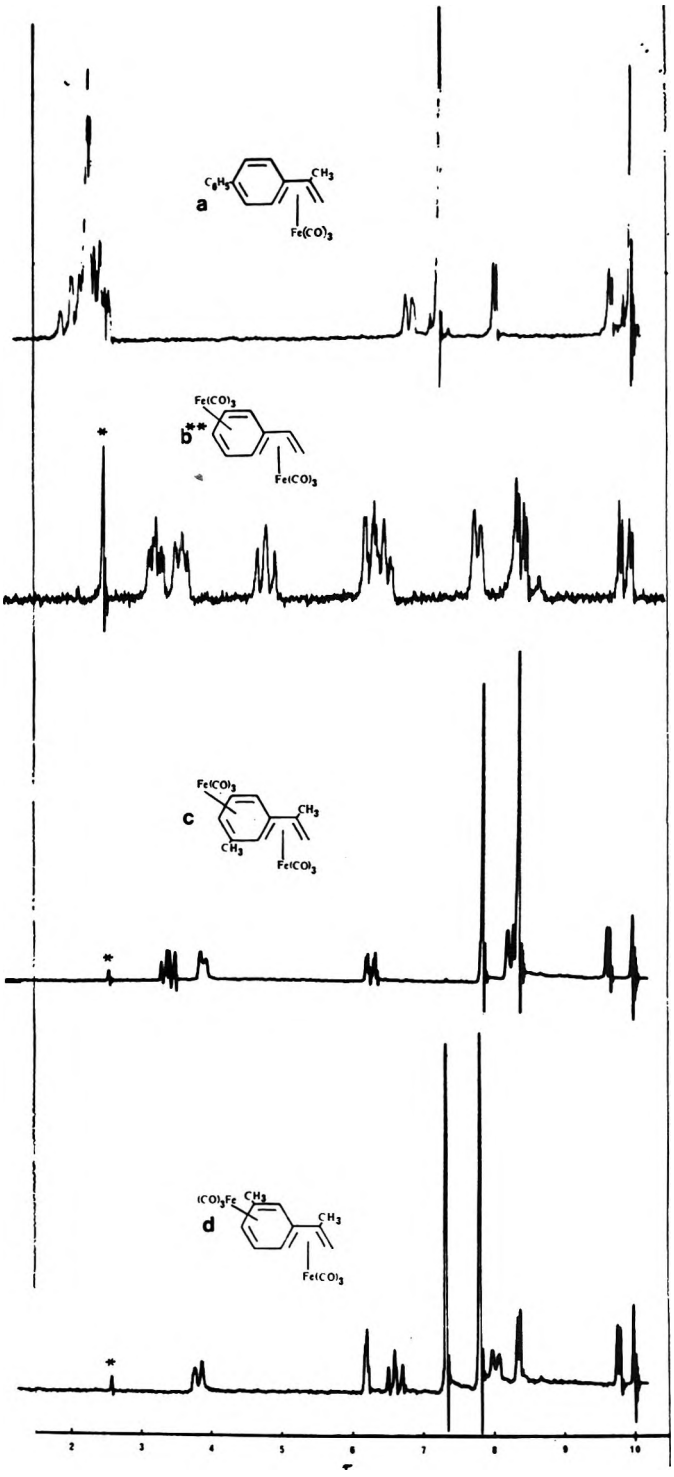


Figure 2.—60-MHz nmr in chloroform-*d* solution: (a) α-methyl-4-phenylstyrene–tricarbonyliron (**9k**); (b) styrene–bistricarbonyliron (**10a**); (c and d) bistricarbonyliron positional isomers of 3,α-dimethylstyrene (**10dI** and **10dII**). *, $CHCl_3$; **, TMS excluded.

and there appears no equilibration between the isomeric complexes. Each trapped structure is also coupled with one of two limiting conformations of the vinyl group, and both conformations should be in the plane of the ring according to the classical diene–tricarbonyliron model.[20] It is further assumed that the two iron moieties in complexes **10** will be in a trans relationship, one above and one below the plane of the ligand, in analogy to bistricarbonyliron complexes of *m*- and *p*-

(20) O. S. Mills and G. Robinson, *Proc. Chem. Soc.*, 421 (1960).

divinylbenzenes (**4** and **5**).[8] X-Ray studies of complexes of types **9** and **10** are in progress, and results will be communicated later.

Experimental Section

Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 237 grating infrared spectrophotometer as hexane solutions for analysis of the metal carbonyl region and as potassium bromide pellets for full spectra. Nuclear magnetic resonance spectra were taken of solutions in $CDCl_3$ on a Jeol C-60H spectrometer. Tetramethylsilane was used as internal standard, and, when samples gave chemical shift near τ 10, this standard was added after the full spectrum was taken. Mass spectra were performed on a MAT CH-5 spectrometer.

Elementary analyses were carried out by A. Bernhardt, Mikroanalytisches Laboratorium, Elbach über Engelskirchen, West Germany.

Apparatus.—The irradiation vessel was equipped with a nitrogen bubbler, a sample outlet, an internal Pyrex or quartz cooling jacket into which the lamp was inserted, and an external condenser. The capacity of the Pyrex vessel to the sample outlet was ~110 ml. The lamp generally employed when monitoring the reaction was a Hanau Q81 lamp, 70 W. A fairly rapid stream of tap water through the internal jacket and the external condenser provided the only source of cooling.

Organic Substrates.—The following substrates were prepared from standard Grignard reactions and dehydration of the carbinols: 2,α-dimethylstyrene (**7c**),[21] 3,α-dimethylstyrene (**7d**),[21] 4-fluoro-α-methylstyrene (**7q**),[22] 4-chloro-α-methylstyrene (**7h**),[22] 4-bromo-α-methylstyrene (**7j**),[22] α-methyl-4-phenylstyrene (**7k**),[23] 4-isopropyl-α-methylstyrene (**7l**),[24] 4-*tert*-butyl-α-methylstyrene (**7m**),[25] 1,1-diphenylethylene (**7n**),[26] 1-(4′-anisyl)-1-phenylethylene (**7o**),[27] 1-(4′-anisyl)-1-cyclopropylethylene (**7p**),[28,29] and 1-phenylpropene (**7q**).[30] The remaining substrates were obtained from commercial sources.

Standard Irradiation Procedure.—Solutions of the organic substrate (~0.05 *M*) and $Fe(CO)_5$ (~0.05 *M*) in hexane were irradiated with magnetic stirring and nitrogen flow for 1–3 hr. Samples of the reaction solution were taken at intervals for ir analysis of the carbonyl region (2100–1800 cm^{-1}). For a normally reactive substrate the appearance of **8** ($\nu_{CO} \simeq 2080$ cm^{-1}) occurred within the first 5 min of irradiation followed closely by **9** ($\nu_{CO} \simeq 2045$ cm^{-1}). While the former reached a fairly steady concentration, the latter increased continuously. After 0.5 to 0.75 hr of irradiation, complex **10** became apparent ($\nu_{CO} \simeq 2055$ cm^{-1}), also increasing in concentration until irradiation was interrupted. Even after 3 hr of irradiation the bulk of the starting material could be recovered on work-up.[31] If complex formation was slow, the inner jacket became coated with $Fe_2(CO)_9$, requiring interruption of the irradiation (at hour intervals) and cleaning of the inner jacket.

Work-Up of Products.—The reaction mixture was filtered, and hexane and unreacted $Fe(CO)_5$ were removed on a rotary evaporator. When extremely air-sensitive complexes were present in the reaction mixture, extensive decomposition was encountered at this stage of work-up. The residue was taken into petroleum ether (bp 40–60°) and eluted by the same solvent on a column of Florisil (~50 g) with a layer of neutral alumina above (~5 g). The order of elution was generally as follows: unreacted substrate **7**, tetracarbonyliron complex **8**, monotricarbonyliron complex **9**, and bistricarbonyliron complex **10**. Further separation of complexes could be effected by fractional recrystallization and by preparative tlc on silica with petroleum ether eluents. Isolation of the monotricarbonyliron complexes of α-methylstyrene (**9b**) and 4-chloro-α-methylstyrene (**9h**) was achieved by removing unreacted substrate from the complex-rich fractions off column chromatography on an oil pump and subliming the complex at low pressure (~0.1 mm) with gentle heating (40–50° bath temperature). From the irradiation of **7p** a red solid, 3-(4′-anisyl)cyclohex-3-enonetricarbonyliron,[1b] was filtered from the reaction mixture, and separation of the evaporated filtrate on column chromatography gave **7p**, **8p**, and **10p** with petroleum ether and 3-(4′-anisyl)cyclohex-2-enone with diethyl ether.

Separation of Isomers.—Column chromatography and preparative tlc in combination were effective in the separation of bistricarbonyliron isomers from 3-chlorostyrene (**10wI**, **10wII**), 3-bromo-α-methylstyrene (**10jI**, **10jII**), and 1-(4′-anisyl)-1-phenylethylene (**10oI**, **10oII**) with more rapid elution of **10wII**, **10jII**, and **10oI** by both techniques. Chromatography was not effective in the separation of isomers from 3,α-dimethylstyrene (**10dI**, **10dII**). Instead, the coprecipitated crystals (pentane solvent) were manually separated according to color (**10dI**, purple; **10dII**, orange) and recrystallized individually.

Stability of Compounds 8, 9, and 10.—A number of air- and heat-sensitive complexes of types 8 and 9 were encountered in the work-up of reaction mixtures. In general, substitution at C-1′ and C-2′ of the original styrene destabilized complexes of type **8**. On the other hand, substitution at C-1′ (CH_3, Ar) increased the stability of the complexes of type **9**, though these too were sensitive to heating and to prolonged standing in solution. Only derivatives of α-methylstyrene were isolated in sufficient purity for spectral analysis, with the order of stability in handling

TABLE IV

PHYSICAL PROPERTIES OF STYRENE–TRICARBONYLIRON COMPLEXES 9 AND STYRENE–BISTRICARBONYLIRON COMPLEXES 10

Complex	Mp (dec), °C	Color	Calcd, % C	Calcd, % H	Found, % C	Found, % H
9b	53	Red-purple	55.85	3.91	32.67[a,b]	3.21
9h[c]	80	Red-purple	49.28	3.10	49.04	2.96
9i	76	Red-purple	42.78	2.69	39.07[a,d]	3.30
9k	104	Red-purple	64.70	4.22	64.85	4.35
10a	121	Orange-red	43.80	2.10	43.98	2.03
10b	131	Red	45.28	2.53	45.43	2.56
10c	90	Orange-red	46.65	2.94	46.82	2.93
10dI	93	Purple	46.65	2.94	46.83	3.04
10dII	116	Orange-red	46.65	2.94	46.77	2.95
10e	119	Orange-red	46.65	2.94	46.82	2.92
10f	136	Orange-red	44.91	2.83	45.07	2.66
10g	106	Orange	43.32	2.18	43.48	2.33
10h[e]	120	Orange-red[f]	41.67	2.10	41.66	2.12
10i	119	Orange	37.78	1.90	38.03	1.70
10jI	108	Red	37.78	1.90	37.88	1.92
10jII	104 (imp)	Orange-red	37.78	1.90	39.88[a,f]	1.83
10k	132	Red-purple	53.21	2.98	52.99	2.96
10l	104	Orange	49.13	3.67	49.28	3.59
10m	107	Orange	50.26	4.00	50.27	3.88
10n	115	Red	52.22	2.63	52.37	2.66
10oI	135	Orange	51.47	2.88	51.34	2.79
10oII	132	Orange-red	51.47	2.88	51.66	2.83
10p	102 (imp)[g]	Orange-red				
10q	116	Orange-red	45.28	2.53	45.43	2.66
10r	109	Orange	44.91	2.83	44.76	2.98
10s	134	Orange-red	52.22	2.63	52.38	2.78
10t	110	Orange-red	41.82	1.73	42.04	1.85
10u	86	Orange-red	40.19	1.69	40.25	1.77
10v	95 (imp)	Orange-red	36.33	1.52	37.55[a,h]	1.69
10wI	93	Orange-red	40.19	1.69	40.34	1.81
10wII	120	Orange	40.19	1.69	40.30	1.86
10x	117	Orange-red	40.19	1.69	40.39	1.79

[a] Sample decomposed in transit. [b] Mass spectrum, M^+ = 258. [c] Calcd: Cl, 12.12; Fe, 19.10. [e] Calcd: Cl, 8.20; Fe, 25.83. Found: Cl, 8.17; Fe, 25.45. [f] Mass spectrum, M^+ = 476, 478. [g] Sample of unsufficient quantity and purity for analysis; mass spectrum, M^+ = 454. [h] Mass spectrum, M^+ = 418, 420.

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(31) Prolonged irradiation resulted in the accumulation of particles of decomposition on the inner jacket and within the solution; thus in no case was the irradiation extended to consumption of either of the reactants.

found to be **9k** (R_4 = C_6H_5) > **9i** (R_4 = Br) > **9h** (R_4 = Cl) > **9b** (R_4 = H).

Complexes of type **10** were generally stable to work-up conditions and repeated recrystallizations. Prolonged exposure to air or heat sometimes resulted in partial decomposition, particularly in those compounds containing halogen on the ring.

Yields.—With the exception of **7p**, which gave 20–30% yields of cyclohexenone derivatives, more than 70% of the organic substrate was recovered on work-up of reaction mixtures. The bistricarbonyliron complexes presented in Table IV were obtained in yields of <1 to 8% after 3-hr irradiation with a 70-W light source. Greater yields (up to 20%) of **2**, **4**, **11**, and **12** were obtained under the same conditions.

Reactions of α-Methylstyrene (7b) under Reflux Conditions. A.—A solution in hexane of **7b** (0.9 g) and $Fe(CO)_5$ (1.05 g) was irradiated for 0.75 hr with water flow in the inner jacket regulated for mild reflux of the reaction solution. Only $Fe(CO)_5$ and $Fe_3(CO)_{12}$ were detected in ir analysis of the metal carbonyl region, and the bulk of **7b** was recovered on work-up.

B.—A solution similar to that in part A was irradiated at room temperature for 1 hr, then refluxed with continued irradiation for an additional 0.5 hr. Work-up of the reaction mixture afforded only **7b** and a small quantity of **10b**.

Reaction of α-Methyl-4-phenylstyrene (7k).—A solution of **7k** (0.1 g) in 15 ml of hexane was stirred with 1.0 g of $Fe_2(CO)_9$ for 48 hr under nitrogen. Ir analysis indicated early formation of **8k** and $Fe_3(CO)_{12}$. Work-up on a short column of Florisil yielded $Fe_3(CO)_{12}$ and a mixture of **7k** and **8k**.

Reaction of 2-Bromostyrenetetracarbonyliron (8v).—A solution of **8v** (0.5 g) in 110 ml of hexane was irradiated for 6 hr and analyzed by ir monitoring of the metal carbonyl region. After 20 min only a small concentration of **8v** was still present while the bands typical of diene–$Fe(CO)_3$ (~2055, 1993, 1983 cm^{-1}, **9v**) were at a maximum. Continued irradiation produced bands characteristic of the diiron complex **10v**. Preparative tlc of the residue after evaporation afforded separation of 2-bromostyrene (**7v**) and two complexes, one identical by ir and melting point with **10v**, and the other identical [mp 120°; ν_{CO} (hexane) 2070, 2036, 2000, 1993 cm^{-1} (sh)] with **13** (see ref 12).

Reactions of 4-Chloro-α-methylstyrenetricarbonyliron (9h). A.—A solution of **9h** (0.10 g) in 110 ml of hexane was irradiated for 3.75 hr. Consumption of **9h** and an increase in bands characteristic of **10h** were observed in the ir throughout the irradiation. Work-up of the residue after evaporation gave **7h** and a considerably smaller amount of **10h**.

B.—Heating a solution similar to that in part A at 45° for 1 hr resulted only in a small decrease in the concentration of **9h**. At reflux temperature of hexane **9h** in this solution decomposed completely within 10 min, and no other organometallic materials were observed.

C.—Irradiation of a solution similar to that in part A with 0.5 g of $Fe(CO)_5$ for 2.5 hr yielded **10h** at a rate greater than that in part A on comparison of ir concentrations of **10h** at any given time.

Reaction of α-Methyl-4-phenylstyrenetricarbonyliron (9k).—A solution of **9k** (0.2 g) in 15 ml of hexane was stirred with $Fe_2(CO)_9$ for 1.5 hr under nitrogen. Carbonyl bands of **10k** and $Fe(CO)_5$ were apparent throughout the period allotted. Work-up of the evaporated residue permitted isolation of **10k** (ir, melting point data).

Acknowledgment.—The authors are grateful to Badische Anilin und Soda Fabrik, Germany, for a gift of iron pentacarbonyl.

Solvomercuration–Demercuration. III. The Relative Rates of Oxymercuration of Representative Olefins in an Aqueous Tetrahydrofuran System

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The relative reactivities of a number of olefins have been determined in aqueous tetrahydrofuran in order to provide a basis for predicting the possibilities of the oxymercuration–demercuration procedure for the selective reaction of one olefin in the presence of a second or the selective reaction of one of the two double bonds in a diene. The results reveal the following reactivity trends with respect to the position of the double bond and the degree of substitution: terminal disubstituted > terminal monosubstituted > internal disubstituted > internal trisubstituted > internal tetrasubstituted. In the case of disubstituted internal olefins, RCH=CHR′, cis olefins are more reactive than the corresponding trans. The rates of oxymercuration reveal marked decreases with increasing branching of the alkyl groups attached to the double bond. This is true irrespective of whether the branched alkyl group is attached to the carbon atom which receives the mercury addendum or the entering hydroxyl group. Inclusion of the double bond in ring systems causes a relatively moderate rate increase which varies modestly with structure: cyclohexene > cyclopentene ≫ cyclooctene; norbornene ≫ bicyclo[2.2.2]oct-2-ene. Conjugation of the double bond with the benzene ring results in a rate decrease. The results can be rationalized in terms of carbonium ion stability, the strain in the double bond, and steric interactions. However, irrespective of the precise interpretations, the results provide a basis for predicting the course of selective oxymercuration–demercuration of mixtures of olefins or unsymmetrical dienes.

In previous papers the broad synthetic utility of the solvomercuration–demercuration process has been indicated. Thus, alcohols,[3] ethers,[4] and amines[5] with the Markovnikov orientation are readily prepared from a wide variety of olefins in excellent yield. Oxymercuration–demercuration has also been extended to dienes and unsaturated alcohols to produce diols, tetrahydrofurans, and tetrahydropyrans.[6]

It then appeared appropriate to undertake a systematic study of the utilization of this procedure for the monohydration of dienes.[7] However, such a study required quantitative data on the effect of modifications in the olefin structure on the rate of oxymercuration under the conditions of the proposed procedure. In this way we could hope to establish the practicality of predicting the point of attack of the reagent in the proposed monohydration of dienes.

Only a limited number of studies have been described in which data have been obtained on the rates of oxymercuration of several nonfunctionally substituted olefins. Indeed, most of the kinetic studies have

(1) National Defense Education Act Fellow (Title IV) at Purdue University, 1965–1968.

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involved methoxymercuration. Thus, the study of Spengler and coworkers involved the reaction of various isomeric hexenes and nonenes with mercuric acetate in methanol.[8] Similarly, Asinger and coworkers examined the reaction of various isomers of *n*-undecene with mercuric acetate in methanol.[9]

Their results are quite interesting. Thus, Spengler, *et al.*,[8] noted that in the case of the normal straight-chain olefins the 1-alkene reacts about ten times faster than the 2-alkene and about 100 times faster than the 3-alkene. Branching in the alkyl group results in a decrease in rate. Thus, 1-hexene is converted to product at four times the rate of 4-methyl-1-pentene. Terminal-disubstituted olefins, such as 2-methyl-1-pentene, react about twice as fast as the monosubstituted isomer, such as 1-hexene. Branching in a remote position has little effect upon the rate, as indicated by the comparable rates for 3,6-dimethyl-1-heptene and 3-methyl-1-octene.

According to the results of Asinger and coworkers,[9] both *cis*- and *trans*-2-undecene react considerably slower than 1-undecene. Moreover, the *trans*-*x*-undecenes always react at a slower rate than the corresponding cis isomer (x = 2, 3, 4, and 5). The rates of reaction of both *cis*- and *trans*-*x*-undecene decrease as x increases, that is, with the positioning of the double bond further toward the center of the chain. Finally, the ratio $k_{\text{cis-}x}/k_{\text{trans-}x}$ increases as x increases.

Halpern and Tinker examined the rates of oxymercuration of a number of unsaturated compounds in aqueous mercuric perchlorate solution.[10] In order to achieve adequate solubility of the substrate in the water medium, most of the olefins utilized carried functional substituents. However, their data do reveal, in agreement with the methoxymercuration data,[8] that terminal-disubstituted olefins react faster than monosubstituted olefins, that internal olefins react slower than terminal olefins, and that cis olefins react faster than the corresponding trans isomer.

We were interested in a far broader range of olefin structures than the previous studies provided. Moreover, we were interested in reactivities for the aqueous tetrahydrofuran system utilized in our general procedure.[3] Accordingly, we decided to undertake a determination of the relative reactivities of a wide variety of representative olefin structures by a competitive technique.

Results and Discussion

The standard oxymercuration–demercuration procedure utilizes a 50:50 (v/v) mixture of water and tetrahydrofuran. In many cases the olefin is only partially soluble in this medium. For the usual oxymercuration–demercuration synthesis, such partial solubility offers no difficulty. However, for the competitive reaction of two olefins or one double bond of a diene it was highly desirable to avoid complications in the data arising from partial miscibility. Accordingly, we adopted for the medium a 20:80 (v/v) mixture of water and THF. Cyclohexene was adopted as the standard (k_r = 1.00) and the relative reactivities of all other olefins referred to this standard.

The standard procedure used to determine the relative reactivities of the various olefins follows. Ten millimoles of each of two olefins was measured volumetrically and introduced into 50 ml of 80% aqueous THF. The solution was cooled to 0°. Generally the solution was observed to be homogeneous at this point. If it was not homogeneous, an additional 50 ml of solvent was added. Then 10 mmol of mercuric acetate was added to the stirred solution. After 1 hr (2 hr if 100 ml of solvent had been used, or if the two olefins were of relatively low reactivity), 10 ml of 3.0 *M* sodium hydroxide was added, followed by 10 ml of 0.5 *M* sodium borohydride in 3.0 *M* sodium hydroxide. A suitable glpc standard was added. After the precipitated mercury had coagulated, the aqueous phase was saturated with sodium chloride and potassium carbonate. A portion of the organic layer was removed, dried with potassium carbonate, and analyzed with a Hewlett-Packard Model 5750 gas chromatograph on a 10 ft × 0.25 in. Carbowax 20M on Chromosorb W (60/80) AW-DMCS column (1% Armeen 18D added).

The relative rates, k_r, were calculated according to the relationship $k_r = \log (A/A_0)/\log (A'/A_0')$, where A_0 and A_0' are the initial concentrations of olefins A and A′, respectively, and A and A' are the final concentrations of olefins A and A′. Both A and A' were measured in terms of the per cent recovery of the respective olefins. Each competitive experiment was run in duplicate. Generally the relative rates from duplicate experiments were well within 5% of the average value, k_r, reported in the tables.

If the conclusions as to the effect of structure on the rate of the oxymercuration stage are to be relied upon, it is necessary to consider both the accuracy and the reliability of the results. The initial olefin concentrations are probably accurate to within ±0.5% by the volumetric method employed. However, the uncertainties of the glpc analysis probably make the uncertainty in the final olefin concentrations to be no greater than ±3%. Moreover, owing to the nature of the relationship between k_r and the initial and final olefin concentrations, the uncertainty in k_r depends not only upon the uncertainty in each of the A terms, but also on the absolute value of each A term. Accordingly, the uncertainty is minimal when the two olefins have approximately the same reactivity, but increases rather severely as the difference in the reactivities of the two olefins become greater.

In order to check the internal consistency of the results, four pairs of olefins for which individual k_r values had been determined previously were oxymercurated competitively, utilizing the standard procedure. The relative reactivities were then calculated from results of the actual experimental data. These experimental relative reactivities were then compared to the relative reactivities calculated from the previously determined values for k_r. The results are summarized in Table I. The data reveal that the experimental and calculated values of the relative reactivities are reasonably consistent.

The olefins we selected for relative rate determinations were chosen to indicate the effects of specific types of structural features on the relative reactivity. Each

(8) V. G. Spengler, H. Frömmel, R. Schäff, P. Faul, and P. Lonsky, *Brennst.-Chem.*, **37**, 47 (1956).

(9) (a) F. Asinger, B. Fell, G. Hadik, and G. Steffan, *Chem. Ber.*, **97**, 1568 (1964); (b) F. Asinger, B. Fell, G. Steffan, G. Hadik, and F. Theissen, *Erdöel Kohle*, **18**, 178 (1965).

(10) J. Halpern and H. B. Tinker, *J. Amer. Chem. Soc.*, **89**, 6427 (1967).

TABLE I

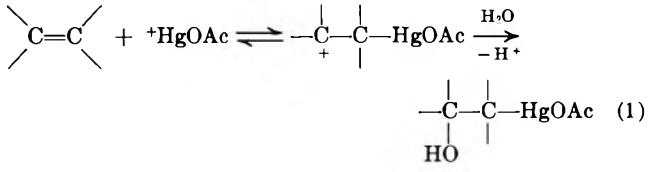
COMPARISON OF THE RELATIVE REACTIVITIES DETERMINED BY DIRECT EXPERIMENTAL COMPARISON AND CALCULATED FROM THE k_r VALUES

Olefin A	k_{r_A}[a]	Olefin B	k_{r_B}[b]	Rel reactivity—Calcd[c]	Rel reactivity—Exptl[d]
3-Methyl-1-butene	2.5	2,4-Dimethyl-2-pentene	0.056	44.7	39.9
1-Hexene	4.8	Cyclopentene	0.78	6.17	6.26
3,3-Dimethyl-1-butene	0.15	*cis*-4-Methyl-2-pentene	0.090	1.66	1.28
1-Pentene	6.6	1-Hexene	4.8	1.37	1.33

[a] Reactivity of olefin A relative to cyclohexene. [b] Reactivity of olefin B relative to cyclohexene. [c] k_{r_A}/k_{r_B}. [d] Calculated from the direct experimental comparison of the pairs of olefins A and B.

of these structural features are considered individually in the following sections.

Although this study was undertaken primarily with the objective of defining structural effects on reactivity, without considering the detailed mechanism of the reaction, it appears desirable at this point to mention the simple working hypothesis we have adopted. The electrophilic nature of the mechanism has been repeatedly demonstrated. The directive effects clearly point to an intermediate with cationlike properties. However, the precise structure of the intermediate ion as well as of the transition state leading to it remains a matter of some debate.[11] In the absence of any definite evidence supporting a mercurinium ion intermediate, we shall view it as essentially a carbonium ion with a large fraction of the charge remaining on the mercury moiety (eq 1). In terms of this hypothesis, the difference in properties of the intermediates produced by adding protons or mercuric ions to olefins is primarily the result of major differences in the amount of positive charge which is transmitted to the cationic centers of the intermediates.



(1)

Effect of Increased Branching in the Alkyl Group of 1-Alkenes.—In the oxymercuration of 1-alkenes the mercury atom invariably becomes attached to the 1-carbon atom and the nucleophile, water, becomes attached to the 2-carbon atom. Increased branching of the alkyl group results in a significant decrease in the relative rates of reaction (Table II).

TABLE II

EFFECT OF INCREASED ALKYL BRANCHING ON THE RELATIVE REACTIVITY

Olefin	Rel reactivity, k_r[a]
1-Pentene	6.6
1-Hexene	4.8
3-Methyl-1-butene	2.5
3,3-Dimethyl-1-butene	0.15

[a] Relative to cyclohexene.

Since the increased branching should not affect significantly the rate of attachment of the mercury atom to the terminal position, the decrease in relative reactivity is presumably the result of a steric retardation of the addition of water.

Effect of the Position of the Double Bond.—The results reveal that 1-alkenes are considerably more reactive than the corresponding 2-alkenes (Table III).

TABLE III

EFFECT OF THE POSITION OF THE DOUBLE BOND

Olefin	Rel reactivity, k_r[a]	k_{cis}/k_{trans}
1-Pentene	6.6	
cis-2-Pentene	0.56	3.29
trans-2-Pentene	0.17	
cis-4-Methyl-2-pentene	0.090	3.46
trans-4-Methyl-2-pentene	0.026	

[a] Relative to cyclohexene.

Effect of Cis–Trans Isomers.—In agreement with the results of previous workers,[9] the cis isomers are considerably more reactive than the trans. Data for two isomeric pairs are given in Table III. The lower rate for the 4-methyl-2-pentene derivatives as compared to the parent 2-pentenes is presumably the result of the larger steric requirements of the more branched alkyl substituent, as discussed earlier.

Effect of the Number of Alkyl Substituents on the Double Bond.—The introduction of a methyl group in the 2 position of a 1-alkene results in a considerable increase in reactivity. Thus the reactivity of 2-methyl-1-pentene is seven times greater than that of 1-pentene. Similarly, the reactivity of 2-methyl-2-pentene is higher than those of *cis*- and *trans*-2-pentene (Table IV). This effect can be rationalized in terms of the fact that the addition of the mercury ion to the less substituted carbon atom in the more reactive systems puts the positive charge at a tertiary position. The relatively small effect which is observed is consistent

TABLE IV

EFFECTS OF SUBSTITUENTS ON THE DOUBLE BOND

Olefin	Rel reactivity, k_r[a]
1-Pentene	6.6
2-Methyl-1-pentene	48
cis-2-Pentene	0.56
trans-2-Pentene	0.17
2-Methyl-2-pentene	1.24
2,4-Dimethyl-2-pentene	0.056
2,4,4-Trimethyl-2-pentene	0.020
2,3-Dimethyl-2-butene	0.061

[a] Relative to cyclohexene.

(11) For a recent review of the literature, see W. Kitching, *Organometal. Chem. Rev.*, **3**, 61 (1968).

with the proposal that very little positive charge is actually transmitted from the mercury ion to the carbon atom in the transition state.

It was earlier pointed out that increased branching in the alkyl group adjacent to the position adding the nucleophile results in decreased reactivity (Table II). The data for 2-methyl-2-pentene and 2,4-dimethyl-2-pentene (Table IV) indicate that steric crowding about the carbon atom to which the mercury atom is becoming attached likewise results in decreased rates. The further decrease observed for 2,4,4-trimethyl-2-butene agrees with this conclusion. It appears, therefore, that branching of the alkyl group attached to the double bond results in a decrease in reactivity irrespective of whether it is located at the carbon atom of the double bond where the mercury atom is becoming attached or at the carbon atom where the nucleophile is adding.

Effect of Ring Systems.—The results reveal that olefins derived from cyclopentyl and cyclohexyl systems exhibit reactivities slightly greater than the corresponding acyclic structures. The reactivity of cyclooctene is quite low. On the other hand, norbornene is quite reactive, while bicyclo[2.2.2]oct-2-ene exhibits a low reactivity.

The results are summarized in Table V.

TABLE V
EFFECT OF RING SYSTEMS

Olefin	Rel reactivity, k_r[a]	Acyclic analog	Rel reactivity, k_r[a]
Cyclopentene	0.78	*cis*-2-Pentene	0.56
Cyclohexene	1.00		
1-Methylcyclopentene	1.86	2-Methyl-2-pentene	1.24
Methylenecyclopentane	59	2-Methyl-1-pentene	48
Cyclooctene	0.002		
Norbornene	3.7		
Bicyclo[2.2.2]-octene	0.01		

[a] Relative to cyclohexene.

It is of interst that cyclooctene, which has an exceptionally low heat of hydrogenation,[12] has the lowest rate of reaction, and norbornene, with a very high heat of hydrogenation, is quite reactive in the oxymercuration reaction. However, with steric effects at both positions of the double bond influencing strongly the relative reactivity, the situation is obviously too complex to permit such simple correlations.

Effect of Conjugation of the Double Bond to a Benzene Ring.—The relative reactivities of four phenyl conjugated olefins are summarized in Table VI.

The results reveal that compared to an alkyl group the phenyl substituent results in a marked rate retardation. For example, styrene reacts only at $^1/_{17}$ the rate of 1-hexene. Conjugative resonance stabilization of the incipient cationic intermediate either is absent or is surpassed in magnitude by some opposing factor. The weak sensitivity of the reaction to stabilization of the incipient carbonium ion by alkyl groups, pointed out earlier, indicates that only a small amount of positive charge is transmitted to the incipient cationic center in the transition state. On this basis, it is not surprising that resonance stabilization by the phenyl substituent fails to dominate the situation. Conjugation of the benzene ring to the double bond should lower the ground state energy and thereby decrease the rate. Secondly, the steric requirements of the aromatic ring may be comparable to those of an isopropyl and *tert*-butyl group. Indeed, the reactivity of styrene falls between that of 3-methyl-1-butene and 3,3-dimethyl-1-butene. Consequently, the observed low rate may in part be due to steric effects.

(12) R. B. Turner, "Theoretical Organic Chemistry," The Kekule Symposium, Butterworths, London, 1959, pp 67–83.

TABLE VI
EFFECT OF CONJUGATION OF THE DOUBLE BOND TO A BENZENE RING

Olefin	Rel reactivity, k_r[a]
Styrene	0.28
α-Methylstyrene	1.18
cis-Propenylbenzene	<0.02
trans-Propenylbenzene	<0.02

[a] Relative to cyclohexene.

Comparison with Previous Data.—Although the present results were obtained under very different conditions, it is of interest to compare them with previous data and conclusions. Spengler and coworkers[8] report that 2-hexene reacts twice as fast as 4-methyl-2-pentene; we find that *trans*-2-pentene reacts six times faster than *trans*-4-methyl-2-pentene. They report that 1-hexene reacts ten times as fast as 2-hexene; we find that 1-pentene reacts 41 times as fast as *trans*-2-pentene and 12 times as fast as *cis*-2-pentene. Finally, Spengler reports that 2-methyl-1-pentene reacts twice as fast as 1-hexene; for these same two olefins we obtain a relative reactivity of seven. Thus, in spite of the fact that Spengler's data refer to the reaction of mercuric acetate in methanol at 20°, whereas ours refers to the addition of the same salt in 80% aqueous THF at 0°, the qualitative agreement is quite good.

The relative reactivities of 1- (1.000), *cis*-2- (0.086), and *trans*-2-undecene (0.022), obtained by Asinger and coworkers for methoxymercuration,[10] are almost identical with our relative reactivity values for the oxymercuration of a related series: 1- (1.000), *cis*-2- (0.085), *trans*-2-pentene (0.024).

Several olefins oxymercurated by Halpern and Tinker[10] exhibit structural features similar to some of those included in the present investigation. A comparison of the two sets of data (Table VII) reveals agreement that can only be considered remarkable in view of the difference in the experimental conditions.

TABLE VII
COMPARISON OF OXYMERCURATION REACTIVITIES

Study of Halpern and Tinker[10]		Present study	
Olefin	Rel reactivity[a]	Olefin	Rel reactivity[b]
2-Methyl-1-propene	>600	2-Methyl-1-pentene	282
1-Butene	47 ± 12	1-Hexene	28
Cyclohexene	2.9 ± 0.6	Cyclohexene	5.9
cis-2-Butene	3.4	*cis*-2-Pentene	3.3
trans-2-Butene	1.00	*trans*-2-Pentene	1.00

[a] Relative to *trans*-2-butene, using aqueous mercuric perchlorate. [b] Relative to *trans*-2-pentene, using 80% aqueous THF.

Conclusion

The oxymercuration–demercuration of olefins has previously been shown to be a highly convenient synthetic method for the Markovnikov hydration of olefins. The present paper has demonstrated a wide range of reactivity accompanying variation of olefin structure. Accordingly, considerable selectivity in the monooxymercuration of dienes is expected. Steric factors play a major role in determining the reactivity of hydrocarbon olefins. Thus, increased substitution on the double bond (as long as the carbonium ion stability remains the same) and increased steric hindrance at the site of hydroxyl or mercury substituent attachment decrease the rate of reaction. Increased stability of the carbonium ion or decreased stability of the olefinic ground state due either to increased cis interactions or constraint in a bicyclic ring system increase the reactivity of the double bond. However, since the situation appears to be relatively complex, it appears best to proceed from experimental data on the relative reactivities of known structures to predict the results of competitive oxymercuration of mixtures of olefins. As will be pointed out in the following paper,[7] the data are helpful in predicting the course of monohydration of dienes.

Experimental Section

Materials.—All olefins used were commercially available and were used as obtained unless vpc or index of refraction data indicated impurities. Mercuric acetate (Mallinckrodt Chemical Works), sodium borohydride (Metal Hydrides, Inc.), and tetrahydrofuran (Fisher Scientific Co.) were used without further purification.

Oxymercuration Procedure.—The general procedure used has been discussed in the text. Cyclohexene was used as the reference olefin in all cases except the following. Norbornene was determined relative to styrene and also relative to 1-pentene. α-Methylstyrene was determined relative to styrene. 2,4,4-Trimethyl-2-pentene, bicyclo[2.2.2]oct-2-ene, and cyclooctene were all determined relative to 2,3-dimethyl-2-butene. In all cases where a reference olefin other than cyclohexene was used, the k_r value was back-calculated to cyclohexene for purposes of presentation in the text.

Control Experiment.—In order to establish that the mercurials do not equilibrate under the reaction conditions employed, the following experiment was performed. Cyclohexene and 1-hexene were oxymercurated separately for 15 min on a 10-mm scale employing 10 mm of mercuric acetate, 10 ml of water, and 10 ml of THF for each olefin; 30 ml of THF was then added to each reaction mixture and the solutions were cooled to 0°. To each reaction mixture was added 10 mm of the other olefin and the solutions were stirred for 8 hr at 0°. Reduction of the mercurials and subsequent vpc analysis showed that no more than 3% of the mercurial from either olefin was converted into the mercurial of the other olefin.

Registry No.—3-Methyl-1-butene, 563-45-1; 1-hexene, 592-41-6; 3,3-dimethyl-1-butene, 558-37-2; 1-pentene, 109-67-1; 2,4-dimethyl-2-pentene, 625-65-0; cyclopentene, 142-29-0; *cis*-4-methyl-2-pentene, 691-38-3; *cis*-2-pentene, 627-20-3; *trans*-2-pentene, 646-04-8; *trans*-4-methyl-2-pentene, 674-76-0; 2-methyl-1-pentene, 763-29-1; 2-methyl-2-pentene, 625-27-4; 2,4,4-trimethyl-2-pentene, 107-40-4; 2,3-dimethyl-2-butene, 563-79-1; cyclohexene, 110-83-8; 1-methylcyclopentene, 693-89-0; methylenecyclopentane, 1528-30-9; cyclooctene, 931-88-4; norbornene, 498-66-8; bicyclo[2.2.2]octene, 931-64-6; styrene, 100-42-5; α-methylstyrene, 98-83-9; *cis*-propenylbenzene, 766-90-5; *trans*-propenylbenzene, 873-66-5; 2-methyl-1-propene, 115-11-7; 1-butene, 106-98-9; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6.

Solvomercuration–Demercuration. IV. The Monohydration of Representative Dienes *via* Oxymercuration–Demercuration

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The oxymercuration–demercuration of dienes with 1 mol of mercuric acetate per mole of diene under standard conditions (80% aqueous tetrahydrofuran) provides a convenient procedure for the Markovnikov monohydration of one of the two double bonds in the diene. In the case of symmetrical nonconjugated dienes, such as 1,5-pentadiene, 1,7-octadiene, and 1,11-dodecadiene, the yield of enol is lower than predicted for a statistical reaction (50% enol) but approaches the statistical value with the longer chains. The yields can be raised by using mercuric trifluoroacetate. In the case of unsymmetrical dienes, such as 2-methyl-1,11-dodecadiene, 11-methyl-1,10-dodecadiene, 4-vinylcyclohexene, and limonene, the yields of enols are higher and involve selective hydration of the double bond whose structural features indicate it to be the more reactive on the basis of the related study of the relative reactivities of representative olefins under these conditions. Good yields of enols can also be realized from conjugated dienes provided that the reaction time is minimized.

Hydroboration–oxidation provides a convenient procedure for the anti-Markovnikov hydration of the carbon–carbon double bonds in olefins and dienes.[5,6] Oxymercuration–demercuration provides an equally convenient procedure for the Markovnikov hydration of the carbon–carbon double bonds in olefins[7] and dienes.[8]

Although there have been a number of reports of the monosolvomercuration of dienes, a systematic study of the synthetic utility of the reaction for the synthesis of enols *via* the monohydration of dienes has not been

(1) National Defense Education Act Fellow (Title IV) at Purdue University, 1965–1968.

(2) Graduate research assistant on a study supported by funds from the Esso Research and Engineering Co.

(3) National Science Foundation Fellow at Purdue University, 1967–1969.

(4) National Science Foundation Trainee at Purdue University, 1969–1971.

(5) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962.

(6) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).

(7) H. C. Brown and P. J. Geoghegan, Jr., *J. Org. Chem.*, **35**, 1844 (1970).

(8) H. C. Brown, P. J. Geoghegan, Jr., J. T. Kurek, and G. J. Lynch, *Organometal. Chem. Syn.*, **1**, 7 (1970/1971).

available. Indeed, much of the previous research involving dienes has been concerned more with the mechanism of either the oxymercuration stage[9] or the reduction stage[10] than with the synthetic application of the reaction.

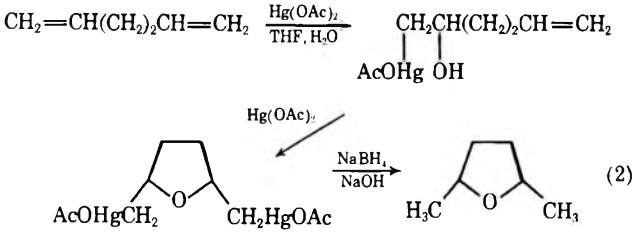
Accordingly, we decided to examine the feasibility of achieving the Markovnikov monohydration of representative dienes utilizing our general procedure.[7,8] Two minor modifications in this procedure were made. In order to minimize possible complications arising from immiscibility of the diene in the reaction mixture, we adopted a less aqueous system, 80% (v/v) tetrahydrofuran–20% water. (The standard procedure utilized a 50:50 mixture.[7,8]) We also utilized a lower temperature, 0°, in many cases in order to enhance the possibility for selective reaction and to minimize the possibilities for side reactions in certain systems. Finally, the 80:20 aqueous THF system and 0° temperature corresponded to the conditions we had utilized in our study of the relative reactivity of various olefin structures.[11]

It should be pointed out that the available data make it clear that several complicating factors may intervene to interfere with the proposed synthesis. If the oxymercuration of a symmetrical diene, such as 1,7-octadiene, were purely statistical, the maximum conversion to the desired 7-octen-2-ol (eq 1) would be 50% (25% diene, 50% enol, 25% diol). However, if the mono-

$$CH_2{=}CH(CH_2)_4CH{=}CH_2 \xrightarrow[2.\ NaOH,\ NaBH_4]{1.\ Hg(OAc)_2,\ THF,\ H_2O} CH_3CH(OH)(CH_2)_4CH{=}CH_2 \quad (1)$$

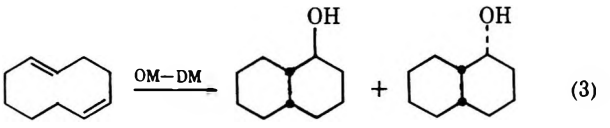
oxymercurated product were more reactive or its further reaction were favored by physical factors, the yield of enol could be greatly diminished.

Participation by the hydroxy group of the initial product can lead to the formation of ethers[8,10d] (eq 2).



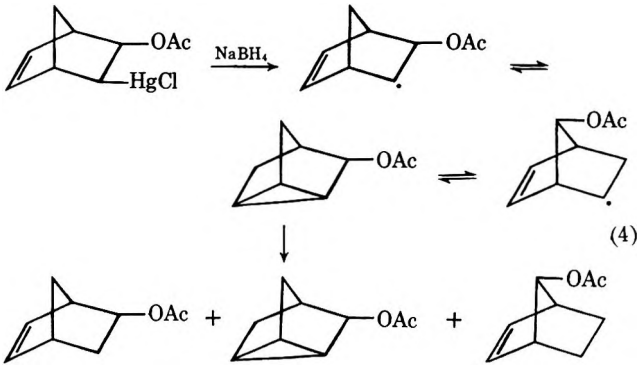
This side reaction can reduce the yield of the desired monohydration product to essentially zero.

Even carbon–carbon double bond participation during the oxymercuration stage is possible in certain instances. For example, the application of our general procedure[7,8] to *cis,trans*-1,5-cyclodecadiene using only 1 mol of mercuric acetate per mole of the diene affords, after reduction, the isomeric *cis,cis*- and *cis,trans*-1-



decalols[12] (eq 3). Similarly, norbornadiene under kinetic control gives only cis-2,3-exo oxymercuration. On the other hand, under thermodynamic control, the intermediate mercurial is nortricyclenic.[13]

The reduction of the oxymercurial apparently proceeds *via* a free radical intermediate. This can react with neighboring carbon–carbon double bonds and produce new structures. For example, the cis-2,3-exo oxymercuration product from norbornadiene is converted into a mixture of at least three isomeric alcohols upon reduction with sodium borohydride[10a–c] (eq 4).



This study was undertaken in the hope of establishing the type of dienes which could be monohydrated without serious interference by these side reactions.

Results and Discussion

The general procedure which was followed was to add 10 mmol of diene to a mixture of 10 ml of water and 40 ml of tetrahydrofuran (THF). The reaction mixture was then brought to reaction temperature, usually 0°, and 10 mmol of mercuric acetate was added. The mixture was stirred for the time indicated (T_2), and 10 ml of a 3 *M* solution of sodium hydroxide was added, followed by 10 ml of a 0.5 *M* solution of sodium borohydride in 3 *M* sodium hydroxide. After 0.5 hr, a suitable glpc standard was added and the aqueous phase was saturated with potassium carbonate. The THF phase was separated, dried, and analyzed by glpc. To achieve more quantitative recovery of certain highly water-soluble products, the aqueous phase was further extracted with THF in some instances.

Symmetrical Nonconjugated Dienes.—1,4-Pentadiene, 1,7-octadiene, and 1,11-dodecadiene were selected for detailed study. [1,5-Hexadiene was not included because it was known from previous work that the oxymercuration stage would lead predominantly to the cyclic ether[8,10d] (eq 2).] The results are summarized in Table I.

It is evident that the yield of enol is considerably lower than the value predicted on the basis of a statistical attack of the mercurating agent on the double bond. As the chain length increases, the yield rises, approaching the 50% yield predicted on the basis of a

(9) The following reviews provide a guide to the voluminous literature: (a) J. Chatt, *Chem. Rev.*, **48**, 7 (1951); (b) N. S. Zefirov, *Usp. Khim.*, **34**, 1272 (1965); *Russ. Chem. Rev.*, **34**, 527 (1965); W. Kitching, *Organometal. Chem. Rev.*, **3**, 61 (1968).

(10) The following papers involve pertinent studies of the mechanism of the reduction stage: (a) G. M. Whitesides and J. S. Filippo, Jr., *J. Amer. Chem. Soc.*, **92**, 6611 (1970); (b) G. A. Grey and W. R. Jackson, *ibid.*, **91**, 6205 (1969); (c) D. J. Pasto and J. A. Gontarz, *ibid.*, **91**, 719 (1969); (d) F. G. Bordwell and M. L. Douglass, *ibid.*, **88**, 993 (1966).

(11) H. C. Brown and P. J. Geoghegan, Jr., *J. Org. Chem.*, **37**, 1937 (1972).

(12) J. G. Traynham, G. R. Franzen, G. A. Knesel, and D. J. Northington, Jr., *ibid.*, **32**, 3285 (1967).

(13) K. C. Pande and S. Winstein, *Tetrahedron Lett.*, 3393 (1964).

TABLE I

MONOOXYMERCURATION–DEMERCURATION OF SYMMETRICAL NONCONJUGATED DIENES WITH MERCURIC ACETATE IN AQUEOUS TETRAHYDROFURAN (80%)

Diene	Temp, °C	Time, t_2,[a] hr	Yield,[b] % Diene	Enol[c]	Diol[d]
1,4-Pentadiene	0	0.5		16	
	0	2.0		16	
	25	0.5	35	12	
	25	2.0	31	13	
1,7-Octadiene	0	0.5		19	28
	0	2.0		18	29
	25	0.5	45	21	37
	25	2.0	45	18	36
1,11-Dodecadiene	0	2.0	33	40	28
	25	1.0	30	41	30

[a] Reaction time for addition of mercuric acetate to addition of base. [b] By glpc analysis. [c] $CH_2{=}CH(CH_2)_nCH(OH)CH_3$. [d] $CH_3CH(OH)(CH_2)_nCH(OH)CH_3$.

statistical oxymercuration of the two identical double bonds.

It is evident from the results for 1,7-octadiene that the low yield is primarily the result of the formation of diol in amounts greater than would be anticipated on a purely statistical basis. With the two reaction centers so widely separated, it is difficult to believe that the oxymercurial moiety at one end can influence the preferred reaction of the remaining double bond at the other end of the chain. It appears more likely that this is primarily the result of physical factors, such as partial miscibility and reaction at interphases. However, this question, interesting as it is, was considered to be beyond the range of our present objectives and was not pursued.

It appeared that the use of a more soluble mercury salt might alter the results. Indeed, the use of mercuric trifluoroacetate did increase the yield of enol (Table II).

TABLE II

MONOOXYMERCURATION–DEMERCURATION OF SYMMETRICAL NONCONJUGATED DIENES WITH MERCURIC TRIFLUOROACETATE IN AQUEOUS TETRAHYDROFURAN (80%)

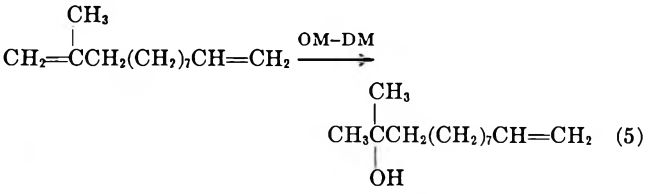
Diene	Temp, °C	Time, t_2,[a] hr	Yield,[b] % Diene	Enol[c]	Diol[d]
1,4-Pentadiene	0	0.5		26	
	0	2.0		27	
	25	2.0		47	
	25	4.0		53	
	25	8.0		57	
1,7-Octadiene	0	0.5		31	16
	0	2.0		31	20
	25	2.0	26	41	19[e]
	25	4.0	26	42	17[e]
1,11-Dodecadiene	0	2.0	37	46	18

[a–d] See corresponding footnotes in Table I. [e] Small amounts (1–4%) of *cis*- and *trans*-2,7-dimethyloxepanes were identified.

At 0° the constancy of the yields with time indicates that these are the kinetic products. However, the increase in the yields of enol with time at 25° indicates that we may be observing an equilibration. In any event, we are approaching essentially the statistically possible yield of 50% enol in all three cases.

Unsymmetrical Nonconjugated Dienes.—2-Methyl-1,11- and 11-methyl-1,10-dodecadiene were selected to test the feasibility of achieving a selective monohydration of unsymmetrical acyclic dienes. Limonene and 4-vinylcyclohexene were selected as examples of unsymmetrical cyclic dienes.

It was previously reported that under these oxymercuration conditions 2-methyl-1-pentene is approximately seven times as reactive as 1-pentene.[11] Similarly, 1-pentene is five times as reactive as 2-methyl-2-pentene.[11] If these relative reactivities can be carried over to the test dienes, the monohydrations should proceed predominantly as indicated in eq 5 and 6.



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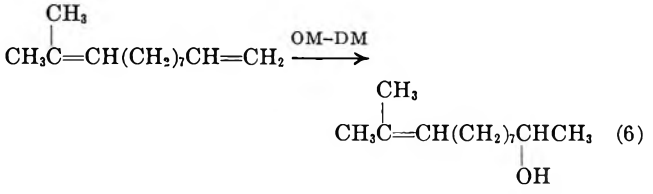

(6)

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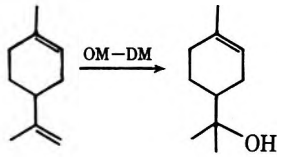
Indeed, this is observed. The enols **1** and **2** are each obtained from their respective dienes in yields of 55%, with the isomeric enols formed in only very minor amounts, 2 and 1%.

The reactivity data for simple olefins[11] predict that the monohydration of limonene should proceed as shown in eq 7. Indeed, the reaction takes the predicted course (Table III).



(7)

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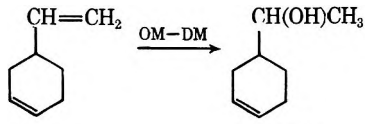
TABLE III

MONOOXYMERCURATION–DEMERCURATION OF UNSYMMETRICAL NONCONJUGATED DIENES WITH MERCURIC ACETATE IN AQUEOUS TETRAHYDROFURAN

Diene	Temp, °C	Time, t_2,[a] hr	Yield,[b] % Diene	Enol[h]	Enol[c]	Diol
2-Methyl-1,11-dodecadiene	25	1.0	16	55[e]	1	15[i]
11-Methyl-1,10-dodecadiene	25	1.0	18	55[f]	2	14[i]
Limonene[d]	25	0.5	19	70[g]		7[j]
4-Vinylcyclohexene	25	0.5	42	12[k]	(2)[l]	22[k]
4-Vinylcyclohexene[d]	25	2.0	37	21[k]	(3)[l]	21[k]

[a,b] See corresponding footnotes in Table I. [c] Isomeric enol. [d] 50% aqueous THF. [e] 1. [f] 2. [g] 3. [h] 4. [i] 2-Methyl-2,11-dodecanediol. [j] Isomeric di-*tert*-diols. [k] Plus approximately 10% bicyclic ethers also formed. [l] Presumably isomeric enols, but not characterized.

Finally, the reactivity data indicate that both unsaturated centers in 4-vinylcyclohexene possess com-



(8)

4

parable reactivity.[11] Consequently, a simple conversion to the secondary alcohol **4** would not be anticipated. Indeed, the results (Table III) reveal that **4** is formed only in modest yield. There are formed both isomeric enols and cyclic ethers. Fortunately, as discussed below, the use of mercuric trifluoroacetate overcomes this difficulty.

Consequently, it is now possible to achieve the Markovnikov monohydration of the exocyclic double bond in limonene and 4-vinylcyclohexene *via* oxymercuration–demercuration. It is of interest to point out that hydroboration of these two dienes with disiamylborane, followed by oxidation with alkaline hydrogen peroxide, yields the corresponding primary enols in these cases.[5,6]

The monohydration of some of these dienes with mercuric trifluoroacetate was also examined. The results are summarized in Table IV.

TABLE IV

MONOOXYMERCURATION–DEMERCURATION OF UNSYMMETRICAL NONCONJUGATED DIENES WITH MERCURIC TRIFLUOROACETATE IN AQUEOUS TETRAHYDROFURAN

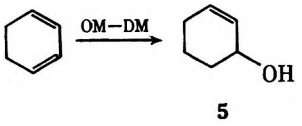
Diene	Temp, °C	Time, $t_{\frac{1}{2}}$,[a] hr	Yield,[b] % Diene	Enol$_1$	Enol$_2$[c]	Diol
2-Methyl-1,11-dodecadiene	0	0.16	24	43[d]	4	17[g]
	25	1.0	26	18[d]	26	22[g]
11-Methyl-1,10-dodecadiene	0	0.16	24	48[e]	5	18[g]
	25	1.0	8	83[e]	1	2[g]
4-Vinylcyclohexene	0	0.1	32	16[f]	(10)[i]	24[h]
	25	0.1	25	37[f]	(4)[i]	18[h]
	25	0.5	18	60[f]	(2)[i]	7[h]
	25	2.0	14	55[f]	(2)[i]	7[h]

[a,b] See corresponding footnotes in Table I. [c] Isomeric enol. [d] 1. [e] 2. [f] 4. [g] 2-Methyl-2,11-dodecanediol. [h] Bicyclic ethers plus diol. [i] Presumably isomeric enols, but not characterized.

Perhaps the most noteworthy feature is the increase in the yield of the enol **2** from 55% under kinetic conditions with mercuric acetate (Table III) to 83% under equilibrating conditions with mercuric trifluoroacetate. Similarly the yield of 62% of enol **4** under these conditions is far higher than that achieved under the kinetic conditions of the reaction involving mercuric acetate. It has been noted in other studies in this laboratory that deoxymercuration of the mercuric trifluoroacetate adduct is considerably more rapid for olefins containing internal di- and trisubstituted double bonds than for terminal olefins. Consequently, the use of mercuric trifluoroacetate at 25° with longer reaction times may provide the basis for a general method to shift the oxymercurial adduct from an internal position to a terminal position.

Conjugated Dienes.—2,3-Dimethyl-1,3-butadiene and 1,3-cyclohexadiene were selected as model compounds of symmetrical conjugated dienes. 2-Methyl-1,3-butadiene and *trans*-1,3-pentadiene were taken as models of unsymmetrical conjugated dienes. These dienes were subjected to the standard monohydration procedure.

1,3-Cyclohexadiene was readily converted into the



(9)

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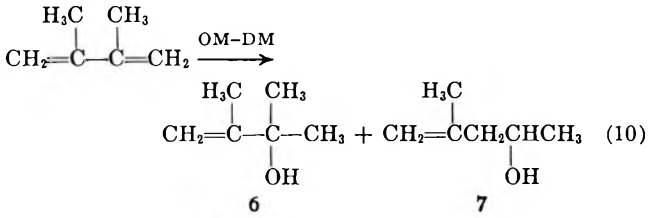
allylic derivative, 2-cyclohexen-1-ol (**5**), in 50% yield (eq 9), essentially the statistical value. We failed to observe the formation of the isomeric homoallylic alcohol, 3-cyclohexen-1-ol. This is in contrast to the report of Moon and coworkers,[14] who reported the formation of both isomers in equal amounts. However, the experimental conditions of this earlier investigation are not identical with those of the present study, so that a direct comparison of results may not be possible. Finally, it should be pointed out that the homoallylic alcohol is readily available *via* hydroboration of 1,4-cyclohexadiene with disiamylborane followed by oxidation with alkaline hydrogen peroxide.[5,6]

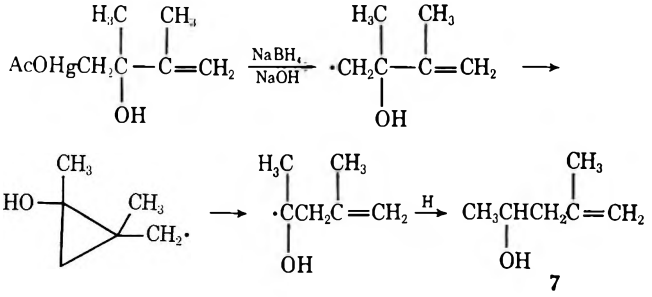
2,3-Dimethyl-1,3-butadiene undergoes reaction to provide a 49% yield of the expected product, 2,3-dimethyl-3-buten-2-ol (**6**), as well as 6% of a product, 4-methyl-4-penten-2-ol (**7**), containing a rearranged carbon structure (eq 10).



(10)

6 7

The results are consistent with an attack of mercury at the terminal position of the diene system, with addition of the nucleophile, water, to the adjacent position. We did not attempt to investigate the mechanism of the reaction responsible for the formation of the rearranged alcohol **7**. However, in view of the evidence that the demercuration step involves formation of a free radical,[10] the following mechanism appears reasonable (eq 11).



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(11)

The yield of the desired product from 2-methyl-1,3-butadiene was relatively low, only 16% of 2-methyl-3-buten-2-ol (**8**). There was also formed a small amount, 2%, of the isomeric enol, 3-methyl-3-buten-2-ol (**9**). The relative amounts of these two isomers correspond to expectations based on the relative reactivities of 2-methyl-1-pentene and 1-pentene.[11] There was also present 9% of a rearranged enol, 4-penten-2-ol (**10**) (eq 12). Presumably, the rearranged alcohol arises from the rearrangement of the intermediate free radical by changes similar to those shown in eq 11.

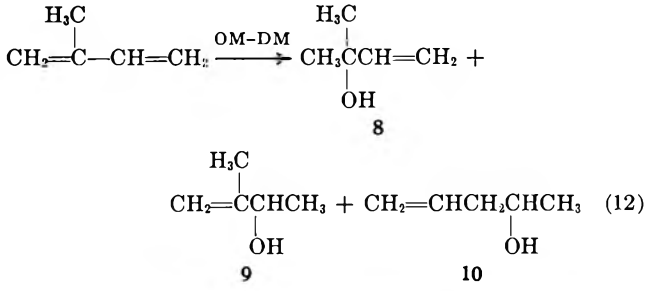
(14) S. Moon, J. M. Takakis, and B. H. Waxman, *J. Org. Chem.*, **34**, 2951 (1969).

TABLE V

MONOOXYMERCURATION–DEMERCURATION OF CONJUGATED DIENES

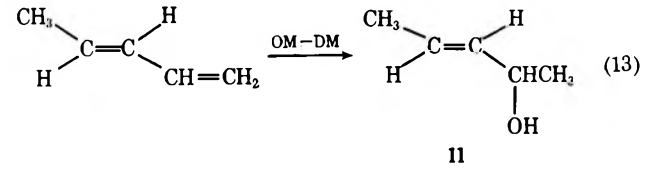
Diene	Temp, °C	Time, t_2,[a] hr	Yield,[b] % Diene	Enol$_1$	Enol$_2$[c]	Enol$_3$[d]	Diol
1,3-Cyclohexadiene	0	0.5		50[e]	0[f]		16[g]
	0	1.0		48[e]	0[f]		19[g]
2,3-Dimethyl-1,3-butadiene	0	0.5	31	49[h]		6[i]	4[i]
2-Methyl-1,3-butadiene	0	2.6		16[k]	2[l]	9[m]	
trans-1,3-Pentadiene	0	1.0		56[n]			

[a,b] See corresponding footnotes of Table I. [c] Isomeric enol. [d] Rearranged enol. [e] 5. [f] 3-Cyclohexenol. [g] Diols similar to those produced in the dihydration of 1,3-cyclohexadiene by this method.[8] [h] 6. [i] 7. [j] Pinacol, plus 2% of other materials assumed to be diols from their retention times. [k] 8. [l] 9. [m] 10. [n] 11.



The low yields of enols from isoprene do not arise as a result of favored conversion to diol. A number of observations were made in the hope of understanding the basis for the low yield, but the problem was not resolved. The observations are reported in the Experimental Section.

Finally, *trans*-1,3-pentadiene is converted into *trans*-3-penten-2-ol (**11**) in 56% yield (eq 13). Consequently, here also attack occurs at the position predicted on the basis of the relative reactivities of 1-pentene and *trans*-2-pentene.



These results are summarized in Table V.

The applicability of mercuric trifluoroacetate for the monohydration of these conjugated dienes was also explored. However, the yields were uniformly poorer; so it is less favorable for this application than mercuric acetate.

Conclusion

The oxymercuration–demercuration procedure appears to provide a convenient general method for the monohydration of dienes. In the case of symmetrical nonconjugated dienes, yields approaching that possible for a statistical reaction, 50%, have been realized. Considerably higher yields are possible in unsymmetrical nonconjugated dienes, where the point of hydration is that double bond whose structural features correspond to a more reactive olefin. The method can be extended to many conjugated dienes, although in some cases the yields are lower owing to certain unusual behavior of the intermediates which is not yet understood.

Experimental Section

Materials.—All dienes used except 11-methyl-1,10-dodecadiene and 2-methyl-1,11-dodecadiene (preparation described below) were commercially available. Mercuric acetate, mercuric oxide, trifluoroacetic acid, and tetrahydrofuran were commercially available and used as obtained.

General Oxymercuration–Demercuration Procedure Using Mercuric Acetate.[15]—To a 100-ml flask equipped with a magnetic stirring bar were added 40 ml of tetrahydrofuran, 10 ml of water, and 10 mmol of diene. The solution was cooled to 0° with an ice–water bath and 10 mmol of mercuric acetate was added to the stirred solution. After an appropriate time interval (t_2) the reaction was completed by adding 10 ml of a 3 *M* NaOH solution followed by 10 ml of a 0.5 *M* $NaBH_4$ solution in 3 *M* NaOH. After stirring for an appropriate time (usually 0.5 hr) a suitable glpc standard was added and the aqueous phase was saturated with K_2CO_3. The upper layer was separated, dried over K_2CO_3, and analyzed by glpc using an appropriate column. In some cases, additional extraction of the aqueous phase was employed.

General Oxymercuration–Demercuration Procedure Using Mercuric Trifluoroacetate.—The procedure was identical with that used with mercuric acetate except that 10 mmol of mercuric oxide followed by 20 mmol of CF_3CO_2H was used in place of mercuric acetate.

Oxymercuration–Demercuration of 1,4-Pentadiene, 1,7-Octadiene, and 1,11-Dodecadiene.—The oxymercuration–demercuration procedure was described above. Identification of the enols from 1,4-pentadiene and 1,7-octadiene was made *via* ir and nmr by isolation of their acetates after acetylating the product from a large-scale preparation. The enol from 1,11-dodecadiene was identified by glpc *via* a mixed injection with an authentic sample of 11-dodecen-2-ol prepared by a published procedure.[16]

The diols listed in the text for these dienes are presumed to be those formed in the dihydration of the respective dienes.[8]

In addition to diene, enol, and diol, two additional components were observed from the 1,7-octadiene reactions using $Hg(O_2CCF_3)_2$. These two components were isolated by preparative glpc and their nmr spectra were recorded. Based on the nmr spectra we believe that the two components are the isomeric *cis*- and *trans*-2,7-dimethyloxepanes.

Preparation of 2-Methyl-11-dodecen-2-ol (1).—In a typical Grignard reaction, 0.358 mol of methyl-10-undecenoate in 40 ml of Et_2O was added to CH_3MgI prepared from 0.807 mol of Mg, 0.803 mol of CH_3I, and 200 ml of Et_2O. After the addition was complete, the solution was heated at reflux for 1.5 hr, cooled, and hydrolyzed with saturated NH_4Cl, and the ether layer was separated, dried (K_2CO_3), concentrated, and distilled, giving 60.9 g (86%) of 1: bp 88–89° (0.6 mm) [lit.[17] bp 130° (10 mm)]; $n^{22}D$ 1.4491; ir (neat) 2.92, 3.21, 6.07, 10.06, 11.00, 13.85 μ; nmr (CCl_4) δ 5.8 (m, 1), 5.0 (m, 2), 2.0 (m, 2), 1.33 and 1.16 (m and s, 21).

Preparation of 11-Methyl-1,10-dodecadiene (12) and 2-Methyl-1,11-dodecadiene (13).—Using the general dehydration

(15) The exact solvent system used varied between 75 and 85% aqueous THF and no significant difference in results was observed within this range.

(16) W. H. Urry, South African Patent 6,706,619 (1968); *Chem. Abstr.*, **70**, 87324a (1969).

(17) V. J. Harding, G. M. Walsh, and C. Weizmann, *J. Chem. Soc.*, **99**, 449 (1911).

method described,[18] 45.6 g of 1 was heated at 130° for 1 hr with 32 g of $(CO_2H)_2$ (oven dried, 110°, 3 hr). The product was taken up in Et_2O and filtered, and the ether phase was washed with $NaHCO_3$ solution, dried (K_2CO_3), concentrated, and distilled, giving 33.2 g (80%) of a mixture of **12** and **13**, bp 102–104° (8.5 mm) [lit.[19] for **12**, bp 94–95° (10 mm)], analyzing by glpc to be 72% **12**, 23% **13**, and 5% of presumably isomeric dienes. Fractionation of 15.5 g of the mixture was then carried out on a 24 mm × 1 m column containing 300 g of silica acid (60/200 mesh) impregnated with 20% $AgNO_3$, using pentane to elute **12**, followed by pentane/Et_2O mixtures to elute **13**. Fractions of desired purity (glpc) were combined and distilled over CaH_2 to give **12** [ir (neat) 3.24, 6.08, 10.08, 11.00, 12.0, 13.85 μ; nmr (CCl_4) δ 4.7–6.1 (m, 4), 1.98 (m, 4), 1.67 (s, 3), 1.58 (s, 3), 1.3 (m, 10)] and **13** [ir (neat) 3.22, 6.05, 10.08, 10.99, 11.28, 13.88 μ; nmr (CCl_4) δ 4.5–6.1 (m, 5), 1.97 (m, 4), 1.68 (s, 3), 1.32 (m, 12)].

Anal. Calcd for $C_{13}H_{24}$: C, 86.59; H, 13.41. Found for **13**: C, 86.45; H, 13.48.

Oxymercuration–Demercuration of 2-Methyl-1,11-dodecadiene (13).—Since 1 mmol of **13** with the standard 5 ml of 80% aqueous THF produced a two-phase system, an additional 1 ml of THF was used to achieve a homogeneous system before the mercuric salt was added. The enol isomer **1** arising from this diene was identified by glpc by mixed injection with a sample of **1** prepared by the Grignard method above. The other enol isomer was isolated by preparative glpc of the reaction of **13** with $Hg(O_2CCF_3)_2$ at 25° for 1 hr and identified as 11-methyl-11-dodecen-2-ol on the basis of the following spectral characteristics: ir (neat) 2.96, 3.21, 6.04, 11.23 μ; nmr (CCl_4) δ 4.67 (m, 2), 3.75 (m, 1), 2.0 (m, 2), 1.70 (approximately s, 3), 1.32 (m, 14), 1.11 (d, 3), 0.9 (s, 1). The diol **14** arising from **13** was identified by glpc by comparison with a sample whose preparation is described below.

Preparation of 2-Methyl-2,11-dodecanediol (14).—Oxymercuration–demercuration of **1** was performed according to the published method for unsaturated alcohols[8] except that $Hg(O_2CCF_3)_2$ was used instead of $Hg(OAc)_2$ and a 1-hr oxymercuration time was employed. The product was purified by sublimination at 90° (0.27 mm) to give **14**: mp 55–56°; ir (mineral oil mull) 2.95 μ; nmr ($CDCl_3$) δ 3.81 (m, 1), 1.50 (shoulder, OH by D_2O exchange), 1.33 (m), 1.21 (s), 1.18 (d, J = 7 Hz).

Anal. Calcd for $C_{13}H_{28}O_2$: C, 72.17; H, 13.04. Found: C, 72.29; H, 13.01.

Oxymercuration–Demercuration of 11-Methyl-1,10-dodecadiene (12).—Since 1 mmol of **12** with the standard 5 ml of 80% aqueous THF produced a two-phase system, an additional 1 ml of THF was used to achieve a homogeneous system before the mercuric salt was added. The minor enol product **1** was well as the diol product **14** arising from oxymercuration–demercuration of **12** were identified by glpc by comparison with authentic samples whose preparations have been described above.

The major enol product **2** was identified by isolation from a preparative reaction as follows. **12** (1.86 g) was oxymercurated–demercurated with 10 mmol of $Hg(O_2CCF_3)_2$ for 1 hr at 25° using 50 ml of THF and 10 ml of H_2O. Evaporation of the dried (K_2CO_3) layer gave a semisolid residue (the solid is probably salts of $CF_3CO_2^-$). The product was taken up in CH_2Cl_2 (the $CF_3CO_2^-$ salts are not as soluble in CH_2Cl_2) and chromatographed on alumina using pentane–Et_2O mixtures as eluent. Fractions analyzing (glpc) for >99% purity were combined and distilled to give **2**: bp 94° (0.5 mm); ir (neat) 2.95, 5.96, 11.95 μ; nmr (CCl_4) δ 5.05 (m, 1), 3.70 (m, 1), 1.88 (m, 2), 1.67 (s, 3), 1.58 (s, 3), 1.42 (s, 1, OH by D_2O exchange), 1.31 (m, 12), 1.12 (d, 3).

Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.79; H, 13.36.

Oxymercuration–Demercuration of Limonene (15).—The enol **3** arising from oxymercuration–demercuration of **15** was identified by comparison of glpc retention time with that of an authentic sample of α-terpineol. The diols arising from **15** were not identified but were presumed to be diols on the basis of glpc retention time.

Oxymercuration–Demercuration of 4-Vinylcyclohexene (16).—The major enol product **4** from oxymercuration–demercuration of **16** with $Hg(O_2CCF_3)_2$ for 1 hr at 25° was identified by isolation and comparison of its retention time and ir and nmr spectra with those of a sample of **4** produced by the reaction of 3-cyclohexene 1-carboxyaldehyde with methyl Grignard: bp 90–92° (18 mm); $n^{20}D$ 1.4836 [lit.[20] bp 93–93.5° (20 mm), $n^{20}D$ 1.4842]; nmr (CCl_4) δ 1.2 (d, 3), 1.8 (m, 7), 3.6 (m, 1), 4.2 (m, 1), 5.7 (s, 2). The minor components were assumed to be a mixture of bicyclic ethers since their retention times were shorter than those of the enol. Preparative glpc separation of this mixture yielded two components in the ratio of 5:1. Both have similar nmr spectra: δ 1.6 (m, 12), 4.2 (m, 2). The methyl doublet is shifted from δ 1.2 in the minor component to δ 1.0 in the major. Based on the recent work of Grubbs and coworkers, it is probable that these are the two 7-methyl-6-oxabicyclo[3.2.1]octanes.[21]

Oxymercuration–Demercuration of 1,3-Cyclohexadiene (17).—The enol **5** arising from oxymercuration–demercuration of **17** was identified by acetylating the evaporated THF extract with Ac_2O and pyridine and comparing glpc retention times with those of authentic samples kindly provided by Mr. P. Burke of 2-cyclohexen-1-yl acetate and 3-cyclohexen-1-yl acetate. None of the isomeric material could be detected. Components of long glpc retention time were presumed to be the diols found for dihydration of this diene.[8]

Oxymercuration–Demercuration of 2,3-Dimethyl-1,3-butadiene (18).—The enol **6** arising from **18** was identified by comparison of the nmr spectrum of a preparative glpc sample with that of an authentic sample prepared by a published procedure.[22] The rearranged enol **7** was identified only on the basis of the nmr spectrum of a preparative glpc sample: nmr (CCl_4) δ 1.15 (d, 3, J = 6 Hz), 1.55 (s, 1), 1.75 (d, 3, J = 1–2 Hz), 2.10 (d plus additional small splitting, 2, J = 6 Hz), 3.87 (sextet, 1, J = 6 Hz), 4.80 (m, 2). Pinacol was identified by glpc with an authentic sample.

Oxymercuration–Demercuration of 2-Methyl-1,3-butadiene (19).—The enols **8**, **9**, and **10** arising from **19** were identified by preparative glpc isolation followed by comparison of their ir and nmr spectra with those spectra of authentic samples of **8**, **9**, and **10** prepared as follows: **8** was prepared by the addition of CH_3Li to methyl vinyl ketone; **9** was prepared by the addition of CH_3Li to methacryladehyde; **10** was prepared by the published procedure.[23]

It should be noted that the **19** used in this study was distilled prior to use and gave only one peak upon glpc analysis under conditions which separated 1,4-pentadiene and *trans*-1,3-pentadiene from **19**. Thus the possibility that the rearranged enol **10** came from contamination of **19** with either of these isomeric dienes is excluded.

Another observation for the oxymercuration–demercuration of **19** was made; namely, that the Hg after reduction was not quantitatively found under the aqueous phase. Thus, 15 min after reduction the THF layer was separated, filtered repeatedly, and then evaporated on the rotary evaporator. Upon evaporation, 42% of the Hg was observed in the residue. This seems to indicate that dialkylmercurials, R_2Hg, are formed substantially in the reduction stage. Dialkylmercurials have previously been observed from $NaBH_4$ reductions of oxymercuration adducts under appropriate conditions.[10d] The presumed R_2Hg would then have to decompose slowly in THF upon standing or rapidly upon evaporation, since Hg precipitates under these conditions. Decomposition would presumably also occur during glpc analysis.[24] The glpc yields listed in the table may therefore be totally misleading with respect to the actual material present in solution. Nevertheless, they should be at least crude approximations to material isolated by normal thermal work-up. Similar considerations may also apply to the other conjugated dienes studied. At this time we have made no attempt to establish the factors responsible for this interesting and peculiar behavior, since it was beyond the scope of the objectives for this study.

Oxymercuration–Demercuration of *trans*-1,3-Pentadiene (20).—The enol **11** formed from the reaction of **20** was isolated by preparative glpc. Its ir spectrum was identical with that pub-

(18) R. B. Carlin and D. A. Constantine, *J. Amer. Chem. Soc.*, **69**, 50 (1947).

(19) D. L. Christman and G. I. Keim, *Macromolecules*, **2**, 358 (1969).

(20) A. A. Petrov and N. P. Sopov, *Zh. Obshch. Khim.*, **22**, 591 (1952); *J. Gen. Chem. USSR*, **22**, 681 (1952).

(21) E. J. Grubbs, R. A. Froehlich, and H. Lathrop, *J. Org. Chem.*, **36**, 504 (1971).

(22) I. N. Rozhkov and S. M. Makin, *Zh. Obshch. Khim.*, **34**, 59 (1964); *J. Gen. Chem. USSR*, **34**, 57 (1964).

(23) W. H. Yanko, H. S. Mosher, and F. C. Whitmore, *J. Amer. Chem. Soc.*, **67**, 666 (1945).

(24) A review on dialkylmercurials has appeared: K. C. Bass, *Organometal. Chem. Rev.*, **1**, 391 (1966).

lished.[25] There was no absorption at 720 cm^{-1}, at which point the cis isomer absorbs strongly.

After reduction of the analytical run, only 55% of Hg was isolated. Addition of acid to the aqueous layer produced evolution of gas (presumably H_2) so that incomplete reduction was not due to insufficient hydride. During the preparative run, Hg was observed to emerge from the separated THF layer during work-up.

(25) B. Heilmann, G. de Gaudemaris, and P. Arnaud, *Bull. Soc. Chim. Fr.*, 123 (1957).

Registry No.—**1**, 34386-60-2; **2**, 34386-61-3; **4**, 17264-01-6; **7**, 2004-67-3; **12**, 18625-77-9; **13**, 34386-65-7; **14**, 34386-66-8; **15**, 138-86-3; **16**, 100-40-3; **17**, 592-57-4; **18**, 513-81-5; **19**, 78-79-5; **20**, 2004-70-8; mercuric acetate, 1600-27-7; 1,4-pentadiene, 591-93-5; 1,7-octadiene, 3710-30-3; 1,11-dodecadiene, 5876-87-9; mercuric trifluoroacetate, 13257-51-7; 11-methyl-11-dodecen-2-ol, 34386-69-1.

Hydroxypropylation

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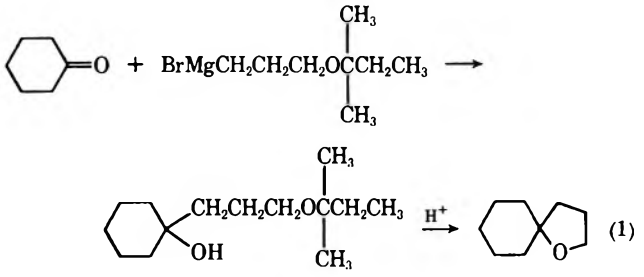
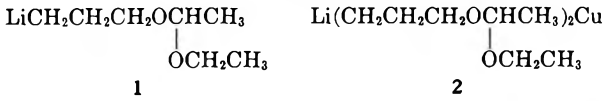
Organometallic reagents (**1**, **2**) useful in Grignard-type addition reactions are readily prepared from ethyl 3-bromopropyl acetaldehyde acetal (**3**). These reagents provide convenient means for the introduction of the hydroxypropyl group and the propionic acid chain.

We recently faced the problem of finding a convenient method for the introduction of the hydroxypropyl group, $-CH_2CH_2CH_2OH$, *via* organometallic-type reactions. Surprisingly, little in the literature is applicable to this problem. Grignard reagents from methyl,[1] ethyl,[2] and *tert*-amyl[3] ethers of 3-bromopropanol have been used in reactions with carbonyl compounds, but subsequent liberation of the primary hydroxyl group from its protecting ether mask cannot be accomplished readily without complication (*e.g.*, eq 1).[3]



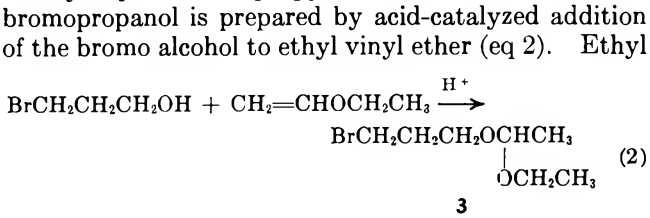
(1)

We report now our simple but exceedingly useful discovery that the organometallic reagents **1** and **2** are



1 **2**

completely satisfactory carriers of the hydroxypropyl group. The parent of these reagents is ethyl 3-bromopropyl acetaldehyde acetal (**3**, alternate name, 1-ethoxyethyl 3-bromopropyl ether). This masked 3-bromopropanol is prepared by acid-catalyzed addition of the bromo alcohol to ethyl vinyl ether (eq 2). Ethyl vinyl ether was chosen for protection of the hydroxyl group rather than the more common reagent dihydropyran as (1) ethoxyethyl ethers are more readily removed by hydrolysis than the corresponding tetrahydropyranyl ethers,[4] and (2) the hydrolysis of an ethoxyethyl ether gives ethanol and acetaldehyde, both volatile and easily removed, whereas a tetrahydropyranyl ether gives the less convenient by-product 5-hydroxypentanal.



(2)

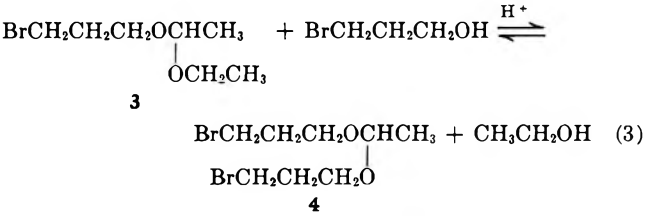
3

(1) H. Erlenmeyer and R. Marbet, *Helv. Chim. Acta*, **29**, 1946 (1946). See also M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Englewood Cliffs, N. J., 1954, p 36, and references cited therein.

(2) L. I. Smith and J. A. Sprung, U. S. Patent 2,421,090; *cf. Chem. Abstr.*, **41**, 5543 (1947).

(3) W. R. Renfrow, D. Oakes, C. Laver, and T. A. Walter, *J. Org. Chem.*, **26**, 935 (1961).

The reaction of 3-bromopropanol with ethyl vinyl ether is nearly quantitative and can be carried out readily on multimole scale if suitable care is exercised in the choice and use of the acid catalyst. Initially we used small amounts of methanesulfonic acid, but on too many occasions this led to explosive polymerization of the vinyl ether or, less disastrously, to production of the symmetrical acetal **4** *via* the exchange reaction shown in eq 3. We now employ dichloroacetic acid as the catalyst and avoid both these problems.



(3)

3 **4**

The lithium reagent **1** can be prepared on mole scale in ethyl ether as easily as a simple Grignard. The reaction of **3** with lithium wire (1% sodium) initiates spontaneously at room temperatures and continues rapidly below 0°.[5] One-molar solutions of **1** in ether are stable for months at −30°. Such solutions can be worked with unhurriedly at room temperature, but slow decomposition does occur to cyclopropane, among other things.

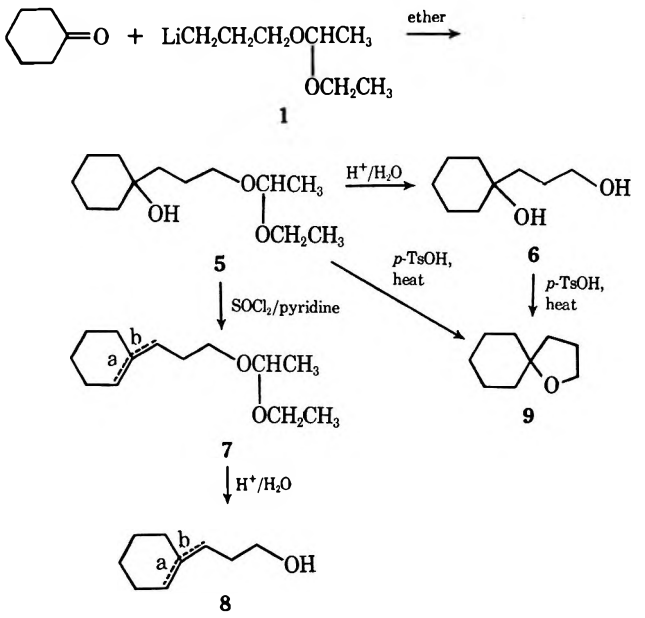
Addition of the lithium reagent **1** to a simple ketone is straightforward and proceeds in excellent yield. The product can be hydrolyzed to the primary alcohol *without* disturbing the nearby tertiary hydroxyl group, or

(4) S. Chladek and J. Smrt, *Chem. Ind.* (London), 1719 (1964).

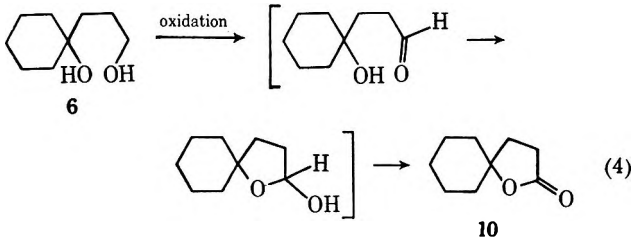
(5) Oddly, the corresponding reaction with magnesium turnings does not proceed at all well in ether solvent. The Grignard can, however, be prepared in tetrahydrofuran. It is less useful than **1**.

if desired, taken to the corresponding unsaturated primary alcohol (protected or free), or cyclized to the tetrahydrofuran (Scheme I).

SCHEME I



Oxidation of the diol produced on hydrolysis of the adduct of 1 with a ketone leads in excellent yield to the γ-lactone, as in eq 4. The oxidation presumably proceeds by way of the corresponding aldehyde and its hemiacetal[6] and is brought about by a large number of oxidizing systems, including chromium trioxide in aqueous acid and the chromium trioxide–pyridine complex in dichloromethane.



The γ-lactones very readily available by the reactions outlined here are useful precursors of substituted cyclopentenones.[7] Hydrolysis and oxidation of the adduct of the lithium reagent 1 to 2-octanone as in Scheme II provides, for example, an alternate approach to the lactone 11 used in the synthesis of dihydrojasmone.[7] We have made good use of equivalent reactions with more complex systems in the synthesis of peristylane as reported elsewhere.[8]

Reaction at −60° of the lithium reagent 1 with 0.5 equiv of cuprous iodide suspended in ether gives the lithium organocuprate 2.[9] We have not taken this organometallic over the full gamut of possible reactions, as this is outside our purpose. Instead, we have shown only that the reagent provides for the conjugate addition of the hydroxypropyl group to 2-cyclopentenone

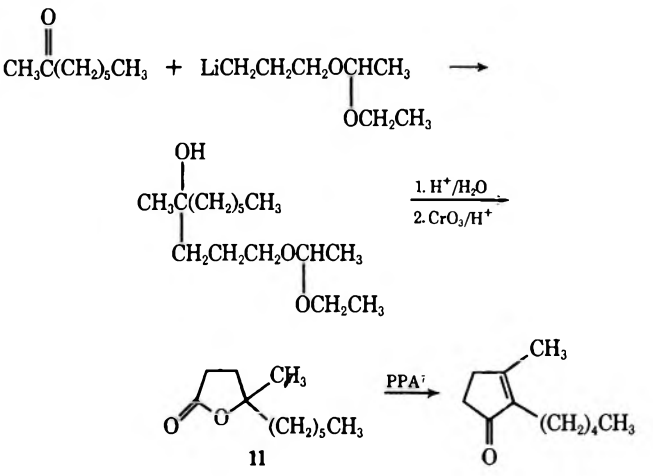
(6) W. A. Mosher and D. M. Preiss, *J. Amer. Chem. Soc.*, **75**, 5605 (1953).

(7) C. Rai and S. Dev, *J. Indian Chem. Soc.*, **34**, 178 (1957), and references cited therein.

(8) P. E. Eaton and R. H. Mueller, *J. Amer. Chem. Soc.*, **94**, 1014 (1972).

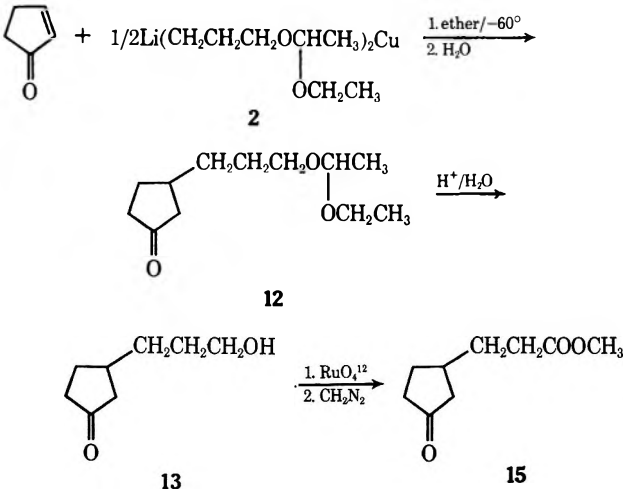
(9) This convenient designation represents only the stoichiometry of the reaction; see E. J. Corey and G. H. Posner, *ibid.*, **90**, 5615 (1968), footnote 7.

SCHEME II



(Scheme III).[10] Oxidation of the keto alcohol from hydrolysis of this adduct and subsequent esterification gives the keto ester 15, a key material in our synthesis of peristylane,[8] and previously available only by lower yield, longer synthetic schemes.[11]

SCHEME III



The hydroxypropyl group can, of course, be oxidized easily to the corresponding acid, as in eq 4 and Schemes II and III. With this small extension, use of the organometallics 1 and 2 offers by far the most convenient way of introducing the propionic acid side chain.[13] The overall scheme should be regarded as

(10) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966), and references cited therein give other examples using different systems.

(11) H. Stetter, I. Krüger-Hansen, and M. Rizk, *Chem. Ber.*, **94**, 2702 (1961).

(12) We thank Dr. B. W. Roberts for calling this oxidation method to our attention.

(13) No Grignard-type carrier of a simply protected (*i.e.*, same oxidation state) propionic acid chain is known. Attempts to prepare such a reagent from 3-bromopropionic acid ortho esters were thwarted by lack of a ready route to these derivatives of this particular acid.[14] Our single attempt to prepare a dihydro-1,3-oxazine[15,16] concealing a 3-bromopropionic acid led to elimination of the halogen; further work here is called for. The Grignard from 3-bromopropionaldehyde ethylene acetal (note oxidation state) is a useful reagent,[17] but it cannot be made in ether nor, as its thermal stability is poor, can it be prepared in quantity in tetrahydrofuran.

(14) J. P. Schroeder, D. C. Schroeder, J. Hardin, and J. K. Marshall, *J. Org. Chem.*, **34**, 3332 (1969).

(15) A. I. Meyers, I. R. Politzer, B. K. Bandlish, and G. R. Malone, *J. Amer. Chem. Soc.*, **91**, 5886 (1969).

(16) J. J. Ritter and E.-J. Tillmans, *J. Org. Chem.*, **22**, 839 (1957).

(17) G. Büchi and H. Wüest, *ibid.*, **34**, 1122 (1969).

cousin to the Reformatsky reaction, so useful in the introduction of the shorter acetic acid side chain.

Experimental Section

Ethyl 3-Bromopropyl Acetaldehyde Acetal (3).—Commercial 3-bromopropanol (1600 g, Eastman), containing water, hydrogen bromide, and organic impurities, was diluted with an equal volume of dichloromethane. The solution was washed in succession once with 200 ml of water, twice with 200-ml portions of saturated aqueous sodium bicarbonate, and once with 200 ml of saturated aqueous sodium chloride, and then dried over sodium sulfate. The solvent was removed *in vacuo*. The residue was neutral to pH paper and was distilled (in four separate batches) to give 3-bromopropanol, bp 60–64° (5 mm), 1250 g, reasonably pure, but acidic to pH paper. The distilled product was stirred over powdered sodium carbonate until the pH was above 5 (*ca.* 6 hr) and then stored until used at −30° over sodium carbonate.

Ethyl vinyl ether (289 ml, 220 g, 3.06 mol) was added to purified, nonacidic 3-bromopropanol (272 g, 1.96 mol) in a 1-l., three-necked flask equipped with a magnetic stirring bar, thermometer, and condenser with drying tube. At first only a small amount of the ether was added to check that there would be no violent reaction. Dichloroacetic acid (2.75 ml) was added. The temperature rose gradually to 50° over 1 hr. An hour later 1 ml more of acid was added and again after an additional 4 hr. The mixture was stirred overnight. In the morning, 8 g of powdered sodium carbonate was added, and the mixture was stirred for several hours. Filtration, removal of excess ethyl vinyl ether *in vacuo*, and vacuum distillation from sodium carbonate gave the required bromo acetal **3** as a colorless liquid, bp 49–51° (1 mm), 379 g, 92% yield. The acetal was stored over powdered sodium carbonate at −30°: nmr (CCl_4) δ 4.63 (1 H, quartet, J = 5.5 Hz), 3.8–3.2 (4 H, complex), 3.48 (2 H, triplet, J = 7 Hz), 2.03 (2 H, pentuplet, J = 6 Hz), 1.23 (3 H, doublet, J = 5.5 Hz), 1.14 ppm (3 H, triplet, J = 7 Hz).

Organolithium 1.—Generation of **1** was accomplished most conveniently using a jacketed, 2-l., three-necked flask with a drain tube at the bottom carrying a glass stopcock and terminating in a male ⅌ joint. The flask was equipped with a mechanical stirrer, low-temperature thermometer, and pressure-equalizing addition funnel topped with a gas inlet and bubbler. The entire apparatus was carefully dried and purged with argon. The flask was charged with 1 l. of dry ether and 18.1 g (2.62 g-atoms) of 0.5-in. lengths of lithium wire (1% sodium). About 25 ml of bromo acetal **3** was added to the stirred mixture. Soon, shiny spots appeared on the lithium wire, and the solution became cloudy. At this point, coolant was pumped from a refrigerated bath through the flask jacket. The temperature of the reaction solution was lowered to −5° and maintained between −5 and −15° as the remaining bromo acetal (total 244 g, 1.15 mol) was added dropwise over 1 hr. The chilled mixture was stirred after the addition was complete until the surface of the residual lithium metal tarnished (about 2 hr). The solution was then drained into a vessel suitable for whatever reaction was next.[18] If desired, the cloudy solution of **1** could be pressure-filtered through a medium porosity frit to give a crystal-clear solution of the organolithium stable for months at −30°. In either case, solutions of **1** prepared by this recipe were regarded as being 1 *M* in organolithium. This underestimates the actual concentration somewhat but provides a convenient guide.

Addition of 1 to Cyclohexanone.—About 70 ml of the ether solution of **1** prepared as just described was run from the preparation flask into a flame-dried, 250-ml, round-bottomed flask equipped for magnetic stirring and flushed with nitrogen. The flask was cooled in an ice bath as a solution of dry cyclohexanone (4.9 g, 0.05 mol) in 20 ml of ether was added dropwise with stirring. The mixture was stirred for 1 hr and then poured into 100 ml of half-saturated aqueous ammonium sulfate solution. After the usual work-up (ether),[19] distillation gave 10.3 g (90%) of colorless adduct **5**, bp 94–95° (0.07 mm).

Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.78; H, 11.38. Found: C, 67.83; H, 11.18.

1-(3-Hydroxypropyl)cyclohexanol (6).—A sample of adduct **5** (24 g), prepared as above but in a larger run, was stirred into 100 ml of a 60:40 mixture of water and ethanol and 4 ml of concentrated hydrochloric acid. After 15 min the homogeneous solution was neutralized by addition of solid potassium carbonate. The mixture was reduced to a small volume under vacuum on a rotary evaporator. The organic material in the residue was taken up in chloroform, and this solution was concentrated under vacuum. Molecular distillation at 100° (0.04 mm) of the residue gave 15.8 g (96%) of the diol **6** as a colorless, extremely viscous oil contaminated (nmr) with traces of chloroform and ethanol. No attempt was made to push the purification process further.

Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 67.88; H, 11.68.

Dehydration of 5. Formation of 7a,b.—The adduct **5** (27.9 g, 0.121 mol) and anhydrous pyridine (150 ml) were mixed together in a 500 ml, three-necked, round-bottomed flask equipped with an addition funnel, drying tube, thermometer, and magnetic stirrer. The solution was cooled to 2° using an ice–water bath. Thionyl chloride (25 ml, 0.346 mol)[20] was added dropwise. The solution was held at 10° by cooling (the reaction is quite exothermic). After the addition was complete, the mixture was stirred for 30 min and then poured onto 200 g of ice. The work-up procedure (ether) was standard except for the addition of three quick washes with 5% hydrochloric acid to remove excess pyridine and a final wash with saturated aqueous sodium bicarbonate solution. Distillation gave 21.3 g (83%) of **7**, bp 61–68° (0.1 mm), containing about 90% **7a** (nmr, vinyl hydrogen δ 5.35 ppm, broadened singlet, no $J > 2$ Hz) and 10% **7b** (δ 5.00 ppm, broadened triplet, $J \sim 8$ Hz).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.35; H, 11.61.

Formation of the Olefin–Alcohols 8a and 8b.—The sequence just described was repeated starting with 18.9 g of adduct **5**. The distillation was omitted; crude **7** was hydrolyzed as described for the conversion of **5** to **6**. Simple distillation of the product gave 10.4 g (90%) of a mixture, bp 60–65° (1 mm), approximately 9 1 in the olefins **8a** and **8b**, respectively, as determined by nmr.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.11; H, 11.58.

1-Oxaspiro[4.5]decane (9).—An 11.1-g sample of distilled adduct **5** was mixed with 70 mg of *p*-toluenesulfonic acid in a 25-ml, round-bottomed flask provided with a magnetic stirring bar. The flask was topped with a 25-cm Vigreux column connected to a simple distilling head with receiver immersed in a Dry Ice bath. The system pressure was reduced to 25 mm (aspirator), and the reaction mixture was heated quickly to 150–200°. The distillate (collected over about 1 hr) was dried and redistilled to give 5.5 g (81%) of the known ether **9**, bp 72–75° (19 mm) [lit.[3] bp 182° (742 mm)], identified spectroscopically.

Formation of Lactone 10.—A small sample of **6** (~1 g) was added slowly with 10 ml of water to a stirred solution of 2 g of chromium trioxide in a mixture of 20 g of water and 20 g of concentrated sulfuric acid. The temperature was held at 5–15°. The crude lactone **10** obtained by a standard work-up (chloroform) was purified by molecular distillation at 50° (0.05 mm), ir (neat) 5.65 μ.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.18; H, 9.38.

Formation of 4-Methyl-4-hydroxydecanoic Acid Lactone (11).—A solution of the lithium reagent **1** was prepared as described earlier using 91.0 g (0.432 mol) of the bromo acetal **3**, 6.9 g (1.0 g-atom) of lithium wire, and 300 ml of ether. A solution of 42.6 g (0.33 mol) of distilled 2-octanone in 100 ml of ether was added dropwise over 30 min to this solution of **1** held at 0°. The reaction mixture was stirred for 1 hr after the addition was complete and then processed as described under the preparation of **5**. The crude adduct was not distilled but was hydrolyzed directly to the corresponding diol as described in the hydrolysis of **5** to **6**. The crude diol was added dropwise to a stirred (Vibromixer) solution of 70.5 g of chromium trioxide and 2 g of manganous sulfate in 500 ml of water and 580 g of concentrated sulfuric acid in a jacketed, 2-l. reaction kettle. Chilled water was passed through the jacket to hold the flask contents below 22°. The crude diol was added as rapidly as consistent with temperature control. After the addition was

(18) Many simple addition reactions can just as well be run without bothering with this transfer (see addition of **1** to 2-octanone). Excess lithium metal does not interfere.

(19) "Usual work-up" is shorthand for extraction with the named solvent, drying the extract with sodium sulfate, filtration, and concentration under vacuum on a rotary evaporator.

(20) This large excess of thionyl chloride is probably not needed.

complete, the mixture was agitated for 1 hr. Standard work-up (chloroform) followed by distillation through a 40-cm spinning band column gave 44.2 g (71%) of pure lactone **11**, bp 75° (0.07 mm) [lit.[7] bp 159–160° (18 mm)].

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.58; H, 10.96.

Preparation of Methyl β-(3-Oxocyclopentyl)propionate (15).

A. Addition of 2 to 2-Cyclopentenone.—The entire apparatus as described earlier for the preparation of the organolithium reagent **1** was assembled atop a jacketed, four-necked, 3-l. reaction kettle. The connection between the two flasks being made *via* the male ⅘ joint terminating the drain tube at the bottom of the upper flask. The lower pot was equipped in addition with a mechanical stirrer, a low-temperature thermometer, and a pressure-equalizing addition funnel topped with a nitrogen inlet and bubbler. Provision was made to cool this flask by forced circulation of acetone through the flask jacket and a heat exchanger (copper coils) immersed in a Dry Ice bath. Care was taken to dry the entire apparatus. A solution of the lithium reagent **1** in ether was prepared under argon in the upper flask exactly as described in the second experiment. This solution was added dropwise to a well-stirred slurry in the lower flask of purified[21] cuprous iodide (136.5 g, 0.72 mol)[22] in 700 ml of dry ether maintained at −60 to −70° throughout the addition. The addition required about 1 hr. Another 1 hr was let pass to ensure complete formation of the lithium cuprate **2**. After this time, a solution of 82.8 g (1.02 mol) of pure, dry 2-cyclopentenone in 100 ml of ether was added dropwise. The reaction mixture was held below −60° throughout this addition, which required about 1.5 hr. (Color changes during the addition varied considerably from run to run. In some runs only a light green or yellow color developed, whereas in others the mixture became brick red and later orange. No obvious correlation with ultimate yield could be made.) After the addition of cyclopentenone had been completed, the mixture was stirred for 1 hr at −65° and then allowed to warm over 30 min to −35°. At this point the reaction was quenched by transferring the mixture by suction through $^3/_{16}$-in.-i.d. polyethylene tubing into a 5-l. flask already containing a well-stirred (Vibromixer) solution of 250 g of ammonium sulfate in 600 ml of water. The main reaction flask was rinsed with 400 ml of ether. The mixture in the quenching flask was agitated for 30 min. The insoluble salts were then removed by filtration. The ether portion of the filtrate was separated; the blue, aqueous layer was extracted with ether (2 × 300 ml). The combined ether solution was washed with saturated aqueous ammonium sulfate solution, dried over sodium sulfate, and concentrated *in vacuo* to give 238 g of crude adduct **12**.

B. Removal of the Protecting Group.—The entire sample of crude adduct **12** was stirred into a solution of 1.5 g of dichloroacetic acid[23] in 750 ml of water contained in a 2-l., single-necked, round-bottomed flask. The mixture went essentially homogeneous after about 1 hr. At this point, the solution was neutralized by addition of solid potassium carbonate. The flask was then attached to a rotary evaporator, and the easily volatile materials (ethanol, acetaldehyde) were removed under vacuum. The residue was saturated with ammonium sulfate. The organic phase was separated, and the aqueous layer was extracted with chloroform (3 × 350 ml). The organic material was combined and concentrated under vacuum to leave 155 g of crude 3-(3-hydroxypropyl)cyclopentanone (**13**). A small sample from this crude product was purified by column chromatography on silica gel followed by molecular distillation at 50° (0.02 mm).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.67; H, 9.90.

C. Oxidation.[17]—A suspension of 616 g (2.68 mol) of potassium metaperiodate and 0.75 g of ruthenium dioxide in 2 l. of water and 1 l. of acetone was made up in a 5-l., jacketed kettle equipped with thermometer, addition funnel, and Vibromixer stirrer. The crude hydroxy ketone **13** was dissolved in 200 ml of acetone, and this solution was added dropwise over 30 min to the well-agitated oxidizing mixture. The reaction is mildly exothermic and was moderated by passing cold water through the kettle jacket. The temperature of the reaction mixture was not allowed to exceed 45°. The progress of the reaction was monitored by nmr analysis of small aliquots, following the signals in the region δ 3.5–3.9 ppm due to starting material. These signals were barely visible after the reaction had run for 2–5 hr. At this point, the insoluble salts were removed by filtration, and the filtrate was concentrated *in vacuo* to remove most of the acetone. The concentrate was saturated with ammonium sulfate, and this was extracted with chloroform (3 × 500 ml). The extract was concentrated *in vacuo*. The residue (which sometimes crystallizes) was mixed with 600 ml of water and titrated with 40% aqueous sodium hydroxide solution to the phenolphthalein end point. The basic solution was extracted twice with chloroform and then acidified with 6 *N* sulfuric acid. Thorough extraction of the acid solution with chloroform followed by evaporation of the solvent under vacuum gave 110 g of crude solid acid. A small part of this was purified by crystallization successively from ethyl ether, *n*-butyl ether, and ethyl ether–pentane to give pure acid **14** as a white, crystalline solid, mp 51–53°.

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.55; H, 7.86.

D. Esterification.—The main part of the crude acid was dissolved in ether (the little that did not dissolve readily was discarded) and converted to the methyl ester **15** by reaction with ethereal diazomethane in the usual way. The ester was purified by distillation, bp 78° (0.005 mm); 85.5 g of pure **15** was obtained, a 50% yield overall from cyclopentenone.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.47; H, 8.23.

Registry No.—**3**, 34399-67-2; **5**, 34399-68-3; **6**, 6963-45-7; **7a**, 34399-70-7; **7b**, 34399-71-8; **8a**, 22516-18-3; **8b**, 4361-24-4; **10**, 699-61-6; **11**, 7011-83-8; **13**, 34399-76-3; **14**, 34399-77-4; **15**, 34399-78-5.

Acknowledgment.—We are grateful to the National Science Foundation for support of this work. R. H. M. thanks the National Institutes of Health for a predoctoral fellowship.

(21) G. B. Kauffman and L. A. Teter, *Inorg. Syn.*, **7**, 9 (1963). The purified cuprous iodide should be finely powdered before use.

(22) Neither the course nor stoichiometry of the addition reaction to cyclopentenone is changed by varying the ratio of cuprous iodide to organolithium from 0.5:1 to 1:1.

(23) The use of stronger acids, *e.g.*, HCl or H_2SO_4, leads to this case to resinification of the product.

Electrolytic Reductive Coupling. XXI.[1] Reduction of Organic Halides in the Presence of Electrophiles

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Controlled potential electrolysis at a mercury cathode was used to effect two-electron reductive cleavages of carbon tetrachloride, ethyl trichloroacetate, ethyl bromoacetate, allyl chloride and bromide, benzyl chloride and bromide, ethyl 4-bromobutyrate, 4-bromobutyronitrile, and chloroacetonitrile in the presence of acrylonitrile, ethyl acrylate, diethyl fumarate, and diethyl maleate. The electrochemically generated anion nucleophilically attacked the acceptor to yield adduct anions. The latter evolved into final products by several routes: (a) by protonation, *e.g.*, 4-trichlorobutyronitrile from CCl_4 and acrylonitrile, (b) by cyclization–displacement of halide, *e.g.*, diethyl 1-chloro-1,2-cyclopropanedicarboxylate from ethyl trichloroacetate and ethyl acrylate, (c) by displacement on halogen of a polyhalo starting material, *e.g.*, diethyl 2,2,4-trichloroglutarate also from ethyl trichloroacetate and ethyl acrylate. The factors that must be considered in the design of these electrochemical syntheses are discussed. Reduction of benzyl chloride in the presence of carbon dioxide led directly to benzyl phenylacetate. Similarly, allyl chloride produced allyl crotonate. Reductive dehalogenative coupling of allyl halides and of ethyl bromoacetate alone are also reported.

Electrolytic reductive cleavage of $E(CH_2)_nL$, in which E is an electron-withdrawing group and L a "leaving" group, in the presence of substituted olefins (*e.g.*, styrene, acrylonitrile) which can trap the radicals or anions resulting from the cleavage has been proposed[2] as a novel synthetic route to polyfunctional molecules. Examples have been presented in which L is phosphonium[3a] or sulfonium.[3b] The present paper concerns related syntheses starting with organic halogen compounds.

There have been numerous studies of the polarography of organic halides in protic and, latterly, in aprotic media[4] and many associated studies concerned with elucidating the mechanism of the cleavage of the carbon–halogen bond.[5] However, not much work has been directed toward involving the dehalogenated fragments in coupling reactions with reagents deliberately added to the electrolysis mixture. As a result of this omission, usually only hydrocarbons, dimers,[6] and symmetrical mercury compounds[7] have been the final products obtained from electrolytic reduction of halides at mercury. Occasionally, electrolyses in the presence of carbon dioxide and identification of the carboxylic acid obtained have been employed, but more as proof that an anionic intermediate had been formed in the reductive cleavage than as a useful synthetic method.[8a] Rifi, however, has obtained acceptable yields of small ring compounds by electrolysis of certain α,ω-dihalides.[9a]

The work reported here was designed to probe the synthetic utility, for preparing coupled products, of reducing certain halides at controlled potential in the presence of an excess of selected acceptors. Carbon tetrachloride (CT), ethyl trichloroacetate (ETA), ethyl bromoacetate (EBA), allyl chloride (AC) and bromide (AB), benzyl chloride (BC) and bromide (BB), ethyl 4-bromobutyrate (EBB), 4-bromobutyronitrile (BBN), and chloroacetonitrile (CAN) were chosen as the halides; acrylonitrile (AN), ethyl acrylate (EA), and diethyl fumarate (DEF)–diethyl maleate (DEM) were the usual acceptors. Occasionally, a halide was reduced in the presence of only starting material or of carbon dioxide. Except where otherwise specified, mercury was the cathode. Yields were not optimized,[9b] and in some cases it was considered sufficient to determine whether or not coupling had occurred.

The organic chemist not conversant with the guidelines of organic electrosynthesis as they apply in this area will be assisted in assessing the rationale of the experiments and the results to be discussed below by considering that[4a] (a) the difficulty of electroreduction—as evidenced by increasing negative voltage required—is iodide < bromide < chloride; (b) monochlorides are reduced in only one discernible two-electron step and are, therefore, cleaved to chloride and a carbanion; (c) controlled potential electrolysis (cpe)[10] allows *gem*-polyhalo compounds to be reduced stepwise with loss of one halide at a time[11]—cpe, likewise, permits one to choose the particular halide–acceptor pair to be used in a coupling experiment so that only the former is reduced at the potential chosen (Table I); (d) the cation of the supporting electrolyte must not be discharged at the voltage needed for the reduction of the halide; (e) slow addition of the halide

(1) Paper XX: M. M. Baizer and J. L. Chruma, *J. Electrochem. Soc.*, **118**, 450 (1971).

(2) M. M. Baizer, *J. Org. Chem.*, **31**, 3847 (1966).

(3) (a) J. H. Wagenknecht and M. M. Baizer, *ibid.*, **31**, 3835 (1966); (b) J. H. Wagenknecht and M. M. Baizer, *J. Electrochem. Soc.*, **114**, 1095 (1967).

(4) (a) M. R. Rifi in "Organic Electrochemistry," M. M. Baizer, Ed., Marcel Dekker, New York, N. Y., Chapter 6; (b) C. K. Mann and K. K. Barnes, "Electrochemical Reactions in Nonaqueous Systems," Marcel Dekker, New York, N. Y., 1970, pp 201–244; (c) I. M. Kolthoff and J. J. Lingane, "Polarography," 2nd ed, Vol. II, Interscience, New York, N. Y., 1952, pp 647–651.

(5) *E.g.*, J. W. Sease, F. G. Burton, and S. L. Nickol, *J. Amer. Chem. Soc.*, **90**, 2595 (1968); P. Zuman, "Substituent Effects in Organic Polarography," Plenum Press, New York, N. Y., 1967; J. Simonet, H. Doupeux, P. Martinet, and D. Bretelle, *Bull. Soc. Chim. Fr.*, 3930 (1970).

(6) M. M. Baizer and J. P. Petrovich in "Progress in Physical Organic Chemistry," Vol. 7, A. Streitwieser, Jr., and R. W. Taft, Ed., Interscience, New York, N. Y., 1970, pp 220–223.

(7) *E.g.*, J. Grimshaw and J. S. Ramsey, *J. Chem. Soc. B*, 60 (1968).

(8) (a) *E.g.*, S. Wawzonek, R. C. Duty, and J. H. Wagenknecht, *J. Electrochem. Soc.*, **111**, 74 (1964). (b) F. H. Covitz, *J. Amer. Chem. Soc.*, **89**, 5403 (1967). (c) L. W. Marple, L. E. I. Hummelstedt, and L. B. Rogers, *J. Electrochem. Soc.*, **107**, 437 (1960), had reported finding two one-electron reductions of BB at 1×10^{-5} to 1×10^{-4} *M* in methanol–water–NaOH; these data were later reinterpreted by L. B. Rogers and A. J. Diefenderfer, *ibid.*, **114**, 942 (1967).

(9) (a) M. R. Rifi, *J. Org. Chem.*, **36**, 2017 (1971). (b) Yields are reported here on the basis of quantity of current passed; *i.e.*, they are current efficiencies for the formation of the given products. Except where otherwise indicated, the electrolyses were interrupted after an arbitrary period. Unreduced halo compound, still available in the catholyte, was not determined quantitatively. While chemical yields are therefore not given, they would deviate from current efficiencies only when mechanical losses or unlikely nonelectrochemical reactions between halo compound and medium occurred.

(10) L. Meites, *Pure Appl. Chem.*, **18**, 35 (1969).

(11) (a) S. Wawzonek and R. C. Duty, *J. Electrochem. Soc.*, **108**, 1135 (1961); (b) M. Nagao, N. Sato, T. Akashi, and T. Yoshida, *J. Amer. Chem. Soc.*, **88**, 3447 (1966); (c) P. Iversen, *J. Chem. Educ.*, **48**, 136 (1971).

TABLE I

POLAROGRAPHIC HALF-WAVE POTENTIALS[a]

Halide	Abbreviation	Electrolyte	$-E_{1/2}$ vs. sce	Electrophile	Abbreviation	Electrolyte	$-E_{1/2}$ vs. sce
Allyl bromide	AB	A[b]	1.29[e]	Acrylonitrile	AN	G[g]	2.15
Allyl chloride	AC	A	2.03	Carbon dioxide	CO_2	H[h]	2.3[i]
Benzyl chloride	BC	F[c]	2.25	Diethyl fumarate	DEF	H	1.54
4-Bromobutyronitrile	BBN	A	1.99	Diethyl maleate	DEM	D[j]	1.52
Chloroacetonitrile	CAN	A	1.45	Ethyl acrylate	EA	A	2.12
Chloroform	CF	C[d]	*1.95[f]				
Carbon tetrachloride	CT	C	*0.75[f]				
Ethyl bromoacetate	EBA	A	0.88				
Ethyl 4-bromobutyrate	EBB	A	2.03				
Ethyl trichloroacetate	ETA	F[c]	0.65[f]				

[a] Taken from the literature (indicated by *) or determined here by standard procedure. Anhydrous DMF, 0.1 *M* supporting electrolyte, 25°. [b] Tetraethylammonium *p*-toluenesulfonate. [c] Tetra-*n*-propylammonium fluoroborate. [d] Tetra-*n*-butylammonium bromide. [e] First wave. Second wave at −1.57 V. [f] First wave. [g] 0.2 *M* tetra-*n*-butylammonium iodide, DMF + 2% water. [h] Tetraethylammonium perchlorate. [i] Acetonitrile as solvent. [j] Lithium chloride.

(at a rate sufficient to maintain a reasonable current) to the catholyte containing an excess of acceptor can be used to favor cross-coupling rather than reaction of reduced halide with starting halide; (f) allylic[12] bromides show two one-electron reductions in aprotic media—benzylic bromides have been reported to exhibit one, presumably two-electron, wave polarographically[8] but to yield products arising from both carbanionic[8a] and presumed radical[7] intermediates[13] in macroelectrolyses; (g) nonallylic and nonbenzylic bromides and iodides are considered to be reduced generally in a single two-electron step;[17] (h) since anodic formation of halogen accompanies cathodic reduction of the halide, a divided cell must be used; (i) when it is desired to trap cathodically produced carbanions usefully, it is necessary to minimize the concentration of proton donors present *ab initio* in the catholyte and/or acquired therein by migration of acidic substances from the anolyte—on the other hand, when carbanions couple with anionically polymerizable acceptors, failure to provide conditions for an early termination will lead to oligomers and polymers rather than to simple condensation products. As will be seen below, polymerization can be aborted by making available suitably a proton donor which does not vitiate the initial condensation or an intra- or intermolecular displacement reaction for termination.

(12) J. P. Petrovich and M. M. Baizer, *Electrochim. Acta*, **12**, 1249 (1967).

(13) This apparent contradiction arises because of the *assumption* that the formation of certain types of products, *e.g.*, bibenzyl and dibenzylmercury (particularly the latter), from a benzyl halide must proceed *via* a benzyl radical. However, an alternate pathway *via* carbanions can be suggested for the reactions of RX in which R can form a relatively stable carbanion (*e.g.*, allylic, benzylic).

Spontaneous[14] or electrolysis-catalyzed[15] partial formation of RHgX yields a species relatively easily reduced in two successive stages.[15]

$$RHgX \xrightarrow[Hg]{e} RHg_n \xrightarrow{e} R^- + nHg$$

Reaction of R^- from the above reaction (or by the 2-e reduction of RX) with RX yields the dibenzyl type of product; displacement of X from RHgX by R^- (or, if RHgX is ionized, reaction of RHg^+ with R^-) yields the dibenzylmercury type without requiring free radicals. Displacements of this type by other stabilized carbanions have been reported.[16]

(14) L. B. Rogers and A. J. Diefenderfer, *J. Electrochem. Soc.*, **114**, 942 (1967).

(15) N. S. Hush and K. B. Oldham, *J. Electroanal. Chem.*, **6**, 34 (1963).

(16) B. L. Dyatkin, S. R. Sterlin, B. I. Martynov, E. I. Mysov, and I. L. Knunyants, *Tetrahedron*, **27**, 2843 (1971); D. Seyberth and J. M. Burlitch, *J. Organometal. Chem.*, **4**, 127 (1965).

(17) However, L. G. Feoktistov and S. I. Zhdanov, *Electrochim. Acta*, **10**, 657 (1965), report two one-electron reductions of 3-iodopropionitrile; J. W. Sease and R. C. Reed, Abstr. 134, Electrochemical Society Meeting, New York (spring 1969), N.Y., obtained hexane, hexene, and dihexylmercury upon reduction of 1-bromohexane.

Results and Discussion

Carbon Tetrachloride (CT).—The stepwise polarographic reduction of CT in dimethylformamide (DMF) has been discussed.[11a]

$$CCl_4 + 2e^- \longrightarrow Cl^- + \underset{1}{CCl_3^-}$$

$$1 + ZH^{18} \longrightarrow Z + \underset{2}{CHCl_3} \text{ (further reduced, second step)}$$

$$1 \rightleftharpoons \underset{3}{CCl_2} + Cl^-$$

$$3 + 2e^- \longrightarrow \underset{4}{CCl_2^{2-}}$$

$$4 + 2ZH^{18} \longrightarrow 2Z + CH_2Cl_2 \text{ (further reduced, third step)}$$

We have attempted to intercept **1** (before it could significantly dissociate or be protonated) by reducing CCl_4 at the potential of its first wave in the presence of an excess of AN, EA, and DEF or DEM. The results are summarized in Table II.

With AN.—Using a medium of tetraethylammonium *p*-toluenesulfonate dissolved in CH_2Cl_2 containing a small amount of water, the expected[19] product, **6a**, was obtained. The current efficiencey varied from 13 to 40% in the course of the run (expt 1). It is

$$1 + CH_2{=}CHX \longrightarrow \underset{5}{(Cl_3CCH_2CHX)^-}$$

$$5 + ZH \longrightarrow \underset{6}{Cl_3CCH_2CH_2X} + Z$$

a, X = CN
b, X = $COOC_2H_5$

evident that in this system substantial protonation occurs *after* coupling as well as before. The hydrophobic properties of the cation of the electrolyte used here have been discussed before.[20] It is also clear that in the "chemical" cyanoethylation of chloroform (CF),[19a] which requires large amounts of 40% aqueous benzyltrimethylammonium hydroxide to achieve even an 11% yield of **5a**, water does not fully inhibit the addition of **1** to AN.

(18) The solvent and/or tetraalkylammonium cation of the supporting electrolyte functioned as proton donors.

(19) (a) H. A. Bruson, W. Niederhauser, T. Riener, and W. F. Hester, *J. Amer. Chem. Soc.*, **67**, 601 (1945); (b) F. Nerdel, W. Brodowski, J. Buddrus, M. Fligge, P. Weyerstahl, K. Ulm, C. Finger, and D. Klamann, *Chem. Ber.*, **101**, 1407 (1968).

(20) *E.g.*, F. Beck, *Ber. Bunsenges. Phys. Chem.*, **72**, 379 (1968).

TABLE II

REDUCTIVE COUPLINGS WITH CARBON TETRACHLORIDE

Expt	Solvent, ml[b-d]	Catholyte Charges: Salt (g)	Catholyte Charges: CCl_4,[e,f] mmol	Catholyte Charges: Acceptor (mmol)	Conditions: −Cath V[g]	Conditions: Temp, °C	Conditions: mF[h]	Conditions: Time, hr	Principal products (%)[a]
1	0.5 H_2O + CH_2Cl_2[b]	A[i] (10.6)	20[f]	AN (300)	1.20	30	3.5	4.5	6a (13)
2	0.5 H_2O + CH_2Cl_2[b]	B[j] (5.75)	20[f]	AN (300)	0.95	27	6.4	6.8	6a (28)
3	CH_2Cl_2[b]	C[k] (11.2)	10[f]	AN (300)	1.00	27	4.6	5.2	2
4	CH_2Cl_2[c]	B (5.0)	10[f]	AN (400)	0.80	30	6.7	6.5	6a (207)
5	24.6 $CHCl_3$ + CH_2Cl_2[b]	B (3.75)	10[f]	AN (300)	1.10	28	9.2	7.0	6a (143)
6	24.6 $CHCl_3$ + 4.0 H_2O[b]	A (16.0)	20[f]	AN (300)	0.98[m]	26	8.0	3.5	6a (347)
7	24.6 $CHCl_3$ + CH_2Cl_2[b]	B (3.75)	30[e]	EA (158)	1.30	16	5.1	3.0	6b (114)
8	0.5 H_2O + DMF[c]	A (20.0)	20[e]	EA (200)	1.30	18	6.4	3.5	6b (9) + 7 (24.6)
9	DMF[b]	D[l] (0.5)	57[f]	EA (58)	1.41	40	9.3	5.5	Traces of product
10	0.8 H_2O + DMF[d]	A (35.0)	250[e]	EA (254)	1.29	24	138.0	23.0	2 + 7
11	DMF[b]	B (2.0)	57[f]	DEF (58)	1.00	40	69.0	25.0	8 (11.8) + 9 (1.7) + 10 (9.6) + 11 (16.2)
12	4.1 $CHCl_3$ + DMF[b]	B (2.0)	51[f]	DEF (58)	1.20	25	29.0	10.5	8 (38) + 9 (28) + 10 (49.5)
13	1.0 H_2O + DMF[b]	A (3.6)	51[f]	DEF (58)	1.60	30	11.4	6.0	2
14	24.6 $CHCl_3$ + CH_2Cl_2[b]	B (3.75)	20[e]	DEM (122)	1.10	17	12.8	6.0	Traces of 8, 9, and 10

[a] Based on current. [b-d] 60, 80, 140 ml total volume of catholyte, respectively. [e,f] Added gradually, at once, respectively. [g] *Vs.* sce. [h] mF = mA-hr/26.8. [i] Tetraethylammonium *p*-toluenesulfonate. [j] Tetraethylammonium chloride. [k] Tetra-*n*-butylammonium bromide. [l] Lithium chloride. [m] Platinum cathode.

Tetraethylammonium chloride could also be used as electrolyte in the preparation of **6a** (expt 2).

An attempt (expt 3) to use tetrabutylammonium ion both as supporting cation and as proton donor was prematurely effective: chloroform but no **6a** was produced.

It appeared that, if chloroform could perform the role of proton donor ZH and, thereby, generate **1**, electroreduction of CCl_4 could serve only a catalytic function, to produce initial quantities of **1** and **5** and, thereafter, to replenish the quantities of **1** which were scavenged by adventitious proton sources. This expectation was realized. **6a** was obtained in greater than 100% current efficiency (expt 4 and 5), even at platinum and in the presence of a saturated aqueous solution of tetraethylammonium *p*-toluenesulfonate (expt 6). Effectively, electroreduction is serving to produce a strong base (**5**); related results have been reported before.[3,21]

Glc analyses of all the above catholytes did not reveal any unknown product corresponding to 2,2-dichlorocyclopropanecarbonitrile which could have been formed by addition of **3** to AN[22] or, alternatively, by intramolecular chlorine displacement–cyclization of **5a**. However, as mentioned below, this type of cyclization was observed in other cases.

With EA.—While electrocatalysis with the system CCl_4–$CHCl_3$ was achieved in one case (expt 7), the results (expt 8–10) were generally less satisfactory than those that had been obtained with AN. Generally, when water was used as the proton donor (expt 8), low yields of **6b** were obtained. The difficulty seemed to reside in the greater criticality of proton-donor control in nucleophilic reactions with EA than with AN:[23] on the one extreme was reduction of CT to chloroform only; on the other, probably oligomerization of EA *via* **5b**. A multiplicity of products was produced. One of these, **7**[24a] (expt 8), is of especial interest because it

$$(Cl_3CCH_2CHCOOC_2H_5)^- + CCl_4 \longrightarrow$$
5b

$$Cl_3CCH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCOOC_2H_5 + CCl_3^-$$
7 **1**

must have arisen by nucleophilic attack of **5b** upon the chlorine of CT. This type of displacement was also noted when ETA was used in couplings (see below). Nonelectrochemically generated anions have been reported to displace upon the chlorine of CT,[25] but in these cases, because of the very alkaline conditions used, the intermediate chloro products analogous to **7** are further transformed.

Our sample of **7**, collected by preparative glc, had the same retention time (including peak enhancement when fortified by authentic sample) and the identical nmr spectrum as the sample prepared according to the literature.[24a]

Since the reaction of **5b** with CT regenerates **1**, the formation of **7** is an electrocatalytic process; there is no over-all redox reaction.

With DEF.—In the absence of purposely added proton donor (expt 11) the products were **8**, **9**, and two olefinic materials, **10** and **11**. **9** could have arisen by cyclization of the adduct anion **12** or by addition of dichlorocarbene to DEF. Our sample of **10**, collected by preparative glc, had the identical glc retention time

(21) P. E. Iversen, *Tetrahedron Lett.*, 55 (1971).

(22) D. Seifert, J. M. Burlitch, R. J. Minasz, J. Y-P. Mui, H. D. Simmons, Jr., A. J. H. Treiber, and S. R. Dowd, *J. Amer. Chem. Soc.*, **87**, 4259 (1965).

(23) M. M. Baizer and J. D. Anderson, *J. Org. Chem.*, **30**, 1357 (1965).

(24) (a) M. Asscher and D. Vofsi, *J. Chem. Soc.*, 1887 (1963), prepared **7** by modulated radical addition of CT to EA. This method has been further studied.[24b] (b) J. Tsuji, XXII IUPAC Congress, Boston, Mass., July 25–30, 1971. (c) Radical additions of methyl dichloroacetate to 1-decene have been reported to give complex mixtures: P. Guerrini, J. Sorba, and D. Lefort, *C. R. Acad. Sci., Ser. C*, **272**, 1690 (1971).

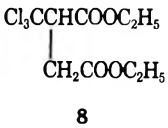
(25) (a) C. Y. Meyers, A. K. Malte, and W. S. Matthews, *J. Amer. Chem. Soc.*, **91**, 7510 (1969); (b) G. Morel, R. Seux, and A. Foucaud, *Tetrahedron Lett.*, 1031 (1971).

TABLE III

REDUCTIVE COUPLINGS WITH ETHYL TRICHLOROACETATE

Expt	Solvent, ml[b,c]	Catholyte charges: Salt (g)	ETA,[f,g] mmol	Acceptor (mmol)	Conditions: −Cath V[h]	Temp, °C	mF[i]	Time, hr	Principal products (%)[a]
15	DMF[b]	D[e] (0.5)	100[f]	AN (200)[f]	0.84	25	40.0	6.5	**18a** (80) + **17a** (20)
16	7.1 $CHCl_2CO_2Et$ + DMF[b]	B[d] (2.0)	12[f]	EA (180)	0.85	27	24.0	6.0	**18b** (99.9) + **17b** (1.1)
17	9.2 $CHCl_2CO_2Et$ + DMF[b]	D (0.5)	12[g]	EA (180)	0.90	28	25.0	7.5	**18b** (110) + **17b** (43.5)
18	DMF[b]	D (0.5)	145[g]	EA (156)	0.90	45	28.0	7.5	**18b** (86) + **17b** (39)
19	9.0 EtOH + DMF[b] 9.2 $CHCl_2CO_2Et$	D (0.5)	12[g]	EA (180)	0.93	30	21.0	7.0	**18b** (73)
20	DMF[b]	D (0.5)	145[f]	EA (200)	0.97	40	122.0	6.5	**18b** (29) + **17b** (11.4)
21	DMF[c]	D (0.5)	145[f]	DEM (158)	0.75	38	119.0	6.0	**19** (55)

[a] Based on current. [b,c] 60, 80 ml total volume of catholyte, respectively. [d] Tetraethylammonium chloride. [e] Lithium chloride. [f,g] Added gradually, at once, respectively. [h] *Vs.* sce. [i] mF = mA-hr/26.8.



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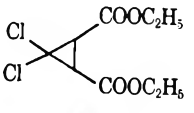
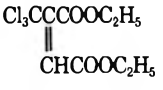


9



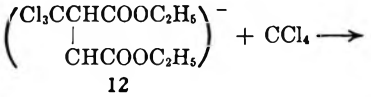
10

$C_9H_{12}Cl_2O_4$

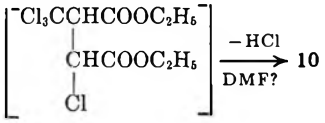
11

and nmr spectrum with the material prepared according to the literature.[26]

It is reasonable to assume that **13**, formed by a process analogous to that which led to **7**, was dehydrohalogenated by the warm DMF.



12



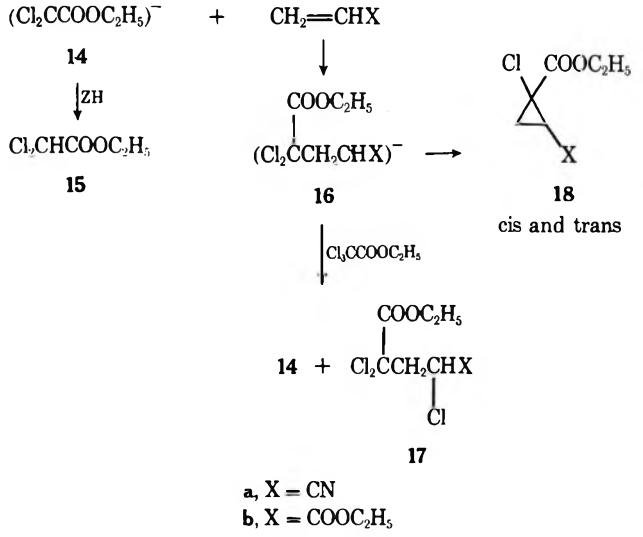
13

The bromotrichloromethyl analog of **13** is converted to **10** by cold triethylamine.[26] **11** is an unsaturated diester (ir and nmr) whose detailed structure is uncertain at present.

When CF was used in the catholyte as proton donor (expt 12), **8**, **9**, and **10** were again obtained. The total yield was better than in expt 11.

With DEM.—No coupling products were obtained when water was present (expt 13). With CF as proton donor, very small quantities of **8** (major), **9**, and **10** were detected. It appears that only the DEF present as an impurity in the DEM had reacted.

Ethyl Trichloroacetate (ETA).—The data are summarized in Table III. Reduction at the first wave yields the carbanion **14**, which has been shown[27] to be a precursor of dichlorocarbene and not of chloroethoxycarbonyl carbene. We, therefore, postulate that in the reductive coupling of ETA with AN and with EA



a, X = CN
b, X = $COOC_2H_5$

the formation of cyclopropyl derivatives **18**[28] arises by addition of **14** to the acceptor, followed by intramolecular elimination of Cl^-. The intermediary of **16** is unequivocally shown in the formation of **17**[24b] by what must be a displacement reaction of **16** upon the chlorine of ETA. That this type of displacement can occur was shown by treating sodio diethyl malonate with ETA; the products were diethyl chloromalonate and tetraethyl 1,1,2,2-ethanetetracarboxylate.[29]

The above experiments yielded only traces of the linear product (protonated **16**) which is the major product in the addition of ethyl dichloroacetate to AN or EA in the presence of alkali metal alkoxides.[30] In the cited reaction, as in typical Michael-type condensations, the donor—in this case alkyl dichloroacetate—can supply protons to react with **16** and regenerate the attacking anion; in the electrochemical reaction, **16** can abstract a proton from solvent or tetraalkylammonium ion (when used) or from adventitious water or, obviously more advantageously, can achieve stabilization by forming **17** and **18**. Including ethyl dichloroacetate alone (expt 16 and 17) or with ethanol (expt 19) did not in these experiments protonate **16b**. This

(26) R. E. Bowman, M. D. Closier, and P. J. Islip, *J. Chem. Soc.*, 3841 (1964).

(27) W. E. Parham and F. C. Loew, *J. Org. Chem.*, **23**, 1705 (1958).

(28) 1-Alkyl-2-chloro-1,2-cyclopropanedicarboxylates have recently been prepared from α-chloroacrylates and ethylzinc chloride: Y. Kawakami and Tsuruta, *Tetrahedron Lett.*, 1173 (1971).

(29) A small yield of dimer was obtained[26b] in the reaction of benzylphenylacetonitrile with carbon tetrachloride and solid potassium hydroxide in *tert*-butyl alcohol.

(30) H. Timmler and R. Wegler, *Angew. Chem.*, **72**, 1001 (1960).

TABLE IV

REDUCTIVE COUPLINGS WITH ETHYL BROMOACETATE

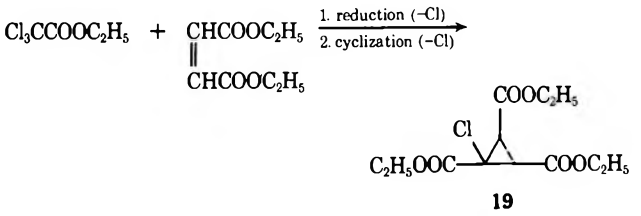
	Catholyte charges				Conditions				
Expt	Solvent, ml[b]	Salt (g)	EBA,[e] mmol	Acceptor (mmol)	−Cath V[g]	Temp, °C	mF[h]	Time, hr	Principal products (%)[a]
22	0.3 H_2O + DMF	A[c] (10.0)	50	Self	1.00	15	48.5	10.8	**20** (19.8) + **21** (51) + **22** (4.3) + **23** (6.6) + **24** (5.7)
23	0.3 H_2O + AN	A (25.0)	50	AN	1.83	20	18.7	5.0	Polymer + **21** + **27a** (34)
24	1.0 H_2O + DMF	A (10.0)	46	AN (300)	1.45	20	50.0	7.0	**21** (95) + **27a** (2.8)
25	0.3 H_2O + DMF	A (10.0)	50	EA (180)	2.00	20	54.0	7.0	**21** (55) + **23** (trace) + **27b** (42.6)
26	0.3 TBP[i] + DMF	A (10.0)	50	EA (180)	1.00	18	25.5	7.5	**21** (73.5)
27	0.3 H_2O + DMF	A (10.0) E[d] (1.0)	37	EA (180)	1.50	20	8.8	7.0	**21** (14.7) + **27b** (76)

[a] Based on current. [b] 60 ml total volume of catholyte. [c] Tetraethylammonium *p*-toluenesulfonate. [d] Tetraethylammonium bromide. [e] Added gradually. [f] Ethyl chloroacetate. [g] *Vs.* sce. [h] mF = mA-hr/26.8. [i] 2,6-Di-*tert*-butylphenol (g).

may reflect a difference in reactivity between the ion pair $16^-R_4N^+$ in DMF present in the electrochemical situation and the pair 16^-Na^+ in toluene present in the "chemical" reaction.[30]

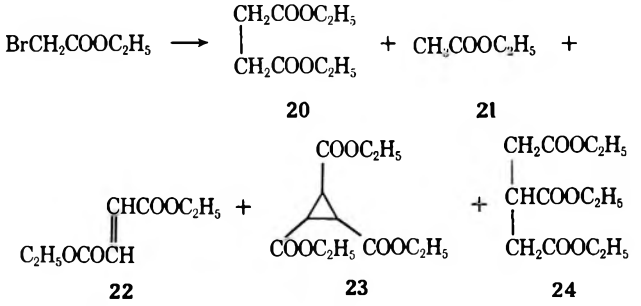
In this case the sequence **14** → **16** → **17** is electrocatalytic, so that the yields reported based on current are not of great significance.

Reductive coupling of ETA with DEM yielded **19** (expt 21).



19

Ethyl Bromoacetate (EBA).—The data are summarized in Table IV. Attempted reductive dehalogenative dimerization (expt 22) in the presence of a small amount of water did, indeed, yield diethyl succinate **20**, but in addition **21**, **22**, **23**, and **24**. By contrast, potassium amalgam reduction of chloroacetic acid



20 **21** **22** **23** **24**

esters is reported to yield *ca.* 70% of succinate esters.[31] Our results are best accommodated by the proposal that **25**, the product of the reduction of EBA, functions

$$BrCH_2COOC_2H_5 \xrightarrow{2e^-} (CH_2COOC_2H_5)^-$$
25

$$25 + EBA \longrightarrow 21 + (BrCHCOOC_2H_5)^-$$
26

as a strong base[3,21] and generates **26**. Thereafter, the reaction course is similar to that proposed by Abushanab,[32a] who prepared **26** from ethyl haloacetate and metal–liquid ammonia. We have identified DEF (which he postulated) among the products; in addition, whereas, according to this scheme **23** arises by attack on DEF of **26** followed by ring closure–elimination, attack on DEF by **25** (formed in the electrochemical but not in the nonelectrochemical sequence) leads also to **24**.

With AN.—The major coupled product isolated (expt 23 and 24) was **27a**; no straight-chain condensation product, *i.e.*, **28a**, was found. The formation of

27 **28**

a, X = CN
b, X = $COOC_2H_5$

both polymer and **27a** in expt 23 may be construed to indicate that **27a** arises *via* addition of **26** to AN followed by ring closure–displacement rather than by prior formation of the carbene from **26**.

With EA.—The major coupled product was **27b** (expt 25). Again, no **28b** was detected. An attempt (expt 26) to favor the formation of the latter by including 2,6-di-*tert*-butylphenol in the catholyte as a proton donor toward the anion which would be formed if **25** added to EA was unsuccessful; **25** was protonated before condensation and yielded only **21**.

Since "activated" chloride is easily displaced by bromide,[8a] it was possible to use ethyl chloroacetate instead of EBA, include bromide ion in the electrolyte, and still reduce at the potential for EBA (expt 27).

Compounds **23**, **27a**, and **27b** have recently been prepared from ethyl (dimethylsulfuranylidene)acetate, and the appropriate olefin,[33a] the bromo analog of **18b**, but not of **18a**, was similarly synthesized.[33b] An analog of **27b** preponderantly in cis form has been prepared[32b] from ethyl chloroacetate, methyl acrylate, and sodium methoxide at −78°. A new synthesis of analogs of **23**, **27a**, **27b** *via* a copper(I) oxide–isonitrile catalyzed reaction of haloacetates with activated olefins has just appeared.[34] All these methods seem less direct and

(31) V. A. Smirnov and A. V. Markova, *Zh. Prikl. Khim.*, **44**, 1364 (1971); *Chem. Abstr.*, **75**, 88065g (1971).

(32) (a) E. Abushanab, *Tetrahedron Lett.*, 2833 (1967), and literature cited therein; (b) A. H. Andrist and P. W. Ford, *Chem. Ind. (London)*, 930 (1971).

(33) (a) G. B. Payne, *J. Org. Chem.*, **32**, 3351 (1967); (b) G. B. Payne and M. R. Johnson, *ibid.*, **33**, 1285 (1968).

(34) T. Saegusa, Y. Ito, K. Yonezawa, Y. Inubushi, and S. Tomita, *J. Amer. Chem. Soc.*, **93**, 4049 (1971).

TABLE V

REDUCTIVE COUPLINGS WITH ALLYL HALIDES

	Catholyte charges				Conditions				
Expt	Solvent, ml[b]	Salt (g)	Halide[f,g] (mmol)	Acceptor (mmol)	−Cath V[i]	Temp, °C	mF[j]	Time, hr	Principal products (%)[a]
28	DMF	A[c] (10.0)	AC (100)[g]	Self	1.845	28	18.5	4.0	**29** (72)
29	DMF	A (10.0)	AC (50)[g]	Self	2.25	20	38.5	23.0	**29** (75)
30	DMF	A (10.0)	AB (100)[g]	Self	1.00	30	27.0	6.5	**29** (53.5)
31	DMF	A (10.0) E[d] (1.0)	AC (32)[g]	Self	1.35	27	22.6	22.0	**29** (33.5)
32	DMF	D (0.5)	AB (50)[g]	Self	1.80	20	56.0	6.5	**29** (78)
33	CH_2Cl_2	E (7.4)	AB (50)[g]	Self	1.62[l]	27	1.2	3.0	**29** (trace)
34	DMF	A (10.0)	AB (50)[g]	Self	1.56[l]	28	5.8	6.5	**29** (35)
35	1.0 TBP[k] + DMF	A (10.0)	AB (27)[f]	AN (300)	1.60	19	24.2	6.0	**30** (13) + **29** (35) + **32** (12.6)
36	0.2 H_2O + DMF	A (10.0)	AB (45)[f]	AN (300)	1.65	28	52.0	7.0	Polymer + **29** (10.5) + **32** (trace)
37	1.0 H_2O + DMF	A (10.0)	AB (50)[f]	AN (300)	1.755	25	52.0	5.5	Polymer + **32** (18)
38	2.0 H_2O + DMF	A (10.0)	AB (38)[f]	AN (300)	1.86	27	43.4	5.5	**30** + **29** + **32**
39	0.3 TBP + DMF	A (10.0)	AB (21)[f]	EA (180)	1.50	21	18.1	6.0	**30** + **29** (55) + **33** (9.3)
40	2.0 H_2O + DMF	A (10.0)	AB (21)[f]	EA (180)	1.80	12	33.0	4.5	**33** (4.2)
41	1.0 H_2O + DMF	A (10.0)	AB (8.3)[f]	DEM (120)	1.25	16	12.4	4.0	**30** + 18 + **34** (trace)
42	0.2 H_2O + DMF	A (10.0)	AB (4.1)[f]	DEM (120)	1.30	17	14.7	7.0	**34** (48.8)
43	DMF	B[e] (2.0)	AC (6.3)[f]	CO_2[h]	2.10	25	145.0	10.5	**35**
44	DMF	B (2.0)	AC (4.2)[f]	CO_2[h]	2.05	26	76.0	8.5	**35**

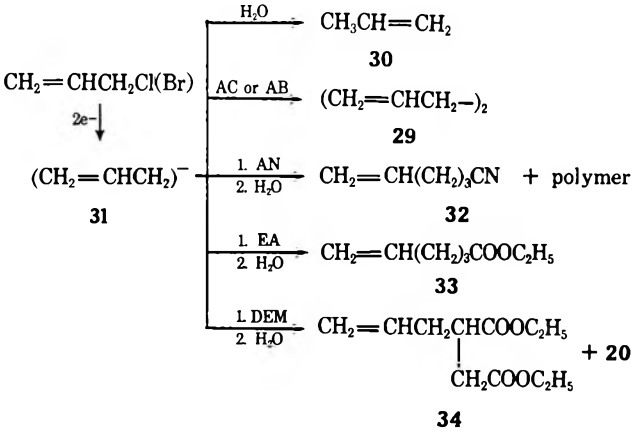
[a] Based on current. [b] 60 ml total volume of catholyte. [c] Tetraethylammonium *p*-toluenesulfonate. [d] Tetraethylammonium bromide. [e] Tetraethylammonium chloride. [f,g] Added gradually, at once. [h] Bubbled continuously through catholyte. [i] *Vs.* sce. [j] mF = mA-hr/26.8. [k] 2,6-Di-*tert*-butylphenol (g). [l] Platinum electrode.

facile than the electrochemical procedure reported here.

Allyl Halides.—The data are summarized in Table V. The dehalogenative coupling of allyl halide to 1,5-hexadiene (**29**) was investigated under a variety of conditions (expt 28–34). Yields were good to excellent; the major by-product was propylene (**30**).

When AC was the halide reduced (expt 28 and 29), a single two-electron step is indicated.[12] The route to **29** is, therefore, *via* the displacement of chloride from AC by the allyl carbanion.[35] The presence of proton donors is injurious to the yield. When, however, allyl bromide (AB)—or AC in the presence of a bromide-containing electrolyte—is used, radical as well as anionic routes to **29** are available. At potentials more anodic than *ca.* −1.5 V (expt 30 and 31) it is likely that **29** was found *via* the electrode product diallylmercury, which easily decomposes on warming.[36,37] The only moderate yields obtained may be due to the difficulty of getting good material and current balances. At potentials more cathodic than *ca.* −1.5 V (expt 32) an anionic course is followed. An attempt to avoid the intervention of mercurials by using a platinum cathode (expt 33 and 34) gave poorer results.

With AN.—The cathode potentials chosen (expt 35–38) were always negative enough to ensure a two-electron[38] reduction of AB. In some cases (expt 37 and 38) they were negative enough to approach AN reduction, since we had previously found[39] that this procedure improves the yield of mixed coupled products. The allyl carbanion **31** formed electrochemically may (a) attack an available proton source to form **30**; (b) attack AB to form **29**; (c) attack AN to form the anion of the coupled product, which anion may be protonated to 5-hexenenitrile (**32**); or (d) react additionally with AN to form polymer. Attempts were made to minimize a (expt 35 and 36) by having a medium of low proton donor availability without encountering d (expt 36 and 37), and to minimize b by adding AB slowly to the catholyte containing an excess of AN. In view of these sometimes contradictory requirements the yields of **32** were low.



With EA.—Reductions at cathode voltages removed from that required for reduction of EA (expt 39) as well as close to it (expt 40) gave poor yields of the coupled product, ethyl 5-hexenoate (**33**).

With DEM.—Because of the relatively positive po-

(35) In the formation of **27** from allyl halides and iron powder in DMF, as reported by D. W. Hall and E. Hurley, Jr., *Can. J. Chem.*, **47**, 1238 (1969), the yield is excellent when allyl bromide is used but poor and not greatly improved by addition of a bromide when allyl chloride is used under moderate conditions.

(36) K. V. Vijayaraghavan, *J. Indian Chem. Soc.*, **17**, 589 (1940); A. Kirrmann and M. Kleine-Peter, *Bull Soc. Chim. Fr.*, 894 (1957).

(37) Our identification and analysis of **20** was based on glc and under these conditions diallylmercury and dibenzylmercury decompose to R–R. See footnote 13.

(38) This would be true whether it is the second wave of AB in an anhydrous system that is involved or the merged single two-electron wave of an aqueous system.

(39) M. M. Baizer, J. P. Petrovich, and D. A. Tyssee, *J. Electrochem. Soc.*, **117**, 173 (1970).

TABLE VI

REDUCTIVE COUPLINGS WITH BENZYL HALIDES

	Catholyte charges				Conditions				
Expt	Solvent[b-d]	Salt (g)	Halide[g,h] (mmol)	Acceptor	−Cath V[j]	Temp, °C	mF[k]	Time, hr	Principal products (%)[a]
45	DMF[c]	F[e] (2.26)	BB (100)[h]	Self	1.24	25	104.0	9.0	**37** (49.6) + **38** (34)
46	DMF[d]	F (2.45)	BB (100)[h]	Self	1.24	22	103.0	9.0	**37** (44) + **38** (32) + **36** (9)
47	DMF[d]	F (2.45)	BB (100)[h]	Self	1.10	24	97.0	20.0	**37** (68) + **39** (trace)
48	DMF[b]	B[f] (2.0)	BC (50)[g]	CO_2[i]	2.37	24	95.0	6.0	**38** (2.5) + **40** (42.8)

[a] Based on current. [b-d] 60, 130, 140 ml total volume of catholyte, respectively. [e] Lithium bromide. [f] Tetraethylammonium chloride. [g,h] Added gradually, at once. [i] Bubbled continuously through catholyte. [j] *Vs.* sce. [k] mF = mA-hr/26.8.

tential required for the reduction of DEM, some of it was coreduced during the reduction of AB (expt 41 and 42). This was evidenced by the presence of a significant background current before AB was added and by the presence of diethyl succinate (**20**) among the products. While only a trace of coupled product, diethyl allylsuccinate (**34**), was formed in expt 41, reducing the amount of water in the catholyte to 0.2 ml (expt 42) resulted in a moderately good yield.

With CO_2.—Electrolysis in the presence of CO_2 has been used as a means of trapping anion radicals[40] and anions from hydrocarbons and halides,[8a] respectively. Good[40a] to very poor[8a] yields of acids have been obtained.

In expt 43 and 44 neither 3-butenoic nor crotonic acid was obtained in more than trace amounts.[41] The major coupling product was allyl crotonate (**35**). While the multiplicity of products did not permit a meaningful determination of the current efficiency, this one-step synthesis of the ester is arresting. It was examined in greater detail in the reduction of benzyl chloride described later.

Reaction of the allyl carbanion with CO_2 yields a carboxylate anion, **36**, which under conditions prevailing in the catholyte[42] must become crotonate rather than 3-butenoate. The counterion is tetraethylammonium. In the presence of excess active halide (AC) the salt is rapidly converted to ester. It was established independently that tetraethylammonium carboxylates are rapidly converted to esters with active and even only moderately active halides in DMF.[43]

$$31 + CO_2 \longrightarrow [CH_2{=}CHCH_2COO^- \rightleftharpoons \underset{\mathbf{36}}{CH_3CH{=}CHCOO^-}]R_4N^+$$

$$\mathbf{36} + AC \longrightarrow \underset{\mathbf{35}}{CH_3CH{=}CHCOOCH_2CH{=}CH_2}$$

Since **35** was present in only dilute solution and since the electrolysis was carried out at too positive a potential for reduction of **35** ($-E_{1/2} = -2.31$ V), no hydrodimerization[42] which would have led to diallyl 3,4-dimethyl adipate occurred.

Benzyl Halides (Table VI).—Dehalogenative coupling of BB at −1.24 V (expt 45 and 46) yielded mainly dibenzylmercury (**37**), toluene (**38**), and in expt 46 a small amount of bibenzyl (**39**). A later run (expt 47), made purely for the purpose of preparing **37**, provided the latter in good yield with only a trace of **39**.[44] Similar results have been reported before using a methanolic LiCl system.[7]

$$C_6H_5CH_2Br \xrightarrow[Hg]{\text{reduction}} \underset{\mathbf{37}}{(C_6H_5CH_2)_2Hg} + \underset{\mathbf{38}}{C_6H_5CH_3} + \underset{\mathbf{39}}{(C_6H_5CH_2)_2}$$

Reduction of BC in the presence of CO_2 (expt 48) at −2.37 V led directly[45] to benzyl phenylacetate (**40**) in good yield. A reported[8a] reduction of 10 ml of BC in DMF containing a bromide electrolyte at "semicontrolled potential" had yielded 0.1 g of phenylacetic acid after 1.68 A-hr of electrolysis. The ester **40** was, undoubtedly, formed by the same circumstances that obtained in the formation of **35** (*vide supra*).

$$2C_6H_5CH_2Cl \xrightarrow[CO_2]{2e^-} \underset{\mathbf{40}}{C_6H_5CH_2COOCH_2C_6H_5} + 2Cl^-$$

Miscellaneous Halides (Table VII).—Since the reduction of this group of halides required rather negative cathode voltages, the electrolyses were carried out at cathode voltages sufficient to reduce the acceptors. It has been shown[1] that this procedure can lead to reductive coupling; self-coupling of the acceptor must now, however, generally be expected.

CAN and/or bromoacetonitrile[8a] with EA (expt 49) gave a mixture of *cis*- and *trans*-**27a** which had previously been obtained (above) from EBA and AN. The two pairs of reagents are, therefore, commutative for the preparation of **27a**. The analytical method did not allow any acetonitrile formed to be differentiated from EA; no diethyl adipate (**41**) or linear condensation product, *i.e.*, **28a**, was found. The sequence leading to **27a** may well be similar to the one discussed above in the EBA experiments.

EBB reduced alone (expt 50) gave ethyl butyrate (**42**), a small yield of ethyl cyclopropanecarboxylate (**43**), and a trace of ethyl 4-acetoxybutyrate (**44**). Since a few drops of acetic acid had been added occasionally to the catholyte to keep it from getting excessively alkaline, **44** is, undoubtedly, an artifact, a solvolysis product of EBB. The formation of *any* **43** under these mild conditions is remarkable. It sug-

$$\underset{\text{EBB}}{Br(CH_2)_3COOC_2H_5} \xrightarrow{\text{trace HOAc}}$$

$$\underset{\mathbf{42}}{CH_3(CH_2)_2COOC_2H_5} + \underset{\mathbf{43}}{\triangle^{COOC_2H_5}} + \underset{\mathbf{44}}{CH_3COO(CH_2)_3COOC_2H_5}$$

(40) (a) S. Wawzonek, E. W. Blaha, R. Berkey, and M. E Runner, *ibid.*, **102**, 235 (1955); (b) R. Dietz and M. E. Peover, *Discuss. Faraday Soc.*, **45**, 154 (1968); (c) J. W. Loveland, U. S. Patent 3,032,489 (1962); *Chem. Abstr.*, **57**, 4470 (1962); S. Wawzonek and D. Wearing, *J. Amer. Chem. Soc.*, **81**, 2067 (1959).

(41) Glc examination of silylated electrolysis products compared with silylated authentic acids.

(42) M. R. Ort and M. M. Baizer, *J. Org. Chem.*, **31**, 1646 (1966).

(43) J. H. Wagenknecht, unpublished work in this laboratory.

(44) Analysis by nmr. In glc **26** decomposes quantitatively to **27**.

(45) Glc analysis of the catholyte. No phenylacetic acid or benzyl alcohol were present.

TABLE VII
REDUCTIVE COUPLINGS WITH MISCELLANEOUS HALIDES

	Catholyte charges				Conditions				
Expt	Solvent, ml[b]	Salt (g)	Halide[e,f] (mmol)	Acceptor (mmol)	−Cath V[g]	Temp, °C	mF[h]	Time, hr	Principal products (%)[a]
49	0.3 H_2O + DMF	A[c] (10.0) E[d] (2.0)	CAN (50)[e]	EA (180)	2.25	15	38.0	6.5	**27a** (43.5)
50	DMF	A (10.0)	EBB (80)[f]	Self	2.28	22	82.0	22.0	**42** (82) + **43** (17) + **44** (1.3 g)
51	0.5 H_2O + DMF	A (10.0)	EBB (40)[e]	EA (180)	2.22	22	55.6	7.0	**41** + **43** + **44**
52	1.0 H_2O + DMF	A (10.0)	EBB (33)[e]	AN (300)	2.31	25	40.0	6.0	Polymer + **45** + **43** + **44**
53	0.5 H_2O + DMF	A (10.0)	BBN (50)[e]	EA (180)	2.22	25	42.5	6.0	**41**
54	1.0 H_2O + DMF	A (10.0)	BBN (50)[e]	AN (300)	2.22	25	40.0	5.5	Polymer + **45**

[a] Based on current. [b] 60 ml total volume of catholyte. [c] Tetraethylammonium *p*-toluenesulfonate. [d] Tetraethylammonium bromide. [e,f] Added gradually, at once. [g] *Vs.* sce. [h] mF = mA-hr/26.8.

$$\text{EBB} \xrightarrow{2e} \underset{\textbf{45}}{^-CH_2CH_2CH_2COOC_2H_5}$$

gests that reduction of EBB yielded the anion **45**, which abstracted a proton from the α position of EBB to yield **42** and **46**; the usual intramolecular elimination–

$$\textbf{45} + \text{EBB} \longrightarrow \textbf{42} + \underset{\textbf{46}}{BrCH_2CH_2\bar{C}HCOOEt}$$

ring closure of **46** formed **43**. "Standard" cyclization of BBN requires either strong alkali, which leads to cyclopropanecarboxylic acid,[46a] or the use of sodium in liquid ammonia if the nitrile is desired;[46b] neither method is probably suitable for preparing **43** directly from EBB.

Reduction of EBB in the presence of EA (expt 51) yielded **43**, **44**, and **41** but no coupled product; in the presence of AN instead of EA (expt 52) only adiponitrile (**45**) was found.

BBN (expt 53 and 54) yielded no coupling products.

Experimental Section[47]

Equipment.—The potentiostat used was a 1.6-A model, Chemical Electronics Co., Newcastle, England. Total current passed was measured using a Lectrocount, Royson Engineering Co., Hatboro, Pa. Polarograms were obtained with a Sargent Model XXI polarograph. Ir spectra were obtained with a Beckman Microspec instrument. Nmr spectra were determined at 60 Mc with a Varian A-56/60 or T-60 spectrometer; the chemical shifts are expressed in δ (parts per million) relative to tetramethylsilane as an internal standard. Analytical glc determinations were made using a Hewlett-Packard 5750 model; preparative glc experiments employed the Model 770 F & M instrument. Electrolysis Cell No. 1 was an H-cell similar to that described by Lingane.[48] The erlenmeyer (cathode) compartment had a minimum capacity of *ca.* 130 ml and was separated from the cylindrical anode compartment by a 30-mm diameter medium-porosity glass frit. The cathode mercury, 50 ml, had an area of 50 cm^2. The anode was a platinum foil cylinder, 20 × 30 cm. Mechanical stirring was used in the cathode chamber, magnetic stirring in the anode chamber. The top of the cathode compartment was fitted with a ground-glass multiport head to which thermometer, buret, condenser, etc., could be attached. The reference sce was held rigidly in place; the salt bridge, drawn to a capillary, was positioned about 1 mm above the mercury. H-Cell no. 2 was constructed of two cylindrical members; the horizontal section contained a 30-mm-diameter medium-porosity glass frit. The cathode (15 ml when mercury) had an area of 15.5 cm^2. The anode was a platinum foil, area 5.8 cm^2. The volume was *ca.* 60 ml on each side. Stirring and auxiliary inlets were similar to those of cell no. 1.

TABLE VIII
WORK-UP AND ANALYSES OF CATHOLYTES

Expt	Work-up procedure-glc column/conditions
1–6, 16, 17, 19, 38, 41, 43	A-I
7,[a] 8,[b] 21,[a,b] 40, 42	D-I
9, 13	A-II
10, 48[d,e]	A-II, then D-II
11,[a,b] 12,[a,b] 14, 15[a,b]	D-II
18,[a,b] 20,[a] 39	A-I, then D-I
22–24, 51–54	D-III
25,[a] 26, 35, 36, 45, 49[a,b]	A-III, then D-III
27, 28, 30–34, 44[d]	A-III
29[a]	B-III
46, 50	A-III, then C, then D-III
47[c]	C

[a] Products also isolated by fractional distillation and structures confirmed. [b] Products also isolated by preparative-scale glc; a 3 ft × 3/4 in. stainless steel column packed with 16% SE-52 on Chromosorb W (60–80 mesh) was used. The carrier flow rate and column temperature were selected to give the highest resolution of components to be collected. Collections were made in cooled glass capillary tubes. [c] Analysis by nmr. [d] Catholyte silylated prior to analysis: to 10 μl in a screw-cap vial was added 20 μl of Regisil (Regis Chemical Co.), and the mixture was warmed 10 min before analysis. [e] Catholyte acidified prior to work-up.

Reagents and Starting Materials.—The DMF was purified as previously described.[49] Allyl bromide (AB), bp 70°, and allyl chloride (AC), bp 45°, were redistilled from high-quality supplies. Acrylonitrile (AN), bp 78°, and ethyl acrylate (EA), bp 99°, were likewise redistilled and stored over a trace of *p*-nitrosodimethylaniline. The stabilizer was not removed before electrolyses. Benzyl bromide (BB), chloroacetonitrile (CAN), diethyl fumarate (DEF), and ethyl bromoacetate (EBA) were all Eastman White Label and used as received. Carbon tetrachloride (CT) and chloroform (2) were Mallinckrodt AR. 4-Bromobutyronitrile (BBN) and 2,6-di-*tert*-butylphenol (DBP) were Aldrich products used as received. Benzyl chloride (BC) was Fisher Reagent Grade and methylene chloride was Fisher Certified. Ethyl trichloroacetate (ETA) was prepared from the acid (Aldrich) by the Fischer–Speyer method. Diethyl maleate (DEM) was MC and B material redistilled, bp 80° (2 mm); glc analysis showed *ca.* 11% DEF content. Ethyl 4-bromobutyrate (EBB) was prepared according to the literature.[50] Tetraethylammonium chloride (Eastman) was dried in a vacuum oven at 100°. Tetraethylammonium bromide (Eastman) was recrystallized from ethanol, and tetraethylammonium *p*-toluenesulfonate (Aldrich) was recrystallized twice from acetone before similar drying. Lithium chloride and bromide (Fisher Certified) were

(46) (a) C. M. McCloskey and G. H. Coleman, *Org. Syn.*, **24**, 36 (1944); (b) M. J. Schlatter, *ibid.*, **23**, 20 (1943).

(47) Melting points are corrected; boiling points are uncorrected.

(48) J. J. Lingane, C. G. Swain, and M. Fields, *J. Amer. Chem. Soc.*, **65**, 1348 (1943).

(49) J. P. Petrovich, M. M. Baizer, and M. R. Ort, *J. Electrochem. Soc.*, **116**, 749 (1969).

(50) H. Lapin, V. Arsenyevic, and A. Horeau, *Bull. Soc. Chim. Fr.*, 1700 (1960).

TABLE IX

ANALYTICAL AND NMR SPECTRAL DATA

Compd	Calcd, % C	Calcd, % H	Calcd, % Cl[a]	Found, % C	Found, % H	Found, % Cl	Solvent	Spectral data,[b] δ, ppm
6b							CCl_4	4.15 (2 H, q, CH_2), 2.91 (4 H, m, 2 CH_2), 1.3 (3 H, t, CH_3)
7							CS_2	2.8–4.6 (5 H, m, 2 CH_2 and CH), 1.3 (3 H, t, CH_3)
8	37.20	4.48	36.70	37.16	4.58	36.06	$CDCl_3$	3.8–4.5 (5 H, m, 2 CH_2 and CH), 3.1 (2 H, m, CH_2), 1.32 (3 H, t, CH_3), 1.25 (3 H, t, CH_3)
9	42.50	4.72	27.80	42.48	4.79	24.13	$CDCl_3$	4.0–4.5 (4 H, m, 2 CH_2), 3.6 (2 H, s, 2 CH), 1.35 (3 H, t, CH_3), 1.25 (3 H, t, CH_3)
10							$CDCl_3$	5.5 (1 H, s, CH), 4.5 (4 H, q, 2 CH_2), 1.33 (6 H, t, 2 CH_3)
11	42.40	4.71	27.90	43.17	5.00	26.97	$CDCl_3$	7.52 (1 H, s, CH), 5.6 (1 H, s, CH), 4.34 (4 H, q, 2 CH_2), 1.36 (3 H, t, CH_3), 1.34 (3 H, t, CH_3)
17a[c]	34.37	3.27	43.53	34.83	3.50	42.93	$CDCl_3$	4.82 (1 H, t, CH), 4.36 (2 H, q, CH_2), 3.28 (2 H, q, CH_2), 1.38 (3 H, t, CH_3)
17b	37.13	4.49	36.48	36.95	4.34	36.27	$CDCl_3$	4.0–4.7 (5 H, m, 2 CH_2 and CH), 2.9–3.6 (2 H, m, CH_2), 1.34 (6 H, 2 t, 2 CH_3)
18a[d]	48.41	4.61	20.46	48.55	4.56	21.08	$CDCl_3$	4.38 (2 H, q, CH_2), 1.6–2.4 (3 H, m, CH_2 and CH), 1.4 (3 H, t, CH_3)
18b	48.98	5.90	16.01	48.96	5.86	16.75	$CDCl_3$	4.15 (4 H, 3 q, 2 CH_2), 1.50–2.80 (3 H, m, CH and CH_2), 1.28 (6 H, 3 t, 2 CH_3)
19	49.23	5.81	12.14	49.17	5.79	12.68	$CDCl_3$	4.2 (6 H, 2 q, 3 CH_2), 3.05 (2 H, q, 2 CH), 1.3 (9 H, 2 t, 3 CH_3)

[a] Compounds with Cl α to ester or nitrile are relatively unstable and tend to give low Cl analyses. *Cf.* data of ref 24. [b] Included, if not previously reported, even for known compounds. [c] Calcd: N, 5.73. Found: N, 5.62. [d] Calcd: N, 8.07. Found: N, 8.19.

dried *in vacuo* at >150°. Tetra-*n*-butylammonium bromide (Eastman) was recrystallized from ethyl acetate and air dried.

Reference Compounds.—The 4-trichlorobutyronitrile (**6a**)[19a] was converted to ethyl 4-trichlorobutyrate (**6b**) *via* the imino ether.[51] Ethyl 2,4,4,4-tetrachlorobutyrate (**7**),[24a] diethyl 2-trichloromethylfumarate (**10**),[26] triethyl cyclopropanetricarboxylate (**23**),[32] ethyl 4-cyanobutyrate (**28a**),[50] 5-hexenenitrile (**32**),[52] ethyl 5-hexenoate (**33**),[52] diethyl allylsuccinate (**34**),[53] benzyl phenylacetate (**40**),[54] and ethyl 4-acetoxybutyrate (**44**)[55] were prepared by the methods cited. Ethyl dichloroacetate (**15**) and triethyl 1,2,3-propanetricarboxylate (**24**) were prepared from the acids (Aldrich) by the Fischer–Speyer method. Allyl crotonate (**35**) was similarly prepared from the acid (Eastman). Diethyl succinate (**20**) (Eastman), ethyl acetate (**21**) (Mallinckrodt), diethyl cyclopropane-1,2-dicarboxylate (**27b**) (Aldrich), diethyl glutarate (**28b**) (Aldrich), 1,5-hexadiene (**29**) (Eastman), propylene (**30**) (Matheson), dibenzylmercury (**37**) (K and K), toluene (**38**) (Mallinckrodt), bibenzyl (**39**) (Eastman), diethyl adipate (**41**) (Aldrich), ethyl butyrate (**42**) (Eastman), ethyl cyclopropanecarboxylate (**43**) (Aldrich), and adiponitrile (**45**) (Textiles Division, Monsanto) were commercially available. Ethyl 2-cyanocyclopropanecarboxylate (**27a**) prepared here had the same boiling point, nmr spectrum, and mass spectrum as reported for this compound in the literature.[33a]

General Electrolysis Procedure.—The cell, which had been oven-dried overnight, was quickly assembled under nitrogen with needed auxiliary equipment (stirrer, thermometer, etc.) and placed in a bath which could be used for warming or cooling. The catholyte charges and the conditions of the electrolyses are indicated in Tables II–VII. The anolyte had the same supporting electrolyte—plus halide, if necessary, to assure that halogen would be preferentially discharged—and solvent as were used for the catholyte; in addition, 1–2 ml of an olefin (*e.g.*, 1-hexene or 1-decene) was included to trap the halogen to be liberated. The catholyte was purged with pure nitrogen for 15–30 min before the beginning of an electrolysis. When it was desired that only the organic halide be reduced, the catholyte was checked in the absence of the organic halide at the cathode voltage to be used, to make sure that only negligible quantities, if any, of other reducible species were present. If, during the electrolysis, there was indication of migration of electrolyte solution (usually anolyte to cathode chamber at high currents), additional supporting electrolyte was added to the chamber that had lost volume. At the end of the electrolysis the catholyte was worked up and analyzed by one or more of several procedures detailed below; the anolyte was examined by glc for olefin dihalides when it appeared that some of the latter may have migrated to the catholyte.

Work-Up and Analyses of Catholytes.—The catholyte was treated in one of the following ways: procedure A, it was analyzed directly by glc; procedure B, it was carefully heated and the distilled materials (at 1 atm) were collected for analysis; procedure C, it was poured onto ice, and the precipitated product was removed by filtration, washed, and dried; procedure D, it was poured onto ice and extracted three times with methylene chloride. The combined extracts were washed, dried over $MgSO_4$, and heated to expel solvent. The residue was analyzed by glc.

Depending on the nature of the products, three different columns and conditions were employed in the glc analyses: (I) 6 ft × 1/8 in. S.S. 3% OV-101 on Chromosorb W (80–100 mesh), 100° → 250° at 20°/min; (II) 6 ft × 1/8 in. S.S. 10% SE-52 on Chromosorb W (80 mesh), 100° → 225° at 10°/min; (III) 10 ft × 1/8 in. S.S. 5% FFAP + 1% Carbowax 20M on Chromosorb G (80–100 mesh), 60° (3 min post-injection interval) → 220° at 30°/min. The work-up and glc analytical procedures used in all experiments are gathered in Table VIII.

Identification of Products.—Comparison of glc retention times under identical conditions including the peak enhancement method was always employed. In addition, in many cases (Table VIII, footnote *b*) preparative glc was used to collect samples of electrolysis products whose physical properties and nmr spectra were compared with those of authentic samples. New analytical and spectral data are given in Table IX.

Detailed Procedure for a Representative Run (Experiment 35, Table V).—To the catholyte compartment of cell no. 2, equipped in this case additionally with a buret, was added the mercury, 15.8 g (0.3 mol) of AN, 1.0 g of 2,6-di-*tert*-butylphenol, 10.0 g of tetraethylammonium *p*-toluenesulfonate, and sufficient DMF to make 60 ml. The buret contained 3.3 g (0.027 mol) of AB. The stirred catholyte was purged with pure nitrogen for 15 min. The anolyte contained the tosylate salt and 1.0 g of tetraethylammonium chloride dissolved in DMF to the same liquid level as in the catholyte. Passage of current at −1.60 V *vs.* sce showed that the "background" current was 6 mA. Addition of AB was then begun at a rate sufficient to maintain a current of 120–140 mA. After the AB had been added, electrolysis was

(51) H. Henecka in Houben-Weyl, "Methoden der Organischen Chemie," 4th ed, Vol. VIII, Georg Thieme Verlag, Stuttgart, 1952, p 536.

(52) F. B. LaFarge, N. Green, and W. A. Gersdorff, *J. Amer. Chem. Soc.*, **70**, 3709 (1948).

(53) K. Alder, F. Pascher, and A. Schmitz, *Ber.*, **76**, 27 (1943).

(54) M. Gomberg and C. C. Buchler, *J. Amer. Chem. Soc.*, **42**, 2059 (1920).

(55) E. V. Spencer and G. F. Wright, *ibid.*, **63**, 1281 (1941).

continued to reduce the residual AB in the catholyte until the current dropped to 12 mA. The total electrolysis time was 6.0 hr; 0.0243 F had been passed.

A sample of the catholyte was directly analyzed by glc for **30** and **29** using *m*-xylene as an internal standard. The catholyte was then poured onto ice and extracted three times with CH_2Cl_2. The combined extracts were washed and dried over $MgSO_4$. The filtered solution was stripped of low-boiling components on a rotary evaporator using an aspirator and warm-water bath. The residue (10.0 g) was examined by glc for **32** using an authentic reference sample and then analyzed quantitatively using ethyl benzoate as an internal standard.

Reaction of Diethyl Malonate with Ethyl Trichloroacetate.—To 50 ml of pure DMF contained in a four-necked 500-ml flask equipped with thermometer, mechanical Trubore stirrer, and drying tube was added 2.2 g (0.05 mol, dry basis) of 54.7% sodium hydride (Metal Hydrides). Then 16.0 g (0.10 mol) of diethyl malonate was added slowly while the temperature was kept below 40° by cooling in an ice–water bath. When hydrogen evolution had ceased, a clear, very pale yellow solution resulted. This was further cooled and then 9.6 g (0.05 mol) of ethyl trichloroacetate was added in 10 min with vigorous stirring at a temperature of 27°. Turbidity appeared a few minutes after addition was complete. Stirring was continued (arbitrarily) for 5 hr at room temperature. The mixture was poured onto 200 g of ice (alkaline solution) and extracted twice with 50-ml portions of CH_2Cl_2. The combined extracts were washed twice with water, dried over $MgSO_4$, filtered, and warmed on a hot water bath to expel CH_2Cl_2. The residual liquid (24.0 g) was analyzed by glc and found to contain (in order of elution) (a) ethyl dichloroacetate (3.2 g), (b) ethyl trichloroacetate (0.42 g), (c) diethyl malonate (6.3 g), (d) diethyl chloromalonate (5.1 g), and (e) tetraethyl ethane-1,1,2,2-tetracarboxylate (3.2 g). A sample of d was collected by preparative glc. Its nmr spectrum ($CDCl_3$) showed δ 4.83 (1 H, s, CH), 4.29 (4 H, q, 2 CH_2), and 1.34 (6 H, t, 2 CH_3) and was virtually identical with Sadtler Spectrum No. 1880 for the bromo analog.

In another similar experiment e was collected by distillation at 125–139° (0.25 mm). The product solidified in the receiver. After crystallization from ethanol, it melted at 75–76°, undepressed when admixed with authentic material.

Registry No.—**6b**, 20101-80-8; **7**, 25335-12-0; **8**, 34405-06-6; **9**, 34405-07-7; **10**, 34405-08-8; **17a**, 34405-09-9; **17b**, 34405-10-2; *cis*-**18a**, 34405-11-3; *trans*-**18a**, 34405-12-4; *cis*-**18b**, 34405-13-5; *trans*-**18b**, 34405-14-6; **19**, 34405-15-7; BC, 100-44-7; BBN, 5332-06-9; CAN, 107-14-2; CF, 67-66-3; CT, 56-23-5; EBA, 105-36-2; EBB, 2969-81-5; ETA, 515-84-4; AN, 107-13-1; CO_2, 124-38-9; DEF, 623-91-6; DEM, 141-05-9; EA, 140-88-5; AB, 106-95-6; AC, 107-05-1.

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Oxidative Carbon–Carbon Coupling. II. The Effect of Ring Substituents on the Oxidative Carbon–Carbon Coupling of Arylmalonic Esters, Arylmalonodinitriles, and Arylcyanoacetic Esters

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Arylmalonic esters and arylmalonodinitriles can be coupled oxidatively to the corresponding bibenzyls. Good yields of dimers are obtained when a para substituent (CH_3, Cl) is introduced, which inhibits the formation of higher oligomers through benzylic C–para C coupling. Substitution at *both* ortho positions and the para position (CH_3) in phenylcyanoacetic esters completely inhibits C–C coupling by steric crowding. Ketene imines are formed instead by C–N coupling. Substitution at *one* ortho position (CH_3) partially gives the usual C–C coupling together with benzylic C–para C coupling (oligomer formation) in case of a free para position and C–N coupling (ketene imine formation) in case of a CH_3-substituted para position. The thermal dissociation of the dimers into radicals is confirmed by esr analysis. From nmr line width measurements kinetic parameters for the dissociation reaction are obtained.

The oxidation of benzyl cyanides, α substituted with ester, acyl, or amide groups to give high yields of C–C dimers, has been described in the previous paper.[1] On thermal treatment the C–C dimers showed a reversible radical dissociation–recombination attended with oligomerization *via* benzylic C–para C coupling in the case of free para positions. Attempts to extend this oxidative dimerization reaction to unsubstituted phenylmalonic esters failed; only low yields of dimers were obtained, presumably owing to formation of higher oligomers. The present paper describes the oxidation of para-substituted arylmalonic esters and arylmalonodinitriles. The effect of both *o*- and *p*-CH_3 substituents on the oxidative coupling of arylcyanoacetic esters is also reported.

Arylmalonic Ester 1a–c.—The oxidation of **1a–c** has been carried out at room temperature with $KMnO_4$, $K_3Fe(CN)_6$, and $[Cu(OH)(TMEDA)]_2Cl_2$–oxygen (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) (*cf.* Table I).

With the first two oxidants, the C–C coupled dimers **2b** and **2c** were formed in high yield, whereas dimer **2a** was only produced as a minor product. In agreement with these results the oxidation of diester **1a** with dibenzoyl peroxide at 100° (neat) has been reported to give only 10% of dimer **2a**.[2] From gel permeation

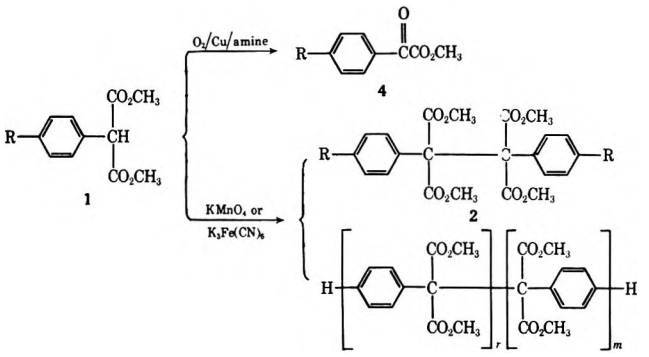
(1) H. A. P. de Jongh, C. R. H. I. de Jonge, and W. J. Mijs, *J. Org. Chem.*, **36**, 3160 (1971).

(2) T. Suehiro, *Nippon Kagaku Zasshi*, **79**, 457 (1958); *Chem. Abstr.*, **54**, 4486g (1960).

TABLE I

PROPERTIES AND YIELDS OF DIMERS 2

Dimer	Oxidant	Solvent	Yield, %	Mp, °C
2a	$KMnO_4$	Acetone/NH_3	10	191–192.5
2a	$K_3Fe(CN)_6$	Aqueous NaOH/CH_2Cl_2	11	
2a	O_2/Cu/amine	Methanol	3.4	
2b	$KMnO_4$	Acetone/NH_3	80	161.1–161.7
2b	$K_3Fe(CN)_6$	Aqueous NaOH/CH_2Cl_2	81	
2b	O_2/Cu/amine	Methanol	13	
2c	$KMnO_4$	Acetone/NH_3	68	167.5–169.5
2c	$K_3Fe(CN)_6$	Aqueous NaOH/CH_2Cl_2	78	



chromatography measurements it followed that about 40% of the oxidation product of **1a** (oxidized with $KMnO_4$) was trimer with about 10% of tetramer, presumably formed by a combination of benzylic C–benzylic C and benzylic C–para C coupling. The structure **3** ($n = 2$, $m = 1$) for the trimer agrees with the presence of extra OCH_3 peaks and a negligible tertiary H signal in the nmr spectrum (see Experimental Section). Similar oligomers are formed in the oxidative coupling of benzyl cyanides, α substituted with ester, acyl, or amide groups.[1]

The Cu/amine/O_2 oxidation system produced only low yields of dimer from **1a** and **1b**, owing to the prevalence of oxygenation over dehydrogenation; the glyoxylic esters **4a** and **4b**, isolated as 2,4-dinitrophenylhydrazones, were the main products. This is especially noteworthy, since the same oxidation system effected nearly quantitative dehydrogenation in the arylcyanoacetic esters series.[1]

The dimers **2** show the same type of radical dissociation–recombination equilibrium on heating (170–200°) as was found earlier with the arylcyanoacetic esters.[1] This was proven by the esr spectrum recorded by heating **2** in diphenyl ether–biphenyl at 202°. The spectrum was found to disappear again on cooling. The esr hyperfine coupling constants are in agreement with the structure of the radicals (Table II).[3] Moreover, dimers **2a** and **2b** were found to be active initiators for the free radical polymerization of styrene at 110°.[4]

Arylmalonodinitriles 5a–c.—Para-substituted arylmalonodinitriles **5b,c** were oxidatively coupled to the symmetrical dimers **6b** and **6c** with Mn(III) acetate in acetic acid and also electrochemically at a Pt anode in 90% acetic acid containing sodium acetate (controlled potential 450 mV/sce). The last two procedures were unsuccessful in producing C–C dimer from the unsubstituted dinitrile **5a**, because a substantial amount of benzylic C-para C oligomers was formed (with n up to 10), as was found with phenylmalonic ester **1a**. Under Hartzler's conditions [oxidation with $K_3Fe(CN)_6$, repeated by us with the same results], dimer **6a** apparently drops out of solution before oligomerization can take place.[5]

TABLE II

ESR HYPERFINE CONSTANTS (IN OERSTEDS) OF THE BENZYL RADICALS FROM THE DIMERS IN DIPHENYL ETHER/BIPHENYL

Radical precursor	Temp, °C	A(N)	A(OCH_3)	A_{ortho}	A_{meta}	A_{para}
2a	202		0.53	4.5	1.6	5.3
2b	202		0.5	4.4	1.5	5.8
6b[a]	83	1.89		4.03	1.23	5.9
8b	160	1.8	0.74	4.0	1.3	5.6
14a[a]	44	2.5	0.9[b]	1.4	1.5	2.7
14b[a]	60	2.5	0.84[b]	1.4	1.55	2.5

[a] In *m*-xylene. [b] OCH_2 (ester).

Dissociation of **6a** and **6b** into radicals occurs at 60°, as indicated by pink coloration, disappearing on cooling. The esr hyperfine splitting of **6b** (*m*-xylene solution at 83°) is consistent with the expected structure of the radicals (Table II).[3] It is noteworthy that Hartzler did not obtain esr spectra from **6a** and its di-*p*-NO_2 derivative. Apparently the lifetime of the radicals is too short in these cases.

Nmr spectra of **6b**, **8a**, and **13a** showed line broadening of all signals at temperatures >80°. McConnell[6] and Johnson[7] developed equations relating line width to rate constants for exchange reactions between diamagnetic and paramagnetic states. The contribution of such an exchange reaction to the width of a given nmr line is

$$\left(\frac{1}{T_2}\right)_{ex} = \frac{1}{\tau_d}\left[\left(\frac{a\tau_p}{2}\right)^2 \Big/ 1 + \left(\frac{a\tau_p}{2}\right)^2\right] \qquad (1)$$

In this equation τ_d and τ_t are the lifetimes of the diamagnetic and paramagnetic states, respectively, and a is the electron–nuclei coupling constant for the group of nuclei whose line width is being measured. In the case where $(a\tau_p/2)^2 \gg 1$, this equation reduces to

(3) W. J. van den Hoek, W. G. B. Huysmans, and J. Smidt, unpublished work.

(4) H. A. P. de Jongh, C. R. H. I. de Jonge, W. G. B. Huysmans, H. J. M. Sinnige, W. J. de Klein, W. J. Mijs, and H. Jaspers, submitted for publication.

(5) H. D. Hartzler, *J. Org. Chem.*, **31**, 2654 (1966).

(6) H. M. McConnell and S. B. Berger, *J. Chem. Phys.*, **27**, 230 (1957).

(7) C. S. Johnson, *ibid.*, **39**, 2111 (1963). See also C. S. Johnson, *Advan. Magn. Resonance*, 33 (1965).

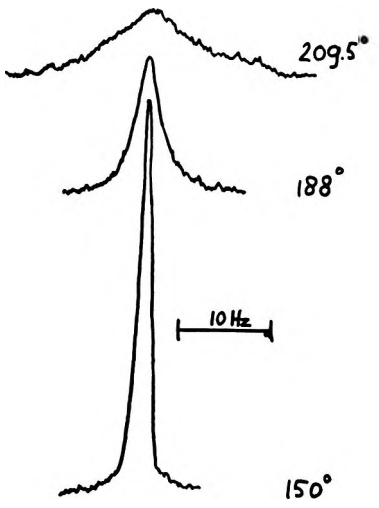


Figure 1.—Nmr spectra of diester **8a** (OCH_3 signal) at 150–210°.

$$\left(\frac{1}{T_2}\right)_{ex} = \frac{1}{\tau_d} \qquad (2)$$

A sufficient condition to use eq 2 is that the esr spectrum of the paramagnetic species shows hyperfine interaction of the group of nuclei whose nmr line broadening is being measured. This condition was fulfilled for all protons of **6b**, **8a**, and **13a** (see Table III and Figure 1).

TABLE III

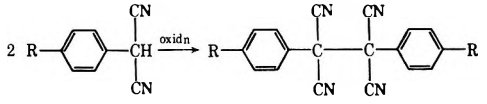
KINETIC PARAMETERS OF THE RADICAL DISSOCIATION REACTIONS, OBTAINED FROM NMR

Dimer	Temp range, °C	k_{diss} at 100°, sec^{-1}	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, eu
6b	80–120	19.8	26	14
8a (dl)	170–210	0.001[a]	31	8
13a	80–120	14.4	14.5	−13

[a] By extrapolation.

From line width measurements of the methyl signal at different temperatures, k_{diss}, $\Delta H^{\pm}$, and $\Delta S^{\pm}$ were obtained in this way for the dissociation reaction of **6b**, **8a**, and **13a** (*cf.* Table III). $\Delta H^{\pm}$ is 5 kcal/mol lower than in the case of the racemic *p*-tolylcyanoacetic ester dimer **8a**, which reflects the greater radical stabilization by the CN groups.

Dimers **6b** and **6c** were found to be active free radical polymerization initiators for styrene at 70°.[3]



a, R = H
b, R = CH_3
c, R = Cl

Methyl-Substituted Phenylcyanoacetic Esters 7 and 11.—Oxidative coupling of *p*-tolylcyanoacetic ester **7a** with O_2–[Cu(OH)(TMEDA)]$_2Cl_2$ in methanol gives dimer **8a** (mixture dl/meso 2:3) in 99% yield.[1]

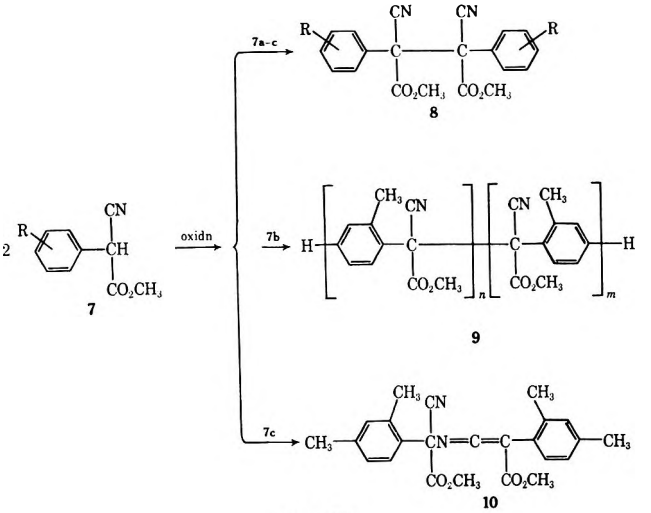
Under identical conditions, the *o*-tolylcyanoacetic ester **7b** consumed twice the amount of oxygen to give a complicated mixture. However, oxidation of **7b** with Ag_2O in benzene gave a 40% yield of C–C dimer **8b** (mixture dl/meso 3:2, determined by nmr;[1] see Experimental Section), together with oligomers. Gel permeation chromatography of the whole mixture showed the presence of about 55% of dimer **8b**, 35% of trimer, and 7% of tetramer. Apparently, the hindrance of the benzylic position by one *o*-CH_3 group promotes benzylic C–para C coupling to give oligomers **9**. The nmr spectrum shows no tertiary H. Oxidation of phenylcyanoacetic methyl ester itself (**7**, R = H) gives 2–4% of trimer as reported before.[1] According to the ir spectrum of the whole oxidation mixture (no C=C=N at 2010 cm^{-1}), no ketene imine similar to **10** could be detected.

As described earlier for **8a**, the kinetic mixture of **8b** (dl/meso 3:2) could be converted into a thermodynamic mixture (dl/meso 97:3 from nmr) by a 5-hr reflux in benzene.

Oxidation of *o*,*p*-dimethylphenylcyanoacetic ester **7c** with the O_2/Cu/amine system in methanol gave a 51% yield of dimer **8c** as one isomer. The dl configuration was assigned to this product on the basis of the nmr spectrum[1] (only *one* OCH_3 singlet at δ 3.88 ppm) and because a 5-hr reflux in benzene left dimer **8c** unchanged (compare dimer **8b**). The oligomerization of **7c** is impeded by the presence of a *p*-CH_3 group.

Oxidation of ester **7c** with Ag_2O in benzene gave a 1:1 mixture of dimer **8c** and ketene imine **10**, as indicated by ir and nmr spectra (see Experimental Section).

Diester **8c** dissociates reversibly into radicals, as shown by the esr spectrum (in diphenyl ether at 120–140°), which is too complex for interpretation in this case.



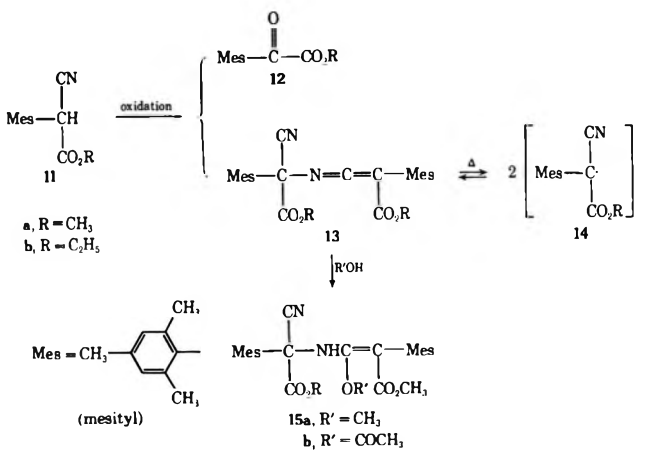
a, R = *p*-CH_3
b, R = *o*-CH_3
c, R = *o*,*p*-di-CH_3

With **11a** and **11b**, however, the steric effect of the two *o*-CH_3 groups seems to inhibit oxidative coupling to the C–C dimer. Oxidation with Ag_2O in benzene now gives exclusively ketene imines **13a** and **13b** *via* C–N coupling. Stuart–Briegleb models show that formation of the usual C–C dimer is inhibited because of the steric effect of the *o*-CH_3 groups. Another example of radical C–N coupling to ketene imines by thermal decomposition of azobisnitriles has been reported by Hammond, *et al.*[8]

(8) C. S. Wu, G. S. Hammond, and J. M. Wright, *Amer. Chem. Soc.*, **82**, 5386 (1960); G. S. Hammond, C. S. Wu, O. D. Trapp, J. Warkentin, and R. T. Keys, *ibid.*, **82**, 5394 (1960).

Oxidation of **11a** with the O_2/Cu/amine system gave only a 9% yield of the ketene imine–methanol adduct **15a**, together with 50% of glyoxylic ester **12a**, (identified as the acid) owing to oxygenation. The methanol adduct **15a** was also formed from ketene imine **13a** by refluxing it in methanol.

Finally, when ester **11a** was oxidized with Mn(III) acetate in acetic acid in the presence of sodium acetate, both ketene imine **13a** and the acetic acid adduct **15b** were formed.



The facile dissociation of ketene imines **13a** and **13b** into radicals **14** is demonstrated by the development of a blue color on heating in solution. The blue color gradually deepens at 40–100° and disappears on cooling to room temperature. The esr hyperfine coupling constants (Table II) of the radicals **14** clearly indicate reduced spin density in the aromatic ring and enhanced spin density at the CN and the ester CH_3 groups[9] compared with the radical from **8a**. The *o*-CH_3 groups apparently reduce coplanarity of the NC–Ċ–CO_2R moiety with the aromatic ring. The oxidative C–N coupling found with **11** is consistent with the enhanced spin density at the N atom, if we assume the same spin density distribution in the transition state of the coupling reaction.

Determination of k_{diss} from nmr line width measurements (as described in the previous section) of the ester CH_3 signal gave for **13** ⇄ **14** a relatively low $\Delta H^{\pm}$ (compared to **8a**) and a negative $\Delta S^{\pm}$ (*cf.* Table III). The lower $\Delta H^{\pm}$ is in agreement with the weaker C–N bond in the ketene imine **13a** compared to the C–C bond in **8a**.

The negative $\Delta S^{\pm}$, surprising at first sight for a dissociation reaction, might be accounted for by the greater freedom of motion in the ketene imine. Molecular models show that rotation of the NC–Ċ–CO_2CH_3 group is severely hindered in the radical **14**, whereas in the ketene imine **13**, the –N=C=C(Mes)CO_2CH_3 group just can rotate freely.

Experimental Section

Physical Methods and Analyses.—The melting points were determined with a melting point microscope (Leitz Model 553215) and are corrected; the boiling points are uncorrected. The ir spectra (KBr disks or neat) were recorded on a Hitachi EPI-G2 and a Perkin-Elmer 457 spectrophotometer. General features: the nitriles **5–15** showed a weak CN bond at 2250 cm^{-1} with varying intensities; the esters **1–4** and **7–15** gave a strong ester C=O band at 1750 cm^{-1}. Nmr spectra were run on an Varian A-60 spectrometer in $CDCl_3$ as solvent. Tetramethylsilane (δ 0) was used as an internal standard. Mass spectra were recorded at 70 eV with a Varian MAT CH-5 spectrometer. Gpc measurements were performed in THF solution on a gel permeation chromatograph, Model 200, manufactured by Waters Associates. The elemental analyses of new compounds were carried out under the supervision of Mr. W. J. Buis of the Micro-Analytical Department of the Institute for Organic Chemistry TNO (Utrecht, The Netherlands).

Esr Measurements.—Esr spectra were taken on a X-band spectrometer developed in our laboratory (Delft), using a TE_{011}-reflection cavity. The spectrometer was equipped with standard variable-temperature accessories. Temperatures were measured with a copper–constantan thermocouple outside the sample tube in the dewar just above the cavity.

Radicals were generated by heating a 0.01 *M* solution of the parent dimeric species under pure nitrogen (somewhat below 1 atm at 20°). The magnetic field was calibrated with Fremy's salt (A_N = 13.09 Oe). In all cases analysis of the spectra was confirmed by computer simulation.

Kinetic Measurements with Nmr Line Broadening.—Nmr line width measurements were recorded at a Jeol JNM-4H 100 MHz spectrometer equipped with a variable-temperature unit and a copper–constantan thermocouple inserted within the nmr tube for direct temperature reading. Temperature recording was accurate within ±0.5°; the temperature stability was better than 0.5°. Line width measurements were performed on the aromatic CH_3 and the ester OCH_3 signals, using α-chloronaphthalene as a solvent. For each of the dimers line width measurements were carried out at at least ten different temperatures relative to tetramethylthiourea, which was added to the solution. The line widths were independant of the dimer concentration.

Least square calculations yielded the Arrhenius activation parameters from the values of ln *k* and $1/T$. Variation coefficients were between 3 and 7%. The accuracy of the $\Delta S^{\pm}$ values was ±2 eu.

Arylmalonic Esters 1a–c.—Dimethyl phenylmalonate (**1a**) was prepared in 77% yield, mp 49.2–50.0°, after the method described by Nelson and Cretcher.[10] According to the same procedure there was obtained dimethyl *p*-tolylmalonate in 82% yield: mp 68.5–69.0°; nmr δ 2.28 (s, 3, *p*-CH_3), 3.67 (s, 6, OCH_3), 4.60 (s, 1, tertiary H), 7.0–7.4 (m, 4, aromatic H).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.86; H, 6.31. Found: C, 65.0; H, 6.5.

Dimethyl (*p*-chlorophenyl)malonate (**1c**) was obtained in 83% yield: mp 75.2–75.8°; nmr δ 3.67 (s, 6, OCH_3), 4.60 (s, 1, tertiary H), 7.0–7.4 (m, 4, aromatic H).

Anal. Calcd for $C_{11}H_{11}O_4Cl$: C, 54.43; H, 4.54; Cl, 14.64. Found: C, 54.6; H, 4.7; Cl, 14.5.

Arylmalonodinitriles 5a–c.—*p*-Tolylmalonodinitrile (**5b**) was prepared by heating *p*-tolylcyanoacetamide[1] with PCl_5 according to a procedure described for phenylmalonodinitrile (**5a**).[11] After crystallization from ethanol there was obtained 40% of **5b**: mp 57–57.5°; nmr (CCl_4) δ 2.40 (s, 3, *p*-CH_3), 5.08 (s, 1, tertiary H), 7.4 (AB system, 4 aromatic H).

Anal. Calcd for $C_{10}H_8N_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 77.0; H, 5.3; N, 17.9.

p-Chlorophenylmalonodinitrile (**5c**) was prepared from *p*-chlorophenylcyanoacetamide as described for **5b**: mp 70.2–70.7°; nmr δ 5.16 (s, 1, tertiary H), 7.60 (s, 4, aromatic H). The *p*-chlorophenylcyanoacetamide was synthesized from methyl *p*-chlorophenylcyanoacetate and ammonia as described for phenylcyanoacetamide,[12] yield 84%, mp 122–124° after one crystallization from ethanol.

Anal. Calcd for $C_9H_5N_2Cl$: C, 61.21; H, 2.85; N, 15.87; Cl, 20.08. Found: C, 60.9; H, 3.0; N, 15.7; Cl, 20.2.

Arylcyanoacetic Esters 7b, 7c, 11a, and 11b.—Methyl *o*-tolylcyanoacetate (**7b**) was prepared in 64% yield from *o*-methylbenzyl cyanide, bp 118–128° (12 mm), and dimethyl carbonate (3 molar excess) with CH_3ONa in refluxing toluene as described for ethyl phenylcyanoacetate:[13] bp 106–114° (0.3 mm); nmr

(9) A theoretical treatment of the esr data will be given elsewhere by W. J. van den Hoek and J. Smidt, Technische Hogeschool, Delft.

(10) W. L. Nelson and L. H. Cretcher, *J. Amer. Chem. Soc.*, **50**, 2760 (1928).

(11) J. C. Hessler, *Amer. Chem. J.*, **32**, 123 (1904).

(12) B. Radziszewski and P. Wispek, *Chem. Ber.*, **18**, 1279 (1885).

(13) N. Rabjohn, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963 p 461.

δ 2.32 (s, 3, o-CH_3), 3.67 (s, 3, OCH_3), 4.83 (s, 1, tertiary H), 7.0–7.5 (m, 4, aromatic H).

Methyl 2,4-dimethylphenylcyanoacetate (**7c**) was prepared in 71% yield from 2,4-dimethylbenzyl cyanide[14] and dimethyl carbonate as described for **7b**, bp 114–120° (0.7 mm). Two crystallizations from methanol–water gave a pure sample: mp 71.3–74.5°; nmr δ 2.30 (s, 3, aromatic CH_3), 2.33 (s, 3, aromatic CH_3), 3.77 (s, 3, OCH_3), 4.87 (s, 1, tertiary H), and 7.0–7.5 (m, 3, aromatic H).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.9; H, 6.5; N, 6.9.

Methyl 2,4,6-trimethylphenylcyanoacetate (**11a**) was prepared from 2,4,6-trimethylbenzyl cyanide[14] and dimethyl carbonate with NaH in dimethoxyethane as described for methyl phenylcyanoacetate.[1] The crude product was not distilled but was immediately recrystallized from ether–cyclohexane (1:9), giving a 21% yield of colorless material, mp 99.6–101.8°. One more recrystallization gave pure ester **11a**: mp 102.3–102.6°; nmr δ 2.28 (s, 3, p-CH_3), 2.37 (s, 6, o-CH_3), 3.78 (s, 3, OCH_3), 5.18 (s, 1, tertiary H), and 6.95 (s, 2, m-H).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.0; H, 7.0; N, 6.4.

Ethyl 2,4,6-trimethylphenylcyanoacetate (**11b**) was prepared from 2,4,6-trimethylphenylbenzyl cyanide[13] and diethyl carbonate with C_2H_5ONa in refluxing toluene as described for ethyl phenylcyanoacetate.[1] There was obtained a 41% yield of crystalline product: bp 124–126° (0.4 mm); mp 61–66°; nmr δ 1.23 (t, 3, ethyl CH_3, J = 7.0 cps), 2.22 (s, 3, p-CH_3), 2.33 (s, 6, o-CH_3), 4.20 (q, 2 ,CH_2, J = 7.0 cps); 5.08 (s, 1, tertiary H), and 6.83 (s, 2, m-H).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 73.0; H, 7.5; N, 6.0.

Tetraesters 2a–c. Oxidative Coupling of 1b with $KMnO_4$ in Acetone–Ammonia.—Dimethyl p-tolylmalonate (**1b**, 4.44 g, 20 mmol) was dissolved in a mixture of 160 ml of acetone and 40 ml of concentrated ammonia. $KMnO_4$ (3.6 g, 23 mmol) was added in small portions over a period of 5 min. The reaction mixture was kept at 20–30° and was stirred magnetically. After 30 min the reaction mixture was acidified with 4 *N* HCl. Extraction with chloroform yielded, after washing three times with 50 ml of water, drying over $MgSO_4$, filtration, and evaporation *in vacuo*, a slightly yellow sirup (4.3 g). Crystallization from methanol afforded 3.5 g (80%) of colorless dimer **2b**: mp 161.1–161.7° (*Anal.* Calcd: C, 65.16; H, 5.88. Found: C, 64.7; H, 6.0.), nmr δ 2.27 (s, 6, aromatic CH_3), 3.77 (s, 12, OCH_3), and 6.8–7.0 (m, 8, aromatic H).

Oxidative Coupling of 1b with $K_3Fe(CN)_6$ in Methanol–Ammonia.—To a solution of 4.44 g (20 mmol) of dimethyl p-tolylmalonate (**1b**) in 80 ml of methanol was slowly added a solution of 6.8 g (21 mmol) of $K_3Fe(CN)_6$ in 60 ml of concentrated ammonia, while stirring at room temperature. After 30 min there was added 100 ml of water and the mixture was extracted with chloroform. After the usual work-up (see previous experiment) there was obtained 3.6 g (81%) of colorless dimer **2b**.

Oxidative Coupling of 1b with O_2/Cu/Amine in Methanol.—The oxidation was carried out in a 250-ml oblong flask with 11.1 g (50 mmol) of dimethyl p-tolylmalonate (**1b**) in 110 ml of methanol at 20° with oxygen using 1.25 g (2.5 mmol) of CuCl–TMEDA as catalyst. The oxygen uptake was followed by means of a gas buret. After 2 hr, 850 ml of oxygen was consumed (calcd 300 ml for an oxidative C–C coupling to give **2b**). The reaction mixture was acidified with 5 ml of 2 *N* HCl and extracted with chloroform. After the usual work-up (see before) there was obtained 11.0 g of a liquid. Crystallization from methanol gave 1.4 g (13%) of dimer **2b**. Treatment of the mother liquor with 2,4-dinitrophenylhydrazine in methanol–sulfuric acid yielded 11.8 g (53%) of the 2,4-dinitrophenylhydrazone of the glyoxylic ester **4b**, mp 168.8–169.2°.

Oxidative Coupling of 1a with $KMnO_4$ in Acetone–Ammonia.—Dimethyl phenylmalonate (**1a**, 4.2 g, 20 mmol) was oxidized according to the procedure described above. After crystallization of the crude product (4.1 g) from methanol there was obtained 0.4 g (10%) of dimer **2a**, mp 191.0–192.5° (reported[2] mp 192°). (*Anal.* Calcd: C, 63.77; H, 5.31. Found: C, 63.7; H, 5.3.); nmr δ 3.80 (s, 12, OCH_3) and 6.8–7.3 (m, 10, aromatic H). Gpc measurements of the mother liquor showed the presence of *ca.* 40% dimer, 40% trimer, and 10% tetramer (shoulder).

Chromatography of the whole oxidation product over silica gel (0.05–0.2 mm) using 3% acetone in CCl_4 as eluent gave besides dimer **2a** also noncrystalline fractions with additional nmr peaks: δ 3.67, 3.73, and 3.77 (s, OCH_3), 4.58 (s, 1.7% of total OCH_3 peaks, tertiary H).

Oxidative Coupling of 1a with $K_3Fe(CN)_6$ in Aqueous NaOH/CH_2Cl_2.—To a mixture of 4.2 g (20 mmol) of dimethyl phenylmalonate (**1a**) dissolved in 50 ml of methylene chloride and 20 ml of 2 *N* NaOH there was added 20 ml of a 1 *N* $K_3Fe(CN)_6$ solution in water and after shaking for 20 min in a separatory funnel the layers were separated. The water layer was extracted three times with 10 ml of methylene chloride. The combined methylene chloride solutions were washed with water and dried over $MgSO_4$.

Evaporation *in vacuo* of methylene chloride and crystallization from methanol gave 0.45 g (11%) of dimer **2a**.

Oxidative Coupling of 1a with O_2/Cu/Amine in Methanol.—Dimethyl phenylmalonate (**1a**, 4.2 g, 20 mmol) was oxidized after the procedure described above. Crystallization from methanol yielded 0.14 g (3.4%) of dimer **2a**. Treatment of the mother liquor with 2,4-dinitrophenylhydrazine in methanol–sulfuric acid gave 2.9 g (42%) of the 2,4-dinitrophenylhydrazone of the glyoxylic ester **4a**, mp 172.2–172.7° (reported[15] mp 173–174°).

Oxidative Coupling of 1c with $KMnO_4$ in Acetone–Ammonia.—Dimethyl (p-chlorophenyl)malonate (**1c**, 4.84 g, 20 mmol) was oxidized after the method described above. Crystallization from methanol afforded 3.3 g (68%) of colorless dimer **2c**: mp 167.5–169.5° (*Anal.* Calcd: C, 54.66; H, 4.14; Cl, 14.70. Found: C, 54.6; H, 4.3; Cl, 14.6.); nmr δ 3.82 (s, 12, OCH_3) and 6.8–7.3 (m, 8, aromatic H).

Oxidative Coupling of 1c with $K_3Fe(CN)_6$ in Methanol-Ammonia.—Dimethyl (p-chlorophenyl)malonate (**1c**, 4.84 g, 20 mmol) was oxidized after the procedure described above. Crystallization from methanol gave 3.8 g (78%) of dimer **2c**.

Tetranitriles 6b and 6c. Oxidative Coupling of 5b with Mn(III) Acetate.—To a solution of 7.8 g (0.050 mmol) of p-tolylmalonodinitrile (**5b**) in 50 ml of acetic acid was added a solution of 11 g (0.048 mmol) of Mn(III) acetate in 100 ml of 98% acetic acid containing 10 g of sodium acetate. The sodium acetate was added to facilitate the dissolution of Mn(III) acetate. The reaction product precipitated, and was filtered and washed with water. Crystallization from toluene gave a 95% yield of tetranitrile **6b**: mp 201–202°; nmr (acetone-d_6) δ 2.50 (s, 6, CH_3), 7.51 (AB spectrum, 8, aromatic H); mass spectrum *m/e* 310 (molecular ion), 155 [p-tolyl-$C(CN)_2$].

Anal. Calcd for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05; mol wt, 310. Found: C, 77.4; H, 4.7; N, 17.8.

Oxidative Coupling of 5c with Mn(III) Acetate.—The oxidation was carried out as described for **5b** and gave a 93% yield of tetranitrile **6c**, mp 215°, nmr δ 7.60 (s, aromatic H).

Electrochemical Coupling of 5b.—A solution of 100 mg (0.64 mmol) of p-tolylmalodinitrile (**5b**) and 0.03 mmol of sodium acetate in 60 ml of 90% acetic acid–water was electrolyzed in a thermostatted cell at 31° at a controlled potential of 450 mV (sce) at a Pt anode. After electrolysis the solution was concentrated to 20 ml and the product was precipitated by the addition of water. The precipitate was filtered, washed with water, and dried to give a 80% yield of dimer **6b** (current yield 85%).

Oxidation of Methyl-Substituted Phenylcyanoacetic Esters 7b and 7c and 11a and 11b. Oxidation of 7b with Ag_2O.—A solution of 9.45 g (0.05 mmol) of methyl o-tolylcyanoacetate (**7b**) in 100 ml of benzene containing 6.0 g (0.026 mmol) of Ag_2O was stirred for 30 min at room temperature. After filtration the benzene was removed *in vacuo*. Chromatography of the residue over 600 g of silica gel (0.05–0.2 mm) gave after elution with 3% ethyl acetate in CCl_4 3.8 g of colorless dimer **8b**. On heating at a rate of 10°/min the dimer (isomer mixture) melted partially at 153°, then it recrystallized completely (conversion to dl isomer): mp 177.4–180.8°; nmr δ 1.81 and 1.98 (s, 6, o-CH_3, ratio 3:2, dl and meso isomer), 3.86 and 3.95 (s, 6, OCH_3, ratio 2:3, meso and dl isomer), 7.0–7.5 (m, 8, aromatic H).

Anal. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.21; H, 5.32; N, 7.45. Found: C, 70.2; H, 5.4; N, 7.4.

Attempts to obtain pure meso isomer by fractional crystallization as described for **7a** failed.

Gpc analysis of the whole reaction mixture corresponded with the presence of *ca.* 55% dimer, 35% trimer, and 7% tetramer.

(14) B. van Zanten and W. T. Nauta, *Recl. Trav. Chim. Pays-Bas*, **79**, 1215 (1960).

(15) P. S. Bailey, S. B. Mainthia, and C. J. Abshire, *J. Amer. Chem. Soc.*, **82**, 6136 (1960).

Nmr of reaction mixture was the same as that of **8b**, except for additional peaks at δ 2.14 and 2.31 (s, *o*-CH_3) and 3.90 (s, OCH_3) and *no* peak at δ 4.83 (tertiary H).

Thermal Equilibration of 8b to Give Racemic Isomer.—A solution of 500 mg of dimer **8b** (dl/meso 3:2) in 20 ml of benzene was refluxed for 1 hr. There was obtained a 93:7 mixture of dl/meso (by nmr). Recrystallization from methanol gave pure dl isomer: mp 180–183°; yield 70%; nmr δ 1.81 (s, 6, *o*-CH_3), 3.95 (s, 6, OCH_3), 7.0–7.4 (m, 8, aromatic H).

Diester 8c by Oxidative Coupling of 7c with Cu/Amine/O_2.—A solution of 160 g (0.79 mol) of ester **7c**, bp 114–120° (0.7 mm), and 5.0 g (11 mmol) of $[Cu(OH)TMDA]_2Cl_2$ in 160 ml of methanol was shaken with oxygen at room temperature in an oblong flask connected with a gas buret. After consumption of the theoretical amount of oxygen (0.2 g-atom in 7.5 min), there was added 1 l. of 0.1 *N* hydrochloric acid and the mixture was extracted two times with $CHCl_3$. The combined chloroform layers were washed with water and dried over molecular sieves. Evaporation of the filtrate *in vacuo* gave a yellow sirup. Addition of about 80 ml of methanol gave immediate crystallization and a first crop of 60 g of colorless, pure diester **8c**, mp 198.4–199°, was obtained. Addition of water to the mother liquor gave 35 g of yellow product, which on recrystallization from methanol gave another 22 g of pure diester **8c**: mp 195.2–197°; total yield 51%; nmr δ 1.77 (s, 6, *o*-CH_3), 2.27 (s, 6, *p*-CH_3), 3.88 (s, 6, OCH_3, dl isomer[1]), 6.8–7.2 (s, 6, aromatic H); mass spectrum *m/e* 404 (molecular ion), 202 (base peak, rupture of central C–C bond).

Anal. Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.0; H, 6.0; N, 6.8.

Thermal Treatment of Diester 8c.—Under conditions in which diester **8a** is equilibrated into 94% dl isomer[1] and diester **8b** into 97% dl isomer (a 5-hr reflux in benzene), diester **8c** is recovered unchanged. Therefore, the dl configuration is assigned to diester **8c**. The presence of a second isomer has never been detected.

Diester 8c and Ketene Imine 10 by Oxidative Coupling of 7c with Ag_2O.—A solution of 2.0 g (10 mmol) of ester **1c** in 100 ml of benzene containing 1.4 g (6 mmol) of Ag_2O was stirred at room temperature for 2 hr. Evaporation of the filtrate *in vacuo* gave 2.0 g of a glassy residue: ir (KBr) 2250 (w, CN), 2025 (m, C=C=N), 1750 (vs, unconjugated C=O), 1720 cm^{-1} (m, conjugated C=O); nmr, same as that of **8c**, except for extra peaks at δ 1.97 (s, *o*-CH_3 of ketene imine moiety) and 3.83 (s, OCH_3 of ketene imine moiety), corresponding to a 1:1 mixture of dimer **8c** and ketene imine **10**.

Crystallization from ligroin (bp 60–80°) gave a first crop of 0.28 g of colorless diester **8c**, mp 193.7–196.5. Upon standing overnight, the mother liquor furnished another 0.80 g of diester **8c**, mp 190–197° (total yield 54%). The ir and nmr spectra of both fractions are identical with those of diester **8c**, prepared before.

Ketene Imine 13a by Oxidative Coupling of 11a with Ag_2O.—A solution of 2.17 g (10 mmol) of ester **11a**, 95–100°, in 75 ml of benzene containing 1.4 g (6 mmol) of Ag_2O was stirred at room temperature for 3 hr. Evaporation of the filtrate gave 2.10 g (97%) of colorless sirup, which was practically pure ketene imine **13** by ir, nmr, and tlc (eluent: benzene–ethyl acetate, 9:1). The sirup was dissolved in boiling ligroin. After intensive scratching at room temperature a very slow crystallization started, and after 2 hr at 0° a first crop was obtained of 0.38 g of colorless ketene imine **13**, mp 116.8–117.3°. Upon standing overnight, the mother liquor furnished another 0.65 g of colorless product: mp 117.5–119.6°; ir 2250 (vw, CN), 2010 (s, C=C=N), 1763 (s, saturated C=O), 1718 (m, C=C–C=O), 1700 cm^{-1} (s, C=C–C=O); nmr δ 2.18, 2.24, and 2.35 (s, 3 × 6, *o*- and *p*-CH_3), 3.71 and 3.82 (s, 2 × 3, OCH_3), 6.83 (s, 4, aromatic H); mass spectrum *m/e* 432 (molecular ion), 216 (strong, rupture of central C–N bond).

Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.52; N, 6.48; mol wt, 432.5. Found: C, 72.1; H, 6.6; N, 6.6.

Oxidation of Ester 11a with Cu/Amine/O_2 to Give 12a and 15a.—A solution of 4.34 g (20 mmol) of ester **11a**, mp 98–101°, and 0.5 g (1.1 mmol) of $[Cu(OH)TMEDA]_2Cl_2$ in 50 ml of methanol was shaken at room temperature with oxygen as described for diester **8c**. After 30 min there was consumed 60 ml (2.5 g-atoms), after 6 hr 220 ml (9 g-atoms) of oxygen. Addition of 500 ml of 0.1 *N* hydrochloric acid followed by chloroform extraction (see diester **8c**) gave 4.7 g of a yellow oil. Chromatography over silica gel (0.05–0.2 mm) with 3% EtOAc in CCl_4 as eluent gave 2.1 g (50%) of a yellow oil, corresponding to methyl 2,4,6-trimethylphenylglyoxylate (**12a**): ir (neat) 1780, 1760, 1740, and 1705 cm^{-1} (C=O); nmr 2.25 (s, 6, *o*-CH_3), 2.29 (s, 3, *p*-CH_3), 3.90 (s, 3, OCH_3), 6.93 (s, 2, *m*-H); mass spectrum *m/e* 206 (molecular ion, very weak), 147 (base peak, Mes-CO), 119 (80% of base peak, Mes).

Hydrolysis of ester **12a** with NaOH in aqueous ethanol (1 hr reflux) gave mesitylglyoxylic acid, which after two recrystallizations from benzene–hexane melted at 115.5–118.5° dec (reported[16] mp 116.7–117.9°).

Further elution gave 0.40 g (9%) of colorless enol ether **15a**: mp 165.8–166.3°; ir 3450 (broad, NH), 3210 and 3150 (m, NH), 2250 (vw, CN), 1775 and 1670 (s, CO), 1620 (sh) and 1595 cm^{-1} (s) (C=C); nmr δ 2.06 (s, 3, aromatic CH_3), 2.21 (s, 3, aromatic CH_3), 2.25 (s, 6, aromatic CH_3), 2.57 (s, 6, aromatic CH_3), 2.87 (s, 3, C=$COCH_3$), 3.62 (s, 3, ester OCH_3), 3.93 (s, 3, ester OCH_3), 6.92 (s, 4, *m*-H); mass spectrum *m/e* 464 (molecular ion).

Anal. Calcd for $C_{27}H_{32}N_2O_5$: C, 69.80; H, 6.94; N, 6.03; mol wt, 464.6. Found: C, 69.8; H, 7.0; N, 5.9.

Methanol Adduct 15a from Ketene Imine 13a.—A solution of 500 mg (1.2 mmol) of ketene imine **13a** in 25 ml of methanol was refluxed until the blue color had disappeared (3 hr).

The solution was concentrated to 10 ml and water was added to the hot solution until a slight turbidity persisted. Upon standing at room temperature, a first crop of 180 mg of product, mp 106–111°, was obtained. From the mother liquor there was obtained a second crop of 230 mg of crystals, mp 98–99.6°, identical with methyl mesitylcyanoacetate (**11a**).

An ether solution of the first crop was shaken with 1 *N* NaOH solution to remove **11a** and the ether layer was dried ($MgSO_4$) and evaporated. Two recrystallizations of the residue from methanol gave the methanol adduct **15a**, mp 160–166°. The ir and nmr spectra are identical with those of **15a**, prepared before.

Oxidation of 11a with Mn(III) Acetate to Give 13a and 15b.—A solution of 1.87 g (8.2 mmol) of Mn(III) acetate and 4.08 g of $NaOAc \cdot 3H_2O$ in 100 ml of acetic acid was slowly added to a solution of 1.02 g (4.7 mmol) of methyl mesitylcyanoacetate (**11a**) and 4.08 g of $NaOAc \cdot 3H_2O$ in 30 ml of acetic acid at 80°. After 10 min the reaction was stopped. After removal of about 70 ml of acetic acid *in vacuo*, the resulting solution was divided into two equal parts.

One part was evaporated to dryness *in vacuo*. The residue was extracted with chloroform and the solvent was slowly evaporated until crystallization just started. There was obtained 100 mg (20%) of a colorless product, mp 118.5–119.2°, the ir and nmr spectra of which are identical with those of ketene imine **13a**, prepared before.

To the second part, water was added until the solution became slightly turbid. After 2 days at 5°, 300 mg (50%) of acetic acid adduct **15b**, mp 164.5–165.2°, was isolated: ir 3450 (broad, NH), 3240 and 3190 (m, NH), 1798 and 1772 (s, CO), 1685 and 1608 cm^{-1} (s, C=C); nmr δ 1.25 (s, 3, $COCH_3$), 2.02 (s, 3, aromatic CH_3), 2.22 (s, 9, aromatic CH_3), 2.53 (s, 6, aromatic CH_3), 3.66 (s, 3, OCH_3), 3.94 (s, 3, OCH_3), 6.87 (s, 4, *m*-H); mass spectrum *m/e* 492 (molecular ion).

Ketene Imine 13b by Oxidation of 11b with Ag_2O.—A solution of 2.3 g (10 mmol) of ester **11b**, mp 61–66°, in 75 ml of benzene containing 1.5 g (6.5 mmol) of Ag_2O was stirred overnight at room temperature. The colorless sirup, obtained on evaporation of the filtrate, was recrystallized from hexane. A first crop of 0.95 g of **13b**, mp 90.1–91.7°, was obtained. Concentration of the mother liquor gave another 0.28 g of product: mp 90–92°; total yield 54%; ir 2230 (vw, CN), 2020 (s, C=C=N), 1770 and 1760 (s, saturated CO), 1722 and 1718 cm^{-1} (s, C=C–C=O); nmr δ 1.18 (t, J = 7.0 cps, 3, ethyl CH_3), 1.23 (t, J = 7.0 cps, 3, ethyl CH_3), 2.20 (s, 12, aromatic CH_3), 2.38 (s, 6, aromatic CH_3), 4.19 (q, J = 7.0 cps, 2, CH_2), 4.23 (q, J = 7.0 cps, 2, CH_2), 6.98 (s, 4, *m*-H); mass spectrum *m/e* 460 (molecular ion), 230 (base peak, rupture of central C–N bond).

Anal. Calcd for $C_{28}H_{32}N_2O_4$: C, 73.02; H, 7.00; N, 6.08; mol wt, 460.6. Found: C, 72.8; H, 7.1; N, 6.1.

Registry No.—**1b**, 34402-91-0; **1c**, 34402-92-1; **2a**, 34404-71-2; **2b**, 34404-72-3; **2c**, 34404-73-4; **4b** 2,4-DNP, 34404-74-5; **5b**, 33534-88-2; **5c**, 32122-64-8;

(16) W. G. Dauben and J. B. Rogan, *J. Amer. Chem. Soc.*, **78**, 4135 (1956).

6b, 34404-77-8; **6c**, 34404-78-9; **7b**, 34404-79-0; **7c**, 34404-80-3; *dl*-**8a**, 30698-38-5; *dl*-**8b**, 34405-36-2; *dl*-**8c**, 34405-37-3; **11a**, 34404-81-4; **11b**, 34404-82-5; **12a**, 34404-83-6; **13a**, 34404-84-7; **13b**, 34404-85-8; **14a**, 34415-49-1; **14b**, 34415-50-4; **15a**, 34404-86-9; **15b**, 34404-87-0.

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Reactions of α-Substituted Polynitrotoluenes. III. 2,4,6-Trinitrobenzyl Anion as a Nucleophile at Aromatic Carbon

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The results of deuterium exchange experiments have shown that 2,4,6-trinitrobenzyl anion is formed from 2,4,6-trinitrotoluene in alkaline tetrahydrofuran–methanol solutions. This carbanion has been utilized as a nucleophile in halogen displacement reactions at aromatic carbon to prepare a series of polynitrodiphenylmethanes.

The previous paper in this series[1] described the preparation of 2,2′,4,4′,6,6′-hexanitrostilbene (**1**) from 2,4,6-trinitrotoluene (**2**) and aqueous hypochlorite in tetrahydrofuran–methanol. It was postulated[1] that, in alkaline media, **2** formed 2,4,6-trinitrobenzyl anion (**3**), which was chlorinated to yield 2,4,6-trinitrobenzyl chloride (**4**). Subsequent reaction of **4** with alkali produced **1**. Evidence to support the intermediacy of **4** in this reaction was obtained by isolating it in 85% yield from a short-stopped reaction.

In the present paper, we present additional evidence for the existence of the anion **3** under our reaction conditions and describe a variety of chemistry based upon its use as a nucleophile in displacement reactions at aromatic carbon. The products of these reactions, polynitrodiphenylmethanes, dissociate in alkaline media to form the corresponding polynitrodiphenylmethide ions. These anions were found to be unreactive in nucleophilic addition reactions.

Results and Discussion

The question of the existence of the anion **3** has been considered by numerous investigators.[2-7] In general, the formation of the anion **3** was disfavored in largely aqueous solvent systems. This conclusion was recently confirmed by Bernasconi,[8] who observed that though the anion **3** is the primary product of the reaction of **2** with alkali in methanol, ethanol, and 50% dioxane–water, there was no evidence to suggest that the anion **3** was present when 10% dioxane–water was used as a solvent.

Since our experimental work[1] had been carried out in tetrahydrofuran–methanol–water, about 1:1:1, our preliminary experiments were designed to determine whether **3** is in fact the primary product formed from **2** upon the addition of alkali. If the anion **3** does form, then in a reaction such as the halogenation of **2**,[1] the formation of **3** should be rate determining.[9a] If halogenation of **3** is rapid relative to its rate of reprotonation by the weak acids water or methanol, then every anion formed will be converted to **4** without returning to **2**. Thus, the conversion of **2** to **4** in a deuterated solvent system should yield **4**-α-H_2.

When **2** in tetrahydrofuran–methanol-*d* was rapidly added to D_2O–OD^- at 0° and the mixture was immediately quenched in DCl–D_2O, the recovered **2** was found to have exchanged 12.4% (nmr) of its methyl protons. Quenching the reaction after a 30-sec equilibration increased the deuterium content of the recovered **2** to 25.5%. However, when the anion **3** was trapped by chlorination[1] in a deuterated solvent system, the halide **4** did not contain any deuterium in the α position. These results are consistent with the proposed slow formation of **3** from **2** (eq 1) followed by a rapid chlorination of the anion **3**.

$$\underset{\mathbf{2}}{\mathrm{PiCH_3}} + \mathrm{OH^-} \longrightarrow \underset{\mathbf{3}}{\mathrm{PiCH_2^-}} + \mathrm{H_2O} \qquad (1)$$

$$\mathrm{PiCH_2^-} + \mathrm{OCl^-} + \mathrm{H_2O} \longrightarrow \underset{\mathbf{4}}{\mathrm{PiCH_2Cl}} + 2\mathrm{OH^-} \qquad (2)$$

Pi = 2,4,6-trinitrophenyl

A similar and perhaps rather surprising result was obtained when *p*-nitrobenzyl bromide was used as the substrate molecule for nucleophilic attack by the anion **3**.[1] From this reaction carried out in tetrahydrofuran–methanol-*d*, we obtained an 83% yield of 2,4,4′,6-tetranitrobibenzyl (**5**). The product had not incorporated deuterium at either of the methylene groups (eq 3). The absence of deuterium in the product sug-

$$\mathrm{PiCH_2^-} + p\text{-}\mathrm{O_2NC_6H_4CH_2Br} \longrightarrow \underset{\mathbf{5}}{p\text{-}\mathrm{O_2NC_6H_4CH_2CH_2Pi}} \qquad (3)$$

gests that the nucleophilic displacement process involving either ionic or ion–radical[9b] intermediates is exceedingly rapid as compared to the recombination of

(1) K. G. Shipp and L. A. Kaplan, *J. Org. Chem.*, **31**, 857 (1966).
(2) K. Bowden and R. Stewart, *Tetrahedron*, **21**, 261 (1965).
(3) E. Buncell, K. E. Russell, and J. Wood, *Chem. Commun.*, 252 (1968).
(4) R. E. Miller and W. F. R. Wynne-Jones, *J. Chem. Soc.*, 2375 (1959).
(5) J. A. Blake, M. J. B. Evans, and K. E. Russell, *Can. J. Chem.*, **44**, 119 (1966).
(6) E. F. Caldin and G. Long, *Proc. Roy. Soc., Ser. A*, **228**, 263 (1955).
(7) K. L. Servis, *J. Amer. Chem. Soc.*, **89**, 1508 (1967).
(8) C. F. Bernasconi, *J. Org. Chem.*, **36**, 1671 (1971).

(9) (a) By analogy with the overall rate of halogenation of other carbon acids: R. G. Pearson and R. L. Dillion, *J. Amer. Chem. Soc.*, **75**, 2439 (1953). Bernasconi[8] reports that the deprotonation of **2** in methanol or ethanol is as slow as in nitroethane. (b) R. G. Kerber, G. W. Urry, and N. Kornblum, *J. Amer. Chem. Soc.*, **87**, 4520 (1965).

3 with protons from the weak acid methanol. We prefer a mechanism involving ionic rather than ion–radical intermediates (eq 4–6) on the following grounds.

$$PiCH_2^- + p\text{-}O_2NC_6H_4CH_2Br \longrightarrow PiCH_2\cdot + p\text{-}O_2NC_6H_4CH_2Br^-\cdot \quad (4)$$

$$p\text{-}O_2NC_6H_4CH_2Br^-\cdot \longrightarrow p\text{-}O_2NC_6H_4CH_2\cdot + Br^- \quad (5)$$

$$p\text{-}O_2NC_6H_4CH_2\cdot + PiCH_2\cdot \longrightarrow p\text{-}O_2NC_6H_4CH_2CH_2CH_2Pi \quad (6)$$

5

Though *p*-nitrobenzyl bromide affords an 83% yield of **5**, the corresponding chloro derivative produced only an 8% yield of **5**. Kornblum[9b] has shown that the rate of carbon alkylation of 2-nitropropyl anion by *p*-nitrobenzyl halides, a reaction which proceeds by an ion–radical mechanism, is quite insensitive to the nature of the leaving group. Therefore, the disparity in the yields of **5** obtained from the bromide and the chloride is better fit by an ionic displacement mechanism, Furthermore, the addition of *p*-dinitrobenzene, an electron acceptor that inhibited the carbon alkylation of 2-nitropropyl anion by *p*-nitrobenzyl chloride,[9b] had no effect on the yield of the nucleophilic displacement product **5**. We therefore concluded that under our reaction conditions **2** forms the anion **3**, which can participate in ionic displacement reactions.

Extending the use of the reagent **3** to aryl halides, we observed that, with picryl chloride as the substrate in tetrahydrofuran–methanol solution, a 90% yield of a crystalline solid, mp 232°, was obtained on acidifying the reaction mixture. Its mode of formation and the results of nmr (Table I), molecular weight, and elemental analytical determinations showed the product to have the structure of the expected, but heretofore unknown, nucleophilic displacement product 2,2′,4,4′,6,6′-hexanitrodiphenylmethane (**6**). With other polynitroaryl halides, halide displacement products analogous to **6** were obtained. These results are summarized in Table I.

Inspection of the yield data in Table I for the mono-, di-, and trinitrophenyl halides shows that the yield of polynitrodiphenylmethane is quite sensitive to the number and orientation of the nitro groups attached to the benzene ring of the aryl halide. As the yield of polynitrodiphenylmethane decreases in the order 2,4,6-$(NO_2)_3 \gg$ 2,4-$(NO_2)_2 >$ 2,6-$(NO_2)_2 >>>>$ 3,5-$(NO_2)_2$ or mononitro, an increase in the yield of 2,2′,4,4′,6,6′-hexanitrobibenzyl (**7**), a bimolecular condensation product of **2**, is obtained. Under these reaction conditions in the absence of aryl halide, **2** affords a 41% yield of **7**. Since the relative reactivity of these polynitroaryl halides toward other nucleophiles is in the same order[10–12] as we have observed for **3**, the inability of mononitro-, 3,5-dinitro-, and 2,6-dinitrophenyl (at mole ratio $ArX/PiCH_3 = 0.5$) halides to form any nucleophilic displacement product analogous to **6** can be attributed to a competing reaction of the anion **3** with **2** to form the bimolecular condensation product **7**. The formation of **7** from **3** and **2** probably involves radical ion intermediates and proceeds by a mechanism similar to that suggested for the formation of 4,4′-dinitrobibenzyl from *p*-nitrotoluene in alkaline media.[13]

The system may therefore be described by the following equations.

$$PiCH_2^- + ArX \xrightarrow{k_N} ArCH_2Pi \quad (7)$$

$$PiCH_2^- + PiCH_2 \xrightarrow{k_B} PiCH_2CH_2Pi \quad (8)$$

As the reactivity of the substrate ArX toward nucleophilic reagents increases, the ratio k_N/k_B will increase. Consequently, the product composition should change from **7** to polynitrodiphenylmethane derivative, passing through a region where a mixed **7**–polynitrodiphenylmethane product is obtained as the susceptibility of the substrate to nucleophilic attack increases. Such an intermediate condition was observed when 1-chloro-2,4-dinitrobenzene was used as a substrate. For a molar ratio $ArX/PiCH_3 = 0.5$, a mixture of **7** and 2,2′,4,4′,6-pentanitrodiphenylmethane (**8**) was obtained (Table I). The displacement reaction (eq 7) competed more effectively on increasing the concentration of the halide substrate. When the $ArX/PiCH_3$ ratio was increased to 1.5, a threefold increase in the partial rate factor $k_N[ArX]/k_B[PiCH_3]$, **8** was the only product formed (Table I).

A change in the product composition similar to that obtained by increasing the concentration of the halide substrate could also be obtained by substituting 1-fluoro-2,4-dinitrobenzene for the chloro derivative. With the fluoro derivative at a mole ratio $ArX/PiCH_3 = 0.5$, the sole reaction product was **8** rather than a mixture of **7** and **8** as was obtained with chloride at this reactant ratio. The rate constant ratio k_{ArF}/k_{ArCl} for the reaction of 2,4-dinitrophenyl halides with anionic nucleophiles of the first row elements is much greater than unity.[14] As only a threefold increase in the partial rate factor $k_N[ArX]/k_B[PiCH_3]$ was required to suppress the formation of **7** in the reaction using the chloride substrate, increasing the reactivity of the substrate ArX by certainly more than a factor of 3[14] should produce the same change in the product composition. These results are consistent with the hypothesis that the formation of the polynitrodiphenylmethanes occurs by an S_N2 ionic displacement mechanism with the anion **3** acting as a nucleophile.

The absence of diphenylmethane product with 2-NO_2, 4-NO_2, 3,5-$(NO_2)_2$, and 2,6-$(NO_2)_2$ phenyl halides at mole ratio $ArX/PiCH_3 = 0.5$ (Table I) is understandable from a consideration of the reaction rates for these substrates with methoxide ion in methanol at 50°.[11,15] The relative rates for 2-NO_2, 4-NO_2, 2,6-$(NO_2)_2$, and 2,4-$(NO_2)_2$ chlorobenzenes are in the order 1:3.4:2900:75,000. With a 20–75,000-fold difference between the reactivity of the mononitro and 2,4-$(NO_2)_2$ substrates toward methoxide ion, displacement of halogen from the mononitro derivatives by **3** (eq 7) should not be able to compete with the formation of **7** (eq 8) at either a larger $ArX/PiCH_3$ ratio or by using the more reactive fluoro substrates. However, with

(10) A. J. Parker and T. O. Read, *J. Chem. Soc.*, 9 (1962)

(11) J. F. Bunnett, *Quart. Rev., Chem. Soc.*, **12**, 1 (1958).

(12) J. Miller, "Aromatic Nucleophilic Substitution," Elsevier, Amsterdam, 1968, Chapters 4 and 5.

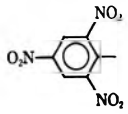
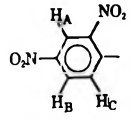
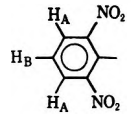
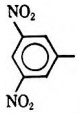
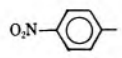
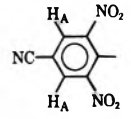
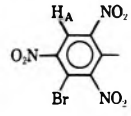
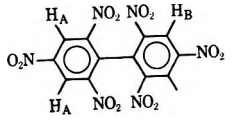
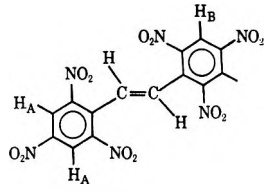
(13) G. A. Russell and E. G. Janzen, *J. Amer. Chem. Soc.*, **84**, 4153 (1962); **89**, 300 (1967).

(14) *Cf.* ref 12, Chapter 5, Section 3b; as examples, k_{ArF}/k_{ArCl} for MeO^- and $p\text{-}O_2NC_6H_4O^-$ with 2,4-dinitrophenyl halides is equal to 890 and 3160, respectively.

(15) Data are not available for the 3,5-$(NO_2)_2$ isomer but it is certainly less reactive than the 2,6-$(NO_2)_2$ isomer and probably less reactive than the 4-NO_2 isomer.

TABLE I

REACTION PRODUCTS, $PiCH_2Ar$, FROM NITROARYL HALIDES AND 2,4,6-TRINITROBENZYL ANION[a]

Ar	X	Yield $PiCH_2Ar$, % THF	THF–DMSO	100-MHz Nmr spectrum[b] Pi	CH_2	CH	H_A	H_B	H_C
	Cl	90	90	(M) 9.06 (A) 8.70	5.12	6.92			
	F	35	84	(M) 9.18	4.78		8.85 (2)	8.38 (4)	7.34 (2)
	Cl	*c*	c	(A) 8.42		7.33	8.73 (2)	8.16 (4)	7.25 (2)
	Cl		28[d]						
	Cl		*e*	(M) 9.00	5.02		8.32 (2)	7.84 (3)	
	Cl		35[f]	(A) 8.30		7.13	8.17 (2)	7.61 (3)	
	I	*e,h*	*e*						
	I		*g,h*						
	F		*e*						
	Br		*e*						
	Br		*g*						
	I	*e,h*	*e,h*						
	I		*g,h*						
	Cl		*e,h*						
	Cl	45	54	(M) 9.04 (A) 8.42[i]	5.09	6.96	8.91 8.65[i]		
	Br		29[i]	(M) 9.10 (A) 8.64	5.00	6.39	9.05 8.95		
	Cl		25	(M) 9.07 (A) 8.86	5.07	6.08	9.29 9.22	9.32 9.01	
	Cl	25	71	(M) 9.08 (A) 8.62	4.99	6.54	9.10 9.10	9.01[k] 8.94[k]	

[a] Unless otherwise noted, mole ratio $ArX/PiCH_3 = 0.5$. [b] Nmr spectra of neutral molecules (M) in DMSO-d_6. For anion (A) spectra, DMSO-d_6 solutions were partially neutralized with MeO^- in methanol. Changes in δ values for neutral molecules after adding base were less than 0.03 ppm. TMS was used as an internal reference. δ Values are in parts per million, multiplicity of lines in parentheses, $J_{o\text{-HH}} \cong 9$ Hz, $J_{m\text{-HH}} \cong 2$ Hz. [c] Mixture of **7** and **8** isolated. [d] Mole ratio $ArX/PiCH_3 = 1.5$. [e] Only **7** isolated. [f] Mole ratio $ArX/PiCH_3 = 6.0$. [g] Mixture of **7** and **1** isolated from reaction carried out at 60°. [h] Mole ratio $ArX/PiCH_3 = 1.0$. [i] Line assignments are questionable. [j] Only one halogen displaced. [k] Lines for vinyl hydrogens at 7.06 (4) ppm in neutral molecule and 7.03 (1) ppm in anion.

only a 25-fold difference in the reactivity of the 2,6-$(NO_2)_2$ and 2,4-$(NO_2)_2$ substrates toward methoxide ion, the synthesis of 2,2′,4,6,6′-pentanitrodiphenylmethane (**9**) from 1-chloro-2,6-dinitrobenzene was realized by increasing the mole ratio $ArX/PiCH_3$ from 0.5 to 6. Under these conditions, a 12-fold increase in the partial rate factor $k_N[ArX]/k_B[PiCH_3]$, the product composition was changed from **7** to **9** (Table I).

The formation of small amounts of **1** together with the bimolecular product **7** in the reactions carried out at 60° with 2-NO_2, 4-NO_2, and 3,5-$(NO_2)_2$ phenyl halides as substrates probably derives from the oxidation of an intermediate in the conversion of **2** to **7** (eq 8). We have obtained similar product compositions from the reaction of **2** and alkali in the absence of nitrophenyl halides.

The improved yields obtained in a mixed tetrahydrofuran–dimethyl sulfoxide solvent system may be due to an increase in the activity of **3** in the presence of dimethyl sulfoxide. This could be accomplished by

either a desolvation of the anion **3**, as dimethyl sulfoxide forms strong hydrogen bonds with both water and methanol, or solvent separation of ion pairs existing in tetrahydrofuran–methanol solution by cation solvation. Similar observations have been noted[16-19] of the effect of dimethyl sulfoxide on the rates and product yields in nucleophilic displacement reactions of nitrophenyl halides.

With a variety of polynitrodiphenylmethanes in hand, we considered the possibility of generating anions from these species for use as nucleophiles. By judicious addition of a solution of sodium methoxide in methanol to dimethyl sulfoxide solutions of the polynitrodiphenylmethanes, intensely colored solutions were obtained. A comparison of the nmr spectra of the solutions prior to and after the addition of base showed that the additional lines in the spectrum of the alkaline solution corresponded in both position and intensity to those of the polynitrodiphenylmethide ion. Unlike alkaline solutions of **2**, partially (about one-half) neutralized solutions of the polynitrodiphenylmethanes were generally stable for at least 24 hr. The nmr spectra of these species are summarized in Table I. When sufficient base was added to neutralize all of the polynitrodiphenylmethane present, the nmr spectrum of the resulting solution became quite complex. The appearance of additional resonances in the aromatic region of the spectrum suggested that, at high base concentrations, the formation of Meisenheimer complexes may be a competing reaction.

We attempted to utilize 2,2′,4,4′,6,6′-hexanitrodiphenylmethide ion as a nucleophile in the addition to formaldehyde. Under reaction conditions in which **2** affords an 85% yield of 2-picrylethanol, 2,2′,4,4′,6,6′-hexanitrodiphenylmethane was recovered quantitatively from the reaction mixture.

Experimental Section

Caution! The compounds described in this work are explosives and may detonate on grinding or impact. Appropriate shielding should be used.

Solvents and Reagents.—Solvents used were Baker Analyzed reagent grade. Methanol-*d*, 99% D, and deuterium oxide, 99.8% D, were from E. Merck. The various halonitrobenzenes, 2,6-dinitrochlorobenzene, 4-chloro-3,5-dinitrobenzonitrile and 3,5-dinitroiodobenzene from Aldrich, 2,4-dinitrofluorobenzene, 4-nitrofluorobenzene, and 2-nitrochlorobenzene from J. T. Baker, and picryl chloride, 4-nitrobromobenzene, 4-nitroiodobenzene, and 2,4-dinitrochlorobenzene from Eastman, were used as received. The following were prepared according to literature procedures: 1,3-dibromo-2,4,6-trinitrobenzene,[20] 3-chloro-2,2′,4,4′,6,6′-hexanitrostilbene,[21] and 3-chloro-2,2′,4,4′,6,6′-hexanitrobiphenyl.[22] Nmr spectra were determined with a Varian HA-100 spectrometer at 30° using internal TMS as a reference.

Equilibration of 2,4,6-Trinitrotoluene (2) with Methanol-*d* and Methoxide.—A solution of 0.01 mol (0.54 g) of NaOMe in 15 ml of D_2O was added all at once to a stirred solution of 0.01 mol (2.27 g) of **2** in 30 ml of tetrahydrofuran and 15 ml of MeOD at 0°. The mixture was immediately quenched by adding an excess of DCl in D_2O. The precipitated oil was extracted with methylene chloride and dried over magnesium sulfate, and the solvent was removed *in vacuo*. The residue, 1.7 g, shown by tlc to consist only of **2**, was assayed for deuterium uptake by comparing the integral of the methyl group with that of the ring protons. Nmr in chloroform-*d* solution: aryl hydrogen δ 8.83 ppm, integral 54 ± 1 mm (2 H), methyl δ 2.70 ppm, integral 71 ± 1 mm (3 H). Per cent methyl hydrogen exchanged: 100(1 − 71/81) = 12.4.

Repeating the above procedure, but allowing the reaction mixture to stand for 30 min prior to quenching, gave a dark red oil. This was extracted with 25 ml of benzene to leave a dark red solid that was shown by tlc to be a mixture of **7** and several unidentified products. The benzene extract, containing a mixture of **7** and **2**, was evaporated to dryness *in vacuo*. The residue was taken up in 1:1 benzene–hexane, and, by careful fractional crystallization, 100 mg (later fractions) of pure **2** was obtained for nmr analysis: in chloroform-*d* solution, aryl hydrogen δ 8.83 ppm, integral 22.2 ± 0.6 mm (2 H), methyl δ 2.70 ppm, integral 24.8 ± 0.8 (3 H). Per cent methyl hydrogen exchanged: 100(1 − 24.8/33.3) = 25.5.

A control experiment in which **2** was dissolved in THF–MeOD–D_2O without base and subsequently quenched in DCl–D_2O showed that none of the methyl hydrogens had exchanged for deuterium.

Chlorination of 2 in a Deuterated Solvent System.—Clean sodium metal, 0.094 g-atom (2.08 g), was dissolved in 50 ml of D_2O under a stream of nitrogen. Dry chlorine gas, 0.079 g-atom (2.80 g), was passed through the resulting solution at such a rate that it was completely absorbed.

To 12.5 ml of the above solution of sodium hypochlorite chilled to 0° was rapidly added with vigorous stirring a solution of 0.0055 mol (1.25 g) of **2** in 12.5 ml of THF and 6.5 ml of MeOD which had been previously chilled to 0°. After 1 min, the dark red mixture was poured into excess DCl–D_2O and the precipitated oil was extracted into methylene chloride. After drying over magnesium sulfate and removing the solvent *in vacuo*, the residual red oil was taken up in benzene–hexane (1:1) and concentrated until crystallization commenced. Recrystallization of the crude product from benzene–hexane (1:1) afforded 0.33 g of **4**. Analysis of the product for deuterium uptake by nmr (chloroform-*d*) gave the following results: aryl hydrogen δ 8.91 ppm, integral 30 ± 1 mm (2 H), methylene hydrogen δ 5.09 ppm, integral 29 ± 0.5 mm (2 H); ratio CH_2/aryl hydrogen = 0.97.

Preparation of 2,4,4′,6-Tetranitrobibenzyl (5) in a Deuterated Solvent System.—To a stirred solution of 0.005 mol (1.13 g) of **2** and 0.005 mol (1.08 g) of 4-nitrobenzyl bromide in 10 ml of THF and 5 ml of MeOD was added a solution of 0.005 mol (0.27 g) of NaOMe in 10 ml of D_2O. After 30 min, the suspended solid was collected by filtration, washed with methanol, and dried. On recrystallizing the crude product (1.5 g, 83%) from methyl ethyl ketone, 1.0 g of **5** was obtained. Deuterium analysis was obtained by nmr spectroscopy (MeCN-d_3): methylene hydrogens δ 3.25 ppm (multiplet), integral 40.0 ± 0.5 mm (4 H), picryl hydrogens δ 8.88 ppm, integral 19.5 ± 0.5 mm (2 H); ratio CH_2/picryl H = 2.05.

Reaction of 3 with *p*-Nitrobenzyl Halides. A. General Procedure.—To a well-stirred solution of 0.01 mol of **2** and 0.01 mol of the *p*-nitrobenzyl halide in 50 ml of THF and 25 ml of methanol was added a solution of 0.01 mol (0.40 g) of sodium hydroxide in 60 ml of water. The wine-colored solution was stirred for 30 min, after which the suspended solid was collected on a Buchner, washed thoroughly with methanol, and dried. The unrecrystallized product was assayed by nmr in DMSO-d_6 solution. The following spectra were observed.

	δ, ppm, internal TMS			
Compd	Pi-H	CH_2	*o*-Ar H	*m*-Ar H
5	9.07	3.18	7.42, 7.51	8.13, 8.22
7	9.04	3.34		

Assays were calculated by subtracting the average of the integrals for the *o*-Ar H and *m*-Ar H from the total integral for the picryl group. Dividing the remainder by two normalized the integral for **7** to that of **5**. The fraction of **5** present in the mixed product could then be calculated by dividing the integral for the picryl hydrogens of **5** by the sum of the integral for the picryl hydrogens of **5** and the normalized integral for the picryl hydrogens of **7**

B. *p*-Nitrobenzyl Bromide.—Using the general procedure, 2.8 g (77%) of a pale yellow solid was obtained. Nmr analysis showed it to be pure **5**.

C. *p*-Nitrobenzyl Chloride.—A 0.54-g yield of crude product

(16) H. Bader, A. R. Hansen, and F. J. McCarty, *J. Org. Chem.*, **31**, 2319 (1966).
(17) J. Miller and A. J. Parker, *J. Amer. Chem. Soc.*, **83**, 117 (1961).
(18) A. J. Parker, *Quart. Rev., Chem. Soc.*, **16**, 163 (1962).
(19) C. A. Kingsbury, *J. Org. Chem.*, **29**, 2363 (1964).
(20) J. C. Dacons and F. Taylor, Jr., *J. Chem. Eng. Data*, **14**, 499 (1969).
(21) K. G. Shipp, *J. Org. Chem.*, **29**, 2620 (1964).
(22) J. C. Dacons, H. G. Adolph, and M. J. Kamlet, *Tetrahedron*, **19**, 791 (1963).

was obtained. This was found to be a mixture of 54 ± 2% **5** and 46 ± 2% **7**. This is equivalent to an 8% yield of **5**.

D. ***p*-Nitrobenzyl Bromide in the Presence of *p*-Dinitrobenzene.**—The general procedure was followed except that 0.002 mol (0.34 g) of *p*-dinitrobenzene was added to the solution of **2** and *p*-nitrobenzyl bromide prior to the addition of alkali. The crude product, 2.7 g (75%), was shown by nmr to consist only of **5**.

E. ***p*-Nitrobenzyl Chloride in the Presence of *p*-Dinitrobenzene.**—The same procedure was followed as in D. The product, 0.63 g, was a mixture of 58 ± 2% **5** and 42 ± 2% **7**. This is equivalent to a 10% yield of **5**.

2,2′,4,4′,6,6′-Hexanitrodiphenylmethane (**6**) was prepared by rapidly adding with vigorous stirring a solution of 0.02 mol (1.32 g) of potassium hydroxide (85%) in 10 ml of methanol to 0.02 mol (4.54 g) of **2** in 50 ml of THF at ambient temperature. Immediately after the addition of alkali, 0.01 mol (2.48 g) of picryl chloride in 25 ml of DMSO[23] was added to the dark red solution. The reaction mixture turned dark blue upon the addition of picryl chloride. After stirring for 30 min, it was quenched in 750 ml of water containing 25 ml of 12 *M* hydrochloric acid. The yellow-orange solid that separated was collected by filtration and washed with hot methanol until the washings were essentially colorless. The residue, 4.0 g (91%), was recrystallized by dissolving it in 35 ml of MeCN, treating the solution with Darco G-60 charcoal, and then adding 50 ml of methanol to the filtrate. On cooling, almost colorless needles of **6**, mp 232° dec, were obtained.

Anal. Calcd for $C_{13}H_6N_2O_{12}$: C, 35.6; H, 1.4; N, 19.2; mol wt, 438. Found: C, 35.5; H, 1.5; N, 18.9; mol wt, 430, 439 (osmometer, MeCN).

2,2′,4,4′,6-Pentanitrodiphenylmethane (**8**) was prepared from 0.02 mol (4.54 g) of **2** and 0.01 mol (1.86 g) of 2,4-dinitrofluorobenzene. The crude product, 3.3 g (84%), was shown by tlc to be a single species. Recrystallization from MeCN–MeOH as described above gave yellow crystals, mp 208–210° dec.

Anal. Calcd for $C_{13}H_7N_5O_{10}$: C, 39.7; H, 1.8; N, 17.8; mol wt, 393. Found: C, 39.5, 39.6; H, 2.0, 1.7; N, 17.7, 17.6; mol wt, 388 (osmometer, MeCN).

With 0.01 mol (2.02 g) of 2,4-dinitrochlorobenzene and 0.02 mol (4.54 g) of **2**, the crude product was shown to be a mixture of **7** and **8** by tlc. Using 0.03 mol (6.06 g) of 2,4-dinitrochlorobenzene and 0.02 mol (4.54 g) of **2**, the crude product, 2.7 g (35%), was shown to be pure **8** by tlc.

2,2′,4,6,6′-Pentanitrodiphenylmethane (**9**) was prepared by the procedure described for the preparation of **6** using 0.12 mol (24.3 g) of 2,6-dinitrochlorobenzene and 0.02 mol (4.54 g) of **2**. A 2.75-g (35%) yield of **9** was obtained. After recrystallization from MeCN–MeOH, the product, pale yellow needles, melted at 188–190° dec.

Anal. Calcd for $C_{13}H_7N_5O_{10}$: C, 39.7; H, 1.8; N, 17.8. Found: C, 39.9, 39.6; H, 2.0, 1.9; N, 18.2, 18.2.

From a reaction mixture consisting of 0.01 mol (2.02 g) of 2,6-dinitrochlorobenzene and 0.02 mol (4.54 g) of **2**, there was obtained 3.25 g (36%) of pure **7**. No **9** could be detected in the crude product from this reaction by tlc techniques.

4-Cyano-2,2′,4′,6,6′-pentanitrodiphenylmethane was prepared by the procedure described for the preparation of **6** from 0.01 mol (2.28 g) of 4-chloro-3,5-dinitrobenzonitrile and 0.02 mol (4.54 g) of **2**. The crude product, 2.25 g (54%), was recrystallized from MeCN–MeOH to yield pale yellow needles, mp 205° dec. The product is very sensitive to light.

Anal. Calcd for $C_{14}H_6N_6O_{10}$: C, 40.2; H, 1.5; N, 20.1. Found: C, 40.7, 40.7; H, 1.6, 1.5; N, 20.0, 19.7.

3-Bromo-2,2′,4,4′,6,6′-hexanitrodiphenylmethane was prepared from 0.01 mol (3.71 g) of 1,3-dibromo-2,4,6-trinitrobenzene and 0.02 mol (4.54 g) of **2**. The red-brown oil that separated upon quenching the reaction mixture was triturated with methanol until it solidified. The crude product, 15 g (29%), was dissolved in acetone and treated with Darco G-60 charcoal, and an equal volume of methanol was added to the filtrate. The resulting solution was heated on a hot plate to remove the acetone, whereupon fine needles of the product, mp 170–172° dec, were obtained.

Anal. Calcd for $C_{13}H_5BrN_6O_{12}$; C, 30.2; H, 1.0; Br, 15.5; N, 16.3. Found: C, 31.0, 30.8; H, 1.8, 1.5; Br, 15.5, 15.5; N, 16.2, 16.1.

3-(2,4,6-Trinitrobenzyl)-2,2′,4,4′,6,6′-hexanitrostilbene was prepared from 0.02 mol (4.54 g) of **2** and 0.01 mol (4.85 g) of 3-chloro-2,2′,4,4′,6,6′-hexanitrostilbene as described previously for the preparation of **6**. The crude product was triturated with methanol and then dissolved in 50 ml of THF and treated with Darco G-60 charcoal. After adding 50 ml of methanol to the hot filtrate, the product, 4.8 g (71%), separated as almost colorless crystals, mp 210–211° dec.

Anal. Calcd for $C_{21}H_9N_9O_{18}$: C, 37.2; H, 1.3; N, 18.8. Found: C, 37.5, 37.7; H, 1.6, 1.5; N, 19.0, 18.4.

3-(2,4,6-Trinitrobenzyl)-2,2′,4,4′,6,6′-hexanitrobiphenyl was prepared from 0.02 mol (4.54 g) of **2** and 0.01 mol (4.58 g) of 3-chloro-2,2′,4,4′,6,6′-hexanitrobiphenyl by the procedure described for **6**. After triturating the crude product with methanol until the extracts were almost colorless, the residue was dissolved in acetone and treated with Darco G-60 charcoal. After addition of an equal volume of methanol to the filtrate, the product, 1.7 g (25%), mp 255–256° dec, separated as pale yellow rods.

Anal. Calcd for $C_{19}H_7N_9O_{18}$: C, 35.1; H, 1.1; N, 19.4. Found: C, 34.9, 34.2; H, 1.6, 1.2; N, 19.2, 18.8.

Registry No.—**2**, 118-96-7; **3**, 34403-92-4; **5**, 5180-52-9; **6**, 32255-27-9; **7**, 5180-53-0; **8**, 32255-28-0; **9**, 32255-29-1; 4-cyano-2,2′,4′,6,6′-pentanitrodiphenylmethane, 32255-30-4; 3-bromo-2,2′,4,4′,6,6′-hexanitrodiphenylmethane, 32255-31-5; 3-(2,4,6-trinitrobenzyl)-2,2′,4,4′,6,6′-hexanitrostilbene, 32255-32-6; 3-(2,4,6-trinitrobenzyl)-2,2′,4,4′,6,6′-hexanitrobibenzyl, 34404-00-7.

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(23) For those runs in the absence of DMSO, it was replaced with an equivalent volume of THF.

Organic Reactions in Liquid Hydrogen Fluoride. III.[1] Carboxylic Acids from Olefins and Carbon Monoxide (Hydrogen Fluoride–Koch Reaction)

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Linear and cyclic olefins are converted to carboxylic acids in 85–95% aqueous hydrogen fluoride under a pressure of 1000–2500 psig of carbon monoxide at 20–50°. 1-Pentene yields a mixture of the "iso" acids, α-ethylbutyric and α-methylvaleric acids, and the "neo" acid, α,α-dimethylbutyric acid. When the reaction product of cyclohexene, HF, and CO is hydrolyzed with water, the chief products are cyclohexanecarboxylic and 1-methylcyclopentanecarboxylic acids. If methanol is added to the reaction, the novel 2-(cyclohexenyl)cyclohexyl cyclohexyl ketone is isolated, in addition to the expected methyl esters of the above acids. Linear long-chain internal olefins, such as 7-tetradecene, give carboxylic acid yields of 65–80%. 2-Methylbutene gives a 57% yield of α,α-dimethylbutyric acid; with cyclododecene, a low yield of the expected 12-membered ring acid admixed with transannular products is obtained. The diolefin 1,5-cyclooctadiene gives the ring-contracted acid bicyclo[3.3.0]octane-2-carboxylic acid in low yield.

As a continuance of our studies on reactions in liquid hydrogen fluoride, we examined the condensation of carbon monoxide with various olefins to produce carboxylic acids. Termed the Koch reaction,[2] carboxylic acids are produced by contacting an olefin, alcohol, or halide with moderate to high pressures (500–2000 psig) of carbon monoxide in the presence of solvent quantities of an acid catalyst, usually sulfuric. Dilution with water liberates the carboxylic acid. Cursory examinations of the Koch reaction using a hydrogen fluoride catalyst solvent system have been reported[3] by various workers, the most extensive work having been done by Takezaki, *et al.* The kinetics of the reaction of propylene with carbon monoxide in HF–H_2O to form isoisobutyric acid was studied.

This report describes the reaction of carbon monoxide with pentene, as a typical linear olefin, and with cyclohexene, as a typical cyclic olefin. Reactions with a few miscellaneous olefins in liquid hydrogen fluoride are also discussed.

HF–Koch Reaction with 1-Pentene.—1-Pentene was employed to investigate various fundamental parameters of the reaction chiefly because only three carboxylic acids are likely: 2-methylvaleric (**1**), 2-ethylbutyric (**2**), and 2,2-dimethylbutyric acid, the "neo" acid (**3**). Current protonation and carbonium ion theories exclude a fourth isomer, *n*-hexanoic acid.

The reaction is carried out by placing HF in a Monel reactor, pressuring the system with the desired amount of carbon monoxide, and then pumping the olefin into the reactor. This method tends to minimize the amount of self-esters and neutral oligomers formed as described by Friedman and Cotton.[3a,b] The significant variable is the molar ratio of HF to pentene (see Table I). Pressure, amount of water present, time, and temperature affect isolated yields of C_6 carboxylic acids to a lesser extent.

Pressure Effects.—Aside from yield data, the variances in pressure can have a pronounced effect on the isomerization of the carbon chain. For example, in comparable runs (runs 1 and 3) the selectivity toward neo acid formation, **3**, decreases from 38 to 14%, as the pressure is increased. This indicates that at higher pressures carbon monoxide tends to intercept the secondary carbonium ion prior to skeletal rearrangement to the tertiary, thus forming enhanced amounts of the "iso" acids.

At lower pressures, thermodynamic equilibrium of the carbonium ions tends to be favored and larger quantities of the "neo" acid are obtained resulting from increased isomerization. More importantly, the higher the ratio of HF to olefin, the greater the total yield of carboxylic acids.

Temperature Effects.—The ideal range for practical carboxylation appears to be 10–50°. Above 50°, polymerization[4] of the olefin becomes predominant and below 10° the reaction is too slow.

Isomerization Studies.—The relative amounts of "neo" and "iso" acids depend both on pressure and amount of contact with the acid phase. Eidus,[5] in a

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(2) For a recent review see J. Falbe, "Carbon Monoxide in Organic Synthesis," Springer-Verlag, New York, N. Y., 1970, p 123 ff.

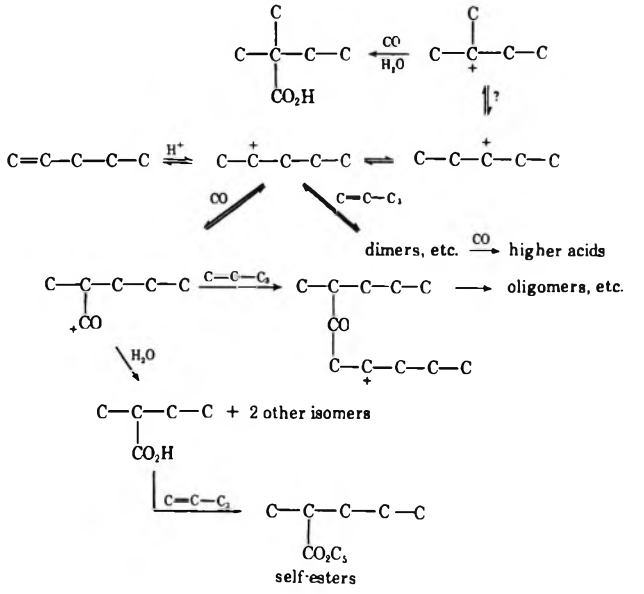
(3) (a) B. S. Friedman and S. M. Cotton, *J. Org. Chem.*, **26**, 3751 (1961); (b) *ibid.*, **27**, 481 (1962); (c) Armour and Co., French Patent 1,477,330 (Mar 6, 1967); (d) Y. Takezaki, Y. Fuchigami, H. Terraishi, N. Sugita, and K. Kudo, *Bull. Jap. Petrol. Inst.*, **8**, 31 (1966); (e) Shell-Internationale Research Maatschappij, N. Y., British Patent 1,167,116 (Oct 15, 1969).

(4) G. A. Olah and Y. Halpern, *J. Org. Chem.* **36**, 2354 (1971).

(5) Y. T. Eidus, K. V. Puzitskii, and O. D. Sterligov, *Zh. Obshch. Khim.*, **30**, 3799 (1960).

carbomethoxylation study on 1-pentene in sulfuric acid and methanol with carbon monoxide, reports only the esters of acids 2 and **3**; no mention is made of the 2 isomer. In contrast, we have found that all three of the possible isomers are present in substantial amounts. The ratio of "neo" to "iso" acid was obtained by glc; however, α-ethylbutyric and α-methylvaleric acids or their methyl esters could not be separated on a 150-ft capillary column. Use of mass spectrometry permitted the quantitative determination of all three acids simultaneously with a $\pm 5\%$ error. Acids **1** and **2** rearrange in the mass spectrometer *via* a McLafferty rearrangement with the former providing propylene and a mass peak of 74 and the latter ethylene and a fragment of 88. Acid **3** cleaves, giving a $C_5H_{12}^+$ of 71 and a $\cdot CO_2H$ fragment. By determining the sensitivity coefficients for pure acids and employing three equations and three unknowns, one can calculate the amount of each acid present based on the above fragmentations. As shown in Table I, both the 2 and 3 isomers were obtained, with substitution at the third carbon prevailing slightly.

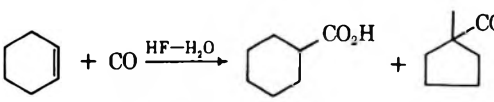
Examination of the over-all picture of the CO carboxylation of 1-pentene indicates a variety of paths.



The above scheme shows that, for optimization of yield, CO pressure should be increased, temperature decreased, and olefin added very slowly to the reaction mixture so as to avoid an excess of olefin. Water is necessary in the system to facilitate hydrolysis of the intermediate acyl fluoride and to prevent extensive oligomerization. The need for a high HF to olefin ratio is not immediately recognized, but the larger amount of HF probably provides a more desirable solvent effect for both the CO and hydrocarbon and gives a higher degree of initial protonation (as was observed in our earlier work on the reaction of olefins and nitriles).[1]

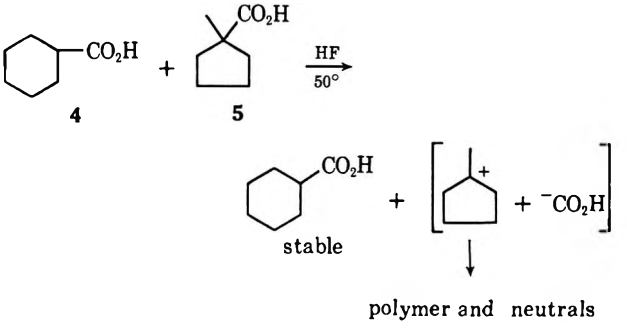
Cyclohexene.—Using cyclohexene as a typical cyclic olefin, its carboxylation was investigated. Earlier, by treating cyclohexene with CO (700 psig) in H_2SO_4, Koch[6] had obtained a 28% yield of a 3:2 mixture of cyclohexanecarboxylic acid (**4**) and 1-methylcyclopentanecarboxylic acid (**5**). Using methanol to quench the reaction mixture, Eidus, *et al.*,[7] obtained a 50% yield of the methyl esters with 1100 psig CO in sulfuric acid the ratio of the cyclohexane to cyclopentanecarboxylic acids being 4:5. Friedman and Cotton[3a] reported a 26% yield of cyclic C_6 acids with CO (500 psig), HF, and water followed by quenching with methanol. In this case the ratio of **4** to **5** was 4:1.

Employing higher CO pressures and an 8:1 ratio of HF to H_2O, we were able to obtain 84% distilled yields of the cyclic acids. The increase in pressure permits CO attack prior to ring contraction.



	4	5	Yield %
1000 psig	73	27	84
2500 psig	89	11	73

If, during the work-up procedure, attempts are made to distil the HF out of the reactor prior to addition of water, the yield of distilled acid is reduced to 30%; however, the isomer ratio becomes 92.5% **4** and 7.5% **5**. The observation is rationalized by assuming that initially similar yields are produced in all cases, but as the fluoride reaction mixture is concentrated by heating at 50° and pulling a water pump vacuum, the tertiary acid **5** decarboxylates and polymerizes or self-esterifies. The cyclohexyl acid, being a secondary acid, is more stable under these conditions and does not degrade. Both **4** and **5** will readily decompose at 100° in HF, but **4** is relatively stable in HF at 50°. Thus, the over-all effect of heating the acid mixture is a decrease in isolated yield, an increase in neutrals, and an increase in percentage of the cyclohexyl acid present.



A new reaction producing a novel ketone occurred when cyclohexene was treated with carbon monoxide in the presence of hydrogen fluoride followed by addition of methanol in place of water. In addition to 37% yield of the methyl esters of cyclohexanecarboxylic acid and 1-methylcyclopentanecarboxylic acid in a 91:9 ratio, there was obtained a 23% yield of the novel ketone, 2-(cyclohexenyl)cyclohexyl cyclohexyl ketone (**6**).

The compound was characterized by noting that the infrared spectrum contained a strong carbonyl band at 5.9 μ. No OH bands at 3.0 μ were found. The nmr spectrum indicated a ketone (τ 7.8) rather than an aldehyde. A broad absorption between τ 7.5 and 9.2 is produced by cyclic methylene groups which shield the protons adjacent to the carbonyl group. A peak

(6) H. Koch, U. S. Patent 2,831,877 (Apr 22, 1958).

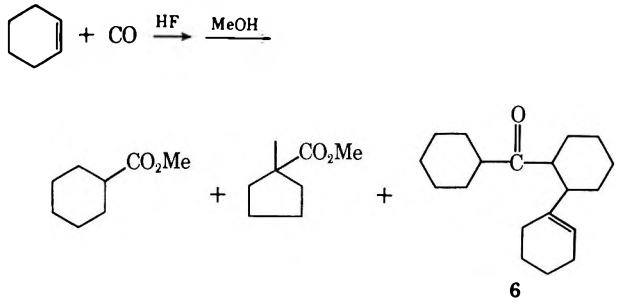
(7) K. V. Puzitskii, Ya. T. Eidus, K. G. Ryabovas, and I. V. Guseva, *Dokl. Akad. Nauk SSSR*, **128**, 555 (1959); *Chem. Abstr.*, **54**, 7584 (1960).

TABLE I

REACTION OF 1-PENTENE WITH CO IN HF

Run	HF/Pentene, mol	CO, psig	Pentene/H_2O, mol	Temp, °C	Time, hr	Hexane solvent, ml	Yield[a] of C_6 acids, %	Selectivity[b] of acids, % DMBA	MVA	EBA
1	4.0	1000	2.4	48	4	0	40	38	28	34
2[c]	4.0	1000	2.4	48	2	0	33	33	29	38
3	4.0	2500	2.4	48	2	0	29	14	37	49
4	7.5	1300	1.0	48	2	200	49	38	27	35
5	8.0	2700	0.9	10	3	0	37	11	44	45
6	8.0	2700	0.9	10	3	200	43	11	37	52
7	8.0	2900	0.9	10	17	200	56	11	37	52
8	15.0	1000	0.9	45	1.5	0	90	36	27	37

[a] Yields are based on distilled C_6 carboxylic acids. [b] DMBA = 2,2-dimethylbutyric acid; MVA = 2-methylvaleric acid; EBA = 2-ethylbutyric acid. [c] 2-Pentene was used in place of 1-pentene.



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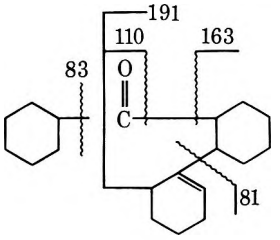
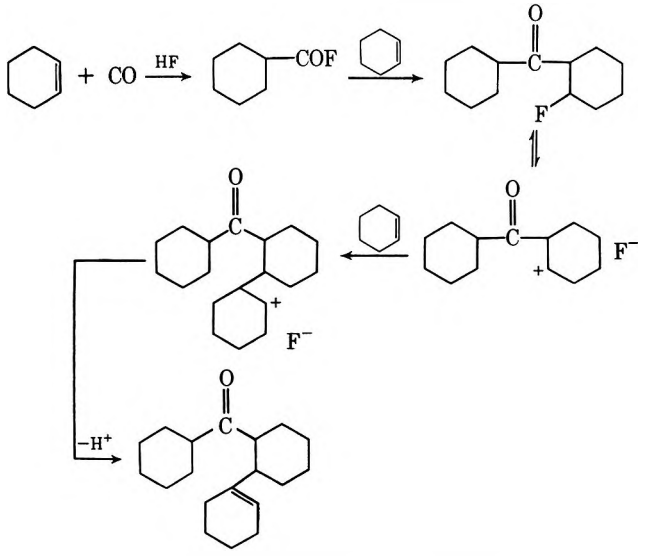
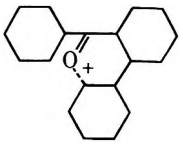
at τ 4.65 indicates the presence of one olefinic proton. The mass spectrum was more indicative in that a parent peak at *m/e* 274 was obtained (calcd 274) and no other peaks were found in that area. All of the major mass spectral peaks can be explained on the basis of the following scissions.



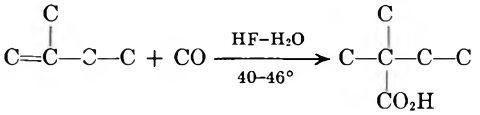
The rationale for formation of the ketone is as shown.



The fact that the oligomerization stops at this point and a fair yield is observed may be due to steric considerations or to an oxonium stabilization of the intermediate carbonium ion of the type shown.

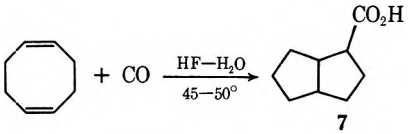


Miscellaneous Olefins.—A tertiary olefin, 2-methyl-2-butene, was treated with CO (1000 psig) in 80% aqueous HF to give a 57% yield of 2-methyl-2-butanecarboxylic acid. With tertiary olefins, whose protonation is more facile than that of a secondary olefin, addi-



tional water should be present to trap the acyl fluoride as it is formed and to prevent a reverse reaction.[1] Some pivalic and higher acids were also obtained as a result of carbon skeleton fragmentation.

On reaction of 1,5-cyclooctadiene and CO (1300 psig) in 90% aqueous hydrogen fluoride, a 17% yield of the transannular product, 2-bicyclo[3.3.0]octane carboxylic acid (**7**), was isolated.



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Cyclododecene provided a 39% yield of a C_{12}-acid mixture distilling at 137–149° (0.4–0.5 mm) which solidified. Recrystallization gave a 17% over-all yield of cyclododecanecarboxylic acid. An olefin, which contains a deeply buried double bond such as that in 7-tetradecene, when treated with 1140 psig CO in 87% aqueous hydrogen fluoride, afforded only a trace of C_{14} acids along with a large amount of a grey-brown but transparent rubbery polymer. If conditions were changed to 3000 psig CO and 94% aqueous HF with a hexane solvent, a 60% distilled yield of tetradecanecarboxylic acids, bp 126–133° (0.05 mm), could be isolated. The individual acids were not separated because of the large number of isomers possible. A mixture of C_7–C_9 linear olefins with the double bond buried in the chains provided an 84% distilled yield of colorless carboxylic acids, bp 76–86° (0.10 mm), using 1200 psig CO. Similarly, a C_{10}–C_{11} fraction of internal olefins under 2600 psig CO gave a 65% yield of carboxylic acids, bp 100–104° (0.15 mm). Yield calcula-

tions were based on the amount of each olefin present in the mixture.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Infracord, nmr spectra were run on a Varian A-60 spectrometer, and the mass spectra were obtained on a CEC mass spectrometer, Model 21-110. Product composition of the carboxylic acids was determined on an F & M Model 500 gas chromatograph with a 5-ft, 16.6% Carbowax 20M on 60–80 mesh acid-washed Chromosorb P, programmed at 100–250° at 15° per minute. Capillary columns used were a 150-ft Carbowax 1540 or Apiezon L in conjunction with a Perkin-Elmer Model 900 gas chromatograph.

Chemicals.—Caution! When handling anhydrous HF, a face shield, rubber gloves with plastic arm bands, and a protective apron should be worn, using excellent hood facilities. Colorless hydrogen fluoride (99% from Air Products, Inc., Allentown, Pa.) was withdrawn in the liquid phase by inverting the cylinder and taking off liquid HF through a Monel Hoke valve in addition to the cylinder valve. The liquid HF was allowed to drip directly into a polyethylene graduate where it readily condenses as a fuming liquid; it was then poured into a 300-ml Monel transfer bomb. No special precautions were required to exclude moisture or air.

Carbon monoxide (99%) was obtained from Matheson and Co., and the olefins were Phillips pure grade when available. Reference samples of the pure acids were obtained from Baker Chemical Co. and Aldrich Chemical Co.

Apparatus.—All reactions were run in a 1-l. Monel magnetically stirred autoclave equipped with a bottom tap. For carbon monoxide pressures of 0–1300 psig, normal cylinder pressure was used. For higher pressures, a Whitey Laboratory Compressor (Model LC-10) was used and the olefin was pumped into the reactor against high pressures with a Whitey Laboratory Feed Pump (Model LP-10).

General Procedure for Reaction of Olefins with Carbon Monoxide in HF.—This following description of the reaction is generalized, the variable data having been recorded under the appropriate heading in Table I. A 300-ml Monel bomb was cooled in ice, and addition of water (when used) was followed by the liquid HF. The bomb, capped with a pressure gauge and a dipstick, was pressured with 50–100 psig of carbon monoxide and the contents were blown into the 1-l. reactor. When hexane solvent was employed, this was added next by means of the Whitey pump. The reactor was then pressured with the desired amount of carbon monoxide and heated with circulating water to the specified temperature. The olefin was then pumped into the reactor over a period of 1 hr while being stirred. Stirring was continued for the specified time at the same temperature as the addition. When the reaction was completed, cold water was circulated through the coils and the excess CO pressure was vented into a hood.

Work-up was generally accomplished by pumping 300–350 ml of water, followed by 150 ml of hexane, into the reactor. The contents were stirred for 15 min and allowed to settle. Essentially an extraction of the acid phase was carried out in the reactor. The liquid was then drained into a plastic separatory funnel and the layers were separated. The upper hexane layer was shaken with a NaOH solution to convert the carboxylic acids to the sodium salt; this was followed by two hexane extractions. Removal of the hexane after drying over $MgSO_4$ gave the "upper basic" layer. The NaOH solution was then acidified with sulfuric acid, extracted with hexane (3 × 250 ml), and dried over $MgSO_4$. After removal of the solvent on a Rotavapor, the crude carboxylic acids ("top acid" layer) were distilled and analyzed.

Reaction of Cyclohexene with Carbon Monoxide and HF at 1000 psig.—The 1-l. Monel reactor was charged with a mixture of HF (160 g, 8 mol) and H_2O (20 g, 1.1 mol) and pressured to 1000 psig with CO. Cyclohexene (82 g, 1 mol) was pumped into the reactor over a period of 1 hr at 50°. A total uptake of 250 psig of CO was noted after the mixture had been stirred for an additional 2.5 hr at 46–50°. The CO was vented, the reactor was cooled to 20°, 350 ml of H_2O and 200 ml of hexane were pumped into the reactor, and the mixture was stirred for 20 min to extract the acid into the hexane phase. The mixture was drained into plastic separatory funnels and the hexane layer which separated was shaken with a dilute NaOH solution to convert the carboxylic acids into the Na salts. Evaporation of the dried hexane solution gave 4.9 g of neutral materials identified as chiefly self-esters by infrared. The NaOH solution was acidified with concentrated H_2SO_4 and extracted with hexane to give 119.5 g (93.5%) of crude, although nearly colorless, carboxylic acids. A small sample was converted to the methyl esters by the method of Metcalfe and Schmitz[8] using BF_3·MeOH complex obtained from Applied Science Laboratories. By glc analysis, this sample was found to contain 27% of the ring-contracted 1-methylcyclopentyl derivative and 73% of the cyclohexyl product. Distillation of 117.2 g of the free acids through a 15-in. Vigreux column gave 107.2 g (84% yield) of colorless acids, bp 75–87° (0.8–1.2 mm), $n^{20}D$ 1.4598, mol wt, 127.9, neut equiv, 7.67 mequiv/g, and a still pot residue, 8.3 g.

Reaction of Cyclohexene with Carbon Monoxide and Anhydrous HF Followed by Methanol Addition.—Hydrogen fluoride (175 g, 8.75 mol) was charged into the 1-l. autoclave and pressured to 100 psig with carbon monoxide. With the temperature maintained at 22–23° by circulating tap water, cyclohexene (82 g, 1 mol) was pumped into the reactor at 1.0–1.8 ml/min. During this time, the pressure fell from 1040 to 820 psig; total addition time was 65 min. After an additional 1 hr of stirring, the CO pressure was released and the HF (147 g) was removed *in vacuo*. Methanol (200 ml) was pumped into the reactor and the mixture was heated with warm water (45°) and stirred for 2 hr. The mixture was drained from the reactor, poured on ice, neutralized with 40% NaOH, and extracted with hexane (3 × 250 ml). Removal of the hexane on a Rotavapor after drying over $MgSO_4$ left 97.7 g of a liquid. The aqueous layer was acidified with concentrated H_2SO_4 to pH 3.0 and extracted with hexane to give 6.2 g of liquid. The extract from the basic solution was distilled through a 15-in. vacuum-jacketed Vigreux column. Considerable foaming occurred and finally 80.2 g of a distillate was obtained which was redistilled as shown in Table II.

TABLE II

Cut	Bp, °C (13 mm)	Wt, g	$n^{20}D$
1	58–61	42.6	1.4413
2	61–130	1.6	
3	130–180	6.9	
4	180–200	21.8	1.5117
Pot residue		6.0	

Cut 1 represents the cyclic methyl esters with the composition being 91% methyl cyclohexanoate and 9% methyl 1-methylcyclopentanoate. The yield of esters normalized to the initial weight is 37%.

Cut 4 was redistilled at 129–130° (0.15 mm), $n^{20}D$ 1.5117, and identified as 2-(cyclohexenyl)cyclohexyl cyclohexyl ketone. See discussion for the nmr and mass spectral data.

Anal. Calcd for $C_{19}H_{30}O$: C, 83.28; H, 11.04; mol wt, 274. Found: C, 82.75; H, 10.94; mol wt, 278 (osmometry).

7-Tetradecene with Carbon Monoxide–HF–H_2O at 3000 psig.—The 1-l. reactor was charged with 160 g (8 mol) of HF, 10 g (0.55 mol) of water, and 200 ml of *n*-hexane and pressured to about 2800 psig with CO. The temperature was maintained 20–22° with circulating water. 7-Tetradecene (78.4 g, 0.40 mol) diluted with an equal volume of *n*-hexane was pumped in the reactor over a period of 1 hr, which raised the pressure to 3000 psig. An additional 50 ml of hexane was added and the mixture was stirred for 4 hr at 20–30°. The CO was vented and 350 ml of water and 150 ml of hexane were charged into the reactor and stirred. The colorless solution was drained into a plastic container and the upper hexane layer was shaken with a NaOH solution. After drying over $MgSO_4$, removal of the hexane gave 21.8 g of neutral components. The NaOH solution was acidified with H_2SO_4 and extracted with hexane to give 64.4 g of colorless acids. Distillation of 61.2 g of the acids gave essentially one cut, 54.8 g (0.23 mol, 58% yield), bp 126–133° (0.05 mm), $n^{20}D$ 1.4450, of colorless C_{14} acids with only 1.0 g of residue.

Anal. Calcd for $C_{15}H_{30}O_2$: C, 74.32; H, 12.47; mol wt, 242. Found: C, 74.54; H, 13.08; mol wt, 237; neut equiv, 4.24 mequiv/g.

Carboxylation of C_{10}–C_{11} Mixture of Internal Olefins.—The

(8) L. D. Metcalfe and A. A. Schmitz, *Anal. Chem.*, **33**, 363 (1961).

olefins employed were a mixture of internal olefins and possessed the following composition: C_9, 10.2; C_{10}, 50.6; C_{11}, 38.1; C_{12}, 1.0; average mol wt, 142.4. The autoclave was charged with 160 g (8 mol) of HF and 10 g (0.55 mol) of H_2O and pressured to 2500 psig with CO. The temperature was 45–50° and 45 min were required to pump in 70 g of olefins used. Distillation of 140 g of HF left a light-colored residue which was poured on ice and made basic with NaOH.

Extraction with hexane gave 3.7 g of neutrals. Acidification of the aqueous solution after hexane extraction gave 69.3 g of crude acids. Distillation of 66.8 g gave essentially one cut weighing 59.1 g (63% yield) of colorless acids, bp 100–104° (0.15 mm), $n^{20}D$ 1.4380, with 2.2 g of heavy residue remaining.

Anal. Found: C, 71.44; H, 12.18; mol wt, 185; neut equiv, 5.18 mequiv/g.

Carboxylation of 1,5-Cyclooctadiene with CO–HF–H_2O.—The 1-l. Monel autoclave was charged with 215 g (10.8 mol) of HF and 25 g (1.4 mol) of H_2O and pressured to 1300 psig with CO. 1,5-Cyclooctadiene (108 g, 1 mol) was added over a period of 2 hr to the mixture heated at 45–50°. After stirring for an additional 1 hr, the CO was vented and the reactor was cooled. HF (176 g) was removed by distillation and the residue was poured on ice and made basic with NaOH followed by extraction with $CHCl_3$. The bottom $CHCl_3$ layer was filtered and dried over $MgSO_4$. An intermediate red-brown layer was very viscous and seemed insoluble in both $CHCl_3$ and H_2O. The top aqueous layer was reextracted with $CHCl_3$ and then acidified with H_2SO_4. Removal of the $CHCl_3$ from the basic extract left 37.7 g of a viscous liquid which was probably the same as the intermediate layer. The acidified layer was extracted with *n*-hexane to give 42.6 g of acids after drying over $MgSO_4$. Distillation of 37.4 g through a 6-in. Vigreux column provided 22.7 g of a heart cut. Redistillation gave the pure acid, bp 91–93° (0.2 mm), $n^{20}D$ 1.4867 [lit.[9] bp 132° (25 mm)]. The nmr spectrum supported the assigned structure, **7**, a singlet at τ −2.7 (RCO_2H) and a multiplet at τ 7–9 in a ratio of 13:1 with no evidence for olefinic protons.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.14; H, 9.15; mol wt, 154. Found: C, 70.00; H, 9.08; mol wt, 152; neut equiv, 6.57 mequiv/g.

Carboxylation of Cyclododecene with CO–HF.—The autoclave was charged with water (10 g) and HF (160 g) and pressured to 2300 psig CO at 45–50°. Cyclododecene (50.4 g, 0.30 mol) dissolved in 100 ml of cyclohexane was added over a period of 40 min. After a reaction time of 3 hr, the reactor was cooled, the CO was vented, and 350 ml of H_2O followed by 150 ml of hexane was added to the autoclave. The contents were drained into a plastic separatory funnel. The upper organic layer was shaken with 10% NaOH to form carboxylic acid salts. Evaporation of the remaining organic layer provided 15.5 g of neutrals. Acidification of the aqueous layer with H_2SO_4 and chloroform extraction gave 42 g of nearly colorless acids. Distillation provided 24.8 g of a heart cut, bp 137–149° (0.3–0.5 mm), of acids which solidified on cooling. Recrystallization (hexane) gave cyclododecanecarboxylic acid, mp 97–98° (lit.[10] mp 97.5°).

Registry No.—**6**, 34402-87-4; **7**, 7403-22-7; HF, 7664-39-3; CO, 630-08-0; 1-pentene, 109-67-1; cyclohexene, 110-83-8; methyl cyclohexanoate, 4630-82-4; 7-tetradecene, 10374-74-0; 1,5-cyclooctadiene, 111-78-4; cyclododecene, 1501-82-2.

Acknowledgment.—The assistance of Mr. Bill Loffer in performing many of the experiments is gratefully recognized.

(9) G. Pregaglia and G. Gregorio, *Chim. Ind. (Milan)*, **45**, 1065 (1963).

(10) G. Bo, P. Perras, and Y. Colleuille (to Rhone-Poulenc), French Patent 1,286,803 (Mar 9, 1962); *Chem. Abstr.*, **57**, 14967 (1962).

The Tiffeneau–Demjanov Reaction on Phenyl-Fused Cyclopentyl Systems

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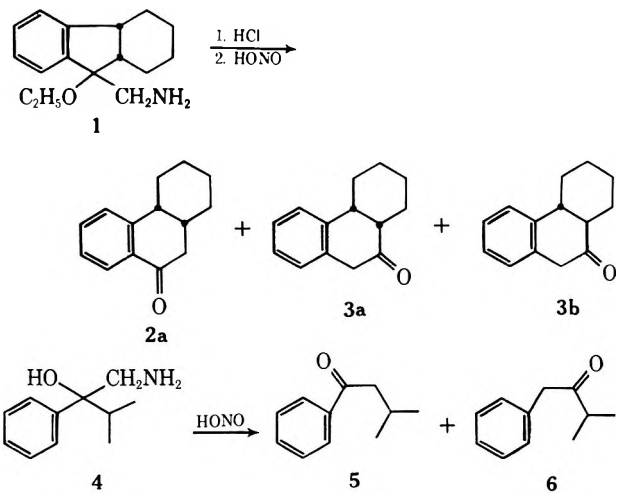
The diastereomeric amine hydrochlorides **10a** and **10b** were prepared and their reactions with nitrous acid were studied. Change of stereochemistry at C-9 in **10** is not a significant factor affecting aryl to alkyl migration in this system; however, it is noted that the ketone product ratios changed markedly changing the ethoxy group at C-9 (in **1**) to hydroxy (**10a** or **10b**).

The Tiffeneau–Demjanov reaction (the action of nitrous acid on β-amino alcohols) of phenyl-fused cyclopentyl systems, in which the migration may be by either the phenyl group or alkyl group, has not heretofore been investigated. A modified Tiffeneau–Demjanov reaction on one diastereomer of the β-amino ether **1** (Scheme I) gave an unusually large ratio of alkyl migration product **2a** to aryl migration product **3**[1] (ratio **2a**/**3** = 1/0.2–0.9) as compared to the analogous monocyclic system **4** (ratio **5**/**6** = 1/31). The observed preferential alkyl migration was attributed to the geometric requirement for phenyl migration. In **1** the phenyl nucleus cannot rotate to the position assumed to be most favorable for migration because of the constraint inherent in the fused system.[1] An alternate explanation, based on dependence of stereochemistry at C-9, was not eliminated, however, since attempts to prepare the other diastereomer of **1** and the two diastereomers **10a** and **10b** were unsuccessful.[1]

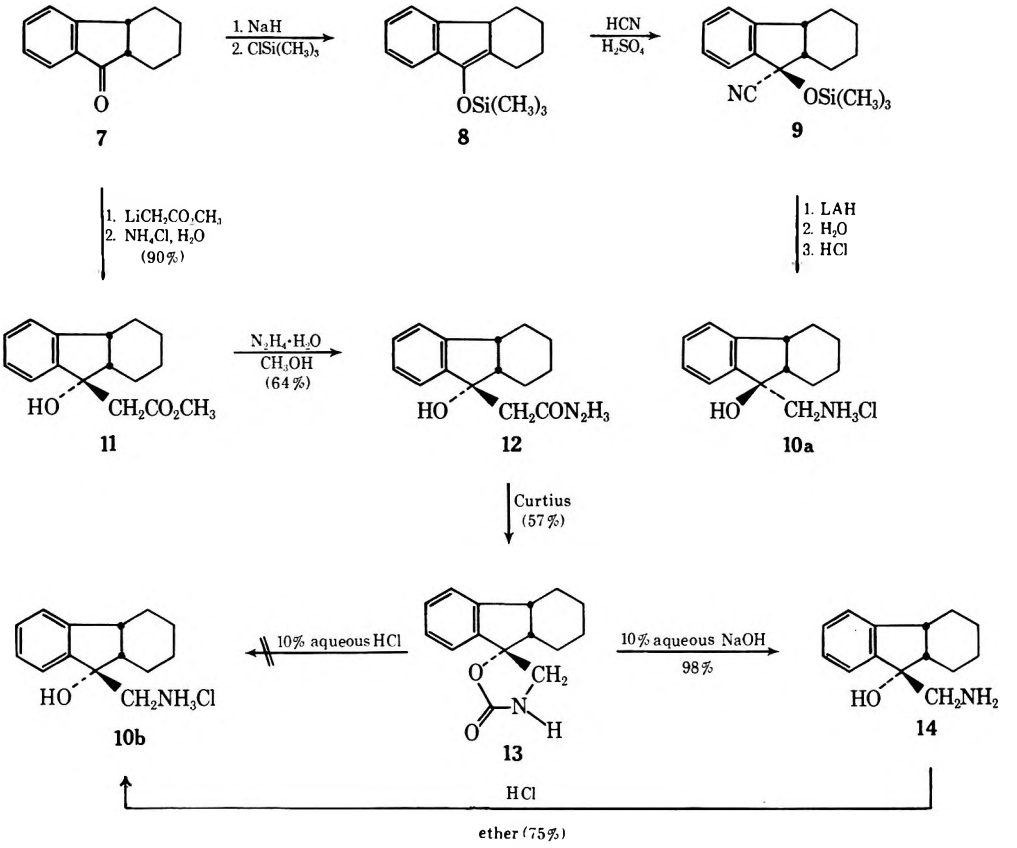
This report describes preparation of the diastereomeric amine hydrochlorides **10a** and **10b** and considers in greater detail factors which affect product ratios in the Tiffeneau–Demjanov reaction in these fused systems.

SCHEME I



(1) W. E. Parham and L. J. Czuba, *J. Amer. Chem. Soc.*, **90**, 4030 (1968).

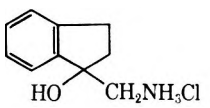
SCHEME II



Results

The two diastereomeric β-amino alcohol hydrochlorides **10a** and **10b** were prepared as shown in Scheme II. The determination and/or assignment of stereochemistry is presented in the Discussion. The amine hydrochloride **10a** was prepared as previously described;[2] **11** was prepared from **7** and lithiomethyl acetate by a modification of the general procedure described by Rathke.[3] Use of methyl acetate rather than ethyl acetate was found to be markedly superior in this system, since the methyl ester **11** gave a higher yield of acid hydrazide **12**; hydrolysis of the intermediate oxazolidone was effected by alkali since use of aqueous hydrochloric acid led to extensive dehydration of **10b**.

The indan derivatives **15** and **16**, analogous to **10** and **1**, were of interest and their preparation is described in the Experimental Section.



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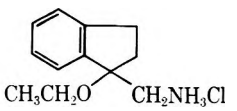


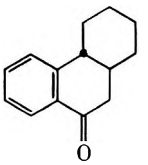
16

The amine hydrochlorides **10a** and **10b** were treated with aqueous sodium nitrite and a catalytic amount of hydrochloric acid. Product identification was effected by ir, gc, and nmr comparisons with authentic samples. Yields were determined by combined gc and nmr analyses and are shown in Table I. The hexahydrophenanthrone **2b** was shown not to be present in the product

TABLE I

YIELDS OF KETONES FROM AMINES

Amine	Yield, % 2a	3a	3b
10a	25.6	55	0.7
10b	32.6	50.3	2.8



2b

by comparison of data obtained from the product with those of an authentic sample of **2b**.[4]

The amino alcohol hydrochloride **15** and the amino ether hydrochloride **16** were treated with sodium nitrite under identical conditions used for **10a** and **10b**; however, no definitive results were obtained. A brown-black solid was obtained in both cases and neither α- nor β-tetralone could be detected. It was subsequently shown that β-tetralone, but not α-tetralone, is unstable to the conditions of reaction; however, owing to the uncertainty of what processes may have occurred it would not seem justifiable to conclude that only β-tetralone was formed in these reactions.

Discussion

Stereochemistry.—The two diastereomeric racemates **10a** and **10b** were prepared from **7** as shown in

(2) W. E. Parham and C. S. Roosevelt, *Tetrahedron Lett.*, 923 (1971).
(3) M. W. Rathke, *J. Amer. Chem. Soc.*, **92**, 3222 (1970).
(4) An authentic sample of **2b** was generously supplied by Professor Wendel E. Nelson, University of Washington.

Scheme II. The stereochemistry of the cyclohexyl–cyclopentyl ring fusion (C-4a and C-9a) was determined by examination of the products from the Tiffeneau–Demjanov reaction on both diastereomers. The Tiffeneau–Demjanov reaction is known[5,6] to proceed with retention of configuration about the migrating carbon atom. The products resulting from migration of the 9a carbon of **10** would then be either ketone **2a** or **2b** depending upon the stereochemistry of the starting material. The ketone resulting from C-9a migration prepared from both diastereomers prepared as shown in Scheme II was found to be the cis ketone **2a**. The two diastereomers of **10** then differed only at the C-9 position, and both have a cis ring fusion.

The stereochemistry of **10a** and **10b** at C-9 was not confirmed, but assignment can be made with reasonable confidence. In the synthesis of **10b** from **7**, the stereochemistry at C-9 was determined by the addition of lithiomethyl acetate to the ketone **7**. By analogy with Cram's rule[7] the lithiomethyl acetate should add across the carbonyl group on the least hindered side. Models clearly show that the least hindered side of **7** contains the 4a-H and 9a-H, *not* the cyclohexyl ring. The addition product should therefore be **11**, and, since none of the subsequent steps would affect the stereochemistry at C-4a, C-9a, and C-9, the amino alcohol hydrochloride can be assigned structure **10b**.

The isomer of **10** prepared by the silyl enol ether route was assigned structure **10a** since other possible structures were excluded by the above arguments. This assignment is also reasonable since the final steric configuration was defined by the addition of hydrogen cyanide to the silyl enol ether **8**. Since the stereochemistry of the product at C-4a and C-9a is known, the proton must first add to **8** to give a cis ring fusion. The nitrile should then add to the less hindered side of the planar carbonium ion. Models show that the trimethylsilyl group is oriented to the side containing the 4a-H and 9a-H, and that the product should be **9**, which would lead to **10a**.

Tiffeneau–Demjanov Reaction.—The ratios of products obtained by aryl to alkyl migration in the Tiffeneau–Demjanov reaction of **10a** and **10b** were 2.17/1 and 1.63/1, respectively. The aryl migration products **3** formed in preference to alkyl migration product **2a** for both diastereomers. By comparison, the open-chain analog **4** gave aryl to alkyl migration in the ratio of 31/1, while the modified Tiffeneau–Demjanov reaction[1] on **1** gave 0.2 to 0.9/1 aryl to alkyl migration.

The large decrease in the aryl to alkyl migration ratio in going from the acyclic compound **4** to the cyclic compound **10** is attributed at least in part to the steric control exerted by the rigid fused system. This same effect has been noted[1] in the modified Tiffeneau–Demjanov reaction involving **1**. In fused systems, such as **10**, rotation of the phenyl group is restricted and the phenyl π orbitals cannot effectively overlap with the empty p orbitals of the developing carbonium ion.[1] The amount of phenyl migration is consequently reduced and the amount of alkyl migration is increased in comparison to nonrestricted acyclic analogs.

The change of stereochemistry at C-9 in **10** is not a significant factor affecting aryl to alkyl migration in this system. Two types of steric control have now been noted that can affect migratory aptitudes of groups in the Tiffeneau–Demjanov reaction. In addition to that discussed above,[1] the second relates to the conformation of the cyclohexyl ring in the transition state[8,9] (*i.e.*, leading to the more stable chair conformation). Failure to observe a significant dependence of stereochemistry at C-9 in **10a** and **10b** on migratory ratios does not assist in assessment of importance of this second steric effect, since, in **10**, the central five-membered ring is relatively flat, which should lead to a six-membered ring transition state that is intermediate between a chair and a boat for either direction of migration.

It is of interest to note that the ketone product ratios were changed markedly by changing the hydroxy group to ethoxy (compare **10** to **1**) with no change in stereochemistry at C-9. Since both intermediates are readily available, this observation is important in synthesis. The only factor that could have caused the difference was the relative effects of ethyl relative to hydrogen. Whether this effect is steric or electronic in nature, or a combination, will be the subject of further study.

Experimental Section

Gas chromatographic analyses were performed on a Varian Aerograph 90-P with thermal conductivity detector; gas flow was 60 cc/min unless otherwise noted. Neither melting points nor boiling points were corrected.

Methyl 9-*trans*-Hydroxy-1,2,3,4,4a-*cis*,9a-*cis*-hexahydrofluoren-9-*cis*-ylacetate (11).—Methyl acetate (7.74 g, 0.104 mol) was added dropwise over a period of 6 min under dry nitrogen to a stirred solution of hexamethyldisilazyllithium[3,10] (0.090 mol) in dry tetrahydrofuran (90 ml) at −78°. Additional tetrahydrofuran (15 ml) was added to the cooled solution, followed by dropwise addition during 30 min of a solution containing 1,2,-3,4,4a-*cis*,9a-*cis*-hexahydrofluoren-9-one (**7**)[1,11] (13.45 g, 0.0725 mol) in tetrahydrofuran (15 ml). The yellow solution was aged for 45 min at −78°. A solution of ammonium chloride 6.55 g, 0.122 mol) in water (55 ml) was added, and the mixture was warmed to room temperature. The tetrahydrofuran layer was separated and combined with two 50-ml ether extractions of the aqueous layer. The yellow solution was dried over magnesium sulfate and concentrated,[12] leaving a yellow oil (21.36 g). A small amount of the oil (2.17 g) was purified by chromatography on a neutral alumina (activity I) column developed with 10% ether and 90% benzene. A white solid was recovered from the column and was used as a seed crystal to crystallize the remaining crude product, which was recovered as a white solid (16.96 g, 90% yield, mp 48–58°). The crude hydroxy ester **11** was purified by recrystallization from petroleum ether (bp 30–60°) to yield the analytically pure sample as a white solid: mp 59–60°; ir (CCl_4) ν 3485 (s, OH), 1724 cm^{-1} (s, C=O); nmr (CCl_4) τ 2.60–3.05 (m, 4 H, C_6H_4), 6.05 (broad s, 1 H, OH), 6.35 (s, 3 H, CH_3), 3.80 (broad s, 1 H, benzo H), 7.40 (s, 2 H, CH_2-CO_2), 7.45–9.35 (m, 9 H, alkyl H); uv (95% ethanol) λ_{max} 260 mμ (ϵ 2175), 265 (2550), 271 (2650).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 74.05; H, 7.93

9-*trans*-Hydroxy-1,2,3,4,4a-*cis*,9a-*cis*-hexahydrofluoren-9-*cis*-ylacetic Acid Hydrazide (12).—Methyl hydroxy ester **11** (5.45 g, 0.0210 mol), methanol (5 ml), and hydrazine hydrate (9 ml)

(5) H. Heussner, P. T. Herzig, A. Furstand, and P. A. Plattner, *Helv. Chim. Acta*, **33**, 1093 (1950).
(6) F. Ramirez and S. Stafiej, *J. Amer. Chem. Soc.*, **77**, 134 (1955).
(7) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 69.
(8) G. DiMaio, *Tetrahedron*, 2291 (1967).
(9) G. DiMaio and P. A. Tardella, *ibid.*, 2069 (1966).
(10) E. H. Amonoo-Neizer, R. A. Shaw, D. O. Slovkin, and B. C. Smith, *J. Chem. Soc.*, 2997 (1965).
(11) S. Dev, *J. Indian Chem. Soc.*, **34**, 169 (1957).
(12) Rotary evaporator under aspirator pressure.

were combined and heated at the reflux temperature for 2 hr. The methanol was removed by distillation and the remaining solution was allowed to cool to room temperature. One volume of water was added and a white, opaque mixture resulted. The crude product was recovered by filtration as a yellow gum, which was crystallized from ether to give the acid hydrazide **12** as a white solid (3.50 g, 64% yield, mp 117–120°). The hydrazide was recrystallized to constant melting point from ether to give the analytically pure sample as a white solid: mp 127.5–128.5°; ir (Nujol) ν 3335 (s), 3240 (s), 1648 cm^{-1} (s); nmr ($CDCl_3$) τ 1.91 (broad s, 1 H, OH), 2.50–3.10 (m, 4 H, C_6H_4), 4.90–6.70 (m, 3 H, NH and NH_2), 6.92 (broad s, 1 H, 4a-CH), 7.25–9.65 (m, 11 H, CH_2 and 9a-CH, acetate CH_2 singlet at τ 7.60).

Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.56. Found: C, 69.06; H, 7.99; N, 10.50.

A repeat of the experiment afforded a 77% yield of crude hydrazide (mp 118–122°) by allowing the opaque, white mixture, formed by addition of one volume of water to the hydrazine hydrate solution, to stand for 24 hr.

Spiro[1′,2′,3′,4′,4a′-*cis*,9a′-*cis*-hexahydrofluorene-9′-*cis*,5-oxazolidin]-2-one (13).—A solution of sodium nitrite (1.07 g, 15.5 mmol) in water (10 ml) was added dropwise over 7 min to a stirred suspension of the hydrazide **12** (2.80 g, 10.8 mmol) in a solution of acetic acid (1.07 g, 17.8 mmol) in water (100 ml) at 0°. After 50 min benzene was added and stirring was continued for an additional 25 min. The mixture was warmed to room temperature and the benzene layer was separated and combined with two 50-ml benzene washings of the aqueous layer. The benzene solution was dried over magnesium sulfite, then heated at the reflux temperature for 30 min. The benzene solution was concentrated[12] to give a yellow oil, which solidified upon standing to give the oxazolidone **13** as yellow crystals (2.40 g, 91% crude yield, mp 135–144°), ir (Nujol) ν 3275 (s), 1755 (s), 1735 cm^{-1} (s). The crude product was recrystallized from ether to give a tan solid: 1.50 g (57% yield); mp 157–157.5°; ir (Nujol) ν 3290 (m), 1753 (s), 1729 cm^{-1} (s); ir ($CHCl_3$) ν 3290 (m), 1730 cm^{-1} (s, broad); nmr ($CDCl_3$) τ 2.40–3.05 (m, 4 H, C_6H_4), 3.05–3.50 (m, 0.5 H, NH), 6.30 (s, 2 H, CH_2N), 6.45–7.20 (m, 1 H, 4a-CH), 7.20–8.90 (m, 9 H, 9a-CH and CH_2); uv (95% ethanol) λ_{max} 258 mμ (ϵ 350), 264 (500), 270 (580).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.83; H, 6.85; N, 5.54.

9-*cis*-Methylamino-1,2,3,4,4a-*cis*,9a-*cis*-hexahydrofluoren-9-*trans*-ol (14).—The oxazolidone **13** (5.65 g, 0.0232 mol) was suspended by stirring in a 10% aqueous sodium hydroxide solution (150 ml) for 16 hr at 110°. The cooled solution was treated with three 100-ml portions of ether. The combined ether portions were dried over magnesium sulfate and concentrated[12] to give a light brown oil (5.31 g). Addition of a small amount of ether caused the oils to crystallize. Removal[12] of the ether left the amino alcohol **14** as a tan solid (5.31 g, 106% crude yield, mp 111–112°), ir (Nujol) ν 3345 (m), 3120 cm^{-1} (broad). Recrystallization of the solid from ether–petroleum ether (bp 60–70°), afforded pure **14** as a white solid: 4.89 g (98% yield); mp 111.5–112.5°; nmr ($CDCl_3$) τ 2.50–3.05 (m, 4 H, C_6H_4), 6.60–7.00 (m, 1 H, 4a-CH), 7.00–7.40 (broad s, 2 H, NH_2), 7.40–9.35 (m, 12 H, OH, CH_2 and 9a-CH).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.16; H, 8.58; N, 6.22.

A portion of the pure amino alcohol (2.54 g, 0.0117 mol) was dissolved in ether (100 ml) and anhydrous hydrogen chloride was bubbled through the solution. Filtration of the mixture gave impure amine hydrochloride **10b**, which was recovered as a white solid (2.24 g, 75% crude yield, mp 209–215°). Recrystallization of this product from ethanol–ether afforded the analytically pure sample as a white powder (mp 229–230° with noticeable decomposition above 183°), ir (Nujol) ν 3340 (m), 3218 (s), 3190 (s), 3100 cm^{-1} (s) (not identical with ir of **10a**, mp 198.5–199.5°[2]).

Anal. Calcd for $C_{14}H_{20}ClNO$: C, 66.26; H, 7.95; N, 5.52; Cl, 13.97. Found: C, 66.39; H, 8.09; N, 5.49; Cl, 13.79.

3-Ethoxyindene.—A mixture of 1-indanone (29.73 g, 0.225 mol), ethanol (100 ml), triethyl orthoformate (40.73 g, 0.275 mol), and hydrochloric acid (two drops) was stirred for 17 hr at room temperature. The resulting red solution was concentrated by distillation at atmospheric pressure until the ethanol and excess triethyl orthoformate were removed. The remaining undistilled red oil was then distilled under vacuum on a spiral wire column (18 × 0.8 cm) to yield the crude product as a clear, colorless oil [18.88 g, 52% crude yield, bp 72–75° (0.15 mm)]. Purification of the crude ether was achieved by chromatography on an alumina (activity III) column, developed with petroleum ether. The pure product was isolated as a cloudy, colorless oil: 16.11 g (45% yield); $n^{28}D$ 1.5448; ir (neat) ν 1615 cm^{-1} (m, C=C); nmr (CCl_4) τ 2.45–3.07 (m, 4 H, C_6H_4), 4.91 (t, J = 2.25 Hz, 1 H, CH), 6.02 (q, J = 6 Hz, 2 H, CH_2CH_3), 6.90 (d, J = 2.25 Hz, 2 H, benzylic CH_2), 8.61 (t, J = 6 Hz, 3 H, CH_3); uv (95% ethanol) λ_{max} 256 mμ (ϵ 8560). The essentially pure sample was distilled again through the spiral wire column to give a clear, colorless oil, bp 63–64° (0.35 mm). An analytical sample was prepared by preparative gas chromatography (3% SE-30 on Chromosorb W, 80–100 mesh, 5 ft × 1/4 in., 140°).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.47; H, 7.55. Found: C, 82.60; H, 7.67.

1-Ethoxyindan-1-ylmethylamine Hydrochloride (16).—3-Ethoxyindene (6.12 g, 0.0387 mol) was added in one lot to hydrogen cyanide[13] (15 ml) containing sulfuric acid (two drops) at ice-bath temperature. The resulting solution was stirred for 3 hr at ice-bath temperature, and then for 12 hr at room temperature. Excess hydrogen cyanide was removed by passing a stream of dry nitrogen gas above the solution. The crude cyano ether was recovered as a dark red oil. The oil was dissolved in ether (25 ml) and the ether solution was added dropwise during 15 min to a stirred suspension of lithium aluminum hydride (1.42 g, 0.0374 mol) in ether (50 ml) heated at the reflux temperature under a dry nitrogen atmosphere. The mixture was stirred for 30 min at room temperature, then 9% aqueous sodium hydroxide (20 ml) was added. The crude product was extracted from the aqueous mixture with three 25-ml portions of ether. The ether solution was dried over magnesium sulfate and concentrated[12] to give a dark green oil (4.87 g). The dark green oil contained unreduced nitrile [ir (neat) ν 2208 cm^{-1} (w, CN)] and was again treated with lithium aluminum hydride (0.61 g, 0.0016 mol) as described above to give a green oil (4.08 g), nmr (CCl_4) two triplets at τ 8.90 and 8.95 in the approximate ratio 3:2. Ether saturated with hydrogen chloride gas was added dropwise at ice-bath temperature to an ether (20 ml) solution of the green oil (1.01 g) until no more solid formed. The amine hydrochloride was obtained as a white solid (0.61 g, 29% yield based on 3-ethoxyindene) which recrystallized twice from ethanol–ether to afford analytically pure **16** as a white powder, mp 145–230° dec.

Anal. Calcd for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97; N, 6.15. Found: C, 63.35; H, 8.02; N, 6.11.

Attempted preparation of **16** by reaction of the amino alcohol with concentrated hydrochloric acid in ethanol led to the isolation of an off-white, platelike solid (41% yield based on **19**, mp 246–247°), which was assumed to be the unsaturated amine hydrochloride.

Anal. Calcd for $C_{10}H_{12}ClN$: C, 66.12; H, 6.66; N, 7.71; Cl, 19.52. Found: C, 66.35; H, 6.63; N, 7.37; Cl, 19.52.

Reaction of Amine Hydrochlorides with Nitrous Acid. A. 10a.—A sample of amine hydrochloride **10a** (0.3317 g, 1.315 mmol) was dissolved in water (8 ml) and cooled to ice-bath temperature. A solution of sodium nitrite (0.2743 g, 3.965 mmol) in water (3 ml) was added with stirring. A catalytic amount of hydrochloric acid (1 drop) was added and the aqueous solution was stirred for 2 hr at ice-bath temperature, and then for 15 hr at room temperature. The product was extracted with three 10-ml portions of ether and the ether solution was dried ($MgSO_4$) and concentrated[12] to yield an orange oil (0.2290 g).

Authentic samples[1] of **2a**, **2b**,[4] **3a**, and **3b** were available. Product identification and analyses were made by gc and nmr analysis similar to the procedure described in detail[1] for mixtures of the same ketones derived from **1**. The yields of products follow: **3a**, 55%; **3b**, 0.7%; **2a**, 25.6%. The reaction was repeated four times; the yields of total ketonic products varied somewhat but the ratio of **3a**, **3b**, and **2a** was essentially the same.

When catalytic amounts of hydrochloric acid were not employed in the diazotization step the total yield of ketonic products was reduced; however, there was essentially no change in ratios of **3a**, **3b**, and **2a**. The aqueous layer obtained from the diazotization contained, in all cases studied, unchanged amine hydrochloride. The only by-product noted was a small amount of ketonic material (ν 1710 cm^{-1}) to 6.3% yield. No **2b** (aromatic protons ortho to carbonyl, τ 1.75–2.10) was present in any products.

(13) K. Ziegler, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1932, p 314.

B. **10b**.—The reaction was conducted as above and gave **2a** (32.6% yield), **3a** (50.3% yield), and **3b** (2.8% yield).

C. **15 and 16**.—The reactions of **15**[2] and **16** were carried out essentially as described above. The product was a brown-black solid; no α- or β-tetralone was detected by gc analysis (comparison with authentic samples, 5% DC-710 on Chromosorb W, 80–100 mesh, 5 ft × 1/4 in., 150°). It was subsequently shown that β-tetralone, but not α-tetralone, reacts readily (to give a black gum) when stirred at 0° with a mixture of 9% aqueous hydrochloric acid to which sodium nitrite is added.

Registry No.—**10b**, 34402-93-2; **11**, 34410-05-4; **12**, 34402-94-3; **13**, 34402-95-4; **14**, 34402-96-5; **16**, 34402-97-6; **19**, 34402-98-7; 3-ethoxyindene, 34402-99-8.

Benzocyclobutene and 2-Phenylethyl Chloride as Alkylating Agents in the Friedel–Crafts Reaction[1]

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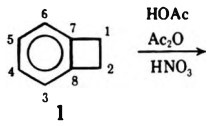
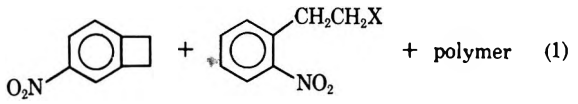
Friedel–Crafts reactions of benzocyclobutene and 2-phenylethyl chloride with benzene and toluene are studied at various temperatures. On the basis of identical product ratios with toluene, lack of positional rearrangement at the aryl rings of 1-chloro-2-*p*-tolylethane and 1-chloro-2-*m*-tolylethane on reaction with benzene, and various stereochemical arguments, it is concluded that in the presence of $AlCl_3$, benzocyclobutene is directly converted to 2-phenylethyl chloride before reaction with the aromatic hydrocarbon. Incomplete reaction of 1,1-dideuterio-2-*p*-tolylethyl chloride with benzene at 40° in the presence of $AlCl_3$ reveals that the starting material undergoes partial isomerization of the CH_2 and CD_2 groups. This differs with previous results with 2-phenylethyl-*1*-^{14}C chloride at −5° and suggests that in our case the intermediate phenonium ion, or its equivalent, reverts in part to starting material.

This paper reports the results of a study of benzocyclobutene (**1**) and 2-phenylethyl chloride (**2**) as alkylating agents under Friedel–Crafts conditions. The reactions of benzocyclobutene (**1**) and its derivatives with electrophilic reagents generally follow two competing pathways.[3] Aromatic substitution may occur, mainly at the 4 position with possibly minor amounts of substitution at the 3 position, or electrophilic attack may occur at a bridgehead carbon to open the four-membered ring and give ortho-substituted 2-phenylethyl derivatives. Some examples are nitration (eq 1),[3a,d] bromination (eq 2),[3f] and reaction with HBr in acetic acid (eq 3).[3d] Lloyd and Ongley have presented

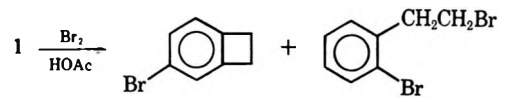


1

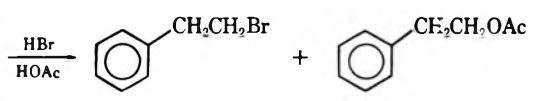


(1)

X = OAc, ONO_2

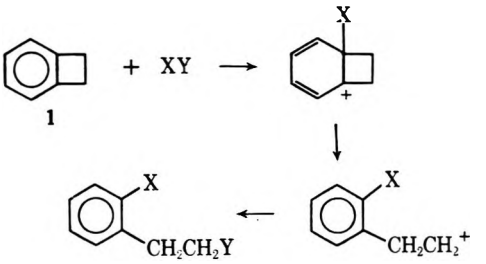


(2)

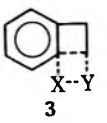


(3)

SCHEME I



arguments concerning the mechanism of the ring-opening reaction.[3f] They have argued that the pathway involving a benzenonium ion (Scheme I) is not involved, since the formation of the benzenonium ion would be precluded by strain effects. It was further argued that this pathway requires generation of an ortho-substituted 2-phenylethyl cation, which is energetically improbable. It was concluded that the mechanism for ring opening involves a multicentered transition state (**3**).



3

The Friedel–Crafts reaction of 2-phenylethyl chloride (**2**) with aromatic hydrocarbons has been studied by isotopic labeling. Lee, Forman, and Rosanthal have found that 2-phenylethyl-*1*-^{14}C chloride with excess $AlCl_3$ in the presence of anisole yields *p*-methoxybibenzyl with the ^{14}C equally distributed between the methylene groups.[4] Two general mechanisms were discussed which could not be distinguished: (1) the same intermediate is involved in rearrangement and alkylation; (2) rearrangement and alkylation occur by separate processes. McMahon and Bunce studied the

(1) Supported in part by grants from the General Faculty Research Committee of the City College of New York and from the City University of New York.

(2) (a) National Science Foundation Undergraduate Research Participant, 1966–1969; (b) City University of New York Research Assistant, 1964–1966; National Aeronautics and Space Administration Trainee, 1966–1967.

(3) (a) L. Horner, H.-G. Schmelzer, and B. Thompson, *Chem. Ber.*, **93**, 1774 (1960); (b) L. Horner, P. V. Subramaniam, and E. Eiben, *Tetrahedron Lett.*, 247 (1965); (c) *Justus Liebigs Ann. Chem.*, **714**, 91 (1968); (d) J. B. F. Lloyd and P. A. Ongley, *Tetrahedron*, **20**, 2185 (1964); (e) *ibid.*, **21**, 2281 (1965); (f) *ibid.*, **21**, 245 (1965).

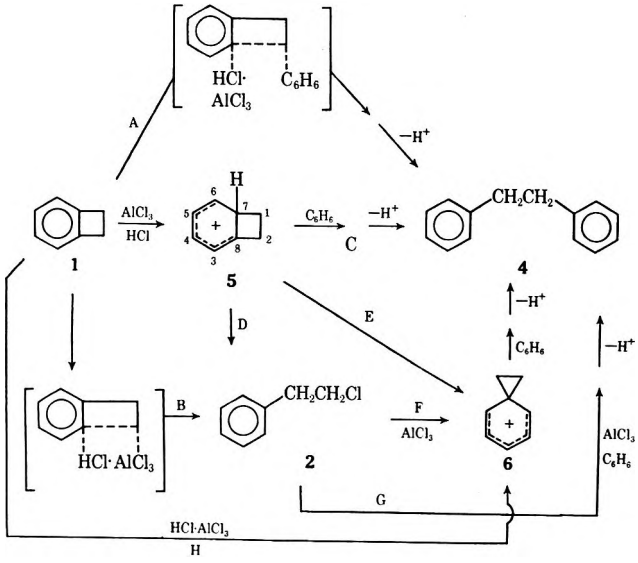
(4) C. C. Lee, A. G. Forman, and A. Rosenthal, *Can. J. Chem.*, **35**, 220 (1957).

reaction of 2-phenylethyl-1-^{14}C chloride with toluene.[5] Recovered starting material was found to be isotopically unrearranged, while the product, 1-phenyl-2-*p*-tolylethane, showed slightly greater than 50% rearrangement of the ^{14}C label. These results were interpreted in terms of a single process for both rearrangement and alkylation. The reaction was pictured as proceeding through a symmetrical phenonium ion which attacked toluene in the rate-determining step.

Results and Discussion

The reaction of benzocyclobutene (**1**) with a large excess of benzene in the presence of approximately 20 mol % $AlCl_3$ at 40° for 0.5 hr gave a quantitative yield of bibenzyl (**4**). A variety of pathways, both multicentered and stepwise, can be envisioned for this reaction. These are shown in Scheme II. Path A

SCHEME II

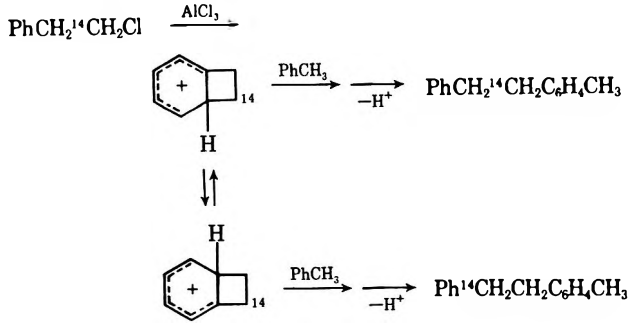


involves a multicentered transition state with direct formation of the product, **4**. Path B involves a multicentered transition state to form 2-phenylethyl chloride (**2**), which yields the product (**4**) either through route F[6] or route G (a direct displacement path). Path C involves direct displacement by benzene at C-1 of benzenonium ion **5**. In addition, ion **5** could lead to the product by directly forming phenonium ion **6** (path E) or by forming 2-phenylethyl chloride (**2**) (path D) which can lead to product as indicated above.

Under the reaction conditions, 2-phenylethyl chloride (**2**) also gave a quantitative yield of bibenzyl (**4**). In an attempt to distinguish between pathways which involve 2-phenylethyl chloride (**2**) (B, D) and those which do not, we studied the reactions of **1** and **2** with toluene. Under identical conditions at 40°, **1** yielded a mixture of 1-phenyl-2-tolylethanes of composition 47.8 ± 0.8% ortho (**7**), 18.2 ± 1.0% meta (**8**), and 34.0 ± 0.2% para (**9**), while **2** yielded a mixture of composition 46.1 ± 0.3% ortho (**7**), 18.8 ± 0.8% meta (**8**), and 35.1 ± 1.1% para (**9**). Suitable control experiments were carried out which established that the products were stable to both the reaction conditions and the subsequent workup procedure. These isomer distributions therefore represent the kinetically controlled products.[7] The identity of the two product mixtures strongly suggests that the reactions of benzocyclobutene (**1**) and 2-phenylethyl chloride (**2**) proceed through a common intermediate. If this is the case, path A is eliminated.

One possible common intermediate is the benzenonium ion **5**. Formation of **5** from **2** would have to involve reversal of either step D or step E (Scheme II). By invoking reversible and rapid 1,2-hydride shifts (or rapid deprotonation–protonation), such an intermediate could accommodate the earlier labeling results of McMahon and Bunce,[5] which were interpreted in terms of a symmetrical phenonium ion. This is shown in Scheme III.

SCHEME III



In an attempt to obtain further information on the possible intermediacy of a benzenonium ion from the 2-arylethyl chloride system, we studied the reaction of 1-chloro-2-*p*-tolylethane (**10**) and 1-chloro-2-*m*-tolylethane (**11**) with benzene. Let us consider a step similar to the reversal of step D. If rapid 1,2-hydride shifts occur in the intermediate benzenonium ion (Scheme III), both **10** and **11** could yield mixtures of 1-phenyl-2-tolylethanes. This is shown in Scheme IV. Careful glc analyses of the reaction products revealed that **10** yielded only 1-phenyl-2-*p*-tolylethane (**9**) and none of the corresponding ortho (**7**) or meta (**8**) isomers, and **11** yielded only 1-phenyl-2-*m*-tolylethane (**8**) and none of the ortho (**7**) or para (**9**) isomers. We interpret these results together with those of previous investigators[8] and the ^{14}C labeling results of McMahon and Bunce[5] as ruling out the reversal of step D followed by step C as the pathway leading from **2** to bibenzyl (**4**). If this were the route leading to the ^{14}C scrambling results of McMahon and Bunce,[5] we would expect to obtain a mixture of products from **10** and **11**.

However, the pathways, reversal of D followed by E, and F followed by the reversal of E, cannot be ruled out unless it is established that under the reaction conditions 1,2-hydride shifts, as pictured in Schemes III and IV, are relatively rapid. These routes could account for the observed ^{14}C scrambling,[5] without the need to invoke shifts of the type pictured in Schemes III and IV. Mixtures of products from **10** and **11**

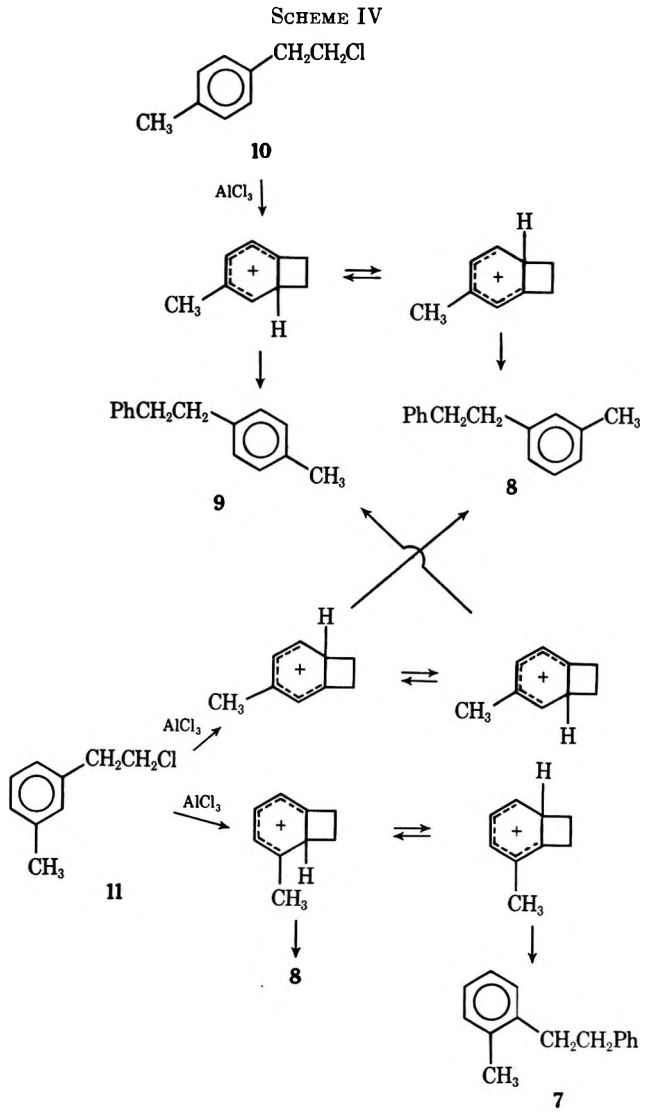
(5) M. A. McMahon and S. C. Bunce, *J. Org. Chem.*, **29**, 1515 (1964).

(6) For simplicity of representation, a phenonium ion (**6**) rather than rapidly equilibrating classical 2-phenylethyl cations is used. This work does not allow these species to be differentiated.

(7) Under somewhat different conditions, McMahon and Bunce[5] found virtually complete para alkylation of toluene by 2-phenylethyl chloride (**2**) at 0°.

(8) The 2-arylethyl system has been the subject of numerous studies in past years. To our knowledge there is no reported case of a substituent on the aromatic ring changing position.

SCHEME IV



would not be required if 1,2-hydride shifts were relatively slow. If such shifts were relatively rapid, **10** would be predicted to yield at least some **8**. This prediction is based on the work of Horner, Schmelzer, and Thompson.[3a] These workers showed that the reaction of 4-acetamidobenzocyclobutene with concentrated HCl yielded, after acetylation, 2-(3-acetamidophenyl)ethyl chloride. The electron-donating acetamido group directs the ring opening toward the meta product. A similar result would be expected from **10**.

Molecular models of ion **5** indicate a small dihedral angle, of the order of 10–15°, between the C_7–H bond and the empty p orbital, and a dihedral angle of approximately 55° between the C_1–C_7 bond and the empty p orbital (Figure 1). Recent work by Brouwer and Hogeveen,[9] Majerski, Schleyer, and Wolf,[10] and Schleyer and coworkers[11] has pointed out the angular requirement for 1,2 shifts between carbonium ions. The difference of five or more orders of magnitude between the rates of 1,2-hydride shifts in the adamantyl ion, on the one hand, and acyclic and monocyclic ions, on

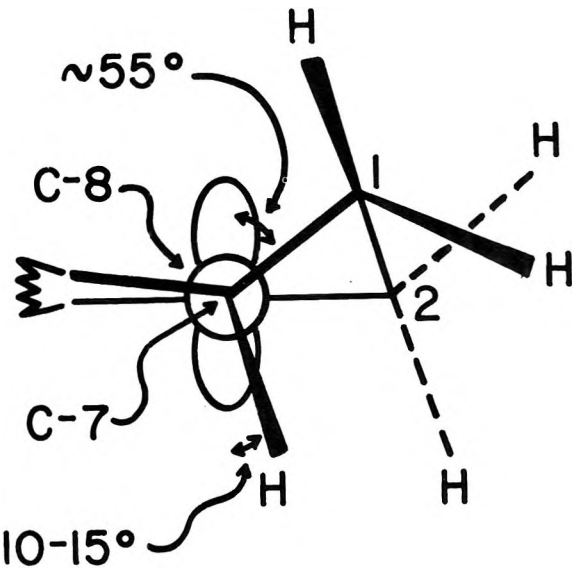


Figure 1.—Molecular model picture of ion **5**.

the other hand, was attributed to unfavorable orbital orientation in the adamantyl ion.[9,11] In order to achieve a most facile rearrangement, the dihedral angle between the sp^3 orbital of the migrating group and the adjacent empty p orbital should be 0°. In the adamantyl case, a 1,2-hydride shift would involve the interconversion of carbonium ions with dihedral angles of 90 and 60°. The mechanism for the interconversion of bridgehead and bridge adamantyl ions was shown to be intermolecular.[11] Similar interconversion of methyladamantyl ions was shown to proceed by skeletal isomerization steps rather than by 1,2-methyl shifts between bridgehead and bridge ions.[10]

Three arguments can be offered against the pathways, reversal of D followed by E, and F followed by the reversal of E. (1) Since orbital orientation in favorable (Figure 1), a 1,2-hydride shift of the type depicted in Schemes III and IV should be relatively facile, especially when such a shift would lead to a more stable ion as in the case of **10**. (2) Both paths under discussion involve the interconversion of ions **5** and **6**. Such a process should be unfavorable, since ion **5** involves a dihedral angle of approximately 55° and ion **6** a dihehdral angle of 60°. The transition state for the interconversion of these ions will be unfavorably twisted.[10,11] (3) Concerning the reversal of step D, to our knowledge, of the many reported studies of the 2-arylethyl system, not a single case of ring closure to a four-membered ring has been found. In an effort to detect such ring closure during the reaction of **2**, we looked for the deprotonation product of **5**, benzocyclobutene (**1**). Careful glc analysis did reveal traces of ethylbenzene and styrene, but no **1** could be found. Based upon the above results and arguments, we conclude that ion **5** is not the common intermediate in the reactions of **1** and **2**.

The remaining possible common intermediates are 2-phenylethyl chloride (**2**) formed from benzocyclobutene (**1**) either through path B or D and phenonium ion **6** formed from **1** either through path E or H. In a number of our early reactions of **1** with toluene, at 40°, glc analysis of the product mixture revealed the presence of very small quantities of 2-phenylethyl chloride

(9) D. M. Brouwer and H. Hogeveen, *Recl. Trav. Chim. Pays-Bas*, **89**, 211 (1970).

(10) Z. Majerski, P. v. R. Schleyer, and A. P. Wolf, *J. Amer. Chem. Soc.*, **92**, 5731 (1970).

(11) P. v. R. Schleyer, L. K. M. Lam, D. J. Raber, J. L. Fry, M. A. McKervey, J. R. Alford, B. D. Cuddy, V. G. Keizer, H. W. Geluk, and J. L. M. A. Schlatmann, *ibid.*, **92**, 5246 (1970).

(2) (<1%). Similar experiments at 0° with equimolar mixtures of **1** and **2** indicated that **2** builds up to approximately 20% of the initial concentration of **1** during the reaction. Since McMahon and Bunce had not found any ^{14}C rearrangement in recovered 2-phenylethyl-*1*-^{14}C chloride (at −5°),[5] which indicated that the reversal of step F does not occur, the formation of **2** from **1** suggested that path B and/or D was being followed *at least* in part. However, since our product distribution (at 40°) was different from that found by McMahon and Bunce (at 0°),[7] we decided to reinvestigate the possibility of rearrangement, under our reaction conditions, of **2** prior to reaction to form product. There are two points that we wished to establish simultaneously: (1) the possibility of rearrangement preceding reaction in the 2-arylethyl system; (2) the possibility of simultaneous isomerization of a substituent on the aromatic ring.[8] The reaction of 1,1-dideuterio-2-*p*-tolylethyl chloride (**10**-*1*-d_2) with benzene was studied at 40° (eq 4). The

$$p\text{-}CH_3C_6H_4CH_2CD_2Cl \xrightarrow[AlCl_3]{C_6H_6} \begin{matrix} p\text{-}CH_3C_6H_4CH_2CD_2C_6H_5 \\ \textbf{9}\text{-}1\text{-}d_2 \\ + \\ p\text{-}CH_3C_6H_4CD_2CH_2C_6H_5 \\ \textbf{9}\text{-}2\text{-}d_2 \end{matrix} \qquad (4)$$

10-*1*-d_2

reaction was quenched after only partial conversion. Analysis of the starting material by glc–mass spectrometry indicated essentially complete equilibration between CH_2 and CD_2 groups (48% H at C-1 and 52% H at C-2). The product showed 47% H at C-2 (**9**-*1*-d_2) and 53% H at C-1 (**9**-*2*-d_2) (53% rearrangement). Glc analysis further established that no positional rearrangement of the methyl group on the aromatic ring had occurred.

We cannot reach a conclusion concerning the difference between our results and those of McMahon and Bunce.[5] This is due to the fact that we used the reaction of a 2-*p*-tolylethyl chloride derivative with benzene rather than a 2-phenylethyl chloride derivative with toluene to investigate the possibility of rearrangement preceding reaction in the 2-arylethyl system. The difference in results could be caused by the different experimental conditions employed, or by the different reactions chosen for study. Furthermore, the fact that we do observe rearrangement in the starting chloride negates our statement in the preceding paragraph that path B and/or D is followed at least in part. Ion **6** might be the only common intermediate in the reactions of **1** and **2** leading to product, and which by reversal of step F could also lead to the formation of **2** from **1**.

The essentially complete equilibration of the methylene groups in the recovered starting material also raised the possibility that the Friedel–Crafts reaction of **10**-*1*-d_2 could be proceeding by a prior equilibration followed by a direct displacement on the starting material (path G, Scheme II). To test this pathway, the rearrangement of the deuterium label was followed in the starting material (**10**-*1*-d_2) and the product (**9**-*1*-d_2 and **9**-*2*-d_2) during the reaction (at 7°) by removing aliquots, separating the starting material from the product by preparative glc, and analyzing by mass spectrometry. The results are shown in Table I. The per cent rearrangement of the starting material increases during the reaction, while the per cent rearrangement of the product is constant throughout. In order to establish that the deuterium distribution of the product was not the result of a subsequent equilibration, **9**-*1*-d_2 was subjected to the reaction conditions (at 40°). Our results indicated little (3–4%), if any, deuterium scrambling. Path G is eliminated, since this route would predict equal scrambling of product and reactant throughout the reaction.

TABLE I

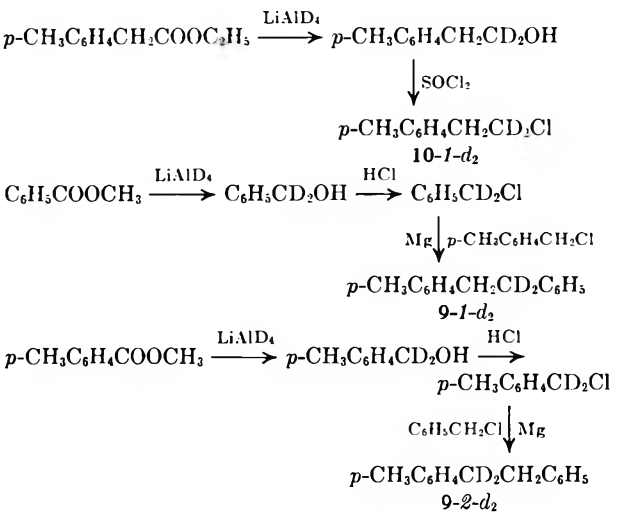
PER CENT REARRANGEMENT OF STARTING MATERIAL AND PRODUCTS DURING THE REACTION OF *p*-$CH_3C_6H_4CH_2CD_2Cl$ (**10**-*1*-d_2) WITH BENZENE (7°)

	Extent of reaction, %	Per cent rearrangement
Starting Material	5	2
	20	6
	70	39
Product	*a*	52

[a] The per cent rearrangement of the product remained invariant throughout the reaction.

The synthesis of **10**-*1*-d_2 and products **9**-*1*-d_2 and **9**-*2*-d_2, which were necessary as standards for mass spectrometry analysis, are outlined in Scheme V and described in the Experimental Section.

SCHEME V



We have already presented an argument against the interconversion of ions **5** and **6** (path E) based on unfavorable twisting in the transition state. A similar argument would apply to path H, where the transition state would have a geometry approaching that of ion **5**. Path D can also be argued against in terms of transition-state strain. A dihedral angle of 0° between the C_1–C_7 bond (Figure 1) and the empty p orbital at C-8 would be most favorable for the conversion of ion **5** to **2**. However, this angle appears to be approximately 55°. Although we cannot offer a quantitative estimation, such a large deviation from the optimum dihedral angle suggests that step D will be an unfavorable process. These arguments lead us to the conclusion that **2** is the common intermediate, and that it arises by way of step B. This is in agreement with the previous conclusion of Lloyd and Ongley[3f] concerning the multicentered nature of the ring opening of benzocyclobutene (**1**).

Experimental Section[12]

Phenyl 2-, 3-, and 4-Methylbenzyl Ketones.—A mixture of 25 g (0.167 mol) of the appropriate tolylacetic acid and 11.5 g (0.084 mol) of PCl_3 were heated under reflux for 1 hr. Anhydrous benzene (119 g, 1.52 mol) was added, and the organic layer was decanted in small portions, with cooling, into a flask containing 25.9 g (0.195 mol) of $AlCl_3$. The mixture was heated under reflux for 1 hr, cooled, and poured into a mixture of 165 g of ice and 65 ml of concentrated HCl. The organic layer was washed with water and dried, and the solvent was removed under vacuum. Distillation afforded the product. Phenyl 2-methylbenzyl ketone (77%) had bp 143–151° (1.3–2.2 mm); mp (from methanol) 67–68°; nmr ($CDCl_3$) δ 2.22 (3 H, s, CH_3), 4.23 (2 H, s, CH_2), 7.12 (4 H, broad s, ArH), 7.2–8.1 (5 H, m, ArH); ir (KBr) 1685 cm^{-1}. Phenyl 3-methylbenzyl ketone (76%) had bp 140–147° (1.5–1.7 mm); nmr ($CDCl_3$) δ 2.20 (3 H, s, CH_3), 4.09 (2 H, s, CH_2), 7.02 (4 H, broad s, ArH), 7.2–8.1 (5 H, m, ArH); ir (liquid) 1678 cm^{-1}. Phenyl 4-methylbenzyl ketone (64%) had bp 150–160° (2.1–2.2 mm); mp (from methanol) 95–96°; nmr ($CDCl_3$) δ 2.27 (3 H, s, CH_3), 4.18 (2 H, s, CH_2), 7.10 (4 H, s, ArH), 7.2–8.1 (5 H, m, ArH); ir (KBr) 1692 cm^{-1}.

1-Phenyl-2-*o*-, -*m*-, and -*p*-tolylethanes (7, 8, 9).—A solution of the appropriate phenyl methylbenzyl ketone (27 g, 0.13 mol), 25.4 g (0.39 mol) of KOH, and 22.5 g (0.45 mol) of hydrazine hydrate in 155 ml of diethylene glycol was heated at reflux for 1.25 hr, distilled until the head temperature reached 198°, and finally heated at reflux for an additional 3.25 hr. After cooling, 150 ml of H_2O was added, and the mixture was extracted with pentane. The pentane solution was washed with water and dried, and the solvent was removed under vacuum. Distillation afforded the product, 1-phenyl-2-*o*-tolylethane (86%): bp 119–120° (2.0–2.2 mm); nmr (CCl_4) δ 2.14 (3 H, s, CH_3), 2.75 (4 H, s, CH_2), 6.95 (4 H, s, ArH), 7.04 (5 H, s, ArH).

Anal. Calcd for $C_{15}H_{16}$: C, 91.78; H, 8.22. Found: C, 91.71; H, 8.48.

1-Phenyl-2-*m*-tolylethane (85%) had bp 118° (2 mm); nmr (CCl_4) δ 2.20 (3 H, s, CH_3), 2.70 (4 H, s, CH_2), 6.65–6.95 (4 H, m, ArH), 7.02 (5 H, s, ArH).

Anal. Calcd for $C_{15}H_{16}$: C, 91.78; H, 8.22. Found: C, 91.73; H, 8.27.

1-Phenyl-2-*p*-tolylethane (92%) had bp 115–119° (1.8–1.95 mm); nmr (CCl_4) δ 2.18 (3 H, s, CH_3), 2.75 (4 H, s, CH_2), 6.87 (4 H, s, ArH), 7.01 (5 H, s, ArH).

Anal. Calcd for $C_{15}H_{16}$: C, 91.78; H, 8.22. Found: C, 92.03; H, 8.11.

Friedel–Crafts Reaction of Benzocyclobutene (1) and 2-Phenylethyl Chloride (2) with Toluene. Product Studies.—The appropriate starting material (1 or 2) (0.0047 mol) was stirred with 500 ml (4.71 mol) of toluene and 0.001 mol of $AlCl_3$ at 40° for 0.5 hr. After quenching with 3 *N* HCl, the organic layer was dried and carefully distilled at atmospheric pressure to remove excess toluene. The residue was subjected to glc analyses. An Apiezon L column (16 ft, 14%, 218°) separated 1-phenyl-2-*m*-tolylethane (8) from the ortho (7) and para (9) isomers, which were not separated. A QF1-0065 column (12 ft, 20%, 189°) separated the ortho isomer from the meta and para isomers. The product distribution from 1 was 47.8 ± 0.8% 7, 18.2 ± 1.0% 8, and 34.0 ± 0.2% 9. In addition, trace amounts of ethylbenzene, styrene, benzocyclobutene (1), and 2-phenylethyl chloride (2) were found. The product distribution from 2 was 46.1 ± 0.3% 7, 18.8 ± 0.8% 8, and 35.1 ± 1.1% 9. Traces of ethylbenzene, styrene, and 2-phenylethyl chloride (2) were also found.

Friedel–Crafts Reactions of 1-Chloro-2-*p*-tolylethane (10) and 1-Chloro-2-*m*-tolylethane (11) with Benzene. A Search for Positional Rearrangement on the Aromatic Ring.—Individually, chlorides 10 and 11 (0.014 mol) were stirred with 0.003 mol of $AlCl_3$ and 300 ml of benzene at 40° for 0.5 hr. After the usual work-up, the products were analyzed by glc. Comparison with known samples indicated that 10 yielded only 9 and 11 yielded only 8.

Stability of the 1-Phenyl-2-tolylethanes (7, 8, 9) under Friedel–Crafts Reaction Conditions.—Two types of experiments were carried out. (1) Various standard mixtures of 7, 8, and 9 were subjected to the reaction conditions described above. Recovery of starting material was essentially quantitative. Analyses by glc showed no alterations in the isomer distributions. (2) Three aliquots were removed at 10-min intervals from a reaction of 2-phenylethyl chloride (2) with toluene (described above). At the 30-min mark, a sample of 9 was added to the reacting mixture. Three additional aliquots were removed at 10-min intervals. Glc analyses indicated the first three aliquots to have identical compositions. The last three aliquots all had the composition expected on the basis of the amount of added 9 and no rearrangement.

1,1-Dideuterio-2-*p*-tolylethyl Alcohol.—Ethyl *p*-tolylacetate (6.89 g, 0.031 mol) was reduced with 1.22 g (0.029 mol) of $LiAlD_4$ in ethyl ether for 5 hr. The nmr spectrum indicated the crude product, which was obtained in 72% yield, to be pure. It was not further purified: nmr ($CDCl_3$) δ 2.25 (3 H, s, CH_3), 2.70 (2 H, broad s, CH_2), 3.62 (1 H, s, OH), 7.05 (4 H, s, ArH).

1,1-Dideuterio-2-*p*-tolylethyl Chloride (10-*1*-d_2).—Thionyl chloride (15 ml) was slowly added to a solution of 5.57 g (0.04 mol) of 1,1-dideuterio-2-*p*-tolylethyl alcohol in 30 ml of pyridine. After heating at 100° for 5 min, the reaction mixture was quenched with 100 ml of cold H_2O and extracted with ether. The ether solution was extracted with H_2O, dilute $NaHCO_3$ solution, and saturated NaCl solution, dried, and evaporated under vacuum. Distillation afforded the product (57%): bp 113° (22 mm); nmr ($CDCl_3$) δ 2.30 (3 H, s, CH_3), 2.97 (2 H, broad s, $ArCH_2$), 7.09 (4 H, s, ArH).

α,α-Dideuteriobenzyl Alcohol.—Methyl benzoate (13.6 g, 0.10 mol) was reduced with 2.53 g (0.055 mol) of $LiAlD_4$ in ethyl ether for 4 hr. The crude alcohol was used without further purification: nmr ($CDCl_3$) δ 2.99 (1 H, s, OH), 7.43 (5 H, s, ArH), 4.66 (1/8 H, s, starting material).

α,α-Dideuteriobenzyl Chloride.—α,α-Dideuteriobenzyl alcohol (10.9 g, 0.10 mol) was shaken intermittently with 200 ml of concentrated HCl for 2 hr and the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O and saturated NaCl solution, dried, and evaporated under vacuum. Distillation afforded the product (20%): bp 173–175°; nmr ($CDCl_3$) δ 7.31 (s, ArH).

1,1-Dideuterio-1-phenyl-2-*p*-tolylethane (9-*1*-d_2).—A solution of 0.87 g (0.01 mol) of α,α-dideuteriobenzyl chloride and 0.97 g (0.01 mol) of 4-methylbenzyl chloride in 40 ml of ether was added over a 0.5-hr period to 0.24 g (0.01 mol) of Mg turnings under a nitrogen atmosphere. The mixture was heated at reflux for 42.5 hr, cooled, and quenched with ice followed by 10% HCl. The ether layer was washed with water, dried, and evaporated under vacuum. The product, 9-*1*-d_2, was separated from the other two possible coupling products by preparative glc (OV-1 column): nmr ($CDCl_3$) δ 2.31 (3 H, s, CH_3), 2.87 (2 H, broad s, CH_2), 7.08 (4 H, s, ArH), 7.22 (5 H, s, ArH).

α,α-Dideuterio-*p*-methylbenzyl Alcohol.—Methyl *p*-toluate (13.2 g, 0.088 mol) was reduced with 2.32 g (0.055 mol) of $LiAlD_4$ in ethyl ether for 5 hr. The crude alcohol, which was obtained in 84% yield, was used without further purification: nmr ($CDCl_3$) δ 2.27 (3 H, s, CH_3), 3.62 (1 H, s, OH), 7.10 (4 H, AA'BB', ArH).

α,α-Dideuterio-*p*-methylbenzyl Chloride.—α,α-Dideuterio-*p*-methylbenzyl alcohol was treated with concentrated HCl as described above for the preparation of α,α-dideuteriobenzyl chloride: bp 99° (52 mm) (64%): nmr ($CDCl_3$) δ 2.29 (3 H, s, CH_3), 7.19 (4 H, AA'BB', ArH).

2,2-Dideuterio-1-phenyl-2-*p*-tolylethane (9-*2*-d_2).—9-*2*-d_2 was prepared from α,α-dideuterio-*p*-methylbenzyl chloride and benzyl chloride as described above for the preparation of 9-*1*-d_2: nmr ($CDCl_3$) δ 2.31 (3 H, s, CH_3), 2.87 (2 H, broad s, CH_2), 7.08 (4 H, s, ArH), 7.22 (5 H, s, ArH).

Friedel–Crafts Reaction of 1,1-Dideuterio-2-*p*-tolylethyl Chloride (10-*1*-d_2) with Benzene at 40°. Incomplete Reaction.—A solution of 1.19 g (0.01 mol) of 10-*1*-d_2 and 0.21 g (0.0016 mol) of $AlCl_3$ in 300 ml benzene were heated at 40° for 0.5 hr. After the usual work-up, the crude product was subjected to glc–mass spectrometry analysis (50 ft × 0.02 in. support-coated open tubular column, Apiezon L, connected through a Watson–Biemann separator to a Hitachi RMU-6E mass spectrometer). Two major peaks whose retention times corresponded to starting material and 1-phenyl-2-*p*-tolylethane were observed.

Analysis of the recovered starting material was based on the corrected relative intensities of the *m/e* 105 ($CH_3C_7H_6$) and 107 ($CH_3C_7H_4D_2$) peaks. For reference, 10 and 10-*1*-d_2 were sub-

(12) Nmr spectra were determined at 60 MHz using a Varian A-60 spectrometer with tetramethylsilane as internal standard. Infrared spectra were determined using a Perkin-Elmer 137 spectrophotometer. Boiling points are uncorrected. Melting points are corrected. All Friedel–Crafts reactions were performed under a dry inert atmosphere with anhydrous solvents (Dri-Na).

jected to identical glc–mass spectrometry analyses. The recovered chloride was found to consist of 52% 10-*1*-d_2 and 48% rearranged material, 10-*2*-d_2.

Analysis of the 1-phenyl-2-*p*-tolylethane fraction was based on the corrected relative intensities of the *m/e* 105 ($CH_3C_7H_6$) and 107 ($CH_3C_7H_4D_2$) peaks. For reference, 9-*1*-d_2 and 9-*2*-d_2 were subjected to identical glc–mass spectrometry analyses. The product was found to consist of 47% 9-*1*-d_2 and 53% 9-*2*-d_2.

Friedel–Crafts Reaction of 1,1-Dideuterio-2-*p*-tolylethyl Chloride (10-*1*-d_2) with Benzene at 7°. Analysis of the Starting Material and Product during the Reaction.—A mixture of 2.09 g (0.011 mol) of 10-*1*-d_2, 0.457 g (0.0034 mol) of $AlCl_3$, 1.385 g of *p*-dichlorobenzene (internal standard for glc analyses, inert), and 300 ml of benzene were stirred at 7° for approximately 1.5 hr. Periodically, 50-ml samples were removed, subjected to the usual work-up conditions, and separated into starting material and product by preparative glc. Mass spectral analyses were performed on these samples as well as on appropriate reference materials by Morgan–Schaffer Corp., Montreal, Canada, using a Hitachi RMU-6 mass spectrometer. The results are reported in Table I.

Registry No.—**1**, 694-87-1; **2**, 622-24-2; 10-*1*-d_2, 34403-01-5; phenyl 2-methylbenzyl ketone, 5033-67-0; phenyl 3-methylbenzyl ketone, 34403-03-7; phenyl 4-methylbenzyl ketone, 2430-99-1; 1-phenyl-2-*o*-tolylethane, 34403-05-9; 1-phenyl-2-*m*-tolylethane, 34403-06-0; 1-phenyl-2-*p*-tolylethane, 14310-20-4; α,α-dideuteriobenzyl chloride, 33712-34-4; α,α-dideuterio-*p*-methylbenzyl chloride, 33712-36-6.

Acknowledgments.—We are indebted to Professor Neil McKelvie, Professor Frank Brescia, and Mr. Sidney Liebgold for their kind assistance.

Dealkylation of Di-*tert*-butylhalo-1,4-benzoquinones

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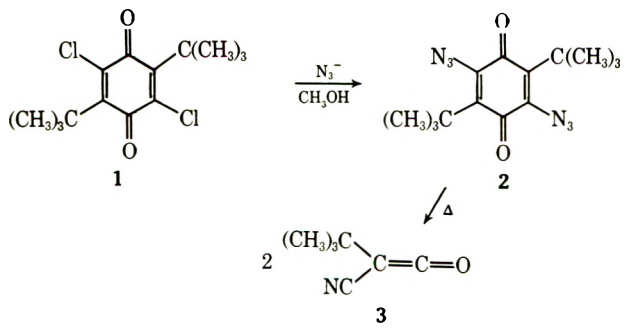
3-Chloro- and 3-bromo-2,5-di-*tert*-butyl-1,4-benzoquinone as well as 3-chloro-2,6-di-*tert*-butyl-1,4-benzoquinone react with anhydrous hydrohalic acids, resulting in dealkylation. This is a synthetically useful reaction for the preparation of 2,3-dihalo-5-*tert*-butyl-1,4-benzoquinones, specifically the 2,3-dichloro-2,3-dibromo-, 3-bromo-2-chloro, and 2-bromo-3-chloro isomers. The mechanism of this dealkylation involves an initial oxidation–reduction yielding the corresponding hydroquinones and molecular halogen. Electrophilic substitution by the halogen then results in elimination of the *tert*-butyl cation.

Recently the synthesis of 2,5-dichloro-3,6-di-*tert*-butyl-1,4-benzoquinone (**1**) was described.[1] This compound upon treatment with sodium azide gives the corresponding 2,5-diazido-3,6-di-*tert*-butyl-1,4-benzoquinone (**2**) which can be pyrolytically cleaved to *tert*-butylcyanoketene (**3**).[2] During our early attempts to synthesize the dichloroquinone **1**, some very interesting de-*tert*-butylation reactions were discovered. These dealkylation reactions are of synthetic utility and can be used to conveniently prepare 2,3-dichloro- (**13**), 2,3-dibromo- (**16**), 3-bromo-2-chloro- (**14**), and 2-bromo-3-chloro-5-*tert*-butyl-1,4-benzoquinone (**15**), from the readily available 2,5- and 2,6-di-*tert*-butyl-1,4-benzoquinones.



1 **2** **3**

The mechanism of these dealkylation reactions is of interest and suggests that the "1,4 addition" of HCl and HBr to certain quinones is not a simple addition, but instead may involve an initial oxidation–reduction to the hydroquinone and molecular halogen followed by electrophilic substitution (halogenation) of the hydroquinone.

(1) H. W. Moore and W. Weyler, Jr., *J. Amer. Chem. Soc.*, **93**, 2812 (1971).

(2) H. W. Moore and W. Weyler, Jr., *ibid.*, **92**, 4132 (1970).

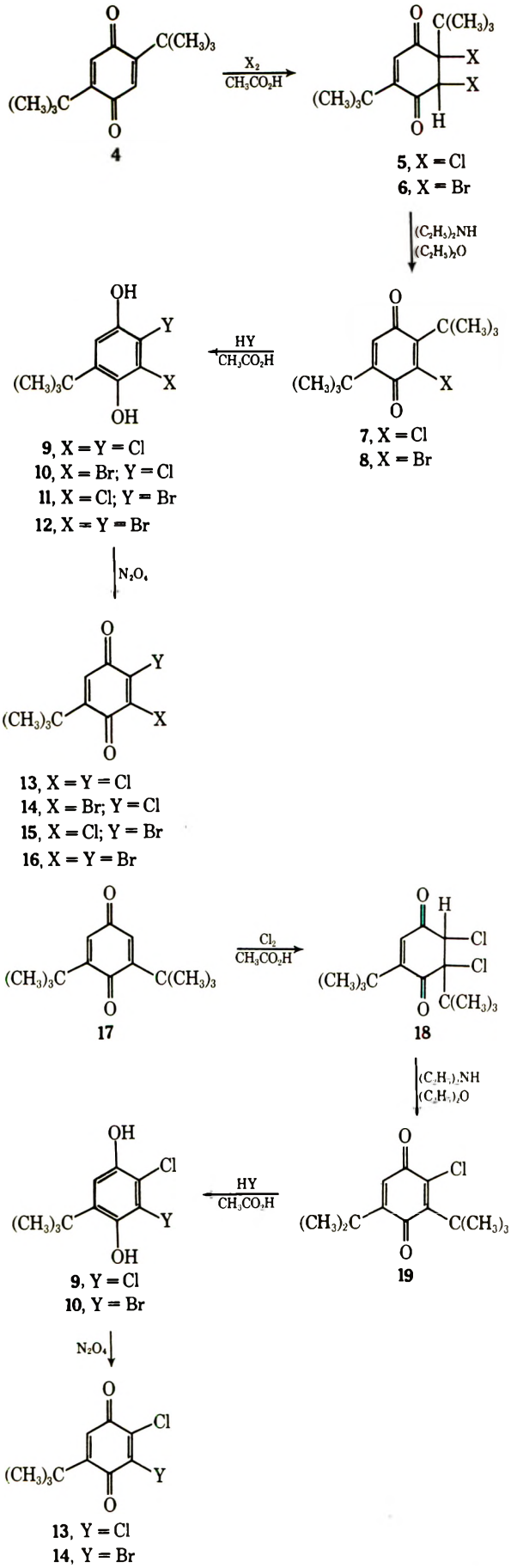
Synthetic Scope.—2,5-Di-*tert*-butyl-1,4-benzoquinone (**4**) was converted to its chloro and bromo derivatives **7** and **8** in high yield. These transformations were accomplished by an initial halogen addition to the carbon–carbon double bond to give the dihalo adducts **5** and **6**. These derivatives were then dehydrohalogenated upon reaction with diethylamine to the 3-halo-2,5-di-*tert*-butyl-1,4-benzoquinones **7** and **8**. Reaction of these haloquinones, 3-chloro-2,5-di-*tert*-butyl- (**7**) and 3-bromo-2,5-di-*tert*-butyl-1,4-benzoquinone (**8**) with anhydrous HCl in glacial acetic acid gave, respectively, 2,3-dichloro- (**9**) and 3-bromo-2-chloro-5-*tert*-butyl-1,4-benzoquinol (**10**). In completely analogous reactions, the monohalo-2,5-di-*tert*-butylquinones, **7** and **8**, were respectively converted to 2-bromo-3-chloro- (**11**) and 2,3-dibromo-5-*tert*-butyl-1,4-benzoquinol (**12**) upon reaction with anhydrous HBr. Oxidation of the above quinols with nitrogen oxides[3] gave the corresponding 2,3-dihalo-5-*tert*-butyl-1,4-benzoquinones, **13**–**16**.

2,3-Dichloro-5-*tert*-butyl-1,4-benzoquinone (**13**) and 3-bromo-2-chloro-5-*tert*-butyl-1,4-benzoquinone (**14**) were also obtained when 2,6-di-*tert*-butyl-1,4-benzoquinone (**17**) was converted to its monochloro derivative and then treated, respectively, with anhydrous HCl and HBr in glacial acetic acid. Oxidation of the resulting quinols gave the quinones in excellent yields.

Structural Assignments.—The structures of the 2,3-dihalo-5-*tert*-butyl-1,4-benzoquinones **13**–**16** are based upon both spectral (Table I) and chemical data. They all react with excess sodium azide to give the same diazide, 2,3-diazido-5-*tert*-butyl-1,4-benzoquinone (**20**),[4]

(3) L. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1967, p 738.

(4) In general, azidoquinones are readily prepared by treating a dilute alcoholic solution of the corresponding halo-substituted quinone with aqueous sodium azide: H. W. Moore, H. R. Shelden, D. W. Deters, and R. J. Wikholm, *J. Amer. Chem. Soc.*, **92**, 1675 (1970).



thus showing the halogens in the four compounds to be in the same orientation. The monoazide, 3-azido-2-bromo-5-*tert*-butyl-1,4-benzoquinone (**21**), was obtained from 2,3-dibromo- (**16**) or 2-bromo-3-chloro-5-*tert*-butyl-1,4-benzoquinone (**15**) upon treatment with 1 equiv of sodium azide. This monoazide underwent the known[5] thermal rearrangement of azidoquinones to give 2-bromo-2-cyano-4-*tert*-butyl-1,3-cyclopentenedione (**22**), which shows a vinyl proton absorption at 7.08 ppm in its nmr spectrum. The fact that this cyclopentene **22** has a vinyl proton rules out 2-azido-5- or 6-bromo-6- or 5-*tert*-butyl-1,4-benzoquinone as possible structures for the monoazidoquinone **21**, since it is known that the substituent adjacent to the azide function in the azidoquinone is found at the sp^3 2 position of the 1,3-cyclopentenedione.

Rearrangement of the monoazidoquinone **21** to the butenolide **23** in concentrated sulfuric acid also aided in its structural assignment. The vinyl proton absorption in the nmr spectrum of the butenolide appears at 7.34 ppm. This is in agreement with structure **23**, while has its alkene proton β to the carbonyl.[6] Consideration of the mechanism of this known[4] acid catalyzed rearrangement reveals that the substituent in the 5 position of a 2-azido-1,4-benzoquinone is located at the β position in the butenolide. As a result, the only reasonable structure for the butenolide **23** precursor is 2-bromo-3-azido-5-*tert*-butyl-1,4-benzoquinone (**21**). These results strongly imply that the halo substituents in the quinones **13**–**16** are in an adjacent 2,3 orientation. This assignment was confirmed by the independent syntheses of 2,3-dibromo-5-*tert*-butyl-1,4-benzoquinone (**16**) starting from *tert*-butyl-1,4-benzoquinone (**31**) as described later.

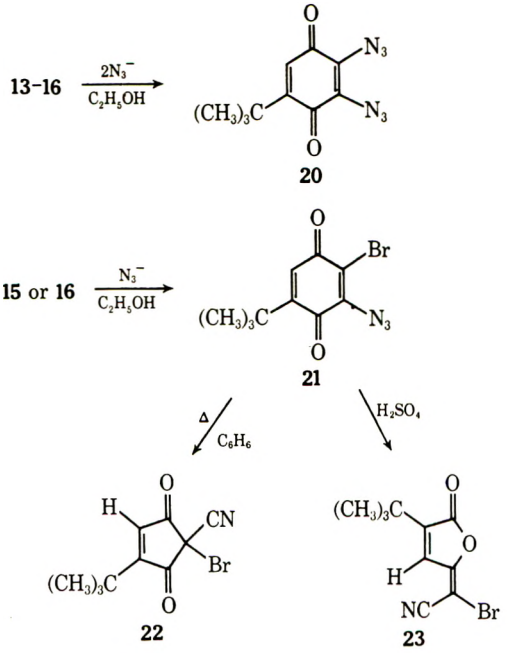
The nmr spectra of the 2,3-dihalo-5-*tert*-butyl-1,4-benzoquinones **13**–**16** are also in accord with their

TABLE I
SPECTRAL PROPERTIES OF NEW COMPOUNDS

Compd	Mp, °C	Ir, cm^{-1}	Nmr, ppm from TMS
5	127–128	1710, 1620	1.25 (9) s, 1.33 (9) s, 4.55 (1) s, 6.21 (1) s
6	112–113	1700, 1620	1.28 (9) s, 1.45 (9) s, 4.85 (1) s, 6.30 (1) s
7	Oil	1680, 1660, 1550	1.30 (9) s, 1.48 (9) s, 6.51 (1) s
8	Oil	1675, 1650, 1550	1.26 (9) s, 1.46 (9) s, 6.43 (1) s
13	89–89.5	1670, 1660, 1580	1.31 (9) s, 6.68 (1) s
14	81–83	1680, 1660, 1580	1.31 (9) s, 6.71 (1) s
15	77–78	1670, 1660, 1570	1.31 (9) s, 6.76 (1) s
16	90–91	1680, 1665, 1575	1.31 (9) s, 6.76 (1) s
18	118–118.5	1685, 1620	1.15 (9) s, 1.46 (9) s, 4.71 (1) d, J = 1.8 Hz, 6.61 (1) d, J = 1.8 Hz
19	Oil	1670, 1550	1.29 (9) s, 1.49 (9) s, 6.50 (1) s
20	104–106	2120, 1670, 1600	1.31 (9) s, 6.50 (1) s
21	71–74	2110, 1660, 1560	1.30 (9) s, 6.77 (1) s
22	91–92	2230, 1700, 1575	1.38 (9) s, 7.08 (1) s
23	102–104	2220, 1780, 1620	1.32 (9) s, 7.34 (1) s
27	167–168	3268, 3333 (sh)	1.25 (9) s, 6.67 (1) s, 6.94 (1) s, 7.32–7.92 (12) m
31	104–107	1700, 1610	1.28 (9) s, 4.60 (2) s, 6.33 (1) s

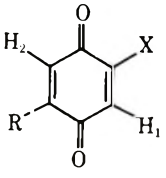
(5) H. W. Moore, W. Weyler, Jr., and H. R. Sheiden, *Tetrahedron Lett.*, 3947 (1969).

(6) The chemical shifts of vinyl protons in the β positions of known γ-cyanoalkylidine-$\Delta^{\alpha,\beta}$-butenolides occur in the range 7.30–7.42 ppm, while those in the α position appear at 4.00–5.67 ppm. See ref 4.



assigned structures. The chemical shifts of the vinyl protons in these compounds appear in the range 6.68–6.75 ppm. This is in good accord with the nmr spectra of other alkylhalo-1,4-benzoquinones having a vinyl proton adjacent to the alkyl substituent (Table II).

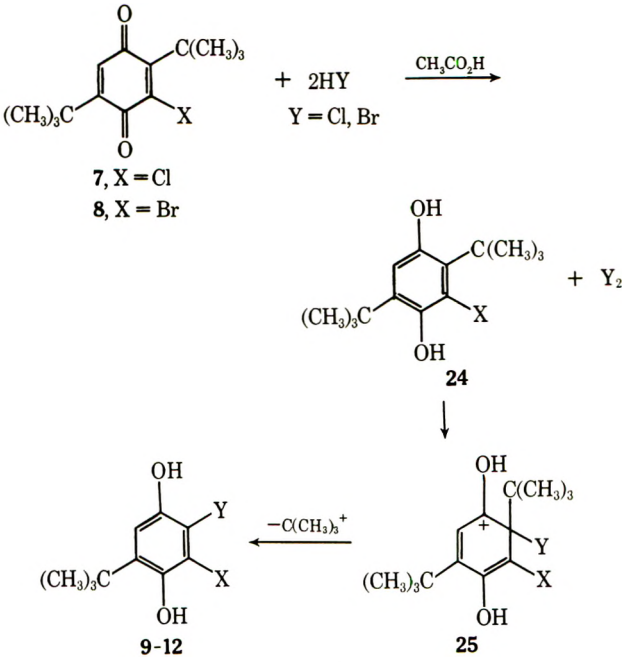
TABLE II[a]
CHEMICAL SHIFTS OF VINYL PROTONS OF ALKYLHALOQUINONES



R	X	H_1	H_2
$(CH_3)_3C$-	Cl	6.88	6.68
$(CH_3)_3C$-	Br	7.10	6.65
CH_3	Cl	6.98	6.73
CH_3	Br	7.25	6.75

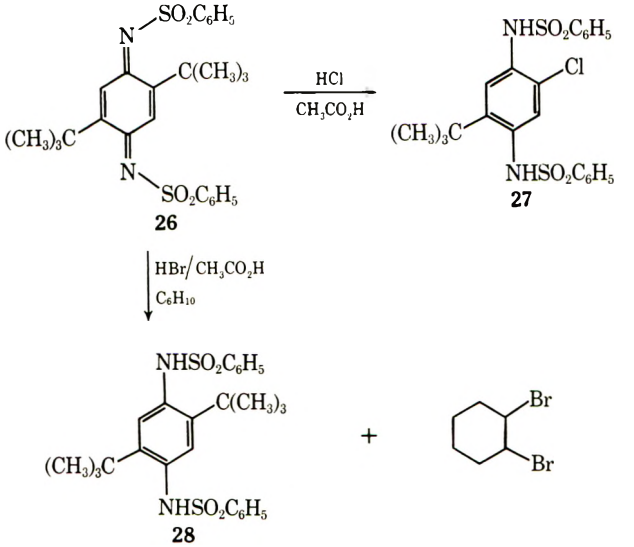
[a] All spectra were obtained for solution of the quinone in CCl_4 solvent.

Mechanism.—The above mechanism is suggested for the de-*tert*-butylation described here. The first step involves an oxidation–reduction to give the hydroquinone **24** and molecular halogen. The hydroquinone then undergoes electrophilic substitution (halogenation) *via* the σ complex **25** to give the hydroquinones **9–12**, which were isolated after N_2O_4 oxidation as the quinones, **13–16**. Data which are consistent with the above mechanism follow. (1) Reaction of 3-bromo-2,5-di-*tert*-butyl-1,4-benzoquinone (**8**) with anhydrous HBr in glacial acetic acid in the presence of excess cyclohexene gave 1,2-dibromocyclohexane (92%) and 3-bromo-2,5-di-*tert*-butyl-1,4-benzoquinol (**24**) (90%). This is in good accord with the first step of the proposed mechanism in which bromine is a product. This oxidation–reduction reaction is of course very dependent upon a balance of redox potentials. This is illustrated by the fact that 2,5-di-*tert*-butyl-1,4-benzoquinone (**4**) does not react with anhydrous HCl in glacial acetic acid. However, this quinone **4** does oxidize anhydrous HBr to bromine under



the same conditions. Substitution of a halogen on the quinone **4** to give **7** or **8** apparently increases their oxidation potential to the point where both hydrohalic acids are oxidized.

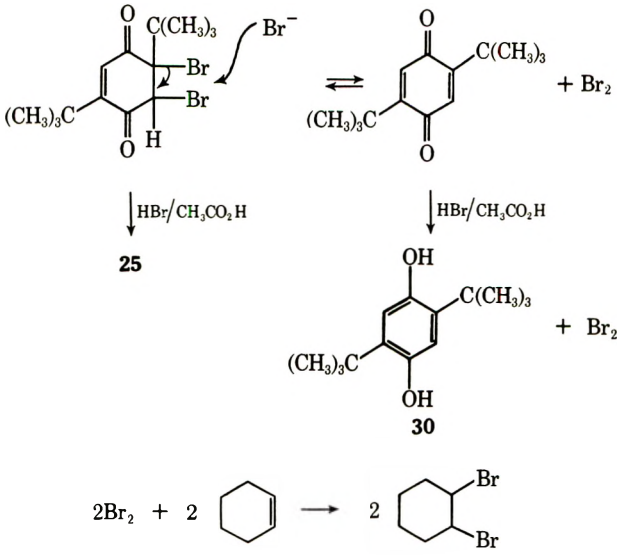
Quinonedibenzenesulfonimides appear to be better oxidizing agents than the corresponding quinones.[7] As a result, one might expect 2,5-di-*tert*-butyl-1,4-benzoquinonedibenzenesulfonimide (**26**)[8] to undergo de-*tert*-butylation upon reaction with HCl in glacial acetic acid. Indeed, such a transformation is readily accomplished. Compound **26** is converted to 5-chloro-2-*tert*-butyl-1,4-benzoquinonedibenzenesulfonamide (**27**) (75%). In addition, when **26** is treated with anhydrous HBr in glacial acetic acid in the presence of excess cyclohexene the reduced diamide **28** and dibromocyclohexane are formed in nearly quantitative yields.



The above transformation of **6** → **12** is not so straightforward as indicated in the preceding reaction scheme. For example, when **6** is treated with anhydrous HBr in glacial acetic acid in the presence of excess cyclohexene, 1,2-dibromocyclohexane (170%, based upon **6** as the

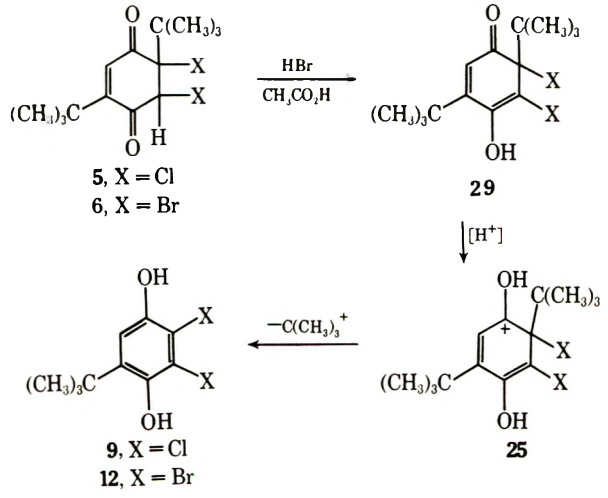
(7) R. Adams and W. Reifschneider, *Bull. Soc. Chim. Fr.*, 23 (1958).
(8) I. Baxter and I. A. Mensah, *J. Chem. Soc. C*, 2604 (1970).

limiting reagent) and 2,5-di-*tert*-butyl-1,4-benzoquinol (**30**) (86%) was formed. Such a transformation can be envisaged as depicted below.

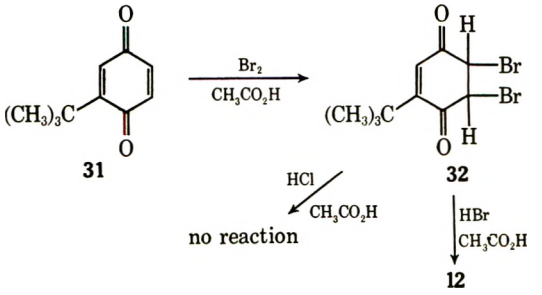


It is, of course, possible that **12** is formed from **6** *via* bromination of the hydroquinone **30**. However, such a reaction sequence is very unlikely for the conversion of the dichlorocyclohexenedione **5** to 2,3-dichloro-5-*tert*-butyl-1,4-benzoquinol (**9**) by the action of anhydrous HBr. For such a reaction sequence to be tenable, at best, a mixture of 2,3-dichloro-, 2,3-dibromo-, 2-bromo-3-chloro-, and 3-bromo-2-chloro-5-*tert*-butyl-1,4-benzoquinol would be anticipated. However, an 80% yield of **9** was obtained. As a result, for the dichloro derivative **5** the σ complex **25** may be generated directly.

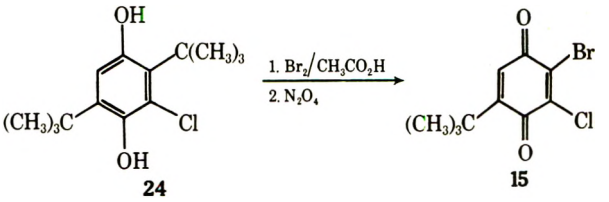
(2) Reaction of the dihalocyclohexenediones **5** and **6** with anhydrous HBr in glacial acetic acid gave, respectively, 2,3-dichloro-5-*tert*-butyl- (**9**) and 2,3-dibromo-5-*tert*-butyl-1,4-benzoquinol (**12**). These transformations presumably arise *via* the σ complex **25**. An acid-catalyzed tautomerism of **5** or **6** would give the dieneone **29**, which upon further protonation would yield the σ complex **25**. Interestingly, these transformations do not take place when **5** or **6** are subjected to the same reaction conditions employing anhydrous HCl as the acid. The fact that HCl is a weaker acid than HBr in acetic acid may account for this observation.



tert-Butyl-1,4-benzoquinone (**31**) reacts with molecular bromine in acetic acid to give the dibromo adduct **32**. This compound is analogous to compound **6** regarding its reactions with HCl and HBr in glacial acetic acid; *i.e.*, it is converted to **12** in the presence of anhydrous HBr but fails to react with anhydrous HCl.



(3) Reaction of 3-chloro-2,5-di-*tert*-butyl-1,4-benzoquinol (**24**) with excess bromine in acetic acid followed by nitrogen oxide gave 2-bromo-3-chloro-5-*tert*-butyl-1,4-benzoquinone (**15**) in excellent yield, thus establishing an analogy for step 2 in the general mechanism presented above.



Experimental Section

2,5-Di-*tert*-butyl-5,6-dichloro-1,4-cyclohexenedione (**5**).—A A 100-g (0.45 mol) portion of 2,5-di-*tert*-butyl-1,4-benzoquinone (**4**) was suspended in 800 ml of glacial acetic acid. Chlorine gas was passed through this vigorously stirred mixture for 50 min. The reaction solution was then allowed to stand at ambient temperature for 4 hr. During this time a white, crystalline precipitate formed and was collected. The mother liquor was poured into water and the resulting white precipitate was collected and combined with the above. The product was dried *in vacuo* to give 127 g (98% yield) of 2,5-di-*tert*-butyl-5,6-dichloro-1,4-cyclohexenedione (**5**), mp 127–128°. The product was readily recrystallized from ether; however, this is not necesssry for the subsequent reactions reported here. It is necessary to avoid hydroxylic solvents and high temperatures (>50°) in the recrystallization; otherwise some dechlorination will result.

Anal. Calcd for $C_{14}H_{20}Cl_2O_2$: C, 57.73; H, 6.92; Cl, 24.35. Found: C, 57.78; H, 6.95; Cl, 24.45.

2,6-Di-*tert*-butyl-5,6-dichloro-1,4-cyclohexenedione (**18**).—A solution of 20 g (0.091 mol) of 2,6-di-*tert*-butyl-1,4-benzoquinone (**17**) in 150 ml of glacial acetic acid was treated with excess chlorine gas for 30 min. The reaction solution was then allowed to stand at ambient temperature for an additional 3 hr and then poured into water. The resulting white, crystalline solid was collected and recrystallized from ice-cold diethyl ether to give 26 g (98%) of **18**, mp 118–118.6°.

Anal. Calcd for $C_{14}H_{20}Cl_2O_2$: C, 57.73; H, 6.92; Cl, 24.35. Found: C, 57.86; H, 6.80; Cl, 24.55.

2,5-Di-*tert*-butyl-5,6-dibromo-1,4-cyclohexenedione (**6**).—A A 10-g (0.045 mol) portion of 2,5-di-*tert*-butyl-1,4-benzoquinone (**4**) was dissolved in 50 ml of glacial acetic acid. A 7-g (0.046 mol) portion of bromine was added and the resulting solution was stirred at room temperature for 12 hr. The resulting light yellow solution was poured into water and the crystalline product was collected. Recrystallization from diethyl ether gave 17 g (97%) of the pale yellow product **6**, mp 112–113°.

Anal. Calcd for $C_{14}H_{20}Br_2O_2$: C, 44.23; H, 5.30; Br, 42.05. Found: C, 44.40; H, 5.34; Br, 41.84.

3-Chloro-2,5-di-*tert*-butyl-1,4-benzoquinone (**7**).—A solution of 118 g (0.41 mol) of 2,5-di-*tert*-butyl-5,6-dichloro-1,4-cyclo-

hexenedione (5) in 1200 ml of anhydrous diethyl ether was cooled to 12°. The solution was vigorously stirred while 30 g (0.41 mol) of diethylamine was slowly added over a period of 10 min. Addition of the base immediately resulted in the precipitation of diethylamine hydrochloride and the formation of a lemon-yellow reaction solution. The reaction mixture was extracted four times with water and dried over sodium sulfate, and the ether was removed *in vacuo* giving 103 g (99%) of **7** as a yellow oil. Vacuum distillation of a small sample gave the analytical sample.

Anal. Calcd for $C_{14}H_{19}ClO_2$: C, 66.00; H, 7.52; Cl, 13.92. Found: C, 66.12; H, 7.47; Cl, 13.88.

3-Chloro-2,6-di-*tert*-butyl-1,4-benzoquinone (19).—A solution of 23 g (0.08 mol) of 2,6-di-*tert*-butyl-5,6-dichloro-1,4-cyclohexenedione (**18**) in 100 ml of diethyl ether was cooled to 0° and 5.9 g (0.08 mol) of diethylamine was slowly added. Diethylamine hydrochloride immediately formed and the solution became yellow. After 10 min the reaction solution was extracted several times with water. The organic layer was then dried over sodium sulfate and the solvent was removed *in vacuo*, leaving 20.8 g of the orange oily quinone **19**. Vacuum distillation of this oil gave 10.6 g (51%) of the analytically pure quinone **19** as a yellow oil.

Anal. Calcd for $C_{14}H_{19}ClO_2$: C, 66.00; H, 7.52; Cl, 13.92. Found: C, 65.83; H, 7.45; Cl, 13.95.

3-Bromo-2,5-di-*tert*-butyl-1,4-benzoquinone (8).—A solution of 48 g (0.126 mol) of 2,5-di-*tert*-butyl-5,6-dibromo-1,4-cyclohexenedione (**6**) in 150 ml of diethyl ether was cooled to 10°. To this vigorously stirred solution was slowly added 9.2 g (0.126 mol) of diethylamine. The reaction mixture was washed four times with water and dried over sodium sulfate, and the solvent was removed *in vacuo*, giving 34 g (96%) of the quinone **8** as a yellow oil. Vacuum distillation of a small sample gave the analytical sample.

Anal. Calcd for $C_{14}H_{19}BrO_2$: C, 56.20; H, 6.40; Br, 26.71. Found: C, 56.41; H, 6.60; Br, 26.59.

2,3-Dichloro-5-*tert*-butyl-1,4-benzoquinone (13). Method A.—Anhydrous HCl was bubbled through a solution of 3 g (0.012 mol) of 3-chloro-2,5-di-*tert*-butyl-1,4-benzoquinone in 50 ml of glacial acetic acid for 30 min. The solution was allowed to stand at ambient temperature for 3 hr and then poured into water. The light yellow oily hydroquinone **9** was extracted into ether. This solution was dried and the solvent was removed *in vacuo*. Glc analysis of this oil showed it to be 86% of the hydroquinone **9**. This oily product was then dissolved in 25 ml of cold chloroform and approximately 3 ml of N_2O_4 was slowly added. The oxidation was complete after 10 min and the excess nitrogen oxides were removed by passing a stream of nitrogen through the reaction mixture for 15 min. The chloroform was dried and removed *in vacuo*, yielding a dark red solid. Recrystallization of this product from 95% ethanol produced 1.8 g (65%) of the quinone **13**, mp 89–89.5°.

Anal. Calcd for $C_{10}H_{10}Cl_2O_2$: C, 51.53; H, 4.32; Cl, 30.42. Found: C, 51.68; H, 4.32; Cl, 30.23.

Method B.—Anhydrous HBr was bubbled through a solution of 10.2 g (0.035 mol) of 2,5-di-*tert*-butyl-5,6-dichloro-1,4-cyclohexenedione (**5**) in 125 ml of glacial acetic acid for 30 min. The reaction solution was allowed to stand at ambient temperatures for an additional 12 hr and then poured into water, giving 10.2 g of the pale yellow hydroquinone **9**. This hydroquinone was oxidized with N_2O_4 as described above to give 7.25 g (80%) of 2,3-dichloro-5-*tert*-butyl-1,4-benzoquinone (**13**) after recrystallization. This compound was identical in all respects with that produced by method A.

Method C.—A 3-g (0.012 mol) portion of 3-chloro-2,6-di-*tert*-butyl-1,4-benzoquinone (**19**) was dissolved in 50 ml of glacial acetic acid. The solution was vigorously stirred while anhydrous HCl was passed through the solution for 45 min. The reaction solution was allowed to stand at room temperature for an additional 3 hr, and then poured into water. The resulting oily hydroquinone **9** was oxidized with N_2O_4 as described above. The resulting quinone **13** was recrystallized from ethanol to give 1.71 g (62%).

2-Chloro-3-bromo-5-*tert*-butyl-1,4-benzoquinone (14).—Anhydrous HCl was rapidly bubbled through a solution of 23 g (0.078 mol) of 3-bromo-2,5-di-*tert*-butyl-1,4-benzoquinone (**8**) in 200 ml of glacial acetic acid for 1 hr. The reaction solution was then poured into water and extracted four times with $CHCl_3$. The combined organic extracts were washed three times with water. The chloroform solution was then dried over anhydrous sodium sulfate and oxidized as described previously with N_2O_4. The chloroform was then removed *in vacuo* to give 18.1 g (85.7%) of the yellow, crystalline quinone **14**, mp 79–83°. This quinone was recrystallized from 95% ethanol to give 16 g (75%) of the pure quinone **14**, mp 81–83°.

Anal. Calcd for $C_{10}H_{10}BrClO_2$: C, 43.27; H, 3.63; Br, 28.81; Cl, 12.77. Found: C, 43.29; H, 3.72; Br, 28.91; Cl, 12.65.

2-Bromo-3-chloro-5-*tert*-butyl-1,4-benzoquinone (15).—Anhydrous HBr was bubbled through a solution of 5.4 g (0.012 mol) of 3-chloro-2,5-di-*tert*-butyl-1,4-benzoquinone (**7**) in 150 ml of glacial acetic acid for 30 min. The reaction solution was allowed to stand at room temperature for an additional 4 hr and then poured into water. The resulting pale yellow oily hydroquinone **11** was dissolved in 25 ml of chloroform and cooled to 0°. An excess, 8 ml, of N_2O_4 was slowly added and the solution was allowed to stand at ambient temperature for an additional 10 min. Nitrogen was vigorously bubbled through the reaction solution for 15 min to remove any excess N_2O_4 and the solvent was then removed *in vacuo*. The resulting red solid was recrystallized from 95% ethanol to give 3.7 g (64%) of the yellow crystalline quinone **15**, mp 77–78°.

Anal. Calcd for $C_{10}H_{10}BrClO_2$: C, 43.27; H, 3.63; Br, 28.81; Cl, 12.77. Found: C, 43.22; H, 3.60; Br, 28.81; Cl, 12.63.

2,3-Dibromo-5-*tert*-butyl-1,4-benzoquinone (16). Method A.—Anhydrous HBr was bubbled through a solution of 3.4 g (0.011 mol) of 3-bromo-2,5-di-*tert*-butyl-1,4-benzoquinone (**8**) in 50 ml of glacial acetic acid for 30 min. The reaction solution was allowed to stand at room temperature for an additional 3 hr and then poured into water. The resulting oily hydroquinone **12** was dissolved in 25 ml of chloroform and cooled to 0°. N_2O_4 (4 ml) was added slowly, resulting in a vigorous reaction which subsided after approximately 10 min. The excess N_2O_4 was then removed by passing a stream of nitrogen through the reaction solution for 15 min. The chloroform was removed *in vacuo* and the resulting red solid was recrystallized from 95% ethanol to give 2 g (55%) of the yellow quinone **16**, mp 90–91°.

Anal. Calcd for $C_{10}H_{10}Br_2O_2$: C, 37.30; H, 3.11; Br, 49.62. Found: C, 37.37; H, 3.07; Br, 49.53.

Method B.—Anhydrous HBr was passed through a solution of 2 g (0.005 mol) of 2,5-di-*tert*-butyl-5,6-dibromo-1,4-cyclohexenedione (**6**) in 50 ml of glacial acetic acid for 30 min. The reaction solution was allowed to stand at ambient temperature for an additional 1 hr and then poured into water. The oily hydroquinone **12** was then oxidized with N_2O_4 as described above to give 1 g (60%) of the purified quinone **16**.

Method C.—A solution of 9.0 g (0.027 mol) of 5,6-dibromo-2-*tert*-butyl-1,4-cyclohexenedione (**32**) in 100 ml of glacial acetic acid was treated with excess anhydrous HBr for 30 min. The reaction solution was then poured into water and the resulting oily hydroquinone **12** was extracted into chloroform. This product was then oxidized with excess N_2O_4 as described above to give 5.2 g (61%) of 2,3-dibromo-5-*tert*-butyl-1,4-benzoquinone (**16**) after recrystallization from 95% ethanol.

2,3-Diazido-5-*tert*-butyl-1,4-benzoquinone (20).—A solution of 4.2 g (15 mmol) of 2,3-dibromo-5-*tert*-butyl-1,4-benzoquinone (**16**) in 50 ml of acetone was treated with 2.0 g (30 mmol) of NaN_3 in 10 ml of water. The resulting deep red solution was stirred at ambient temperature for 20 min and then cooled to 0°, and 100 ml of 95% ethanol was added. The resulting fine red crystalline precipitate was collected, giving 2.85 g (77%) of **20**, mp 104–106°.

Anal. Calcd for $C_{10}H_{10}N_6O_2$: C, 48.78; H, 4.06; N, 34.14. Found: C, 48.92; H, 4.08; N, 33.77.

The same diazide **20** was prepared in a completely analogous manner starting with 2,3-dichloro- (**13**), 2-bromo-3-chloro- (**15**), or 3-bromo-2-chloro-5-*tert*-butyl-1,4-benzoquinone (**14**).

3-Azido-2-bromo-5-*tert*-butyl-1,4-benzoquinone (21).—A solution of 0.284 g (1 mmol) of 2-bromo-3-chloro-5-*tert*-butyl-1,4-benzoquinone in 10 ml of acetone was treated with 0.068 g (1.06 mmol) of NaN_3 in 5 ml of water. After 5 min the product precipitated as a red oil. The oil was dissolved in aqueous ethanol and then the solution was cooled to 0°. The resulting red precipitate was collected, giving 0.142 g (50%) of **21**, mp 71–74°.

Anal. Calcd for $C_{10}H_{10}BrN_3O_2$: C, 42.25; H, 3.52; N, 14.78. Found: C, 42.36; H, 3.55; N, 14.90.

The same azidoquinone **21** could be formed in 64% isolated yield starting with 2,3-dibromo-5-*tert*-butyl-1,4-benzoquinone (**16**).

2-Bromo-2-cyano-4-*tert*-butyl-1,3-cyclopentenedione (22).—A solution of 4.2 g (0.015 mol) of 3-azido-2-bromo-5-*tert*-butyl-1,4-benzoquinone (**21**) in anhydrous toluene was refluxed for 2 hr.

During this time nitrogen evolved and the color of the reaction solution changed from deep red to light orange. The solvent was then removed *in vacuo* and the resulting solid was recrystallized from cyclohexane and then sublimed to give 2.8 g (75%) of **22** as a light orange solid, mp 91–92°.

Anal. Calcd for $C_{10}H_{10}BrNO_2$: C, 46.87; H, 3.90; N, 5.46. Found: C, 46.78; H, 3.99; N, 5.48.

α-*tert*-Butyl-γ-cyanobromomethylene-$\Delta^{\alpha,\beta}$-butenolide (23).—3-Azido-2-bromo-5-*tert*-butyl-1,4-benzoquinone (**21**), 2 g (0.007 mol), was slowly (20 min) added to 40 ml of vigorously stirred cold (0–5°) concentrated sulfuric acid. The reaction solution became a deep blue upon addition of the azide and nitrogen slowly evolved. Upon disappearance of the color the solution was poured into ice water, causing the butenolide to precipitate, yield 1.55 g (86%), mp 102–104. Recrystallization from ether–petroleum ether (bp 30–60°) gave an analytical sample.

Anal. Calcd for $C_{10}H_{10}BrNO_2$: C, 46.87; H, 3.90; N, 5.46; Br, 31.24. Found: C, 46.78; H, 3.87; N, 5.56; Br, 31.13.

Reaction of 3-Bromo-2,5-di-*tert*-butyl-1,4-benzoquinone (8) with HBr in the Presence of Cyclohexene.—3-Bromo-2,5-di-*tert*-butyl-1,4-benzoquinone (**8**) was dissolved in 20 ml of glacial acetic acid and 5 ml of cyclohexene. This solution was vigorously stirred at ambient temperature and saturated with anhydrous HBr. The solution immediately lightened in color and after 2 min it was quenched with water and extracted with diethyl ether. The ether extract was backwashed twice with water and then dried over anhydrous sodium sulfate. The solvent was then removed *in vacuo*, giving a light yellow oil. This oil was analyzed by gas chromatography using known standards of 1,2-dibromocyclohexane and 3-bromo-2,5-di-*tert*-butyl-1,4-benzoquinol, showing 0.337 g (92.5%) of the former and 0.404 g (90.5%) of the latter.

2-Chloro-5-*tert*-butyl-1,4-benzoquinonedibenzenesulfonamide (27).—Anhydrous HCl was bubbled through a solution of 180 mg (0.36 mmol) of 2,5-di-*tert*-butyl-1,4-benzoquinonedibenzenesulfonimide in 10 ml of glacial acetic acid for 4 min and the mixture was then allowed to stand at room temperature for 21 hr. The reaction solution was then poured into ice–H_2O and the resulting white precipitate (130 mg, 75%) was collected and washed with acetic acid, mp 162–166°. Recrystallization from acetone–ether gave the analytical sample.

Anal. Calcd for $C_{22}H_{23}ClN_2S_2O_4$: C, 55.17; H, 4.80; N, 5.85. Found: C, 55.22; H, 4.83; N, 5.98.

Reaction of 2,5-Di-*tert*-butyl-1,4-benzoquinonedibenzenesulfonimide with Anhydrous HBr in the Presence of Cyclohexene.—A suspension of 249 mg (0.52 mmol) of 2,5-di-*tert*-butyl-1,4-benzoquinonedibenzenesulfonimide (**26**) in 7 ml of glacial acetic acid and 4 ml of cyclohexene was treated with anhydrous HBr for 3 min. The reaction solution was then allowed to stand at ambient temperature for 7 hr. During this time the original yellow color disappeared and a white solid precipitated. The reaction solution was poured into water and basified with 1% NaOH. An ether extract of this mixture was analyzed by vpc, which showed 1,2-dibromocyclohexane. The basic solution was acidified with dilute HCl. The white solid (230 mg, 92%), mp 261–264°, was collected and recrystallized from acetone, giving pure 2,5-di-*tert*-butyl-1,4-benzoquinonedibenzenesulfonamide, mp and mmp 265–266°.

2-*tert*-Butyl-5,6-dibromo-1,4-cyclohexenedione (32).—A solution of 10 g (0.061 mol) of 2-*tert*-butyl-1,4-benzoquinone (**31**) was dissolved in 100 ml of glacial acetic acid. This solution was then treated with 9.7 g (0.061 mol) of bromine. The halogen was added over a period of 2 min. The bromine immediately reacted with the quinone, as evidenced by the disappearance of the bromine color. The reaction solution was then poured into water and the resulting precipitate was filtered to give 18.9 g (91%) of the dibromo derivative **32**, mp 103–106°. Recrystallization from diethyl ether gave 12.8 (61%), mp 104–106°.

Anal. Calcd for $C_{10}H_{12}Br_2O_2$: C, 33.63; H, 3.36; Br, 49.38. Found: C, 33.58; H, 3.42; Br, 49.27.

Reaction of 2,3-Dibromo-2,5-di-*tert*-butyl-1,4-cyclohexenedione (6) with HBr/CH_3CO_2H in the Presence of Cyclohexene.—2,3-Dibromo-2,5-di-*tert*-butyl-1,4-cyclohexenedione (**6**) (4.0 g, 0.0105 mol) was dissolved in 75 ml of glacial acetic acid and 10 ml of cyclohexene. Anhydrous HBr was slowly passed through the vigorously stirred solution for 45 min. The reaction was then quenched with water and extracted twice with ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, and concentrated by removal of the solvent *in vacuo* to give 2.0 g (86%) of 2,5-di-*tert*-butyl-1,4-benzoquinol (**30**). This hydroquinone **30** was identified by comparison of its ir spectrum with that of an authentic sample as well as by a mixture melting point. The mother liquor contained 4.3 g (170%) of 1,2-dibromocyclohexane as determined by glc analysis.

Registry No.—**5**, 33611-72-2; **6**, 34403-11-7; **7**, 33611-70-0; **8**, 33611-71-1; **13**, 34403-14-0; **14**, 34403-15-1; **15**, 34403-16-2; **16**, 25762-86-1; **18**, 34403-18-4; **19**, 34403-19-5; **20**, 34403-20-8; **21**, 34403-21-9; **22**, 34403-22-0; **23**, 34403-23-1; **27**, 34403-24-2; **28**, 30221-31-9; **31**, 24197-48-6.

The Ortho Alkylation of Anisole

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Aluminum chloride catalyzed alkylation of anisole with a series of olefins and with γ-valerolactone is demonstrated to result primarily in the formation of ortho-substituted products. The extent of ortho alkylation is shown to be a function of solvent and of basic functionality in the alkylating agent.

The aluminum chloride catalyzed alkylation of aromatic compounds with olefins[2] and γ-lactones[3] is a well-documented reaction. Application of this reaction to anisole has generally been reported to result in a mixture of ortho and para isomers, with the para isomer predominating.[2] An unusual exception exists in the literature, however. This consists of a report that reaction of anisole with ethyl allylmalonate in the presence of $AlCl_3$ affords a product consisting of approximately 90% of the ortho isomer.[4] In view of this, we have carefully examined the isomer distribution produced on $AlCl_3$-catalyzed alkylation of anisole with a series of olefins and with γ-valerolactone (**7**). The results (Table I) demonstrate that, with all those alkylating agents studied, the ortho isomer is either the principal or nearly by exclusive alkylation product.

(1) National Science Foundation College Teacher Research Participant summer 1970.

(2) (a) S. H. Patinkin and B. S. Friedman in "Friedel–Crafts and Related Reactions," Vol. II, Part 1, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, Chapter XIV; (b) R. Koncos and B. S. Friedman, Chapter XV.

(3) (a) J. F. Eijkman, *Chem. Zentr.*, **75**, I, 1416 (1904); (b) R. T. Arnold, J. S. Buckley, and J. Richter, *J. Amer. Chem. Soc.*, **69**, 2322 (1947); (c) R. V. Christian, *ibid.*, **74**, 1591 (1952); (d) W. L. Mosby, *ibid.*, **74**, 2564 (1952); (e) W. E. Truce and C. E. Olson, *ibid.*, **74**, 4721 (1952); (f) D. B. Bruce, A. J. S. Sorrie, and R. H. Thomson, *J. Chem. Soc.*, 2403 (1953); (g) J. I. Brauman and A. J. Pandell, *J. Amer. Chem. Soc.*, **89**, 5421 (1967); (h) D. W. Waples and J. I. Brauman, *Chem. Commun.*, 1075 (1971); (i) E. J. Eisenbraun, C. W. Hinman, J. M. Springer, J. W. Burnham, and T. S. Chou, *J. Org. Chem.*, **36**, 2480 (1971).

(4) A. S. Gupta, K. L. Murthy, and S. Dev, *Tetrahedron*, **23**, 2481 (1967).

TABLE I

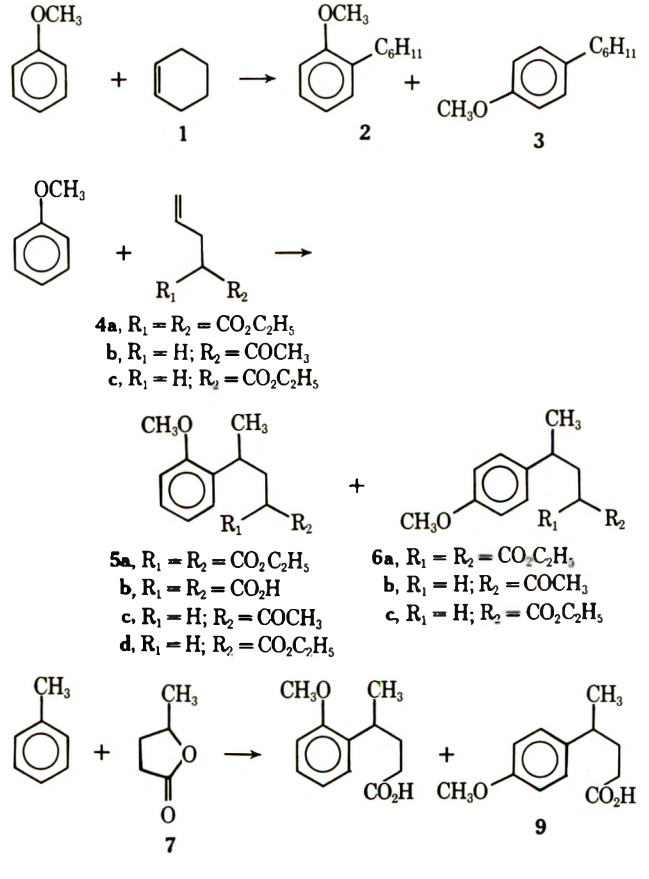
ALUMINUM CHLORIDE CATALYZED ALKYLATION OF ANISOLE

Alkylating agent	Product	Solvent	Time, hr[a]	Isolated yield, %	Isomer distribution, %[b] Ortho	Para
Cyclohexene (1)	$CH_3OC_6H_4(C_6H_{11})$	Hexane	3	63	66	34
		Anisole	3	78	64 (68[c])	36 (32[c])
Ethyl allylmalonate (4a)	$CH_3OC_6H_4CH(CH_3)CH_2CH(CO_2C_2H_5)_2$	Hexane	31	31	86	14
		Anisole	16	36	65[c]	35[c]
		1-Nitropropane	24	30	55[c]	45[c]
5-Hexen-2-one (4b)	$CH_3OC_6H_4CH(CH_3)CH_2CH_2COCH_3$	Hexane	25	33	97 (98[d])	3 (2[d])
		Anisole	2	10	94	6
		Anisole	6.3	20	93[e]	7[e]
Ethyl 4-pentenoate (4c)	$CH_3OC_6H_4CH(CH_3)CH_2CH_2CO_2C_2H_5$	Hexane	19	40	95	5
		Anisole	2.5[f]	2.4	86	14
		Anisole	18	23	87 (82[c])	13 (18[c])
γ-Valerolactone (7)	$CH_3OC_6H_4CH(CH_3)CH_2CH_2CO_2H$	Hexane	12[g]	24	81	19
		Anisole[h]	1.8[i]	41	67	33

[a] At room temperature unless otherwise incidcated. [b] Per cent of isolated product determined by nmr except where indicated. [c] Determined by gas chromatography on a 5 ft × 0.25 in. column packed with 15% silicone SF-96 on Chromosorb P. [d] Determined by gas chromatography on a 5 ft × 0.25 in. column packed with 15% Carbowax 20M on Chromosorb P. [e] Determined by gas chromatography on a 15 ft × 0.25 in. column packed with 10% silicone QF-1 on Chromosorb P. [f] At ice bath temperature. [g] At reflux. [h] A 1.00:0.50:0.52 mole ratio of anisole:γ-valerolactone:$AlCl_3$ was employed in this reaction. [i] At 90–100° bath temperature.

The alkylations were carried out using either hexane, excess anisole, or 1-nitropropane as a diluent. Reactions in hexane were conducted with a 1.28:1.00:0.20 mole ratio of $AlCl_3$:anisole:alkylating agent and were heterogeneous. Under these conditions, ethyl allylmalonate (**4a**), 5-hexen-2-one (**4b**), ethyl 4-pentenoate (**4c**), and γ-valerolactone (**7**) each afforded an alkylation product consisting of >80% of the ortho isomer. The essentially exclusive (98%) ortho alkylation obtained with 5-hexen-2-one (**4b**) appears to be without precedent. Cyclohexene (**1**), however, afforded only a modest 66% of the ortho isomer (Scheme I).

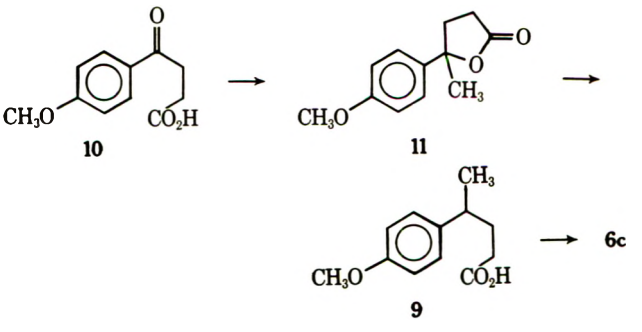
SCHEME I



When excess anisole was substituted for hexane as the solvent, a ratio of $AlCl_3$:anisole:alkylating agent of 0.20:1.00:0.10 was employed, and the reaction mixtures were homogeneous. The stereoselectivity of the reaction was reduced under these conditions with each alkylating agent except cyclohexene (**1**). This reduction in stereoselectivity is not large for 5-hexen-2-one (**4b**), which still affords 93–94% of the ortho isomer.[5] Alkylation with ethyl allylmalonate (**4a**) in excess anisole, however, demonstrates a somewhat more dramatic reduction in the stereoselectivity of alkylation. In the single experiment employing 1-nitropropane as solvent, the ratio of $AlCl_3$:anisole:ethyl allylmalonate (**4a**) was the same as that used for reactions carried out in hexane. This reaction demonstrates a further reduction in stereoselectivity to a point where the amounts of ortho and para isomers formed are essentially equal.

4-(*p*-Methoxyphenyl)valeric acid (**9**) and its ethyl ester **6c**, obtained as products in the reaction of anisole with γ-valerolactone (**7**) and ethyl 4-pentenoate (**4c**) respectively, were identified by comparison with authentic compounds prepared by independent synthesis (Scheme II). Conversion of keto acid **10** to γ-lactone

SCHEME II



11 was accomplished in 67% yield by reaction with 2.1 equiv of methylmagnesium iodide. Subsequent hydrogenolysis of **11** afforded 4-(*p*-methoxyphenyl)valeric

(5) The product of reaction of 5-hexen-2-one with anisole under similar conditions has been previously described in the literature[6] but was incorrectly regarded as consisting exclusively of the para isomer.

(6) S. M. Mukherji, O. P. Vig, and N. K. Maheshwary, *J. Indian Chem. Soc.*, **34**, 9 (1957).

acid (9). Fischer esterification with ethanol and sulfuric acid then gave the corresponding ethyl ester **6c**.

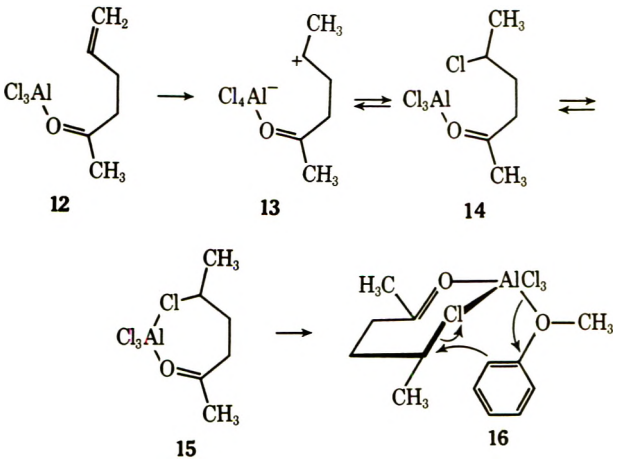
4-(*o*-Methoxyphenyl)valeric acid (**8**) and its ethyl ester **5d** were also identified by comparison with authentic compounds. Reaction products resulting from alkylation of anisole with cyclohexene (**1**), ethyl allylmalonate (**4a**), and 5-hexen-2-one (**4b**) were identified by isolation and characterization.

Discussion

The exclusive or nearly exclusive electrophilic ortho substitution of aromatic compounds is an uncommon reaction with interesting synthetic potential. Reactions of this type include the Kolbe–Schmitt reaction,[7] alkylation of phenol[8] and aromatic amines[9] with olefins, bromination of phenol,[10] and thallation of suitably substituted benzene derivatives.[11] A cyclic mechanism has been proposed for each of these examples.

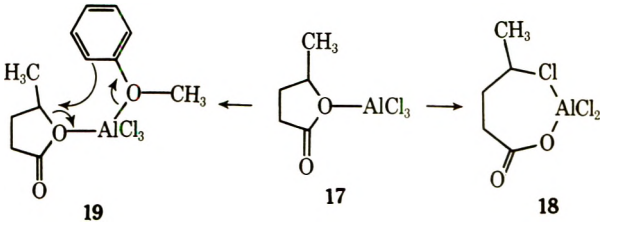
The results in Table I indicate that, with properly chosen alkylating agents, the $AlCl_3$-catalyzed alkylation of anisole represents still another example of near exclusive ortho substitution. The fact that extensive ortho alkylation is observed only with those alkylating agents which represent potential sources of reactive intermediates carrying a positive charge γ to a carbonyl, carbethoxy, or carboxyl group suggests that the oxygen-containing functional groups assume more than a passive role in the reaction. In hexane solution, the amount of $AlCl_3$ used was slightly greater, on a mole basis, than the combined amounts of anisole and alkylating agent. In view of the ability of $AlCl_3$ to form stable complexes with ethers, ketones, and esters,[12] it may be assumed that little free anisole or alkylating agent is present. The unusual amount of ortho alkylation further suggests that both reactants may be associated with the same aluminum atom and that the alkylating agent is delivered through a cyclic process. In the case of 5-hexen-2-one (**4b**) (Scheme III), the coordinated ketone **12** could react with adventitious HCl to give species such as **13**, **14**, or **15**.[13] Structure **15** may be the best representation, however, since the chelate structure would be anticipated to afford a modest amount of stability. Coordination of anisole with $AlCl_3$ should reduce its reactivity toward electrophilic reagents and, in addition, any increase in electrophile

SCHEME III



stability would be expected to further reduce the rate of reaction. Therefore, although attack by **15** on the $AlCl_3$·anisole complex should produce a mixture of ortho and para products, the rate of reaction should not be large. Alternatively, coordination of a molecule of anisole with the aluminum of **15** would afford **16** in which ortho alkylation of the aromatic ring could take place by way of a six-center cyclic mechanism. A similar sequence of events can also be postulated for esters **4a** and **4c**. γ-Valerolactone (**7**), however, requires a slight modification (Scheme IV). In this case, cleavage

SCHEME IV



of the lactone ring could provide the intermediate **18**,[3g] which is analogous to **15**. Coordination of one or two molecules of anisole with the aluminum atom of **18** would then permit ortho alkylation to proceed by way of a cyclic process as depicted for **16**. Alternatively, coordination of anisole with the aluminum atom of **17** would afford **19**, which could also permit an intramolecular delivery of the alkylating agent. The relatively low yield (81%) of ortho product **8** obtained in this reaction may be a consequence of the higher reaction temperature required.

Reduction of the stereoselectivity produced by use of excess anisole as solvent is presumably a result of the availability of substantial amounts of free anisole. The free anisole should be more reactive than the $AlCl_3$·anisole complex toward electrophilic reagents and result in an increase in the extent of intermolecular reaction, which would be anticipated to be less stereoselective than an intramolecular process. The independence of isomer ratio from reaction time in anisole solution for both **4b** and **4c** suggests that selective destruction of one isomer is not responsible for the still substantial amount of ortho product obtained.

Transition to 1-nitropropane as the solvent would be expected to result in a low ortho/para ratio as a result

(7) A. S. Lindsey and H. Jeskey, *Chem. Rev.*, **57**, 583 (1957).

(8) (a) A. J. Kolka, J. P. Napolitano, A. H. Filbey, and G. G. Ecke, *J. Org. Chem.*, **22**, 642 (1957); (b) R. Stroh, R. Seydel, and W. Hahn, *Angew. Chem.*, **69**, 699 (1957); (c) E. A. Goldsmith, M. J. Schlatter, and W. G. Toland, *J. Org. Chem.*, **23**, 1871 (1958).

(9) (a) G. G. Ecke, J. P. Napolitano, A. H. Filbey, and A. J. Kolka, *ibid.*, **22**, 639 (1957); (b) R. Stroh, J. Ebersberger, H. Haberland, and W. Hahn, *Angew. Chem.*, **69**, 124 (1957).

(10) D. E. Pearson, R. D. Wysong, and C. V. Breder, *J. Org. Chem.*, **32**, 2358 (1967).

(11) E. C. Taylor, F. Kienzle, R. L. Robey, A. McKillop, and J. D. Hunt, *J. Amer. Chem. Soc.*, **93**, 4845 (1971).

(12) N. N. Greenwood and K. Wade in "Friedel–Crafts and Related Reactions," Vol. I, G. A. Olah, Ed., Interscience, New York, N. Y., 1963, Chapter VII.

(13) Stable compounds containing four-coordinate and six-coordinate aluminum are well known.[14] Five-coordination of aluminum is less common, but examples have been documented.[15] Therefore, postulation of a five-coordinate aluminum compound as a reactive intermediate, such as **13** or **15**, does not appear unreasonable.

(14) P. J. Durrant and B. Durrant, "Introduction to Advanced Inorganic Chemistry," 2nd ed, Wiley, New York, N. Y., 1970, pp 564–579.

(15) (a) I. Pattison and K. Wade, *J. Chem. Soc. A*, 2618 (1968); (b) C. W. Heitsch and R. N. Kniseley, *Spectrochim. Acta*, **19**, 1385 (1963); (c) G. W. Fraser, N. N. Greenwood, and B. P. Straughan, *J. Chem. Soc.*, 3742 (1963).

of competition between solvent and anisole for coordination sites on aluminum. Under these conditions, intramolecular delivery of alkylating agent should be almost entirely suppressed in favor of an intermolecular reaction pathway. This appears to be substantiated by the reaction of ethyl allylmalonate (**4a**) with anisole in this solvent to provide only 55% of ortho product **5a**.

The relatively small amount of ortho product obtained with cyclopentene,[16] where it represents the minor product, and with cyclohexene (64–68%) argues strongly against the operation of a cyclic mechanism where participation by a neighboring oxygen-containing functional group is not possible. The apparent lack of solvent dependence of the isomer distribution in the case of cyclohexene provides additional evidence for the importance of such neighboring functionality. The composite of these results indicates that upon proper selection of an alkylating agent, manipulation of the reaction conditions can afford a substantial degree of control over the orientation of substitution.

Experimental Section[17]

Analyses.—Analyses were accomplished either by integration of the nmr singlets produced by methoxyl protons of the isomeric products or by gas chromatography.

4-(*p*-Methoxyphenyl)-4-hydroxyvaleric Acid Lactone (11).—A solution of methylmagnesium iodide was prepared under nitrogen by dropwise addition of 73.0 g (0.515 mol) of methyl iodide in 350 ml of anhydrous ether to a flask containing 13.11 g (0.540 g-atom) of magnesium turnings over a period of 2 hr with mechanical stirring at ice bath temperature. Stirring was continued at room temperature for an additional 45 min after addition was complete. After cooling again at ice bath temperature, a solution of 50.0 g (0.240 mol) of 3-(*p*-methoxybenzoyl)propionic acid (**10**),[18] mp 148.5–150.0°, in 1 l. of tetrahydrofuran (freshly distilled from $LiAlH_4$) was added dropwise over a period of 110 min with mechanical stirring. The mixture was then heated at reflux under nitrogen with mechanical stirring for 14 hr. After cooling, the mixture was decomposed with 800 ml of 3 *M* HCl. The aqueous layer was separated and extracted twice with 700-ml portions of ether. The combined ether layers were washed once with 300 ml of 5% sodium bisulfite solution, once with 500 ml of water, once with 300 ml of 10% aqueous K_2CO_3, once with 500 ml of water, and once with 300 ml of saturated sodium chloride solution, and dried over anhydrous $MgSO_4$. Removal of solvent *in vacuo* afforded 34.05 g of brown oil which was fractionated through a 9-cm Vigreux column to give 25.2 g (51%) of γ-lactone **11** as a pale yellow oil, bp 137.0–139.0° (0.30 mm) [lit.[4] bp 140–142° (1.5–2 mm)]. Acidification of the potassium carbonate wash afforded 12.1 g of recovered 3-(*p*-methoxybenzoyl)propionic acid (**10**), mp 145.0–148.0°, indicating a 67% yield of γ-lactone **11** based on recovered starting material.

4-(*p*-Methoxyphenyl)valeric Acid (9).—Hydrogenolysis of 25.18 g (0.122 mol) of γ-lactone **11** over 3.00 g of 5% palladium on carbon powder at 60 psi in 200 ml of absolute ethanol was complete after 2 hr. After filtration, concentration of the filtrate *in vacuo* followed by distillation of the residue afforded 22.64 g (89%) of 4-(*p*-methoxyphenyl)valeric acid (**9**) as a colorless oil which solidified on standing: bp 135.0–139.0° (0.2 mm); mp 38.0–40.5° (lit.[4] mp 39–40.5°); nmr (CCl_4) δ 1.22 (3 H, d J = 7 Hz, $CHCH_3$), 3.68 (3 H, s, OCH_3) and 6.57–7.15 (4 H, symmetrical A_2B_2 m, aromatic CH).

Ethyl 4-(*p*-Methoxyphenyl)valerate (6c).—To a solution of 3.040 g (14.6 mmol) of 4-(*p*-methoxyphenyl)valeric acid (**9**) in 25.0 ml of absolute ethanol was added 0.50 ml of concentrated sulfuric acid and the mixture was heated at reflux for 6.5 hr. After cooling, the resulting mixture was diluted with 75 ml of water and extracted with 75 ml of benzene. The benzene extract was washed once with 75 ml of saturated $NaHCO_3$ solution and once with 75 ml of water, and dried over anhydrous $MgSO_4$. Concentration of the resulting solution *in vacuo* followed by distillation afforded 3.019 g (88%) of ethyl 4-(*p*-methoxyphenyl)valerate (**6c**) as a colorless liquid: bp 112.0–116.0° (0.4 mm); ir (neat) 1734 (ester C=O) and 836 cm^{-1} (aromatic CH); nmr (CCl_4) δ 1.17 (3 H, t, J = 7 Hz, CH_2CH_3), 1.21 (3 H, d, J = 7 Hz, $CHCH_3$), 3.68 (3 H, s, OCH_3), 4.00 (2 H, q, J = 7 Hz, OCH_2CH_3), and 6.58–7.17 (4 H, symmetrical A_2B_2 m, aromatic CH).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.31; H, 8.76.

4-(*o*-Methoxyphenyl)valeric Acid (8).—Using the procedure of Fourneau and Baranger,[19] pure **8** was obtained as large white crystals: mp 66.0–67.0° (lit.[4,19] mp 63–65°); nmr (CCl_4) δ 1.22 (3 H, d, J = 7 Hz, $CHCH_3$), 3.74 (3 H, s, OCH_3), and 6.60–7.25 (4 H, complex, m, aromatic CH).

Ethyl 4-(*o*-Methoxyphenyl)valerate (5d).—Using the procedure employed for the para isomer, 4-(*o*-methoxyphenyl)-valeric acid (**8**) was converted to the ethyl ester **5d**, which was obtained in 90% yield as a colorless liquid: bp 98.0–99.0° (0.25 mm); ir (neat) 1735 (ester C=O) and 760 cm^{-1} (aromatic CH); nmr (CCl_4) δ 1.16 (3 H, t, J = 7 Hz, CH_2CH_3), 1.20 (3 H, d, J = 7 Hz, $CHCH_3$), 3.74 (3 H, s, OCH_3), 3.99 (2 H, q, J = 7 Hz, OCH_2CH_3), and 6.62–7.24 (4 H, complex m, aromatic CH).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.49; H, 8.45.

Oxidation of 0.493 g (2.09 mmol) of **5d** with 3.004 g (19.0 mmol) of $KMnO_4$ in 60 ml of 0.32% aqueous NaOH afforded 0.050 g of crude acidic product. Sublimation (85° bath temperature at 0.35 mm) followed by crystallization from benzene–hexane afforded 0.035 g (11%) of *o*-methoxybenzoic acid, mp 102.5–104.0°, undepressed on admixture with authentic material.

Alkylation of Anisole with 5-Hexen-2-one (4b) in Excess Anisole.—The following preparation is representative of the general procedure using excess anisole as the solvent. Under a $CaCl_2$ drying tube, 26.7 g (0.20 mol) of anhydrous aluminum chloride was added to 108.1 g (1.00 mol) of anisole with mechanical stirring over a period of 11 min. To this was added a solution of 9.815 g (0.10 mol) of 5-hexen-2-one (**4b**) in 10.0 g (0.093 mol) of anisole over a period of 28 min at room temperature with stirring. Stirring was then continued at room temperature for 6.3 hr. The resulting brown mixture was decomposed with 100 g of ice and extracted with 100 ml of hexane. The hexane extract was washed with four 100-ml portions of water and dried over anhydrous $MgSO_4$. Hexane was removed at aspirator pressure, and the residue was fractionated through a 10-cm Vigreux column to give 4.019 g (20%) of 5-anisylhexan-2-one, bp 95.0–102.0° (0.4 mm). Gas chromatography[20] indicated the presence of two isomers in a 93:7 ratio.

The principal component, 5-(*o*-methoxyphenyl)hexan-2-one (**5c**), was obtained as a colorless liquid after preparative gas chromatography[20] followed by short path distillation (0.2 mm and 92° bath): ir (neat), 1717 (C=O) and 760 cm^{-1} (aromatic CH); nmr (CCl_4) δ 1.18 (3 H, d, J = 7 Hz, $CHCH_3$), 1.90 (3 H, s, $COCH_3$), 3.73 (3 H, s, OCH_3), and 6.62–7.24 (4 H, complex m, aromatic CH).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.87; H, 8.69.

The minor component, 5-(*p*-methoxyphenyl)hexan-2-one (**6b**), was obtained as a pale yellow liquid after preparative gas chromatography[20] followed by short path distillation (0.2 mm and 95° bath): ir (neat) 1715 (C=O) and 836 cm^{-1} (aromatic CH); nmr (CCl_4) δ 1.18 (3 H, d, J = 7 Hz, $CHCH_3$), 1.90 (3 H, s, $COCH_3$), 3.68 (3 H, s, OCH_3), and 6.62–7.17 (4 H, symmetrical A_2B_2 m, aromatic CH).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.65; H, 8.53.

Alkylation of Anisole with Cyclohexene (1) in Hexane.—The following preparation is representative of the general procedure

(16) P. Cagniant, A. Deluzarche, and G. Chatelus, *C. R. Acad. Sci.*, **224**, 1064 (1947).

(17) Melting points are uncorrected. The infrared spectra were recorded with either a Beckman IR-8 or a Perkin-Elmer 257 infrared spectrophotometer. Nmr spectra were determined with a Varian A-60 spectrometer using tetramethylsilane as internal standard. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich.

(18) Y. S. Rao and R. A. Kretchmer, *Org. Prep. Proced. Int.*, **3**, 177 (1971).

(19) E. Fourneau and P. M. Baranger, *Bull. Soc. Chim. Fr.*, **49**, 1161 (1931).

(20) A 15 ft × 0.25 in. column packed with 10% silicone QF-1 on Chromosorb P was employed.

using hexane as the solvent. Under a $CaCl_2$ drying tube, 85.0 g (0.64 mol) of anhydrous aluminum chloride was added to a solution of 54.0 g (0.50 mol) of anisole in 140 ml of hexane over a period of 12 min with mechanical stirring. To this was added a solution of 8.22 g (0.10 mol) of cyclohexene (1) in 10.0 ml of hexane over a period of 67 min with stirring. The resulting mixture was stirred at room temperature for 3 hr, then decomposed with 100 g of ice. The organic layer was separated, washed five times with 100-ml portions of water, and dried over anhydrous $MgSO_4$. The solution was concentrated *in vacuo* and the residue was fractionated through a 10-cm Vigreux column to give 11.98 g (63%) of cyclohexylanisole, bp 108.5–117.0° (2.5 mm). Integration of the nmr singlets at δ 3.68 and 3.63 indicated a 66:34 mixture of ortho and para isomers.

The major isomer, *o*-cyclohexylanisole (2), was isolated from the product of an analogous reaction by preparative gas chromatography[21] as a colorless liquid, ir (neat) 760 cm^{-1} (aromatic CH). The minor isomer, *p*-cyclohexylanisole (3), was obtained in similar fashion as a white solid, mp 55–56° (lit.[22] mp 57–58°), ir (KBr) 824 cm^{-1} (aromatic CH).

Ethyl [2-(Methoxyphenyl)propyl]malonate.—The minor (35%) isomer, ethyl [2-(*p*-methoxyphenyl)propyl]malonate (6a), produced on monoalkylation of anisole with ethyl allylmalonate (4a) in excess anisole, was isolated after preparative gas chromatography[21] and short path distillation (0.5 mm and 160° bath) as a colorless liquid: ir (neat) 1748, 1732 (ester C=O), and 836 cm^{-1} (aromatic CH); nmr (CCl_4) δ 1.18 (3 H, t, J = 7 Hz, CH_2CH_3), 1.24 (3 H, t, J = 7 Hz, CH_2CH_3), 1.24 (3 H, d, J = 7 Hz, $CHCH_3$), 3.71 (3 H, s, OCH_3), 4.04 (2 H, q, J = 7 Hz, OCH_2CH_2), 4.12 (2 H, q, J = 7 Hz, OCH_2CH_3), and 6.60–7.15 (4 H, symmetrical A_2B_2 m, aromatic CH).

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.57; H, 7.86.

The major (65%) isomer, ethyl [2-(*o*-methoxyphenyl)propyl]malonate (5a), was also isolated by preparative gas chromatography[21] as a colorless liquid: ir (neat) 1750, 1734 (ester C=O), and 760 cm^{-1} (aromatic CH); nmr (CCl_4) δ 1.14 (3 H, t, J = 7 Hz, CH_2CH_3), 1.18 (3 H, t, J = 7 Hz, CH_2CH_3), 1.22 (3 H, d, J = 7 Hz, $CHCH_3$), 3.73 (3 H, s, OCH_3), 4.02 (2 H, q, J = 7 Hz, OCH_2CH_2), 4.11 (2 H, q, J = 7 Hz, OCH_2CH_3), and 6.67–7.30 (4 H, complex m, aromatic CH). Characterization was accomplished by saponification to [2-(*o*-methoxyphenyl)-propyl]malonic acid (5b), mp 148.0–149.5° dec (lit.[4] mp 143–144°).

(21) A 5 ft × 0.25 in. column packed with 15% silicone SF-96 on Chromosorb P was employed.

(22) D. Bodroux, *Ann. Chim. (Paris)*, **11**, 511 (1929).

Registry No.—**1**, 110-83-8; **4a**, 2049-80-1; **4b**, 109-49-9; **4c**, 1968-40-7; **5a**, 34399-51-4; **5c**, 34399-52-5; **5d**, 34399-53-6; **6a**, 34399-54-7; **6b**, 34399-55-8; **6c**, 34399-56-9; **7**, 108-29-2; **10**, 3153-44-4; $AlCl_3$, 7446-70-0; anisole, 100-66-3.

General Acid Catalysis of Ortho Ester Hydrolysis

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The rates of hydrolysis of diethylphenyl orthoformate, diphenylethyl orthoformate, and diphenylethyl orthoacetate have been determined in 50% dioxane–H_2O (v/v) at 25 and 45°. A pronounced general acid catalysis is observed in the hydrolysis of these compounds. The value of the Brønsted coefficient α is 0.47, 0.68, and 0.49, respectively. Thus, general acid catalysis is more favorable with very weak acids in the case of diethylphenyl orthoformate in comparison with diphenylethyl orthoformate even though the latter compound is of lower basicity. This is due to the more stable oxocarbonium ion produced from diethylphenyl orthoformate which causes the bond-breaking process to be more facile.

It has long been known that certain types of ortho esters are subject to general acid catalyzed hydrolysis in aqueous solution.[2] The pseudo-first-order rate constants for hydrolysis of ethyl orthocarbonate, ethyl orthoacetate, and ethyl orthopropionate are dependent on buffer acid concentration at constant pH.[2] The hydrolysis of methyl orthobenzoate was reported to be catalyzed by general acids in aqueous methanol,[3] and general acid catalysis was claimed for hydrolysis of triethyl orthoformate in 70% dioxane–H_2O but not in H_2O.[4] However, it has recently been shown that this result was possibly due to specific salt effects in aqueous dioxane.[5] Bunton and DeWolfe[6] stressed relatively low basicity of ortho esters as a feature responsible for general acid catalysis. The Brønsted coefficient α for general acid catalyzed hydrolysis of ethyl orthocarbonate[2,7] and also methyl orthobenzoate[3] is approximately 0.7. It has been considered that ortho ester hydrolysis will generally be characterized by high α values.[8]

General acid catalysis has also been observed in acetal and ketal hydrolysis with 2-(substituted phenoxy)-tetrahydropyrans,[9] tropone diethyl ketal,[10] and benzaldehyde di-*tert*-butyl acetals.[11] Electron withdrawal in the leaving group of a phenoxytetrahydropyran will both lower basicity and increase the ease of C–O bond breaking. With tropone diethyl ketal[10] the leaving group is poor, but the great stability of the intermediate carbonium ion makes C–O bond breaking relatively easy. In the case of the benzaldehyde di-*tert*-butyl acetals[11] the bond breaking process is facilitated by relief of ground state strain during the hydrolytic reaction. With all of these compounds, ease of bond breaking is most likely the predominant feature giving rise to general acid catalysis.[9–12]

Triphenyl orthoformate, an ortho ester with which basicity would be very low and with which the leaving group would be reasonably good, has been studied.[13]

(1) Postdoctoral Fellow, Department of Biochemistry, University of Southern California.

(2) J. N. Brønsted and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **25**, 59 (1929).

(3) H. Kwart and M. B. Price, *J. Amer. Chem. Soc.*, **82**, 5123 (1960).

(4) R. H. DeWolfe and R. M. Roberts, *ibid.*, **76**, 4379 (1954).

(5) M. Lahti and A. Kankaanpera, *Acta Chem. Scand.*, **24**, 706 (1970).

(6) C. A. Bunton and R. H. DeWolfe, *J. Org. Chem.*, **30**, 1371 (1965).

(7) A. J. Kresge and R. J. Preto, *J. Amer. Chem. Soc.*, **87**, 4593 (1965).

(8) E. H. Cordes, *Progr. Phys. Org. Chem.*, **4**, 1 (1967).

(9) T. H. Fife and L. K. Jao, *J. Amer. Chem. Soc.*, **90**, 4081 (1968).

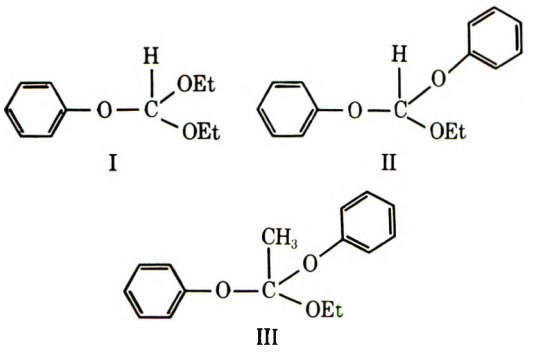
(10) E. Anderson and T. H. Fife, *ibid.*, **91**, 7163 (1969).

(11) E. Anderson and T. H. Fife, *ibid.*, **93**, 1701 (1971).

(12) T. H. Fife and L. H. Brod, *ibid.*, **92**, 1681 (1970).

(13) M. Price, J. Adams, C. Lagenaur, and E. H. Cordes, *J. Org. Chem.*, **34**, 22 (1969).

The rates of hydrolysis of that compound are quite slow, and a search for general acid catalysis by buffer acids was not reported.[13] In that case the intermediate carbonium ion would not be highly stabilized by the adjoining phenoxy groups with the result that the bond-breaking process would still be difficult. Ortho esters possessing both a good leaving group and a reasonably stable carbonium ion intermediate have not been studied. It was felt that, in view of the results obtained in acetal hydrolysis reactions,[9-12] such an ortho ester should show a pronounced general acid catalysis with a relatively low Brønsted coefficient. We have therefore studied the hydrolysis of diethylphenyl orthoformate (I), and, for comparison purposes, diphenylethyl orthoformate (II) and diphenylethyl orthoacetate (III).



Experimental Section

Materials.—Diethylphenyl orthoformate was obtained commercially from Aldrich Chemical Co. and distilled before use, boiling at 75° (0.1 mm), $n^{23}D$ 1.4813. Diphenylethyl orthoformate was prepared by the method of Stetter and Reske[14] and boiled at 154° (0.3 mm), $n^{23}D$ 1.5391. Diphenylethyl orthoacetate was prepared by the method of Smith,[15] except that a molar ratio of phenol to ethyl orthoacetate of 3:1 was used and the forerun of diethylphenyl orthoacetate was rejected. The product boiled at 140° (0.3 mm), $n^{23}D$ 1.5323.

Dioxane was purified by the method of Fieser[16] and was stored frozen in brown bottles. Deuterium oxide (99.8%) was obtained from Bio-Rad Laboratories. Standard HCl solutions were made from "Dilut-it" concentrated analytical reagent by dilution with boiled deionized water. Other chemicals were A. R. grade materials.

Kinetic Measurements.—Fresh stock solutions of ortho ester in acetonitrile were made up before each series of kinetic runs. The rates of hydrolysis were determined at 25 and 45° with a Gilford 2000 recording spectrophotometer by following the increase in absorbance at 272.3 mμ due to the phenol product. The solvent was 50% dioxane–H_2O (v/v) and ionic strength was maintained at 0.1 with KCl. To initiate the reactions 7 μl of stock solution was added to 3 ml of buffer solution in the cuvette. The reactions were followed to completion, and pseudo-first-order rate constants were calculated by a rigorous least-squares procedure with an IBM 360-40 computer. In the cases of II and III, 2 equiv of phenol was released. The pH of each solution was measured with a Model 22 Radiometer pH meter. The glass electrode gives the correct pH reading in dioxane–H_2O mixtures.[17]

Product Analysis.—The appropriate ortho ester was added from a microsyringe to 1 ml of the appropriate 50% dioxane buffer (0.01 *N* HCl or 0.1 *M* CH_3CO_2H–0.1 *M* $CH_3CO_2^-$) to form a 0.01 *M* solution. After hydrolysis was complete, 1 μl of the solution was chromatographed on a Hewlett-Packard flame ionization chromatograph equipped with a Hewlett-Packard digital integrator. Flow rates were, He, 25 cc/min; H_2, 15 cc/min; air, 150 cc/min. Temperatures were, injection block, 55°; detector, 250°; oven, 100–150° at 10°/min. The column was 6-ft OV 17 on Chromosorb P. Retention times (min) were, ethyl acetate, 0.79; dioxane, 1.20; phenol, 3.58; ethyl formate, 0.64. The observed retention times were the same to ±0.02 min as obtained with authentic samples, and addition of the authentic materials to the solutions gave no further peaks. In the case of I, the products were solely ethanol, phenol, and ethyl formate. With II and III, the products were solely phenol and either ethyl formate or ethyl acetate in a molar ratio of 1.8 ± 0.3/1.

(14) H. Stetter and E. Reske, *Chem. Ber.*, **103**, 643 (1970).
(15) B. Smith, *Acta Chem. Scand.*, **10**, 1006 (1956).
(16) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath, Boston, Mass., 1956, p 284.
(17) H. P. Marshall and E. Grunwald, *J. Chem. Phys.*, **21**, 2143 (1953).

Results

It would be expected that the initial C–O bond broken in hydrolysis would be that involving the phenoxyl group, since that would result in a good leaving group and formation of the most stable carbonium ion. That phenol is the leaving group is easily demonstrated for the present compounds. Product analysis after the hydrolysis of II and III under actual hydrolytic conditions (excepting a tenfold increase in concentration) by glc shows the products to be solely phenol and either ethyl formate or ethyl acetate. Initial ethoxyl cleavage would require the products to be ethanol, phenol, and phenyl formate or phenyl acetate. Product analysis shows the products of the hydrolysis of I to be ethanol, phenol, and ethyl formate. This is, however, not conclusive evidence for phenoxyl cleavage with I. Therefore, the acetic acid catalyzed methanolysis of I and the dimethyl analog, dimethylphenyl orthoformate, prepared by the method of Smith,[15] was studied. In 0.1 *M* acetic acid in absolute methanol, I solvolyzes four times faster than dimethylphenyl orthoformate, excluding the latter as an intermediate. Pseudo-first-order kinetics were obeyed to 7 half-lives, making the intercession of a stable intermediate highly unlikely. Furthermore, the rate constant for solvolysis of I in methanol is close to that for catalysis by 0.1 *M* acetic acid in water, 5.8×10^{-3} sec^{-1} *vs.* 1.63×10^{-2} sec^{-1}, indicating that the mechanism is very likely the same.

A very large general acid catalysis is observed in the hydrolysis of the ortho esters I, II, and III. For example, in acetic acid buffers at HA = A^-/2 (pH 6.38), 0.05 *M* acetic acid produced a 12.7-fold enhancement in the pseudo-first-order rate constant for hydrolysis of diethylphenyl orthoformate in comparison with the intercept value. Catalysis is by the acid species of the buffer since identical second-order rate constants were obtained from plots of k_{obsd} *vs.* buffer acid concentration at three different acetic acid/acetate buffer ratios and at two different formic acid/formate buffer ratios. A plot is shown in Figure 1 of k_{obsd} for hydrolysis of diethylphenyl orthoformate *vs.* total acetate buffer concentration. Values of the second-order rate constants for general acid catalysis are given in Table I. In Figure 2 a plot is shown of log k_{HA} *vs.* the pK_a of the catalyzing acid in the hydrolysis of diethylphenyl orthoformate. The slope of this plot is −0.47 with a correlation coefficient of 0.993. In this correlation cacadylic acid was included with the six carboxylic acids. The slopes of plots of log k_{HA} *vs.* pK_a for hydrolysis of diphenylethyl orthoformate and diphenylethyl orthoacetate were −0.68 (r = 0.997) and −0.49 (r = 0.981), respectively.

Rate constants for hydronium ion catalysis were determined in HCl solutions and are reported in Table I. The point for hydronium ion in Figure 2 falls con-

TABLE I

RATE CONSTANTS k_{HA} (M^{-1} sec^{-1}) FOR GENERAL ACID CATALYZED HYDROLYSIS OF DIETHYLPHENYL ORTHOFORMATE, DIPHENYLETHYL ORTHOFORMATE, AND DIPHENYLETHYL ORTHOACETATE IN 50% DIOXANE–H_2O (v/v) WITH μ = 0.1, MAINTAINED WITH KCl

Acid	pK_a[a]	Diethylphenyl orthoformate[b]	Diphenylethyl orthoformate[c]	Diphenylethyl orthoacetate[b]
H_3O^+		74.0[d]	1.35[d]	35.3[d]
D_3O^+		64.6	1.48	30.9
Dichloroacetic	2.60		0.085	
Cyanoacetic	3.74	2.29	0.0195	0.68
Chloroacetic	4.00	1.57	0.0103	0.367
Formic	4.80	0.535	0.00299	0.171
Formic (D_2O)			0.0014	
Glycolic	4.95	0.388	0.0023	0.108
Acetic	6.06	0.154		0.0497
Acetic (D_2O)		0.073		0.0214
Succinic	6.90	0.078		
Cacadylic	7.50	0.03		

[a] Determined by half-neutralization at 25°. [b] At 25°. [c] At 45°. [d] The second-order constant is k_{obsd}/a_H.

siderably below the line and was omitted from the correlation. This was also the case in the similar plots of log k_{HA} *vs.* pK_a for hydrolysis of diphenylethyl orthoformate and diphenylethyl orthoacetate.

Rate constants were also determined in 50% dioxane–D_2O in these reactions and are reported in Table I. It will be noted that second-order rate constants for buffer acid catalysis are approximately twofold less in 50% dioxane–D_2O. The rate constants for hydronium ion catalysis show a slight change when the solvent is changed from 50% dioxane–H_2O to 50% dioxane–D_2O, the ratio $k_{D_3O^+}/k_{H_3O^+}$ being 0.87, 1.10, and 0.88 for hydrolysis of I, II, and III.

Salt and ionic strength effects are reasonably small in the hydrolysis of these orthoesters. The second-order rate constant for acetic acid catalyzed hydrolysis of diphenylethyl orthoacetate at 25° is 0.06 M^{-1} sec^{-1} when ionic strength is held constant at 0.5 M with KCl, approximately 20% greater than the rate constant obtained when ionic strength is 0.1. Likewise, the rate constant for acetic acid catalyzed hydrolysis of diethylphenyl orthoformate is only slightly greater when ionic strength is held constant at 0.5 M with $NaClO_4$, being 0.214 M^{-1} sec^{-1}.

Discussion

It has been observed that some of the reports of general acid catalysis in ortho ester hydrolysis reactions are possibly due to specific salt effects.[5,18] It would be expected that such effects would be most pronounced in media with a high percentage of organic solvent. The rate enhancements produced by small concentrations of buffer acids in the present study are certainly much too large to be attributable to specific salt effects. Furthermore, it was ascertained that greatly increasing the ionic strength to 0.5 M, held constant with KCl or with $NaClO_4$, gave rise to small increases in the second-order rate constants for buffer catalysis. At such high ionic strengths the contribution of the buffer anion to the total ionic strength is quite small. The

(18) P. Salomaa, A. Kankaanpera, and M. Lahti, *J. Amer. Chem. Soc.*, **93**, 2084 (1971).

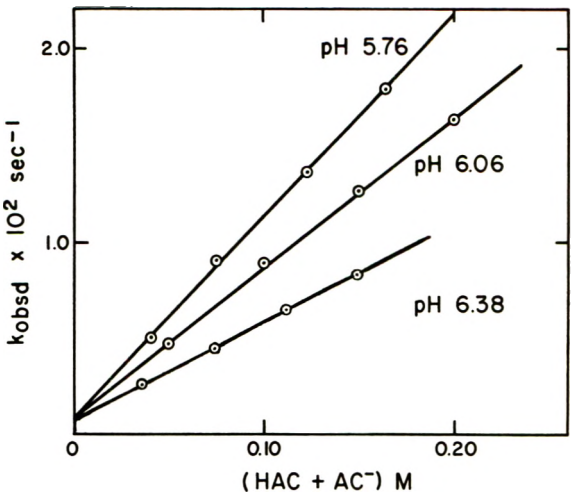


Figure 1.—Plots of k_{obsd} for hydrolysis of diethylphenyl orthoformate *vs.* total acetate buffer concentration in 50% dioxane–H_2O at 25° (μ = 0.1).

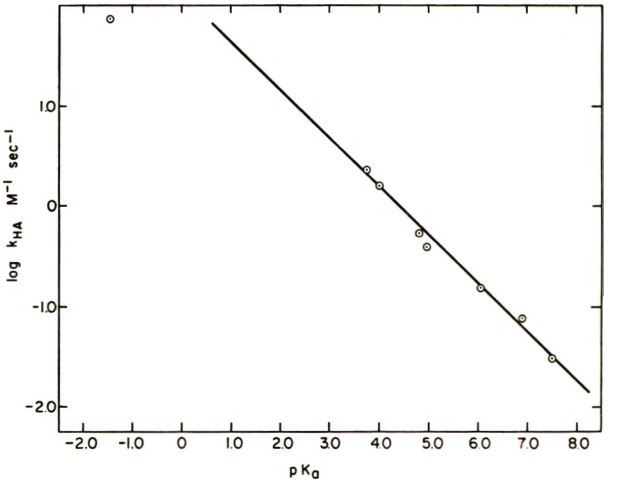


Figure 2.—Plot of log k_{HA} for general acid catalyzed hydrolysis of diethylphenyl orthoformate *vs.* the pK_a of the catalyzing acid in 50% dioxane–H_2O at 25° (μ = 0.1).

observed rate enhancements produced by increasing the buffer concentration at constant ionic strength and pH are then due to genuine general acid catalysis.

The Brønsted coefficient α of 0.47 for diethylphenyl orthoformate is considerably less than previously observed values of ~0.7 in ortho ester hydrolysis.[2,3,7] It is also less than observed in hydrolysis of the acetal 2-(*p*-nitrophenoxy)tetrahydropyran in 50% dioxane–H_2O (0.69).[12] The relatively fast rates of hydrolysis of diethylphenyl orthoformate in comparison with triphenyl orthoformate[13,19] and the pronounced general acid catalysis in comparison with the lack of general acid catalysis in the hydrolysis of triethyl orthoformate[4] must be due in part to the fact that with diethylphenyl orthoformate the leaving group is good and the intermediate carbonium ion is well stabilized by the adjoining ethoxy groups. Thus, as with acetals[9-12] ease of bond breaking appears to be a key factor in facilitating general acid catalysis.

This interpretation is strongly supported by the data for hydrolysis of diphenylethyl orthoformate with which

(19) The value of k_{obsd} for hydrolysis of triphenyl orthoformate in 40% dioxane–H_2O at 25° with 1 M HCl is 7.8 × 10^{-4} sec^{-1}. Therefore, although experimental conditions are different, the hydronium ion catalyzed hydrolysis of diethylphenyl orthoformate must proceed approximately 10^3 times more rapidly.

the leaving group is the same as with diethylphenyl orthoformate but where the intermediate carbonium ion should be less stable and where basicity will be considerably less because of the electron-withdrawing ability of the phenoxy group relative to ethoxy.[20] This ortho ester is also subject to general acid catalysis, but it will be noted in Table I that the magnitude of the rate constants is much less at 45° than in the case of diethylphenyl orthoformate at 25°. The rate constant for hydronium ion catalysis is 55-fold less. Of critical importance is the fact that the slope of the Brønsted plot of log k_{HA} *vs.* pK_a is much greater (−0.68). Thus, proton transfer is very likely occurring to a considerably greater extent in the transition state. General acid catalysis is therefore much less favorable with weak acid catalysts even though basicity is less.

Greatly increasing the stability of the oxocarbonium ion intermediate in the diphenylethyl system by employing diphenylethyl orthoacetate as the substrate led to a large reduction in the magnitude of the Brønsted coefficient (0.49). This again illustrates the importance of oxocarbonium ion stability and the ease of bond breaking in facilitating general acid catalysis in these reactions. From knowledge of the structural features leading to general acid catalysis in acetal and ketal hydrolysis,[9-12] it has therefore been possible to predict what types of ortho esters would show pronounced general acid catalysis and also the relative magnitudes of the Brønsted coefficients. Thus, the conclusion that ease of bond breaking is the critical feature in these reactions in regard to general acid catalysis would appear to be well established and general in application.

(20) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 556.

Registry No.—I, 14444-77-0; II, 25801-57-4; III, 33712-25-3.

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Acetolysis of 1-Tosyloxy-2,2-dideuteriobicyclopropyl

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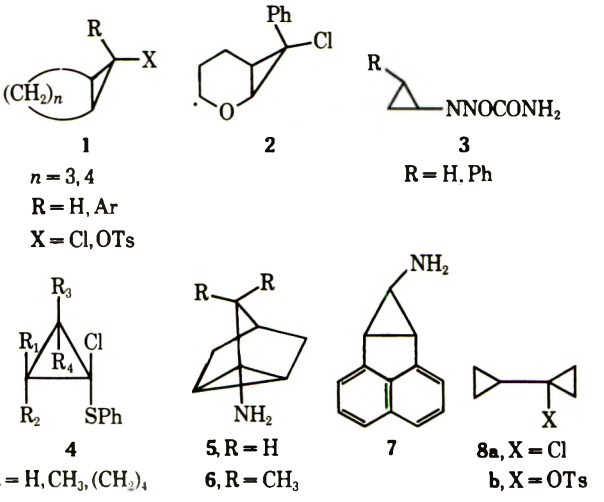
Acetolysis of 1-tosyloxy-2,2-dideuteriobicyclopropyl at 25° for 120 hr in the presence of sodium acetate produced a mixture of acetates **13** and **16** in which the position of the deuterium atoms eliminated the possibility of any of the degenerate rearrangements shown in Scheme I.

Examples of cyclopropyl derivatives that form stabilized cyclopropyl cations in solvolytic reactions and do not entirely undergo ring cleavage to allylic products are few. Unrearranged products have been obtaned in the solvolysis of exo-substituted bicyclo[*n*.1.0]-derivatives **1**, **2**,[1] cyclopropyl-*N*-nitrosoureas **3**,[2] cyclopropyl thioethers **4**,[3] the nitrous acid deamination of apotricyclylamine (**5**),[4a] 1-aminonortricyclene (**6**),[4b] and 3-amino-1,2-cyclopropanoacenaphthene (**7**),[4c] and solvolysis of bicyclopropyl derivatives **8**.[5]

Steric prohibition of the favored electrocyclic transformation[6] to an allylic system is justification[1c,d,6b] for the nonrearranged products of the solvolysis of compounds **1**, **2**, **5**, **6**, and **7**; however, a free-radical mechanism has been suggested[7] for compounds **5**, **6**, and **7**, and, although it might be extended to **3**, a carbonium ion mechanism has also been invoked for the latter.[2] Of all of the aforementioned systems, bicyclopropyl derivatives remain among the most interesting because substantial amounts of both ring-opened and ring-closed products are found.



Although acetolysis of **8a** in the presence of silver ion produced a mixture of **9**, **10**, and **11**,[5b,8] the use of **8b** with acetic acid and sodium acetate resulted in a mixture of **9** and **12** in addition to several minor products.[5c]

(1) (a) U. Schöllkopf, K. Fellenberger, M. Patsch, P. v. R. Schleyer, T. Su, and G. W. Van Dine, *Tetrahedron Lett.*, 3639 (1967); (b) U. Schollköpf, *Angew. Chem., Int. Ed. Engl.*, **7**, 588 (1968); (c) D. B. Ledlie and E. A. Nelson, *Tetrahedron Lett.*, 1175 (1969); (d) D. T. Clark and G. Smale, *Chem. Commun.*, 868, 1050 (1969); (e) D. B. Ledlie and W. H. Hearne, *Tetrahedron Lett.*, 4837 (1969).

(2) (a) W. Kirmse and H. Schütte, *Chem. Ber.*, **101**, 1674 (1968); (b) W. Kirmse and H. Schütte, *J. Amer. Chem. Soc.*, **89**, 1284 (1967).

(3) U. Schöllkopf, E. Ruban, P. Tonne, and K. Riedel, *Tetrahedron Lett.*, 5077 (1970).

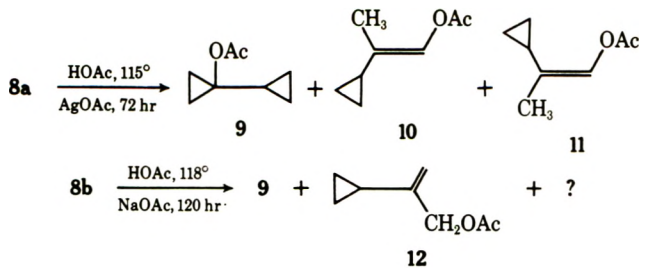
(4) (a) P. Lippe and C. Padberg, *Chem. Ber.*, **54**, 1316 (1921); (b) H. Hart and R. A. Martin, *J. Amer. Chem. Soc.*, **82**, 6362 (1960); (c) R. Petit, *ibid.*, **82**, 1972 (1960).

(5) (a) J. A. Landgrebe and L. W. Becker, *ibid.*, **89**, 2505 (1967); (b) J. A. Landgrebe and L. W. Becker, *ibid.*, **90**, 395 (1968); (c) B. A. Howell and J. C. Jewett, *ibid.*, **93**, 798 (1971).

(6) (a) R. B. Woodward and R. Hoffmann, *ibid.*, **87**, 395 (1965); (b) C. H. DePuy, L. G. Schnack, J. W. Hausser, and W. Wiedemann, *ibid.*, **87**, 4006 (1965).

(7) K. V. Scherer, Jr., and R. S. Lunt, III, *ibid.*, **88**, 2860 (1966).

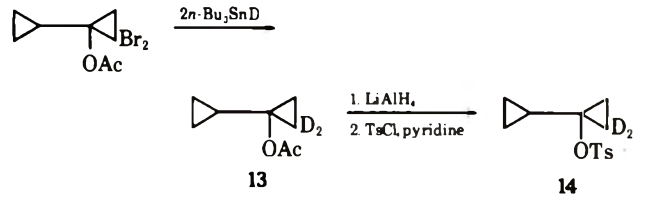
(8) An error in our original report[5b] resulted in enol acetate structures in which methyl and acetoxy groups were interchanged. However, the nmr spectra clearly establish the structures shown for **10** and **11**.



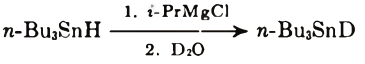
In the present study attention is focused on establishing whether or not there are degenerate rearrangements occurring during the solvolysis of **8b**.

Results and Discussion

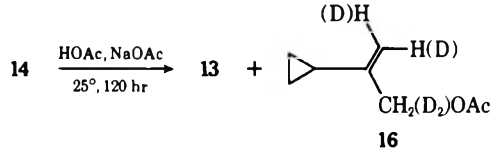
2,2-Dideuteriobicyclopropyl tosylate (**14**) was synthesized by a variation of the method previously described for the preparation of the undeuterated compound.[5a,b]



The reducing agent, tri-*n*-butyltin deuteride (**15**), was prepared by the deuterolysis of tri-*n*-butyltinmagnesium chloride,[9] which resulted in a product of *ca.* 99.8% deuterium content.



Acetolysis of deuterated tosylate **14** at 25° for 120 hr in the presence of sodium acetate produced a 1:2.5 mixture of bicyclopropyl acetate (**13**) and deuterated 2-cyclopropylallyl acetate (**16**) in comparable yield to

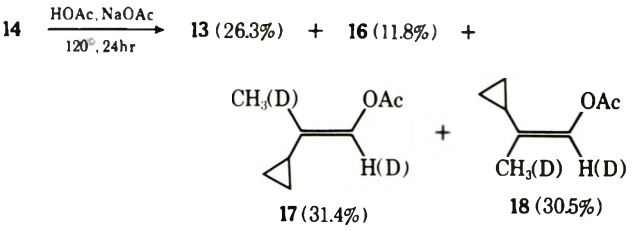


that reported by Howell and Jewett.[5c] Whether **16** forms directly from **14** or from the solvolysis of 2-cyclopropylallyl tosylate was not ascertained.

The location of the deuterium atoms in allyl acetate **16** was determined from an nmr spectrum of a sample isolated by preparative vapor phase chromatography. Chemical shift values agreed with those for undeuterated 2-cyclopropylallyl acetate.[10] Comparison of the integrated area for each type of proton with the acetate methyl as a three-proton internal standard revealed that the vinyl- and acetoxy-substituted carbon atoms contained all the deuterium atoms of the molecule about equally distributed between the two possible locations.

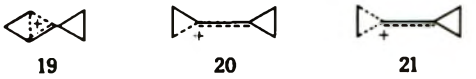
Analysis of the deuterium location in a collected sample of bicyclopropyl acetate (**13**) was accomplished by the use of 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctan-4,6-dionatoeuropium.[11] The cis and trans protons (relative to acetoxy) at C-2 and C-3 appeared as two distinct AX doublets sufficiently removed from the multiplet assigned to the protons of the other cyclopropyl ring to allow a quantitative integration of the nmr spectrum and comparison with the acetate methyl. Proton assignments were confirmed by comparison with the nmr spectra of authentic **13** and undeuterated acetate **9** in the presence of the shift reagent. In the latter example, the cis and trans protons of C-2 and C-3 appeared as a pair of symmetrical multiplets containing four protons. Solvolysis product **13** had 95–100% of the deuterium atoms in the acetoxy-substituted ring, the small uncertainty being the result of an impurity and some line broadening caused by the nmr shift reagent.

The acetolysis of **14** in the presence of sodium acetate at 120° for 24 hr produced a mixture of **13**, **16**, *trans*-2-cyclopropylpropenyl acetate (**17**), and *cis*-2-cyclopropylpropenyl acetate (**18**) as well as three unidentified products which comprised no more than 3–5% of the total yield. Although the enol acetates **17** and **18**



were not individually isolated, an nmr spectrum of the product mixture indicated the presence of two deuterium atoms distributed between the allylic methyl group and the vinyl position. 2-Cyclopropylallyl acetate has been suggested as a precursor to the observed enol acetates[5c] but was never detected in their presence until shorter reaction times were used. In our work it has been observed that **16** readily formed a mixture of **17** and **18** on vapor phase chromatographic columns unless precautions were taken.

Although the observed lack of deuterium scrambling does not clearly distinguish between possible cationic intermediates such as **19**,[12] **20**,[13] or **21**,[14] it



does eliminate symmetrical species such as **22** and further indicates the lack of degenerate rearrangements represented by path a and path bcde of Scheme I. Evidence against path b (and e) is consistent with the observations of Wiberg[15] for the solvolysis of 4-tosyloxyspirohexane (**23**), which gives a variety of products,

(9) (a) J.-C. Lahournere and J. Valade, *J. Organometal. Chem.*, **22**, C3 (1970).

(10) The spectrum was kindly supplied by Professor J. Jewett, Ohio University.

(11) (a) C. C. Hinckley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969); (b) J. K. M. Sanders and D. H. Williams, *Chem. Commun.*, 422 (1970); (c) R. E. Sievers and R. Rondeau, ARL Report 70-0285, 1970, Twelfth Experimental Nmr Conference, Gainesville, Fla., Feb 18, 1971.

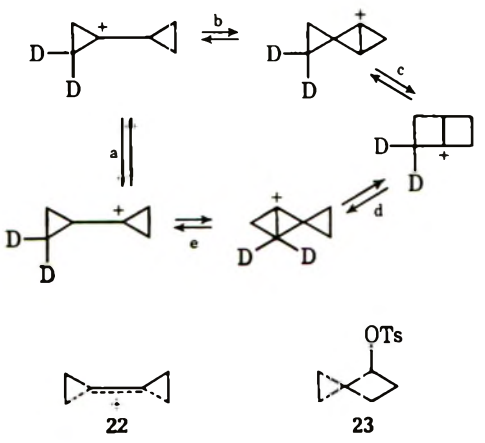
(12) R. H. Mazur, W. N. White, D. A. Semenow, C. C. Lee, M. S. Silver, and J. D. Roberts, *J. Amer. Chem. Soc.*, **81**, 4399 (1959).

(13) S. Winstein and E. M. Kosower, *ibid.*, **81**, 4399 (1959).

(14) (a) C. U. Pittman, Jr., and G. A. Olah, *ibid.*, **87**, 5123 (1965); (b) H. G. Richey, Jr., and J. M. Richey, *ibid.*, **88**, 4971 (1966); (c) P. v. R. Schleyer and G. W. Van Dine, *ibid.*, **88**, 2321 (1966).

(15) K. B. Wiberg and J. E. Hiatt, *ibid.*, **90**, 6495 (1968); see also D. E. Applequist and W. A. Bernett, *Tetrahedron Lett.*, 3005 (1968), and K. B. Wiberg and J. E. Hiatt, *ibid.*, 3009 (1968).

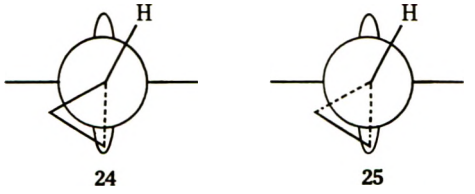
SCHEME I



22 23

none of which correspond structurally to those observed for the solvolysis of tosylate **14** under mild conditions.[16] It remains to be shown why the interconversion represented by path b is so energetically unfavorable.

In view of the case of hydride migrations in various carbonium ions,[17a-c] the lack of an observable 1,2-hydride shift (path a) in the cation presumed to form during the solvolysis of **14** is significant. One possible explanation is that the preferred conformations for ions such as **20** and **21** (depected in structures **24** and **25**, respectively) result in dihedral angles between the methine C–H bond and the adjacent vacant orbital substantially different from the angle of 0° which is favored for hydride migration.



24 25

Experimental Section[18]

Tri-*n*-butyltin Deuteride (15).—This reagent was prepared by the method of Lahournere and Valade.[9a] To a stirred solution of isopropylmagnesium chloride (0.15 mol) in ether was added dropwise tri-*n*-butyltin hydride (10.0 g, 0.034 mol). The mixture was stirred at room temperature for 2.5 hr and then brought to reflux for 20 min. The contents were hydrolyzed with deuterium oxide and the resultant gel was slowly filtered and washed with ether. The ethereal solution was dried (Na_2SO_4), concentrated, and distilled to give 6.8 g (0.023 mol, 68%) of tri-*n*-butyltin deuteride, bp 78–70° (0.6 mm). The infrared spectrum (film) contained a Sn–D absorption at 1805 cm^{-1}.

2,2-Dideuteriobicyclopropyl Acetate (13).—The compound was obtained by a modification of the method described for the synthesis of bicyclopropyl acetate.[5b] Crude 2,2-dibromobicyclopropyl acetate was reduced by stirring it with tri-*n*-butyltin deuteride for 72–90 hr at 25° or overnight at 85° to give acetate **13** in 50% yield. The nmr spectrum (CCl_4) displays a complex multiplet at τ 9.2–9.85 (6 H) consistent with the introduction of two deuterium atoms and the nmr spectrum previously reported for bicyclopropyl acetate. More detailed nmr assignments are given in the description of the acetolysis.

2,2-Dideuteriobicyclopropyl Tosylate (14).—Acetate **13** (1.42 g, 0.010 mol) in ether (15 ml) was reduced with lithium aluminum hydride (0.95 g, 0.025 mol) in ether (50 ml) in a manner reported[5b] for the preparation of 1-hydroxybicyclopropyl to give 0.92 g (91.5%) of 1-hydroxy-2,2-dideuteriobicyclopropyl. The alcohol (0.92 g, 0.009 mol) and dry pyridine (18 ml) were chilled and tosyl chloride (3.43 g, 0.018 mol) was added; after dissolution, the mixture was stored at −20° for 5 days. Crystalline, long, white needles of tosylate **14** (1.28 g, 55.9%), mp 40.8–41.8°, were obtained from a work-up suggested by Fieser and Fieser.[19] The nmr spectrum (CCl_4) had absorptions at τ 2.23–2.7 (4 H, A_2B_2, para-substituted phenyl), 7.57 (3 H, singlet, tolyl methyl), and 8.13–9.95 (7 H, multiplet, cyclopropyl). An undeuterated sample of the tosylate was analyzed.

Anal. Calcd for $C_{13}H_{16}SO_3$: 61.88; H, 6.39. Found: C, 61.93; H, 6.38.

Acetolysis of 2,2-Dideuteriobicyclopropyl Tosylate (14) at 25°.—A mixture of tosylate **14** (1.017 g, 0.004 mol), anhydrous sodium acetate (0.492 g, 0.006 mol), and glacial acetic acid (180 ml) was stirred at 25° for 5 days. The solution was diluted with water (180 ml) and extracted with pentane (5 × 40 ml). The combined pentane solutions were washed with saturated aqueous sodium bicarbinate solution and concentrated to give 0.810 g of an oil which contained two components in a ratio of 1:2.5 by vpc analysis with a 5 ft, 10% OV-101 on 60/80 Gas-Chrom Q column at 100°. The two products were collected individually with a 6 ft, 10% OV-210 on 100/120 Gas-Chrom Q glass column at 75°. The product of shorter retention time and lower yield proved indistinguishable from authentic acetate **13** with both of the above columns. The nmr spectrum of the other compound agreed (neglecting proton integration) with the nmr spectrum of 2-cyclopropylallyl acetate.[10] The nmr spectrum (CCl_4) contained absorptions at τ 5.09 and 5.20 (broad singlets with some fine structure, $C{=}CH_2$), 5.48 (singlet, CH_2OCOCH_3), 7.97 (singlet, $OCOCH_3$), 8.4–9.0 (multiplet, methine proton), and 9.2–9.7 (multiplet; other cyclopropyl protons). The integration of the combined areas of the peaks represented by vinyl plus allylic protons compared to the acetate methyl as 2:3.

Addition of tris-1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctan-4,6-dionatoeuropium (Pierce Chemical Co., 15 mg) to the other product produced a simplified spectrum which was essentially identical with that of authentic **13** measured under similar conditions. The cis and trans C-4 protons appeared as two separated AX doublets which corresponded to 95–100% deuterium retention in the acetoxy-substituted ring. These assignments were confined by the addition of the shift reagent (50 mg) to bicyclopropyl acetate (**9**) (40.6 mg) in carbon tetrachloride (0.5 ml) which gave a spectrum that contains two almost identical five-peak multiplets (4 H) and an upfield multiplet (4 H) in addition to the acetoxy methyl.

Acetolysis of 2,2-Dideuteriobicyclopropyl Tosylate (14) at 120°.—A mixture of tosylate **14** (383 mg, 1.50 mmol), anhydrous sodium acetate (175 mg, 2.13 mmol), and glacial acetic acid (70 ml) was stirred at 120° for 24 hr. The mixture was cooled, diluted with water (70 ml), and extracted with pentane (5 × 60 ml). The combined pentane solution was washed with saturated sodium bicarbonate solution, dried (Na_2SO_4), and concentrated to give 205 mg (96%) of crude products. Four products representing 90% of the product mixture were identified by vpc and nmr data as 2,2-dideuteriobicyclopropyl acetate (**13**) (26.3%), 2-cyclopropylallyl acetate (**16**) (11.8%), *trans*-2-cyclopropylpropenyl acetate (**17**) (31.4%), and *cis*-2-cyclopropylpropenyl acetate (**18**) (30.5%). Allylic acetate **16** readily isomerized to a mixture of **17** and **18** on vpc columns unless buildup of decomposition products on the column was minimized by use of very small samples. Columns were treated frequently with Silyl-8 conditioner (Pierce Chemical Co.).

Registry No.—**13**, 34839-53-7; **14**, 34839-54-8; **15**, 6180-99-0.

(16) Solvolysis of **14** at 120° did produce three very minor unidentified products which represented 3–5% of the total product mixture.

(17) (a) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill, New York, N. Y., 1968, pp 786–789, 795–797; (b) Y. Pocker in "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 13; (c) J. A. Berson, *ibid.*, pp 140–145.

(18) Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained with a Beckman IR-8 double grating spectrophotometer and nmr spectra were obtained with a Varian A-60 spectrometer. Chemical analyses were performed with an F & M Model 180 Carbon, Hydrogen, Nitrogen Analyzer, Department of Medicinal Chemistry, University of Kansas, Lawrence, Kans.

(19) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N. Y., 1967, p 1180.

Homolysis of Some Radical Initiators. Viscosity Dependence and Cage Return[1]

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Our previously derived viscosity test for distinguishing one-bond from multi-bond initiators has been applied to the homolysis of nine peroxy compounds in alkane solvents (Table I). The results are consistent with findings by other authors (Table II), and the viscosity test appears to offer a fast and convenient method for initial screening of all types of initiators. The amounts of cage return for acetyl peroxide (Ac_2O_2), propionyl peroxide (PPO), and benzoyl peroxide (Bz_2O_2) are compared with those of the corresponding *tert*-butyl peroxy esters (Table VII). In each pair, the diacyl or diaroyl peroxide undergoes the smaller amount of cage return. This can be explained for the Ac_2O_2/*tert*-butyl peroxyacetate and PPO/*tert*-butyl peroxypropionate pairs by the higher stability of the *tert*-butoxy radical of the peroxy ester compared to the acyloxy radical of the diacyl peroxide (Table VI). However, for the Bz_2O_2/*tert*-butyl peroxybenzoate pair both the *t*-BuO· and the $PhCO_2$· radicals undergo β scission too slowly to compete with diffusion from the cage (Table VI); the small amount of cage return for Bz_2O_2 appears to be an anomaly. Some CO_2 trapping experiments for the *tert*-butyl peroxy esters RCO_2OBu-*t*, where R is methyl, ethyl, or *tert*-butyl, support the kinetic data (Table II). These experiments also indicate that *tert*-butyl peroxyisobutyrate (R = isopropyl) is a two-bond initiator. However, the viscosity test shows a small amount of cage return (~1%). Therefore, we conclude that this compound either decomposes by both mechanisms (but mainly two-bond) or undergoes only a small amount of cage return due to the high instability of the $C_3H_7CO_2$· radical. *tert*-Butoxy radicals from the decomposition of di-*tert*-butyl peroxide (TOOT) undergo negligible amounts of β scission or disproportionation in the cage. The viscosity dependence of k_{obsd} for TOOT can be used to calculate the fraction of cage return, f_r, from eq 2 and 3, and the values are compared with those of Kiefer and Traylor.

The effect of solvent viscosity on the observed rate constant for homolysis of radical initiators can be used to determine the number of bonds which break at the transition state.[5] There are two possibilities: homolysis may involve the cleavage of only one bond, or several bonds may undergo simultaneous cleavage. To further test these ideas, we have studied the viscosity dependence of the rates of decomposition of the peroxy compounds which are listed in Table I. (The abbreviations given there for the names of the compounds will be used throughout this article.)

TABLE I

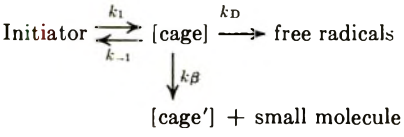
PEROXY COMPOUNDS WHICH HAVE BEEN STUDIED

Formula[a]	Name	Abbreviations for peroxy compounds
$[PhC(O)O-]_2$	Benzoyl peroxide	Bz_2O_2
$[EtC(O)O-]_2$	Propionyl peroxide	PPO
MeC(O)OOBu-*t*	*tert*-Butyl peroxyacetate	TAc
EtC(O)OOBu-*t*	*tert*-Butyl peroxypropionate	TPr
$Me_2CHC(O)OOBu$-*t*	*tert*-Butyl peroxyisobutyrate	TiBu
$Me_3CC(O)OOBu$-*t*	*tert*-Butyl peroxypivalate	TPiv
PhC(O)OOBu-*t*	*tert*-Butyl peroxybenzoate	TBz
[*t*-BuCOOC(O)]$_2$	Di-*tert*-butyl peroxyoxalate	TOx
(*t*-BuO-)$_2$	*tert*-Butyl peroxide	TOOT
(*n*-BuO-)$_2$	*n*-Butyl peroxide	NOON
$[EtCH(Me)O-]_2$	*sec*-Butyl peroxide	SOOS

[a] The following abbreviations are used: Ph, C_6H_5; Et, C_2H_5; Me, CH_3; Bu, C_4H_9.

For a one-bond initiator, the generalized mechanism for homolysis is shown in Scheme I, where [cage] represents the geminate pair of radicals produced by the scission of one bond, and [cage'] is the pair of radicals produced by some β-scission process. In terms of this mechanism, the observed rate constant k_{obsd} is given by eq 1, where k_1 is the rate constant for bond homolysis, k_{-1} is the rate constant for cage return, k_D is the rate constant for diffusive separation of the geminate radicals, and k_β is the rate constant for β scission. The fraction of geminate radicals which combine to reform the initiator is defined in eq 2.

SCHEME I



$$k_{obsd} = \frac{k_1(k_D + k_\beta)}{k_{-1} + k_D + k_\beta} \quad (1)$$

$$f_r = k_{-1}/(k_{-1} + k_D + k_\beta) \quad (2)$$

For a multi-bond initiator the decomposition involves the simultaneous cleavage of two or more bonds, and we assume that the three or more species formed cannot combine to re-form the initiator. Therefore, the observed rate constant would be expected to be independent of the cage lifetime and, consequently, of the solvent viscosity.

We have derived an equation (eq 3) which relates

$$1/k_{obsd} = 1/k_1 + [k_{-1}/A_D k_1][\eta/A_v]^\alpha \quad (3)$$

k_{obsd} to solvent viscosity.[5] For a one-bond initiator, a fraction, f_r, of the geminate radicals recombines to reform the initiator, and f_r is viscosity dependent. For a multi-bond initiator, $k_{-1} = 0$ and the value of $1/k_{obsd}$ in eq 3 will be independent of viscosity and equal to $1/k_1$. The derivation of eq 3 is based on the assumptions that k_D is the only rate constant in Scheme I

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(2) Address all correspondence to this author. John Simon Guggenheim Fellow, 1970–1971; NIH Special Postdoctoral Fellow, summer 1971.

(3) E. Morkved was a Postdoctoral Fellow on NSF Grant GP-3820 from June 1969 to December 1969 and from June 1970 to February 1971.

(4) H. T. Bickley was a Predoctoral Fellow on NSF Grant GP-3820 from January 1966 to May 1969 and on NIH Grant GM 11908 from May 1969 to December 1970.

(5) (a) W. A. Pryor and K. Smith, *J. Amer. Chem. Soc.*, **89**, 1741 (1967); (b) *ibid.*, **92**, 5403 (1970); (c) *Intra-Sci. Chem. Rep.*, **3**, 255 (1969).

which is viscosity sensitive, that $k_\beta < k_D$, that $k_D = A_D \exp(-E_D/RT)$, that $\eta = A_v \exp(E_v/RT)$, and that $E_D = \alpha E_v$ where α is a proportionality constant. Equation 3 predicts a linear relationship between $1/k_{obsd}$ and $(\eta/A_v)^\alpha$, and k_1 can be determined from the intercept if the value of α is known. We suggested an α value of 0.5 as a convenient value for initial work,[5b] and this choice has been justified by theoretical arguments by Koenig.[6] However, recent diffusion experiments in these laboratories[7] gave an α value of 0.72 when benzene was used as a model for caged radical fragments, and an analysis of literature data gave α values of 0.74 for toluene and 0.76 for iodine. We were surprised to find that all three of these solutes had such similar α values; we previously had suggested[5b] that α might vary for each initiator. It is not clear at present whether all initiators have α values near 0.7, or whether the similarities in the data now available result from the fact that the solutes studied to date (benzene, toluene, and iodine) all have similar size and polarity. Our present position is that it is a worthwhile working hypothesis to assume that the α value for all initiators will be near 0.7 and to calculate cage return data for initiators using this value. However, until α values are known with more confidence, we also will continue to calculate the amount of cage return for $\alpha = 0.5$.

We also have applied the technique of Shine, *et al.*,[8a,b] to distinguish one-bond from multi-bond initiators. This technique involves the use of cyclohexene as a solvent to scavenge acyloxy radicals before they decarboxylate. Shine[8b] has shown, for example, that acetyl peroxide gives a larger yield of CO_2 in benzene as a solvent than in cyclohexene, indicating that the $CH_3CO_2\cdot$ radical can be scavenged, and that acetyl peroxide is a one-bond initiator.[9] We applied this method to the series of peroxy esters RCO_2OBu-*t*, where R = methyl, ethyl, isopropyl, or *tert*-butyl.

Results and Discussion

We will discuss separately each of the three classes of peroxy compounds which we have studied: the diaroyl peroxide, the *tert*-butyl peroxy esters, and the dialkyl peroxides. For convenience, we have summarized all of our results in Table II. This table shows the comparison between the mode of decomposition for each compound as concluded from the viscosity test, the CO_2 trapping experiments, and that suggested by other workers using different methods.

TABLE II
MODE OF DECOMPOSITION FOR SOME PEROXY COMPOUNDS

	Mode of decomposition[b]		
Compd[a]	Viscosity test	CO_2 Trapping	Other work
Diaroyl Peroxide			
Bz_2O_2	1		1[c]
Diacyl Peroxide			
PPO[d]	*d*		1[e]
Peroxy Esters			
TAc	1	1	1[f]
TPr	1	1	1[g]
TiBu	1[h]	2	
TPiv	2	2	2[i]
TBz	1		1[j]
TOx	multi		multi[k]
Dialkyl Peroxides			
TOOT	1		1[l]
NOON	1		

[a] For explanation of abbreviations, see Table I. [b] The number of bonds which initially are broken are referred to as follows: 1 for one bond, 2 for two bonds, and "multi" if there is a possibility for homolysis of more than two bonds. [c] G. S. Hammond and L. M. Soffer, *J. Amer. Chem. Soc.*, **72**, 4711 (1950); A. E. Nicholson and R. G. W. Norrish, *Discuss. Faraday Soc.*, **22**, 97 (1956); C. Walling and J. Pellon, *J. Amer. Chem. Soc.*, **79**, 4786 (1957), J. K. Kochi, *ibid.*, **84**, 1572 (1962); H. J. Shine, J. A. Waters, and D. M. Hoffman, *ibid.*, **85**, 3613 (1963); J. C. Martin and J. H. Hargis, *ibid.*, **91**, 5399 (1969). [d] See footnote 10 for a discussion of our incomplete studies of propionyl peroxide. [e] J. C. Martin and J. H. Hargis, submitted for publication. [f] P. D. Bartlett and R. R. Hiatt, *J. Amer. Chem. Soc.*, **80**, 1398 (1958); T. Koenig and M. Deinzer, *ibid.*, **90**, 7014 (1968); T. Koenig, J. Huntington, and R. Cruthoff, submitted for publication. [g] No α-D secondary isotope effect was found in the decomposition of TPr: J. P. Stanley, Louisiana State University, private communication, 1968. [h] The viscosity test indicates a small amount (1%) of cage return for TiBu. However, both mechanisms (one-bond and two-bond scission) might occur simultaneously for this compound. See footnote 20c. [i] P. D. Bartlett and D. M. Simons, *J. Amer. Chem. Soc.*, **82**, 1753 (1960); T. Koenig and R. Wolf, *ibid.*, **89**, 2948 (1967). [j] P. D. Bartlett and R. R. Hiatt, *ibid.*, **80**, 1398 (1958); R. C. Neuman and J. V. Behar, *ibid.*, **91**, 6024 (1969); T. Koenig, M. Deinzer, and J. A. Hoobler, *ibid.*, **93**, 938 (1971). [k] P. D. Bartlett, E. P. Benzing, and R. E. Pincock, *ibid.*, **82**, 1762 (1960); R. Hiatt and T. G. Traylor, *ibid.*, **87**, 3766 (1965); H. Kiefer and T. G. Traylor, *ibid.*, **89**, 6667 (1967). [l] C. Walling and G. Metzger, *ibid.*, **81**, 5365 (1959); C. Walling and H. P. Waits, *J. Phys. Chem.*, **71**, 2361 (1967); H. Kiefer and T. G. Traylor, *J. Amer. Chem. Soc.*, **89**, 6667 (1967); E. S. Huyser and R. M. VanScoy, *J. Org. Chem.*, **33**, 3524 (1968).

Benzoyl Peroxide (Bz_2O_2).[10,11]—This compound is known to be a one-bond initiator.[12-14] Firstly, an almost quantitative yield of benzoic acid is obtained from the decomposition of Bz_2O_2 in wet carbon tetra-

(6) T. Koenig, *J. Amer. Chem. Soc.*, **91**, 2558 (1969).

(7) (a) The diaphragm cell technique was used to measure the diffusion coefficients D at 32° for 0.02–0.03 M solutions of benzene in the alkanes with carbon numbers 6, 7, 8, 10, 12, 14, and 16. (The method and equations are given in ref 5c.) The D values are correlated by the equation $\log D = A - \alpha \log \eta$ (where A and α are disposable parameters) with a correlation coefficient of −0.9992. Using our new data for benzene and literature data for toluene and iodine, values of A and α are as follows: benzene, −6.13, 0.72; toluene,[7b] −6.22, 0.74; iodine, [7b,c] −6.29, 0.76. (b) P. Chang and C. R. Wilke, *J. Phys. Chem.*, **59**, 592 (1955). (c) R. H. Stokes, P. J. Dunlop, and J. R. Hall, *Trans. Faraday Soc.*, **49**, 866 (1953).

(8) (a) H. J. Shine and J. R. Slagle, *J. Amer. Chem. Soc.*, **81**, 6309 (1959). (b) H. J. Shine, J. A. Waters, and D. M. Hoffman, *ibid.*, **85**, 3613 (1963). (c) Instead of cyclohexene, used by Shine and coworkers,[8a,b] we used 4MC because of its higher boiling point.

(9) J. C. Martin, J. W. Taylor, and E. H. Drew, *J. Amer. Chem. Soc.*, **89**, 129 (1967), have argued that the unusually fast reaction between acetoxy radicals and cyclohexene (rate constant of the order 10^8 l. mol^{-1} sec^{-1}) is explained by the initial formation of a π complex in the cage. The π complex would subsequently react with a cage partner, or diffuse out of the cage and thereafter abstract a hydrogen atom from the solvent. The π complex would decarboxylate less readily than the acetoxy radical itself, explaining the lower CO_2 yields.

(10) We also have studied[11] the viscosity dependence of k_{obsd} for the two diacyl peroxides, propionyl peroxide and lauroyl peroxide. Our studies indicate that the values of k_{obsd} for both are independent of viscosity. However, it is difficult to distinguish a small, finite slope in eq 3 from no slope, and we have collected an insufficient amount of data for these two compounds to distinguish between the two possibilities. Propionyl peroxide previously was shown to undergo 9% cage return at 80° in isooctane.[12]

(11) H. T. Bickley, Ph.D. Dissertation, Louisiana State University, 1971.

(12) J. C. Martin and J. H. Hargis, submitted for publication.

(13) (a) A. E. Nicholson and R. G. W. Norrish, *Discuss. Faraday Soc.*, **22**, 97 (1956); (b) C. Walling and J. Pellon, *J. Amer. Chem. Soc.*, **79**, 4786 (1957); (c) R. C. Neuman and J. V. Behar, *ibid.*, **91**, 6024 (1969).

(14) (a) G. S. Hammond and L. M. Soffer, *ibid.*, **72**, 4711 (1950); (b) J. K. Kochi, *ibid.*, **84**, 1572 (1962); (c) J. C. Martin and J. H. Hargis, *ibid.*, **91**, 5399 (1969).

chloride in the presence of iodine.[14a] Secondly, a 94% yield of *sec*-butyl benzoate is obtained when Bz_2O_2 and *cis*-butene-2 are heated in benzene.[14b] Thirdly, Martin and Hargis find that some ^{18}O scrambling has occurred in Bz_2O_2 recovered after partial decomposition;[14c] surprisingly, however, the amount of scrambling is anomalously small. Fourthly, high-pressure studies[13a,b] of Bz_2O_2 have been summarized by Neuman and Behar,[13c] and they conclude that the large activation volumes for Bz_2O_2 indicate initial scission of one bond.

Table III indicates some decrease in k_{obsd} for Bz_2O_2 with increasing solvent viscosity in the solvents hexane through hexadecane.[15] Analysis of these data using eq 3 (with $\alpha = 0.7$) gives a slope of 139 sec with a confidence level of 97.8%. Similar calculations for the known two-bond initiator TPiv (this compound will be discussed in detail later) give a slope of 3.6 sec with a confidence level of 64%. Since pure chance could yield a positive slope with a confidence level of 50%, the difference between Bz_2O_2 and TPiv is significant. From the magnitude and confidence level of the slope for Bz_2O_2, we conclude that Bz_2O_2 is a one-bond initiator.[16]

TABLE III
DECOMPOSITION OF BENZOYL PEROXIDE, Bz_2O_2, AT 80° IN ALKANE SOLVENTS[a]

Carbon no. of alkane	$10^5 k_{obsd}$, sec^{-1}		
6	2.85	2.85[b]	
7	2.57		
7	2.75	2.71[b]	2.98[c]
7	2.80		
iso-8	2.79	2.79[b]	
10	2.53	2.53[b]	
14	2.64		
14	2.64	2.64[b]	
14	2.63		
16	2.51	2.51[b]	2.70[c]

[a] Disappearance of initiator measured by the disappearance of its infrared carbonyl absorption. Concentration of initiator was 2×10^{-2} *M*. We also have measured $k_{obsd} = 2.94 \times 10^{-5}$ sec^{-1} in Nujol. This value has been disregarded, since induced decomposition might occur in this highly viscous solvent: J. C. Martin and J. H. Hargis, *J. Amer. Chem. Soc.*, **91**, 5399 (1969). [b] Average k_{obsd} values in each solvent. [c] 0.2 *M* styrene added.

The amount of cage return for Bz_2O_2 in isooctane can be calculated from these data, and 0.4% return is obtained. This value certainly cannot be very accurate, but it is in qualitative agreement with the finding of Martin that only a small fraction (4%) of the benzoyloxy radicals give cage return. It is puzzling that 35% of the acetoxy radicals from acetyl peroxide recombine in the cage under the same conditions where only about 4% of the benzoyloxy radicals from Bz_2O_2 do so.[17] Recent studies by Martin and Hargis[12] rule out the possibility that Bz_2O_2 undergoes significant amounts of return without scrambling of its oxygens. These authors also considered the possibility that the low value of f_r is due to electrostatic repulsive forces between the benzoyloxy radicals. To probe this, they carried out ^{18}O scrambling studies for three symmetrically substituted benzoyl peroxides, and their results indicate that there is no correlation between f_r and polar substitutent effects. The possibility that a larger activation barrier exists for the combination of the benzoyloxy radicals than for the acetoxy radicals has not been ruled out, but the reason why such a barrier might exist is not clear at present.[18]

tert-**Butyl Peroxy Esters.**—We have studied the decomposition of six peroxy esters in alkane solvents. Three of the peroxy esters, *tert*-butyl peroxyacetate (TAc), *tert*-butyl peroxypropionate (TPr), and *tert*-butyl peroxybenzoate (TBz), show decreasing values of k_{obsd} with increasing solvent viscosity; therefore, these peroxy esters are one-bond initiators (Table IV). This is in agreement with work by other authors.[13c,19a,b,c,g] The two peroxy esters, *tert*-butyl peroxypivalate (TPiv) and di-*tert*-butyl peroxyoxalate (TOx), show values of k_{obsd} that are independent of solvent viscosity and, therefore, behave as multi-bond initiators. The last compound, *tert*-butyl peroxyisobutyrate (TiBu), shows a small and somewhat irregular decrease in k_{obsd} with increasing solvent viscosity. When the data for TiBu are analyzed using eq 3 ($\alpha = 0.7$), a slope of 26 sec is found (confidence level 91%) and the amount of cage return is calculated to be about 1% in isooctane.

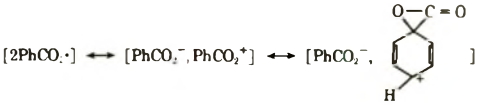
We also applied the acyloxy trapping technique[8a,b] to the alkyl series of peroxy esters, RCO_2OBu-*t*, where R varies from methyl (TAc) to ethyl (TPr) to isopropyl (TiBu) to *tert*-butyl (TPiv). The CO_2 yields from the decompositions of these peroxy esters in 4-methyl-1-cyclohexene (4MC)[8c] were measured gravimetrically, and these yields are listed in Table V together with the CO_2 yields from decompositions of the peroxy esters in alkane solvents under the same conditions. TAc and TPr give a smaller amount of CO_2 when decom-

(15) We have disregarded the k_{obsd} value in Nujol (Table III, footnote *a*), since other workers[14c] also have had inconsistent results, probably caused by induced decomposition, in this highly viscous solvent.

(16) Induced decomposition is not affecting the data of Table III importantly since the addition of styrene hardly changes k_{obsd}. We normally measured these rates under 1 atm air; degassing of the reaction mixtures increased k_{obsd} by 40–50% ($k_{obsd} = 3.84 \times 10^{-5}$ sec^{-1} in heptane, 4.14×10^{-5} sec^{-1} in tetradecane), indicating that induced decomposition of Bz_2O_2 occurs in the absence of air. Apparently there is enough oxygen present under atmospheric conditions to scavenge the radicals which cause induced decomposition.

(17) (a) J. W. Taylor and J. C. Martin, *J. Amer. Chem. Soc.*, **88**, 3650 (1966). (b) *ibid.*, **89**, 6904 (1967). (c) Martin and Taylor's data[17a,b] have been critized recently by M. J. Goldstein and H. A. Judson, *ibid.*, **92**, 4119 (1970). However, J. C. Martin has reevaluated Goldstein's data using very high ^{18}O levels and has obtained results in good agreement with his own previously published data. Private communication from J. C. Martin to W. A. Pryor, Jan 1971.

(18) One possibility which has not been suggested is that a complex between a carboxylate group of one fragment and the aromatic ring of another keeps the alignment of the two caged fragments such that they are poorly disposed to recombine. The Hammett correlation of the decomposition of benzoyl peroxides as well as Walling's recent mechanism for the induced decomposition provide some evidence for this: C. Walling and Ž. Čeković, *J. Amer. Chem. Soc.*, **89**, 6681 (1967). Resonance structures involving charge transfer can be written for the geminate pair.



(19) (a) P. D. Bartlett and R. R. Hiatt, *J. Amer. Chem. Soc.*, **80**, 1398 (1958). (b) T. Koenig, J. Huntington, and R. Cruthoff, submitted for publication. (c) No α-D secondary isotope effect was found in the decomposition of TPr: J. P. Stanley, Louisiana State University, private communication, 1968. (d) P. D. Bartlett and L. B. Gortler, *J. Amer. Chem. Soc.*, **85**, 1864 (1963). (e) P. D. Bartlett and D. M. Simons, *ibid.*, **82**, 1753 (1960). (f) T. Koenig and R. Wolf, *ibid.*, **89**, 2948 (1967). (g) T. Koenig, M. Deinzer, and J. A. Hoobler, *ibid.*, **93**, 938 (1971). (h) T. Koenig and M. Deinzer, *ibid.*, **90**, 7014 (1968).

TABLE IV

RATE CONSTANTS, $10^5 k_{obsd}$, sec^{-1}, FOR HOMOLYSIS OF PEROXY ESTERS, RCO_2O-*t*-Bu, IN ALKANE SOLVENTS[a]

Carbon no. of alkane	R / Temp, °C	CH_3[b] (TAc) 100	CH_3CH_2 (TPr) 100	$(CH_3)_2CH$ (TiBu) 100	$(CH_3)_3C$ (TPiv) 80	$(CH_3)_3C$[c] (TPiv) 80	C_6H_5 (TBz) 115	$(CH_3)_3COOC(O)$ (TOx) 41
7						23.3	7.21	
8		2.07	2.03	15.9	23.4	23.4	7.06	17.9
10		1.95	1.82	14.6	23.8	21.8	6.77	17.5
12		1.78	1.78	15.6	20.0	23.8	6.44	18.1
14		1.67	1.68	15.2	21.6	22.7	6.03	17.1
16		1.55	1.58	14.7	24.4	23.9	5.97	

[a] All rate constants were obtained by directly observing the disappearance of peroxy ester except for di-*tert*-butyl peroxyoxalate (TOx), where the excess scavenger technique was used and with galvinoxyl as the scavenger. Most rate constants are the average of at least three separate runs. [b] Rate constants from Ph.D. Dissertation of K. W. Smith, Louisiana State University, 1969. [c] 74% peroxy ester in mineral spirits as purchased from Lucidol. The purities of the peroxy esters TPr, TiBu, and TPiv were determined by iodometric titration, using the method by L. S. Silbert and D. Swern, *Anal. Chem.*, **30**, 385 (1958); 95% pure peroxy ester was considered satisfactory.

TABLE V

CO_2 YIELDS FROM DECOMPOSITIONS OF PEROXY ESTERS, RCO_2O-*t*-Bu

R	Solvent	Temp, °C	CO_2, %[a]
CH_3	Isooctane	80	97
	Isooctane	100	103
(TAc)	Decane	130	100, 102
	4MC[b]	80	75, 76, 77
	4MC	100	70, 74, 77, 77, 78, 78, 79
CH_3CH_2	Isooctane	100	92
	Decane	130	95
(TPr)	4MC	80	48, 59
	4MC	100	54, 55, 57, 61, 65
$(CH_3)_2CH$	Isooctane	80	92, 94
	Isooctane	100	100
(TiBu)	4MC	80	98, 101
	4MC	100	104
$(CH_3)_3C$[c]	Isooctane	80	95, 101
(TPiv)	4MC	80	103, 103, 91

[a] Purity of the peroxy esters was determined by iodometric titration, method by L. S. Silbert and D. Swern, *Anal. Chem.*, **30**, 385 (1958). The CO_2 yields were corrected for less than 100% pure peroxy ester; theoretical molar ratio of CO_2 to peroxy ester is 1:1. [b] 4-Methyl-1-cyclohexene. [c] 15% Mineral spirits present in the peroxy ester before dissolving in isooctane or 4MC.

TABLE VI

RATE CONSTANTS FOR β SCISSION OF SOME RADICALS[a]

Reaction	Rate constant, sec^{-1}	Temp, °C
$CH_3CO_2\cdot \longrightarrow CH_3\cdot + CO_2$	1.6×10^{9}[b]	60
$C_2H_5CO_2\cdot \longrightarrow C_2H_5\cdot + CO_2$	1.6×10^{9}[c]	60
t-$BuO\cdot \longrightarrow CH_3\cdot + CH_3COCH_3$	2×10^{5}[d]	80
$C_6H_5CO_2\cdot \longrightarrow C_6H_5\cdot + CO_2$	10^{4}–10^{5}[e,f]	80

[a] The rate constant for diffusion of a radical from a solvent cage is of the order of 10^{10} sec^{-1}. [b] W. Braun, L. Rajbenbach, and F. R. Eirich, *J. Phys. Chem.*, **66**, 1591 (1962). [c] This rate constant is not smaller than that for the acetoxy radical; decarboxylation of the acetoxy and propionyloxy radicals has $\Delta H = -15$ and -17 kcal/mol [S. W. Benson, "Thermochemical Kinetics," Wiley, New York, N. Y., 1968, pp 178–181; S. W. Benson in "Organic Peroxides," Vol. I, D. Swern, Ed., Wiley-Interscience, New York, N. Y., 1970, p 121; G. P. Adams, D. H. Fine, P. Gray, and P. G. Laye, *J. Chem. Soc. B*, 720 (1967)]. [d] Calculated using an A factor of $10^{13.4}$ sec^{-1} and E_a = 13 kcal/mol (P. Gray, R. Shaw, and J. C. J. Thynne in "Progress in Reaction Kinetics," Vol. 4, G. Porter Ed., Pergamon Press, Oxford, 1967, pp 79, 81, and 97). A rate constant of 10^3 sec^{-1} at 160° was measured for this reaction in the gas phase by F. W. Birss, C. J. Danby, and C. Hinshelwood, *Proc. Roy. Soc., Ser. A*, **239**, 154 (1957). [e] D. F. DeTar, *J. Amer. Chem. Soc.*, **89**, 4058 (1967). [f] J. C. Bevington and J. Toole, *J. Polym. Sci.*, **28**, 413 (1958).

posed in 4MC than in decane or isooctane, whereas TiBu and TPiv give close to theoretical amounts of CO_2 when decomposed in both 4MC and in alkane solvents. Thus, the acyloxy fragments from TAc and TPr can be trapped[20a] and these peroxy esters are one-bond initiators, whereas TiBu and TPiv behave as multi-bond initiators. Literature results for TAc,[19a,b,h] TPr,[19c] and TPiv[19e,f] support these conclusions (Table II). The nonconcerted decomposition of TAc and TPr clearly is due to the fact that $CH_3CO_2\cdot$ and $C_2H_5CO_2\cdot$ are sufficiently stable so that cage return can compete with decarboxylation (Table VI).

The viscosity and the CO_2 scavenging data for TiBu do not agree, and this compound requires more extensive discussion. The rate of decomposition of TiBu is sensitive to solvent viscosity, but the i-$PrCO_2\cdot$ radical from it cannot be scavenged by 4MC. In the series of peroxy esters RCO_2OBu-*t*, where R is Me, Et, *i*-Pr, or *t*-Bu, the first two compounds decompose by a one-bond mechanism, the fourth by a two-bond path, and the third compound is borderline (see Table

(20) (a) Martin and Dombchik[20b] were unable to find any cyclohexyl propionate from the decomposition of acetyl propionyl peroxide in cyclohexene, and, therefore, the reduced amount of CO_2 from the decomposition of TPr in 4MC is unexpected. We cannot explain the difference in our results and Martin's. We did not isolate any products from the reaction of TPr in 4MC, but infrared analysis of the crude reaction mixture showed that the disappearance of the perester carbonyl absorption at 1787 cm^{-1} coincided with the appearance of an absorption at 1743 cm^{-1}, typical of an ester carbonyl group. We also cannot explain why we observe a greater reduction in CO_2 yields for TPr than for TAc, opposite of what would be expected. However, our results are not due to induced decomposition, since the rate constants for decomposition of both TAc and TPr were the same in the alkane solvents and 4MC. (b) J. C. Martin, private communication. Also see J. C. Martin and S. A. Dombchik, *Advan. Chem. Ser.*, **75**, 269 (1968). (c) It is conceivable that an initiator exists which has relative energies for one- and two-bond scission such that the two processes can occur simultaneously. (Even if the transition state for one has a slightly higher energy than the other, differing trajectories on the region of the reaction surface where the two paths divide would not be improbable for molecules having different kinetic energies.) If this were to describe the behavior of TiBu, then an overall 1% return could result, for example, from the average of 10% return by 10% of the peroxy ester plus 0% return by 90% of the material which undergoes two-bond scission. (d) We have discussed the case of an initiator which decarboxylates ten times faster than does acetyl peroxide but undergoes diffusion and cage recombination at the same rate as Ac_2O_2. Such a compound would appear to be a two-bond initiator by the viscosity test even if it were a one-bond. See ref 5b, Table I. (e) T. W. Koenig and W. D. Brewer, *Tetrahedron Lett.*, **No. 32**, 2773 (1965). (f) The only data in the literature relevant to the mechanism of decomposition of TiBu is the measurement by Bartlett and Gortler[19d] of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values. This allows the application of the isokinetic test to this compound, and the method predicts that the peroxy ester is a two-bond initiator. However, the lack of reliability of this method has recently been discussed, and it is extremely doubtful if the isokinetic plot can be used to decide the number of bonds which initially break in peroxy ester decompositions.[20g] (g) W. A. Pryor and K. Smith, *Int. J. Chem. Kinet.*, **3**, 387 (1971).

TABLE VII

COMPARISON OF AMOUNTS OF CAGE RETURN FOR DIACYL OR DIAROYL AND RELATED PEROXY ESTERS[a]

R	Cage return, % (Temp, °C)[b] RC(=O)OOC(=O)R	RC(=O)OO-*t*-Bu
CH_3	18[b,c] (80)	18[b,d] (100)
C_2H_5	9[e] (80)	15[d] (100)
Ph	4[f] (80)	11[d] (115)

[a] Decomposition of PPO and Bz_2O_2 in isooctane, all the other compounds in octane. [b] All the peroxy esters were decomposed at higher temperatures than the related peroxides. Therefore, since the amount of cage return increases with decreasing temperature, TAc (R = CH_3) would give more than 18% return at 80°. [c] By viscosity test, α = 0.7: W. A. Pryor and K. Smith, *J. Amer. Chem. Soc.*, 92, 5403 (1970). [d] By viscosity test, α = 0.7. [e] J. C. Martin and J. H. Hargis, submitted for publication. [f] J. C. Martin and J. H. Hargis, *J. Amer. Chem. Soc.*, 91, 5399 (1969).

IV). The stability of the *i*-$PrCO_2\cdot$ radical is such that its rate of decarboxylation is comparable to its rate of cage recombination; nevertheless, the viscosity test indicates a very small amount of cage return.[20c,d]

The lack of agreement of the scavenging and viscosity data for TiBu is not unexpected, since the viscosity test should be more sensitive than the CO_2 scavenging method. One-bond behavior will be registered by the viscosity test if radical recombination in the cage is able to compete with decarboxylation; the CO_2 scavenging method, however, requires that addition of the acyloxy radical to an olefin compete with decarboxylation. Since radical recombination is much faster than addition of a radical to an olefin, it is not surprising that the more sensitive viscosity test can detect one-bond behavior for a borderline compound such as TiBu, although the intermediate acyloxy radical cannot be trapped by 4MC.

Two further features of the behavior of this peroxy ester are worthy of mention. Firstly, no study has yet been made by more reliable methods to determine whether this is a one- or two-bond initiator. Both the secondary deuterium isotope effect test[20e] and the ^{18}O method[20b] should be applied to TiBu to test the prediction from our viscosity test.[20f] Secondly, the amount of cage return in octane calculated for TiBu from the data in Table IV is 1%. Despite the moderate confidence level for this slope (91%), the data are sufficiently scattered and the total change in k_{obsd} values from octane to hexadecane is so small (*ca.* 8%) that the intercept of a plot of eq 3 predicts the return to be 1 ± 2%. Thus, the conclusions based on the viscosity data, although reasonable, must be taken as tentative.

Comparison of Peroxy Esters and Diacyl or Diaroyl Peroxides.—It is interesting to compare the amount of cage return for some of the peroxy esters and the corresponding diacyl or diaroyl peroxides which we have studied. Table VII lists three peroxides and the related peroxy esters and shows that each peroxy ester undergoes cage return to a larger extent than the corresponding peroxide (see also Table VIII). In the two cases where R is an alkyl group, methyl or ethyl, this can be explained. Table VI gives rate constants for β scission of acetoxy, propionyloxy, *tert*-butoxy, and benzoyloxy radicals; only the first two radicals undergo β scission fast enough to compete with cage return. Therefore, in going from Ac_2O_2 to TAc, one of the unstable acetoxy fragments is replaced with the relatively stable *tert*-butoxy, and the peroxy ester would be expected to undergo a larger amount of cage return. However, for Bz_2O_2 and TBz, both the $PhCO_2\cdot$ and the *t*-BuO· radicals are stable on the time scale of cage processes. Thus, the smaller amount of cage return for Bz_2O_2 relative to TBz can be explained only by assuming that two $PhCO_2\cdot$ radicals combine more slowly than do a $PhCO_2\cdot$ and a *tert*-butoxy. It is not obvious why this should be true,[12] but it may be related to the ambident nature of the benzoyloxy radicals.[18]

TABLE VIII

CAGE RETURN, f_r, OF ONE-BOND INITIATORS DECOMPOSED IN ALKANE SOLVENTS

Initiator[a]	Carbon no. of alkane	Temp, °C	f_r[b] By viscosity test using α = 0.5	α = 0.7	By ^{18}O
Ac_2O_2	8	80	0.28[c]	0.18	0.35[d]
TAc	8	100	0.30[e]	0.18	
TAc	9	130	0.12[e]	0.09	
TAc	Nujol	100	0.67[e]	0.61	0.38[f]
TAc	Nujol	130	0.47[e]	0.40	
TPr	8	100	0.23	0.15	
Bz_2O_2	iso-8	80	0.02	0.004	0.04[g]
TBz	8	115	0.17	0.11	0.06[h]
NOON	8	80	0.79[i]	0.49[i]	
TOOT	8	80	0.32	0.20	
TOOT	9	80	0.36	0.22	
	9	100	0.33	0.20	
	9	110	0.18	0.07	
	9	120	0.16	0.07	
	9	130	0.11	0.06	

[a] Acetyl peroxide is listed as Ac_2O_2, and for the other abbreviations, see Table I. [b] The value of f_r was calculated from eq 16, footnote c of this table. [c] W. A. Pryor and K. Smith, *J. Amer. Chem. Soc.*, 92, 5403 (1970). [d] Calculated from eq 19, ref 5b, using the k_s value of J. C. Martin and S. A. Dombchik, *Advan. Chem. Ser.*, 75, 269 (1968). The solvent is isooctane. [e] Data from Ph.D. Dissertation by K. Smith, Louisiana State University, 1969. [f] T. Koenig and M. Deinzer, *J. Amer. Chem. Soc.*, 90, 7014 (1968). [g] J. C. Martin and J. H. Hargis, *ibid.*, 91, 5399 (1969). [h] Calculated as in footnote d using data of T. Koenig, M. Deinzer, and J. A. Hoobler, *ibid.*, 93, 938 (1971); temperature is 130° and solvent is isooctane. [i] These values are too high; see the discussion in the text.

TABLE IX

RATE CONSTANT, $10^7 k_{obsd}$, SEC^{-1}, FOR HOMOLYSIS OF DIALKYL PEROXIDES, ROOR, IN ALKANE SOLVENTS[a]

Carbon no. of alkane	R	$(CH_3)_3C$[b] (TOOT)	$(CH_3)_3C$[c] (TOOT)	$(CH_3)_3C$[c] (TOOT)	*n*-C_4H_9[b] (NOON)
	Temp, °C	80	110	130	80
6		0.164	21.7		
7		0.144	21.9		0.204
8		0.148	21.9		0.158
9		0.136	20.1	254 (250)	
10		0.139	20.1	248	0.143
12		0.129	18.7	244 (246)	0.117
14		0.112	18.2	238 (214)	0.096
16		0.107	18.2	233	0.088

[a] Most rate constants are the average from at least three separate runs. We also measured k_{obsd} for TOOT in Nujol: 110°, 12.9 × 10^{-7} sec^{-1}; 130°, 166 × 10^{-7} sec^{-1}. [b] Rate constant by excess initiator method; iodine was used as the scavenger. [c] Disappearance of peroxide measured directly by the disappearance of an infrared absorption peak at 878 cm^{-1}. The numbers in parenthesis are by excess scavenger technique, using iodine as the scavenger.

Dialkyl Peroxides.—*tert*-Butyl peroxide (TOOT) and *n*-butyl peroxide (NOON) were decomposed in alkane solvents, and k_{obsd} for both initiators decreases with increasing solvent viscosity (Table IX). There-

TABLE X
DECOMPOSITION PRODUCTS FROM ALKYL PEROXIDES, ROOR, IN ALKANE SOLVENTS AT 130°

R	Carbon no. of alkane	10^2 [ROOR]$_0$, M	% ROH[a]	% Acetone[a]	ROH/Acetone	ROH/MEK[b]
$(CH_3)_3C$	Benzene[c]	10.14	23.3	76.0		
(TOOT)	iso-8	9.44	98.9			
	8	7.82	96.8	2.5	38.7	
	12	9.45	93.0	2.4	38.8	
	14	9.51	95.8	2.0	47.9	
	16	10.66	93.9	2.3	40.8	
$C_2H_5CH(CH_3)$	12	4.65				1.73
(SOOS)	14	4.79				1.60
	Nujol	4.87				1.05

[a] Based on 2 mol of product per mole of peroxide. [b] The decomposition of *sec*-butyl peroxide was carried out to only one half-life, but the ratio ROH/MEK was checked at different times during the decomposition and was found to be constant. [c] The ratio ROH/acetone = 0.3 from this decomposition of TOOT in benzene compares well with the ratio of 0.6 obtained when TOOT was decomposed in *tert*-butyl benzene at 125°: J. H. Raley, F. F. Rust, and W. E. Vaughan, *J. Amer. Chem. Soc.*, **70**, 1336 (1948).

fore, these peroxides are one-bond initiators, in agreement with chemical intuition and with the results of other workers.[21]

Our studies of the decomposition products from TOOT in alkanes at 130° (Table X) show that *tert*-butyl alcohol is formed in almost quantitative yield. This indicates that essentially no β scission of the *tert*-butoxy radical occurs, and also that no cage disproportionation occurs between two *tert*-butoxy radicals. We found no *tert*-butyl methyl ether[22] in the reaction products; this also implies that β scission of the *tert*-butoxy radicals does not occur. Calculation from our viscosity data of f_r for TOOT at 80° in octane gives 20–32% cage return, depending on the α value used (see Table VIII). Kiefer and Traylor[23] have studied the photolytic decomposition of TOOT at 45° and have concluded that TOOT undergoes 12% cage return in isooctane. This value is fairly close to the range suggested by our studies, but several facts should be kept in mind when our work and Kiefer and Traylor's are compared. Firstly, our choice of α value of either 0.5 or 0.7 is still somewhat arbitrary. We have shown[7] that several small molecules, including benzene and iodine, diffuse with an α value of 0.7, but we have not studied the diffusion of a molecule which was specifically chosen as a model for *tert*-butoxy radicals (*e.g.*, *tert*-butyl alcohol). Secondly, the procedure used by Kiefer and Traylor can be criticized. They measured the amount of TOOT formed as a cage product from the thermal decomposition of di-*tert*-butyl hyponitrile (DBH) and di-*tert*-butyl peroxyoxalate (TOx) in alkanes at 45°. Decreasing amounts of TOOT were formed from these two compounds with decreasing solvent viscosity, and both compounds gave the same yield of TOOT (4%) in pentane. They then *assumed* that this could be taken as the f_r value for TOOT in pentane, and they used this value together with the k_{obsd} value found by photolysis of TOOT to calculate 12% cage return for TOOT in octane. One weakness of this approach is that even though the same yield of TOOT is produced as a cage product when one N_2 molecule separates two *t*-BuO· radicals (as in DBH) or when two CO_2 molecules do so (as in TOx), it does not necessarily follow that the same yield of TOOT will be produced by cage return when no molecules at all separate the geminate pair. This could be a very different situation and could produce a larger yield of "cage product" from TOOT relative to DBH or TOx. A second weakness of Traylor's approach is that DBH and TOx were thermalized, but, in order to achieve similar rates, TOOT was photolyzed. It is not safe to assume that thermolysis and photolysis of an initiator give the same extent of cage return. Radicals formed by photolysis can be kinetically excited ("hot"), and their diffusion apart may be enhanced relative to their combination.[24a,b] Clearly, therefore, our measured values of f_r for TOOT are not necessarily in conflict with the results of Kiefer and Traylor.

The amount of cage return for di-*n*-butyl peroxide (NOON), as calculated from our viscosity data, is more than twice as large as f_r for TOOT (Table VIII). We could not follow the disappearance of NOON directly, since there is no significant change in its absorption spectra upon decomposition. Therefore, the excess scavenger technique[5b] was employed. When this method is used, disproportionation of the initially formed radicals in the cage could reduce the yield of scavengable radicals and lower the apparent observed rate constant for decomposition. The amount of this cage disproportionation could increase with solvent viscosity, and part of the viscosity dependence of k_{obsd} could be caused by this. Unfortunately, the decomposition of NOON was not studied by any other method. When we attempted to probe whether the *n*-butoxy radicals undergo cage disproportionation, we found one of the expected products, butyraldehyde, to be unstable in the presence of radicals. Therefore, we studied the decomposition of di-*sec*-butyl peroxide (SOOS) under identical conditions and found that there is a significant amount of cage disproportionation of the *sec*-butoxy radicals. Firstly, a significant amount of methyl ethyl ketone (MEK) is formed, and, secondly, the ratio of *sec*-butyl alcohol to MEK decreases with in-

(21) E. S. Huyser and R. M. VanScoy, *J. Org. Chem.*, **33**, 3524 (1968); C. Walling and G. Metzger, *J. Amer. Chem. Soc.*, **81**, 5365 (1959); C. Walling and H. P. Waits, *J. Phys. Chem.*, **71**, 2361 (1967).

(22) We analyzed the products by glc and an amount of 3×10^{-5} M of *tert*-butyl methyl ether could be detected.

(23) H. Kiefer and T. G. Traylor, *J. Amer. Chem. Soc.*, **89**, 6667 (1967).

(24) (a) W. A. Pryor and R. W. Henderson, *ibid.*, **92**, 7234 (1970), have compared the reaction products from *tert*-butyl peroxyformate when the compound was decomposed thermally and photolytically. Photolysis gave more CO_2 and less formic acid than thermolysis. This can be interpreted as implying that the photolysis is a two-bond process whereas thermolysis is one-bond. (b) Kiefer and Traylor show that both photochemical and thermal decomposition of DBH give the same cage yield of TOOT. However, DBH, an azo compound, probably decomposes from an excited singlet state. If TOOT were to decompose *via* a triplet, then the photochemical and thermal cage return yields would be expected to be different. At present, there is no reason to exclude photodecomposition of TOOT from a triplet state.

creasing solvent viscosity (Table X). We conclude from these results that cage disproportionation also occurs during the decomposition of NOON. Therefore, the amount of cage return calculated from our viscosity data on NOON is too high.[25]

Conclusion.—Thus we conclude that the viscosity test gives the "correct" answer for all the compounds which we have studied. However, for peroxides such as Bz_2O_2 which undergo a very small amount of cage return, the viscosity test may not always be capable of distinguishing one-bond from multi-bond scission.

Experimental Section

Hydrocarbons.—Technical grade alkanes from Phillips Petroleum Co. were purified as previously described.[5b]

Radical Scavengers.—Triply sublimed iodine from W. H. Curtin and Co. was used without further purification. Galvinoxyl was synthesized by the procedure of Kharasch and Joshi.[26] 4-Methyl-1-cyclohexene from Aldrich Chemical Co. was used without further purification. Styrene (Aldrich) was washed with 10% sodium hydroxide and water, dried, and distilled three times under reduced pressure.

Diaroyl Peroxide.—Benzoyl peroxide (Bz_2O_2) (Lucidol) was recrystallized several times from CCl_4 and methanol.

***tert*-Butyl Peroxy Esters.**—*tert*-Butyl peroxyacetate (TAc) and *tert*-butyl peroxyisobutyrate (TiBu), Lucidol, were distilled under reduced pressure at 25°. *tert*-Butyl peroxypropionate (TPr) was prepared by the method of Bartlett and Hiatt[19a] for TAc. A 75% solution of *tert*-butyl peroxypivalate (TPiv) in mineral spirits was purchased from Lucidol. The boiling points of the peroxy ester and the solvent were too close to allow separation by distillation. Chromatography, three passages, on Woelm neutral alumina grade 1, and with hexane as eluent, gave about 10% of 91% pure peroxy ester. The mineral spirits were eluted from the column very shortly before the peroxy ester. *tert*-Butyl peroxybenzoate (TBz), 98% pure (Lucidol), was used without further purification. Di-*tert*-butyl peroxyoxalate (TOx) was prepared by the method of Bartlett, Benzing, and Pincock.[27] The compound was recrystallized from pentane at −78°. (This compound is susceptible to detonation.) The peroxy esters TPr, TiBu, and TPiv were analyzed by iodometric titration.[28]

Dialkyl Peroxides.—*tert*-Butyl peroxide (TOOT), Lucidol, was used without further purification. *n*-Butyl peroxide (NOON) was prepared by the method of Mosher, *et al.*[29] *sec*-Butyl peroxide (SOOS) was synthesized by the method of Pryor and coworkers.[30]

Determination of CO_2 from Homolysis of Peroxy Esters.—Round-bottom ampoules (25 ml, Kontes) with two sealed tip side arms, 7 × 100 mm, were used as reaction vessels. The peroxy ester solution and a Teflon stir bar were introduced into the ampoule through its 10 × 70 mm neck, which was connected to a vacuum pump during the degassing procedure and thereafter was sealed off. The sealed ampoules were immersed in a constant-temperature bath and after complete reaction, the CO_2 was measured by absorption on Ascarite, KOH on asbestos (A. H. Thomas Co.) by the method of Shine and coworkers.[8b]

Procedure for Kinetic Runs.—We have used three methods for obtaining rate constants for homolysis of radical initiators: direct observance of initiator disappearance, first-order disappearance of scavenger, or zero-order disappearance of scavenger. These methods have been described previously,[5b] and the raw data were treated by a computer program to obtain a least squares fit of the data to the applicable rate law. Tables III, IV, and IX indicate the method used to find the rate constant for each peroxy compound. Our estimate of the accuracy of the rate constants is ±6% as determined from the probable error in each rate constant and the random variation in k_{obsd} with solvent viscosity for the multi-bond initiators in Table IV.

Registry No.—Benzoyl peroxide, 94-36-0; TAc, 107-71-1; TPr, 14206-05-4; TiBu, 109-13-7; TPiv, 927-07-1; TBz, 614-45-9; TOx, 1876-22-8; Ac_2O_2, 110-22-5; NOON, 3849-34-1; TOOT, 110-05-4; SOOS, 4715-28-0.

(25) (a) β Scission of the *n*-BuO· radical to formaldehyde and a propyl radical is considered negligible, since no β scission occurs for the *t*-BuO· radical, and both reactions have the same activation energy (13 kcal/mol) and preexponential (~10^{14} sec^{-1}) for β scission.[25b] The other decomposition mode of the *n*-BuO· radical to form a hydrogen atom and butyraldehyde will occur with even less probability.[25b] (b) P. Gray, R. Shaw, and J. C. J. Thynne in "Progress in Reaction Kinetics," Vol. 4, G. Porter, Ed., Pergamon Press, Oxford, 1967, pp 92–93.

(26) M. S. Kharasch and B. S. Joshi, *J. Org. Chem.*, **22**, 1435 (1957).

(27) P. D. Bartlett, E. P. Benzing, and R. E. Pincock, *J. Amer. Chem. Soc.*, **82**, 1762 (1960).

(28) L. S. Silbert and D. Swern, *Anal. Chem.*, **30**, 385 (1958).

(29) F. Welch, H. R. Williams, and H. S. Mosher, *J. Amer. Chem. Soc.*, **77**, 551 (1955).

(30) W. A. Pryor, D. M. Huston, T. R. Fiske, T. L. Pickering, and E. Ciuffarin, *ibid.*, **86**, 4237 (1964).

The Synthesis and Properties of Phosgene Phenylhydrazones

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Methods for the synthesis of phosgene phenylhydrazones, a new group of imidoyl chlorides, are described. Chlorination of various 2,3,4-pentanetrione 3-phenylhydrazones gave ring-substituted 1,1-dichloro-1-phenylazo-2-propanones that were readily hydrolyzed to the corresponding phosgene phenylhydrazones. Chlorination of glyoxylic acid 2-[(2,4,6-trichlorophenyl)hydrazone] (**19**) and formaldehyde (*p*-nitrophenyl) hydrazone (**23**) gave phosgene (2,4,6-trichlorophenyl)hydrazone (**10a**) and phosgene (2-chloro-4-nitrophenyl)hydrazone (**26**), respectively. Phosgene phenylhydrazones react relatively slowly with nucleophilic reagents with displacement of both acid chloride substituents; products formed by displacement of only one chlorine atom were not detected.

The chemistry of imidoyl halides has received considerable attention in the past and has recently been reviewed by Ulrich.[1] In the course of studies on the chlorination of phenylhydrazones we have discovered a new group of imidoyl chlorides, the phosgene phenylhydrazones (**2**); the preparation and properties of these compounds are detailed herein.

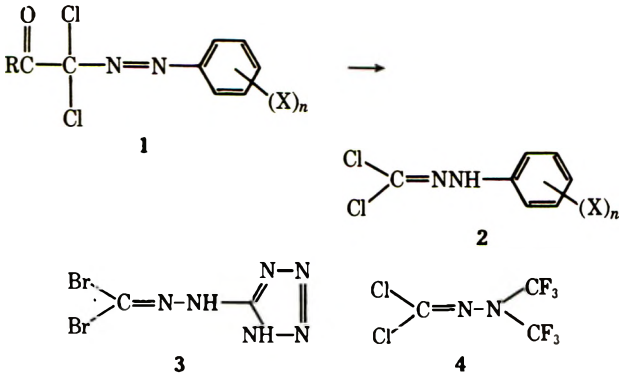
While synthesis of the carbonyl halide hydrazones **3**[2] and **4**[3] and preparation of a variety of carbonyl halide azines have been described,[2,4] no phosgene phenylhydrazone had been reported prior to our description of phosgene (2,4,6-trichloro-*m*-tolyl)hydrazone, which was prepared by refluxing ethyl dichloro[(2,4,6-tri-

(1) H. Ulrich, "The Chemistry of Imidoyl Halides," Plenum Press, New York, N. Y., 1968.

(2) J. Thiele, *Justus Liebigs Ann. Chem.*, **303**, 57 (1898).

(3) R. C. Dobbie and H. J. Emeleus, *J. Chem. Soc. A*, 933 (1966).

(4) (a) H. Reimlinger, *Chem. Ber.*, **97**, 3505 (1964); (b) R. A. Mitsch and P. H. Ogden, *J. Org. Chem.*, **31**, 3833 (1966); (c) F. L. Scott and D. A. Cronin, *Chem. Ind. (London)*, 1757 (1964); (d) F. L. Scott, J. Donovan, and J. K. O'Halloran, *Tetrahedron Lett.*, 4079 (1970).



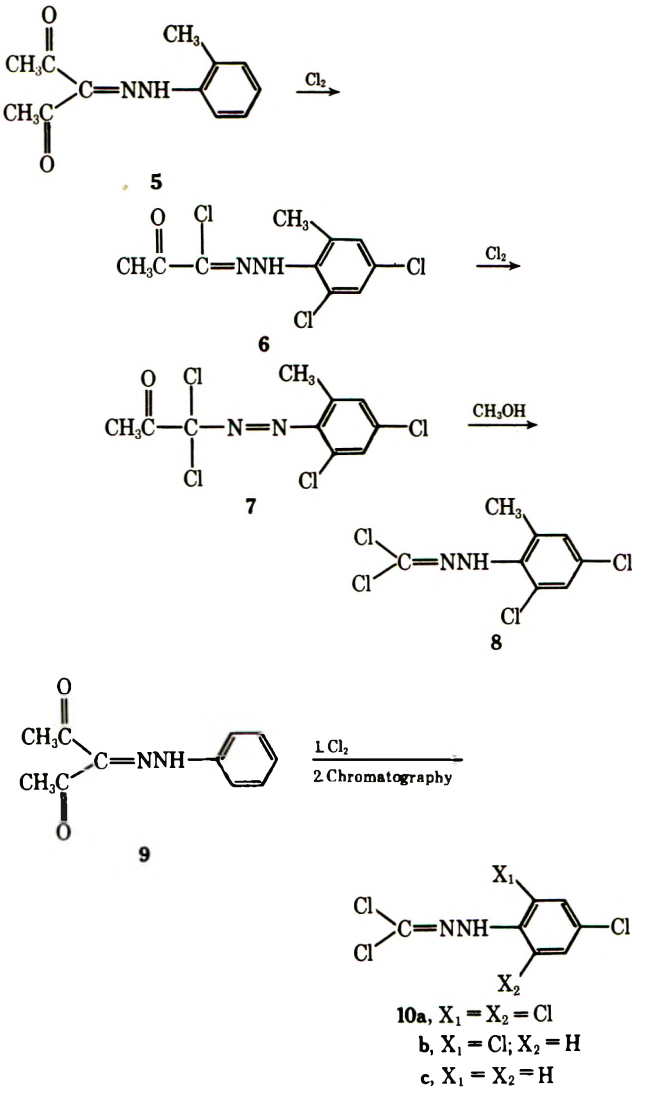
chloro-*m*-tolyl)azo]acetate (general formula **1**, R = OC_2H_5) in acetic acid for 4 hr.[5] This reaction, a new example of the Japp–Klingemann reaction,[6] may alternately be effected at room temperature by treating the azo ester with 1 equiv of morpholine in methanol.

The most convenient synthesis of phosgene phenylhydrazones found to date is a modification of this method. The hitherto unreported azo ketones of structure **1** (R = CH_3), prepared by chlorination of 2,3,4-pentanetrione 3-phenylhydrazones, readily undergo Japp–Klingemann cleavage to phosgene phenylhydrazones when heated in methanol or when chromatographed on silica gel; azo esters of structure **1** are stable under these reaction conditions. Thus 2,3,4-pentanetrione 3-(*o*-tolylhydrazone) (**5**), prepared from 2,4-pentanedione and *o*-tolyldiazonium chloride, reacted in chloroform with 3 molar equiv of chlorine to give pyruvoyl chloride 1-[(4,6-dichloro-*o*-tolyl)hydrazone][7] (**6**) and with excess chlorine to give 1,1-dichloro-1-[(4,6-dichloro-*o*-tolyl)azo]-2-propanone (**7**). Compound **7**, an orange oil, decomposed with gas evolution on attempted distillation at reduced pressure; the structure of the crude product (>90% pure) was supported by nmr and ir spectra (no NH absorption, carbonyl band at 1735 cm^{-1}).[8] When **7** was heated in methanol, or treated with 1 equiv of morpholine in methanol, phosgene (4,6-dichloro-*o*-tolyl)hydrazone (**8**) was obtained (71% yield from **5**).

A disadvantage of this synthetic method is that a pentanetrione phenylhydrazone may give on chlorination and subsequent Japp–Klingemann cleavage mixtures of ring-chlorinated azo ketones (**1**) and phosgene phenylhydrazones. For example, 2,3,4-pentanetrione 3-(phenylhydrazone) gave on chlorination a mixture of azo ketones that decomposed when chromatographed on silica gel to a separable mixture of phosgene (2,4,6-trichlorophenyl)hydrazone (**10a**), phosgene (2,4-dichlorophenyl)hydrazone (**10b**), and phosgene (*p*-chlorophenyl)hydrazone (**10c**).

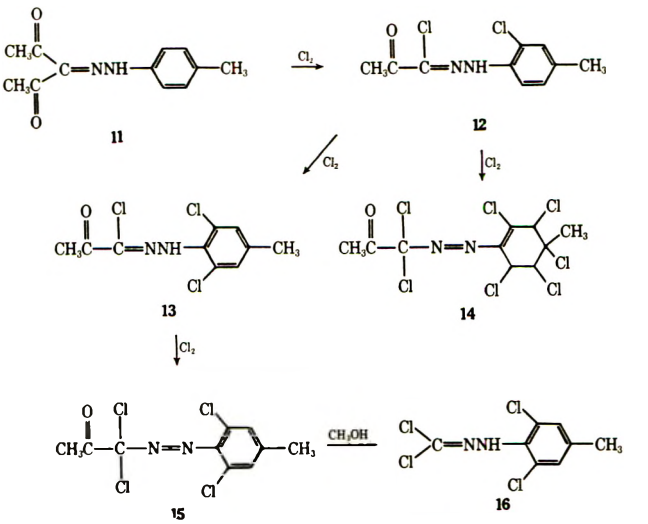
A mixture of products was also obtained on chlorination of 2,3,4-pentanetrione 3-(*p*-tolyhydrazone) (**11**) and the yield of phosgene (2,6-dichloro-*p*-tolyl)hydrazone (**16**) was low (37%). A major by-product in the reaction was found to be **14** and, using limited amounts of chlorine, the reaction was shown to proceed according to Scheme I; formation of a perchlorinated product related to **14** during phenylhydrazone chlorination was recently reported.[5]

Pentanetrione phenylhydrazones may also be brominated to afford carbonyl bromide phenylhydrazones.



10a, $X_1 = X_2 = Cl$
b, $X_1 = Cl; X_2 = H$
c, $X_1 = X_2 = H$

SCHEME I



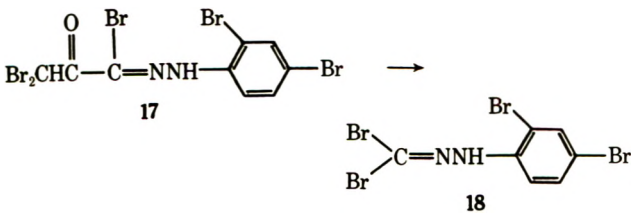
(5) M. W. Moon, *J. Org. Chem.*, **37**, 386 (1972); an alternate name for phosgene (2,4,6-trichloro-*m*-tolyl)hydrazone is (2,4,6-trichloro-*m*-toluidino)-imidocarbonyl chloride.

(6) R. R. Phillips, *Org. React.*, **10**, 143 (1959); azo compounds previously known to undergo the Japp–Klingemann reaction all have at least two unsaturated groups (*e.g.*, ketone, ester, or nitrile) attached to the α-carbon atom.

(7) Pyruvoyl chloride 1-phenylhydrazones have previously been obtained by chlorination of 2,3,4-pentanetrione 3-phenylhydrazones; see F. D. Chattaway and D. R. Ashworth, *J. Chem. Soc.*, 939 (1934).

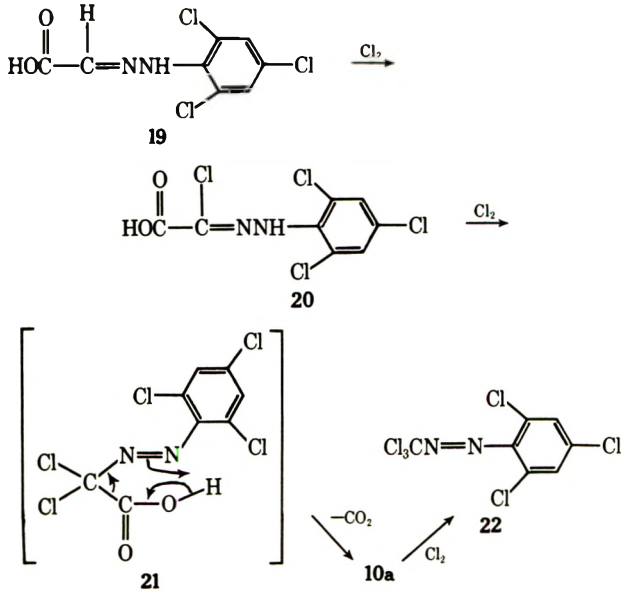
(8) Related compounds have recently been shown to be azo compounds and not *N*-chloro compounds; see ref 5 and M. W. Moon, *J. Org. Chem.*, **37**, 383 (1972).

Thus **9** reacted with bromine to give dibromopyruvoyl bromide (2,4-dibromophenyl)hydrazone (**17**)[9] and this was treated with *N*-bromosuccinimide in methanol, giving carbonyl bromide (2,4-dibromophenyl)hydrazone (**18**).

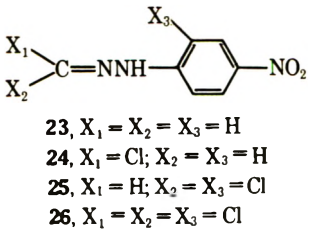


Phosgene phenylhydrazones may also be prepared by chlorination of glyoxylic acid phenylhydrazones and formaldehyde phenylhydrazones. These alternate syntheses have the disadvantage that chlorination gives the phosgene phenylhydrazones directly and these can react further with chlorine to give azo compounds, particularly when acetic acid is used as the reaction solvent.

Glyoxylic acid 2-[(2,4,6-trichlorophenyl)hydrazone] (**19**) reacted with chlorine in acetic acid to give chloroglyoxylic acid 2-[(2,4,6-trichlorophenyl)hydrazone] (**20**)[10] and this was further chlorinated to phosgene (2,4,6-trichlorophenyl)hydrazone (**10a**), presumably by formation and *in situ* decomposition of the unstable azo acid **21**.[11] Partial chlorination of **10a** gave 1′,1′,1′,2,4,6-hexachlorobenzeneazomethane (**22**) as a by-product.



Phosgene (2-chloro-4-nitrophenyl)hydrazone (**26**) was prepared by chlorination of formaldehyde (*p*-nitrophenyl)hydrazone (**23**) in chloroform. The chlorination proceeds sequentially *via* formyl chloride (*p*-nitrophenyl)hydrazone (**24**)[12] and formyl chloride (2-chloro-4-nitrophenyl)hydrazone (**25**). Formaldehyde phenylhydrazone, only recently characterized in its monomeric

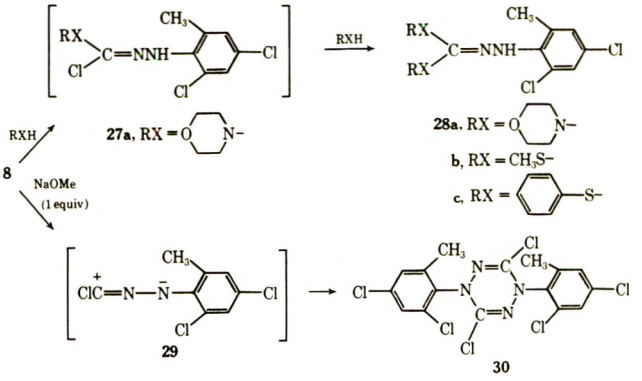


23, $X_1 = X_2 = X_3 = H$
24, $X_1 = Cl$; $X_2 = X_3 = H$
25, $X_1 = H$; $X_2 = X_3 = Cl$
26, $X_1 = X_2 = X_3 = Cl$

form,[13] reacted with 5 equiv of chlorine to give phosgene (2,4,6-trichlorophenyl)hydrazone (**10a**) (33%) and considerable amounts of unidentified tar.

The chemical properties of phosgene (4,6-dichloro-*o*-tolyl)hydrazone (**8**) are representative for the phosgene phenylhydrazones described in this report. This compound reacted slowly with morpholine at room temperature with formation of the bismorpholine derivative **28a**.[14] The monoadduct **27a** was not detected either when the reaction was carried out using limited amounts of morpholine, or using excess morpholine and a short reaction period. When **8** was treated with the sodium salts of thiophenol or methanethiol in methanol the products again were bisadducts, **28b** and **28c**, respectively. A complex mixture was obtained when a solution of **8** in tetrahydrofuran was treated with 1 equiv of sodium methoxide. From the highly colored reaction mixture **30** was isolated in low yield; this product can arise by elimination of hydrogen chloride from **8** followed by dimerization of the resulting dipolar intermediate **29** (Scheme II).

SCHEME II



The low reactivity of the phosgene phenylhydrazones contrasts with the properties of the related imidoyl chloride, *N*-phenyl imidocarbonyl chloride ($Cl_2C{=}N{-}C_6H_5$), which is highly reactive and readily reacts with nucleophiles with displacement of either one or both of the chlorine atoms.[15]

Experimental Section

Mass spectra were recorded at 70 eV on an Atlas CH4 spectrometer. Other analytical and chlorination procedures are as described in ref 8, Experimental Section.

Phosgene (2,4,6-Trichloro-*m*-tolyl)hydrazone.—Morpholine (0.87 g, 0.01 mol) was added to a solution of methyl dichloro[(2,4,6-trichloro-*m*-tolyl)azo]acetate (3.65 g, 0.01 mol) in methanol (20 ml). After 2 hr the solution was cooled to −10°

(9) F. D. Chattaway and R. G. Lye, *Proc. Roy. Soc., Ser. A*, **137**, 489 (1932).

(10) F. D. Chattaway and F. G. Daldy, *J. Chem. Soc.*, 2759 (1928).

(11) Related azo acids decompose spontaneously: see G. Favrel, *Bull. Soc. Chim. Fr.*, **41**, 1494 (1927).

(12) For an alternate synthesis of **24** see R. Huisgen and H. J. Koch, *Justus Liebigs Ann. Chem.*, **591**, 200 (1955).

(13) C. H. Schmidt, *Chem. Ber.*, **103**, 986 (1970).

(14) Products related to **28a** have been prepared by alternate routes. See (a) H. E. Neubauer, M. Seefelder, and H. Widinger, *Chem. Ber.*, **97**, 1232 (1964); (b) F. Runge, A. El-Hewehi, H. J. Renner, and E. Taeger, *J. Prakt. Chem.*, **11**, 284 (1960).

(15) W. R. Smith, *J. Amer. Chem. Soc.*, **16**, 372 (1894).

and the precipitate of phosgene (2,4,6-trichloro-*m*-tolyl)hydrazone (1.82 g, mp 35–37°) was filtered off; ir, nmr, and tlc of the product were identical with those of an authentic sample.[5]

2,3,4-Pentanetrione 3-(*o*-Tolylhydrazone) (5).—A solution of sodium nitrite (345 g, 5.0 mol) in water (800 ml) was added over 10 min to a stirred mixture of *o*-toluidine (535 g, 5.0 mol), concentrated hydrochloric acid (1.1 l., 11.0 mol), and water (1 l.) maintained at 0°. Sodium acetate trihydrate (680 g, 5.0 mol) in water (1.5 l.) was added to the reaction mixture. A cooled solution of 2,4-pentanedione (500 g, 5.0 mol) and sodium hydroxide (200 g, 5.0 mol) in 3 l. of 50% aqueous ethanol was then added rapidly to the reaction solution. After 10 min the precipitate that had formed was filtered off, washed well with water, washed further with methanol (4 l.), and air dried to give 784 g of 2,3,4-pentanetrione-3-(*o*-tolylhydrazone), mp 114–117°. Recrystallization of a sample from methanol and then ethyl acetate gave the analytical sample, mp 115–117°.

Anal. Calcd for $C_{12}H_{24}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.92; H, 6.34; N, 13.03.

Pyruvoyl Chloride 1-[(4,6-Dichloro-*o*-tolyl)hydrazone] (6).—Chlorine (137 ml, 3.0 mol) was added over 10 min to a stirred solution of 2,3,4-pentanetrione 3-(*o*-tolylhydrazone) (218 g, 1.0 mol) in chloroform (1 l.) at −50°. The solution was allowed to warm to −20° during the addition and was then held at 15° for 30 min. Evaporation of the solvent under reduced pressure gave a solid that was recrystallized from methanol to give 188 g of **6**, mp 95–99°. A sample was recrystallized from methanol and finally ethyl acetate for analysis: mp 100–101.5°; ir (Nujol) 1685 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.43 (s, 3, CH_3), 2.50 (s, 3, CH_3), 7.12 (d, 1, J = 2 Hz, ArH), 7.23 (d, 1, J = 2 Hz, ArH), and 8.60 (s, 1, NH).

Anal. Calcd for $C_{10}H_9Cl_3N_2O$: C, 42.96; H, 3.24; Cl, 38.05; N, 10.02. Found: C, 43.17; H, 3.43; Cl, 38.19; N, 9.75.

1,1-Dichloro-1-[(4,6-dichloro-*o*-tolyl)azo]-2-propanone (7).—Chlorine (350 ml, 7.6 mol) was slowly added to a stirred, cooled solution of 2,3,4-pentanetrione 3-(*o*-tolylhydrazone) (279 g, 1.28 mol) in chloroform (1.25 l.). After addition of the chlorine was complete, the reaction solution was held at room temperature for 2 hr. The chloroform was then removed by evaporation to give **7** as an orange oil having the following properties: ir (film) 1735 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.30 (s, 3, CH_3), 2.50 (s, 3, CH_3), 7.13 (d, 1, J = 2 Hz), ArH) and 7.35 (d, 1, J = 2 Hz); λ_{max}^{hexane} 235 mμ (ε 7000), 295 (7950), and 418 (365).

Phosgene (4,6-Dichloro-*o*-tolyl)hydrazone (8). Method A.—The total product **7** from the above reaction was dissolved in methanol (500 ml) and was heated to 40° for 15 min. The solution was then cooled to −10° and the precipitate of **8** (157 g, mp 57–59°) was filtered off and washed with methanol. A further crop of **8** (65 g, mp 55–57°) formed when the methanolic mother liquors were allowed to stand at room temperature for 7 days. An aliquot was recrystallized twice from petroleum ether (bp 30–60°) to give the analytical sample: mp 57.5–59.5°; nmr ($CDCl_3$) δ 2.38 (s, 3, CH_3), 7.08 (d, 1, J = 2 Hz, ArH), 7.21 (d, 1, J = 2 Hz, ArH), and 7.66 (s, 1, NH).

Anal. Calcd for $C_8H_6Cl_4N_2$: C, 35.33; H, 2.22; Cl, 52.15; N, 10.30. Found: C, 35.60; H, 2.25; Cl, 51.99; N, 10.25.

Method B.—Morpholine (87 ml, 1.0 mol) was slowly added to a solution of compound **7** prepared as described earlier from 218 g of 2,3,4-pentanetrione 3-(*o*-tolylhydrazone) in methanol (1 l.). The temperature of the reaction solution rose to 50° during the addition. After cooling to 0°, 192 g (71%) of **8** was filtered off, mp 57–59°.

Chlorination of 2,3,4-Pentanetrione 3-(Phenylhydrazone) (9).—Chlorine (56 ml, 1.2 mol) was added to a cooled solution of 2,3,4-pentanetrione 3-phenylhydrazone[16] (40.8 g, 0.2 mol) in chloroform (400 ml). After 18 hr at room temperature the reaction solution was evaporated to an oil and hexane (100 ml) was added. The precipitate (18.6 g, a mixture of pyruvoyl chloride phenylhydrazones) that formed was filtered off and the hexane solution was chromatographed on silica gel (1500 g). Elution with hexane (4 l.) gave 8.2 g of phosgene (2,4-dichlorophenyl)hydrazone (**10b**). Two recrystallizations from petroleum ether gave the analytical sample: mp 59–60°; nmr ($CDCl_3$) δ 7.20 (m, 3, ArH) and 7.90 (s, 1, NH); mass spectrum m/e for ^{35}Cl (rel intensity, number of chlorine atoms in ion) 256 (71, 4), 160 (100, 2), 159 (71, 2), and 133 (71, 2).

Anal. Calcd for $C_7H_4Cl_4N_2$: C, 32.59; H, 1.56; N, 10.86. Found: C, 32.55; H, 1.60; N, 10.86.

Further elution with 2 l. of benzene–hexane (1:3) gave 4.1 g of phosgene (2,4,6-trichlorophenyl)hydrazone (**10a**). Recrystallization twice from petroleum ether gave the analytical sample: mp 29–30°; nmr ($CDCl_3$) δ 7.25 (s, 2, ArH) and 7.49 (s, 1, NH).

Anal. Calcd for $C_7H_3Cl_5N_2$: C, 28.75; H, 1.03; N, 9.58. Found: C, 28.88; H, 0.98; N, 9.64.

Continued elution with the same solvent gave 1.1 g of phosgene (*p*-chlorophenyl)hydrazone (**10c**). Recrystallization from Skellysolve B gave the analytical sample: mp 50–54°; nmr ($CDCl_3$) δ 6.96 (d, 2, J = 9 Hz, ArH), 7.27 (d, 2, J = 9 Hz, ArH), and 7.48 (s, 1, NH); mass spectrum m/e for ^{35}Cl (rel intensity, number of chlorine atoms in ion) 222 (13, 3), 187 (3, 2), 152 (7, 1), 126 (80, 1), and 125 (100, 1).

Anal. Calcd for $C_7H_5Cl_3N_2$: C, 37.61; H, 2.26; N, 12.54. Found: C, 37.99; H, 2.44; N, 12.37.

Pyruvoyl Chloride 1-[(2-Chloro-*p*-tolyl)hydrazone] (12).—To a stirred solution of 2,3,4-pentanetrione 3-(*p*-tolylhydrazone)[17] (55.5 g, 0.25 mol) in chloroform at −40° was added chlorine (28 ml, 0.55 mol). After 15 min at −40° the solvent was removed under reduced pressure and the residual oil was crystallized from hexane (200 ml) to give 38.5 g (63%) of **12**, mp 100–102°. Recrystallization from hexane gave the analytical sample: mp 102–104°; ir (Nujol) 1690 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{10}Cl_2N_2O$: C, 49.00; H, 4.11; Cl, 28.93; N, 11.43. Found: C, 49.10; H, 4.04; Cl, 28.81; N, 11.22.

Pyruvoyl Chloride 1-[(2,6-Dichloro-*p*-tolyl)hydrazone] (13).—Chlorine (50 ml, 1.1 mol) was added to a solution of 2,3,4-pentanetrione 3-(*p*-tolylhydrazone)[17] (43.6 g, 0.2 mol) in methylene chloride (250 ml). The solution was held at −30° for 1 hr and the methylene chloride was then removed. The residual oil was crystallized from 120 ml of hexane–ethyl acetate (5:1) to give 15.1 g of pyruvoyl chloride 1-[(2,6-dichloro-*p*-tolyl)hydrazone]. Two recrystallizations from hexane–ether gave the analytical sample: mp 93–95°; nmr ($CDCl_3$) δ 2.30 (s, 3, CH_3), 2.48 (s, 3, CH_3), 7.20 (s, 2, ArH), and 8.44 (s, 1, NH).

Anal. Calcd for $C_{10}H_9Cl_3N_2O$: C, 42.96; H, 3.24; Cl, 38.04; N, 10.08. Found: C, 42.64; H, 3.18; Cl, 38.69; N, 9.81.

The mother liquor from the original crystallization was evaporated to an oil and this was dissolved in benzene–hexane (1:1) and chromatographed on silica gel (800 g). The column was eluted with 6 l. of benzene–hexane (1:1), the eluate being discarded. Continued elution with the same solvent mixture gave 9 g of **14**. The compound was recrystallized several times from hexane to give the analytical sample: mp 114–117°; ir (Nujol) 1710 cm^{-1} (C=O); λ_{max}^{hexane} 239 mμ (ε 17,500) and 265 (inflection, 3400); nmr δ 2.10 (s, 3, CH_3) and 2.69 (s, 3, CH_3) with cyclohexene ring protons at 4.85 (d, 1, J = 7 Hz), 5.04 (d, 1, J = 7 Hz), and 5.42 (s, 1).

Anal. Calcd for $C_{10}H_9Cl_7N_2O$: C, 28.50; H, 2.15; Cl, 58.90; N, 6.65. Found: C, 28.52; H, 2.32; Cl, 59.46; N, 6.99.

Phosgene (2,6-Dichloro-*p*-tolyl)hydrazone (16).—Chlorine (100 ml, 2.2 mol) was passed into a solution of 2,3,4-pentanetrione 3-(*p*-tolylhydrazone) (30 g, 0.14 mol) in chloroform (300 ml). After 24 hr excess chlorine and the chloroform were removed by evaporation and the residual oil was chromatographed on silica gel. Elution with benzene–hexane (1:9) gave 13.9 g of phosgene (2,6-dichloro-*p*-tolyl)hydrazone. The crystalline product was recrystallized from methanol and finally from hexane to give the analytical sample: mp 52–54°; nmr ($CDCl_3$) δ 2.25 (s, 3, CH_3), 7.12 (s, 2, ArH), and 7.47 (s, 1, NH).

Anal. Calcd for $C_8H_6Cl_4N_2$: C, 35.33; H, 2.22; Cl, 52.15; N, 10.30. Found: C, 35.46; H, 2.31; Cl, 51.89; N, 10.26.

Chlorination of Pyruvoyl Chloride (2,6-Dichloro-*p*-tolyl)-hydrazone (13).—Chlorine (10 ml, 0.22 mol) was added to a stirred solution of **13** (5 g, 0.018 mol) in chloroform (50 ml). The resulting solution was stirred at room temperature for 2 hr and the chloroform was then evaporated. The product was identified as **15** from its nmr spectrum: nmr ($CDCl_3$) δ 2.33 (s, 3, CH_3), 2.47 (s, 3, CH_3), and 7.18 (s, 2, ArH). The compound decomposed when heated in methanol to give phosgene (2,6-dichloro-*p*-tolylhydrazone) as the sole product.

Carbonyl Bromide (2,4-Dibromophenyl)hydrazone (18).—A mixture of dibromopyruvoyl bromide (2,4-dibromophenyl)-

(16) C. Beyer and L. Claisen, *Chem. Ber.*, **21**, 1697 (1888).

(17) G. Bülow and W. Spengler, *ibid.*, **58**, 1375 (1928).

hydrazone[8] (53 g, 0.1 mol), *N*-bromosuccinimide (50 g, 0.28 mol), chloroform (250 ml), and methanol (250 ml) was stirred at room temperature for 30 min. The solvents were then evaporated and the residue was extracted with hexane. The hexane-soluble fraction was chromatographed on silica gel. Elution with hexane gave 6.9 g of carbonyl bromide (2,4-dibromophenyl)hydrazone as a crystalline solid. Recrystallization from ethyl acetate and finally from hexane gave the analytical sample: mp 89–91°; nmr ($CDCl_3$) δ 7.26 (m, 2, ArH), 7.53 (d, 1, J = 2 Hz, ArH), and 8.08 (s, 1, NH).

Anal. Calcd for $C_7H_4Br_4N_2$: C, 19.29; H, 0.92; Br, 73.35; N, 6.43. Found: C, 19.38; H, 0.91; Br, 73.06; N, 6.38.

Chlorination of Chloroglyoxylic Acid 2-[(2,4,6-Trichlorophenyl)hydrazone] (20).—To a stirred suspension of chloroglyoxylic acid 2-[(2,4,6-trichlorophenyl)hydrazone] (15.0 g, 0.05 mol) in acetic acid (100 ml) was added chlorine (5 ml, 0.11 mol). The solid dissolved after 4 hr; after 6 hr the acetic acid was removed by evaporation at reduced pressure. The residual oil was dissolved in Skellysolve B and was chromatographed on silica gel. Elution of the column with Skellysolve B gave 3.2 g of 1′,1′,1′,2,4,6-hexachlorobenzeneazomethane (22) as the first fraction. The product, an orange oil, was analyzed after evaporation at 100° (10 mm): nmr ($CDCl_3$) singlet absorption at δ 7.45; mass spectrum m/e for ^{35}Cl (rel intensity, number of chlorine atoms in ion) 289 (16, 5), 207 (66, 3), and 179 (100, 3).

Anal. Calcd for $C_7H_2Cl_6N_2$: C, 25.72; H, 0.62; N, 8.57. Found: C, 26.44; H, 1.04; N, 8.43.

Continued elution of the column gave 7.5 g of phosgene (2,4,6-trichlorophenyl)hydrazone identical with the sample of **10a** prepared earlier.

Chlorination of Formaldehyde Phenylhydrazone.—To a stirred solution of formaldehyde phenylhydrazone (5.5 g, 0.05 mol) in chloroform (100 ml) at −40° was added chlorine (11.5 ml, 0.25 mol) over a period of 10 min. The violet-colored reaction solution was allowed to warm to room temperature and, after an additional 30 min, was evaporated. The product was chromatographed on silica gel to give 4.4 g (33%) of phosgene (2,4,6-trichlorophenyl)hydrazone identical with the sample previously prepared by nmr, ir, and tlc analysis.

Formyl Chloride (*p*-Nitrophenyl)hydrazone (24).—*tert*-Butyl hypochlorite (9.0 ml, 0.075 mol) was added to a stirred suspension of formaldehyde (*p*-nitrophenyl)hydrazone[18] (8.2 g, 0.05 mol) in chloroform (200 ml). The temperature of the solution rose to about 45° and a homogeneous solution was obtained within 5 min. The solution was then evaporated and the solid product was recrystallized from benzene–hexane to give 4.5 g of formyl chloride (*p*-nitrophenyl)hydrazone, mp 135–138°. Recrystallization from methanol and finally benzene–hexane gave the analytical sample: mp 140–143°; nmr ($CDCl_3$) δ 6.96 (s, 1, N=CHCl), 7.13 (d, 2, J = 9 Hz, ArH), 8.18 (d, 2, J = 9 Hz, ArH), and 8.45 (s, 1, NH).

Anal. Calcd for $C_7H_6ClN_3O_2$: C, 42.12; H, 3.03; Cl, 21.05; N, 17.77. Found: C, 42.38; H, 3.00; Cl, 20.94; N, 17.85.

Formyl Chloride (2-Chloro-4-nitrophenyl)hydrazone (25).—Chlorine (10 ml, 0.22 mol) was slowly added to a stirred suspension of formaldehyde (*p*-nitrophenyl)hydrazone (16.5 g, 0.1 mol) in chloroform (200 ml) at −40°. The solution was allowed to warm to room temperature. After 1 hr the reaction mixture was filtered to remove insoluble tars and the chloroform was evaporated. The residue was crystallized from methanol to give **25**, mp 122–125°. The product was recrystallized from ethyl acetate to afford 7.8 g of product: mp 124–126°; nmr ($CDCl_3$) δ 7.10 (s, 1, N=CHCl), 7.50 (d, 1, J = 8.5 Hz, ArH), 8.13 (d of d, 1, J = 2 and 8.5 Hz, ArH), 8.26 (d, 1, J = 2 Hz, ArH), and 8.75 (s, 1, NH).

Anal. Calcd for $C_7H_3Cl_2N_3O_2$: C, 35.92; H, 2.15; Cl, 30.30; N, 17.95. Found: C, 35.99; H, 2.39; Cl, 30.39; N, 17.67.

Phosgene (2-Chloro-4-nitrophenyl)hydrazone (26).—Chlorine (5 ml, 0.11 mol) was added to a stirred solution of formyl chloride (2-chloro-4-nitrophenyl)hydrazone (**25**, 5.3 g, 0.023 mol) in chloroform (100 ml) at 0°. After 3 hr the chloroform was removed, and the residue was dissolved in methanol and cooled to −10° to give 2.7 g of phosgene (2-chloro-4-nitrophenyl)-hydrazone, mp 96–102°. Recrystallization twice from hexane and finally from methanol gave the analytical sample: mp 102–104°; nmr ($CDCl_3$) δ 7.43 (d, 1, J = 8 Hz, ArH), 8.08 (d of d, 1, J = 2 and 8 Hz, ArH), 8.17 (d, 1, J = 2 Hz, ArH), and 8.30 (s, 1, NH).

Anal. Calcd for $C_7H_4Cl_3N_3O_2$: C, 31.31; H, 1.50; Cl, 39.62; N, 15.62. Found: C, 31.54; H, 1.66; Cl, 40.08; N, 15.63.

4,4′-Carbonyldimorpholine (4,6-Dichloro-*o*-tolyl)hydrazone (28a).—A mixture of phosgene (4,6-dichloro-*o*-tolyl)hydrazone (9 g, 0.03 mol) and morpholine (20 ml) in chloroform (50 ml) was allowed to stand at room temperature for 2 days. The chloroform solution was then washed well with water, dried over sodium sulfate, and evaporated. Skellysolve B was added to the residual oil and the crystalline product (10.1 g, mp 115–120°) was filtered off. It was recrystallized from ethyl acetate to give 6.9 g of **28a**, mp 128–131°. Recrystallization from methanol gave the analytical sample, mp 130–132°.

Anal. Calcd for $C_{16}H_{22}Cl_2N_4O_2$: C, 51.48; H, 5.94; Cl, 19.00; N, 15.01. Found: C, 51.70; H, 6.04; Cl, 19.09; N, 15.50.

Diphenyl (4,6-Dichloro-*o*-toluidino)dithioimidocarbonate (28c).—A solution of thiophenol (7.3 g, 0.066 mol) in 2 *N* sodium methoxide (33 ml) was added to a stirred solution of phosgene (4,6-dichloro-*o*-tolyl)hydrazone (9 g, 0.03 mol) in methanol. An oily layer separrated and this was extracted into benzene. The benzene extract was washed well with water, dried over sodium sulfate, and evaporated. The residual oil was dissolved in Skellysolve B and, after cooling to −10°, 7.6 g of **28c**, mp 33–35°, was filtered off. Recrystallization from Skellysolve B and finally petroleum ether gave the analytical sample, mp 35–37°.

Anal. Calcd for $C_{20}H_{16}Cl_2N_2S_2$: C, 57.27; H, 3.85; Cl, 16.90; N, 6.68; S, 15.28. Found: C, 57.42; H, 3.84; Cl, 16.68; N, 6.65; S, 15.30.

Dimethyl (4,6-Dichloro-*o*-toluidino)dithioimidocarbonate (28b).—A solution of phosgene (4,6-dichloro-*o*-tolyl)hydrazone (6.1 g, 0.02 mol) in chloroform (10 ml) was slowly added with stirring to 50 ml of a solution of sodium thiomethylate (18%) in methanol. The precipitate that formed was filtered off and dried to give 5.8 g of **28c**, mp 63–66°. Recrystallization from petroleum ether and finally from methanol gave the analytical sample, mp 65–67°.

Anal. Calcd for $C_{10}H_{12}Cl_2N_2S_2$: C, 40.68; H, 4.10; Cl, 24.02; N, 9.49; S, 21.72. Found: C, 40.51; H, 3.94; Cl, 23.97; N, 9.48; S, 21.37.

Preparation of 30.—To a stirred solution of phosgene (4,6-dichloro-*o*-tolyl)hydrazone (18 g, 0.066 mol) in a mixture of tetrahydrofuran (50 ml) and methanol (25 ml) was added 66 ml of 2 *N* sodium methoxide in methanol. After 15 min the dark reaction solution was evaporated, water was added, and the resulting solution was extracted into benzene. The benzene extract was dried, concentrated, and chromatographed on silica gel. Elution with benzene gave in the early fractions 1.3 g of **30**, mp 235–240°. Two recrystallizations from ethyl acetate gave the analytical sample: mp 245–248°; mass spectrum m/e for ^{35}Cl (rel intensity, number of chlorine atoms in ion) 468 (54, 6), 433 (5, 5), and 398 (10, 4).

Anal. Calcd for $C_{16}H_{10}Cl_6N_4$: C, 40.80; H, 2.14; N, 11.90. Found: C, 40.67; H, 2.26; N, 11.50.

Registry No.—**5**, 24756-03-4; **6**, 34387-69-4; **7**, 34387-70-7; **8**, 34387-71-8; **10a**, 34387-72-9; **10b**, 34402-62-5; **10c**, 34387-73-0; **12**, 34387-74-1; **13**, 34387-75-2; **14**, 34387-76-3; **15**, 34387-77-4; **16**, 34387-78-5; **18**, 34387-79-6; **22**, 34387-80-9; **24**, 34387-81-0; **25**, 34387-82-1; **26**, 34387-83-2; **28a**, 34387-84-3; **28b**, 34387-85-4; **28c**, 34387-86-5; **30**, 34387-87-6; phosgene (2,4,6-trichloro-*m*-tolyl)hydrazone, 32974-73-5.

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(18) E. Bamberger, *Chem. Ber.*, **32**, 1807 (1899).

Synthesis and Reactions of 3-Indolyl β Ketones

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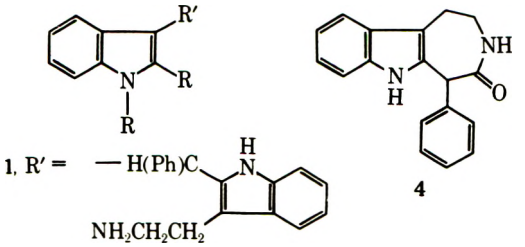
Reaction of indoles with free 3 position (**5**) with α-halo ketones (**6**) in acidic solutions affords 3-indolyl ketones (**7**). This novel reaction conveniently offers versatile starting materials for indolylcyclohexyl oximes (*e.g.*, **16**), amines (*e.g.*, **23**), alcohols (*e.g.*, **25**), indolylazabicycloheptanes ((*e.g.*, **21**), and indolyl fatty acids (*e.g.*, **19**), as well as pyrano[3,4-*b*]indoles (*e.g.*, **12**).

Alkylation of indoles in aqueous acid with phenylindolylcarbinols,[1] allyl bromide,[2] and ethyl bromoacetate,[3] and, intramolecularly, of haloacyltryptamines[4] has led to the facile formation of compounds **1**–**4**, respectively.



1, R′ = —H(Ph)C— (with H, N, $NH_2CH_2CH_2$)

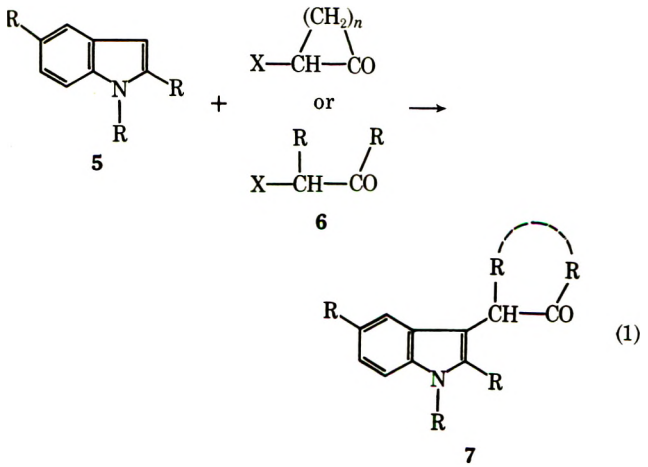
2, R′ = $-CH_2CH{=}CH_2$

3, R′ = $-CH_2COOC_2H_5$

4

We wish to report the extension of this reaction to α-halo ketones leading to indolyl ketones. A number of these novel indole derivatives are convenient starting materials for a variety of tryptamine and serotonin related compounds of potential biological interest.

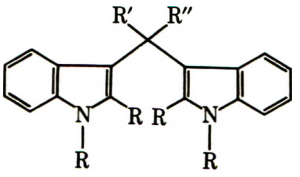
Synthesis.—On heating of an indole **5** and an α-halogen ketone **6** in a mixture of glacial acetic acid and phosphoric acid (2 *N*), a variety of substituted indolyl ketones **7** was obtained according to eq 1. Many of these compounds **7**, listed in Tables I–III, may be difficult to obtain by conventional indole synthesis. (For a review see ref 5a; also *e.g.*, ref 6.)



5 + 6 (or) → 7 (1)

(1) K. Freter, H. H. Hübner, H. Merz, H. Detlef Schroeder, and K. Zeile, *Justus Liebigs Ann. Chem.*, **684**, 159 (1965).
(2) K. R. Freter, *Can. J. Chem.*, **45**, 2628 (1967).
(3) K. R. Freter, German Patent Application P1,963,845.0.
(4) K. Freter, *Justus Liebigs Ann. Chem.*, **721**, 101 (1969).
(5) R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, N. Y., 1970: (a) p 412; (b) p 39; (c) p 47.
(6) P. Rosenmund, D. Sauer, and W. Trommer, *Chem. Ber.*, **103**, 496 (1970).

The dimerization to diindolylmethane derivatives (**8**), well documented for the reaction of indoles with aldehydes and ketones under acidic conditions,[5b] was observed as a minor side reaction only in a few cases, and as main reaction only, when the indole was unsubstituted (see **9** below). Also, when ω-bromoacetophenone was employed, the diindolylmethane **8** (R_1 = C_6H_5, R_2 = CH_2Br) was the sole reaction product and no ketone **7** was observed.

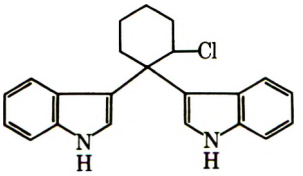


8

Bromoacetone, 2-bromo-3-butanone, and 2-chlorocyclohexanone proved to be suitable examples for **6** in this reaction.

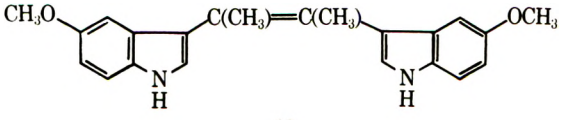
With bromoacetoacetate, bromocyanoacetate, and bromomaleate no carbonyl-containing reaction products could be isolated. It appeared as if these compounds acted as brominating agents on the indoles.

A variety of substituted indoles was subjected to the above procedure. Generally, best results were achieved with 1,2-disubstituted indoles; with indoles unsubstituted in the 1 position the yields were lower. Indole itself reacted differently: on treatment with chlorocyclohexanone the diindolylchlorocyclohexane **9** was obtained (see Experimental Section).



9

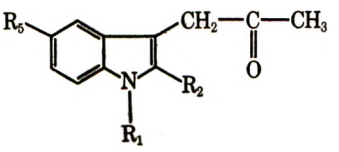
The reaction of 5-methoxyindole with 2-bromo-3-butanone proceeded in a different manner, yielding a diindolylbutene (**10**), according to spectral and analytical data.



10

The heating of 1-*p*-chlorobenzyl-5-methoxy-2-methylindole with ethyl bromopyruvate did not give the expected indolyl pyruvate according to eq 1, but the

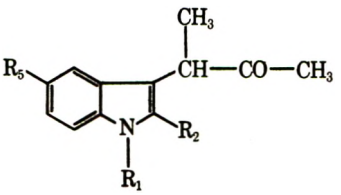
TABLE I



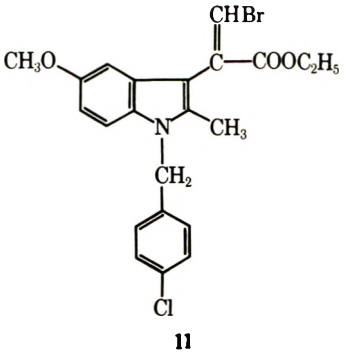
7	R_1	R_2	R_5	Time, min	Temp, °C	Yield, %	Empirical formula		C, %	H, %	N, %	Mp, °C	Mp, oxime, °C	Mp, thiosemicarbazone, °C
a	CH_3	CH_3	H	30	20	33	$C_{13}H_{15}NO$	Calcd	77.58	7.51	6.96	44	137	219
								Found	77.84	7.63	6.92			
b	H	CH_3	CH_3O	10	20	30	$C_{13}H_{15}NO_2$	Calcd[a]	57.92	6.25	19.30	Oil		203
								Found	58.10	6.35	19.31			
c	p-$ClC_6H_4CH_2$	CH_3	CH_3O	30	60	20	$C_{20}H_{20}ClNO_2$	Calcd	70.27	5.90	4.10	111		
								Found	69.98	5.66	4.19			

[a] Calculated for the thiosemicarbazone $C_{14}H_{18}N_4OS$.

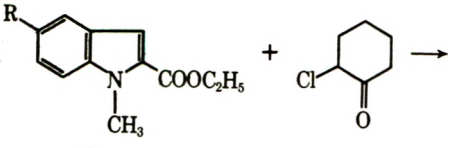
TABLE II



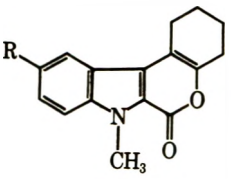
7	R_1	R_2	R_5	Time, min	Temp, °C	Yield, %	Empirical formula		C, %	H, %	N, %	Mp, °C	Mp, oxime, °C	Mp, thiosemicarbazone, °C
d	CH_3	CH_3	H	30	60	70	$C_{14}H_{17}NO$	Calcd	78.10	7.96	6.51	70	183	209
								Found	78.10	8.29	6.69			
e	H	CH_3	OCH_3	25	90	65	$C_{14}H_{17}NO_2$	Calcd	72.70	7.41	6.06	79	140	165
								Found	72.48	7.30	6.10			
f	CH_3	CH_3	CH_3	45	80	79	$C_{15}H_{19}NO_2$	Calcd	73.44	7.81	5.71	85	177–185	195–201
								Found	73.79	8.06	5.40			
g	CH_3	C_6H_5	H	40	80	35	$C_{19}H_{19}NO$	Calcd	82.28	6.91	5.05	106	177	205
								Found	81.96	7.29	5.30			
h	p-$ClC_6H_4CH_2$	CH_3	OCH_3	90	100	58	$C_{21}H_{22}ClNO_2$	Calcd	70.87	6.24	3.93	110	169	134
								Found	71.11	6.10	4.09			



11

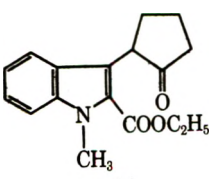


R = H or CH_3O

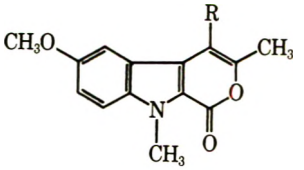


(2)

12, R = H
13, R = CH_3O



14



15a, R = H
b, R = CH_3

bromoacrylate **11** instead. This is in agreement with the reported reaction of 1,2-dimethylindole with ethyl pyruvate.[7]

The reaction of indolyl-2-carboxylates with, *e.g.*, chlorocyclohexanone produced the pyrone derivatives **12** and **13** (eq 2) in reasonable yields.

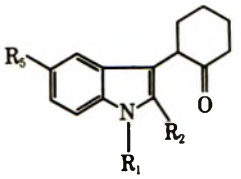
The interesting reactions of these compounds are discussed below. With chlorocyclopentanone, the expected keto ester (**14**) did not ring close and could be isolated in 63% yield. The pyrones resulting from the reaction with bromoacetone or bromobutanone were obtained only in small amounts (**15a** and **b**).

(7) S. H. Zee, Ph.D. Thesis with W. E. Noland, University of Minnesota, 1966; *Diss. Abstr.*, **27**, 123 (1967). See also ref 5c.

Reactions.—The ketones **7** form oximes and thiosemicarbazones in the usual manner in yields ranging from 70 to 90%.

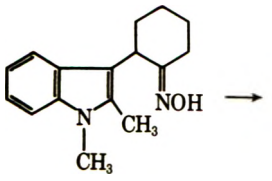
The oximes, on treatment with benzenesulfonyl

TABLE III

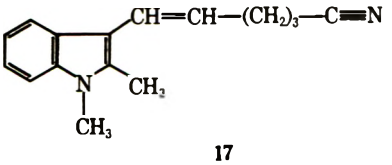


7	R1	R2	R5	Time, min	Temp, °C	Yield, %	Empirical formula		C, %	H, %	N, %	Mp, °C	Mp, oxime, °C	Mp, thiosemicarbazone, °C
j	H	CH_3	H	90	60	27	$C_{15}H_{17}NO$	Calcd	79.26	7.54	6.16	139		
								Found	79.38	7.65	6.32			
k	CH_3	CH_3	H	60	100	50	$C_{16}H_{19}NO$	Calcd	79.63	7.94	5.80	161	226–232	192
								Found	79.75	7.67	5.78			
l	H	CH_3	CH_3O	240	20	32	$C_{16}H_{19}NO_2$	Calcd	74.68	7.44	5.44	163	187	196
								Found	74.39	7.23	5.71			
m	CH_3	CH_3	CH_3O	30	100	36	$C_{17}H_{21}NO_2$	Calcd	75.24	7.80	5.16	138		213
								Found	75.04	8.04	5.24			
n	CH_3	*p*-C_6H_4Cl	CH_3O	30	100	45	$C_{22}H_{22}ClNO_2$	Calcd	71.83	6.03	3.81	196		179
								Found	71.48	6.22	3.84			
o	*p*-$ClC_6H_4CH_2$	CH_3	CH_3O	30	100	36	$C_{23}H_{24}ClNO_2$	Calcd	72.40	6.33	3.67	157	202	
								Found	72.59	6.17	3.84			

chloride in pyridine, underwent a Beckmann rearrangement of the second order.[8] From the oxime **16**, for example, the unsaturated nitrile **17** was obtained in good yield.

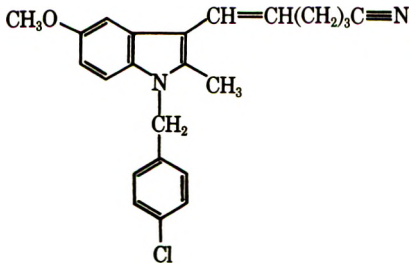


16



17

The nitrile **18** was obtained analogously from the oxime of ketone **7o**.

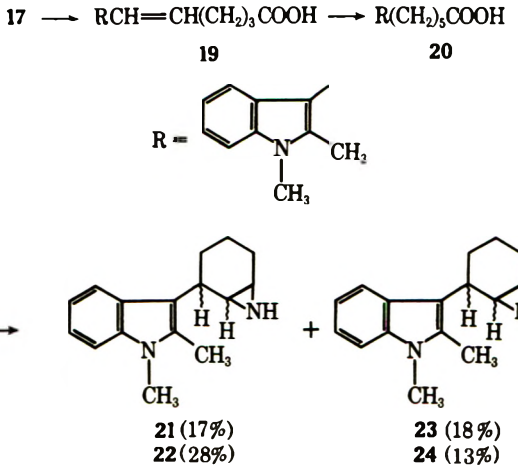


18

Saponification of the nitrile **17** followed by hydrogenation led to the ω-(1,2-dimethyl-3-indolyl)hexenoic acid (**19**) and -caproic acid (**20**), respectively.

The reduction of **16** with $LiAlH_4$ resulted in the formation of four basic compounds, which were separated by chromatography.

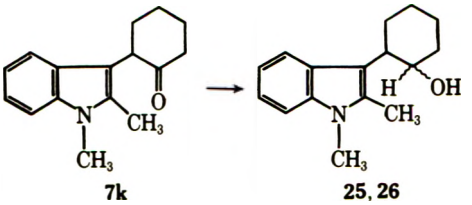
The analytical data indicate that **21** and **22** are the isomeric indolylazabicycloheptanes with regard to the relative position of the aziridine ring to the indolyl



substitutent and **23** and **24** the corresponding isomeric cyclohexylamines.

The formation of aziridines as result of oxime reductions has been recorded.[9] Since both aziridines and amines were obtained, it seems likely that the oxime **16** was a mixture of the syn and anti forms.[10]

The reduction of the ketones **7** with $LiAlH_4$ proceeded normally. In the case of **7k** the two isomeric cyclohexanols **25** and **26** were obtained in equal amounts.



7k **25, 26**

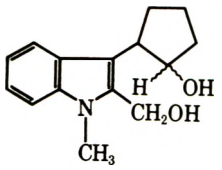
Two products, also, were obtained as expected after reduction of **14** with $LiAlH_4$ (**27**, **28**).

The situation was different when the lactones **12** or **13** were subjected to treatment with excess lithium aluminum hydride. Here the reduction stopped at the stage of the semiketals (**29**, **30**). Their structures were

(8) Houben-Weyl, "Methoden der Organischen Chemie," Vol. X-4, Georg Thieme Verlag, Stuttgart, 1968, p 229.

(9) K. Kitahonoki, Y. Takano, A. Matsuura, and K. Kotera, *Tetrahedron*, **25**, 335 (1969).

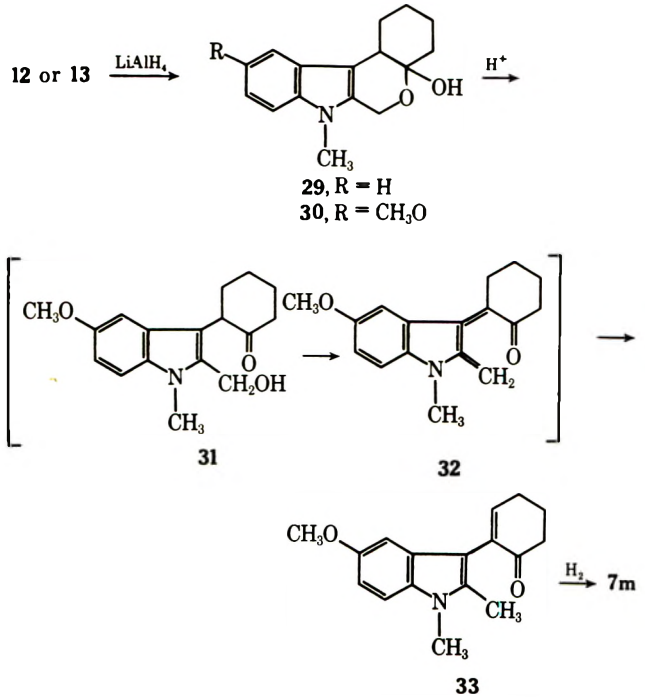
(10) J. L. M. A. Schlatmann, J. G. Korlsloot, and J. Schut, *ibid.*, **26**, 949 (1970).



27, 28

established on grounds of ir (no carbonyl absorption, OH at 3440 cm^{-1}), nmr spectra (distinct CH_2 singlet, one exchangeable OH proton), analyses, and mass spectra. Compounds **29** and **30** belong to a group of 8a-hydroxyhexahydrochromans, which are usually prepared from and are in equilibrium with the open-chain hydroxy alkyl ketones.[11] The formation of hydroxyisochromans on lithium aluminum hydride reduction of comparable enol-lactones has been recorded and discussed recently.[12]

The ring-open keto alcohol **31** could not be isolated. On treatment of **30** with dilute acid at room temperature, rearrangement to **33** took place. A possible mechanism may involve elimination of water from **31** *via* **32**, but this question was not pursued further.



29, R = H
30, R = CH_3O

The structure of **33** followed from the spectral data and was confirmed by hydrogenation, which led to the indolyl ketone **7m**, identical with the ketone arrived at according to eq 1.

Experimental Section

Melting points were determined on a Fisher–Johns block and are uncorrected. Microanalyses were performed by Dr. A. B. Gygli, Toronto, or Dr. C. Daessle, Montreal. Mass spectra were recorded on an RMU-6D instrument by Morgan Schaffer Corp., Montreal, and nmr spectra were taken on a Varian T-60 instrument, except for the 220-MHz study, kindly performed by Dr. A. A. Grey of the Canadian 220 MHz NMR Centre, Toronto.

(11) J. Colonge, J. Dreux, and M. Thiers, *Bull. Soc. Chim. Fr.*, 1459 (1959).

(12) J. Schneckenburger and R. Kaufmann, *Arch. Pharm. (Weinheim)*, **303**, 760 (1970).

The preparation of oximes and thiosemicarbazones is not recorded in the Experimental Section. Their melting points are included in Tables I–III. Satisfactory analyses were obtained for these compounds.

General Procedure for the Preparation of β-(3-Indolyl) Ketones (7).—The indole (0.1 mol) and the halo ketone (0.25 mol) were heated in 300 ml of acetic acid and 100 ml of 2 *N* phosphoric acid for the time and at the temperature indicated in Tables I–III. The mixture was poured on 1.5 l. of ice and 500 ml of ammonia. The resulting precipitate was either filtered and recrystallized or extracted with ethyl acetate, dried, and evaporated to dryness and then crystallized. In some cases, notably for the open-chain ketones **7a–h**, purification *via* chromatography on silica was advantageous.

2,2-(Di-3-indolyl)-1-chlorocyclohexane (9).—A mixture of indole (5 g), chlorocyclohexanone (6 ml), acetic acid (90 ml), and 2 *N* H_3PO_4 (30 ml) was stirred at 100° for 2 hr. After cooling, the crystals were collected, washed, and recrystallized from dimethylformamide–ether: yield 2.6 g (35%); mp 220–235°; ir, no carbonyl absorption.

Anal. Calcd for $C_{22}H_{21}ClN_2$: C, 75.71; H, 6.08; Cl, 10.18; N, 8.03. Found: C, 75.73; H, 6.28; Cl, 10.46; N, 8.30.

2,3-Di(5-methoxy-3-indolyl)-2-butene (10).—A mixture of 5-methoxyindole (10 g), 2-bromo-3-butanone (12 ml), glacial acetic acid (200 ml), and 2 *N* phosphoric acid (100 ml) was heated in an oil bath of 110° for 4 hr. It was poured on ice–ammonia and extracted with ethyl acetate, and the extract was washed, dried, and evaporated. The residue was chromatographed on silica with benzene–methanol (97:3). The main fraction crystallized from ethanol: yield 5.5 g (47%); mp 205–208°; nmr ($CDCl_3$) δ 8.1–7.9 (m, 2), 7.5–6.7 (m, 6), 3.99 (s, 3), 3.81 (s, 3), 3.25 (s, 2, exchangeable), 2.90 (s, 3), 2.26 (s, 3).

Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.27; H 6.40; N, 8.09. Found: C, 75.98; H, 6.72, N, 8.17.

Ethyl β-Bromo-α-(1-*p*-chlorobenzyl-5-methoxy-2-methyl-3-indolyl)acrylate (11).—1-*p*-Chlorobenzyl-5-methoxy-2-methylindole (5 g), 10 ml of ethyl bromopyruvate, 150 ml of acetic acid, and 10 ml of 2 *N* phosphoric acid were stirred at 40° for 5 min. The reaction mixture was poured on excess ice–ammonia and extracted with ether, and the extracts were washed, dried, and evaporated to dryness. The residue was chromatographed on silica, using benzene–methanol (99.5:0.5) as eluent. The fraction corresponding to an R_F of 0.6 on tlc plates using the same eluent was crystallized from methanol: yield 2 g (25%) of **11**; mp 105–107°; nmr ($CDCl_3$) δ 7.4–6.8 (m, 7), 6.70 (s, 1), 5.22 (s, 2), 4.34 (q, 2, J = 7.5 Hz), 3.83 (s, 3), 2.27 (s, 3), 1.32 (*t*, 3, J = 7.5 Hz).

Anal. Calcd for $C_{22}H_{21}BrClNO_3$: C 57.20; H, 4.57; Br, 17.27; Cl 7.66; N, 3.03. Found: C, 57.45; H, 4.43; Br, 16.95; Cl 7.95; N, 3.14.

7-Methyl-1,2,3,4-tetrahydroindolo[2,3-*c*]coumarin (12).—Ethyl 1-methylindole-2-carboxylate (10 g), 40 ml of 2-chlorocyclohexanone, 80 ml of glacial acetic acid, and 20 ml of 2 *N* H_3PO_4 were heated for 2 hr at 130°. The mixture was poured on ice–ammonia, and the resulting precipitate was filtered, washed with water and cold ethanol, and then crystallized from chloroform–ether: yield 6.5 g (52%); mp 217–218°; ir (KBr) 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 8.1–7.1 (m, 4), 4.13 (s, 3) 3.1–2.4 (m, 4), 2.1–1.5 (m, 4); mass spectrum (70 eV) *m/e* (rel intensity) 253 (100), 225 (93), 196 (85).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.13; H, 6.21; N, 5.42.

10-Methoxy-7-methyl-1,2,3,4-tetrahydroindolo[2,3-*c*]coumarin (13).—Ethyl 5-methoxy-1-methylindole-2-carboxylate (15 g), 60 g of 2-chlorocyclohexanone, 120 ml of glacial acetic acid, and 30 ml of 2 *N* H_3PO_4 were heated for 2 hr in an oil bath of 120°. The mixture was worked up as described for **12**, and the residue was purified on silica, using chloroform as eluent: yield 8.5 g (46%); mp 145–148°; ir (KBr) 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.4–7.1 (m, 3), 4.00 (s, 3), 3.88 (s, 3), 3.0–2.4 (m, 4), 2.0–1.7 (m, 4).

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 72.03; H, 5.97; N, 4.99.

Ethyl 3-(Cyclopentanon-2-yl)-1-methylindole-2-carboxylate (14).—Ethyl 1-methylindole-2-carboxylate (17 g), 2-chlorocyclopentanone (30 ml), glacial acetic acid (140 ml), and 2 *N* H_3PO_4 (35 ml) were heated for 150 min at 90–100°. The mixture was worked up as usual, and the crude reaction product was slurried with ethanol and crystallized from chloroform–petroleum ether (bp 30–60°): yield 15 g (63%); mp 181–184°; nmr

($CDCl_3$) δ 7.6–6.9 (m, 4), 4.36 (q, J = 7.0 Hz, 2), 3.94 (s, 3), 3.0–1.7 (m, 7), 1.32 (t, 3); ir (KBr) 1724, 1675 cm^{-1}.

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.67; H, 6.83; N, 5.00.

The thiosemicarbazone of **14** was obtained, mp 193°.

Anal. Calcd for $C_{18}H_{22}N_4O_2S$: C, 60.32; H, 6.19; N, 15.63; S, 8.93. Found: C, 60.09; H, 6.33; N, 15.53; S, 8.96.

6-Methoxy-3,9-dimethylpyrano[3,4-*b*]indol-1-one (15a).—Ethyl 5-methoxy-1-methylindole-2-carboxylate (10 g), 80 ml of acetic acid, 20 ml of 2 N H_3PO_4, and bromoacetone (15 ml) were heated to 100° for 5 hr. The mixture was worked up as usual and chromatographed on silica with chloroform as eluent. The above reaction product was obtained in 5% yield (0.5 g), after crystallization from ethanol: mp 135–137°; ir (KBr) 1700 cm^{-1}; nmr ($CDCl_3$) δ 7.6–7.2 (m, 3), 7.1 (m, 1), 4.16 (s, 3), 3.92 (s, 3), 2.42 (d, J = 1.0 Hz, 3). The latter signal of the 3-methyl group is split, possibly because of long-range coupling with the C^4 proton.

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.34; H, 5.63; N, 5.91.

6-Methoxy-3,4,9-trimethylpyrano[3,4-*b*]indol-1-one (15b).—The preparation was identical with that of 15a, replacing bromoacetone by 2-bromobutanone (**3**): yield 7%; mp 123–126°; ir (KBr) 1710 cm^{-1}; nmr ($CDCl_3$) δ 7.5–7.0 (m, 3), four methyl singlets at 4.03, 3.89, 2.34, and 2.30.

Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.09; H, 5.76; N, 5.39.

1,2-Dimethyl-3-(5-cyanopenten-1-yl)indole (17).—2-(1,2-Dimethyl-3-indolyl)cyclohexanone oxime (**16**) (14 g, 0.055 mol), prepared from **7k** and hydroxylamine hydrochloride, ethanol, and $NaHCO_3$ in the usual manner, was dissolved in 140 ml of dry pyridine. Benzenesulfonyl chloride (14 ml, 0.11 mol) was added under stirring and cooling. After standing at room temperature for 16 hr, the mixture was poured on ice and 6 N hydrochloric acid, and the reaction product was extracted with ethyl acetate. The residue after drying and evaporation was slurried with cold methanol and filtered, yield 10.6 g (81%), mp 97–100°. This product was sufficiently pure for further reactions.

An analytical sample was prepared by recrystallization from acetone–water: mp 97–100°; ir ($CHCl_3$) 2230 cm^{-1}; nmr ($CDCl_3$) δ 8.0–7.7 (m, 1), 7.3–7.0 (m, 3), 6.64 (d, J = 16 Hz, 1), 5.96 (d, J = 16 Hz, split further to t, J = 7 Hz, 1), 3.50 (s, 3), 2.7–1.2 (m, 6), 2.30 (s, 3).

Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.41; H, 8.01; N, 11.55.

1-*p*-Chlorobenzyl-5-methoxy-2-methyl-3-(5-cyanopenten-1-yl)indole (18).—This nitrile was prepared from the oxime of **7o** in the same manner as **17**, yield 30%, mp 101°.

Anal. Calcd for $C_{23}H_{23}ClN_2O$: C, 72.90; H, 6.12; Cl, 9.36; N, 7.40. Found: C, 72.58; H, 6.12; Cl, 9.40; N, 7.19.

6-(1,2-Dimethyl-3-indolyl)-5-hexenoic Acid (19).—The nitrile **17** (4 g) was heated to reflux in 50 ml of ethanol and 5 ml of 50% KOH for 14 hr. About 100 g of ice were added and the mixture was acidified with dilute hydrochloric acid. The precipitate was recrystallized from ethanol, yield 3.2 g (75%), mp 154–158°.

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.49; H, 7.70; N, 5.20.

ε-(1,2-Dimethyl-3-indolyl)caproic Acid (20).—The unsaturated acid **19** (1 g) was hydrogenated in 100 ml of ethanol with palladium/charcoal at room temperature and atmospheric pressure in the usual way. The residue after filtration and evaporation crystallized from ethanol–water, yield 0.9 g (90%), mp 74°.

Anal. Calcd for $C_{16}H_{21}NO_2$: C 74.10; H, 8.16; N, 5.40. Found: C, 74.12; H, 8.13; N, 5.76.

LiAlH$_4$ Reduction of 2-(1,2-Dimethyl-3-indolyl)cyclohexanone Oxime (16).—Lithium aluminum hydride (4 g, 0.11 mol) was added under nitrogen to a stirred solution of the oxime **16** (20 g, 0.078 mol) in 500 ml of anhydrous tetrahydrofuran. The mixture was refluxed for 4 hr and worked up in the usual manner. The residue after evaporation was transferred to a silica column (30 × 10 cm, approximately 1 kg of silica gel) and chromatographed with chloroform–methanol–concentrated ammonia (97:2.8:0.2). Four major fractions were obtained which corresponded to the four spots with basic character (blue with iodo plateate[13]) of the R_f values 0.6, 0.5, 0.2, and 0.1 on thin layer silica plates, using the same eluent.

2-(1,2-Dimethyl-3-indolyl)-7-azabicyclo[4.1.0]heptane (21, *cis*- or *trans*-).[14]—The fraction of the above column, corresponding to R_f 0.6, was evaporated to dryness, yielding 3.2 g (17%) and crystallized from ethanol: mp 173°; nmr ($CDCl_3$) δ 8.2–8.0 (m, 1), 7.3–6.9 (m, 3), 3.62 (s, 3), 3.5–3.0 (m, 1), 2.49 (s, 3), 2.4–1.0 (m, 8), 0.8–0.4 (s, 1, exchangeable); mass spectrum (70 eV) m/e (rel intensity) 240 (76), 223 (100), 208 (57), 197 (49), 182 (68).

Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39; N, 11.66. Found: C, 80.07; H, 8.31; N, 11.30.

2-(1,2-Dimethyl-3-indolyl)-7-azabicyclo[4.1.0]heptane (22, *trans*- or *cis*-).—The fraction of the above column, which corresponded to R_f 0.5, was evaporated to dryness, yielding 5.2 g (28%), and crystallized from ether–petroleum ether (bp 30–60°): mp 153°; nmr ($CDCl_3$) δ 7.8–7.5 (m, 1), 7.3–6.9 (m, 3), 3.61 (s, 3), 3.5–2.8 (m, 1), 2.40 (s, 3), 2.5–1.1 (m, 8), 0.6–0.5 (s, 1, exchangeable); mass spectrum (70 eV) m/e (rel intensity) 240 (100), 223 (19), 212 (37), 197 (81), 182 (80).

Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39; N, 11.66. Found: C, 80.25; H, 8.59; N, 11.33.

2-(1,2-Dimethyl-3-indoyl)cyclohexylamine (23, *cis*- or *trans*-).—The fraction corresonding to R_f 0.2 was evaporated to dryness and dissolved in ether and the hydrochloride was precipitated with ethereal HCl, yielding 3.8 g (18%). Recrystallization from ethanol gave mp 250–255°; nmr (free base in $CDCl_3$) δ 7.9–7.6 (m, 1), 7.3–6.9 (m, 3), 3.55 (s, 3), 3.3–1.3 (m, 10), 2.34 (s, 3) 1.19 (s, 2, exchangeable); mass spectrum (free base) (70 eV) m/e (rel intensity) 242 (95), 184 (100), 171 (99), 158 (100), 145 (96).

Anal. Calcd for $C_{16}H_{22}N_2 \cdot HCl$: C, 68.89; H, 8.32; N, 10.04. Found: C, 68.91; H, 8.22; N, 9.57.

2-(1,2-Dimethyl-3-indolyl)cyclohexylamine (24, *trans*- or *cis*-).—The fraction corresponding to R_f 0.1 was converted to the hydrochloride as described for **23**: yield 2.7 g (13%); mp 310–320° (from ethanol); nmr (free base in $CDCl_3$) δ 7.8–7.5 (m, 1), 7.3–6.8 (m, 3), 3.60 (s, 3), 3.5–0.8 (m, 10), 2.39 (s, 3), 1.15 (s, 2, exchangeable); mass spectrum (free base) (70 eV), m/e (rel intensity) 242 (100), 184 (82), 171 (65), 158 (100), 145 (95)

Anal. Calcd for $C_{16}H_{22}N_2 \cdot HCl$: C, 68.89; H, 8.32; N, 10.04. Found: C, 68.42; H, 8.25; N, 9.93.

2-(1,2-Dimethyl-3-indolyl)cyclohexanol, *cis*- and *trans*- (25 and 26).—2(1,2-Dimethyl-3-indolyl)cyclohexanone (**7k**) (11.5 g) was dissolved in 150 ml of dry tetrahydrofuran and this solution was added dropwise under stirring and cooling and in an atmosphere of nitrogen to a suspension of 4 g of $LiAlH_4$ in 50 ml of tetrahydrofuran. After refluxing for 3 hr the mixture was worked up as usual and the residue after evaporation (11.0 g) was applied on a silica column and chromatographed with chloroform.

Cis Isomer (25).—The fraction corresponding to a tlc R_f of 0.4 crystallized from ethanol: yield 4.0 g (35%); mp 143–146°; ir (KBr) 3570 cm^{-1}; nmr ($CDCl_3$) δ 8.0–7.7 (m, 1), 7.3–6.9 (m, 3), 3.95 (s, broad, no splitting pattern discernible, 1), 3.62 (s, 3), 2.94 (s, broad, slight indication of a triplet, 1), 2.39 (s, 3), 2.2–1.2 (m, 9).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C 79.26; H, 8.57; N, 5.63.

Trans Isomer (26).—The second fraction (R_f 0.2) yielded 4 g (35%) after crystallization from ethanol: mp 190–193°; ir (KBr) 3450 cm^{-1} (broad); nmr ($CDCl_3$) δ 7.8–7.5 (m, 1), 7.4–6.8 (m, 3), 4.02 (t, J = 10 Hz, further split into doublets, J = 4.8 Hz, 1), 3.57 (s, 3), 2.70 (pattern is like signal at δ 4.02, 1), 2.35 (s, 3), 2.3–0.9 (m, 9).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.33; H, 8.83; N, 5.62.

2-(2-Hydroxymethyl-1-methyl-3-indolyl)cyclopentanols (27 and 28).—The keto ester **14** (15 g) was reduced with $LiAlH_4$ (5 g) analogously to the preparation of **25** and **26**. After the same work-up, the mixture of the two isomers was separated on silica, using chloroform–methanol (97:3) as eluent. The stereochemistry was not established. Fraction 1 (R_f 0.55), 9 g crude, was crystallized from ethanol–petroleum ether: yield 6.5 g (50%); mp 93–94°; nmr ($CDCl_3$) δ 7.8–7.5 (m, 1), 7.4–6.9 (m, 3), 4.68 (s, 2), 4.2–3.9 (m, 1), 3.62 (s, 3), 3.6–3.0 (m, 1), 2.8–1.0 (m, 2 + 6).

(13) "Anfärbereagenzien für Dünnschicht und Papierchromatographie," E. Merck, Darmstadt, p 29.

(14) A definite assignment of the stereochemistry could not be made with the data available. A 220-MHz nmr study, kindly performed by the Canadian 220-MHz NMR Centre, Director Dr. A. A. Grey, could not solve the problem either; it was possible in compound **21** to decouple the C_1 H signal (1.94 ppm) wiping out a 4-Hz coupling at the C_2 H signal (3.25 ppm) but the equivalent decoupling in **22** could not be performed due to experimental limitations.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.88; H, 7.70; N, 5.87.

Fraction 2 (R_f 0.35), 2.7 g crude, was crystallized as above: yield 1.2 g (9%); mp 133–134°; nmr ($CDCl_3$) δ 7.7–7.4 (m, 1), 7.3–6.8 (m, 3), 4.60 (d, J = 3 Hz, 2), 4.6–4.1 (m, 1), 3.80 (s, 2, exchange with D_2O), 3.55 (s, 3), 3.1–2.6 (m, 1), 2.3–1.3 (m, 6).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 74.05; H, 7.77; N, 5.79.

4a-Hydroxy-7-methyl-1,2,3,4,4a,11c-hexahydro[1]benzopyrano[3,4-*b*]indole (29).—A suspension of 8 g of the lactam **12** in 100 ml of tetrahydrofuran was added under stirring and cooling in an atmosphere of nitrogen to a mixture of $LiAlH_4$ (3.6 g) and 20 ml of tetrahydrofuran. After stirring for 2 hr at 0°, the reaction products were worked up as usual and separated on a silica column, using $CHCl_3$–MeOH (97:3) as eluent. The main fraction, corresponding to an R_f of 0.5 on tlc, was crystalline after evaporation (5 g). Recrystallization from ethanol–petroleum ether yielded 4 g (50%) of **29**: mp 135–139°; ir (KBr) 3440 cm^{-1}; nmr ($CDCl_3$) δ 7.7–7.0 (m, 4), 4.95 (s, 2), 3.55 (s, 3), 3.2–1.5 (m, 10); mass spectrum (70 eV) parent 257.

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 75.01; H, 7.69; N, 5.65.

4a-Hydroxy-10-methoxy-7-methyl-1,2,3,4,4a,11c-hexahydro-[1]benzopyrano[3,4-*b*]indole (30).—The reduction of **13** was performed analogously to the one described for the preparation of **29**. In this case, the reaction was carried out at room temperature and the reaction product was crystallized without chromatography in 68% yield from chloroform: mp 165–168°; nmr (DMSO-d_6) δ 7.4–6.6 (m, 3), 5.70 (s, 1, exchange), 4.85 (s, 2), 4.55 (broad s, 1), 3.73 (s, 3), 3.48 (s, 3), 3.0–0.9 (m, 8).

Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.02; H, 7.35; N, 5.07.

2-(5-Methoxy-1,2-dimethyl-3-indolyl)cyclohex-2-enone (33).—A solution of the semiketal **30** (8 g) in dioxane (80 ml) containing 4 ml of 4 N HCl was allowed to stand for 30 min at room temperature. It was diluted with 100 ml of 2 N Na_2CO_3 and extracted with two 200-ml portions of ethyl acetate. The residue after washing, drying, and evaporation (8 g) was chromatographed on silica using $CHCl_3$–CH_3OH (99:1) as eluent. A main fraction was obtained crystalline in 50% yield (4 g). After recrystallization from ethanol, 1.9 g (25%) of the unsaturated ketone **33** was obtained analytically pure: mp 107–108°; ir (KBr) 1675 cm^{-1}; nmr ($CDCl_3$) δ 7.3–6.6 (m, 4), 3.78 (s, 3), 3.57 (s, 3), 2.8–2.0 (m, 6), 2.22 (s, 3).

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H 7.11; N, 5.20. Found: C, 75.65; H, 7.17; N, 5.20.

2-(5-Methoxy-1,2-dimethyl-3-indolyl)cyclohexanone (7m).—The unsaturated ketone **33** (0.5 g) was hydrogenated in ethanol (50 ml) with palladium (5%) on carbon at room temperature and atmospheric pressure in the usual way. The residue after filtration and evaporation yielded crystals from ethanol, which were identical (melting point, ir, nmr, tlc) with the material obtained according to eq 1 (see Table III).

Registry No.—**7a**, 32544-44-8; **7a** oxime, 32500-86-0; **7a** thiosemicarbazone, 32500-87-1; **7b**, 32500-88-2; **7b** thiosemicarbazone, 32500-89-3; **7c**, 32500-90-6; **7d**, 32500-91-7; **7d** oxime, 32500-92-8; **7d** thiosemicarbazone, 32500-93-9; **7e**, 32500-94-0; **7e** oxime, 32500-95-1; **7e** thiosemicarbazone, 32500-96-2; **7f**, 32500-97-3; **7f** oxime, 32500-98-4; **7f** thiosemicarbazone, 32500-99-5; **7g**, 32544-45-9; **7g** oxime, 32501-00-1; **7g** thiosemicarbazone, 32501-01-2; **7h**, 32500-28-0; **7h** oxime, 32500-29-1; **7h** thiosemicarbazone, 32500-30-4; **7i**, 32605-77-9; **7k**, 32544-46-0; **7k** oxime, 32500-31-5; **7k** thiosemicarbazone, 32500-32-6; **7l**, 32500-33-7; **7l** oxime, 32500-34-8; **7l** thiosemicarbazone, 32500-35-9; **7m**, 32500-36-0; **7m** thiosemicarbazone, 32500-37-1; **7n**, 32500-38-2; **7n** thiosemicarbazone, 32500-39-3; **7o**, 32500-40-6; **7o** oxime, 32500-41-7; **9**, 32500-42-8; **10**, 32500-43-9; **11**, 32500-44-0; **12**, 32500-45-1; **13**, 32500-46-2; **14**, 32544-47-1; **14** thiosemicarbazone, 32500-47-3; **15a**, 32500-48-4; **15b**, 32500-49-5; **17**, 32500-50-8; **18**, 32500-51-9; **19**, 32500-52-0; **20**, 32500-53-1; *cis*-**21**, -**22**, 32500-54-2; *trans*-**21**, -**22**, 32500-55-3; *cis*-**23**, -**24**, 32500-56-4; *trans*-**23**, -**24**, 32500-57-5; *cis*-**25**, 32500-58-6; *trans*-**26**, 32500-59-7; *cis*-**27**, -**28**, 32500-60-0; *trans*-**27**, -**28**, 32500-61-1; **29**, 32500-62-2; **30**, 32500-63-3; **33**, 32500-64-4.

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Synthesis of Dinitroxides

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The synthesis of seven stable nitroxide biradicals has been completed. Five of these compounds, namely, *N*-(1-oxyl-2,2,6,6-tetramethylpiperidyl)-*N'*-(1-oxyl-2,2,6,6-tetramethyl-4-methoxycarbonylpiperidyl)urea, 1-oxyl-2,2,5,5-tetramethylpyrrolyl-4-*N*-(1-oxyl-2,2,5,5-tetramethylpyrrolidyl-3-methylene)carboxamide, 1-oxyl-2,2,5,5-tetramethylpyrrolidine-3-*N*-(1-oxyl-2,2,6,6-tetramethylpiperidyl-4)carboxamide, 1,2-bis(1-oxyl-2,2,6,6-tetramethyl-4-methoxycarbonylpiperidyl-4)oxalic acid diamide, and 1,2-bis(1-oxyl-2,2,6,6-tetramethylpiperidyl-4)-succinic acid diamide, fulfill the two conditions which are postulated for their application as a flexible strain gauge in biological material: a distance of 7–11 Å between the two radical units in order to guarantee an interaction between the two unpaired electrons and a certain rigidity in the connecting chain in order to achieve a high resolution of the esr spectrum.

In this paper we describe the synthesis of new stable biradicals in the class of nitroxides of pyrrolines, pyrrolidines, and piperidines. Stable biradicals have been proposed as a flexible strain gauge, which would be attached to a biological sample (membrane or macromolecule) at two points, deform together with the support, and transduce the strain into the interaction-dependent features of the esr spectrum.[4,5]

***N,N'*-Bis(1-oxyl-2,2,6,6-tetramethyl-4-cyano-4-piperidyl)diaminoethane (I).**—This biradical in the class of the bis(α-imino acid nitriles) was obtained by a

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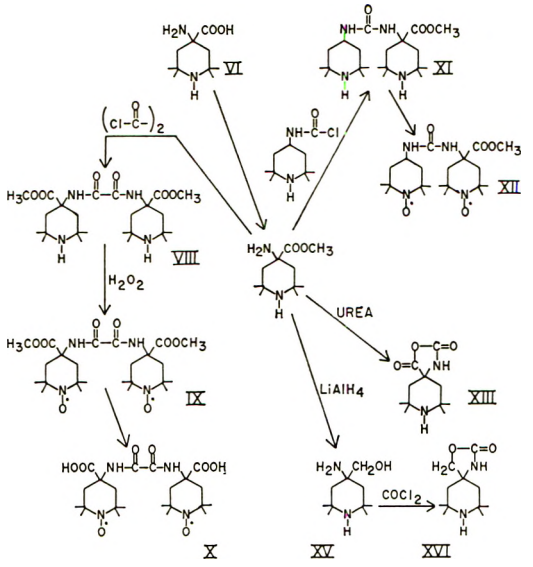
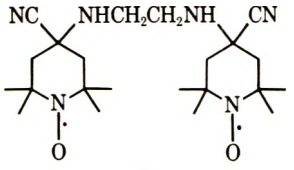


Figure 1.—Synthetic scheme for derivatives of 2,2,6,6-tetramethyl-4-carboxypiperidine (VI).

modified synthesis according to Strecker with 1-oxyl-2,2,6,6-tetramethyl-4-piperidone and ethylenediamine. Compound I is very easily hydrolyzed back to its starting materials, and is, therefore, not useful for biological applications.



I

1-Oxyl-2,2,5,5-tetramethylpyrrolyl-4-*N*-(1-oxyl-2,2,5,5-tetramethylpyrrolidyl-3-methylene)carboxamide (III).—This compound was prepared by acylation of 2,2,5,5-tetramethyl-3-aminomethylpyrrolidine (V) with 1-oxyl-2,2,5,5-tetramethyl-3-chloroformylpyrroline (IV), to 1-oxyl-2,2,5,5-tetramethylpyrrolyl-4-*N*-(1-oxyl-2,2,5,5-tetramethylpyrrolidyl-3-methylene)carboxamide (III), followed by oxidation. Compound V was prepared by reduction of 2,2,5,5-tetramethylpyrrolidine-3-carboxamide with lithium aluminum hydride.

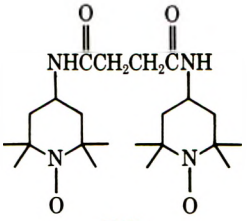
Derivatives of 2,2,6,6-Tetramethyl-4-amino-4-carboxypiperidine (VI).—Figure 1 gives a summary of the derivatives of VI. We prepared three biradicals from VI, which is described by Rassat,[6] namely, the amides IX, X, and XII, using the methyl ester of VI (VII) as a key intermediate.

***N*,*N*′-Bis(1-oxyl-2,2,6,6-tetramethyl-4-methoxycarbonylpiperidyl-4)oxalic acid diamide (IX)** was prepared by acylation of VII with oxalyl chloride, which yields the diamide VIII. It is converted to IX by oxidation with hydrogen peroxide. Mild alkaline hydrolysis yields 1,2-bis(1-oxyl-2,2,6,6-tetramethyl-4-carboxypiperidyl-4)oxalic acid diamide (X).

***N*-(1-oxyl-2,2,6,6-tetramethylpiperidyl-4)-*N*′-(1-oxyl-2,2,6,6-tetramethyl-4-methoxycarbonylpiperidyl-4)-urea (XII).**—We obtained XII by selective acylation of VII with the carbamic acid chloride of 2,2,6,6-tetramethyl-4-aminopiperidine and oxidation of the unsymmetrical *N*,*N*′-disubstituted urea XI with hydrogen peroxide in 60% yield. The inverse procedure, namely, the reaction of the carbamic acid chloride of VII with 2,2,6,6-tetramethyl-4-aminopiperidine, gave only 30% XI.

We obtained the hydantoin XIII exclusively in our attempts to prepare the *symmetrical urea* XIV by melting together 2 mol of VII and 1 mol of urea. Neither did we get the urea which could be expected from the reaction of 2 mol of 2,2,6,6-tetramethyl-4-amino-4-hydroxymethylpiperidine (XV) with 1 mol of phosgene or urea, but we did obtain the oxazolidone XVI in good yield.

Derivatives of 2,2,6,6-Tetramethyl-4-aminopiperidine (XVII). *N*,*N*-Bis(1-oxyl-2,2,6,6-tetramethylpiperidyl-4)succinic Acid Diamide (XIX).—We obtained XIX by condensation of 2 mol of XVII with 1 mol of succinyl chloride to XVIII and oxidation of XVIII with hydrogen peroxide. Rozantsev obtained



XIX

XIX by condensing succinyl chloride with 1-oxyl-2-2,6,6-tetramethyl-4-aminopiperidine.[7]

1-Oxyl-2,2,5,5-tetramethylpyrrolidine-3-*N*-(1-oxyl-2,2,6,6-tetramethylpiperidyl-4)carboxamide (XX).—We prepared XX by acylation of XVII with 1-oxyl-2,2,5,5-tetramethylpyrrolidine-3-carboxylic acid and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and oxidation with hydrogen peroxide.

Experimental Section

Biradical I.—Ethylenediamine (0.02 mol) was almost neutralized with HCl (pH 8) and 2.20 g (0.046 mol) of NaCN was added. After mixing, 5 ml of ethanol was added and the mixture was cooled at −10°. Within 2 hr a saturated solution of 6.84 g (0.04 mol) of 2,2,5,5-tetramethylpiperidine(1)oxyl in 90% ethanol was added, while the reaction mixture was kept at −10 to 0° and stirred. The resulting clear orange mixture was stirred for 0.5 hr with the same volume of ice, whereupon compound I precipitated. After the addition of 5 ml of water, I was separated by filtration and washed with water. The product was almost pure and has a melting point of 126° after drying over P_2O_5 *in vacuo* at room temperature. It can be recrystallized in benzene, ir 3300 ($-NH_2$) and 2219 cm^{-1} (CN).

Anal. Calcd: C, 63.15; H, 9.1; N, 20.1. Found: C, 63.14; H, 9.13; N, 20.24.

Biradical III.—Five grams of 2,2,5,5-tetramethyl-4-carbamidopyrrolidine and 2.5 g of $LiAlH_4$ were refluxed for 2 days in absolute ether. Water and solid KOH were added, and the solvent was evaporated from the filtered reaction mixture. The residue was fractionated *in vacuo*. The yield was 3 g of a colorless liquid at 90–92° (12 Torr), ir 3365, 3305, 3180, 1583 cm^{-1}.

A mixture of 2,2,5,5-tetramethyl-4-carboxypyrroline-1-oxyl and 0.1 ml of pyrridine in 3 ml of benzene was cooled to 0° and 0.09 ml of thionyl chloride was slowly added. After standing at room temperature for 1 hr, the solution of the acid chloride was separated from the pyridine–HCl with a filter pipette and concentrated in the argon stream, until the mixture did not smell of $SOCl_2$ anymore. The material was cooled at 0°, and 155 mg of 2,2,5,5-tetramethyl-4-aminomethylpyrrolidine was added. After

(6) A. Rassat and P. Rey, *Bull. Soc. Chim. Fr.*, 815 (1967).

(7) E. G. Rozantsev and V. I. Suskina, *Izv. Akad. Nauk SSSR., Ser. Khim.*, **9**, 2148 (1968).

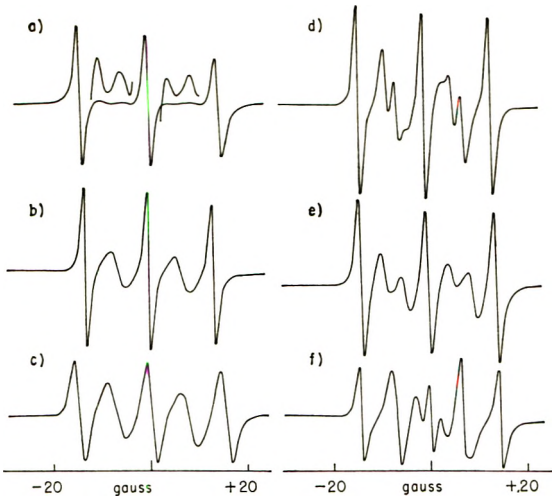


Figure 2.—First-derivative esr spectra of biradicals III, IX, XIX, and XX in different solvents: IX (a) in water and (b) in chloroform; XIX (c) in water and (d) in chloroform; III (e) and XX (f) in water. The spectra of oxygen-free solutions of III and XX in chloroform show the same resolution.

stirring for 2 hr at room temperature, the precipitated hydrochloride was brought into solution by adding 1 *M* NaOH. The organic layer was washed with water and the solvent was evaporated. The residue was oxidized with hydrogen peroxide without purification,[8] yield 250 mg of raw product, yellow needles, mp 182.5° (cyclohexane–benzene), ir 3448, 3360, 1664, 1615 cm^{-1} (double bond).

Anal. Calcd: C, 64.14; H, 9.20; N, 12.51. Found: C, 64.15; H, 9.22; N, 12.60.

Amino Acid Ester VIII.—Two grams of VI was dissolved in 20 ml of absolute methanol and the mixture was saturated with HCl gas. Methanol was removed *in vacuo* after 10 hr and the same procedure was repeated. The residue of the amino acid methyl ester hydrochloride was made alkaline with 15% KOH at 0°, and the free ester was extracted with chloroform. After washing with water, drying, and evaporating the chloroform, the residue crystallized as large, colorless crystals, mp 88–89°. After recrystallization in cyclohexane–petroleum ether (bp 30–60°) the melting point was 91.5°, yield 60% over-all, ir 3375 (-NH), 3300 ($-NH_2$), 1725 cm^{-1} (C=O).

Anal. Calcd: C, 62.0; H, 9.88; N, 13.13. Found: C, 62.08; H, 10.04; N, 13.02.

Biradical IX.—To a solution of 107 mg of amino acid ester VII in 2 ml of chloroform, 0.021 ml of oxalyl chloride was added under argon at −5°. After 2 hr at 0° and 24 hr at 20° the white precipitate was separated by filtration and recrystallized in petroleum ether and cyclohexane, yield 70–80%, mp 179.5°.

Anal. Calcd: C, 59.9; H, 8.9; N, 11.65. Found: C, 60.03; H, 8.96; N, 11.77.

IX was obtained by the usual oxidation procedure, according to Rozantsev,[10] mp 231°, ir 3390, 1741, 1685 cm^{-1}.

Biradical X.—A solution of 79 mg of diester IX in 2.5 ml of 0.5 *M* NaOH and 2 ml of methanol was kept at 40° for 3 hr and then at 20° for an additional 3 hr. The reaction mixture was acidified very carefully to pH 3–4 with HCl. The bright yellow diacid X precipitated and was collected by filtration and recrystallized in acetone under pressure at 100°, yield 70%, mp 230° dec, ir 3200, 2500, 1720, 1670 cm^{-1}.

Anal. Calcd: C, 54.55; H, 7.48; N, 11.58. Found: C, 54.50; H, 7.39; N, 11.37.

Biradical XI.—To a mixture of 155 mg of XVII in 2 ml of chloroform under argon, 0.8 ml of a 12.5% solution of phosgene in benzene was added at −20°. The mixture was warmed up to 0° and after 10 min 214 mg of amino acid ester VII in 1 ml of chloroform was slowly injected. The reaction mixture was stirred for 2 hr at 0° and for 30 min at 70°. Chloroform was evaporated *in vacuo*, and the residue was dissolved in 2 ml of 1 *M* HCl, kept at 60° for 30 min, cooled to 0°, and made alkaline to pH 12 with concentrated KOH. The white precipitate was filtered and washed with water, yield 200 mg, mp 260–270°.

(8) E. G. Rozantsev, "Free Nitroxyl Radicals," Plenum Press, New York, N. Y., 1970.

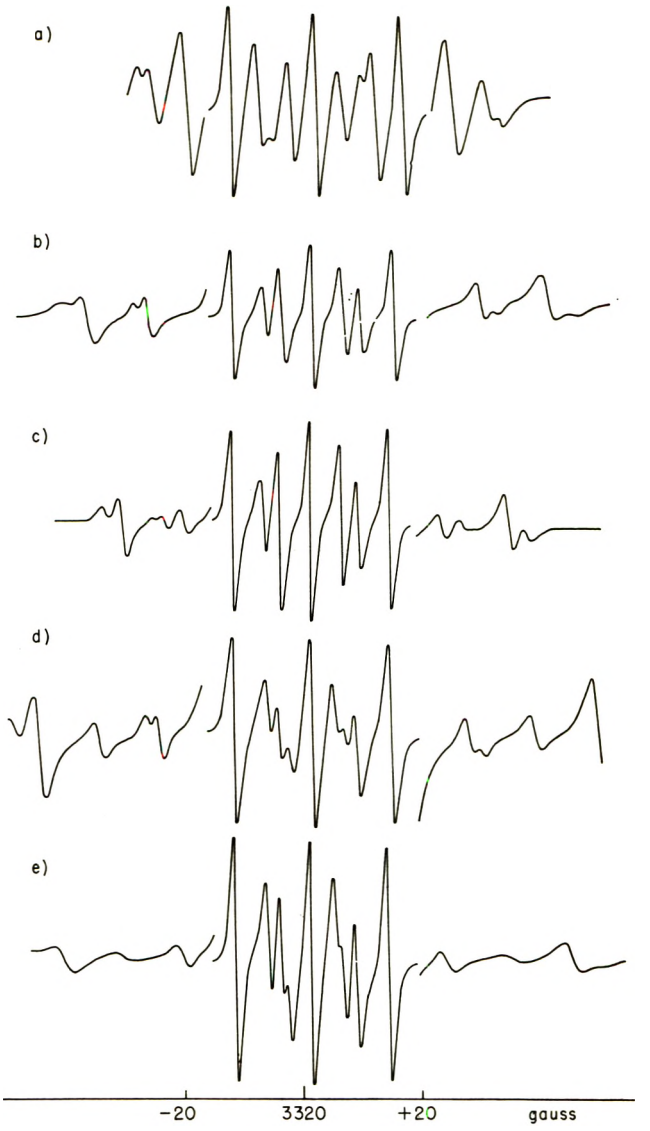


Figure 3.—First derivative esr spectra of biradical XII in (a) water, (b) chloroform, (c) benzene, (d) carbon tetrachloride, and (e) *n*-hexane. The *J* resonances ("side bands") are recorded at 10 times higher gain.

Oxidation with H_2O_2 and recrystallization of the crude biradical from methanol–cyclohexane and benzene yielded 120 mg of red needles, mp 241°, ir 3460, 3430, 3360, 1763, 1700 (s), 1507 cm^{-1}.

Anal. Calcd: C, 59.1; H, 8.95; N, 13.15. Found: C, 59.58; H, 8.73; N, 13.50.

Biradical XIX.—To 1.56 g of XVII in 20 ml of chloroform, 0.78 g of succinoyl chloride in 5 ml of chloroform was added slowly. After 1 hr, the white precipitate was filtered and 10% aqueous NaOH solution was added. The free base was extracted with chloroform, and the extract was washed with saturated sodium chloride solution and dried with sodium sulfate. After recrystallization in isopropyl alcohol, the white amide dihydrate melted at 204°. Oxidation with hydrogen peroxide yielded 90% XIX, mp 180° (lit. mp 178.5–180°).

Anal. Calcd: C, 62.7; H, 9.50; N, 13.25. Found: C, 62.75; H, 9.61; N, 13.37.

Biradical XX.—A mixture of 186 mg (1 mmol) of 2,2,5,5-tetramethyl-4-carboxypyrrolidine-1-oxyl, 200 mg (1.05 mmol) of 1-ethyl-3-(dimethylaminopropyl)carbodiimide HCl, and 155 mg (1 mmol) of XVII in 5 ml of chloroform was kept overnight at 40° under argon. After evaporation of the solvent the residue was oxidized by the usual method overnight with hydrogen peroxide without any purification. The crude red biradical was recrystallized once from benzene–cyclohexane, yield 30% over-all, mp 179.5°, ir 3425, 3332, 1667 cm^{-1}.

Anal. Calcd: C, 62.9; H, 9.54; N, 12.93. Found: C, 63.00; H, 9.60; N, 12.94.

Hydantoin XII by a Substitution with Urea.—Two moles of

VII and 1 mol of urea were mixed together and heated to 160–170° in 15 min. At 140° the mixture started evolving NH_3, and became turbid. After 30 min at 170° the mixture was a white solid. After cooling down, about 120 mg of starting material VII was extracted with toluene. The residue consisted of pure hydantoin XIII (identified by comparison of its ir spectrum with the ir spectrum of hydantoin obtained by a Strecker synthesis with 2,2,6,6-tetramethyl-4-oxopiperidine).

The oxazolidone XVI was made in an analogous procedure with amino alcohol XV.

Amino Alcohol XV.—Amino acid ester VII (214 mg) and 115 mg of $LiAlH_4$ were stirred in 5 ml of ether for 15 min. Water (0.8 ml) was added and then 30 ml of ether. Filtration and evaporation of the solvents yielded 200 mg of XV, mp 121.5° (petroleum ether–benzene), ir (Nujol) 3620, 3340, 3160, 1580 cm^{-1}.

Anal. Calcd: C, 64.5; H, 11.8; N, 15.05. Found: C, 64.85; H, 11.98; N, 15.04.

Esr Spectra.—The spectra described here have been taken at X band in a Varian E-3 spectrometer. Some preliminary studies were done with different solvents. The solutions were degassed and sealed off in a vacuum line. Radical concentrations were sufficiently low to eliminate intermolecular exchange broadening. The spectra were taken at 20°.

A selection of spectra of biradicals III, IX, XIX, and XX is shown in Figure 2. Figure 3 shows the spectra of biradical XI in five solvents of different polarities. Biradicals I and X showed three sharp lines and two broad lines inbetween. This type of spectrum has been discussed by Ferruti and coworkers.[5]

Registry No.—I, 34386-54-4; III, 34386-55-5; VII, 34386-56-6; IX, 34402-55-6; X, 34386-57-7; XI, 34402-56-7; XV, 32923-90-3; XIX, 21184-43-0; XX, 34386-59-9.

Sulfur Dioxide Extrusion from 2,5-Diaryl-4-hydroxy-3-ketotetrahydrothiophene 1,1-Dioxides. A Novel Synthesis of 1,4-Diarylbutane-2,3-diones[1]

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Five 2,5-diaryl-4-hydroxy-3-keto-2,3-dihydrothiophene 1,1-dioxides (**4a–e**) were prepared and reduced with zinc dust in acetic acid–ethanol–THF at 5–10° to 2,5-diaryl-4-hydroxy-3-ketotetrahydrothiophene 1,1-dioxides (**5a–e**). These products, in acetic acid–sodium acetate solution at 100–110°, underwent fragmentation to 1,4-diarylbutane-2,3-diones (**6a–e**) with loss of sulfur dioxide. Nmr analysis showed that the latter products consisted of mixtures of diketo and monoenol forms, with the monoenol predominating. It is proposed that the fragmentation reaction proceeds *via* a concerted elimination of sulfur dioxide from a 3-sulfolene intermediate.

α diketones have found a wide range of use in organic synthesis. However, one class of α diketones, the 1,4-diarylbutane-2,3-diones, appears infrequently in the chemical literature. The synthesis of only two compounds of this type has been reported: 1,4-diphenylbutane-2,3-dione and the 1,4-bis(4′-methoxyphenyl) analog. The former was prepared[2] by reaction of benzylmagnesium chloride with phenylacetaldehyde cyanohydrin, followed by hydrolysis and oxidation of the resulting acyloin with cupric acetate. The acyloin condensation has been reported to fail with ethyl phenylacetate.[3] According to a more recent report,[4] however, the reaction of ethyl 4′-methoxyphenylacetate proceeds in good yield to the corresponding acyloin, which upon oxidation gives 1,4-bis(4′-methoxyphenyl)-butane-2,3-dione.

For the general synthesis of substituted 1,4-diarylbutane-2,3-diones, the cyanohydrin method suffers from the lengthy preparation of intermediates. The acyloin method appears limited in its scope and is certainly unsuitable for the synthesis of analogs with halogen substituents since it involves the use of metallic sodium. We report here a new method for the synthesis of 1,4-diarylbutane-2,3-diones, which is fairly general in its scope and uses readily available starting materials. This method involves the intermediate synthesis of 2,5-diaryl-4-hydroxy-3-keto-2,3-dihydrothiophene 1,1-dioxides (*e.g.*, **4**), a class of compounds first prepared by Overberger and coworkers.[5]

Following the general route of Overberger[5a,c] (see Scheme I), treatment of 3,4-dimethylbenzyl chloride **1a** with sodium sulfide in aqueous ethanol yielded the sulfide **2a** (95%), which was oxidized with 30% hydrogen peroxide in acetic acid to sulfone **3a** (92%). Condensation of **3a** with excess diethyl oxalate in the presence of sodium ethoxide gave the cyclic diketo sulfone **4a** (80%), which exists in the tautomeric forms indicated.

We were interested in determining if compounds such as **4a** could be converted into 1,4-diarylbutane-2,3-diones by the action of reducing agents which are known to cause reductive cleavage of β-keto sulfones to ketones.[6] When **4a** was treated with zinc dust in acetic acid–ethanol–THF mixtures at 5–10° for 30 min, the major product isolated was the hydroxy-keto sulfone **5a** (73%) rather than the butanedione **6a**. Thin layer chromatography (silica gel, benzene) of samples of the reaction mixture indicated the formation of only a minor amount of **6a** as a fast-moving spot. At higher temperatures further reduction of these products becomes a significant side reaction. The structure of

(1) This investigation was supported in part by Research Contract DADA-17-71-C-1001 from the U. S. Army Medical Research and Development Command, Office of the Surgeon General. This is Publication No. 1031 from the Army Research Program on Malaria.

(2) (a) P. Ruggli and B. Hegedüs, *Helv. Chim. Acta*, **25**, 1285 (1942); (b) P. Ruggli and P. Zeller, *ibid.*, **28**, 741 (1945).

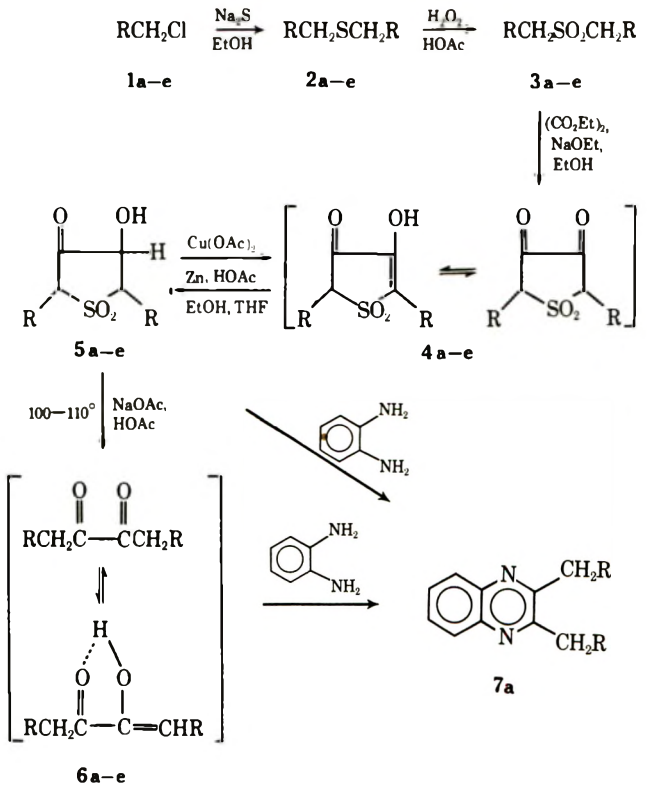
(3) N. R. Campbell, J. N. Dunsmuir, and M. E. H. Fitzgerald, *J. Chem. Soc.*, 2743 (1950).

(4) I. Hagedorn, U. Eholzer, and A. Lüttringhaus, *Chem. Ber.*, **93**, 1584 (1960).

(5) (a) C. G. Overberger, S. P. Ligthelm, and E. A. Swire, *J. Amer. Chem. Soc.*, **72**, 2856 (1950); (b) C. G. Overberger and J. M. Hoyt, *ibid.*, **73**, 3305, 3957 (1951); (c) C. G. Overberger, R. A. Gadea, J. A. Smith, and I. C. Kogon, *ibid.*, **75**, 2075 (1953).

(6) (a) E. J. Corey and M. Chaykovsky, *ibid.*, **86**, 1640 (1964); **87**, 1345 (1965). (b) H. O. House and J. K. Larson, *J. Org. Chem.*, **33**, 61 (1968).

SCHEME I



a, R = 3,4-$(CH_3)_2C_6H_3$–
b, R = 4-ClC_6H_4–
c, R = 3,4-$Cl_2C_6H_3$–
d, R = 3-$CF_3C_6H_4$–
e, R = 2-naphthyl

5a was verified by nmr spectrometry[7] and by reoxidation to **4a** with cupric acetate in aqueous methanol–acetic acid solution (93%).

When **5a** was heated under nitrogen in acetic acid at 100–110°, a slow decomposition occurred, with loss of sulfur dioxide and formation of butanedione **6a**, along with other products. In the presence of excess sodium acetate, however, sulfur dioxide extrusion occurred cleanly and rapidly at this temperature, with almost quantitative conversion into **6a**. The oily solid product thus isolated was found, by nmr spectrometry, to be a mixture of diketo (28%) and monoenol (72%) tautomeric forms. Product composition was determined by comparing the integral ratio of the diketo and monoenol methylene singlets (see Experimental Section). The existence of any significant amount of a doubly enolized tautomer was discounted since only one signal appeared in the vinyl region of the spectrum, which was attributed to the monoenol methine (half the integral area of the monoenol methylene). Verification of this was accomplished by determining the spectrum of the pure monoenol tautomer, isolated by fractional crystallization from hexane. Further proof that the fragmentation reaction proceeded cleanly to **6a** was shown by conversion of the crude mixture of tautomers into the quinoxaline **7a** (95%) upon treatment with *o*-phenylenediamine in refluxing ethanol; **7a** was also obtained (88%) when **5a** was refluxed with the diamine in ethanol–acetic acid.[8,9]

Following the same reaction scheme, four other cyclic diketo sulfones (**4b–e**) were prepared and transformed in good yield into the corresponding butanediones (**6b–e**). In each instance the products were isolated as a mixture of diketo and monoenol tautomers with the latter predominating. All the intermediate hydroxy keto sulfones were isolated and characterized except for **5e** (R = 2-naphthyl), which proved to be somewhat unstable during work-up and was therefore converted directly into **6e**. Steric factors may play an important role in the fragmentation of the 2-naphthyl compound. In fact, overall yields of butanediones in all of these examples may be improved by eliminating the isolation of the hydroxyketo sulfones. There was always some fragmentation during work-up of the reduction mixture, due presumably to the presence of acetic acid and zinc acetate.

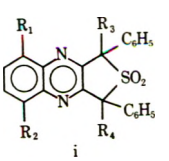
The mechanism of sulfur dioxide extrusion from compounds such as **5** has not been fully investigated. However, in light of what is known about the thermal fragmentation of 2,5-dihydrothiophene 1,1-dioxides (3-sulfolenes) to dienes and sulfur dioxide,[10] it seems attractive, in this instance, to propose that a 3-sulfolene-type intermediate may be involved. According to this view, in acetic acid at 100–110° in the presence of excess sodium acetate, compounds **5a–e** undergo rapid equilibration to tautomeric enol and enediol forms. At this temperature[11] the latter tautomer, which can be considered a 3-sulfolene, undergoes fragmentation with concerted elimination of sulfur dioxide and formation of **6a–e**. Consistent with this mechanism is the finding that the reaction occurs only slowly in acetic acid alone, or in ethanol–sodium acetate solution. It appears that both an acid and a base are necessary for the reaction to occur rapidly, presumably because they promote enolization to the sulfolene.

Inasmuch as cyclic diketo sulfones such as **4a–e** can be prepared easily in large quantities and in excellent yields, we believe this method to be a practical preparation of 1,4-diarylbutane-2,3-diones. Also, since these cyclic sulfones can be alkylated at a methine position,[5b] the method is applicable in principle to the

(7) The vicinal methine protons in compounds **5a–d** appear as a pair of doublets in deuterioacetone and deuteriopyridine with J = 6.8–7.0 Hz. By analogy to values found for 2,3-dihydrothiophene (J_{trans} = 7.5 Hz; J_{cis} = 10.0 Hz) we tentatively assign a trans configuration for the vicinal methines in **5a–d**. See R. J. Abraham in "Nuclear Magnetic Resonance for Organic Chemists," D. W. Mathieson, Ed., Academic Press, New York, N. Y., 1967, p 142.

(8) In the reaction of **5a** with *o*-phenylenediamine, a dark green color develops, which changes to orange as the reaction progresses. It is possible that this signals the transient appearance of an enamine which undergoes fragmentation, with loss of sulfur dioxide, prior to cyclization to the quinoxaline.

(9) Moriconi and coworkers have used compounds of type **4** for the preparation of thienoquinoxaline dioxides (i) and have studied the pyrolytic,

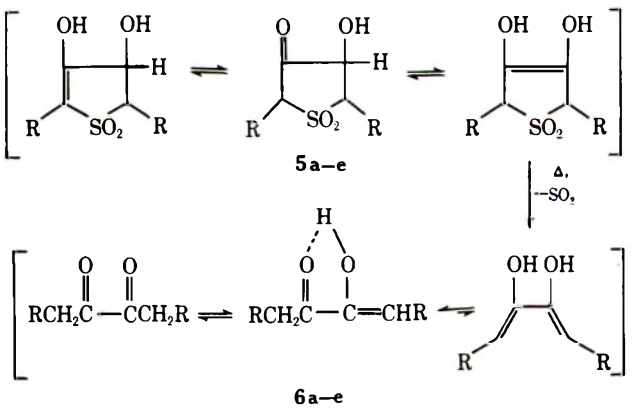


i

photolytic, oxidative, and reductive extrusion of sulfur dioxide from these compounds. See E. J. Moriconi, R. E. Misner, and T. E. Brady, *J. Org. Chem.*, **34**, 1651 (1969); **36**, 479 (1971).

(10) For recent work on the stereoelectronic course of these fragmentations, see (a) W. L. Mock, *J. Amer. Chem. Soc.*, **88**, 2857 (1966); (b) S. D. McGregor and D. M. Lemal, *ibid.*, **88**, 2858 (1966), and references cited therein.

(11) It has been shown[10a] that *cis*-2,5-dimethyl-2,5-dihydrothiophene 1,1-dioxide undergoes fragmentation with vigorous gas evolution at 100°, while the trans isomer requires a temperature of 150° or higher.[10] Under the equilibrating conditions of our system, the facile elimination of sulfur dioxide at 100° is understandable.



preparation of 1,4-diarylbutane-2,3-diones substituted at one of the methylene positions.

Experimental Section[12]

Bis(3,4-dimethylbenzyl) Sulfide (2a).—To a stirred solution of 3,4-dimethylbenzyl chloride[13] (186 g, 1.2 mol) in ethanol (360 ml), at 50°, was added slowly a solution of sodium sulfide (60% technical flakes, 78 g, 0.6 mol) in water (100 ml), at such a rate as to maintain reflux (~30 min). The mixture was stirred under reflux for 18 hr, cooled, and poured into a mixture of crushed ice and water (1.2 l.). Filtration gave a white solid (154 g, 95%), mp 45–50°. Recrystallization of a sample twice from ethanol gave colorless plates, mp 67–68°.

Anal. Calcd for $C_{18}H_{22}S$: C, 79.94; H, 8.20; S, 11.86. Found: C, 79.88; H, 8.35; S, 12.03.

Bis(3,4-dimethylbenzyl) Sulfone (3a).—To a stirred solution of **2a** (150 g, 0.556 mol) in glacial acetic acid (800 ml) was added slowly 30% hydrogen peroxide (340 g, 3.0 mol) at such a rate as to maintain the temperature at 70–80° (~45 min). After being stirred at 70° for an additional 3 hr, the mixture was cooled, and water (500 ml) was added. The white solid was filtered, washed thoroughly with water, and dried (155 g, 92.3%, mp 147–150°). Recrystallization of a sample twice from ethanol gave white crystals, mp 160–162°.

Anal. Calcd for $C_{18}H_{22}O_2S$: C, 71.48; H, 7.33; S, 10.60. Found: C, 71.40; H, 7.46; S, 10.42.

Bis(3,4-dichlorobenzyl) Sulfone (3c).—Following the above procedure, **2c**[14] gave the sulfone as a white solid (89%), mp 187–188° (from ethanol).

Anal. Calcd for $C_{14}H_{10}Cl_4O_2S$: C, 43.77; H, 2.62; Cl, 36.92; S, 8.33. Found: C, 43.70; H, 2.63; Cl, 37.01; S, 8.49.

Bis(3-trifluoromethylbenzyl) Sulfide (2d) and Sulfone (3d).—To a stirred solution of *m*-trifluoromethylbenzyl chloride[15] (100 g, 0.514 mol) in alcohol (500 ml) was added slowly sodium sulfide (60% technical flakes, 33.4 g, 0.257 mol) in water (50 ml). The mixture was heated under reflux for 5 hr, cooled, and poured into 1 l. of water. Extraction of the oily mixture with dichloromethane and evaporation of the combined extracts under vacuum afforded **2d** (90 g, quantitative yield) as a yellow oil. The oil was dissolved in glacial acetic acid (700 ml), and the solution was heated to 70–80° and stirred while 30% hydrogen peroxide (148 g, 1.3 mol) was added slowly. After 5 hr at 70–80°, the mixture was cooled and poured into crushed ice and water (1.2 l.). The white solid was filtered, washed thoroughly with water, and dried (86.5 g, 88%, mp 141–145°). Recrystallization from benzene gave colorless needles, mp 148–149°.

Anal. Calcd for $C_{16}H_{12}F_6O_2S$: C, 50.26; H, 3.16; F, 29.81; S, 8.38. Found: C, 50.16; H, 3.04; F, 30.19; S, 8.46.

2,5-Bis(3′,4′-dimethylphenyl)-4-hydroxy-3-keto-2,3-dihydrothiophene 1,1-Dioxide (4a).—A solution of sodium ethoxide was prepared from sodium (10.9 g, 0.475 g-atom) and absolute ethanol (600 ml). To this was added **3a** (65.5 g, 0.216 mol) and diethyl oxalate (63.1 g, 0.432 mol). The mixture was refluxed for 8 hr, cooled, and poured into water (1 l.). Some insoluble material was filtered off and the filtrate was acidified with concentrated hydrochloric acid to pH 2. The aqueous phase was decanted, and the remaining sticky solid was triturated with 50% aqueous ethanol. Filtration gave a light tan solid (53.5 g, mp 240–245°). An additional 8 g of material was obtained by extracting the aqueous phase with chloroform (total yield 80%). Recrystallization of a sample twice from ethanol gave colorless needles: mp 251–252°; ir ($CHCl_3$) 5.90 (s), 7.41 (s), 7.62 (s), 8.60 (m), 8.98 (m), 9.15 μ (m).

Anal. Calcd for $C_{20}H_{20}O_4S$: C, 67.39; H, 5.66; S, 9.00. Found: C, 67.52; H, 5.74; S, 8.89.

2,5-Bis(3′,4′-dichlorophenyl)-4-hydroxy-3-keto-2,3-dihydrothiophene 1,1-Dioxide (4c).—A solution of sodium ethoxide was prepared from sodium (3.75 g, 0.163 g-atom) and absolute alcohol (230 ml). To this was added sulfone **3c** (28.5 g, 0.0741 mol) and diethyl oxalate (43.3 g, 0.296 mol). The reaction mixture was refluxed for 7 hr, cooled, and poured into water (2 l.). The insoluble material was filtered off and the filtrate was acidified with concentrated hydrochloric acid to pH 2. The solid was filtered and dried (30 g, 92.3%), mp 262–265°. Recrystallization twice from ethyl acetate–hexane gave white crystals: mp 266–268°; ir (KCl) 5.81 (s), 6.81 (m), 7.33 (s), 7.80 (s), 8.62 (s), 8.89 (s), 9.22 μ (s).

Anal. Calcd for $C_{16}H_8Cl_4O_4S$: C, 43.86; H, 1.84; Cl, 32.37; S, 7.31. Found: C, 43.72; H, 1.71; Cl, 32.55; S, 7.19.

2,5-Bis(3′-trifluoromethylphenyl)-4-hydroxy-3-keto-2,3-dihydrothiophene 1,1-Dioxide (4d).—To a solution of sodium ethoxide prepared from sodium (1.26 g, 0.0548 g-atom) and absolute ethanol (70 ml) was added **3d** (10 g, 0.0261 mol) and diethyl oxalate (15.2 g, 0.104 mol). After being refluxed for 4 hr, the solution was cooled, poured into water (300 ml), and acidified with concentrated hydrochloric acid to pH 2. Filtration gave a white solid (11.1 g, 97.5%), mp 202–204°. Recrystallization from benzene gave white crystals: mp 203–205°; ir (KCl) 5.83 (s), 7.32 (s), 7.52 (s), 7.80 (s), 8.52 (s), 8.90 (s), 9.08 (s), 9.30 μ (s).

Anal. Calcd for $C_{18}H_{10}F_6O_4S$: C, 49.54; H, 2.31; F, 26.12; S, 7.34. Found: C, 49.57; H, 2.00; F, 26.21; S, 7.39.

2,5-Bis(3′,4′-dimethylphenyl)-4-hydroxy-3-ketotetrahydrothiophene 1,1-Dioxide (5a).—A stirred solution of **4a** (21.4 g, 0.06 mol) in glacial acetic acid (75 ml), ethanol (75 ml), and tetrahydrofuran (75 ml) was cooled to 5° in an ice bath, and zinc dust (19.5 g, 0.3 g-atom) was added.[16] After 10 min the temperature rose to 9°, and after 30 min the greenish yellow color of the mixture became gray and the temperature subsided. The mixture was filtered immediately under suction, and the filtered solids were washed with ethanol (50 ml). The combined filtrates were concentrated under vacuum to about one-third volume, and water (400 ml) was added slowly with stirring. The precipitated cream-colored solid was filtered, washed with water, and dried (20 g), mp 178–183° dec. Recrystallization from ethyl acetate–hexane gave colorless prisms (15.7 g, 73%), mp 204–206° dec. One more recrystallization furnished the analytical sample: mp 206–207° dec; ir (KCl) 6.02 (m), 7.82 (s), 8.92 (s), and 9.18 μ (s). The nmr spectrum (deuterioacetone) showed the two vicinal methine hydrogens as a pair of doublets centered at δ 4.47 and 5.22 (J = 6.8 Hz); in deuteriopyridine they appear at δ 5.15 and 5.70 (J = 6.8 Hz).

Anal. Calcd for $C_{20}H_{22}O_4S$: C, 67.01; H, 6.19; S, 8.95. Found: C, 66.95; H, 6.10, S, 9.02.

Oxidation of 5a to 4a.—A mixture of **5a** (0.5 g, 1.4 mmol) and copper acetate monohydrate (0.560 g, 2.8 mmol) in 50% aqueous acetic acid (25 ml) and methanol (10 ml) was refluxed for 2 hr. The cooled mixture was diluted with water (100 ml) and extracted with chloroform. The extracts were washed with water, dried over sodium sulfate, and evaporated to leave **4a** as a pale yellow solid (0.463 g, 93%), mp 244–246°, identified by its ir spectrum.

2,5-Bis(4′-chlorophenyl)-4-hydroxy-3-ketotetrahydrothiophene 1,1 Dioxide (5b).—A stirred solution of **4b**[5a] (9.6 g, 0.026 mol) in glacial acetic acid (80 ml), ethanol (80 ml), and tetrahydrofuran (80 ml) was cooled to 7° in an ice bath, and zinc dust (8.44 g, 0.13 g-atom) was added. After about 12 min the color of the

(12) Ir spectra were taken with a Perkin-Elmer Model 137B double-beam recording spectrophotometer. Nmr spectra were determined on a Varian A-60 instrument, with tetramethylsilane as the internal standard. Melting points were measured in Pyrex capillary tubes in a Mel-Temp apparatus (Laboratory Devices, Inc., Cambridge, Mass.) and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by Werby Laboratories, Boston, Mass.

(13) Aldrich Chemical Co., Inc., Milwaukee, Wis.

(14) M.G. Voronkov, A. N. Pereferkovich, and S. V. Mikhailova, *Zh. Prikl. Khim* (Leningrad), **42**, 1155 (1969); *Chem. Abstr.*, **71**, 80852h (1969).

(15) Pierce Chemical Co., Rockford, Ill.

(16) Tetrahydrofuran is added to increase the solubility of the cyclic sulfones. The zinc dust used was purchased from Fisher Scientific Co.

mixture changed from greenish yellow to gray. The mixture was filtered immediately under suction and the solids were washed with ethanol (50 ml). The combined filtrates were evaporated under vacuum to a yellow oil, to which was added ethanol (10 ml). After further addition of water (150 ml), filtration gave a pale yellow solid (6.7 g). Trituration of this solid with 1:1 ethyl acetate–hexane (50 ml) and filtration gave almost colorless crystals (5.15 g, 53%), mp 238–244° dec. Recrystallization from ethyl acetate–hexane gave colorless prisms: mp 242–245° dec; ir (KCl) 6.02 (m), 6.72 (m), 7.82 (s), 8.85 (s) and 9.19 μ (s); nmr (deuteriopyridine) δ 5.18 (d) and 5.64 (d) (J = 6.8 Hz, vicinal methine protons).

Anal. Calcd for $C_{16}H_{12}Cl_2O_4S$: C, 51.76; H, 3.26; Cl, 19.10; S, 8.64. Found: C, 51.95; H, 3.14; Cl, 18.97; S, 8.42.

2,5-Bis(3′,4′-dichlorophenyl)-4-hydroxy-3-ketotetrahydrothiophene 1,1-Dioxide (5c).—A stirred solution of **4c** (8.76 g, 0.020 mol) in glacial acetic acid (50 ml), ethanol (50 ml), and tetrahydrofuran (50 ml) was cooled to 5° in an ice bath, and zinc dust (6.5 g, 0.1 g-atom) was added. The temperature was maintained at 5–10° for 1 hr and 5 min, after which the color changed from greenish yellow to gray. The mixture was filtered immediately and the solids were washed with ethanol (50 ml). The combined filtrates were evaporated to one-third volume, water (150 ml) was added, and the mixture was extracted with ethyl acetate. The extracts were washed with water, dried over sodium sulfate, and evaporated to leave a yellow oil. The oil was dissolved in benzene (30 ml) and scratched to induce crystallization. Cooling and filtration gave a white solid (3.55 g), mp 205–207° dec. Addition of hexane (20 ml) to the filtrate and cooling gave additional solid (1.4 g), mp 197–202° dec (total yield 56.2%). Recrystallization from ethyl acetate–hexane gave colorless prisms: mp 206–207° dec; ir (KCl) 6.07 (m), 6.82 (s), 7.37 (s), 7.83 (s), 8.88 (s), 9.16 μ (s); nmr (deuteriopyridine) δ 5.18 (d) and 5.62 (d) (J = 7.0 Hz, vicinal methine protons).

Anal. Calcd for $C_{16}H_{10}Cl_4O_4S$: C, 43.66; H, 2.29; Cl, 32.22; S, 7.29. Found: C, 43.32; H, 2.13; Cl, 32.50; S, 7.29.

2,5-Bis(3′-trifluoromethylphenyl)-4-hydroxy-3-ketotetrahydrothiophene 1,1-Dioxide (5d).—A stirred solution of **4d** (8.7 g, 0.02 mol) in glacial acetic acid (50 ml), ethanol (50 ml), and tetrahydrofuran (50 ml) was cooled to 3° in an ice bath, and zinc dust (6.5 g, 0.1 g-atom) was added. The temperature rose to ~10° after 16 min, and the color changed from greenish yellow to gray. The mixture was filtered immediately and the solids were washed with ethanol (50 ml). The combined filtrates were evaporated under vacuum to one-third volume, water (150 ml) was added, and the mixture was extracted with ethyl acetate. The extracts were washed with water, dried over sodium sulfate, and evaporated to a yellow oil. Trituration with a warm mixture of benzene (20 ml) and hexane (10 ml), cooling, and filtering gave a white solid (6.85 g, 78%), mp 195–199° dec. Recrystallization from ethyl acetate–hexane afforded colorless prisms: mp 197–200° dec; ir (KCl) 6.08 (m), 7.40 (s), 7.55 (s), 7.85 (s), 8.55 (s), 8.90 (s), 9.30 μ (s); nmr (deuterioacetone) δ 4.85 (d) and 5.48 (d) (J = 7.0 Hz); nmr (deuteriopyridine) δ 5.37 (d) and 5.76 (d) (J = 7.0 Hz, vicinal methine protons).

Anal. Calcd for $C_{18}H_{12}F_6O_4S$: C, 49.32; H, 2.76; F, 26.00; S, 7.32. Found: C, 49.31; H, 2.49; F, 26.26; S, 7.57.

Preparation of 1,4-Diarylbutane-2,3-diones.—The general procedure for the fragmentation reaction was to dissolve 1 to 2 g of **5a–d** and 5 molar equiv of sodium acetate in 20–30 ml of glacial acetic acid. With nitrogen bubbling through, the mixture was heated to 100–110° for 30 min. Completion of the reaction was monitored by tlc (silica gel, benzene). The solution was cooled, water (70 ml) was added, and the mixture was extracted with benzene. The extracts were washed three times with water, dried over sodium sulfate, and evaporated to a yellow solid (or an oil which crystallized when scratched) consisting of a mixture of diketo and monoenol (hydrogen bonded) forms. Nmr spectra were taken to determine product composition and the solids were recrystallized for analysis. The results are summarized below.

6a was obtained in 98% yield: oily solid; nmr (CCl_4, 0.5 M) δ 3.74 (s, diketo CH_2), 3.88 (s, monoenol CH_2), 6.36 (s, =CH–), 7.13 (s, hydrogen bonded –OH); 72% monoenol form. Recrystallization twice from hexane gave very pale yellow prisms: mp 85–86° (monoenol); ir ($CHCl_3$) 2.90 (m), 6.02 (s), 6.17 (s), 7.27 μ (s).

Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.28; H, 7.80.

6b was obtained in 97.6% yield: mp 115–131°; nmr ($CDCl_3$, 0.5 M) δ 3.93 (s, diketo CH_2), 4.07 (s, monoenol CH_2), 6.47 (s, =CH–); 86% monoenol form. Recrystallization twice from isopropyl ether gave very pale yellow prisms: mp 130–132° (monoenol); ir ($CHCl_3$) 2.92 (m), 6.03 (s), 6.17 (s), 6.77 (s), 7.26 (s), 9.20 (s), 9.90 μ (s).

Anal. Calcd for $C_{16}H_{12}Cl_2O_2$: C, 62.56; H, 3.74; Cl, 23.08. Found: C, 62.47; H, 3.85; Cl, 22.86.

6c was obtained in 97.5% yield: oily solid; nmr ($CDCl_3$, 0.25 M) δ 3.96 (s, diketo CH_2), 4.07 (s, monoenol CH_2), 6.40 (s, =CH–); 83% monoenol form. Recrystallization twice from benzene–hexane gave pale yellow prisms: mp 155–157° (monoenol); ir ($CHCl_3$) 2.91 (m), 6.0 (s), 6.12 (s), 6.83 (s), 7.25 (s), 7.64 (s), 8.87 (s), 9.72 μ (s).

Anal. Calcd for $C_{16}H_{10}Cl_4O_2$: C, 51.10; H, 2.68; Cl, 37.71. Found: C, 51.16; H, 2.51; Cl, 37.90.

6d was obtained in 97.6% yield: mp 67–72°; nmr ($CDCl_3$, 0.5 M) δ 4.07 (s, diketo CH_2), 4.20 (s, monoenol CH_2), 6.57 (s, =CH–); 77% monoenol form. Recrystallization twice from hexane gave very pale yellow needles: mp 76–80° (mixture of diketo and monoenol); ir ($CHCl_3$) 2.90 (m), 5.82 (m), 6.0 (m), 6.12 (m), 6.92 (m), 7.21 (m), 7.55 (s), 8.59 (s), 8.85 (s), 9.30 μ (s).

Anal. Calcd for $C_{18}H_{12}F_6O_2$: C, 57.76; H, 3.23; F, 30.46. Found: C, 57.64; H, 3.16; F, 30.60.

1,4-Bis(2′-naphthyl)butane-2,3-dione (6e).—A stirred solution of **4e**[17] (4.0 g, 0.01 mol) in glacial acetic acid (100 ml), ethanol (50 ml), and tetrahydrofuran (200 ml) was cooled to 8° in an ice bath, and zinc dust (3.25 g, 0.05 g-atom) was added. The temperature was maintained at 8–10° for 1 hr and 5 min, at which time the greenish yellow color changed to gray. The mixture was filtered immediately and the solids were washed with 40 ml of ethanol. The combined filtrates were evaporated under vacuum to ~125 ml, and sodium acetate (4.1 g, 0.05 mol) was added. The mixture was heated at 100–110° for 30 min, with nitrogen bubbling through, and then cooled. Addition of water (150 ml), with stirring, and filtration of the granular precipitate yielded a light tan solid (3.1 g, 91.6%): mp 172–178°; nmr ($CDCl_3$, 0.125 M) δ 4.11 (s, diketo CH_2), 4.32 (s, monoenol CH_2), 6.78 (s, =CH–); 78% monoenol form. Recrystallization from ethyl acetate gave yellow prisms: mp 174–179° (mixture of diketo and monoenol); ir (KCl) 5.85 (s), 6.02 (m), 6.12 (m), 6.68 (m), 7.21 (m), 7.38 (m), 7.62 μ (m).

Anal. Calcd for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36. Found: C, 84.83; H, 5.54.

2,3-Bis(3′,4′-dimethylbenzyl)quinoxaline (7a) from (5a).—A mixture of **5a** (0.717 g, 0.002 mol) and *o*-phenylenediamine (0.216 g, 0.002 mol) in ethanol (10 ml) and glacial acetic acid (2 ml) was heated to reflux. The color of the solution became dark green and changed to orange after 5 min. After being refluxed for 3 hr, the solution was cooled, water (30 ml) was added, and the mixture was neutralized with dilute aqueous sodium hydroxide. Filtration gave the quinoxaline as a tan solid (0.646 g, 88%), mp 95–99°. Recrystallization twice from ethanol gave colorless needles, mp 108–110°. The solid gave a purple quinoxaline test with concentrated sulfuric acid.[18]

Anal. Calcd for $C_{26}H_{26}N_2$: C, 85.20; H, 7.15; N, 7.65. Found: C, 85.07; H, 7.45; N, 7.43.

7a from 6a.—When the crude fragmentation product **6a** was refluxed with 1 molar equiv of *o*-phenylenediamine in ethanol, the quinoxaline was obtained in 95% yield.

Registry No.—**2a**, 34277-82-2; **3a**, 34277-83-3; **3c**, 34277-84-4; **3d**, 34277-85-5; **4a**, 34277-86-6; **4c**, 34277-87-7; **4d**, 34277-88-8; **5a**, 34277-89-9; **5b**, 34277-90-2; **5c**, 34277-91-3; **5d**, 34277-92-4; **6a** diketone, 34277-93-5; **6a** monoenol, 34297-65-9; **6b** diketone, 34277-94-6; **6b** monoenol, 34277-95-7; **6c** diketone, 34297-66-0; **6c** monoenol, 34277-96-8; **6d** diketone, 34277-97-9; **6d** monoenol, 34277-98-0; **6e** diketone, 34277-99-1; **6e** monoenol, 34278-00-7; **7a**, 34278-01-8.

(17) Compound **4e** was prepared by the method of Overberger,[5a] except that the intermediate β-naphthylmethyl sulfone was obtained from the corresponding sulfide by oxidation with 30% hydrogen peroxide in acetic acid (84%), rather than by oxidation with chromic anhydride.

(18) W. J. Hickinbottom, "Reactions of Organic Compounds," 3rd ed, Longmans, Green and Co., London, 1957, p 439.

The Reaction of Sulfonyl Azides with Pyridines and Fused Pyridine Derivatives

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The thermal reaction of sulfonyl azides with pyridines, quinoline, isoquinoline, and acridine has been reexamined and the course of the reaction established unambiguously. In many cases, sulfonylaminopyridines are formed and in most *N*-sulfonyliminopyridinium ylides are obtained. The orientation of the former has been determined and implicates the intervention of a sulfonyl nitrene intermediate. Quinaldine, 1-methylisoquinoline, and 6-methylphenanthridine behave differently and give 1,2,3-triazolo[1,5-*a*]quinoline, 1,2,3-triazolo[5,1-*a*]isoquinoline, and 1,2,3-triazolo[1,5-*f*]phenanthridine, respectively, in high yields. Possible mechanisms for these reactions are discussed as are the spectral properties of the products.

The reaction of sulfonyl azides with pyridine was first studied by Curtius and coworkers,[2] who reported the isolation of compounds they formulated as 2-, 3-, or 4-aminopyridine derivatives. They also obtained the hydrogen abstraction product, the unsubstituted sulfonamide. For example, hydrolysis of the product from 2-naphthylsulfonyl azide and pyridine with hydrochloric acid was said to give 2-aminopyridine (identified as its chloroplatinate) and 2-naphthalenesulfonic acid. Other products were not so characterized. From the reaction of *p*-acetamidobenzenesulfonyl azide with pyridine an aminopyridine derivative was obtained which, by analogy with Curtius' work, was assumed to be the 3 isomer.[3] This reaction was reinvestigated by Buchanan and coworkers,[4a] and by Datta,[4b] who proved, both by degradation and by unambiguous synthesis, that the product was actually *N*-(*p*-acetamidobenzenesulfonimido)pyridinium ylide (**1**). The hydrogen-abstraction product **2** was also obtained, as well as a product of ipso substitution (**3**) by the sulfonyl nitrene, and a compound $C_{13}H_{15}N_3O_3S$ of unknown structure.[4a] The latter needs reinvestigation, since the molecular formula corresponds to a dihydro derivative of **1** or of a *C*-aminopyridine derivative. By implication, it has since been assumed that no aminopyridines were actually formed in the reactions studied by Curtius.[5] Attempts to obtain the corresponding 1-aminoquinolinium derivatives led only to tar formation and the isolation of the hydrogen-abstraction product.[2,6]

In view of the above apparent contradictions, and of our need for 1-iminopyridinium *N*-sulfonyl ylides as potential non azide precursors for the generation of sulfonyl nitrenes, we have reinvestigated the reaction of pyridine and some substituted pyridines with a number of sulfonyl azides, and have extended these studies to quinoline, isoquinoline, acridine, and phenanthridine derivatives.

Thermolysis of methane-, benzene-, or *p*-toluenesulfonyl azide in pyridine itself gave only two identifiable products, the 1-sulfonylimidopyridinium ylide and the unsubstituted sulfonamide. In no case could any product of substitution at carbon be detected, even by tlc or glc. The benzene- and *p*-toluenesulfonylimino ylides are known compounds but the 1-mesyliminopyridinium ylide (**4**) was not and its structure was confirmed by its nmr spectrum and its synthesis from 1-aminopyridinium iodide or sulfate.

$$MeSO_2N_3 + C_5H_5N \xrightarrow{\Delta} MeSO_2NH_2 + C_5H_5\overset{+}{N}\text{—}\overset{-}{N}SO_2Me \xleftarrow{MeSO_2Cl} C_5H_5\overset{+}{N}NH_2X^-$$

4

On the other hand, thermal decomposition of benzenesulfonyl azide in 2- and 4-picoline, in 2,6-lutidine, and in 2,4,6-collidine gave both the C_3- (**5**) and the N-amination products (**6**), in addition to benzenesulfonamide. No 6-benzenesulfonamido-2-methylpyridine could be detected in the reaction with 2-picoline. No C-amination products were formed, however, in the thermolyses in 3-picoline, 3,5-ludidine, and 4-cyanopyridine, only the ylide **6** and benzenesulfonamide being obtained. The results are summarized in Table I.

The structures of the sulfonamides **5** and the *N*-ylides **6** were determined by spectral and analytical measurements, as well as by the synthesis of authentic samples in some cases.

Infrared Spectra.—The sulfonamides **5** exhibited the two strong SO_2 bands in the normal range[7] of 1320–1340 and 1160–1170 cm^{-1}. The NH stretching band did not appear in its usual position but, instead, a very broad absorption in the 2880–2650 cm^{-1} region was evident (KBr disks of the compounds), suggesting that the sulfonamides existed predominantly in the zwitterionic form **5'** in the solid state. In contrast to the sulfonamides **5**, the *N*-sulfonylimino ylides **6** exhibited two strong bands due to SO_2 in the 1270–1285 and 1130–1140 cm^{-1} regions. This bathochromic shift may be

(1) Postdoctoral Fellow, 1969–1970, on leave from Osaka Prefecture University.

(2) T. Curtius, *J. Prakt. Chem.*, **125**, 303 (1930); T. Curtius and J. Rissom, *ibid.*, **125**, 311 (1930); T. Curtius and G. Kraemer, *ibid.*, **125**, 323 (1930); T. Curtius and K. Vorbach, *ibid.*, **125**, 340 (1930); T. Curtius and H. Derlon, *ibid.*, **125**, 420 (1930).

(3) B. S. Alamela and K. Ganapathi, *Curr. Sci.*, **12**, 119 (1943); *Chem. Abstr.*, **38**, 5492 (1944).

(4) (a) J. N. Ashley, G. L. Buchanan, and A. P. T. Eason, *J. Chem. Soc.*, 60 (1947); G. L. Buchanan and R. M. Levine, *ibid.*, 2248 (1950); (b) P. K. Datta, *J. Indian Chem. Soc.*, **24**, 109 (1947).

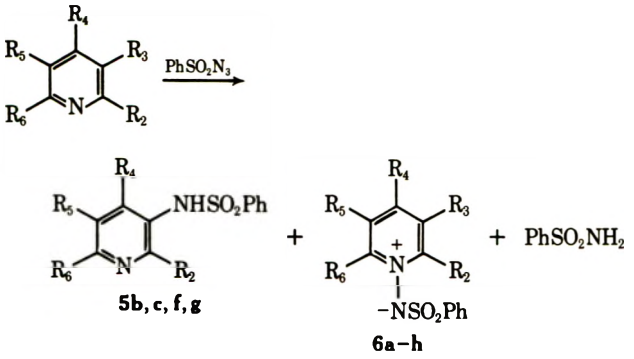
(5) D. S. Breslow in "Nitrenes," W. Lwowski, Ed., Interscience, New York, N. Y., 1970, p 245.

(6) R. J. W. Cremlyn, *J. Chem. Soc.*, 1132 (1965).

(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1958.

TABLE I

PRODUCTS (%) OBTAINED FROM THERMOLYSIS OF BENZENESULFONYL AZIDE IN PYRIDINES[a]

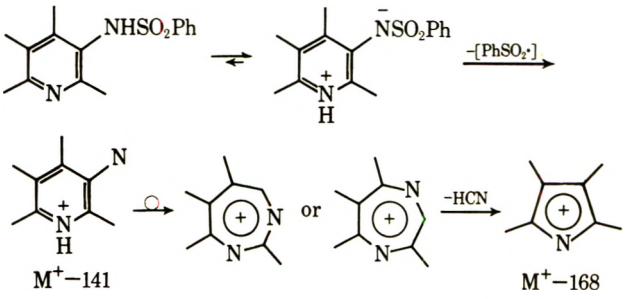


	5	6	$PhSO_2NH_2$	Overall yield, %
a		30	>18	>48
b, R_2 = Me; R_6 = H	8.8[b]	37	45	91
c, R_4 = Me	5	18	62	85
d, R_3 = Me		49	23	72
e, R_3 = R_5 = Me		54	37	91
f, R_2 = R_6 = Me	13	18	57	88
g, R_2 = R_4 = R_6 = Me	15	15	61	91
h, R_4 = CN		17	>30	>47

[a] All R_n = H unless specified. [b] Mixture of 3- and 5-benzenesulfonamido-2-methylpyridine.

and orientation in the case of **5**. The chemical shifts and coupling constants are summarized in Tables II and III. From the ratio of the intensities of the two methyl peaks observed in the nmr spectrum of the unresolved mixture of **5b** the molar ratio of 3-benzenesulfonamido-2-methyl- and 5-benzenesulfonamido-2-methylpyridine was determined to be 0.41.

In the mass spectra of the sulfonamides the main fragment ions in addition to M^+ are $M^+ - 141$ ($-C_6H_5SO_2$), $M^+ - 168$ ($-C_6H_5SO_2 - HCN$), and $C_6H_5^+$.

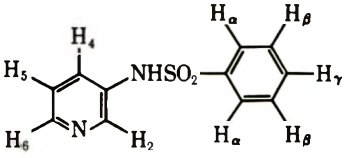


The mass spectral fragmentations of the ylides will be discussed in a future paper.

Authentic samples of the sulfonamides **5** were prepared from the 3-aminopyridine and benzenesulfonyl chloride in pyridine. Some of the ylides **6** were synthesized by the reaction of the appropriate 1-aminopyridinium salt with benzenesulfonyl chloride in the presence of a base. **6f** could not be prepared in this way, though the desired amine was obtained readily. **6g** was more conveniently prepared by the reaction of the 2,4,6-trimethylpyrylium salt **7** with benzenesulfonylhydrazide and a base. The corresponding 2,4,6-triphenylpyrylium salt did not react with benzenesulfonylhydrazide and was recovered unchanged.

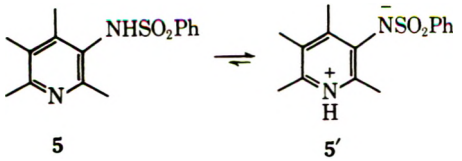
TABLE II

NMR SPECTRA (τ) OF 3-BENZENESULFONAMIDOPYRIDINES IN $CDCl_3$



Compd	H_2	H_4	H_5	H_6	H_α	H_β	H_γ
5b[a] (2,5-)	1.90 d ($J_{2,4}$ 1.5 Hz)	2.50 m	2.95 d ($J_{4,5}$ = 8 Hz)	7.63 (3 H, s, CH_3)	2.42 m		2.50–2.65 m
5b[a] (2,3-)	7.83 (3 H, s, CH_3)	2.50 m	3.00 q ($J_{4,5}$ = $J_{5,6}$ = 8 Hz)	1.80 dd ($J_{5,6}$ = 8; $J_{4,6}$ = 1.5 Hz)	2.42 m		2.50–2.65 m
5c[b]	1.50 s	7.57 (3 H, s, CH_3)	2.37 d ($J_{5,6}$ = 5 Hz)	1.32 d ($J_{5,6}$ = 5 Hz)		1.93 (5H, s)	
5f	7.83 (3 H, s, CH_3)	2.44 d ($J_{4,5}$ = 8 Hz)	3.07 d ($J_{4,5}$ = 8 Hz)	7.54 (3 H, s, CH_3)	2.26 (2 H, dd) ($J_{\alpha\beta}$ = 8 Hz; $J_{\alpha\gamma}$ = 2 Hz)		2.50 (3 H, m)
5g	8.00 (3 H, s, CH_3)	8.18 (3 H, s, CH_3)	3.13 s	7.54 (3 H, s, CH_3)	1.96 (2 H, dd) ($J_{\alpha\beta}$ = 8 Hz; $J_{\alpha\gamma}$ = 2 Hz)		2.44 (3 H, m)

[a] Unresolved mixture of 2,3 and 2,5 isomers. [b] DMSO-d_6 used as solvent in this case.



due to the delocalization of the electron pair on the imino nitrogen onto the sulfonyl group, rather than partially towards the pyridine ring (as in **5** or **5'**), so that back-donation may not be important in these ylides.

Nmr and Mass Spectra.—The nmr spectra of **5** and **6** permit clear-cut assignments of the structures

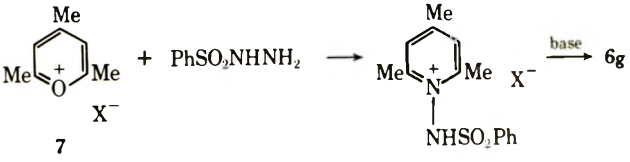
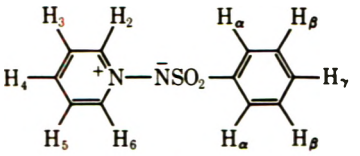


TABLE III

NMR SPECTRA (τ) OF *N*-BENZENESULFONYLIMINOPYRIDINIUM YLIDES IN $CDCl_3$[a]



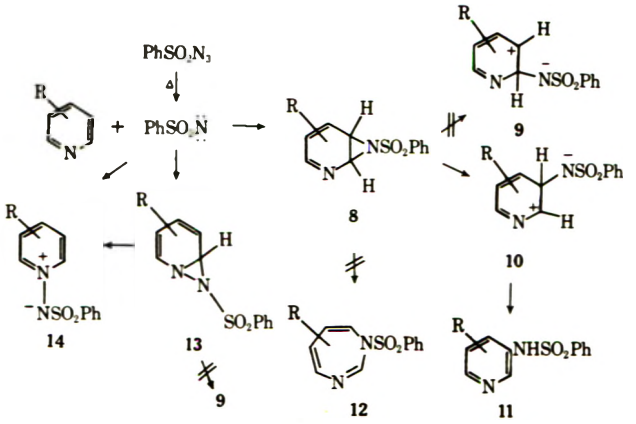
Compd	H_2	H_3	H_4	H_5	H_6	H_α	H_β	H_γ
6b	7.58 (3 H, s, CH_3)	2.28–2.69 m	2.08 t ($J_{3,4}$ = 8 Hz)	2.28–2.69 m	1.41 d ($J_{5,6}$ = 8 Hz)		2.28–2.69 m	
6c	1.70 d ($J_{2,3}$ = 8 Hz)	2.43–2.67 m	7.46 (3 H, s, CH_3)	2.43–2.67 m	1.70 d	2.27 (2 H, d) ($J_{\alpha\beta}$ = 8 Hz)		2.43–2.67 m
6d	1.70 s	7.60 (3 H, s, CH_3)	2.07–2.35 m	2.41–2.70 m	1.74 d ($J_{5,6}$ = 8 Hz)	2.07–2.35 m		2.41–2.70
6e	1.95 s	7.69 (3 H, s, CH_3)	2.45 s	7.69 (3 H, s, CH_3)	1.95 s	2.30 (2 H, dd), ($J_{\alpha\beta}$ = 8 Hz; $J_{\alpha\gamma}$ = 2 Hz)		2.63 (3 H, m)
6f	7.44 (3 H, s, CH_3)	2.58–2.71 m	2.22–2.39 t	2.58–2.71 m	7.49 (3 H, s, CH_3)	2.29–2.39 m		2.58–2.71 m
6g	7.55 (3 H, s, CH_3)	2.81 s	7.63 (3 H, s, CH_3)	2.81 s	7.55 (3 H, s, CH_3)	2.24 (2 H, dd), ($J_{\alpha\beta}$ = 8 Hz, $J_{\alpha\gamma}$ = 2 Hz)		2.62 (3 H, m)

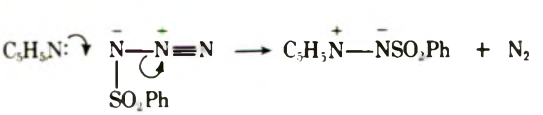
[a] Where a range of τ is indicated this means that overlapping peaks due to more than one type of proton could not be resolved.

The methanesulfonyl derivative corresponding to **6g** was also most readily prepared in this way from **7** and $MeSO_2NHNH_2$. In contrast to a recent report,[8] we experienced no difficulty in preparing 1-*N*-mesyliminopyridinium ylide, albeit in poor yields, either from the *N*-aminopyridinium salt or from methanesulfonyl azide and pyridine (in the latter case, together with a 70% yield of $MeSO_2NH_2$).

The formation of a 3-sulfonamidopyridine in a number of cases is clearly indicative of the intermediacy of a singlet sulfonyl nitrene in these reactions. Indeed, the exclusive substitution of the 3 position would eliminate a triplet electrophilic nitrene from consideration, since the latter, behaving as an electrophilic radical, might be expected to attack not only the 3, but the 2 and 4 positions as well,[9] but be consistent with the expected behavior of a singlet electrophilic species. The rate-determining step following the elimination of nitrogen would be the addition of the singlet sulfonyl nitrene to the pyridine ring to give a pyridoaziridine intermediate (**8**),[10] which in a fast, product-determining step would undergo ring opening under thermodynamic control conditions[11] to give the observed substitution products.

Ring opening of **8** and **9** would yield a dipolar intermediate in which the developing positive charge would be delocalized over the highly electronegative pyridine ring nitrogen atom, while **8** → **10** would not. The latter route is therefore favored and leads to **11** following a prototropic shift. A similar argument would account for the formation of **11** but no 4-sulfonamidopyridine from a nitrene adduct to the pyridine "3,4 double bond." Formation of the ylide **14** could be accounted for in a similar manner by the selective ring opening of **13**, but more likely (since no **9** is formed; *cf.* ref 11a) by a direct trapping of the electrophilic nitrene intermediate, or by a concerted attack of the pyridine nitrogen lone pair on the azide function with elimination of nitrogen.





It should be possible to distinguish between these possibilities by studying the kinetics of the formation of the ylides. If a nitrene intermediate is a precursor, then the rate of ylide formation should be independent of the pyridine concentration, while a bimolecular process is involved in the concerted process. Such studies are under way now.

No 1,3-diazepine (**12**), the expected product of kinetic control,[11] was observed under our conditions, nor was it possible to trap it, say with TCNE as was used with the *N*-sulfonylazepines,[11] since this trapping agent forms relatively stable charge-transfer complexes with pyridines. Similarly, none of the product of photoisom-

(8) J. Epsztajn, E. Lunt, and A. R. Katritzky, *Tetrahedron*, **26**, 1665 (1970).

(9) R. A. Abramovitch and J. G. Saha, *J. Chem. Soc.*, 2175 (1964); R. A. Abramovitch and M. Saha, *J. Chem. Soc. B*, 733 (1966); R. A. Abramovitch, G. N. Knaus, and V. Uma, *J. Amer. Chem. Soc.*, **91**, 7532 (1969); R. A. Abramovitch, *Intra-Sci. Chem. Rep.*, **3**, 211 (1969).

(10) R. A. Abramovitch, J. Roy, and V. Uma, *Can. J. Chem.*, **43**, 3407 (1965); R. A. Abramovitch and R. G. Sutherland, *Fortsch. Chem. Forsch.*, **16**, 1 (1970).

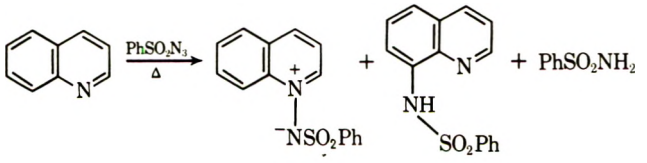
(11) (a) R. A. Abramovitch and V. Uma, *Chem. Commun.*, 797 (1968); (b) J. A. Moore, E. J. Volker, and C. M. Kopay, *J. Org. Chem.*, **36**, 2676 (1971).

erization of **13**, the *N*-sulfonyl-1,2-diazepine,[12] was observed under our thermolysis conditions.

As expected on the basis of an attack of the pyridine nucleus by an electrophilic singlet nitrene, the yield of **5** increased slightly with the presence of electron-donating substituents in the pyridine nucleus and dropped to zero when a 4-cyano group was present. While our mechanism will account readily for the fact that no C-substitution product was observed with 3,5-lutidine, we have no explanation for the lack of formation of **5e** from 3-picoline which still has a vacant β position, unless it is that the methyl group is not in a position where it can delocalize the developing positive charge and hence that the pyridine ring is not nucleophilic enough to undergo addition by the electrophilic sulfonyl nitrene (pyridine itself does not undergo C substitution; see Table I). Alkyl groups at the α and γ positions can delocalize the positive charge (say in **10**) and hence lead to substitution products. If this is so, it might suggest that the transition state for the substitutions resembles an unsymmetrical species whose structure is intermediate between **8** and **10**, *i.e.*, one in which one C–N bond is more developed than the other. That the yields of **6f** and **6g** were not higher than they were may be attributed to steric hindrance by the 2,6-dimethyl group to the attack on the lone pair on nitrogen.

It was shown[10] that the hydrogen abstraction product from the reaction of methanesulfonylnitrene and an aromatic nucleus does not arise by the abstraction of one hydrogen atom at a time (which would lead to the simultaneous production of aryl radicals, for the intermediacy of which no evidence was found) but that two hydrogens were abstracted simultaneously, or almost simultaneously. No bipyridyls were detected in the present study (a small amount of a dipyridylethylene was observed in one case), so that the mechanism of formation of RSO_2NH_2 is not clear.

The reaction was next extended to the fused pyridine derivatives, quinoline, isoquinoline, and acridine. Isoquinoline gave only the hydrogen-abstraction product together with much tar. No ylide could be isolated. Quinoline also gave the hydrogen-abstraction product together with the ylide **15** (12%) and 8-benzenesulfonamidoquinoline (**16**, 1%). No other substitution product was detected, but small amounts of diphenyl disulfide were also obtained. Authentic samples of **15** and **16** were prepared from the 1- and 8-

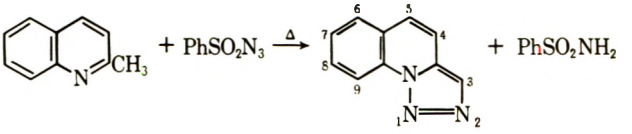


15 **16**

aminoquinoline derivatives, respectively. It thus appears that the benzene ring is more susceptible to C attack by the electrophilic nitrene than is the pyridine ring, which is not unexpected. Nitration of quinoline gives the 5- and 8-nitro derivatives, with the former predominating slightly.[13] Acridine gave a low yield (2%) of *N*-benzensulfonyliminoacridinium ylide (**17**) together with some benzenesulfonamide. Again, the low yield of **17** may be attributed to steric hindrance to the approach of the ring nitrogen.

17

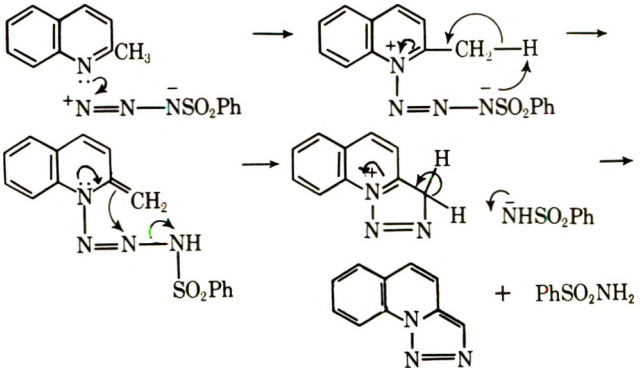
The reaction with α-methylated fused pyridine derivatives gave an unexpected but interesting result. Thus, when quinaldine was heated with benzenesulfonyl azide, benzenesulfonamide was formed, but none of the expected ylide. Instead, a good yield of 1,2,3-triazolo-[1,5-*a*]quinoline (**18**) was obtained. The triazole, which undoubtedly arises from the ring–chain tautomerism of 2-diazomethylquinoline, has previously been obtained less conveniently by the silver oxide oxidation of quinoline-2-aldehyde hydrazone.[14] The triazole ring CH appeared as a singlet at τ 1.96.



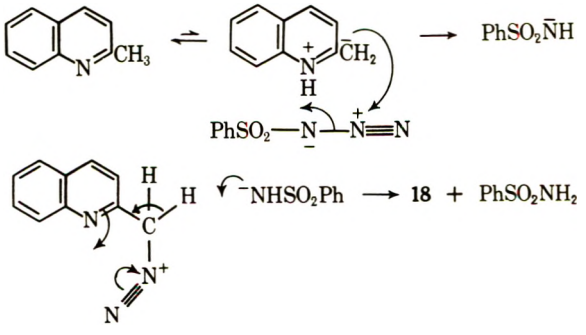
18

One can write two plausible routes leading from quinaldine to **18**, and these sketched in Schemes I and II. Other routes are conceivable as well.

SCHEME I



SCHEME II

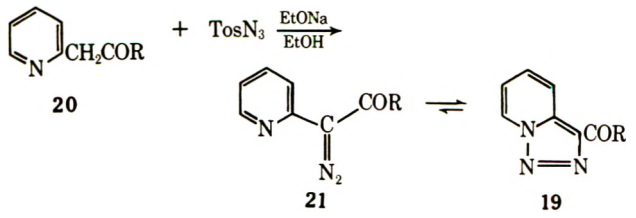


The mechanism outlined in Scheme II is somewhat similar to that proposed for the formation of the keto-triazole **19** by the reaction of an alkyl or aryl (2-pyridyl)-methyl ketone (**20**) with *p*-toluenesulfonyl azide in the

(12) J. S. Streith and J. M. Cassal, *Tetrahedron Lett.*, 4541 (1968); R. A. Abramovitch and T. Takaya, unpublished results.

(13) L. F. Fieser and E. B. Hershberg, *J. Amer. Chem. Soc.*, **62**, 1640 (1940); M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.*, 2521 (1957).

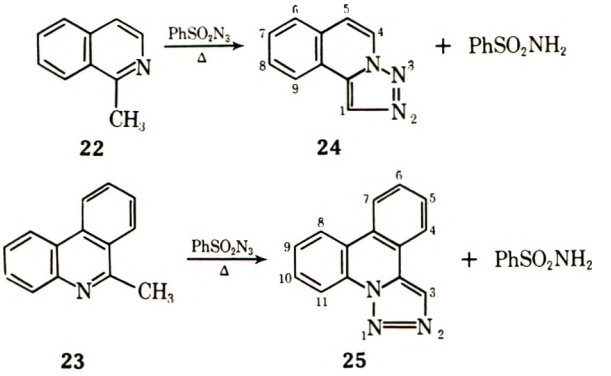
(14) J. H. Boyer, R. Borgers, and L. T. Wolford, *J. Amer. Chem. Soc.*, **79**, 678 (1957).



presence of a strong base *via* the diazo ketone intermediate **21**.[15]

It should be pointed out that no such product was observed here in the reactions of the alkylated pyridines themselves with the sulfonyl azides, and that no added base was necessary in the reaction with quinaldine. This confirms that the α-methyl group is much more reactive when attached to a quinoline than to a pyridine nucleus.

The generality of this new reaction was tested by carrying out the decomposition of benzenesulfonyl azide in 1-methylisoquinoline (**22**) and 6-methylphenanthridine (**23**). In both cases the desired 1,2,3-triazolo derivatives were obtained in good yields, together with benzenesulfonamide.

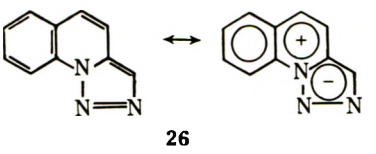


The triazoloisoquinoline **24** exhibited a singlet at τ 1.70 attributed to the triazole ring proton, a 1 H doublet at τ 1.64 ($J_{4,5}$ = 8 Hz) assigned to C_4 H (see numbering above) of the isoquinoline ring, a 1 H doublet at τ 2.98 ($J_{4,5}$ = 8 Hz) assigned to C_5 H, and a 1 H doublet at τ 2.07 ($J_{8,9}$ = 6 Hz) attributed to C_9 H of the isoquinoline ring. **25** exhibited at singlet at τ 2.50 due to the triazole ring proton and a 1 H doublet at τ 0.92 (J = 5 Hz) assigned to C_{11} H of the phenanthridine ring.

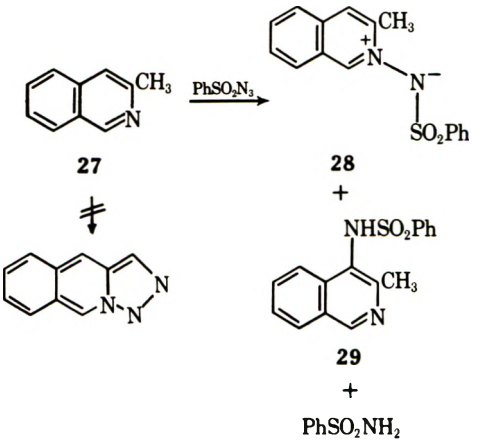
The mass spectra of **18**, **24**, and **25** all exhibited strong parent ions, as well as ($M^+ - N_2$) and ($M^+ - N_2 - H$) fragment ions. In the cases of **18** and **24** the ($M^+ - N_2$) ions were the base peaks while the ($M^+ - N_2 - H$) ion was the base peak in **25**.

1,2,3-Triazolo[1,5-*a*]quinoline (**18**) proved to be remarkably stable, as was also **25**. The stability of **24** was not investigated. Thus, **18** and **25** were recovered following irradiation in a variety of solvents with light of wavelengths of 2537, 3000, or 3500 Å with or without triplet sensitizers. Attempted thermal decomposition of **18** in solution at temperatures up to 180° with or without a copper catalyst also failed. We are continuing to probe the possible decomposition of these triazoles, whose stability is undoubtedly due to aromatic delocalization as shown in **26** below.

(15) M. Regitz and A. Liedhegener, *Chem. Ber.*, **99**, 2918 (1966); M. Regitz, *Angew. Chem., Int. Ed. Engl.*, **6**, 733 (1967).



It is suggested that this aromatic stabilization is an important driving force in the success of this diazo-transfer reaction. On this basis, and also of the fact that the α-methyl group in 3-methylisoquinoline (**27**) would not be expected to be so reactive as that in **22**, we anticipated that such a diazo-transfer reaction would not occur with **27**.[16] Indeed, this has been found to be the case. When **27** was heated with benzenesulfonyl azide, the ylide **28** and benzenesulfonamide were formed, together with a C-substituted sulfonamido derivative. The structure of **28** was unambiguously assigned on the basis of its spectral properties (see Experimental Section). The substitution product has been tentatively identified, mainly on the basis of its nmr spectrum, as being 4-benzenesulfonamido-3-methylisoquinoline (**29**). An authentic sample



of 5-benzenesulfonamido-3-methylisoquinoline had quite different physical properties (but was too unsoluble to permit a determination of its nmr spectrum). **29** exhibited peaks corresponding to C_1 H (s, τ 0.56), C_3 CH_3 (3 H, s, τ 7.45), and C_8 H [d, τ 1.65 (J = 7 Hz) with each branch showing much fine structure]. 3-Methylisoquinoline and 5-amino-3-methylisoquinoline both exhibited a 1 H singlet (in addition to the singlet at lower field due to C_1 H) at τ 2.43 and 2.78, respectively, which is due to C_4 H, as well as multiplets due to C_8 H. No signal corresponding to C_4 H was observed in the spectrum of **29**. If this structural assignment is correct it would indicate that a methyl group in the pyridine ring that can assist the delocalization of the developing charge in the transition state for substitution may stabilize this transition state sufficiently to cause attack of the pyridine ring to be favored over addition to the benzene ring, as was observed in the case of quinoline. In this connection, it would be of interest to study the reaction with 4-methylquinoline to see whether attack takes place in the benzene or pyridine ring and also to see whether or not a diazomethyl compound can be prepared under these conditions when it cannot undergo stabilization by tau-

(16) For such a reaction to occur would require a disruption of the aromatic character of the benzene ring in **27**, allowing other processes to compete effectively with the diazo transfer process.

tomerization to the aromatic species, as can the 2-diazomethyl derivative.

Experimental Section

Melting points are uncorrected. Infrared spectra were determined using a Perkin-Elmer 337 spectrophotometer using KBr disks of the compounds, while nmr spectra were obtained on a Varian HA-100 spectrometer, using deuteriochloroform solutions of the compounds (unless otherwise stated) and TMS as the internal standard.

Reagents.—2-, 3-, and 4-picoline, 2,6- and 3,5-lutidine, and 2,4,6-trimethylpyridine (Reilly Tar and Chemical Corp.) were dried over potassium hydroxide and distilled, as were quinoline and isoquinoline. 1-Methylisoquinoline was prepared by the action of methyllithium on isoquinoline, followed by dehydrogenation of the dihydro derivative at 190° with palladium on charcoal suspended in Freon E-3. It had bp 78–80° (0.8 mm); mass spectrum *m/e* (rel intensity) 143 (100, M^+); picrate mp 216° (lit.[17] mp 225–226°). 6-Methylphenanthridine was prepared by an extension of the method of Taylor and Kalenda.[18] 3-Amino-2,6-lutidine and 3-amino-2,4,6-collidine were prepared by reduction of the corresponding nitro compounds.[19]

Thermal Decomposition of Benzenesulfonyl Azide in Pyridines.

A. In 2-Picoline.—A stirred solution of benzenesulfonyl azide (6.1 g) in freshly distilled 2-picoline (156 g) was heated in an oil bath at 125–130° until no more nitrogen was evolved (48 hr). The excess 2-picoline was distilled *in vacuo* and the pasty black residue was chromatographed on a column (2.5 × 30 cm) of silica gel (60–200 mesh). Elution with light petroleum ether (bp 30–60°)–ether (5:1 and then 1:1, v/v) gave benzenesulfonamide (2.31 g, 45%), mp 152–154° (from aqueous EtOH). Elution with ether gave a mixture of 3- and 5-benzenesulfonamido-2-methylpyridine (0.72 g, 8.7%). Fractional crystallization from benzene–methanol and benzene–chloroform gave **5-benzenesulfonamido-2-methylpyridine**, mp 181–182° (from benzene–MeOH), as the insoluble fraction, followed by 3-benzenesulfonamido-2-methylpyridine, mp 146–148° (from benzene–acetone) (insufficient quantities of pure material to permit analysis, but structure confirmed by nmr and mass spectroscopy). The 2,5 isomer was identical with an authentic sample prepared from 5-amino-2-picoline and benzenesulfonyl chloride: mass spectrum *m/e* (rel intensity) 248 (30, M^+), 107 (100) ($M^+ - C_6H_5SO_2$), 80 (16, $M^+ - C_6H_5SO_2 - HCN$), 77 (50, Ph), 53 (60), 52 (23), 51 (39), 39 (16).

Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87. Found: C, 57.67; H, 4.56.

Elution with $CHCl_3$–MeOH (10:1, v/v) gave **1-benzenesulfonylimino-2-methylpyridinium ylide** (3.07 g, 37%), which was purified for analysis by preparative thin layer chromatography on silica gel PF_{254} (Merck AG) [developed with $CHCl_3$–MeOH (10:1, v/v)] and recrystallization from benzene–$CHCl_3$ to give colorless crystals, mp 153–155°, identical with an authentic sample prepared as outlined below.

Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87. Found: C, 58.18; H, 5.04.

Elution with MeOH gave a brown pasty product (0.31 g) which was not investigated further.

B. In 2,6-Lutidine.—The decomposition of benzenesulfonyl azide (40 g) in freshly distilled 2,6-lutidine (70 g) was carried out and worked up as described above for 2-picoline. Elution of the silica gel column with light petroleum ether (bp 60–90°)–ether (10:1, v/v) gave a product (15 mg), mp 111–112° (from light petroleum ether), mass spectrum *m/e* (rel intensity) 210 (16, M^+), 209 (100, $M^+ - 1$), which is probably 1,2-bis(6-methyl-2-pyridyl)ethylene. Elution with benzene–ether (1:1, v/v) afforded benzenesulfonamide (1.92 g, 57%), mp 152–154°. Elution with ether gave **3-benzenesulfonamido-2,6-dimethylpyridine** (0.765 g, 13%), mp 155.5–156.5° (from benzene–CCl_4), identical in all respects with a sample synthesized from 3-amino-2,6-lutidine and benzenesulfonyl chloride in pyridine: mass spectrum *m/e* (rel intensity) 262 (18, M^+), 121 (100, $M^+ - C_6H_5SO_2$), 94 (23, $M^+ - C_6H_5SO_2 - HCN$), 77 (14), 53 (39), 43 (27).

Anal. Calcd for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38. Found: C, 59.86; H, 5.54.

Elution with $CHCl_3$–MeOH (10:1, v/v) gave **1-benzenesulfonylimino-2,6-dimethylpyridinium ylide** (1.0 g, 18%), mp 172–176°, which, after purification by tlc, had mp 177° (benzene–EtOH).

Anal. Calcd for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38. Found: C, 59.17; H, 5.54.

Elution with methanol gave black tarry material (0.17 g).

C. In 3-Picoline.—The reaction was carried out as above to give benzenesulfonamide (23%) and **1-benzenesulfonylimino-3-methylpyridinium ylide** (49%), mp 165–166° (benzene–ethyl acetate).

Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87. Found: C, 58.02; H, 4.79.

Methanol eluted a brown tar (1.3 g).

D. In 4-Picoline.—Carried out as above the reaction yielded benzenesulfonamide (62%) and **3-benzenesulfonamido-4-methylpyridine** (5%): mp 185–186° (benzene–EtOH); mass spectrum *m/e* (rel intensity) 248 (30, M^+), 107 (100, $M^+ - C_6H_5SO_2$), 80 (19, $M^+ - C_6H_5SO_2 - HCN$), 77 (25), 53 (48), 51 (25).

Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87. Found: C, 58.22; H, 4.90.

Elution with Et_2O–CH_2Cl_2 gave **1-benzenesulfonylimido-4-methylpyridinium ylide** (18%), mp 138–139° (benzene–ethyl acetate).

Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87. Found: C, 58.01; H, 4.84.

Elution with methanol gave a brown, intractable solid, mp >280°.

E. In 3,5-Lutidine.—Two products were obtained: benzenesulfonamide (37%) and **1-benzenesulfonylimido-3,5-dimethylpyridinium ylide** (54%), mp 211–212° (benzene–EtOH), identical with an authentic sample prepared from 1-amino-3,5-dimethylpyridinium iodide and benzenesulfonyl chloride in the presence of aqueous KOH.

Anal. Calcd for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38. Found: C, 59.30; H, 5.54.

F. In 2,4,6-Trimethylpyridine.—From the decomposition of benzenesulfonyl azide (6.1 g) in 2,4,6-collidine (200 g) there was obtained a product (59 mg) of unknown structure, mp 54–58°, M^+ 218 [eluted with light petroleum ether (10:1, v/v)]. Elution with light petroleum ether (1:1, v/v) gave **3-benzenesulfonamido-2,4,6-trimethylpyridine** (1.11 g, 12%), mp 127–128° (cyclohexane), identical with an authentic sample prepared from 3-amino-2,4,6-collidine and benzenesulfonyl chloride in pyridine: mass spectrum *m/e* (rel intensity) 276 (14, M^+), 135 (100, $M^+ - C_6H_5SO_2$), 108 (30, $M^+ - C_6H_5SO_2 - HCN$), 77 (7), 67 (21), 41 (14).

Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84. Found: C, 60.78; H, 5.89.

Elution with petroleum ether–ether (1:3, v/v) and then ether gave benzenesulfonamide (3.51 g, 61%). Elution with $CHCl_3$ gave **1-benzenesulfonimido-2,4,6-trimethylpyridinium ylide** (1.41 g, 15%), mp 145° after purification by preparative tlc and recrystallization from benzene. The product was identical with that obtained from 2,4,6-trimethylpyrylium perchlorate and benzenesulfonylhydrazide as described below.

Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84. Found: C, 60.68; H, 6.15.

A black, gummy tar (0.37 g) was obtained on elution with MeOH.

G. In 4-Cyanopyridine.—A mixture of 4-cyanopyridine (25 g) and benzenesulfonyl azide (9.2 g) was stirred and heated to 110° (the mixture became homogeneous at 60°) and kept at 110–120° until N_2 evolution ceased (50 hr). The excess cyanopyridine was mostly removed by vacuum distillation and the residue was chromatographed on a column (2.5 × 30 cm) of basic alumina. Elution with light petroleum ether (1:1, v/v) gave unchanged 4-cyanopyridine (3.7 g). Elution with ether gave benzenesulfonamide (2.36 g, 30%), while elution with chloroform gave **1-benzenesulfonylimino-4-cyanopyridinium ylide** (2.22 g, 17%): mp 160–161° (from benzene–cyclohexane); ir (KBr) 2250 cm^{-1} (C≡N); mass spectrum *m/e* 259 (M^+); nmr τ 1.17 (dd, $J_{2,3}$ = 7, $J_{2,4}$ = 1.5 Hz, 2 H, C_2 H, C_6 H), 1.82 (dd, $J_{3,4}$ = 7.5, $J_{2,4}$ = 1.5 Hz, 2 H, C_3 H, C_5 H), 2.21 (dd, 2 H, ortho CH), 2.51 (m, 4 H, meta CH, para CH).

Anal. Calcd for $C_{12}H_9N_3O_2S$: C, 55.72; H, 3.50. Found: C, 55.83; H, 3.58.

***N*-Benzenesulfonyliminoacridinium Ylide.**—A mixture of

(17) "Dictionary of Organic Compounds," 4th ed, Vol. 4, Eyre and Spottiswoode, 1965.

(18) E. C. Taylor, Jr., and N. W. Kalenda, *J. Amer. Chem. Soc.*, **76**, 1699 (1954).

(19) E. Plazek, *Ber.*, **72**, 577 (1939).

acridine (18 g) and benzenesulfonyl azide (9 g) was heated and stirred at 125–130° for 50 hr. The tacky mixture was dissolved in hot MeOH, and the solution was concentrated and chromatographed on alumina (2.5 × 70 cm). Elution with light petroleum and with light petroleum ether (1:1, v/v) gave acridine (1.60 g). Elution with ether gave the ylide (335 mg, 2%): mp 211–212° (from benzene–cyclohexane); ir (KBr) 3180 (w), 3060 (w), 1530 (w), 1460 (m), 1420 (m), 1360 (s), 1295 (m), 1285 (w), 1165 (s), 1135 (w), 1095 (s), 1075 (w), 1045 (m), 950 (s), 910 (s), 880 (w), 850 (m), 810 (w), 750 (s), and 685 cm^{-1} (s); mass spectrum m/e (rel intensity) 334 (35, M^+), 270 (6), 194 (16), 193 (100), 167 (9), 166 (45), 140 (8), 77 (7).

Anal. Calcd for $C_{19}H_{14}N_2O_2S$: C, 68.25; H, 4.22. Found: C, 68.38; H, 4.31.

Elution with ether–chloroform (8:2, v/v) gave benzenesulfonamide (350 mg, 4.5%).

1-Methanesulfonyliminopyridinium Ylide. A. From 1-Aminopyridinium Salt.—A solution of hydroxylamine-*O*-sulfonic acid (5.7 g) in water (50 ml) was neutralized with KOH (2.8 g) in water (10 ml) at 5°, and the resulting solution was added dropwise to pyridine (20 g) at 70–80°. The solution was kept at that temperature for another 30 min and K_2CO_3 (7 g) was then added with cooling. Water and pyridine were evaporated below 40° and the residue was dissolved in ethanol (150 ml). The inorganic salts were filtered. K_2CO_3 (10 g) was added to the filtrate and, after 1 hr, methanesulfonyl chloride (5.8 g) was added and the solution was stirred at room temperature for 12 hr. It was filtered, the filtrate was concentrated *in vacuo*, and the residue was chromatographed on a column of alumina. Elution with $CHCl_3$ gave the ylide (1.66 g, 19%): mp 177–178° (EtOH–ethyl acetate); ir (KBr) 3100 (w), 3080 (w), 3050 (w), 3000 (w), 2920 (w), 1612 (m), 1475 (s), 1430 (w), 1330 (w), 1270 (s), 1160 (m), 1115 (s), 1080 (m), 1030 (w), 920 (s), 810 (s), 785 (m), 725 (w), and 690 cm^{-1} (s); λ_{max}^{EtOH} 245 nm (ϵ 8300), 308 (2000); mass spectrum m/e (rel intensity) (30, M^+); nmr (DMSO-d_6) τ 1.03 (dd, $J_{2,3}$ = 7, $J_{2,4}$ = 1.3 Hz, 2 H, C_2 H and C_6 H), 1.51 (m, $J_{3,4}$ = 6.5, $J_{2,4}$ = 1.3 Hz, 1 H, C_4 H), 1.87 (dd, $J_{2,3}$ = 7, $J_{3,4}$ = 6.5 Hz, 2 H, C_3 H and C_5 H) and 7.11 (s, 3 H, CH_3).

Anal. Calcd for $C_6H_8N_2O_2S$: C, 41.85; H, 4.68. Found: C, 42.03; H, 4.74.

B. From Methanesulfonyl Azide.—A solution of methanesulfonyl azide (9.0 g) in dry pyridine (30 g) was boiled under reflux for 30 hr, the excess pyridine was distilled *in vacuo*, and the black residue was chromatographed on a column of basic alumina (3 × 40 cm) to give methanesulfonamide (4.97 g, 70%), mp 91.5–92.5°, and 1-methanesulfonyliminopyridinium ylide (0.38 g, 3%), mp 175°, identical with the sample obtained above.

3-Benzenesulfonamido-2,4,6-trimethylpyridine.—Benzenesulfonyl chloride (1.96 g) was added dropwise to a solution of 3-amino-2,4,6-collidine (1.36 g) in dry pyridine (5 ml) below 45°, and the solution was then heated on a steam bath for 40 min. Aqueous NaOH (3%, 10 ml) was added and the mixture was heated for 20 min. The solvent was evaporated and the residue was triturated with water (10 ml) to give the sulfonamide (1.47 g, 53%), mp 128° (from benzene–cyclohexane).

3-(*N*,*N*-Dibenzenesulfonyl)amino-2,4,6-trimethylpyridine.—A solution of the amine (0.61 g) and benzenesulfonyl chloride (1.0 g) in dry pyridine (5 ml) was boiled under reflux for 20 min. Aqueous NaOH (3%, 10 ml) was added and the mixture was heated for 20 min. The solvent was evaporated and the yellow residue (0.90 g, 45%) was recrystallized from light petroleum ether (bp 60–90°)–benzene to give the disulfonamide: mp 168.5–169.5°; ir (KBr) 3070 (w), 3030 (w), 2970 (w), 2940 (w), 1600 (s), 1550 (w), 1480 (w), 1450 (s), 1360 (s), 1300 (w), 1220 (m), 1165 (s), 1080 (s), 1025 (w), 955 (w), 930 (w), 905 (m), 880 (s), 855 (w), 760 (m), 750 (s), 730 (s), 720 (m), 715 (s), 685 (s), and 640 cm^{-1} (s); nmr τ 8.17 (s, 3 H, CH_3), 8.00 (s, 3 H, CH_3), 7.53 (s, 3 H, CH_3), 2.32–2.56 (m, 6 H, meta and para ArH), 2.13 (s, 1 H, C_5 H), 1.95 (dd, ortho, meta J = 8 Hz, ortho, para J = 2 Hz, 4 H, ortho ArH); mass spectrum m/e 275 (M^+).

Anal. Calcd for $C_{20}H_{20}N_2O_4S_2$: C, 57.67; H, 4.85. Found: C, 57.42; H, 4.70.

2-Benzenesulfonamido-6-methylpyridine.—Prepared from 2-amino-6-methylpyridine and benzenesulfonyl chloride in dry pyridine on a steam bath, it was obtained in 87% yield: mp 139–140°; ir (KBr) (main peaks only) 3225 (m), 1610 (s), 1530 (s), 1370 (s), 1270 (s), 1135 (s), 1090 (s), 855 (s), 790 (s), 770 (s), 745 (s), 710 (m), and 700 cm^{-1} (s); mass spectrum m/e 248 (M^+).

Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87. Found: C, 58.16; H, 4.99.

1-Benzenesulfonyliminopyridinium Ylide.—This was prepared in 84% yield from 1-aminopyridinium iodide, potassium carbonate, and benzenesulfonyl chloride, mp 154–155°. It was identical with the product obtained from the thermolysis of benzenesulfonyl azide in pyridine.

1-Benzenesulfonylimino-2-methylpyridinium Ylide.—An ice-cold solution of 1-amino-2-methylpyridinium iodide[20] (0.472 g) in water (10 ml) was basified at 0–5° with solid K_2CO_3 and this solution was added portionwise to a solution of benzenesulfonyl chloride (0.360 g) in dry acetone (10 ml). After stirring the solution at room temperature overnight the acetone was evaporated and the solid was filtered. Recrystallization from benzene–methylene chloride gave the ylide (0.240 g, 49%), mp 154–155°, identical with the product obtained from 2-picoline and the sulfonyl azide.

1-Benzenesulfonylimino-2,4,6-trimethylpyridinium Ylide.—A mixture of 2,4,6-trimethylpyrylium perchlorate[21] (2.22 g) and benzenesulfonylhydrazide (1.72 g) was boiled under reflux in absolute EtOH (60 ml) for 12 hr. Unreacted pyrylium salt was filtered from the hot solution, which was then concentrated *in vacuo* to give 1-benzenesulfonamido-2,4,6-trimethylpyridinium perchlorate (2.20 g, 60%): mp 116–120°; ir (KBr) (main peaks only) 2700–2600 (br m), 1600 (s), 1430 (s), 1330 (s), 1160–1060 (br s), 855 (br s), 750 (m), 715 s, 680 (s), and 620–550 cm^{-1} (br s).

The perchlorate (1.88 g) was dissolved in methanol (20 ml), the ice-cold solution was added portionwise to KOH (2 g) in water (7 ml), and methanol (10 ml) was then added. Potassium perchlorate precipitated and was filtered, and the filtrate was evaporated to dryness. The residue was chromatographed on a column of basic alumina (1.5 × 20 cm). Elution with $CHCl_3$ gave the desired ylide (1.32 g), mp 145–146°.

Reaction of Benzenesulfonyl Azide with Quinoline.—A mixture of quinoline (7.80 g) and benzenesulfonyl azide (5.49 g) was heated in an oil bath at 125° with stirring for 65 hr. The product was chromatographed on basic alumina (3 × 30 cm). Elution with light petroleum ether–ether (9:1, v/v) gave diphenyl disulfide (56 mg), mp 60°, identical with an authentic sample. Elution with light petroleum ether–ether (3:7, v/v) gave **8-benzenesulfonamidoquinoline** (280 mg, 1%), mp 134–135° (CCl_4), identical with a sample prepared in 99% yield from 8-aminoquinoline and benzenesulfonyl chloride in pyridine on a steam bath: ir (KBr) (main peaks only) 3200 (m, NH), 1360 (s), 1308 (s), 1170 (s), 1095 (s), 980 (s), 860 (s), 825 (m), 793 (s), 755 (s), 725 (s), and 691 cm^{-1} (s); mass spectrum m/e (rel intensity) (19, M^+), 220 (49), 219 (33), 143 (100), 116 (60), 89 (22), 77 (28), 63 (13), 51 (22), and 39 (17); nmr τ 1.34 (dd, $J_{2,3}$ = 4.5 Hz, $J_{2,4}$ = 1.8 Hz, 1 H, C_2 H), 2.01 (dd, $J_{3,4}$ = 8.5, $J_{2,4}$ = 1.8 Hz, 1 H, C_4 H), 2.19 (dd, ortho, meta J = 9.5, ortho, para J = 2.0 Hz, 2 H, ortho CH), 2.21 (dd, $J_{5,6}$ = 8.5, $J_{5,7}$ = 1 Hz, 1 H, C_5 H), and 2.63–2.79 (m, 6 H, C_3 H, C_6 H, C_7 H, meta CH, para CH).

Anal. Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.16. Found: C, 63.47; H, 4.36.

Elution with petroleum ether–ether (1:9, v/v) gave benzenesulfonamide (1.41 g, 30%). Elution with $CHCl_3$ gave **1-benzenesulfonyliminoquinolinium ylide** (1.019 g, 12%), mp 183° (ethyl acetate–ethanol), identical with an authentic sample prepared as described below: ir (KBr) (main peaks only) 1296 (s), 1218 (s), 1140 (s), 1092 (s), 927 (s), 836 (s), 817 (m), 774 (s), 737 (m), and 704 cm^{-1} (m); mass spectrum m/e 284 (21, M^+); nmr τ 0.91 (dd, $J_{2,3}$ = 6, $J_{2,4}$ = 1 Hz, 1 H, C_2 H), 1.51 (overlapping dd, J = 7, 1 Hz, 2 H, C_4 H and C_8 H); λ_{max}^{EtOH} 365 nm (infl, ϵ 2500), 324 (6000), 293 (infl, 2000), 259 (infl, 5900), 234 (31,900).

Anal. Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.16. Found: C, 63.33; H, 4.37.

Elution with MeOH gave black, gummy material (2.04 g) which was not investigated further.

1-Benzenesulfonyliminoquinolinium Ylide.—A solution of hydroxylamine-*O*-sulfonic acid (20 g) and potassium hydroxide

(20) R. Gösl and A. Meuwsen, *Chem. Ber.*, **92**, 2523 (1959).

(21) G. N. Derofenko and S. V. Krivun, *Metody Poluch. Khim. Reaktivov Prep.*, No. 17, 149 (1967); *Chem. Abstr.*, **71**, 61161 (1969); O. Diels and K. Alder, *Ber.*, **60**, 716 (1927).

(10 g) in water (60 ml) was added to quinoline (45 g) at 70–80°, and the reaction mixture was stirred for another 30 min at that temperature. A solution of potassium carbonate (12 g) in water (40 ml) was added, and the mixture was washed with ether (2 × 100 ml) and concentrated to a small volume below 40°. Potassium carbonate (30 g) and ethanol (200 ml) were added, the mixture was stirred at room temperature for 1 hr, and then benzenesulfonyl chloride (34 g) was added. After the mixture was stirred overnight at room temperature, the inorganic solids were filtered, and the filtrate was concentrated and chromatographed on a column (3 × 30 cm) of basic alumina. Elution with $CHCl_3$ gave the ylide (10.86 g, 20%), mp 183°.

5-Benzenesulfonamidoquinoline.—This was prepared from 5-aminoquinoline (0.5 g) and benzenesulfonyl chloride (0.5 g) in pyridine (2 ml) to give the sulfonamide (0.70 g): mp 207–208° (ethyl acetate); mass spectrum *m/e* (rel intensity) 284 (24, M^+), 143 (100), 116 (70), 89 (30), 77 (33), 63 (14), 51 (23), 40 (20), 39 (15); ir (KBr) (main peaks only) 2670 (br w), 1394 (s), 1336 (br s), 1170 (s), 1094 (s), 810 (s), 770 (s), and 735 cm^{-1} (m).

Anal. Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.16. Found: C, 63.10; H, 4.40.

Reaction of Benzenesulfonyl Azide with Isoquinoline.—The reaction was carried out as described for quinoline above; 51.7% of the isoquinoline was recovered; and benzenesulfonamide (51%) was also obtained. The remainder of the products resembled black coal.

Reaction of Benzenesulfonyl Azide with 3-Methylisoquinoline.—3-Methylisoquinoline (21.45 g) was heated with benzenesulfonyl azide (5.49 g) at 125–130° for 12 hr. The isoquinoline (16.55 g) was recovered. Chromatography on basic alumina and elution with petroleum ether–ether (2:8, v/v) gave benzenesulfonyl azide (112 mg). Elution with ether gave benzenesulfonamide (1.245 g, 27.6%). Elution with $CHCl_3$ gave **2-benzenesulfonylimino-3-methylisoquinolinium ylide** (1.790 g, 20.9%): mp 210–211° (benzene–ethyl acetate); ir (KBr) (main peaks only) 1294 (s), 1280 (s), 1265 (s), 1145 (s), 1090 (s), 940 (s), 770 (s), 757 (s), 721 (m), and 700 cm^{-1} (m); mass spectrum *m/e* (rel intensity) 298 (20, M^+); nmr τ 0.56 (s, 1 H, C_1 H), other aromatic C H's, complex multiplets at 1.95–2.75, 7.57 (s, 3 H, CH_3).

Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.70. Found: C, 64.50; H, 4.91.

Elution with ethyl acetate gave **4-benzenesulfonamido-3-methylisoquinoline** (1.06 g, 12.4%): mp 234.5–235° (benzene–ethanol); ir (KBr) 3265 (s, NH), 3100–3050 (w), 1620 (m), 1578 (m), 1480 (w), 1450 (s), 1430 (w), 1385 (s), 1325 (s), 1250 (m), 1180 (m), 1165 (s), 1042 (s), 968 (w), 926 (m), 905 (w), 870 (m), 794 (s), 780 (m), 762 (s), 740 (w), 728 (m), 696 (m), and 670 cm^{-1} (w); mass spectrum *m/e* (rel intensity) 298 (12, m^+), 157 (100), 103 (17), 89 (30), 77 (24), 63 (11), 51 (15), 44 (16), 39 (13); nmr (DMSO-d_6) τ 0.56 (s, 1 H, C_1 H), 1.65 (md, $J_{7,8}$ = 7 Hz, C_8 H), 2.00–2.20 (m, 9 H), and 7.45 (s, 3 H, CH_3).

Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.70. Found: C, 64.29; H, 4.91.

Elution with methanol gave a black, intractable solid (1.5 g).

5-Benzenesulfonamido-3-methylisoquinoline.—5-Amino-3-methylisoquinoline (1.60 g) and benzenesulfonyl chloride (2.00 g) were heated on a steam bath for 1 hr, NaOH (0.6 g) in water (3 ml) was added, and heating was continued for 10 min. The solution was evaporated to dryness and the residue was triturated with water (15 ml) to give the desired sulfonamide (2.08 g, 70%): mp 195–196° (ethyl acetate); ir (KBr) (main bands only) 2780 (br m), 2730 (br m), 1630 (s), 1590 (s), 1430 (br s), 1330 (br s), 1160 (br s), 1087 (s), 916 (s), 880 (s), 735 (br s), and 690 cm^{-1} (br s); mass spectrum *m/e* (rel intensity) 298 (14, M^+), 157 (100), 130 (20), 77 (34), 51 (17), 45 (11); the compound was too insoluble in $CDCl_3$, $(CD_3)_2CO$, and DMSO-d_6 to permit the determination of its nmr spectrum.

Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.70. Found: C, 64.23; H, 4.79.

1,2,3-Triazolo[1,5-*a*]quinoline.—A solution of benzenesulfonyl azide (5.49 g) in quinaldine (25 g) was stirred and heated at 110–115° for 40 hr. The excess quinaldine (18 g) was distilled off at 1 mm below 100°, and the residue was dissolved in methylene chloride and chromatographed on a column of alumina (3 × 40 cm). Elution with petroleum ether–ether (1:1, v/v) gave the triazoloquinoline (3.60 g, 72%): mp 81.5–82° [from ether–light petroleum ether (bp 60–80°)] (lit.[14] mp 81°); ir (KBr) (main bands only) 1613 (s), 1468 (s), 1450 (s), 1398 (s), 1285 (s), 1143 (s), 1107 (s), 975 (s), 817 (s), 800 (m), and 750 cm^{-1} (s); λ_{max}^{EtOH} 246 nm (ϵ 16,900), 252 (16,300), 261 (9600), 287 (6500), 295 (6900), 316 (6300), 330 (5900); mass spectrum *m/e* (rel intensity) 169 (42, M^+), 141 (100, $M^+ - N_2$), 140 (68), 114 (53), 88 (15), 63 (21), 41 (23), 39 (16); nmr τ 1.28 (d, $J_{7,8}$ = 8 Hz, 1 H, C_9 H), 1.96 (s, 1 H, C_3 H), 2.20–2.56 (m, 5 H).

Anal. Calcd for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found: C, 70.90; H, 4.34; N, 24.89.

Elution with petroleum ether–ether (1:9, v/v) gave benzenesulfonamide (4.20 g, 89%). A similar result was obtained when the thermolysis was carried out at 125–130°.

1,2,3-Triazolo[5,1-*a*]isoquinoline.—A mixture of 1-methylisoquinoline (4.29 g) and benzenesulfonyl azide (5.49 g) was heated at 125° for 20 hr and worked up as described for quinaldine above. Elution of the column with light petroleum ether–ether (8:2, v/v) gave diphenyl disulfide (80 mg), mp 59–60°, identical with an authentic sample. Further elution with this solvent afforded **1,2,3-triazolo[5,1-*a*]isoquinoline** (2.881 g, 64%): mp 110–111° (benzene–cyclohexane); ir (KBr) (main bands only) 3105 (w), 1395 (s), 1205 (s), 968 (s), 838 (s), 806 (s), 775 (s), 763 (w), 753 (m), and 695 cm^{-1} (w); mass spectrum *m/e* (rel intensity) 169 (42, M^+), 141 (100, $M^+ - N_2$), 140 (74), 114 (70), 113 (27), 88 (20), 87 (14), 63 (27), 62 (26), 51 (17), 50 (16), 39 (22); nmr τ 1.64 (d, $J_{4,5}$ = 8 Hz, 1 H, C_4 H), 1.70 (s, 1 H, C_1 H), 2.07 (d, $J_{8,9}$ = 6 Hz, 1 H, C_9 H), 2.53 (dd, $J_{8,9}$ = 6, $J_{7,8}$ = 5.5 Hz, 1 H, C_8 H) 2.32–2.46 (m, 2 H, C_6 H and C_7 H), 2.98 (d, $J_{4,5}$ = 8 Hz, 1 H, C_5 H); λ_{max}^{EtOH} 241 nm (ϵ 34,400), 248 (33,500), 255 (25,000), 299 (2100), 306 (2000), 313 (3400), 327 (3400).

Anal. Calcd for $C_{10}H_7N_3$: C, 70.99; H, 4.17. Found: C, 71.15; H, 4.32.

Elution with $CHCl_3$ gave benzenesulfonamide (4.332 g, 92%).

1,2,3-Triazolo[1,5-*f*]phenanthridine.—6-Methylphenanthridine (2.90 g) and benzenesulfonyl azide (2.75 g) were heated at 125° for 15 hr and worked up as described above for quinaldine. Elution of the column with light petroleum ether–ether (5:1, v/v) gave unchanged 6-methylphenanthridine (77 mg, 2.6%). Elution with light petroleum ether–ether (4:1, v/v) gave the triazolophenanthridine (2.797, 88%): mp 187–188° (benzene–cyclohexane); ir (KBr) (main peaks only) 3115 (w), 1460 (s), 1445 (s), 1050 (m), 825 (m), 753 (s), and 724 cm^{-1} (s); mass spectrum *m/e* (rel intensity) 219 (31, M^+), 191 (83), 190 (100, $M^+ - N_2 - H$), 164 (27), 163 (24), 95 (15), 82 (29), 81 (20), 69 (21), 63 (22), 57 (22), 55 (25), 51 (15), 50 (15), 43 (22), 41 (29), 39 (34); nmr τ 0.92 (d, $J_{10,11}$ = 5 Hz, 1 H, C_{11} H), 2.51 (s, 1 H, C_3 H); λ_{max}^{EtOH} 243 nm (infl, ϵ 45,000), 248 (50,000), 299 (5000), 306 (4500), 312 (4700), 319 (2800), 327 (4700).

Anal. Calcd for $C_{14}H_9N_3$: C, 76.70; H, 4.13. Found: C, 76.85; H, 4.28.

Elution with ether gave benzenesulfonamide (2.30 g, 99%).

Registry No.—**4,** 34456-51-4; **5b** (2,3 isomer), 34456-52-5; **5b** (2,5 isomer), 34456-53-6; **5c,** 34456-54-7; **5f,** 34456-55-8; **5g,** 34456-56-9; **6a,** 28460-28-8; **6b,** 34456-58-1; **6c,** 34456-59-2; **6d,** 34456-60-5; **6e,** 34456-61-6; **6f,** 34456-62-7; **6g,** 34456-63-8; **6h,** 34456-64-9; **15,** 34456-65-0; **16,** 16082-59-0; **17,** 34456-67-2; **18,** 235-21-2; **24,** 34456-69-4; **25,** 34456-70-7; **28,** 34456-71-8; **29,** 34456-72-9; 1,2-bis(6-methyl-2-pyridyl)ethylene, 34456-73-0; methanesulfonamide, 3144-09-0; 3-(*N*,*N*-dibenzenesulfonyl)amino-2,4,6-trimethylpyridine, 34456-74-1; 2-benzenesulfonamido-6-methylpyridine, 34456-75-2; 5-benzenesulfonamidequinoline, 34298-61-8; 5-benzenesulfonamido-3-methylisoquinoline, 34456-77-4.

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The Synthesis of Some New Azabenzo[a]pyrenes and Monomethylazabenzo[a]pyrenes[1a]

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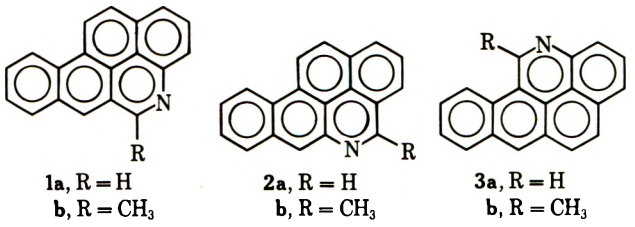
4-Azabenzo[a]pyrene (**1a**), 5-methyl-4-azabenzo[a]pyrene (**1b**), 12-azabenzo[a]pyrene (**3a**), 11-methyl-12-azabenzo[a]pyrene (**3b**), 5-azabenzo[a]pyrene (**2a**), and 4-methyl-5-azabenzo[a]pyrene (**2b**) were obtained in good yields by the Bischler–Napieralski cyclodehydration of the appropriate amides with polyphosphoric acid. The ultraviolet absorption and nuclear magnetic resonance spectra of all six compounds were consistent with their assigned structures. These compounds are being submitted for both carcinogenic and carcinostatic testing.

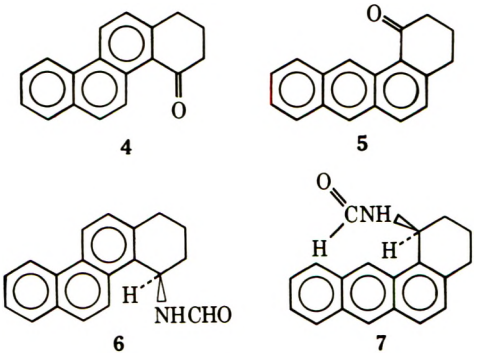
Benzo[a]pyrene and many of its derivatives have been shown to be powerful carcinogens, and a study of the carcinogenic activity of some methylated benzo[a]pyrenes prepared in this laboratory has been reported recently.[2] In addition, benzo[a]pyrene has been shown to exhibit antitumor action.[3-5] Several years ago we initiated a program to synthesize a number of azabenzo[a]pyrenes for use in carcinogenic and carcinostatic studies in the hope that such compounds would exhibit a lower carcinogenic activity and possibly a higher carcinostatic activity than the parent hydrocarbon. The substitution of methyl groups in the 1, 2, 3, 4, 5, 6, 11, and 12 positions gives monomethylbenzo[a]pyrenes which are highly carcinogenic. It was felt that a study should be made of compounds with nitrogen heteroatoms in these positions. The 1-, 3-, and 6-aza derivatives should be of particular interest since these positions are attacked in metabolism in rats whereby the animal oxidizes the carcinogen.[6]

The syntheses of only three of the possible 12 azabenzo[a]pyrenes have been reported; namely, 10-azabenzo[a]pyrene,[7,8] 8-azabenzo[a]pyrene,[8] and 7-azabenzo[a]pyrene.[8] We are reporting herewith the synthesis of three new azabenzo[a]pyrenes, namely the 4-, 5-, and 12-aza derivatives (**1a**, **2a**, and **3a**, respectively) as well as the 5-methyl-4-, 4-methyl-5-, and 11-methyl-12-azabenzo[a]pyrenes (**1b**, **2b**, and **3b**, respectively).

Of particular interest are the 4- and 5-azabenzo[a]pyrenes and their methyl derivatives, since they are the first azabenzo[a]pyrenes to be prepared in which the annular nitrogen atom is located in the K region of the benzo[a]pyrene skeleton.

4-Keto-1,2,3,4-tetrahydrochrysene (**4**) and 1-keto-1,2,3,4-tetrahydrobenz[a]anthracene (**5**) were prepared according to previously described procedures to be converted, respectively, to 4-formamido-1,2,3,4-tetrahydrochrysene (**6**) and 1-formamido-1,2,3,4-tetrahydrobenz[a]anthracene (**7**) *via* the Leuckart reaction.[9] Indeed, 4-keto-1,2,3,4-tetrahydrochrysene (**4**) afforded the formamide **6** in 85% yield *via* the Leuckart reaction with formamide and formic acid. All attempts to cyclize the formamide **6** to 1,2,3,3a-tetrahydro-4-azabenzo[a]pyrene failed with the usual Bischler–Napieralski reagents.





Examination of molecular models of the amide **6** indicated that the formamido group was not in a conformation suitable for facile attack at the aromatic ring carbon. It has been reported by Cook and Thomson[10] that the cyclization of 4-formamidophenanthrene (**8**) with phosphorus pentoxide in refluxing xylene gave 4-azapyrene (**9**) in 33% yield. Studies in this laboratory of the Bischler–Napieralski cyclization of 4-formamido-1,2,3,4-tetrahydrophenanthrene (**10**) to 1,2,3,3a-tetrahydro-4-azapyrene (**11**) showed this amide to be equally as inert towards cyclodehydration as the amide **6**.[11] We, therefore, abandoned the approach *via* the tetrahydroamides **6** and **7**, and turned our attention to aromatized amides similar to 4-formamidophenanthrene.

The ketones **4** and **5** were converted to their respective azines **12a** and **12b** in nearly quantitative yields by heating with 95% hydrazine in alcohol containing hydrochloric acid.[12] Dehydrogenation of the

(1) (a) From the dissertation presented by Richard E. Phillips, Jr., to the graduate faculty of the University of New Mexico in partial fulfillment of the requirements for the degree of Doctor of Philosophy. This investigation was supported in part by a Research Grant (C-4714) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service. (b) National Science Foundation Trainee, 1965–1969. (c) Author to whom inquiries should be directed. (d) Graduate Research Assistant, Feb 1960 to June 1962.

(2) A. Lacassagne, F. Zajdela, N. P. Buu-Hoi, O. Chalvet, and G. H. Daub, *Int. J. Cancer*, **3**, 238 (1968).

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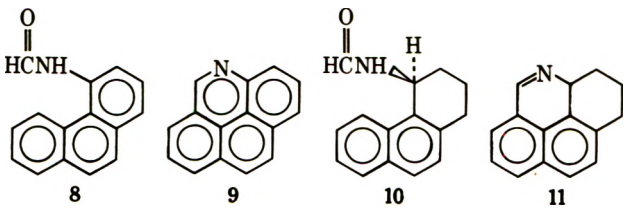
(9) "Organic Reactions," Vol. V, Wiley, New York, N. Y., 1949, p 321.

(10) J. W. Cook and W. H. S. Thomson, *J. Chem. Soc.*, 395 (1945).

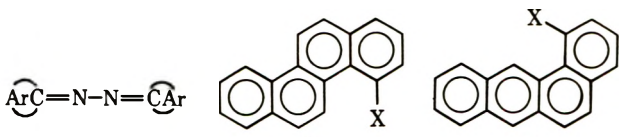
(11) G. H. Daub and R. L. Taber, unpublished work.

(12) M. J. S. Dewar and W. H. Poesche, *J. Org. Chem.*, **29**, 1259 (1964).



8 9 10 11

azines **12a** and **12b** with 10% palladium on charcoal in refluxing triethylbenzene afforded the amines **13b** and **14b**, isolated as their hydrochlorides, **13a** and **14a**, in 59 and 48% yields, respectively.



12a, azine from **4**
b, azine from **5**

13

14

a, X = NH_3Cl
b, X = NH_2
c, X = NH(C=O)H
d, X = $NH(C=O)CH_3$

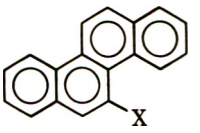
Liberation of the free amines from the hydrochloride salts with aqueous ammonia followed by acylation with formic acid or acetyl chloride afforded 4-formamidochrysene (**13c**), 4-acetamidochrysene (**13d**), 1-formamidobenz[*a*]anthracene (**14c**), and 1-acetamidobenz[*a*]anthracene (**14d**) in 76, 72, 68, and 44% yields, respectively (see Table I).

TABLE I
PHYSICAL PROPERTIES AND YIELDS FOR THE FORMAMIDES AND ACETAMIDES[c]

$ArNH_2$	ArNHCOR	Yield, %	Mp, °C
Ar = 4-Chrysenyl (**13b**)	**13c**,[a] R = H	76	246.5–247.5
	13d,[a] R = CH_3	72	245–246
Ar = 1-Benz[*a*]-anthracenyl (**14b**)	**14c**,[a] R = H	68	268–268.5
	14d,[a] R = CH_3	44	265–266
Ar = 5-Chrysenyl (**15d**)	**15e**,[b] R = H	77	253–253.5
	15f,[b] R = CH_3	71	250–251

[a] Sublimed at reduced pressure and crystallized from ethyl acetate. [b] Crystallized from ethyl acetate. [c] Satisfactory analytical data (±0.4% for C and H) were reported for all new compounds listed in the table.

The amides **15e** and **15f** were prepared *via* chrysene-5-carboxylic acid (**15a**), which was readily available using the method of Fieser and Joshel.[13] The Schmidt reaction of chrysene-5-carboxylic acid (**15a**) with sodium azide in a mixture of trifluoracetic acid, trifluoroacetic anhydride, and chloroform was carried out in a manner similar to that described by Rutherford and Newman.[14] The expected chrysene-5-isocyanate (**15b**) and 5-trifluoroacetamidochrysene (**15c**) were obtained, the latter product probably resulting from reaction of the isocyanate **15b** with trifluoroacetic acid. The crude mixture of **15b** and **15c** upon hydrolysis with alcoholic potassium hydroxide afforded 5-aminochrysene (**15d**) in 92% overall yield from **15a**. Formylation and acetylation of the amine **15d** afforded 5-formamidochrysene (**15e**) and 5-acetamidochrysene (**15f**) in 77 and 71% yields, respectively (see Table I).



15a, X = COOH
b, X = N=C=O
c, X = $NH(C=O)CF_3$
d, X = NH_2
e, X = NH(C=O)H
f, X = $NH(C=O)CH_3$

A study of the Bischler–Napieralski cyclodehydration of the formamide **8** to 1-azapyrene (**9**) using a variety of reagents (*e.g.*, phosphorus pentoxide in refluxing xylene, anhydrous hydrofluoric acid, polyphosphate ester, phosphorus oxychloride, aluminum chloride in methylene chloride, and polyphosphoric acid) showed polyphosphoric acid to be the most effective. Cannon and Webster[15] also showed polyphosphoric acid to be a more effective Bischler–Napieralski catalyst than the more classical condensing agents in a study of the cyclization of some *N*-acylphenylethylamines to the corresponding 3,4-dihydroisoquinolines.

Thus, cyclization of the amides **13c**, **13d**, **14c**, **14d**, **15e**, and **15f** to the corresponding azabenzo[*a*]pyrenes **1a**, **1b**, **3a**, **3b**, **2a**, and **2b** was accomplished by heating with polyphosphoric acid, the crude products being obtained in excellent yields (see Table II).

TABLE II
THE BISCHLER–NAPIERALSKI CYCLODEHYDRATION OF THE AMIDES TO THE AZABENZO[a]PYRENES WITH POLYPHOSPHORIC ACID[e]

Amide	Azabenzo[a]-pyrene	Reaction time, hr	Reaction temp, °C	Yield,[a] %	Mp, °C
13c	**1a**[b,c]	2.0	150	66	173.5–174
13d	**1b**[b,d]	2.0	150	59	160.5–161.5
14c	**3a**[c]	1.5	130	80	230–231
14d	**3b**[c]	1.5	130	53	184–185.5
15e	**2a**[c]	1.5	130	75	225–226.5
15f	**2b**[c]	1.5	130	80	190.5–191.5

[a] Yield of purified material. In all cases the crude yields were in the range of 96% of material with melting points not more than 10° below that of pure material. [b] Chromatographed on Woelm alumina (basic); column eluted with 7.5:1 benzene–ethyl acetate. [c] Recrystallized from ethyl acetate. [d] Recrystallized from benzene. [e] Satisfactory analytical data (±0.4% for C, H, and N) were reported for all new compounds listed in the table.

The similarity of the ultraviolet absorption spectra of these new azabenzo[*a*]pyrenes to that of benzo[*a*]pyrene[16] strongly supports their structures. The ultraviolet absorption spectra of these new compounds were in no way similar to those of chrysene and benz[*a*]anthracene.

The nuclear magnetic resonance spectra of these compounds also substantiates their assigned structures. Each of the unsubstituted azabenzo[*a*]pyrenes (**1a**, **2a**, and **3a**) has a one-proton singlet absorption with a δ value of between 10.24 and 10.46 ppm appear-

(13) L. F. Fieser and L. M. Joshel, *J. Amer. Chem. Soc.*, **62**, 1211 (1940).
(14) K. G. Rutherford and M. S. Newman, *ibid.*, **79**, 213 (1957).
(15) J. G. Cannon and G. L. Webster, *J. Amer. Pharm. Ass.*, **47**, 353 (1958).
(16) "U. V. Atlas of Organic Compounds," Vol. IV, Plenum Press, New York, N. Y., 1968, E6/20.

ing downfield from the other aromatic protons. These other aromatic protons appear as multiplets with δ values between 7.69 and 8.94 ppm. These singlet protons have been assigned to the position adjacent to the nitrogen atom in each of the three unsubstituted compounds, owing to the fact that this absorption peak disappears in the spectrum of each of the three monomethyl derivatives (**1b**, **2b**, and **3b**), and is replaced by a sharp three-proton singlet between δ values of 2.99 and 3.58 ppm. This sharp singlet is, of course, assigned to the methyl group in each case. The remaining aromatic protons of the monomethyl derivatives appear as a multiplet between δ values of 7.60 and 8.80 ppm.

Experimental Section[17]

4-Formamido-1,2,3,4-tetrahydrochrysene (6).—A mixture of 9.84 g (0.04 mol) of 4-keto-1,2,3,4-tetrahydrochrysene (**4**), mp 119–122°,[18-20] 80 ml of formamide, and 1.0 ml of 90% formic acid was heated at 175° in a 200-ml round-bottomed flask equipped with a stirrer, thermometer, and take-off condenser as described in "Organic Reactions,"[9] an additional 1.0 ml of formic acid being added every 2 hr over a period of 8 hr until a total of 5.0 ml of formic acid had been added. The reaction mixture was heated at 175° for a total of 13 hr, after which time it was cooled and the solid which separated was collected, washed with water, and air dried, affording 9.46 g (85.5% yield) of light tan crystals, mp 206–210°. Crystallization from benzene gave a first crop of 7.83 g of 4-formamido-1,2,3,4-tetrahydrochrysene (**6**) as a colorless solid, mp 211.5–212.5°. An analytical sample, mp 211.5–212.5°, was obtained by further recrystallization from benzene.

Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22. Found: C, 83.13; H, 6.22.

4-Keto-1,2,3,4-tetrahydrochrysene Azine (12a) and 1-Keto-1,2,3,4-tetrahydrobenz[*a*]anthracene Azine (12b).—To a mixture of 3.2 g (0.013 mol) of 4-keto-1,2,3,4-tetrahydrochrysene (**4**) and 20 ml of 95% ethanol was added 0.35 ml (0.01 mol) of 95% hydrazine and 20 drops of concentrated hydrochloric acid.[12,21] The mixture was refluxed for 24 hr, after which time the precipitate was collected, triturated with hot ethanol, and dried to give 3.17 g (99.8% yield) of 4-keto-1,2,3,4-tetrahydrochrysene azine (**12a**) as a yellow solid, mp 309–310° (evacuated tube).

Anal. Calcd for $C_{36}H_{28}N_2$: C, 88.49; H, 5.78. Found: C, 88.44; H, 5.86.

Similar treatment of 1-keto-1,2,3,4-tetrahydrobenz[*a*]anthracene (**5**)[22] afforded a quantitative yield of orange 1-keto-1,2,3,4-tetrahydrobenz[*a*]anthracene azine (**12b**), mp 328.5–329° (evacuated tube).

Anal. Calcd for $C_{36}H_{28}N_2$: C, 88.49; H, 5.78. Found: C, 88.04; H, 5.76.

4-Aminochrysene Hydrochloride (13a) and 1-Aminobenz[*a*]anthracene Hydrochloride (14a).—To a refluxing solution of 2.0 g (4.1 mmol) of 4-keto-1,2,3,4-tetrahydrochrysene azine (**12a**) in 150 ml of triethylbenzene (redistilled technical grade) was slowly added 0.6 g of 10% palladium on charcoal catalyst (Matheson Coleman and Bell, #5865).[12,21] The mixture was refluxed for 1 hr, after which time the hot mixture was filtered and the residue was washed with hot benzene. The combined filtrate and washings were allowed to cool and the small amount of yellow fluorescent precipitate which appeared was collected, washed with benzene, and discarded. The filtrate was saturated with dry hydrogen chloride and the precipitate which formed was collected, washed with ether, and dried. The dark green 4-aminochrysene hydrochloride (**13a**) thus obtained amounted to 1.35 g (59% yield). Attempts to obtain the pure amine from the hydrochloride were met with difficulty and therefore it was isolated and analyzed as its formyl and acetyl derivatives as described below.

Similar treatment of 1-keto-1,2,3,4-tetrahydrobenz[*a*]anthracene azine (**12b**) (reflux 1.5 hr) afforded a 48% yield of 1-aminobenz[*a*]anthracene hydrochloride (**14a**), which was directly converted to its acetyl and formyl derivatives as described below.

5-Aminochrysene (15d).—To a cold swirling solution (4°) of 1.0 g (3.7 mmol) of chrysene-5-carboxylic acid (**15a**),[13,23] mp 222.5–223.5°, 8.2 ml of trifluoroacetic acid, 8.2 ml of trifluoroacetic anhydride, and 25 ml of chloroform was slowly added 0.48 g (7.4 mmol) of sodium azide.[15] This mixture was stirred in the cold for 35 min, during which time a gray precipitate appeared. The mixture was filtered and the gray precipitate thus collected was washed with water, a portion of the precipitate being water soluble. The gray material which remained was dried and weighed 0.5 g, mp 160–161°. A small portion of this material was crystallized from ethyl acetate to give chrysene-5-isocyanate (**15b**) as a white, flocculent solid, mp 160–161°.

Anal. Calcd for $C_{19}H_{11}NO$: C, 84.74; H, 4.12. Found: C, 85.01; H, 4.27.

The organic solvents were removed from the filtrate above under reduced pressure, leaving 0.5 g of a brown solid, mp 230–250°. A small portion of this material was crystallized from ethyl acetate to give a solid, mp 247–247.5°. This compound was shown to contain fluorine by elemental analysis, and has been identified as 5-trifluoroacetamidochrysene (**15c**).

Anal. Calcd for $C_{20}H_{12}NOF_3$: C, 70.80; H, 3.54. Found: C, 71.20; H, 3.17.

The crude isocyanate **15b** and crude trifluoroacetamide **15c** were combined and mixed with 50 ml of 70% ethanol and 0.7 g of potassium hydroxide.[15] This mixture was refluxed for 4 hr, after which time it was poured over ice and allowed to stand overnight. The yellow precipitate which appeared was collected, washed with water, and dried to afford 0.74 g (92% yield) of crude 5-aminochrysene (**15d**), mp 141–148°. This material was crystallized from cyclohexane, yielding 0.64 g of yellow needles, mp 148.5–149.5°.

Anal. Calcd for $C_{18}H_{13}N$: C, 88.86; H, 5.39. Found: C, 88.88; H, 5.59.

General Procedure for the Preparation of the Formamides and Acetamides.—The appropriate amine hydrochloride (**13a** or **14a**) was decomposed with excess dilute ammonia or sodium carbonate solution and the liberated amine was extracted into ether. The ether solution was dried ($MgSO_4$) and the ether was removed. The crude amine (**13b** or **14b**) thus prepared or 5-aminochrysene (**15d**), mp 144–148°, was heated with an excess (5:1) of 97% formic acid on a steam bath until the excess formic acid had evaporated. The crude formamide (**13c**, **14c**, or **15e**) was triturated with water or 5% sodium carbonate solution, filtered, washed with water, dried, and purified as indicated in Table I.

The crude amine **13b**, **14b**, or **15d** was allowed to react with an excess (2:1) of acetyl chloride in pyridine solution (stirring) in an ice bath for 10–45 min, after which time the reaction mixture was allowed to warm to room temperature. The mixture was poured over ice, and the precipitate was collected, washed with dilute hydrochloric acid and water, and dried. The crude acetamide thus obtained was purified as indicated in Table I.

General Procedure for the Preparation of the Azabenzo[*a*]pyrenes and Their Methyl Derivatives.—The amides **13c**, **13d**, **14c**, **14d**, **15e**, and **15f** were cyclized with polyphosphoric acid (prepared according to Gilmore and Horton[24] from 24.8 g of phosphorus pentoxide and 16 ml of 85% phosphoric acid) by stirring a mixture of 1 g of amide with the acid for 1.5–2 hr at 125–130 for amides **13c**, **13d**, **14c**, and **14d** and 145–150° for amides **15e** and **15f**. The viscous reaction mixture was poured into ice water, stirred, and made basic with concentrated ammonia, and the precipitated azabenzo[*a*]pyrene was collected, washed with water, and dried. The crude products thus obtained were purified as shown in Table II.

(17) All melting points were taken in Pyrex capillary tubes in a Hoover-Thomas melting point apparatus and are uncorrected. Ultraviolet spectra were taken in 95% ethanol solution and were run on a Cary Model 14 spectrophotometer. Nmr spectra were run on a Varian Associates Model A-60A spectrometer in deuteriochloroform.

(18) A. Burger and E. Mosettig, *J. Amer. Chem. Soc.*, **59**, 1302 (1937).

(19) D. Phillips, *ibid.*, **75**, 3223 (1953).

(20) W. E. Bachmann and W. S. Struve, *J. Org. Chem.*, **4**, 456 (1939).

(21) E. C. Horning and M. G. Horning, *J. Amer. Chem. Soc.*, **69**, 1907 (1947).

(22) J. W. Cook and A. M. Robinson, *J. Chem. Soc.*, 505 (1938). Using 2 mol of aluminum chloride per mole of succinic anhydride in the Friedel-Crafts reaction with anthracene almost doubled the yield reported by these workers, who used these reagents in a 1:1 ratio.

(23) De Los F. De Tar, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 730.

(24) R. C. Gilmore and J. W. Horton, *J. Amer. Chem. Soc.*, **73**, 1411 (1951).

Registry No.—**1a**, 24499-89-6; **1b**, 34440-84-1; **2a**, 24496-61-5; **2b**, 34440-86-3; **3a**, 24496-65-9; **3b**, 34440-88-5; **6**, 34440-89-6; **12a**, 34440-90-9; **12b**, 34440-91-0; **13c**, 34440-94-3; **13d**, 34440-92-1; **14c**, 34440-93-2; **14d**, 34440-95-4; **15b**, 34440-96-5; **15c**, 34440-97-6; **15d**, 34440-98-7; **15e**, 34440-99-8; **15f**, 34441-00-4.

Acknowledgment.—The authors are indebted to the U. S. Public Health Service (Grant No. C-4714 from the National Cancer Institute of the National Institutes of Health) and to the National Science Foundation (NSF traineeship) for generous financial support of this work.

Notes

Cycloalkanones. I. The Stereochemistry of α,α'-Dibenzylcycloalkanones

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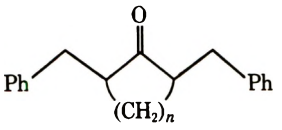
In the course of investigation of cycloalkanones for possible drug uses,[2] it became necessary to establish the stereochemistry of the series of α,α'-dibenzylcycloalkanones **1**–**4**. The *cis*- (**2a**) and *trans*- (**2b**) cyclo-



1, $n = 2$ **3**, $n = 4$
2, $n = 3$ **4**, $n = 5$

hexanones are known in the literature.[3,4] Both *cis*- (**1a**) and *trans*- (**1b**) cyclopentanone have been reported,[5] but the sterochemistry has not been established. A liquid dibenzylcycloheptanone has been reported[6] as well as its oxime.[7] The cis (**3a**) and trans (**3b**) isomers have not been isolated previously. Neither *cis*- (**4a**) nor *trans*- (**4b**) dibenzylcyclooctanone is known. In the present work, all four pairs of isomers were isolated and their configurations established.

The configurations of the isomeric ketones were established by lithium aluminum hydride reduction. Analysis for the number of alcohols obtained in each case was by vpc. The results are given in Table I. The assignment of the cyclohexanone isomers was consistent with the literature.[3] As a further check on the analysis, samples of the alcohols from both isomers of the cyclohexanone and cyclooctanone compounds were isolated by preparative vpc and used for mass spectral analysis. All showed the correct molecular ion peak. The molecular ion peak was small in all cases, but each had a large P − 18 peak, confirming that the compounds seen by vpc were the alcohols.

TABLE I
NUMBERS OF ALCOHOLS PRODUCED ON $LiAlH_4$ REDUCTION OF α,α'-DIBENZYLCYCLOALKANONES

Compd	Mp, °C	No. of alcohols[a]	Assigned configuration
1a	39–40	2	cis
1b	54–55	1	trans
2a	119–122	2	cis
2b	55	1	trans
3a	*b*	2	cis
3b	*c*	1	trans
4a	84–85	2	cis
4b	82–83	1	trans

[a] From $LiAlH_4$ reduction. [b] First ketone isolated during column chromatography. [c] Second ketone isolated during column chromatography.

As it was necessary for biological correlation to know which isomer predominated in an equilibrating system, one isomer of each pair of ketones was equilibrated in 0.1 *M* NaOEt, in ethanol. Samples were taken at 24-hr intervals until no change was seen. The cyclohexanones and cyclooctanones were separable as the ketones, but the cycloheptanones had to be reduced to the alcohols with $NaBH_4$. The equilibrium concentration of the cyclopentanones was not obtained owing to the inability to separate either the ketones or the alcohols on a variety of columns. The two alcohols from the cis ketone could be separated, but one of them overlapped the alcohol from the trans ketone. The equilibrium concentrations are given in Table II.

TABLE II
EQUILIBRIUM CONCENTRATIONS OF α,α'-DIBENZYLCYCLOALKANONES IN 0.1 *M* NaOEt IN ETHANOL

Compd	cis, %	trans, %
2	88	12
3	35	65
4	40	60

Experimental Section

All melting points are uncorrected and were obtained on a Mel-Temp apparatus. Analytical vpc utilized a Packard model 800 and preparative vpc utilized a Varian Aerograph Model 202. The α,α'-dibenzylidenecycloalkanones were prepared by base-catalyzed condensations of benzaldehyde with the appropriate

(1) (a) To whom inquiries should be addressed. (b) Smith, Kline and French Postdoctoral Fellow. (c) Predoctoral trainee supported by Public Health Service Training Grant 5T01-GM01770-02 from the National Institute of General Medical Sciences, National Institutes of Health.

(2) Publication in preparation.

(3) R. Cornubert, M. Andre, M. Demo, R. Joly, and A. Strebel, *Bull. Soc. Chim. Fr.*, **6**, 103 (1939).

(4) E. J. Corey, T. H. Topie, and W. A. Wozniak, *J. Amer. Chem. Soc.*, **77**, 5416 (1955).

(5) R. Cornubert, M. Demo, R. Joly, and A. Strebel, *Bull. Soc. Chim. Fr.*, **6**, 132 (1939).

(6) W. Borsche, *Chem. Ber.*, **45**, 46 (1912).

(7) N. J. Leonard, L. A. Miller, and J. W. Berry, *J. Amer. Chem. Soc.*, **79**, 1482 (1957).

cyclic ketone.[2] Elemental analysis was made of all compounds.[2]

cis-**2,5-Dibenzylcyclopentanone**.—Hydrogenation of 2,5-dibenzylidenecyclopentanone[2] in EtOAc over 10% Pd/C gave a mixture of saturated ketone and alcohol (ir). Chromatography on silica gel gave an oil which later crystallized on standing in an open dish, mp 39–40° (lit.[5] mp 39°).

trans-**2,5-Dibenzylcyclopentanone**.—Isomerization of the cis isomer in methanolic KOH after Cornubert, *et al.*,[5] gave the trans isomer, mp 54–55° (lit.[5] mp 58°). By tlc (C_6H_6/$CHCl_3$, 95:5) this material was free of the cis isomer.

cis-**2,6-Dibenzylcyclohexanone**.—Crystallization of the crude mixture from hydrogenation (10% Pd/C in EtOAc) of 2,6-dibenzylidenecyclohexanone[2] from MeOH gave the cis isomer, mp 119–122° (lit.[3] mp 122°).

trans-**2,6-Dibenzylcyclohexanone**.—The trans isomer was isolated from the mother liquor from crystallization of the cis isomer, after several batches of cis isomer were removed, mp 55° (lit.[3] mp 55°).

cis- **and** *trans*-**2,7-Dibenzylcycloheptanone**.—Hydrogenation of 2,7-dibenzylidenecycloheptanone[2] (10% Pd/C in EtOAc) gave an oil which failed to crystallize. Chromatography of 1 g of the oil on a 2-cm column using 60 g of 75–325 mesh silica gel and C_6H_6 eluent gave first the cis isomer, followed by the trans. Neither isomer was ever obtained as a solid.

trans-**2,8-Dibenzylcyclooctanone**.—Crystallization of the crude mixture from hydrogenation (10% Pd/C in EtOAc) of 2,8-dibenzylidenecyclooctanone[2] from MeOH gave the trans isomer, mp 82–83°.

cis-**2,8-Dibenzylcyclooctanone**.—Isomerization of trans isomer was carried out using 0.1 *M* NaOEt in EtOH,[2] yielding cis isomer, mp 84–85°. These were not the same compounds by mixture melting point, ir, and nmr.

Lithium Aluminum Hydride Reductions.—Each isomeric ketone (50 mg) was reduced with 50 mg of $LiAlH_4$ in anhydrous Et_2O by standard procedures.

Equilibration of Isomers.—One gram of one isomer of each pair was dissolved in 0.1 *M* NaOEt in EtOH and stirred at room temperature. Samples were analyzed at 24-hr intervals until no change in concentration was seen. The samples of the cycloheptanones had to be reduced to the alcohols with $NaBH_4$ before analysis. This was done by adding 50 mg of $NaBH_4$ to the aliquot, allowing it to stand overnight, and extracting into Et_2O after acidifying with 1 *N* HCl.

Vapor Phase Chromatography.—The cyclooctanones were separated on a 5 ft × 0.25 in. o.d. glass column packed with 3% OV-225 on Chromosorb W-AW-DMCS. The cyclohexanones were separated on a 5 ft × 0.25 in. o.d. glass column packed with 3% OV-17 on Chromosorb W-AW-DMCS. The alcohols obtained from the ketones were separated on the OV-225 column. The two alcohols from the *cis*-2,5-dibenzylcyclopentanone were separable but the alcohol from the trans isomer had the same retention time as one of the alcohols from the cis ketone.

Registry No.—**1a**, 34403-27-5; **1b**, 34403-28-6; **2a**, 7382-09-4; **2b**, 7382-10-7; **3a**, 34403-31-1; **3b**, 34410-06-5; **4a**, 34403-32-2; **4b**, 34403-33-3.

Acknowledgment.—We would like to express our gratitude to Smith, Kline and French Laboratories, Philadelphia, Pa., for support of this work.

Noble Metal Catalysis. I. Synthesis of Succinates from Olefins

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Dialkyl succinates[1] can be prepared in good yields by the oxidative carbonylation of olefins in the presence of alcohols with a palladium redox system, according to eq 1.

$$C_2H_4 + 2CO + {}^1/_2O_2 + 2ROH \longrightarrow RO_2CCH_2CH_2CO_2R + H_2O \quad (1)$$

The palladium redox system is somewhat similar to the one used in acetaldehyde synthesis[2] but optimum results are achieved by restricting both the amounts of excess hydrogen ion and chloride ion. Both iron and copper chlorides were shown to be useful as redox reagents for palladium, according to the following equations (for copper).

$$PdCl_2 + 2CO + CH_2{=}CH_2 + 2ROH \longrightarrow RO_2CCH_2CH_2CO_2R + Pd^0 + 2HCl \quad (2)$$

$$2CuCl_2 + Pd^0 \longrightarrow Cu_2Cl_2 + PdCl_2 \quad (3)$$

$$Cu_2Cl_2 + 2HCl + {}^1/_2O_2 \longrightarrow 2CuCl_2 + H_2O \quad (4)$$

However, it was quickly found that palladium chloride with either cupric chloride or ferric chloride alone gave a very poor catalyst system for succinate synthesis. The problem was found to be due to the presence of hydrogen chloride generated by eq 2. To the extent that eq 2 and 3 are faster than 4, then large amounts of cupric chloride give large amounts of hydrogen chloride. It was found that, when cuprous chloride was added, the excess chloride ion could be tied up. In the iron system, ferrous chloride was more effective than even a mixture of ferrous and ferric chlorides.

The oxidation of ferrous chloride by air was already known to be much faster in alcohols than in water and to increase in rate with increasing molecular weight of the alcohol.[3] The presence of water or small amounts of mineral acid in the solution reduced the rate of oxidation considerably. The rate of oxidation was related to the square of the concentration of ferrous chloride. The reaction was thought to be eq 5. Some oxidation

$$2FeCl_2 + {}^1/_2O_2 \longrightarrow FeCl_3 + FeOCl \quad (5)$$

of the ethanol solvent to acetaldehyde and ethyl acetate was also observed.

The acid–base effect is illustrated in Table I, where

TABLE I

EFFECT OF ACID AND BASE[a]

Acid or base	Wt, of acid or base, g	Mol of product produced: Methyl succinate	Carbon dioxide	Other
	0	0.17	0.17	Methyl formate, 0.02
Sodium acetate	3	0.22	0.10	
37% Hydrochloric acid	1	0.04	0.26	Methyl formate, 0.02 Methylal, 0.1

[a] At 300 psig CO, 700 psig C_2H_4, methanol to 400 ml in a 0.5-gal stirred titanium autoclave with 1 g of $PdCl_2$, 10 g of $FeCl_2 \cdot 4H_2O$, and oxygen addition to 125–175 psig in increments at 85°.

it is seen that in the synthesis of methyl succinate the addition of small amounts of sodium acetate (organic bases such as pyridine are also effective) increases the yield of succinate and decreases the yield of carbon dioxide, the chief by-product. On the other hand, hydrogen chloride has just the opposite effect.

The other product produced along with the succinate

(1) D. M. Fenton, U. S. Patents 3,481,845; 3,397,225; 3,397,226.

(2) J. Smidt, *Angew. Chem.*, 176 (1959).

(3) J. R. Pound, *J. Phys. Chem.*, **43**, 955, 969 (1939).

is water. Although small amounts of water do not prevent succinates from forming, water definitely increases the production of carbon dioxide, as seen in Table II.

TABLE II
EFFECT OF ADDITION OF ORTHOFORMATE[a]

Wt of methyl orthoformate, g	Mol of product produced: Methyl succinate	Carbon dioxide	Other
0	0.17	0.17	Methyl formate, 0.02
100	0.33	0.068	
200	0.18	0.0044	
200[b]	0.24[b]	0.0088	Ethyl acetate, 0.19

[a] At 300 psig CO, 700 psig C_2H_4, methanol to a total of 400 ml in a 0.5-gal stirred titanium autoclave with 1 g of $PdCl_2$, 10 g of $FeCl_2 \cdot 4H_2O$, and oxygen addition to 125–175 psig in increments at 85°. [b] The corresponding ethyl esters and ethyl alcohol.

Alkyl orthoformates can be added to suppress the carbon dioxide formation. In this way yields of succinate of over 90% based upon both ethylene and carbon monoxide are achieved.

Although eq 1 shows the need for 2 mol of carbon monoxide for 1 mol of ethylene, it was shown that slightly higher partial pressures of ethylene to carbon monoxide give better yields of succinates, as shown in Table III, for butyl succinate. Also, lower yields of

TABLE III
EFFECT OF CHANGES IN THE CARBON MONOXIDE–ETHYLENE RATIO[a]

Pressure, psig: Carbon monoxide	Ethylene	CO/C_2H_4	Wt of butyl succinate product, g
300	700	0.43	0[b]
500	750	0.67	26
500	400	1.25	23
800	500	1.60	12

[a] 1 g of $PdCl_2$, 5 g of $CuCl_2$, 5 g of LiCl, and 400 ml of butanol, at 125–150° in a 0.5-gal stirred steel autoclave with 150–200 psig oxygen added in increments. [b] 15 g of butyl acrylate produced.

carbon dioxide are produced at lower CO/C_2H_4 ratios. However, at still lower CO/C_2H_4 ratios, instead of succinates, acrylates are produced. However, with the same carbon monoxide–ethylene ratio using the ferrous system without excess chloride ion, succinates were made (Tables I and II). Thus the product distribution depends significantly on the CO/C_2H_4 ratio. This dependence on CO/C_2H_4 ratio was previously noted for the synthesis of acrylic acid[4] starting from ethylene and carbon monoxide, according to eq 6,

$$CH_2{=}CH_2 + CO + {}^1/_2O_2 \longrightarrow CH_2{=}CHCO_2H \quad (6)$$

using a similar palladium redox catalyst with an acetic acid solvent. Here β-acetoxypropionic acid was also produced, particularly at higher temperatures and pressures and also at higher CO/C_2H_4 ratios. However, succinic acid was not a significant product.

Other olefins may also be used in place of ethylene. The results of two of these runs are shown in Table IV.

(4) D. M. Fenton, K. L. Olivier, and G. Biale, *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, **14** (4), C77 (1969).

TABLE IV
USE OF OTHER OLEFINS[a]

Olefin	Wt, g: Olefin	Ethyl orthoformate	Pressure, psig carbon monoxide	Wt of products, g
Propylene	238	200	600	Diethyl methylsuccinate, 30; Ethyl crotonate, 30
1-Octene	100	100	700	Diethyl hexylsuccinate, 22

[a] 1 g of $PdCl_2$, 5 g of $CuCl_2$, 5 g of LiCl, and enough ethanol to make 600 ml of liquid, in a 0.5-gal stirred steel autoclave at 125–150° with 100–200 psig oxygen.

Experimental Section

The reactions were carried out in 0.5-gal stirred autoclaves made of either steel or titanium. The steel autoclaves exhibited some corrosion and so titanium was preferred. The catalyst and liquids were charged to the autoclave and ethylene (where used) and carbon monoxide were added to the desired pressures. Stirring was commenced and the autoclave was heated to the desired temperature. Oxygen was then added (controlled from behind a suitable barracade) in 10-psig increments. In almost all cases an immediate exotherm was noted and cooling water was circulated to bring the temperature under control. Pressure drops were noted. Oxygen was added until 150–200 psi had been added or until the reaction slowed down. In those cases where no noticeable reaction occurred no more than 40 psi of oxygen was added. After oxygen addition, the autoclave was cooled to room temperature and the gases were collected and analyzed by gas chromatography. The liquid was weighed and analyzed by gas chromatography and occasionally by distillation.

Registry No.—Palladium chloride, 7647-10-1; sodium acetate, 127-09-3; hydrochloric acid, 7647-01-0; methyl orthoformate, 34405-39-5; carbon monoxide, 630-08-0; ethylene, 74-85-1.

Effect of α-Methyl Substitution in the Beckmann and Schmidt Rearrangement of 1-Hydrindanones[1]

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In this paper we report the results of a study of (1) the Beckman rearrangement on the oximes of *cis*- and *trans*-1-hydrindanones (**1**), *cis*- and *trans*-8-methyl-1-hydrindanones (**4**), *cis*- and *trans*-2,8-dimethyl-1-hydrindanones (**8**), and 16-methylestrone 3-methyl ether (**13**); and (2) the Schmidt reaction on *cis*- and *trans*-**8**.

cis- and *trans*-**1**,[3] *cis*- and *trans*-**4**[4–6] and **13** are known compounds, and the oximes of the former, respectively

(1) This research was supported by Public Health Service Grant No. 5RO1 AI-108063-01-03 from the National Cancer Institute.

(2) Graduate Research Assistant (1963–1967) on grants[1] supported by NIH; taken entirely from the Ph.D. Thesis of M. A. Stemniski, Fordham University, New York, N. Y., 1967.

(3) W. Hückel and W. Egerer, *Justus Liebigs Ann. Chem.*, **645**, 162 (1961).

(4) W. S. Johnson, *J. Amer. Chem. Soc.*, **65**, 1317 (1943).

(5) W. S. Johnson, *ibid.*, **66**, 215 (1944).

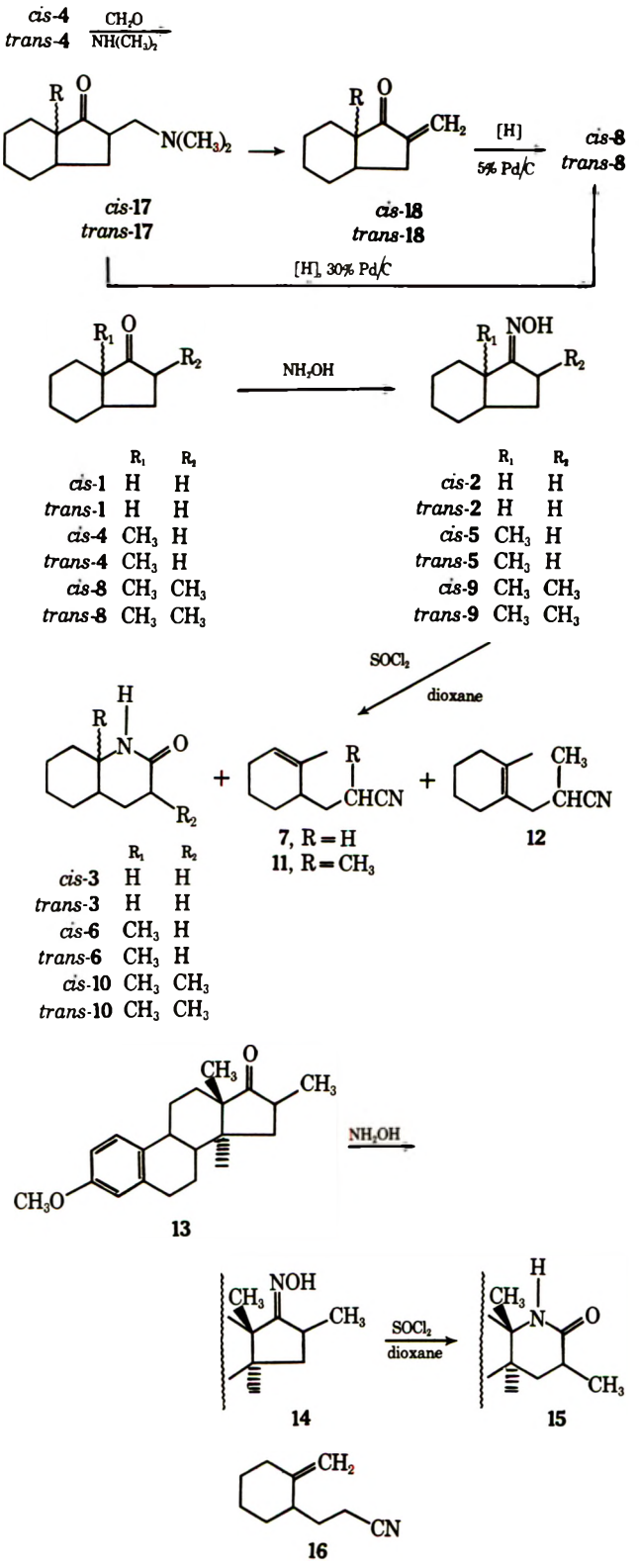
(6) W. E. Bachmann and S. Kushner, *J. Amer. Chem. Soc.*, **65**, 1963 (1943).

cis- and *trans*-2[7] and *cis*- and *trans*-5,[5,6] also have been reported. Conventional treatment of **13** with hydroxylamine afforded oxime **14**. Ketones *cis*- and *trans*-**8** were prepared from *cis*- and *trans*-**4**, respectively, *via* the well-trod Mannich pathway.[8,9] Thus, treatment of *cis*- and *trans*-**4** with dimethylamine hydrochloride and paraformaldehyde in 95% ethanol afforded the Mannich bases *cis*- (61%) and *trans*-**17** (39%), respectively. Since the Mannich reaction proceeds *via* the enol tautomer, recovery of considerable starting material from the trans reaction suggests that *cis*-**4** can enolize more readily than the trans isomer. Decomposition of *cis*- and *trans*-**17** either by steam distillation or refluxing in acetic acid–acetic anhydride led to *cis*- (55–57%) and *trans*-2-methylene-8-methyl-1-hydrindanone (**18**) (61–62%), respectively. Both *cis*- and *trans*-**18** were unstable and polymerized on standing at room temperature. Reduction of *cis*- and *trans*-**18** over 5% Pd/C led to *cis*- and *trans*-**8**, respectively, both isolated as stable oils (85%). Alternatively, both *cis*- and *trans*-**8** were prepared directly from the Mannich bases, respectively *cis*- (56%) and *trans*-**17** (46%), by hydrogenolysis over 30% Pd/C. The stereochemistry of the C-2 methyl substituent in *cis*- and *trans*-**8** is unknown. Since models indicate equal ease of hydrogen attack on both sides of both *cis*- and *trans*-**18**, it is assumed that each isomer of **8** is a mixture of α and β configurations. Oximation of *cis*- and *trans*-**8** occurred slowly (steric hindrance by the α,α'-methyl groups) and yields of oximes *cis*- (25%) and *trans*-**9** (46%) were comparatively low.

Models suggest less congestion in the geometric isomer of both *cis*- and *trans*-**9**,[10] and **14** where the hydroxyl group is anti to the six-membered ring.[11] In this configuration, the oximino group occupies a staggered conformation relative to the C-2 hydrogen and methyl substituents.

Beckmann rearrangement (thionyl chloride in dioxane) of oximes *cis*- and *trans*-**2** and **14** afforded the expected lactams *cis*- (66%)[12] and *trans*-3,4,4a,5,6,7,8,-8a-octahydrocarbostyril (**3**, 66%)[13] and 16-methyl-17a-aza-D-homoestrone 3-methyl ether (**15**, 32%).[14]

Rearrangement of *cis*-**5** led to lactam *cis*-8a-methyl-3,4,4a,5,6,7,8,8a-octahydrocarbostyril (**6**, 40%) and fragmentation product 3-(2-cyanoethyl)-2-methylcyclohexene (**7**, 40%). Di Maio and Permutte[15] have noted in passing that treatment of *cis*-**5** with PCl_5 in ether afforded *cis*-**6** and 3-(2-methylenecyclohexyl)-propanenitrile (**16**) in undisclosed yields.[16] Since the latter authors easily converted *cis*-**6** to **16** under the



(7) W. Hückel, M. Sachs, J. Yantschulewitsch, and F. Nerdel, *Justus Liebigs Ann. Chem.*, **518**, 155 (1935).

(8) F. A. Kincl and M. Garcia, *Ber.*, **92**, 595 (1959).

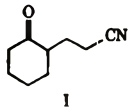
(9) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 230–234.

(10) *trans*-**9** is configurationally identical with the trans-fused C,D rings in **14**.

(11) P. T. Lansbury and N. R. Mancuso, *Tetrahedron Lett.*, 2445 (1965); P. T. Lansbury, J. G. Colson, and N. R. Mancuso, *J. Amer. Chem. Soc.*, **86**, 5225 (1964); P. T. Lansbury and N. R. Mancuso, *ibid.*, **88**, 1205 (1966).

(12) Identical with the lactam obtained by C. A. Grob, H. P. Fischer, H. Link, and E. Renk, *Helv. Chim. Acta*, **46**, 1190 (1963), on treatment of the tosylate of *cis*-**2** with base.

(13) *trans*-**3** has been obtained (1) as one of the products of the Schmidt reaction on a mixture of *cis*- and *trans*-**1** [G. DiMaio and P. A. Tardella, *Gazz. Chim. Ital.*, **91**, 1345 (1961), and (2) *via* cylization of 2-(2-cyanoethyl)-cyclohexanone (I) with formic acid and sodium formate [A. N. Kost,



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T. A. Shelegoleva, and L. G. Yudin, *Zh. Obshch. Khim.*, **25**, 2464 (1955); *Chem. Abstr.*, **50**, 9410i (1956)].

(14) B. M. Regan and F. N. Hayes, *J. Amer. Chem. Soc.*, **78**, 639 (1956).

(15) G. DiMaio and V. Permutti, *Tetrahedron*, 2059 (1966).

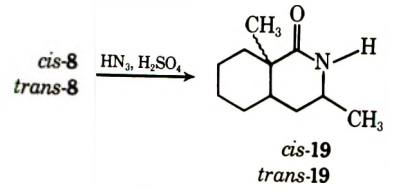
(16) A comparison of the properties of **7** and **16** is not possible since the authors[15] proved the structure of **16** by hydrolysis to 3-(2-methylenecyclohexyl)propanoic acid and then transformed the latter into its benzylisothiouronium salt. Our **7** clearly showed both a single vinyl proton at δ 4.61 coupled to the adjacent CH_2 and a CH_3 singlet at δ 2.29. The discrepancy between our melting point for *cis*-**6** (82–84°) and that reported by Di Maio and Permutti (mp 48–49°) should be noted.

reaction conditions,[15] the latter is a secondary reaction product and not a true Beckmann fragmentation product, as is **7**.

Similarly, Beckmann rearrangement of *trans*-**5** afforded *trans*-**6** (37%) and **7** (35%).

Finally, rearrangement of *cis*- and *trans*-**9** produced lactams *cis*- (41%) and *trans*-3,8a-dimethyl-3,4,4a,5,6,-7,8,8a-octahydrocarbostyril (**10**, 40%), respectively. In the former case, fragmentation product 3-(2-cyanopropyl)-2-methylcyclohexene (**11**, 12%) was also obtained; in the latter an inseparable mixture of **11** and the isomeric 2-(2-cyanopropyl)-1-methylcyclohexene (**12**) was isolated in 17% yield.

Treatment of benzene solutions of *cis*- and *trans*-**8** with hydrazoic acid in the presence of concentrated sulfuric acid afforded the expected lactams, *cis*- (27%) and *trans*-3,8a-dimethyl-3,4,4a,5,6,7,8,8a-octahydroisocarbostyril (**19**, 30%), respectively. Worthy of



comparison is the position of the C-3 methine proton in the nmr. In carbostyrils *cis*- and *trans*-**10**, this proton appears as a complex multiplet in the range δ 2.65–1.90. In isocarbostyrils *cis*- and *trans*-**19**, it is deshielded by the adjacent N and appears downfield at δ 3.70–3.25.

To sum up a general observation, models indicated and these experiments confirmed that methyl substituents on C-2,8 of **1** have little or no effect on the direction of the Beckmann rearrangement (aryl migration) leading to carbostyril products. In the Schmidt reaction, however, methyl substitution on C-2,8 of **1** led *via* alkyl migration to isocarbostyrils.

Experimental Section[17]

In the preparation of *cis*-1-hydrindanone (**1**),[3] reduction of 1-indanone was accomplished at 60 psi using 5% rhodium on alumina catalyst.[18] The reduction product mixture containing *cis*-1 and 1-hydrindanol was oxidized with chromic acid to yield *cis*-1 in 73% overall yield.

Oxime of 16-Methylestrone 3-Methyl Ether (14).—A mixture of 2.8 g (9.4 mmol) of 16-methylestrone 3-methyl ether (**13**), mp 90–93° (lit.[19] mp 95–96°), 1.40 g (20 mmol) of $NH_2OH \cdot HCl$, and 3.0 g of NaOAc in 300 ml of 95% C_2H_5OH was stirred and refluxed for 3 hr. The reaction was diluted with H_2O and cooled to yield a white solid which was filtered and air dried. Several recrystallizations from 95% C_2H_5OH gave white crystals of **14** (1.3 g, 44%): mp 181–185° dec (15–20 min); ir (KBr) 6.25 μ (C=N); nmr ($CDCl_3$) δ 8.70 (s, 1, NOH), 7.32–6.60 (m, 3, aromatic), 3.78 (s, 3, OCH_3), 3.10–1.34 (m, 14, CH_2 and CH), 1.22 (d, J = 6.5 Hz, 3, CH_3), and 1.07 (s, 3, CH_3).

Anal. Calcd for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.54; H, 8.70; N, 4.58.

(17) Melting points and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 337 grating spectrophotometer. Potassium bromide wafers were used for all solid compounds and sodium chloride plates were used for all liquid compounds. The nmr spectra were obtained on a Varian Associates A-60 spectrometer; chemical shifts are expressed in parts per million (δ) downfield from TMS as an internal standard. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(18) A. I. Meyers, W. Beverung, and G. Garcia-Munoz, *J. Org. Chem.*, **29**, 3427 (1964).

(19) D. A. Tyner, U. S. Patent 3,049,555 (1962); *Chem. Abstr.*, **59**, 1712*h* (1963).

cis-**2-(Dimethylaminomethyl)-8-methyl-1-hydrindanone (17).**—A mixture of 5.0 g (33 mmol) of *cis*-8-methyl-1-hydrindanone (**4**), bp 70° (3 mm) [lit.[5] bp 106° (20 mm)], 5.0 g (0.17 mol) of paraformaldehyde, 17.8 g (0.22 mol) of $(CH_3)_2NH \cdot HCl$, and 85 ml of 95% C_2H_5OH was stirred and refluxed for 3 hr. An additional 5.0 g (0.17 mol) of paraformaldehyde was added to the clear solution and refluxing was continued for an additional 15–17 hr. Evaporation *in vacuo* afforded a semisolid residue to which was added 100 ml of 10% HCl, and the whole was extracted with ether. The aqueous layer was neutralized with concentrated NH_4OH and extracted with ether. The ether extracts were dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give 4.2 g (61%) of *cis*-**17** as a colorless oil: bp 108–110° (2 mm); ir (neat) 5.76 μ (C=O); nmr (CCl_4) δ 2.75–2.21 (m, 3, CH_2 and CH), 2.17 [s, 6, $N(CH_3)_2$], 2.00–1.00 (m, 11, CH_2 and CH), and 0.93 (s, 3, CH_3).

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69; Found: C, 74.49; H, 11.04; N, 6.99.

trans-**2-(Dimethylaminomethyl)-8-methyl-1-hydrindanone (17).**—Similar treatment of *trans*-8-methyl-1-hydrindanone (**4**, 2.0 g, 13 mmol), bp 64–65° (1.5 mm) [lit.[5] bp 109° (20 mm)], afforded *trans*-**17** (1.1 g, 39%): bp 105–109° (2 mm); ir (neat) 5.76 μ (C=O); nmr (CCl_4) δ 2.90–2.25 (m, 3, CH_2 and CH), 2.15 [s, 6, $N(CH_3)_2$], 1.95–1.20 (m, 11, CH_2 and CH), and 0.89 (s, 3, CH_3).

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.52; H, 10.97; N, 6.69.

cis-**2-Methylene-8-methyl-1-hydrindanone (18).**—Indirect steam distillation (short path distillation head) of 1.75 g of *cis*-**17** into ice-cold ether was continued until the distillate was a single phase. The ether solution was extracted with 10% HCl, dried (Na_2SO_4), and evaporated *in vacuo* to an oil which was fractionated to give *cis*-**18** (0.78 g, 57%), bp 75–76° (2.5 mm).

Alternatively, 1.75 g (8.3 mmol) of *cis*-**17** in 10 ml each of glacial acetic acid and acetic anhydride was heated on a steam bath for 2 hr. After the solvent was evaporated *in vacuo*, the residue was dissolved in ether and successively washed with 10% NaOH, H_2O, and a saturated solution of NaCl. Evaporation of solvent ether *in vacuo* then fractionation gave 0.75 g (55%) of *cis*-**18**: bp 74–76° (2.5 mm); ir (neat) 5.78 (C=O) and 6.11 μ (C=C); nmr (CCl_4) δ 6.08 (distorted q, J = 2.5 Hz, 1, =CH), 5.34 (distorted q, J = 2.5 Hz, 1, =CH), 2.85–1.22 (m, 11, CH_2 and CH), and 1.02 (s, 3, CH_3).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.24; H, 10.05.

trans-**2-Methylene-8-methyl-1-hydrindanone (18).**—Similar treatment of *trans*-**17** (2.6 g, 12 mmol) afforded *trans*-**18** in 62% yield by steam distillation and 61% *via* acetic acid–acetic anhydride reflux: bp 69–70° (0.8 mm) and 76–78° (2 mm); ir (neat) 5.78 (C=O) and 6.10 μ (C=C); nmr (CCl_4) δ 5.92 (distorted q, J = 2.5 Hz, 1, =CH), 5.25 (distorted q, J = 2.5 Hz, 1 =CH), 2.50–1.20 (m, 11, CH_2 and CH), and 0.85 (s, 3, CH_3).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.26; H, 9.62.

cis-**2,8-Dimethyl-1-hydrindanone (8). Hydrogenation of *cis*-18.**—A mixture of 4.0 g (12 mmol) of *cis*-**18** in 150 ml of absolute C_2H_5OH and 2.0 g of 5% Pd/C was hydrogenated (10 psi) in a Paar apparatus for 2 hr. After catalyst removal by filtration through Filter-cel, the solvent was removed *in vacuo* and the oily residue was distilled to give 3.44 g (85%) of *cis*-**8** as a colorless oil, bp 58° (0.6 mm).

Hydrogenolysis of *cis*-17.—The 30% Pd/C catalyst (2.0 g) in 200 ml of absolute C_2H_5OH was reduced under 45 psi H_2 pressure for 2 hr. To this suspension was added 3.8 g (18 mmol) of *cis*-**17** and reduction was continued at 30 psi for 24 hr. After catalyst and solvent removal, the residual oil was dissolved in ether and washed with 10% HCl. Neutralization of the aqueous layer followed by extraction led ultimately to recovery of 1.15 g of unreacted *cis*-**17**. The ether layer was evaporated *in vacuo* and distilled to give 1.70 g (56%) of *cis*-**8**: bp 67–68° (2 mm); ir (neat) 5.75 μ (C=O); nmr (CCl_4) δ 2.40–1.31 (m, 12, CH_2 and CH), 1.12 (d, J = 6.5 Hz, 3, CH_3), and 1.04 (s, 3, CH_3).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.65; H, 10.68.

trans-**2,8-Dimethyl-1-hydrindanone (8).**—Similar hydrogenation of *trans*-**18** (2.0 g, 12 mmol) and hydrogenolysis of *trans*-**17** (3.75 g, 18 mmol) afforded *trans*-**8** in 85 and 46% yields, respectively, as a colorless oil: bp 63° (0.7 mm) and 67–68° (1 mm); ir (neat) 5.75 μ (C=O); nmr (CCl_4) δ 2.20–1.25 (m, 12, CH_2 and CH), 1.13 (d, J = 6.5 Hz, 3, CH_3), and 0.78 (s, 3, CH_3).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.37; H, 10.63.

cis-**2,8-Dimethyl-1-hydrindanone Oxime (9).**—A mixture of 2.0 g (12 mmol) of *cis*-**8**, 1.64 g (24 mmol) of $NH_2OH \cdot HCl$, 3.74 g of NaOAc, and 100 ml of 95% C_2H_5OH was refluxed for 7 hr. The solution was diluted with an equal volume of H_2O and cooled to precipitate crude *cis*-**9**. Several recrystallizations of this material from 95% C_2H_5OH afforded 0.55 g (25%) of *cis*-**9**: mp 114–116°; ir (KBr) 6.90 μ (C=N); nmr ($CDCl_3$) δ 9.75 (s, 1, OH), 3.20–2.60 (broad s, 1, CH_2 or CH), 1.44 (s, 11, CH_2 and CH), 1.40 (d, downfield peak hidden under band at δ 1.44, J = 6.5 Hz, 3, CH_3), and 1.18 (s, 3, CH_3).

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.72. Found: 72.85; H, 10.39; N, 7.48.

trans-**2,8-Dimethyl-1-hydrindanone Oxime (9).**—Similar treatment of *trans*-**8** (0.50 g, 3.0 mmol) with $NH_2OH \cdot HCl$ (0.41 g, 5.9 mmol) and NaOAc (0.94 g) in 25 ml of 95% C_2H_5OH ultimately afforded *trans*-**9** (0.25 g, 46%): mp 114–116° (from CH_3OH); ir (KBr) 6.83 μ (C=N); nmr ($CDCl_3$) δ 9.03 (s, 1, OH), 3.15–2.55 (m, 1), 2.10–1.37 (m, 11, CH_2 and CH), 1.30 (d, downfield peak partially obscured by band at CH_2 resonances, J = 6.5 Hz, 3, CH_3), and 0.93 (s, 3, CH_3).

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 73.18; H, 10.61; N, 7.69.

Beckmann Rearrangements.—The general procedure was as follows. Thionyl chloride (5–10 molar equiv) was added slowly to a solution of the oxime in anhydrous, freshly distilled dioxane at room temperature. The temperature of the resulting yellow solution rose 8–10°. After stirring for 10–20 min, the solution was decomposed with aqueous $NaHCO_3$ solution and extracted with $CHCl_3$ or ether. The extracts were dried (Na_2SO_4) and evaporated to dryness, leaving a residue that was recrystallized (solid) or distilled (liquid). Variations on isolation and purification procedure are noted under each oxime.

cis-**2** (2.0 g, 13 mmol), mp 97–99° (lit.[6] mp 100°), in 140 ml of dioxane and 5 ml (67 mmol) of $SOCl_2$ afforded crude *cis*-**3,4,4a,5,6,7,8,8a-octahydrocarbostyril** (**3**) as a crude solid after liquid–liquid extraction with ether for 48 hr. Recrystallization from acetone gave pure *cis*-**3**, mp 127–129° (lit.[12] mp 128–130°).

Similarly, *trans*-**2** (1.0 g 6.5 mmol), mp 145–147° (lit.[6] mp 146°), 70 ml of dioxane, and 2.5 ml (34 mmol) of $SOCl_2$ gave 0.66 g (33%) of *trans*-**3,4,4a,5,6,7,8,8a-octahydrocarbostyril** (**3**), mp 151.5–153° (from acetone) (lit.[13] mp 151°). After liquid–liquid extraction with ether and evaporation, the initial crude *trans*-**3** had been isolated as white crystals in a brown oil. This negligible amount of residual oil showed the presence of a nitrile and unreacted *trans*-**2**.

cis-**5** (2.0 g, 12 mmol), mp 85–87° (lit.[7] mp 85.5–87°), in 140 ml of dioxane and 4.5 ml (62 mmol) of $SOCl_2$ led after evaporation of the ether extract (liquid–liquid extractor) to a viscous brown residual oil. Vacuum distillation of this material afforded two fractions. Fraction i consisted of **3-(2-cyanoethyl)-2-methylcyclohexene** (**7**, 0.71 g, 40%): bp 57° (0.10 mm); ir (neat) 4.46 (C=N) and 6.10 μ (C=C); nmr (CCl_4) δ 4.61 (d, J = 6.5 Hz, 1, C=CH), 2.20–1.80 (m, 5, CH_2 and CH), 1.63 (s, 6, CH_2), and 2.29 (s, 3, CH_3).

Anal. Calcd for $C_{10}H_{15}N$: C, 80.48; H, 10.13; N, 9.38. Found: C, 80.47; H, 10.06; N, 9.23.

Fraction ii, bp 118–120° (0.15 mm), gave 0.80 g (40%) of a nearly colorless viscous oil which gradually crystallized on standing. Recrystallization of this material from ether gave *cis*-**8a-methyl-3,4,4a,5,6,7,8,8a-octahydrocarbostyril** (**6**): mp 82–84°; ir (KBr) 3.14 (NH) and 6.02 μ (C=O); nmr (CCl_4) δ 7.53 (s, 1, NH), 2.50–2.18 (m, 2, CH_2) 2.12–1.31 (m with sharp peak at 1.50, 11, CH_2 and CH) and 1.26 (s, 3, CH_3).

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.24; N, 8.37. Found: C, 72.00; H, 10.10; N, 8.60.

Similarly, *trans*-**5** (2.0 g, 12 mmol), mp 115–116° (lit.[7] mp 113–115°), in 140 ml of dioxane and 5 ml (67 mmol) of $SOCl_2$ gave, after evaporation of the $CHCl_3$ extracts, a residual brown oil from which crystals separated on standing. The crystals were filtered and washed with ether; the ether wash was slowly evaporated to yield an additional crop of crystals in a brown oil. The combined solids were recrystallized from acetone to give 0.75 g (37%) of *trans*-**8a-methyl-3,4,4a,5,6,7,8,8a-octahydrocarbostyril** (**6**): mp 150–152°; ir (KBr) 3.12 (NH), 6.01 and 6.15 μ (C=O); nmr (CCl_4) δ 9.20 (s, 1, NH), 2.40–2.10 (m, 2, CH_2), 1.90–1.35 (m, 11, CH_2 and CH), and 1.13 (s, 3, CH_3).

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.24; N, 8.37. Found: C, 71.82; H, 10.01; N, 8.62.

Fractional distillation of the brown oil afforded **7** (0.63 g, 35%) as a colorless oil, bp 71° (0.80 mm).

cis-**9** (1.0 g, 5.5 mmol) in 60 ml of dioxane and 4.0 ml (55 mmol) of $SOCl_2$ led, after evaporation of the $CHCl_3$ extracts, to an oil which gradually crystallized on standing. The filtered crystals were washed with cold ether and dried. Slow evaporation of the ether wash yielded an additional crop of crystals in a viscous oil. The combined solids were recrystallized from acetone to give 0.41 g (41%) of *cis*-**3,8a-dimethyl-3,4,4a,5,6,7,8,8a-octahydrocarbostyril** (**10**): mp 149–151°; ir (KBr) 3.12 (NH) and 6.01 μ (C=O); nmr (CCl_4) δ 8.10 (s, 1, NH), 2.40–1.90 (m, 1, CH), 1.85–1.40 (m, 11, CH_2 and CH), 1.30 (s, 3, CH_3), and 1.16 (d, J = 6.5 Hz, 3, CH_3).

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.72. Found: C, 72.71; H, 10.63; N, 7.48.

Fractional distillation [pot temperature 95–100° (1.2 mm)] of the viscous oil afforded 0.11 g (12%) of **3-(2-cyanopropyl)-2-methylcyclohexene** (**11**): ir (neat) 4.47 (C≡N) and 6.10 μ (C=C); nmr (CCl_4) δ 4.62 (d, J = 6.5 Hz, 1, =CH), 2.80–2.40 (m, 1, CH), 2.40–2.00 (m, 3, CH_3), 2.00–1.48 (m, 9, CH_2 and CH), and 1.30 (d, J = 6.5 Hz, 3, CH_3).

Anal. Calcd for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.58. Found: C 81.07; H, 10.62; N, 8.83.

Similar treatment of *trans*-**9** (1.0 g, 5.6 mmol) in 60 ml of dioxane and 4.0 ml (55 mmol) of $SOCl_2$ ultimately afforded 0.40 g (40%) of *trans*-**3,8a-dimethyl-3,4,4a,5,6,7,8,8a-octahydrocarbostyril** (**10**): mp 158–160° (from acetone); ir (KBr) 3.15 (NH), 6.00 and 6.23 μ (C=O); nmr ($CDCl_3$) δ 6.44 (s, 1, NH), 2.65–2.10 (m, 1, CH), 1.98–1.38 (m, 11, CH_2 and CH), 1.24 (d, upfield peak under CH_3 resonance, J = 6.5 Hz, 3, CH_3), and 1.16 (s, 3, CH_3).

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.72. Found: C, 72.60; H, 10.61; N, 7.71.

Fractional distillation of the oil [pot temperature 90–100° (0.8 mm)] afforded 0.15 g (17%) of a mixture (nmr) of **11** and **2-(2-cyanopropyl)methylcyclohexene** (**12**): ir (neat) 4.48 (C≡N) and 6.12 μ (C=C); nmr (CCl_4) δ 4.62 (d, J = 6.5 Hz, =CH), 2.40–1.79 (m, CH_3), 1.64 (s, CH_2), 1.30 (d, J = 6.5 Hz), and 1.25 (d, J = 6.5 Hz).

Oxime **14** (0.88 g, 2.8 mmol) in 35 ml of dioxane rearranged in 15 min with 1.0 ml (14 mmol) of $SOCl_2$. After decomposition with 100 ml of saturated aqueous $NaHCO_3$, the precipitate which formed was filtered and dried. Repeated recrystallization from CH_3OH gave 0.28 g (32%) of **16-methyl-17a-aza-*D*-homoestrone 3-methyl ether** (**15**): mp 212–214°; ir (KBr) 3.13 (NH) and 6.02 μ (C=O); nmr ($CDCl_3$) δ 7.21–6.71 (m, 3, aromatic), 6.32 (s, 1, NH), 3.75 (s, 3, OCH_3), 3.00–1.40 (m, 14, CH_2 and CH), 1.20 (d, upfield peak under CH_3 resonance, J = 6.5 Hz, 3, CH_3), and 1.15 (s, 3, CH_3).

Anal. Calcd for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.69; H, 8.64; N, 4.33.

Schmidt Reaction on *cis*- **and** *trans*-**8.**—Concentrated H_2SO_4 (5.6 ml) was added to a cooled (<10°), stirred solution of 2.0 g (12 mmol) of *cis*-**8** in 96 ml of anhydrous C_6H_6. Twenty milliliters of a solution of freshly prepared HN_3 [13 g (0.20 mol) of NaN_3, 13 ml of H_2O, 100 ml of C_6H_6, and 9.8 g (0.10 mol) of concentrated H_2SO_4] in benzene was added to the yellow solution over a 1-hr period. The temperature was maintained at 6–7° during addition and for 30 min more until N_2 evolution ceased. The reaction mixture was poured onto 300 ml of ice water and extracted with a large excess of $CHCl_3$. The combined organic extracts were successively washed with 2 *N* NaOH solution and H_2O and dried (Na_2SO_4). Filtration and evaporation of solvent *in vacuo* left a brown oil which crystallized on standing. The crystals were washed with cold ether and dried. Recrystallization from acetone (or CH_3OH) gave 0.58 g (27%) of *cis*-**3,8a-dimethyl-3,4,4a,5,6,7,8,8a-octahydroisocarbostyril** (**19**): mp 112–114°; ir (KBr) 3.14 (NH) and 6.04 μ (C=O); nmr ($CDCl_3$) δ 6.17 (s, 1, NH), 3.70–3.25 (broad mound, 1, CH), 2.26–1.37 (m, 11, CH_2 and CH), 1.28 (s, 3, CH_3), and 1.15 (d, J = 6.5 Hz, 3, CH_3).

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.72. Found: C, 72.30; H, 10.73; N, 7.76.

Some unidentified material (0.20 g, 10%) was isolated from the mother liquors.

Similar treatment of *trans*-**8** (2.0 g, 12 mmol) in 96 ml of benzene with 5.6 ml of concentrated H_2SO_4 and 20 ml of a freshly prepared solution of HN_3 in C_6H_6 provided 0.67 g (31%) of *trans*-**3,8a-dimethyl-3,4,4a,5,6,7,8,8a-octahydroisocarbostyril** (**19**): mp 121–123° (from acetone); ir (KBr) 3.13 (NH) and 6.05 μ (C=O);

nmr (CCl_4) δ 8.09 (s, 1, NH), 3.70–3.25 (broad mound, 1, CH), 1.60–1.30 (m, 11, CH_2 and CH), 1.18 (d, J = 6.5 Hz, 3, CH_3), and 1.08 (s, 3, CH_3).

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.72. Found: C, 72.76; H, 10.53; N, 7.84.

Registry No.—*cis*-**6**, 34387-94-5; *trans*-**6**, 34387-95-6; **7**, 34387-96-7; **8**, 34387-97-8; **9**, 34387-98-9; **10**, 34387-99-0; **11**, 34388-00-6; **14**, 34388-01-7; **15**, 34388-02-8; **17**, 34388-03-9; *cis*-**18**, 34388-04-0; *trans*-**18**, 34388-05-1; **19**, 34388-06-2.

Intramolecular Cyclization of *N*-Alkyl-3,3′,4,4′-tetrahydro-1,1′-biisoquinolinium Salts

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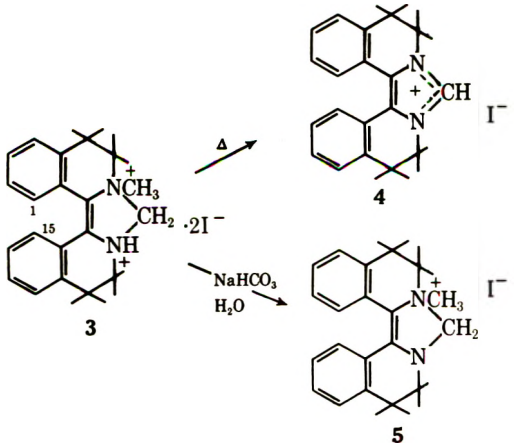
The preparation and chemiluminescence of 2,2′-dimethyl-3,3′,4,4′-tetrahydro-1,1′-biisoquinolinium diiodide (**1**) have recently been described.[1] Although 3,3′,4,4′-tetrahydro-1,1′-biisoquinoline (**2**) very readily forms a monomethiodide, its conversion to the dimethiodide requires more drastic reaction conditions. As a consequence, a competing, intramolecular cyclization, which will be described in this note, also occurs.

When **2** and excess methyl iodide were refluxed in acetonitrile for 18 hr, in addition to **1** (52% yield), there was recovered in approximately 10% yield an isomeric compound whose ^1H nmr spectrum and chemical behavior are consistent with those expected for 7-methyl-5,6,10,11-tetrahydro-8*H*-diisoquino[1,2-*c*:2′,1′-*e*]imidazolidiinium diiodide (**3**). The proton count on **3** indicated only one methyl group. The nmr spectrum was characterized by two other significant changes. One was the appearance of an AB quartet, which, although it is the chemical shift region assigned to 3 and 4 protons in 1,2-dihydroisoquinoline derivatives,[2] is due to the methylene in the imidazole ring, split because of the adjacent asymmetric nitrogen atom in the fused ring system. The other is a marked downfield shift of two of the aromatic ring protons, ascribed to an overlap of the 1,15 protons in the rigid, fused ring system of **3**.



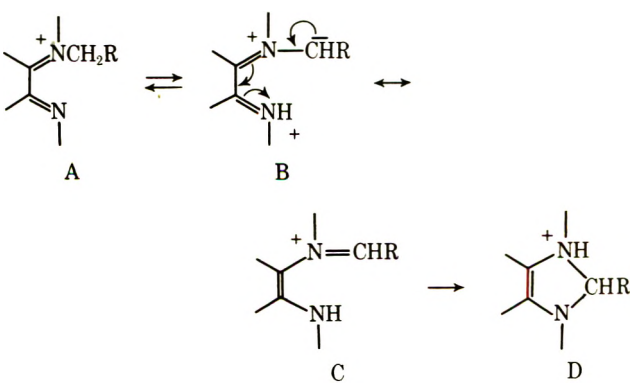
In **1**, rotation about the 1,1′ bond can still occur and the 8,8′ protons do not overlap.

When **3** was heated to 165–170°, both loss of methyl iodide and oxidation occurred to give 5,6,10,11-tetrahydrodiisoquino[1,2-*c*:2′,1′-*e*]imidazolium iodide (**4**). Its ^1H nmr spectrum (see Experimental Section) reflected these changes. Heating an aqueous solution of **3** with sodium bicarbonate yielded the monoquaternary salt **5**, whose nmr spectrum, except for one less proton, was the same as that for **3**.

It appears that the cyclization which leads to **3** can occur in either of two ways. (1) The monomethiodide of the 1,1′-biisoquinoline cyclizes intramolecularly and the resulting product is further methylated. (2) The dimethiodide **1** is first formed and then undergoes cyclization. There is evidence for both routes. For example, when preformed monomethiodide was refluxed in dry acetonitrile for various lengths of time, the proton nmr spectra on the recovered mixture of salts showed decreasing methyl signals, increasing signals characteristic of a methylene group, and the downfield shift of two aromatic protons as a consequence of the 1,15 proton overlap which develops as the fused ring system forms. Similarly, when 2-benzyl-3,3′,4,4′-tetrahydro-1,1′-biisoquinolinium bromide was refluxed in acetonitrile, the benzyl methylene signal disappeared; in addition the generally complicated nmr spectrum of the starting compound (because of unsymmetrical substitution) became simpler and more symmetrical as the cyclization occurred. One of the products recovered from this latter reaction was the 8-phenyl-5,6,10,11-tetrahydrodiisoquino[1,2-*c*:2′,1′-*e*]imidazolium salt (as the perchlorate).

When purified dimethiodide **1** was refluxed in methanol, ethanol, or 2-propanol, the dark red-orange colored solutions gradually faded. Although the recovered pale yellow product was a difficultly separable mixture, one compound isolated and identified was **5**.

2-Benzyl-1,1′-biisoquinolinium bromide remains essentially unchanged under conditions which effect the complete loss of the corresponding 3,3′,4,4′-tetrahydro compound. This fact suggests that the greater basicity of the 3,4-dihydroisoquinoline moiety over that of the unreduced isoquinoline is an important factor in the cyclization process. One possible route for cyclization of a monoalkyl salt is depicted in the following simplified scheme.



Abstraction of a proton from the alkyl group on A leads to the ylide B, which through charge redistribution gives the immonium salt C. Intramolecular addition of the nucleophile to the latter in a manner

(1) R. A. Henry and C. A. Heller, *J. Luminescence*, **4**, 105 (1971).

(2) J. L. Neumeyer, M. McCarthy, K. K. Weinhardt, and P. L. Levins, *J. Org. Chem.*, **33**, 2890 (1968).

analogous to the formation of pseudobases from isoquinolinium salts furnishes D. Although proton abstraction from A has been written here as an intramolecular process, it could occur equally well as an intermolecular one. Cyclization by a similar sequence would then give unprotonated D. Only the cis configuration has been shown for C, since it would be the form to cyclize; any trans isomer would through the equilibrium revert to B and ultimately back to *cis*-C.

This reaction scheme is similar to one proposed for the reduction of bisquaternary 1,1′-biisoquinolinium salts by base to air-reactive olefins.[1,3]

Experimental Section

7-Methyl-5,6,10,11-tetrahydro-8*H*-diisoquino[1,2-*c*:2′,1′-*e*]-imidazolidiinium Diiodide.—3,3′,4,4′-Tetrahydro-1,1′-biisoquinoline[1] (**2**, 5.2 g, 0.02 mol) and 8 ml of methyl iodide were refluxed in 100 ml of acetonitrile under a 0° condenser for 18 hr; after the solution had been chilled to 5°, the previously described,[1] dark red dimethiodide was removed, yield 5.7 g (52%).

Addition of ether to the above acetonitrile mother liquors and cooling gave 2.2 g of a mixture of materials. One of these (**3**), comprising about half of the mixture, was less soluble in 80% ethanol than either the monomethiodide or the dimethiodide (both of which were also present) and after several recrystallizations was obtained as pale purple needles with an orange-red hue. The melting point was very indefinite; partial melting, then resolidification at 160–165° with a change in color from purple to pale yellow. (This new solid decomposed at 240–265°.) When plunged into a hot bath at 190–195°, it completely melted; if plunged into a bath at 165°, it partially melted before resolidifying (see following experiment). This compound in methanol did not chemiluminesce in air when made basic: nmr (DMSO-d_6) τ 6.56 (s, 3, $-NCH_3$), 6.4–7.7 (m, 7), 5.8–6.3 (m, 2, H_6, H_6), 5.22 (d, 1, J = 7.0 Hz, H_8), 4.75 (d, 1, J = 7.0 Hz, H_8), 2.57–2.97 (m, 6, H_2, H_3, H_4, H_{12}, H_{13}, H_{14}), 2.10–2.57 (m, 2, H_1, H_{15}).

Anal. Calcd for $C_{20}H_{22}N_2I_2$: C, 44.15; H, 4.07; N, 5.15; I, 46.64. Found: C, 44.38; H, 3.80; N, 5.10; I, 46.75.

When some of **3** was dissolved in a minimum volume of boiling water and treated with excess sodium bicarbonate, cooling gave a pale yellow solid **5**. Recrystallization from water furnished coarse yellow needles or prisms, mp 177–178° dec; an aqueous solution had an intense blue fluorescence. The ^1H nmr spectrum in DMSO-d_6 was almost identical with that for **3** except that the total proton count was one less. Surprisingly, a mass spectrum showed a small parent peak, m/e 416, with the base peak at m/e 290. The presence of a parent peak suggests opening of the imidazole ring by the nucleophile, iodide ion, to give an iodomethylene derivative.

Anal. Calcd for $C_{20}H_{21}N_2I$: C, 57.70; H, 5.08; N, 6.73; I, 30.49. Found: C, 57.85, 57.80; H, 5.03, 5.08; N, 6.62, 6.73; I, 30.64, 30.35.

The monopicrate from **5** melted at 170–171° after two recrystallizations from absolute ethanol.

Anal. Calcd for $C_{26}H_{23}N_5O_7$: N, 13.53. Found: N, 13.61.

Decomposition of 3.—When **3** was heated for 10 min at 155–165°, there was a 22% loss in weight (theory, 26% for one CH_3I); further heating caused very little more loss. Even when heated at 94° (25 mm) there was an 18% loss of weight in 5 days. The crude product decomposed at 240–260°. Recrystallization from 2-propanol gave yellow blades of 5,6,10,11-tetrahydroiisoquino[1,2-*c*:2′,1′-*e*]imidazolium iodide (**4**): mp 296–298° dec; nmr (DMSO-d_6) τ 6.83 (t, 4, J = 6.0 Hz, H_5, H_{11}), 5.67 (t, 4, J = 6.0 Hz, H_6, H_{10}), 2.5–2.9 (m, 6, H_2 H_3, H_4, H_{12}, H_{13}, H_{14}), 2.05–2.36 (m, 2, H_1, H_{15}), 0.70 (s, 1, CH in imidazolium ring, H_8).

Anal. Calcd for $C_{19}H_{17}N_2I$: C, 57.01; H, 4.28; N, 7.00; I, 31.71. Found: C, 56.80; H, 4.36; N, 6.93; I, 32.10.

The picrate decomposed at 241–242°.

Anal. Calcd for $C_{25}H_{19}N_5O_7$: N, 13.97. Found: N, 14.00.

Decomposition of 1 in Methanol.—A solution of 0.86 g of 1 in 100 ml of absolute methanol was refluxed for 26.5 hr while protected from moisture. The initially dark red-orange solution became pale orange in color. Cooling for 2 days at 5° deposited 0.36 g of starting compound, mp 208–209° dec; an additional 0.15 g was recovered by evaporating the mother liquors to 20 ml and cooling. Further evaporation to 4–5 ml and cooling gave a mixture of 1 and yellow needles, mp *ca.* 150°, which were separated mechanically. Additional amounts of the latter compound can be isolated by reworking the mother liquors. Recrystallization from 2-propanol gave pale yellow needles, mp 166–167°; the ^1H nmr indicated a mono-2-propanolate. A sample was desolvated at 70° (25 mm) for 24 hr prior to analysis. The nmr spectrum and the analytical data agree with those for **5**.

Anal. Calcd for $C_{20}H_{21}N_2I$: C, 57.70; H, 5.08; N, 6.73; I, 30.49. Found: C, 57.46; H, 5.05; N, 6.67; I, 30.56.

5,6,10,11-Tetrahydro-8-phenyldiisoquino[1,2-*c*:2′,1′-*e*]-imidazolium Perchlorate.—2-Benzyl-3,3′,4,4′-tetrahydro-1,1′-biisoquinolinium bromide[1,4] (0.76 g) in 25 ml of acetonitrile was refluxed for 72 hr. The cooled solution was diluted with a large volume of ether to precipitate a hygroscopic, amorphous solid which was filtered and dried, mp 110–150°; the ^1H nmr spectrum in either $CDCl_3$ or DMSO-d_6 revealed the complete disappearance of the benzyl methylene signal. Since attempts to recrystallize this product were unsatisfactory, it was dissolved in a small volume of water, filtered from insoluble material, and converted to the perchlorate by adding excess sodium perchlorate. This salt, when dry, was easily recrystallized from 2-propanol. The cream-colored crystals turned dark at *ca.* 270° and decomposed at 283–285°: nmr ($CDCl_3$) τ 6.87 (t, 4, J = 6.5 Hz, H_5, H_{11}), 5.83 (t, 4, J = 6.5 Hz, H_6, H_{10}), 2.60 (s, 5, phenyl), 2.16–2.70 (m, 6, H_2, H_3, H_4, H_{12}, H_{13}, H_{14}), 1.94–2.16 (m, 2, H_1, H_{15}).

Anal. Calcd for $C_{25}H_{21}ClN_2O_4$: Cl, 7.89; N, 6.24. Found: Cl, 7.50; N, 6.11.

2-Benzyl-1,1′-biisoquinolinium Bromide.—1,1′-Biisoquinoline (0.6 g) and benzyl bromide (0.4 g) (equimolar ratio) in 10 ml of dry acetonitrile stood at room temperature for 6 days. The former compound gradually dissolved as benzylation occurred. Addition of ether precipitated the monoquaternary salt, which was recrystallized twice from 2-propanol as needles, mp 136–137° dec. The nmr spectrum indicated one propanol of crystallization. The desolvated compound decomposed at 195–197°: nmr (DMSO-d_6) τ 4.18 (s, 2, benzyl CH_2), 2.35–3.22 (complex multiplet, 9, benzyl C_6H_5, H_5', H_6', H_7', H_8'), 2.67 (d, 1, J = 7.0 Hz, H_5), 2.14 (t, 1, J = 7.0 Hz, H_6), 1.73 (t, 1, J = 7.0 Hz, H_7), 1.64 (d, 1, J = 5.5 Hz, H_4'), 1.37 (d, 1, J = 7.0 Hz, H_8), 1.11 (d, 1, J = 5.5 Hz, H_3'), 0.97 (d, 1, J = 7.0 Hz, H_4), 0.62 (d, 1, J = 7.0 Hz, H_3).

Anal. Calcd for $C_{25}H_{19}BrN_2 \cdot C_3H_8O$: C, 68.99; H, 5.58; Br, 16.39; N, 5.75. Found: C, 69.11; H, 5.40; Br, 16.55; N, 5.77.

Refluxing some of the desolvated salt in dry acetonitrile for 72 hr caused no change; the recovered product melted at 194.5–196° and its nmr spectrum was the same as that of the starting material.

Registry No.—**1**, 34414-11-4; **3**, 34410-07-6; **4**, 34414-12-5; **4** monopicrate, 34414-13-6; **5**, 34414-14-7; **5** monopicrate, 34414-15-8; 5,6,10,11-tetrahydro-8-phenyldiisoquino[1,2-*c*:2′,1′-*e*]imidazolium perchlorate, 34414-16-9; 2-benzyl-1,1′-biisoquinolinium bromide, 34414-17-0.

(3) C. A. Heller and R. A. Henry, unpublished work.

(4) Nmr (DMSO-d_6) τ 6.90 (t, 2, J = 7.5 Hz, H_4'), 6.25–6.72 (m, 2, H_{4eq}, H_{4ax}), 6.10 (t, 1, J = 10.0 Hz, H_{3ax}), 5.82 (doubled triplet, 2, J_t = 7.5 Hz, J_d = 3.0 Hz, H_3'), 5.60 (m, 1, H_{3eq}), 4.55 (s, 2, benzyl CH_2), 2.08–2.70 (m, 5, benzyl C_6H_5).

An Improved Synthesis of *N*-Amino Imides

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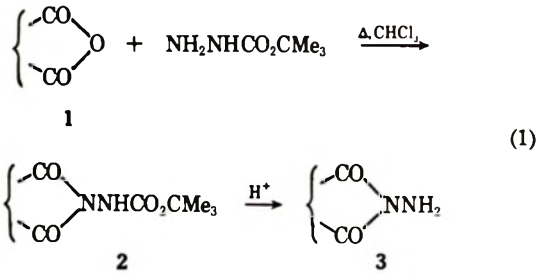
Depending upon reaction conditions, the reaction of five-membered ring anhydrides with hydrazine can proceed with formation of the cyclic hydrazide, the bis-

hydrazide, the *N*-amino imide, or a mixture of these.[1] Of these products the *N*-amino imide is often the most difficult to obtain. Employing *tert*-butyl carbazate, we have developed a procedure which provides the *N*-amino imide from each of the cyclic anhydrides examined thus far. The series of reactions in generalized form is shown in eq 1.[2] Overall yields are in the range

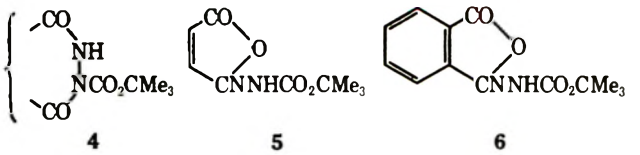


(1)

of 40–80%, and purification of the *N*-*tert*-butyloxycarbonyl amino derivatives **2** is unnecessary for conversion to the *N*-amino imides **3**.

N-Amino imides prepared by this procedure include the *N*-amino derivatives of succinimide **3a**, maleimide **3b**, phthalimide **3c**, *cis*-1,2-cyclohexanedicarboximide **3d**, 3,4-dihydro-1,2-naphthalenedicarboximide **3e**, and 1,2-naphthalenedicarboximide **3f**. The *N*-amino imides **3a–d** had physical properties identical with the literature values. The compounds **3e** and **3f** are new and were characterized by their isomerization to the corresponding cyclic hydrazides which are known[1a] and by their ir spectra. The coupled carbonyl absorptions observed at 1705 and 1760 cm^{-1} for **3e** and at 1720 and 1770 cm^{-1} for **3f** are characteristic of *N*-amino maleimides.[1a]

Proof of the structures for **2a–f** as formulated in eq 1 rather then structures of the type **4** includes the fact that all carbonyl absorptions are above 1700 cm^{-1}. This indicates five-membered rather than six-membered lactam rings, for which carbonyl positions are characteristically in the range 1650–1670 cm^{-1}.[1a] Isomaleimide structures of the type **5** are also untenable in view of the uv spectra of **2b**, **2c**, **2e**, **2f**, **3e**, and **3f**. Maleimides are known to absorb in the uv at about 220 (log ϵ 4–4.25) and 300 nm (log ϵ 2.7), while isomaleimides absorb at 300 nm (log ϵ 4.3).[3] All of the compounds in question have intense uv absorption between 217 and 229 nm (log ϵ 4–4.5) and weak absorption at 300 nm (log ϵ 3.4) and, in this respect, resemble the maleimides. The structure of **2c** is certainly not of the isomaleimide type, since this specific compound **6** has been reported,[2] and the reported melting point of **6** is 55° lower than our observed melting point for **2c**.



We feel that the method outlined in eq 1 will prove to be generally applicable for the conversion of five-membered ring anhydrides to *N*-amino imides, thereby obviating the difficulties normally encountered in their preparation from the anhydride and hydrazine.

Experimental Section

Infrared spectra were recorded in Nujol; ultraviolet spectra were recorded in 95% ethanol.

N-**Aminosuccinimide** (**3a**).—Succinic anhydride (0.01 mol) and *tert*-butyl carbazate (0.01 mol) were dissolved in 15 ml of chloroform. The solution was refluxed for 3 hr, and the solvent was evaporated *in vacuo* to leave an oil, ir 1720 cm^{-1}, which was dissolved in 5 ml of methanol without purification. The solution was cooled to 5°, and a slow stream of anhydrous hydrogen chloride was passed into the solution for 10 min. The resulting mixture was left to stand at 20° for 2 hr and diluted with 20 ml of ether. The solid was filtered at the pump and treated with 10 ml of an anhydrous solution of ammonia in methanol. The precipitated NH_4Cl was removed by filtration, and the filtrate was evaporated to dryness to yield 0.9 g (80%) of **3a**, which was identified as the diacetate, mp 73–74° (lit.[4] mp 70–72°).

N-**Aminomaleimide** (**3b**).—This compound was prepared as described above from maleic anhydride and was isolated in 75% yield as the hydrochloride salt, mp 145–148° (lit.[5] mp 150°). As before, the residue resulting upon evaporation of the chloroform was an oil which was not purified before treatment with HCl–methanol. This oil had ir 1700 cm^{-1}, uv 220 nm (log ϵ 4.15).

N-*tert*-**Butyloxycarbonylaminophthalimide** (**2c**).—This compound was prepared from phthalic anhydride as described above in 85% yield: mp 185–186° (ethanol); ir 1710 and 1780 cm^{-1}; uv 220 nm (log ϵ 4.49) and 295 (3.45).

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.69. Found: C, 59.45; H, 5.31; N, 10.80.

N-**Aminophthalimide** (**3c**).—The entire product **2c** from above was treated with HCl–methanol to obtain the hydrochloride salt of **3c**, which was converted to the free imide upon treatment with aqueous $NaHCO_3$ in 95% yield: mp 200–205°, solidifies and remelts at 338–340° (lit.[6] mp 200–205°, solidifies and remelts at 340°); ir 1715 and 1775 cm^{-1}; uv 222 nm (log ϵ 4.49) and 298 (3.38).

cis-*N*-**Amino-1,2-cyclohexanedicarboximide** (**3d**).—The compound **2d**, which resulted upon reaction of *tert*-butyl carbazate and *cis*-1,2-cyclohexanedicarboxylic acid anhydride, was obtained as a gummy material which was not characterized except for its ir spectrum, 1715 and 1785 cm^{-1}. Successive treatment of **2d** with HCl–methanol and NH_3–methanol as described above gave **3d** in 85% yield, mp 60–63° (lit.[1c,7] mp 63–64°).

N-*tert*-**Butyloxycarbonylamino-3,4-dihydro-1,2-naphthalenedicarboximide** (**2e**).—This compound was prepared from the corresponding anhydride as described above in 90% yield: mp 172–173° (benzene–hexane); ir 1730 and 1780 cm^{-1}; uv 229 nm (log ϵ 4.19) and 365 (3.60).

Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.77; N, 8.91. Found: C, 65.17; H, 6.09; N, 8.84.

N-**Amino-3,4-dihydro-1,2-naphthalenedicarboximide** (**3e**).—The product **2e** was treated with 10 ml of hydrofluoric acid at 40° until gas evolution ceased. The solution was poured into ice–water, and the solid was filtered at the pump, washed with aqueous $NaHCO_3$ solution, and air dried to give **3e** (70%): mp 156–158°; ir 1705 and 1760 cm^{-1}; uv 234 nm (log ϵ 4.0) and 374 (3.43).

Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.70; N, 13.08. Found: C, 67.01; H, 4.82; N, 12.90.

Compound **3e** was further characterized by its isomerization in refluxing *n*-butyl alcohol to the corresponding cyclic hydrazide, mp 230–234° (lit.[1a] mp 231–232°).

N-*tert*-**Butyloxycarbonylamino-1,2-naphthalenedicarboximide** (**2f**).—This compound was prepared from the corresponding anhydride in 90% yield: mp 207–209° (benzene–hexane); ir

(1) (a) F. G. Baddar, M. F. El-Newaihy, and M. R. Salem, *J. Chem. Soc. C*, 716 (1971); (b) H. Feuer, G. B. Bachman, and E. H. White, *J. Amer. Chem. Soc.*, **73**, 4716 (1951); (c) E. Grovenstein, D. V. Rao, and J. W. Taylor, *ibid.*, **83**, 1705 (1961).

(2) A similar but less convenient procedure utilizing benzyl carbazate in place of *tert*-butyl carbazate has been reported by L. A. Carpino, *J. Amer. Chem. Soc.*, **79**, 98 (1957).

(3) E. Hedaya, R. L. Hinman, and S. Theodoropulos, *J. Org. Chem.*, **31**, 1311 (1966).

(4) Th. Curtius, *J. Prakt. Chem.*, **92**, 80 (1915).

(5) H. Hinterbauer, Austrian Patent 176,563 (Nov 10, 1953).

(6) H. D. K. Drew and H. H. Hatt, *J. Chem. Soc.*, 16 (1937).

(7) M. Ishikawa, M. Fujimoto M. Sakai, and A. Matsumoto, *Chem. Pharm. Bull.*, **16** (4), 618 (1968).

1735 and 1785 cm^{-1}; uv 217 nm (log ϵ 4.47), 258 (4.47), and 345 (3.43).

Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.28; H, 5.23; N, 9.05.

N-Amino-1,2-naphthalenedicarboximide (3f).—This compound was prepared from 2f by the same method used for preparation of 3e. The yield was 80% for 3f: mp 196–197°; ir 1720 and 1770 cm^{-1}; uv 218 nm (log ϵ 4.59), 258 (4.51), and 346 (3.32).

Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.98; H, 3.81; N, 13.32.

Compound 3f was further characterized by its isomerization in refluxing *n*-butyl alcohol to the corresponding cyclic hydrazide, mp 332–335° (lit.[1a] mp 340°).

Registry No.—2c, 34387-89-8; 2e, 34387-90-1; 2f, 34387-91-2; 3e, 34387-92-3; 3f, 34387-93-4.

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Hydrogen Abstraction from Arylmethanes by Bromine Atom

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An excellent correlation of the relative rates of hydrogen abstraction from a series of arylmethanes by the trichloromethyl radical with the change in SCF–π-binding energies between the incipient radicals and the arylmethanes recently has been reported.[2] No such correlation was found for abstraction by *tert*-butoxy radical.[2] Unruh and Gleicher[2] interpret this as evidence that the transition state for hydrogen abstraction by the trichloromethyl radical must strongly resemble the intermediate free radical while that for abstraction by *tert*-butoxy radical probably has a structure between the reactant and the intermediate. We wish to report a similar study in which bromine atom is the abstracting species.

Competitive brominations were carried out at 75.5° using standard techniques.[3] Analysis of the resulting arylmethyl bromides was done by nmr techniques so that ring substitution in arenes by bromine atom was not an analytical problem. The results are reported in Table I. Unfortunately, 2-methylanthracene, 9-methylanthracene, and 1-methylpyrene did not afford benzylic bromination but rather a rapid ring substitution reaction. As a result, the kinetic results have a spread of only about six.

Table I
Relative Rates of Hydrogen Abstraction by Bromine in Benzene at 75°

Arylmethane	No. of expt	k/k_0[a]
Toluene		(1.00)
2-Methylphenanthrene	3	2.03 ± 0.03
2-Methylnaphthalene	3	2.72 ± 0.01
3-Methylphenanthrene	6	3.19 ± 0.32
1-Methylphenanthrene	3	4.00 ± 0.13
1-Methylnaphthalene	3	5.69 ± 0.05

[a] Experimental error represents average deviation of the number of experiments shown.

Table II
Correlations of the Relative Rates of Hydrogen Abstraction from Unsubstituted Arylmethanes by Bromine Atom with Various Molecular Orbital Parameters

Parameter	Correlation coefficient
HMO charge density	0.947
SCF ΔE_π[a]	0.935
SCF charge density	0.934
HMO free valence	0.899
HMO ΔE_π	0.898

[a] Values taken from ref 2.

Correlation of the natural logarithms of the relative rates of hydrogen abstraction with some calculated molecular orbital parameters are shown in Table II. While none of the correlations are as excellent as that obtained by Unruh and Gleicher[2] for trichloromethyl radical with SCF ΔE_π, it is interesting to note that all are good. Charge density calculations[4] were made using an arylmethyl cation as a model and the correlation was made with charge density at the methyl carbon atom. It is not clear what such a correlation represents, especially from the somewhat surprising result that the Hückel method gives better results than does the SCF approach. One is tempted to explain the correlation with charge density on the basis of the suggestion of Russell and Williamson[5] of stabilization of the transition state by a significant contribution of a polar canonical structure I. On the basis of the rather good

$$ArCH_2H\cdot X \longleftrightarrow \underset{I}{Ar\dot{C}H_2\overset{+}{H}X^-} \longleftrightarrow ArCH_2\dot{H}\text{-}X$$

correlation with the SCF ΔE_π parameter and the interpretation given to such a correlation by Unruh and Gleicher,[2] the transition state for the hydrogen abstraction by bromine atom must strongly resemble the radical intermediate.

Experimental Section

All methylarenes were commercially available. Toluene and benzene were distilled as constant-boiling heart cuts.

Brominations were run at 75.5° in a 50-ml, three-necked flask fitted with a nitrogen bubbling tube, a water condenser, and an addition funnel. Hydrocarbons to be studied were weighed into the flask and benzene was added so that the total initial concentration was about 0.2 *M*. After the flask was placed in the constant-temperature bath the solution was degassed with bubbling nitrogen. A benzene solution of bromine was added slowly with irradiation of the solution with 275-W Sylvania sunlamp. The rate of addition was adjusted so that the reacting solution remained nearly colorless. Evolved hydrogen bromide was entrained by bubbling nitrogen through the solution, which also served to agitate the solution. Upon completion of the reaction, about 15 min, the mixtures were reduced to a volume of approximately 2 ml on a rotary evaporator at room temperature and 80–140 mm pressure. Ethylene dichloride was weighed into the concentrated solution as a standard and the arylmethyl

(1) (a) National Science Foundation, COSIP participant; (b) National Science Foundation, URP participant.

(2) J. D. Unruh and G. J. Gleicher, *J. Amer. Chem. Soc.*, **93**, 2008 (1971).

(3) R. D. Gilliom and B. F. Ward, Jr., *ibid.*, **87**, 3944 (1965).

(4) HMO calculations were made utilizing the program of J. R. Howles and R. D. Gilliom, "Huckel," Program 132, Quantum Chemistry Program Exchange, Indiana University. SCF charge density calculations were made using J. E. Bloor and B. R. Gilson, "SCFCIO-Closed-Shell SCF-LCAO-MO," Program 71.2, Quantum Chemistry Program Exchange, Indiana University, rewritten in SPS for calculations on an IBM 1620-40K.

(5) G. A. Russell and R. C. Williamson, Jr., *J. Amer. Chem. Soc.* **86**, 2357 (1964).

bromides were quantitatively analyzed by integration on a Varian HA-60IL nmr spectrometer. Each integration was performed at least ten times. Reactions were run with varying quantities of bromine to ensure consistent results. Relative rate constants were calculated using the standard equation[3]

$$k/k_0 = \ln [(A_0 - X)/A_0]/\ln [(T_0 - Y)/T_0]$$

where A_0 and T_0 are initial moles of hydrocarbon and toluene and X and Y are the corresponding moles of bromides obtained upon completion of the reaction. No reaction was carried beyond consumption of 30% of the methylarenes.

Registry No.—Hydrogen, 1333-74-0; bromine, 7726-95-6; 2-methylphenanthrene, 2531-84-2; 2-methylnaphthalene, 91-57-6; 3-methylphenanthrene, 832-71-3; 1-methylphenanthrene, 832-69-9; 1-methylnaphthalene, 90-12-0.

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Reductive Conversion of 1-Aryl-3-hydroxymethyl-3,4-dihydro-2-naphthoic Acid Lactones into Substituted Tetrahydro-1*H*-cyclopropa[*a*]naphthalenes[1a]

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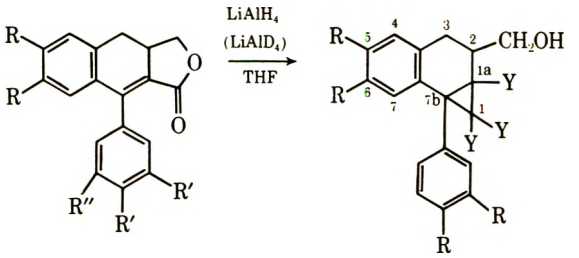
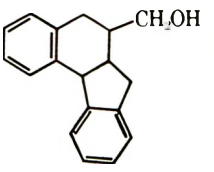
The ease of synthesis of cyclolignan lactones of the 3,4-dihydronaphthalene type **1** by means of the intramolecular Diels–Alder reaction[2,3] prompted us to investigate the formation of reduction products of **1**. Cis and trans addition of hydrogen to the α,β-unsaturated lactone system of γ-apopicropodophyllin (**1c**) by means of catalytic[4] and electrochemical[3] processes, respectively, have been described previously. We now report the chemical reduction of **1a** and **1b** by means of excess lithium aluminum hydride in tetrahydrofuran.

Isolated from the chemical reduction of **1a** was a crystalline product A, molecular formula $C_{18}H_{18}O$, in 70% yield. The infrared spectrum of A indicated the presence of an alcoholic OH group. The mass spectrum showed prominent peaks at m/e values of 250 $(M)\cdot^+$, 232 $(M - H_2O)\cdot^+$, and 219 $(M - CH_2OH)^+$. A was readily converted into a crystalline monoacetate and a crystalline monotosylate. The absence of an alkenic double bond in A was apparent from chemical

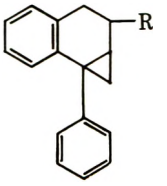


1a, R = R′ = R″ = H
b, R = R′ = CH_3O; R″ = H
c, R = OCH_2O; R′ = R″ = CH_3O

2a, R = H; Y = H
b, R = H; Y = D
c, R = CH_3O; Y = H



3



4a, R = H
b, R = CH_2OAc
c, R = CH_2OTs
d, R = CH_3

tests on the acetate, the failure of A to absorb hydrogen in the presence of Pd/C at room temperature and pressure, and the relatively low extinction coefficient of the acetate (ϵ_{244} 1540, ϵ_{282} 160) compared to that of styrene (ϵ_{244}^{max} 12,000, ϵ_{282}^{max} 450)[5] in the wavelength range of 240–285 nm. A Kuhn–Roth determination on A showed no *C*-methyl group. Two structures, **2a** and **3**, seemed plausible on the basis of these data, though the former was preferred because of precedent for reduction of cinnamate esters to phenylcyclopropane[6] under conditions similar to those used on **1a**.

Careful integration of the pmr spectrum of A showed the presence of equal numbers of aromatic and aliphatic protons—a situation consistent with structure **2a** but not with **3**. However, the signal at highest field consisted of a multiplet for three protons at δ 1.1–1.7 (Figure 1), considerably downfield from the value of *ca.* 0.2 expected for protons in a cyclopropane ring magnetically unperturbed by the molecular environment.[7] The pmr spectra of A acetate and A tosylate also exhibited similar multiplets. Reduction of **1a** with lithium aluminum deuteride gave trideuterated A, a compound which showed almost exactly the same pmr spectrum as A itself, except for the absence of the high-field multiplet. Construction of a Stuart–Briegleb molecular model of **2a** indicated that protons at C-1 and C-1a should lie in the deshielding zone of the aromatic rings, and hence might be subject to the observed downfield shift.[8] On this basis the structures of A, its acetate, its tosylate, and its trideuterio derivative were assigned as **2a**, **4b**, **4c** and **2b**, respectively (where the stereochemical relationship between substituents at C-1a and C-2 remains undetermined).

(1) (a) This investigation was supported by Research Grants No. CY-3097 from the National Cancer Institute and No. GM 12730 from the National Institute of General Medical Sciences, U. S. Public Health Service. (b) Research Assistant, 1962–1964. (c) Research Associate, 1966–1967. (d) Research Associate, 1969–1970. (e) On leave from the Department of Chemistry, Weizmann Institute of Science, Rehovoth, Israel, 1964–1969. (f) Research Assistant, 1970–1971.

(2) L. H. Klemm, K. W. Gopinath, D. H. Lee, F. W. Kelly, E. Trod, and T. M. McGuire, *Tetrahedron*, **22**, 1797 (1966); L. H. Klemm, D. H. Lee, K. W. Gopinath, and C. E. Klopfenstein, *J. Org. Chem.*, **31**, 2376 (1966); L. H. Klemm and P. S. Santhanam, *ibid.*, **33**, 1268 (1968).

(3) L. H. Klemm, D. R. Olson, and D. V. White, *ibid.*, **36**, 3740 (1971).

(4) A. W. Schrecker and J. L. Hartwell, *J. Amer. Chem. Soc.*, **75**, 5916 (1953).

(5) A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," Edward Arnold, London, 1960, p 141.

(6) M. J. Jorgensen and A. W. Friend, *J. Amer. Chem. Soc.*, **87**, 1815 (1965); R. T. Uyeda and D. J. Cram, *J. Org. Chem.*, **30**, 2083 (1965); E. I. Snyder, *ibid.*, **32**, 3531 (1967).

(7) K. B. Wiberg and B. J. Nist, *J. Amer. Chem. Soc.*, **83**, 1226 (1961).

(8) *Cf.* the pmr spectrum of 1-methyl-2,2-diphenylcyclopropane [H. M. Walborsky and A. E. Young, *J. Amer. Chem. Soc.*, **86**, 3288 (1964); J. N. Pierce and H. M. Walborsky, *J. Org. Chem.*, **33**, 1962 (1968)] which shows a complexity of signals for three cyclopropane protons at δ 1.00–1.83 in CCl_4.

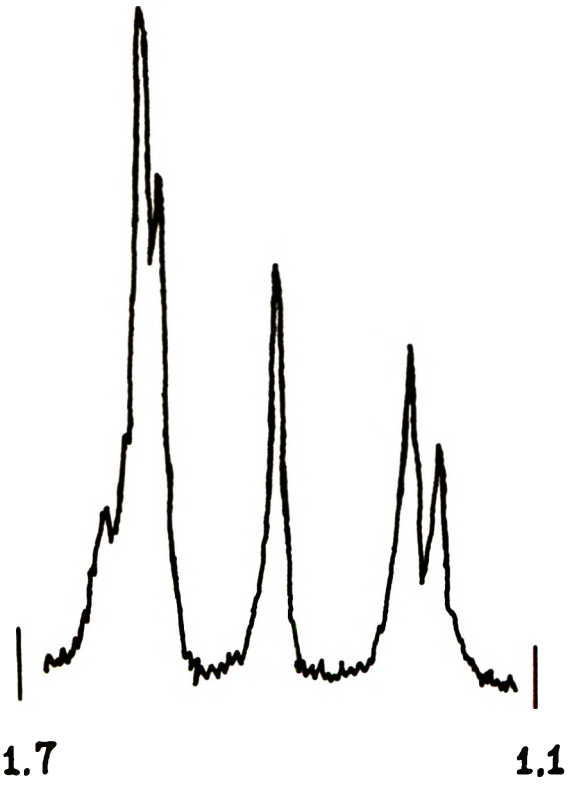


Figure 1.—Pmr spectrum for protons on the cyclopropane ring of 2a; solvent $CDCl_3$.

To confirm these assignments the model compound **4a** was synthesized by means of Simmons–Smith methylenation of the known 1-phenyl-3,4-dihydronaphthalene.[9] This compound also exhibited a three-proton multiplet at δ 1.1–1.6 and gave negative tests for alkenic unsaturation. Further structural confirmation was obtained from examination of the infrared spectra of **2a**, **4a** and **4b**, especially in the short-wavelength region. Thus, each of these three compounds showed an absorption band at 1.635 μ for cyclopropyl C–H stretching,[10] while the deuterated compound **2b** did not absorb in this region.

In extensions of these studies, tosylate **4c** was reduced by means of lithium aluminum hydride to hydrocarbon **4d** and the tetramethoxycyclolignan lactone **1b** was converted into the benzonorcarene derivative **2c**. Compound **2c** likewise showed a multiplet at δ 0.9–1.5 and an absorption band at 1.645 μ. Its mass spectrum exhibited prominent peaks at *m/e* 151 $[(CH_3O)_2C_7H_5]^+$, 339 (M − CH_3O or M − CH_2OH)$^+$, and 370 (M)$\cdot^+$.

Experimental Section[11]

7b-Phenyl-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene (4a).—To the mixture which resulted from stirring 1.4 g of zinc–copper couple (Alfa Inorganics), 8 ml of ether, and a crystal of iodine[12] was added dropwise a mixture of 4 g of 1-phenyl-3,4-dihydronaphthalene,[9] 2 ml of methylene iodide, and 10 ml of ether. The reaction mixture was refluxed, with stirring, for 24 hr and filtered. The ether layer plus washings of the solid residue was dried (Na_2SO_4) and distilled to give a viscous liquid, bp 128–134° (0.8 mm), separated into nearly equal parts of starting hydrocarbon and product **4a** by means of vpc at 185° with a stationary phase of 10% silicone DC-550 on 60–80 mesh Chromosorb W. Repetitive vpc gave an analytically pure sample of **4a**: negative permanganate test, inert to a mixture of 5% Pd/C and hydrogen gas at room temperature and pressure; pmr δ 1.1–1.6 (m, 3, H-1a plus 2 H-1), 2.0–2.9 (m, 4, 2 H-2 plus 2 H-3), 6.6–7.3 (m, 9, aromatic protons, including a five-proton singlet at δ 7.25 for the phenyl group); mass spectrum *m/e* 220 (M, 100%).

Anal. Calcd for $C_{17}H_{16}$: C, 92.68; H, 7.32. Found: C, 92.55; H, 7.58.

2-Hydroxymethyl-7b-phenyl-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene (2a).—To a stirred slurry of 0.8 g (21 mmol) of lithium aluminum hydride in 30 ml of tetrahydrofuran was slowly added a solution of 1.2 g (4.6 mmol) of 1-phenyl-3-hydroxymethyl-3,4-dihydro-2-naphthoic acid lactone (**1a**)[3] in 30 ml of the same solvent. The mixture became warm and developed a red-brown color, which disappeared in 30 min. The mixture was refluxed for 3 hr, cooled, and treated first with 1:1 (v/v) ether–EtOAc and then with water. The organic layer, plus ether extracts of the aqueous phase, was dried (Na_2SO_4) and evaporated to give a liquid, which crystallized from ether–petroleum ether (bp 30–60°) as prisms: mp 97–98°; yield 0.8 g (70%); pmr δ 1.1–1.7 (m, 3, H-1a plus 2 H-1),[13] 2.17 (s, 1, disappears on shaking with D_2O, OH), 2.24–2.63 (m, 1, H-2), 2.73 (d, 2, J = 5 Hz, 2 H-3), 3.51 and 3.62 (2 overlapping d of d, 2 total, AB portion of ABX system, J_{AB} = −10.5 Hz, a' = 3.2 Hz, a = 2.3 Hz, CH_2OH),[14] 6.5–7.2 (m, 4, H-4 to H-7), 7.27 (s, 5, phenyl group); ir ($CHCl_3$) 3460 and 3620 cm^{-1} (OH); mass spectrum[15] *m/e* (rel intensity) 250 (M, 47), 232 (36), 231 (30), 219 (100).

Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25; *C*-methyl, none. Found:[16] C, 86.00; H, 7.12; *C*-methyl, none.

2-Hydroxymethyl-7b-phenyl-1,1,1a-trideuterio-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene (2b).—Reaction of lithium aluminum deuteride with **1a** in the preceding manner gave a liquid, purified by evaporative distillation at 150° (0.1 mm) (single spot in tlc on silica gel with 1:1 benzene–ether) and then crystallization from ether–pentane as plates: mp 96–97.5°; pmr δ 1.99 (s, 1, OH), 2.1–2.43 (m, 1, H-2), 2.76 (split d, 2, J = 5 Hz, 2 H-3), 3.53 and 3.65 (two overlapping d of d, 2 total, AB portion of ABX system, J_{AB} = −10.1 Hz, a' = 3 Hz, a = 2.3 Hz, CH_2OH),[14] 6.5–7.2 (m, 4, H-4 to H-7), 7.27 (s, 5, phenyl group); ir ($CHCl_3$) 3470 and 3620 cm^{-1} (OH); mass spectrum[15] *m/e* 253 (M, 72%), 222 (M − CH_2OH, 100), 221 (43), 204 (38), 93 ($C_7H_5D_2$, 45).

Anal. Calcd for $C_{18}H_{15}D_3O$: 16.67 atom % excess D. Found:[17] 15.75 atom % excess D.

Acetylation of 2a.—A mixture of 0.56 g of alcohol **2a**, 5 ml of pyridine, and 3 ml of acetic anhydride was refluxed for 1 hr and then poured into ice–water. A $CHCl_3$ extract of the mixture was washed with 2% HCl and then water, dried, and evaporated. The residue crystallized from MeOH to give 0.62 g (95%) of prisms (acetate **4b**): mp 95–97°, raised to 100.5–101° on recrystallization; negative tests with Br_2–CCl_4 and $KMnO_4$ in acetone; λ_{max}^{EtOH} 253 nm (ϵ 534), 260 (595), 266 (608), 269 (600), 278 (472), plus stronger, short-wavelength end absorption; pmr δ 1.1–1.7 (m, 3, H-1a plus 2 H-1), 1.96 (s, 3, Ac), 2.3–2.9 (m, 3, H-2 plus 2 H-3), 4.05 and 4.16 (2 d of d, 2 total, AB portion of ABX system, J_{AB} = −10.8 Hz, a' = 8.7 Hz, a = 8.6 Hz, CH_2OAc),[14] 6.5–7.1 (m, 4, H-4 to H-7), 7.29 (s, 5, phenyl group).

(9) R. Weiss, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 729.

(10) P. G. Gassman and F. V. Zalar, *J. Org. Chem.*, **31**, 166 (1966).

(11) Unless otherwise noted, microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill., and M-H-W Laboratories, Garden City, Mich. Ultraviolet spectra were obtained by means of a Cary Model 11 spectrophotometer; pmr spectra, by means of a Varian A-60 spectrometer with $CDCl_3$ as solvent (unless otherwise noted) and tetramethylsilane as internal standard; and mass spectra, by means of a CEC Model 21-110 instrument at 70 eV.

(12) R. D. Smith and H. E. Simmons, *Org. Syn.*, **41**, 72 (1961).

(13) Thanks to Mr. Ronald Merrill of this laboratory, this multiplet was resolved (by use of a europium shift reagent) into two other multiplets for H-1a at lower field and 2 H-1 at higher field. Fuzziness in the multiplets, however, prevented clear assignment of coupling constants to these signals.

(14) See P. L. Corio, "Structure of High-Resolution NMR Spectra," Academic Press, New York, N. Y., 1966, pp 299–305. The negative sign of J_{AB} is assumed. Constant a' denotes the separation of the two central lines of the upfield d of d. Constant a gives the respective information for the downfield d of d.

(15) Only peaks of intensity ≥30% of the most abundant peaks are reported.

(16) Analyses by Clark Microanalytical Laboratory, Urbana, Ill.

(17) Analysis by Josef Nemeth, Urbana, Ill.

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.15; H, 6.89; sapon equiv, 292. Found: C, 82.04; H, 7.05; sapon equiv,[18] 292.

Basic hydrolysis of acetate **4b** gave recovery of alcohol **2a**.

Tosylation of 2a.—To a solution of 1.48 g (5.9 mmol) of alcohol **2a** in 10 ml of pyridine at 0° was added dropwise (with swirling) a solution of 2.3 g (12 mmol) of *p*-toluenesulfonyl chloride in 10 ml of pyridine. The mixture was kept at −20° for 24 hr, then poured onto ice and processed as in the preceding acetylation. The residue, 2.24 g (94%) of tosylate **4c**, mp 119–120.5°, formed prisms from benzene–hexane: mp 122–123°; pmr δ 1.1–1.7 (m, 3, H-1a plus 2 H-1), 2.43 (s, 3, tosylate CH_3), *ca.* 2.70 (broadened s, 3, H-2 plus 2 H-3), 3.8–4.2 (irregular t, 2, CH_2OTs), 6.6–7.9 (m, 13, aromatic protons); ir (KBr) 1180 and 1350 cm^{-1} (sulfonate).

Anal. Calcd for $C_{25}H_{24}O_3S$: C, 74.24; H, 5.96; S, 7.93. Found: C, 74.15; H, 6.02; S, 8.00.

2-Methyl-7b-phenyl-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene (4d).—To a stirred slurry of 0.75 g (20 mmol) of $LiAlH_4$ in 50 ml of tetrahydrofuran at 0° was added dropwise a solution of 1.57 g (3.9 mmol) of tosylate **4c** in 100 ml of the same solvent. The mixture was then stirred at 25° for 30 min, refluxed for 6 hr, treated dropwise with water, brought to pH 1, and extracted with ether. Evaporation of the water-washed, dried extract gave a liquid which formed prisms (0.91 g, 99%) from hexane–ether: mp 70–72° (raised to 72–73° on recrystallization); mass spectrum[15] *m/e* (rel intensity) 234 (M, 100), 219 (M − CH_3, 73), 205 (M − C_2H_5, 33), 192 (M − $CH_3CH{=}CH_2$, 43).

Anal. Calcd for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.49; H, 7.50.

5,6-Dimethoxy-2-hydroxymethyl-7b-(3,4-dimethoxyphenyl)-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene (2c).—In the same manner as used for the synthesis of **2a**, tetramethoxy compound **1b**[3] was reduced to **2c**. The oily product was chromatographed by means of Florisil and (in succession) eluents of benzene and benzene–$CHCl_3$ (1:1, v/v). From the latter eluent was obtained a 36% yield of **2c** (single spot on tlc), converted to light yellow prisms on crystallization from hexane: mp 45–46°; pmr (CCl_4) δ 0.9–1.5 (m, 3, cyclopropane protons), *ca.* 2.6 (broad signal, disappears on shaking with D_2O, OH) which overlaps 2.1–3.0 (complex, 3, H-2 plus 2 H-3), 3.50 (s, 3, OCH_3 at C-6), 3.68, 3.74, 3.77 (3s, other OCH_3 groups) which obscure signals for CH_2OH, 6.30 (s, 1, H-7), 6.52 (s, 1, H-4), 6.57–6.9 (broad s plus m, 3, H-2′, H-5′, and H-6′); ir ($CHCl_3$) 3500 cm^{-1} (broad, OH); mass spectrum[15] *m/e* 370 (M, 69%), 339 (100), 151 (36), 57 (32).

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.61; H, 7.16.

Infrared Spectra.—Spectral examination of samples in the near infrared region of the spectrum was made by means of a Cary model 14 spectrophotometer, with a concentration of *ca.* 50 mg of substrate per milliliter of solvent, CCl_4. Compounds **2a**, **2c**, **4a**, and **4b** (but not deuterated compound **2b**, nor the impure product from catalytic hydrogenolysis of **4d**) showed prominent absorption shoulders or peaks at 1.635–1.645 μ. Extinction coefficients for **2a**, **4a**, and **4b** were 0.35, 0.19, and 0.32, respectively.

The regular infrared spectra (obtained in CS_2 as solvent, by means of a Beckman IR-7 spectrophotometer) of **2a**, **4a**, and **4b** also showed a medium band at 1016–1021 cm^{-1} (ascribed to cyclopropane ring deformation)[19,20] and a weak band at 820–844 cm^{-1} (ascribed to cyclopropane ring CH_2 rocking).[20,21] The latter band was clearly resolved in all compounds, though the former band was sharp only in hydrocarbon **4a**. For **2a** it occurred only as a shoulder on the strong C–O stretching band at 1035 cm^{-1}, but some better resolution was found in the spectrum of **4b**.

Registry No.—**2a**, 34599-28-5; **2b**, 34566-27-3; **2c**, 34566-28-4; **4a**, 34566-29-5; **4b**, 34566-30-8; **4c**, 34566-31-9; **4d**, 34566-32-0.

(18) Analysis by Geller Laboratories, Charleston, W. Va.

(19) J. M. Derfer, E. E. Pickett, and C. E. Boord, *J. Amer. Chem. Soc.*, **71**, 2482 (1949); C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press, New York, N. Y., 1963, p 146, and references cited therein.

(20) S. A. Liebman and B. J. Gudzinowicz, *Anal. Chem.*, **33**, 931 (1961); M. Hanack, H. Eggensperger, and S. Kang, *Chem. Ber.*, **96**, 2532 (1963).

(21) H. A. Szymanski, "Interpreted Infrared Spectra," Vol. 1, Plenum Press, New York, N. Y., 1964, pp 143–162.

Acknowledgment.—The authors are grateful to Professor H. M. Walborsky of Florida State University for providing us with a pmr comparison spectrum of 1-methyl-2,2-diphenylcyclopropane and to Dr. T. M. McGuire (formerly of this laboratory) for obtaining definitive pmr spectra on some of our products.

Structure of a New Fungal Lactone, LL-P880α, from an Unidentified *Penicillium* sp.

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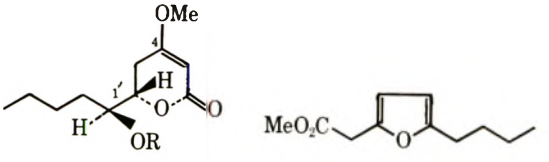
In a continuing program seeking useful pharmacologically active compounds from microorganisms, we had occasion to examine the fermentations of culture P880, an unidentified *Penicillium* species. This report describes the structure, stereochemistry, and some rearrangements of the metabolite LL-P880α.[1] This metabolite, $C_{11}H_{18}O_4$, is characterized by a uv maximum at 235 nm (ε 12,000) and strong ir absorption at 1710 and 1625 cm^{-1} which suggests the presence of the 4-alkoxy-5,6-dihydro-α-pyrone moiety.[2] The nmr spectrum supports this conclusion with a methoxy signal at δ 3.80, the C_3 vinyl proton signal at δ 5.16 ($J_{3,5a}$ = 2 Hz), a 1 H multiplet at δ 4.33 due to the proton of C_6, an eight-line pattern at δ 2.67 (J_{gem} = 18, $J_{3,5a}$ = 2, $J_{5a,6}$ = 11 Hz), and a four-line system at δ 2.23 (J_{gem} = 18, $J_{5e,6}$ = 4 Hz) due to the geminal C_5 protons. In addition, a primary C–Me signal at δ 0.92 as a characteristic 3 H triplet and a 1 H multiplet due to a second



I, R = H
II, R = Ac

III

proton on a carbon bearing an oxygen atom at δ 3.70 are observed. The hydroxy nature of this remaining oxygen is indicated by the formation of acetate II, $C_{13}H_{20}O_5$.

The major fragmentation in the mass spectrum of I results from the loss of the five-carbon side chain, giving the base peak at *m/e* 127. The ion at *m/e* 157 is consistent with cleavage between $C_{1'}$ and $C_{2'}$ and expulsion of the *n*-butyl unit. This evidence, in conjunction with the foregoing, unequivocally indicates I as the structure of the metabolite.

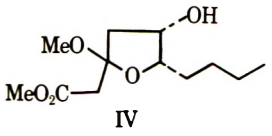
The chemistry of I under acidic or basic conditions is characterized by a marked propensity to rearrange to the furanoid system or derivatives thereof. Thus hydrolysis of I in methanolic hydrochloric acid gave the furan ester III, $C_{11}H_{16}O_3$. Its nmr spectrum shows the two ring-proton signals at δ 6.08 and 5.90 as two dou-

(1) After this work was completed, a note by Y. Kimura, K. Katagiri, and S. Tamura appeared in *Tetrahedron Lett.*, **No. 33**, 3137 (1971), which describes the same compound from *Pestalotia cryptomeriaecola*.

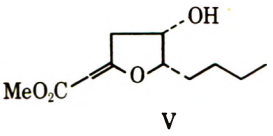
(2) H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 3628 (1950).

blets, J = 3 Hz. A 2 H singlet at δ 3.63 is attributed to the C_2 methylene protons. The methoxy signal resonates at δ 4.71, and the C_6 methylene hydrogens at δ 2.61 as a broad triplet.

Treatment of I with sodium methoxide in dry methanol under reflux with rigorous exclusion of moisture gave IV, $C_{12}H_{22}O_5$, and V, $C_{11}H_{18}O_4$, by ether extraction of the crude concentrate. Acidification during the work-up provided III.



IV



V

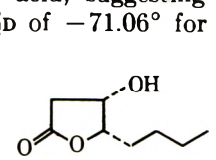
The nmr of IV shows the C_4 geminal hydrogens as a sharp 2 H doublet (J = 4 Hz) at δ 2.29 and the C_2 geminal hydrogens as a 2 H quartet at δ 2.64 and 2.93 (J_{gem} = 16 Hz). The C_5 and C_6 proton signals are buried under the C_3 methoxy signal at δ 3.17 and the ester methoxy signal occurs at δ 3.70.

Although IV is a colorless oil, V is highly crystalline. Two four-line nmr patterns at δ 2.86 and 3.19 ($J_{4,4}$ = 19, $J_{2,4a}$ = 2, $J_{4a,5}$ = 5 Hz) in the spectrum of V are assigned to the pseudoaxial proton signal of C_4. Only one of the signals of the pseudoequatorial C_4 proton is seen at δ 3.45 as a triplet ($J \cong$ 1.5 Hz), since the remaining portion at δ 3.68 is obscured by the methoxy signal. The C_2 olefinic proton is seen at δ 5.37 as a complex multiplet.

An internal Michael addition of the $C_{1'}$ hydroxyl group in I followed by methanolysis of the resulting bicyclic lactone and elimination of the C_4 methoxyl, or other related combinations, will lead to the observed products. A related situation was observed in the chemistry of rubratoxin.[3]

The stereochemistry at C_6 and $C_{1'}$ depicted in I is based on several pieces of evidence, all of which are mutually consistent. The axial nature of the C_6 hydrogen is known from the coupling constant of 11 Hz between the C_{5a} and C_6 hydrogens. A negative Cotton effect (Δε −7.90) at 243 nm in the CD spectrum of I[4] determines the absolute stereochemistry at C_6 as S. Application of the Horeau method[5] to V, in which the lactone ether oxygen is now a secondary alcohol, confirms the CD results. Thus treatment of the latter with (±)-α-phenylbutyric anhydride liberated (−)-α-phenylbutyric acid.

Treatment of I with the racemic anhydride also liberated the (−) acid, suggesting the S configuration at $C_{1'}$. An $[\alpha]_D$ of −71.06° for the lactone VI (obtained by ozonolysis of V) on the basis of the Hudson lactone rule[6] confirms this assignment, as does the Δε of −0.53 at 216 nm in the CD[7] spectrum of VI.



VI

Experimental Section

All melting points were determined on a Fisher-Johns melting point block and are uncorrected. Nmr spectra were recorded with a Varian A-60D in $CDCl_3$; shifts are expressed as δ values (parts per million) from tetramethylsilane as internal standard, and coupling constants are expressed in cycles per second (hertz). Infrared spectra were taken on a Perkin-Elmer Model 137 infracord and ultraviolet spectra on a Cary Model 11. Circular dichroism curves were obtained on a Cary 60 spectropolarimeter with a CD attachment. In nmr descriptions, s = singlet, d = doublet, t = triplet, m = multiplet, dd = double doublet, and q = quartet.

Isolation of I.—The whole mash from a 300-l. fermentation was extracted at pH 6 with a 0.5 volume of ethyl acetate. This was concentrated to an oily residue, which was taken up in methanol. The methanol solution was washed with heptane and then reconcentrated to give 9 g of a dark, semisolid residue. Column chromatography over silica gel (250 g) and elution with methylene chloride gave a crystalline residue which on recrystallization from benzene–hexane gave 3.8 g of I. The analytical sample had mp 84–85°; $[\alpha]_D$ −86.2° (c 0.14, MeOH); λ_{max}^{MeOH} 235 nm (ε 12,000); ir (KBr) 1710 and 1625 cm^{-1}; nmr δ 0.92 (CMe, t), 2.23 (H_{5e}, dd, $J_{5a,5e}$ = 18, $J_{5e,6}$ = 4 Hz), 2.67 (H_{5a}, dd, $J_{5a,5e}$ = 18, $J_{3,5a}$ = 2, $J_{5a,6}$ = 11 Hz), 3.80 (OMe, s), 4.33 (H_5, m), 5.16 (H_3, d, $J_{3,5a}$ = 2 Hz), 3.70 ($H_{1'}$, m); CD (0.82 mg in 10 cc of MeOH) $\Delta\epsilon_{243}$ −7.90; mass spectrum m/e 214 ($C_{11}H_{18}O_4$).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.78; H, 8.19.

Acetate II.—A solution containing 100 mg of I in 0.5 ml of acetic anhydride and 0.5 ml of pyridine was allowed to stand at room temperature overnight. The reaction was evaporated to dryness under reduced pressure to give a yellow gum. This was chromatographed on acid-washed silica gel with 25% ether–methylene chloride as the eluent to give 93 mg of a colorless, viscous oil which showed only one spot on silica gel tlc (20% ethyl acetate–benzene); $[\alpha]_D$ −98.5° (c 0.53, MeOH); λ_{max}^{MeOH} 233 nm (ε 13,300); ir (smear) 1740, 1710, and 1625 cm^{-1}; nmr δ 1.00 (CMe, t), 2.15 (OAc, s), 2.25 (H_{5e}, dd, $J_{5a,5e}$ = 18, $J_{5e,6}$ = 4 Hz), 2.65 (H_{5a}, dd, $J_{5a,5e}$ = 18, $J_{3,5a}$ = 2, $J_{5a,6}$ = 11 Hz), 3.78 (OMe, s), 4.50 (H_6, m), 5.06 ($H_{1'}$, m), 5.20 (H_3, d, $J_{2,5a}$ = 2 Hz); mass spectrum m/e 256 ($C_{13}H_{20}O_5$).

Conversion of I to III with Methanolic Hydrochloric Acid.—A solution of 20 ml of methanol and five drops of concentrated hydrochloric acid containing 300 mg of I was refluxed overnight. Removal of the solvent and distillation[8] at 100° (80 μ) gave an almost quantitative yield of III: ir (KBr) 1740 cm^{-1}; nmr δ 0.92 (CMe, t), 2.62 (H_7, t), 3.63 (H_2, s), 3.72 (OMe, s), 5.90 and 6.08 (H_4 and H_5, dd, J = 3 Hz); mass spectrum m/e 196 ($C_{11}H_{16}O_3$).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 66.90; H, 8.04.

Conversion of I to IV and V.—To a solution of 5 g of I in 100 ml of dry methanol (dried over molecular sieves) was added 2 g of sodium methoxide in 50 ml of dry methanol. The solution was refluxed overnight with the rigorous exclusion of moisture. The methanol was evaporated and the gummy suspension was treated with ether and filtered. The filtrate was evaporated to an oil which was chromatographed over 180 g of silica gel and eluted with 5% ethyl acetate–hexane with fraction volumes of 80–85 ml. Fractions 9–16 gave 2.5 g of a colorless oil which was further purified by partitioning over 220 g of acid-washed Celite using the solvent system heptane–acetonitrile. This provided

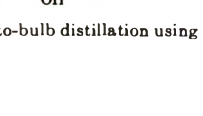
(3) G. Büchi, K. M. Snader, J. D. White, J. Z. Gougouatas, and S. Singh, *J. Amer. Chem. Soc.*, **92**, 6638 (1970).

(4) G. Snatzke, *Angew. Chem.*, **80**, 14 (1968).

(5) A. Horeau and H. B. Kagan, *Tetrahedron*, **20**, 2431 (1964).

(6) C. S. Hudson, *J. Amer. Chem. Soc.*, **32**, 338 (1910); 1525 (1939). The same argument has been used to assign the S configuration to the γ-propylbutyrolactone obtained from oudenone: M. Ohno, M. Okamoto, N. Kawabe, H. Umezawa, T. Takeuchi, H. Iinuma, and S. Takahashi, *J. Amer. Chem. Soc.*, **93**, 1285 (1971).

(7) This is on the basis that VI exists as in the projection; see A. F. Beecham, *Tetrahedron Lett.*, **No. 32**, 3591 (1968); F. I. Carrol, H. Sobti, and R. Meck, *ibid.*, No. 5, 405 (1971), and references cited therein.



(8) Evaporative bulb-to-bulb distillation using a Büchi kugelrohrofen.

1.8 g of pure IV: $[\alpha]D$ −66.3° (*c* 1.09, MeOH); ir (smear) 1740 cm^{-1}; 100-MHz nmr (CCl_4) δ 0.95 (CMe, t), 2.29 (H_1, d, J = 4 Hz), 2.80 (H_2, q, J = 16 Hz), 3.17 (C_3OMe, s), 3.70 (C_1 OMe, s).

Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.51; H, 9.00. Found: C, 58.34; H, 8.80.

Fractions 17–28 from the silica gel column mentioned above gave, on concentration, 350 mg of white solid which was recrystallized from ether–hexane to give the analytical sample of V: mp 105–106°; $[\alpha]D$ −169° (*c* 0.72, MeOH); λ_{max}^{MeOH} 245 nm (ε 22,250); ir (KBr) 3450, 1720, and 1600 cm^{-1}; nmr δ 0.97 (CMe, t), 2.86 and 3.19 (H_{4a}, q, $J_{4,4}$ = 19, $J_{2,4a}$ = 2, $J_{4a,5}$ = 5 Hz), 3.45 (H_{4e}, 1 H, t, $J \cong$ 1.5 Hz), 4.25 (m, H_5 and H_6), 5.37 (H_2, m); mass spectrum *m/e* 214 ($C_{11}H_{18}O_4$).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 62.04; H, 8.45.

Conversion of I to III with Sodium Methoxide.—A solution of 1.07 g of I and 270 mg of sodium methoxide in 20 ml of methanol was gently warmed on a steam bath for 30 min. The solution was concentrated and the resultant oil was taken up in ethyl acetate and washed with 4 *N* hydrochloric acid. The ethyl acetate phase was dried and concentrated to an oil which was passed over 80 g of acid-washed silica gel and eluted with 10% ethyl acetate in hexane. This provided 550 mg of a colorless oil from which 150 mg was distilled[8] at 80° (100 μ) to give III. This material was identical in all respects with that obtained above.

Ozonolysis of V.—Ozone was passed through a solution of 400 mg of V in methanol at −70°. The reaction was worked up by the dimethyl sulfide procedure.[9] After removal of the solvent, the residual oil was distilled[8] at 135° (100 μ) to give 100 mg of colorless oil: $[\alpha]D$ −71.1 (*c* 0.73, MeOH); ir (smear) 1770 cm^{-1}; CD (2.44 mg/ml MeOH) $\Delta\epsilon_{216}$ −0.53.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.88; H, 8.79.

Application of Horeau's Method to I.—A solution of 59 mg of I and 215 mg of (±)-α-phenylbutyric anhydride in 3 ml of pyridine was allowed to stand over the weekend at ambient temperature. Then 1 ml of water was added with the consequent generation of heat. After 1 hr, 20 ml of water was added and the mixture was extracted three times with ether. The ether extracts were back-extracted twice with 10 ml of 10% sodium carbonate solution. The aqueous alkaline solution was washed with ether and then acidified and extracted once again with ether. This was dried over magnesium sulfate and evaporated to 154 mg of a colorless oil which solidified in the refrigerator. Tlc using benzene–dioxane–acetic acid (50:50:2) showed this material to be α-phenylbutyric acid as did the ir and nmr, $[\alpha]D$ −0.17 ± 0.07° (*c* 2.90, benzene).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.26; H, 7.20.

Application of Horeau's Method to V.—To 3 ml of pyridine was added 65 mg of V and 218 mg of (±)-α-phenylbutyric anhydride. The solution was allowed to stand over the weekend at room temperature and then worked up as described above to give 145 mg of the acid, $[\alpha]D$ −2.27 ± 0.07° (*c* 2.9, benzene).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.24; H, 7.46.

Registry No.—I, 34565-32-7; II, 34565-33-8; III, 34565-34-9; IV, 34565-35-0; V, 34565-36-1; VI, 34565-37-2; α-phenylbutyric acid, 938-79-4.

Acknowledgments.—We wish to thank our colleagues for their assistance in particular, Dr. H. Tresner and Miss Jean Hayes for culture isolation and identification, Mr. A. J. Shay for large-scale fermentations, Mr. M. Dann for large-scale work-ups, Mr. L. Brancone for microanalytical data, Mr. W. Fulmor for spectral data and optical rotations, and Miss Pat Mullen of Cyanamid Stamford Laboratories for the CD curves.

(9) J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966).

Photoreduction of Conjugated Cyclopropyl Ketones in Isopropyl Alcohol[1]

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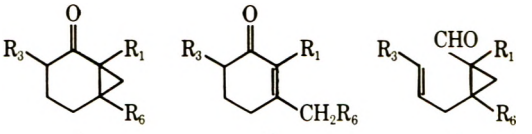
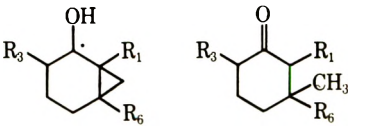
Previous photochemical studies of substituted bicyclo[4.1.0]heptan-2-ones (**1**) under photoisomerization conditions, *i.e.*, *tert*-butyl alcohol used as solvent, have established that the relative efficiencies of three possible reaction pathways from **1** in the triplet state are affected by the pattern of substitution on the ring system.[2] The general photoisomerization of such a conjugated system (**1**, R_3, R_6 = H) to a 3-substituted cyclohex-2-en-1-one (**2**, R_3, R_6 = H) is blocked when R_6 is an alkyl group; in such a case only efficient intersystem crossing from the excited triplet state to the singlet ground state of the starting material occurs. However, with substitution at R_3, the Norrish type I cleavage to an aldehyde **3** becomes the favored primary photoprocess.



1 **2** **3**

On the other hand, irradiation of **1** (R_1, R_3 = H, R_6 = H or CH_3) in isopropyl alcohol, *i.e.*, photoreduction conditions, has been shown to lead to a selective reductive opening of the outside bond of the cyclopropyl ring.[3] In this photoreduction, the intervention of the α-hydroxycyclopropylcarbinyl radical **4** (R_1, R_3 = H, R_6 = H or CH_3) has been established and it is its collapse which leads to a 3-substituted 3-methylcyclohexanone **5** (R_1, R_3 = H). The effect of the pattern of substitution of the ring system on this photoreduction process has now been investigated.



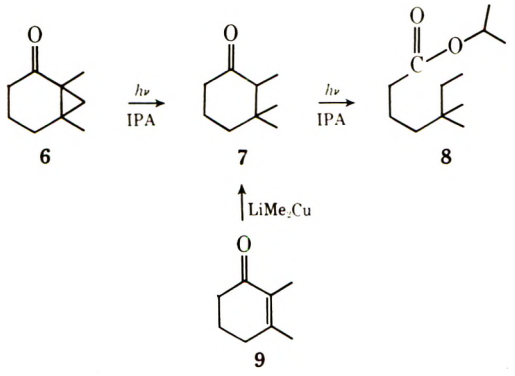
4 **5**

It was found that the disubstituted derivative 1,6-dimethylbicyclo[4.1.0]heptan-2-one (**6**) upon irradiation in isopropyl alcohol was rapidly transformed to isopropyl 5,5-dimethylheptanoate (**8**). When the irradiation was monitored using infrared spectroscopy, it was found that the expected 2,3,3-trimethylcyclohexanone (**7**) was the first photoproduct formed. This latter ketone **7**, prepared from 2,3-dimethylcyclohex-2-en-1-one (**9**) and lithium dimethylcopper, upon ir-

(1) This work was supported by Public Health Service Grant No. 00709, National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

(2) W. G. Dauben, G. W. Shaffer, and E. J. Deviny, *J. Amer. Chem. Soc.*, **92**, 6273 (1970).

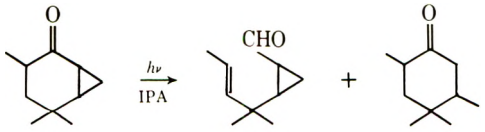
(3) W. G. Dauben, L. Schutte, R. E. Wolf, and E. J. Deviny, *J. Org. Chem.*, **34**, 2512 (1969).



6 7 8 9

radiation in isopropyl alcohol rapidly yielded ester **8**.[4] Thus, these experiments show that hydrogen abstraction by the triplet of ketone **6** is more efficient than intersystem crossing to the ground-state singlet. It also is of interest to note that, whereas the 2,3,3-trimethylcyclohexanone undergoes a rapid type I photolysis, the related cyclopropyl ketone **6** does not undergo α cleavage.

To evaluate the relative efficiencies of the type I cleavage and the hydrogen abstraction from solvent, 3,5,5-trimethylbicyclo[4.1.0]heptan-2-one (**10**) was studied, since it had been found earlier[2] that in *tert*-butyl alcohol type I cleavage was the sole reaction pathway. Irradiation of **10** in isopropyl alcohol was found to yield, in a ratio of 1.5:1, the unsaturated aldehyde **11** from the cleavage route and 2,4,4,5-tetra-



10 11 12

methylcyclohexanone (**12**) from the reduction route. Thus, the hydrogen abstraction process is more efficient than photoisomerization and the resulting α-hydroxycyclopropylcarbinyl radical still leads to the selective opening of the outside bond of the cyclopropane ring.

Further information with regard to the nature of this type of radical intermediate has been obtained by study of the two isomeric 4,5-methanocholestan-3-ones **13** and **15**.[5] It was found that when the 4β,5β isomer **13** was irradiated in isopropyl alcohol the sole product of the reaction was the 5β-methyl derivative **14** (eq 1). Irradiation of the isomeric 4α,5α-methano compound **15**, however, yielded a mixture of products which was shown to contain only 15% of the expected 5α-methyl isomer **16** and quite surprisingly 85% of the 5β isomer **14**. Such a result can be visualized as involving the symmetrical homoallylic radical **17**, which can collapse to either **14** or **16**. That previous isomerization of **15** to **13** had not occurred was shown by the stability of the material upon irradiation in benzene.

Experimental Section

Unless otherwise noted, the following general conditions were used in all reactions. Infrared spectra were recorded in carbon tetrachloride using either a Perkin-Elmer 137 Infracord or a 237 grating spectrometer. Nmr spectra were obtained with a Varian T-60 spectrometer using carbon tetrachloride as the solvent and tetramethylsilane as an external reference. Mass spectral analyses and elementary analyses were obtained from the Analytical Laboratory, College of Chemistry, University of California, Berkeley, Calif.

Irradiation Procedure.—Irradiations were conducted in deaerated 0.2–0.5% solutions in 125 ml of isopropyl alcohol, using a Corex filter with a 450 W Hanovia lamp. The reactions were monitored by vpc (10% Carbowax). After termination of the irradiation, the solvent was rotary evaporated and the products were collected by chromatography.

Irradiation of 1,6-Dimethyl[4.1.0]heptan-2-one (6).—The solution of **6**[6] was irradiated for 8 hr, at which time 50% of the starting material had disappeared. The photoproduct (~80% based upon recovered starting material) was isolated by preparative vpc and identified as isopropyl 5,5-dimethylheptanoate (**8**) by comparison with an authentic sample (see below). The material spectral properties were: ir (CCl_4) 1724, 1258, and 1110 cm^{-1}; mass spectrum (70 eV) *m/e* 185 (M − CH_3), 171 (M − C_2H_5), 141 (M − C_3H_7O), and 129 (M − C_5H_{11}).

When the reaction was monitored by infrared spectrometry, the carbonyl absorption at 1705 cm^{-1} of 2,3,3-trimethylcyclohexanone (**7**) was present at the early stages of the irradiation and then remained at a low concentration, steady-state intensity.

2,3,3-Trimethylcyclohexanone (7).—A solution of lithium dimethylcopper was prepared by the addition of 80 ml of a 2 *M* ethereal solution of methyl lithium to 11.6 g of cuprous bromide.[7] To the ice-cooled mixture there was added 2.0 g of 2,3-dimethyl-2-cyclohexenone (**9**) in 20 ml of ether. The reaction was stirred for 2 hr at ice temperature, and refluxed for 2 hr. The mixture was processed in the standard fashion[6] to yield 2 g of a 2:8 mixture of two compounds. The materials were separated by alumina chromatography (Woelm neutral, activity III), pentane eluting the minor product, tentatively identified as 1,2,3-trimethyl-1,3-cyclohexadiene. The ketone **7** was eluted with chloroform: yield 1.5 g (67%); ir (CCl_4) 1705, 1445, 1080, and 935 cm^{-1}; nmr (CCl_4) δ 2.50–1.45 (m, 7), 1.03 (s, 3), 0.87 (d, 3, J = 7 Hz), and 0.73 (s, 3); mol wt, 140 (mass spectrum).

Irradiation of the ketone **7** under the standard conditions gave ester **8**, whose properties are reported above.

Irradiation of 3,5,5-Trimethylbicyclo[4.1.0]heptan-2-one (10).—The solution of **10**[2] was irradiated for 2 hr, at which time 50% of the starting material had disappeared and two major products, **11** and **12**, appeared in a ratio of 1.5:1; the total yield by vpc was 80%, based upon reacted starting material. The photoproducts were separated by vpc and identified by comparison with authentic samples.

2,3-Methano-4,4-dimethyl-*trans*-Δ^5-heptanal (11).—The material was prepared as previously described[2] by irradiation of 3,5,5-trimethylbicyclo[4.1.0]heptan-2-one in *tert*-butyl alcohol and purified by vpc on two columns (10% Carbowax and 5% XF 1150 Cyanosilicone).

2,4,4,5-Tetramethylcyclohexanone (12).—The material was prepared from 4,4,6-trimethyl-2-cyclohexenone and lithium dimethylcopper following the procedure described for **7**: yield 90%; ir (CCl_4) 1690, 1450, 1375, 1365, 1135, and 1065 cm^{-1}; nmr (CCl_4) δ 1.8–2.8 (m, 3), 1.2 (br s, 3), 0.95 (s, 6), and 0.81 (d, 3, J = 4 Hz); mol wt, 154 (mass spectrum).

Irradiation of 4β,5β-Methanocholestan-3-one (13).—A solution of 0.5 g of **13**[5] in 125 ml of isopropyl alcohol was irradiated with a 200-W Hanovia lamp (Vycor filter) for 90 min, at which time 65% of the starting material had been consumed. The reaction mixture was chromatographed on 500 g of silica gel (Brinkmann 7734) according to the procedure of Duncan[8] using the solvent system benzene–acetone (9:1). In the early eluates there was obtained the photoproduct, which was recrystallized from methanol–acetone, yield 225 mg, mp 87–88°. The material was identical in all respects with the known 5β-methylcholestan-3-one (**14**).[9] In the later fraction there was obtained 155 mg of starting ketone.

Irradiation of 4α,5α-Methanocholestan-3-one (15).—A solution of 0.5 g of **15**[5] in 125 ml of isopropyl alcohol was irradiated for

(4) The ketone **7** and the ester **8** were not separable on the vpc columns used in this research.

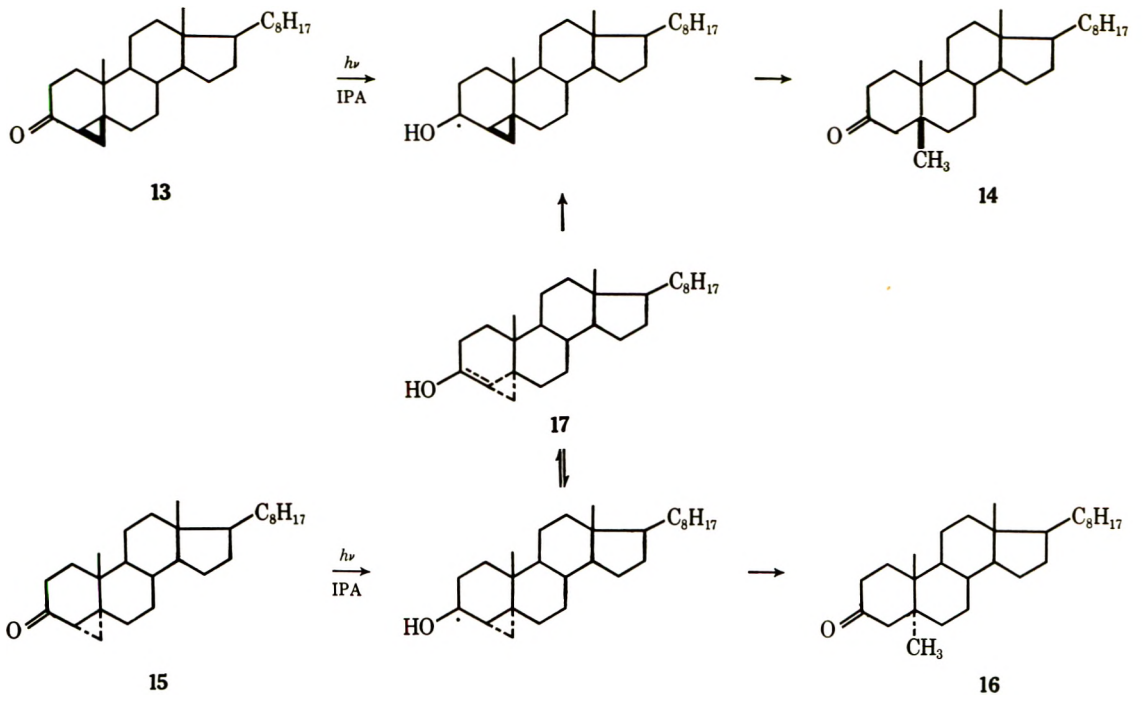
(5) W. G. Dauben, P. Laug, and G. H. Berezin, *J. Org. Chem.*, **31**, 3869 (1966).

(6) W. G. Dauben and G. H. Berezin, *J. Amer. Chem. Soc.*, **89**, 3449 (1967).

(7) H. O. House and W. F. Fisher, *J. Org. Chem.*, **33**, 949 (1968).

(8) G. R. Duncan, *J. Chromatogr.*, **8**, 37 (1962).

(9) W. G. Dauben and E. J. Deviny, *J. Org. Chem.*, **31**, 3794 (1966); W. Nagata, H. Hirai, H. Itazaki, and K. Takeda, *Justus Liebigs Ann. Chem.*, **641**, 196 (1961).



(1)

2.5 hr as described for the 4β,5β isomer **13**, at which time 80% of the starting material had been consumed. The reaction mixture was chromatographed by the Duncan procedure[8] to yield 290 mg of reaction product and 80 mg of starting ketone. The reaction product was recrystallized from absolute ethanol to yield a granular solid, mp 76–132°, mol wt, 400 (mass spectrum).

Anal. Calcd for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 83.99; H, 11.91.

The product was analyzed by vpc and found to be composed of 85% of 5β-methylcholestan-3-one (**14**) and 15% of 5α-methylcholestan-3-one (**16**) by coinjection with authentic samples.[9]

Registry No.—**6**, 14845-43-3; **7**, 34562-14-6; **10**, 29750-24-1; **12**, 34562-16-8; **13**, 2429-48-3; **15**, 2602-40-6; isopropyl alcohol, 67-63-0.

Cycloaddition Reactions with *anhydro*-1,3-Dimethyl-4-hydroxy-1,2,3-triazolium Hydroxide[1]

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In a previous communication,[2] *anhydro*-3-aryl-4-hydroxy-1-methyl-1,2,3-triazolium hydroxides (**1**, R = aryl) were reported to undergo cycloaddition reactions with dimethyl acetylenedicarboxylate to the corresponding pyrazole. Reactive olefinic-type dipolarophiles such as ethyl azodicarboxylate also gave 1:1 adducts with the ring system and tetracyanoethylene formed "ene" type substitution products. Particularly noteworthy, however, was the lack of reaction with phenyl isocyanate and phenyl isothiocyanate, even over extended reaction periods.

The 3-aryl substituent would be expected to have considerable effect on the electron density associated with the nucleus of **1**. The inability of **1** (R = aryl) to form the corresponding methyl ether with methyl iodide whereas the 3-methyl compound **1** ($R = CH_3$) underwent ready methylation with methyl iodide[3] may be attributed to substituent effect. We have now found that replacement of the 3-aryl substituent with a methyl group facilitates cycloaddition reactions with this ring system and greatly extends the scope of the reaction.

anhydro-1,3-Dimethyl-4-hydroxy-1,2,3-triazolium hydroxide (**1**, $R = CH_3$) underwent reaction with dimethyl acetylenedicarboxylate in refluxing benzene (1 hr), giving dimethyl 1-methylpyrazole-3,4-dicarboxylate (**3**) in 60% yield, presumably *via* the intermediate **2** which lost methyl isocyanate under the reaction conditions. An equally facile reaction of **1** ($R = CH_3$) with ethyl azodicarboxylate also occurred, giving ethyl 6,7-dimethyl-5-oxo-1,2,3,6,7-pentaazabicyclo[2.2.1]heptane-2,3-dicarboxylate (**4**) in 95% yield. The assignment of this structure to the cycloadduct is based on analytical and spectral data (see Experimental Section) and is analogous to the structure of the product from **1** (R = aryl) and the ester.

Both phenyl isocyanate and phenyl isothiocyanate gave 1:1 cycloadducts with **1** ($R = CH_3$). In the former case, structure **5**, 2,7-dimethyl-3,5-dioxo-6-phenyl-1,2,6,7-tetraazabicyclo[2.2.1]heptane, was assigned to the product. The bridgehead proton at C-4 resonated at τ −0.23, broadened slightly by coupling with the bridge NCH_3 group,[2,4] and is at extremely low field consistent with it being deshielded by the carbonyl groups in the 3 and 4 positions. This would appear to exclude from consideration the isomeric 2,7-dimethyl-3,6-dioxo-5-phenyl-1,2,5,7-tetraazabicyclo[2.2.1]heptane formed by reverse addition of the phenyl isocyanate to **1**. Such a reverse addition has been observed with sydnone.[5] The adduct with phenyl isothiocyanate was assigned the analogous structure **6**.

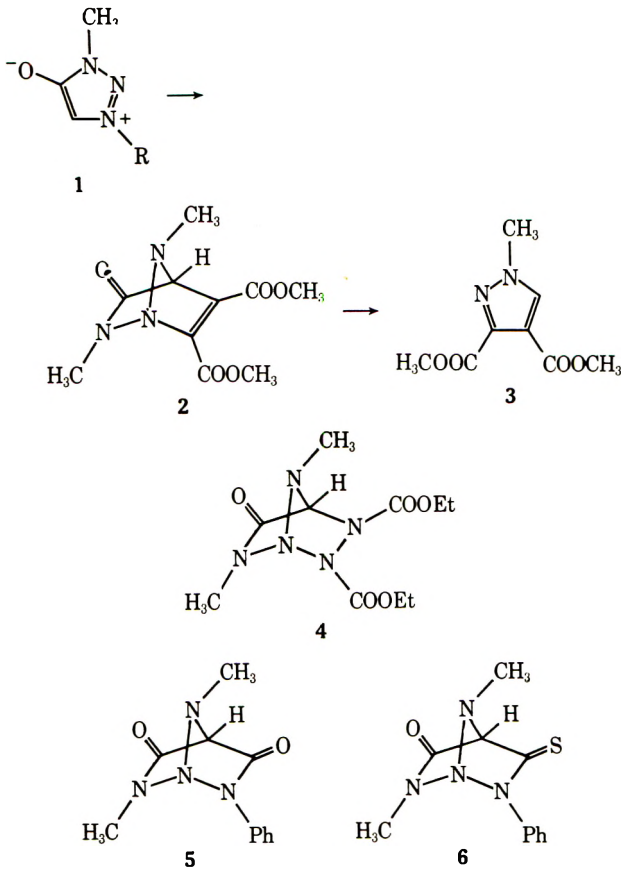
(1) (a) Support of this work by U. S. Public Health Service Research Grant CA 08495, National Cancer Institute, is gratefully acknowledged. (b) Part XVII in the series, Mesoionic Compounds.

(2) K. T. Potts and S. Husain, *J. Org. Chem.*, **35**, 3451 (1970).

(3) M. Begtrup and C. Pedersen, *Acta Chem. Scand.*, **20**, 1555 (1966); M. Begtrup and P. A. Kristensen, *ibid.*, **23**, 2733 (1969).

(4) D. E. Ames and B. Novitt, *J. Chem. Soc. C*, 2355 (1969).

(5) H. Kato, S. Sato, and M. Ohta, *Tetrahedron Lett.*, 4261 (1967).



In this case the bridgehead proton at C-4 underwent a large downfield shift to τ −2.5 which can be attributed to the increased deshielding of the thiocarbonyl group.[6]

Experimental Section[7]

Methyl 1-Methylpyrazole-3,4-dicarboxylate (3).—*anhydro*-1,3-Dimethyl-4-hydroxy-1,2,3-triazolium hydroxide[3] and dimethyl acetylenedicarboxylate (equimolar amounts) were refluxed in benzene for 1 hr. The reaction mixture was chromatographed directly on neutral alumina and the ester was eluted with benzene, yield 60%, mp 68–69° (lit.[8] mp 68–69°). This product was identical[9] with an authentic sample.

Ethyl 6,7-Dimethyl-5-oxo-1,2,3,6,7-pentaazabicyclo[2.2.1]heptane-2,3-dicarboxylate (4).—Equimolar amounts of 1 and ethyl azodicarboxylate were refluxed in xylene for 1 hr. Evaporation of the solvent and trituration of the residue with ether gave a colorless, crystalline product which crystallized from benzene–petroleum ether (bp 40–60°) as colorless, irregular prisms: mp 166–168°; yield 95%; ir (KBr) 3150, 2975 (CH), 1750 (sh), 1725, 1650 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 282 nm (log ϵ 3.86); nmr ($CDCl_3$) τ 8.77 (t, 3, J = 7.0 Hz, CH_2CH_3), 8.73 (t, 3, J = 7.0 Hz, CH_2CH_3), 6.3 (s, 3, NCH_3), 5.95 (s, 3, NCH_3), 5.86 (q, 2, J = 7.0 Hz, CH_2CH_3), 5.78 (q, 2, J = 7.0 Hz, CH_2CH_3), 0.47 (s, 1, 4-CH); mass spectrum m/e (rel intensity) M·+ 287 (17).

Anal. Calcd for $C_{10}H_{17}N_5O_5$: C, 41.81; H, 5.96; N, 24.38. Found: C, 42.08; H, 5.95; N, 24.10.

2,7-Dimethyl-3,5-dioxo-6-phenyl-1,2,6,7-tetraazabicyclo[2.2.1]heptane (5).—*anhydro*-1,3-Dimethyl-4-hydroxy-1,2,3-triazolium hydroxide (0.20 g) and phenyl isocyanate (1.0 g) in xylene (5 ml) were refluxed for 10 hr. After cooling, water (5 ml) was added and the next day the solvent was removed under reduced pressure. The solid residue was dissolved in hot benzene and chromatographed on neutral alumina (activity I) and finally eluted with chloroform. It crystallized from benzene as colorless needles: yield 287 mg (70%); mp 167–168°; ir (KBr) 3005 (CH), 1690 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 336 nm (log ϵ 3.76), 312 (4.29); nmr ($CDCl_3$) τ 6.34 (s, 3, NCH_3), 5.74 (s, 3, NCH_3), 2.61 (m, 5, aromatic), −0.23 (broad s, 1, 4-CH); mass spectrum m/e (rel intensity) M·+ 232 (80).

Anal. Calcd for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.13. Found: C, 57.12; H, 4.99; N, 24.47.

6,7-Dimethyl-5-oxo-2-phenyl-1,2,6,7-tetraazabicyclo[2.2.1]heptane-3-thione (6) was prepared as above using phenyl isothiocyanate. The yellow product was eluted using benzene–chloroform (1:1) and crystallized from benzene–petroleum ether as yellow needles: yield 258 mg (59%); mp 148–150°; ir (KBr) 2900 (CH), 1670 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 340 nm (log ϵ 4.39), 240 (3.94); nmr ($CDCl_3$) τ 6.28 (s, 3, NCH_3), 5.47 (s, 3, NCH_3), 2.5 (m, 5, aromatic), −2.5 (broad s, 1, 4-CH); mass spectrum m/e (rel intensity) M·+ 248 (100).

Anal. Calcd for $C_{11}H_{12}N_4SO$: C, 53.22; H, 4.87; N, 22.57. Found: C, 53.65; H, 4.82; N, 22.44.

Registry No.—1 (R = CH_3), 13273-71-7; **4**, 34407-45-9; **5**, 34407-46-0; **6**, 34407-47-1.

(6) K. T. Potts and R. Armbruster, *J. Org. Chem.*, **36**, 1846 (1971); R. Hull, *J. Chem. Soc. C*, 1777 (1968).

(7) Spectral characterization of products was carried out on the following instrumentation: ir, Perkin-Elmer Model 337 spectrophotometer; uv, Cary Model 14 spectrophotometer; nmr, Varian A-60, T-60, and HA-100 spectrometers using TMS as internal standard; mass spectra, Hitachi Perkin-Elmer RMU-6E mass spectrometer using the direct inlet probe at about 165°. All evaporations were done under reduced pressure using a rotavap apparatus and melting points were taken in capillaries. Microanalyses are by Instranal Laboratories, Inc., Rensselaer, N. Y.

(8) K. T. Potts and U. P. Singh, *Chem. Commun.*, 66 (1969).

(9) Criteria for product equivalency were superimposable infrared spectra, not more than 1° depression in mixture melting point, and identical R_f values.

Reduction of Nitroxides to Amines by Sodium Sulfide

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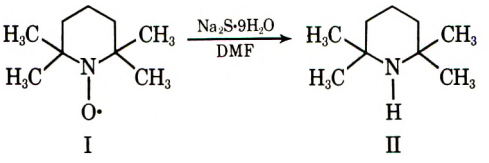
We report the facile reduction of nitroxides to amines. This reduction takes place at room temperature and, despite our relatively cursory study of the matter, the yields of pure products range from 50 to 81%. Thus, the nitroxide I on treatment with sodium sulfide in dimethylformamide for 11 hr gives a 50% yield of the tetramethylpiperidine II. Reduction also occurs



(1)

smoothly in dimethyl sulfoxide; the nitroxide III is reduced to the amine IV in 81% yield. Our third example is the conversion of di-*tert*-butyl nitroxide to di-*tert*-butylamine (65% yield).[1,2]

These reductions have several interesting characteristics. They exhibit an induction period and they are accelerated by elementary sulfur. Table I records

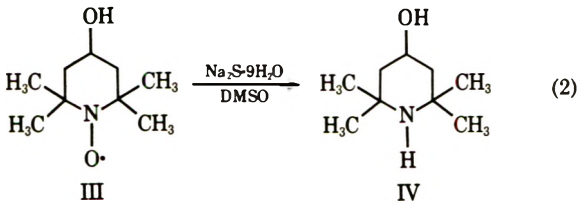
(1) This is the best route to di-*tert*-butylamine. Compare F. Klages and H. Sitz, *Ber.* **92**, 2606 (1959); N. C. Deno, R. Fishbein, and J. C. Wyckoff, *J. Amer. Chem. Soc.*, **93**, 2066 (1971).

(2) The use of zinc (or iron) and refluxing hydrochloric acid has been reported to convert nitroxides to amines in a few isolated cases; the yields are 35% or less [N. C. Deno, private communication; H. Wieland and K. Roth, *Ber.*, **53**, 210 (1920)]. Recently, the catalytic hydrogenation, over Raney nickel, of di-*tert*-butyl nitroxide to di-*tert*-butylamine (60% yield) was reported by E. G. Rozantsev and R. S. Burmistrova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2364 (1968).

TABLE I
EFFECT OF SULFUR ON THE REACTION OF DI-*tert*-BUTYL NITROXIDE WITH SODIUM SULFIDE NONAHYDRATE IN DMF IN THE LIGHT[a]

Time, hr	% Reaction	(100 Atom % of S[b] Added)
0.5	0	26
1.0	1	100
2.0	8	
4.0	35	
8.0	100	

[a] By vpc. [b] Relative to nitroxide.



III IV (2)

data for the di-*tert*-butyl nitroxide case. While these reductions go in the dark, they proceed more rapidly in the light. For example, in 14 hr the reduction of eq 1 goes only 21% in the dark whereas a duplicate experiment employing two ordinary 20-W fluorescent lights is 83% complete in this time. All this suggests that the sulfide reduction of nitroxides may well be a chain process involving radical intermediates.

Aside from its value as a synthetic and degradative procedure, the reaction of nitroxides with sodium sulfide is of interest because nitroxides are employed as mechanistic probes in a variety of ways.[3] One wonders, therefore, what other nucleophiles will reduce nitroxides. Preliminary experiments in hexamethylphosphoramide reveal that di-*tert*-butyl nitroxide is also destroyed by sodium thiophenoxide at room temperature (ordinary room light); on the other hand, the nitroxide is not affected by sodium azide, sodio malonic ester, sodium nitrite, sodium benzenesulfinate, and the lithium salt of 2-nitropropane.[4]

Experimental Section

Reduction of Di-*tert*-butyl Nitroxide.—Di-*tert*-butyl nitroxide[5] (5.66 g, 39.2 mmol), sodium sulfide nonahydrate (50 g, 208 mmol), and sulfur (1.33 g, 0.0416 g-atom) were stirred under nitrogen in 150 ml of DMF between two 20-W fluorescent light bulbs for 2 hr and the resulting mixture was then poured into *ca.* 200 ml of ice–water. The aqueous phase was saturated with potassium carbonate and extracted with pentane, and the pentane solution was washed with water and dried over anhydrous magnesium sulfate. Distillation gave 3.25 g (65% yield) of pure di-*tert*-butylamine: bp 119–120°; n^{24}D 1.4100; ir (neat) 3.0, 6.8, 7.2, 7.3, 8.2 μ; nmr (CCl_4) δ 0.45 (1 H, broad), 1.18 (18 H); mass spectrum (75 eV) *m/e* (rel intensity) 131 (0.15), 130 (0.38), 129 (M, 3.63), 114 (14.1), 58 (100).

Anal. Calcd for $C_8H_{19}N$: C, 74.34; H, 14.82; N, 10.84. Found: C, 74.50; H, 15.00; N, 10.96.

Reduction of 2,2,6,6-Tetramethylpiperidine Nitroxide (I).—A solution of 5.55 g (35.6 mmol) of 2,2,6,6-tetramethylpiperidine nitroxide[6] (I) in 120 ml of DMF was stirred with sodium sulfide nonahydrate (42.7 g, 178 mmol) under N_2 between two 20-W fluorescent lights for 11 hr. On work-up 2.5 g (50% yield) of pure 2,2,6,6-tetramethylpiperidine was isolated: bp 57.5–58.5° (9.5 mm); n^{20}D 1.4451; ir (neat) 3.0, 3.45, 6.9, 7.3, 8.1 μ; nmr (CCl_4) δ 0.6 (1 H), 1.1 (12 H), 1.5 (6 H). A small-scale reaction was greatly accelerated by the addition of 100 atom % of sulfur (relative to I).

Reduction of 2,2,6,6-Tetramethyl-4-piperidinol Nitroxide (III).—This nitroxide[6] (3.70 g, 21.4 mmol) and sodium sulfide nonahydrate (26.4 g, 110 mmol) were stirred in 75 ml of DMSO under nitrogen while exposed to the fluorescent lights. After 63 hr the reaction mixture was poured into ice–water and continuously extracted with pentane. After washing with water and drying the solvent was removed and the crude product was chromatographed on acid-washed alumina. Vacuum sublimation gave 2.57 g (81% yield) of white crystals: mp 127.5–128.5°, and a mixture melting point with authentic 2,2,6,6-tetramethyl-4-piperidinol (mp 128–128.5°) was undepressed; ir ($CHCl_3$) 3.0, 3.4, 6.9, 7.3, 8.2 μ; nmr (CCl_4) δ 0.8 (0.5 H), 1.0 (0.5 H), 1.15 (6 H), 1.2 (6 H), 1.8 (2 H), 2.0 (2 H), 4.0 (1 H). A small-scale reaction in DMF was greatly accelerated by the addition of 100 atom % of sulfur (relative to III).

Registry No.—II, 768-66-1; IV, 2403-88-5; di-*tert*-butylamine, 21981-37-3.

Acknowledgment.—We thank Eli Lilly and Company and the National Science Foundation for generous support.

(3) N. Kornblum and S. D. Boyd, *J. Amer. Chem. Soc.*, **92**, 5784 (1970); N. Kornblum, S. D. Boyd, H. W. Pinnick, and R. G. Smith, *ibid.*, **93**, 4316 (1971); E. G. Janzen, *Accounts Chem. Res.*, **4**, 31 (1971).

(4) These experiments were monitored by esr.

(5) A. K. Hoffmann, A. M. Feldman, E. Gelblum, and A. Henderson, *Org. Syn.*, **48**, 62 (1968).

(6) R. Briere, H. Lemaire, and A. Rassat, *Bull. Soc. Chim. Fr.*, 3273 (1965).

A Convenient Method for the Preparation of Naphthyl Ethers and Sulfides[1]

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We have recently reported the reactions of the monohalonaphthalenes with alkoxide[3,4] and mercaptide[5] bases in dimethyl sulfoxide (DMSO). The products of these reactions were the alkylnaphthyl ethers[3,4] and sulfides.[5]

Aromatic ethers in general are easy to prepare. The appropriate naphthol is treated with an alkyl halide in the presence of sodium hydroxide.[6] *tert*-Butyl ethers cannot be prepared in this manner. Sahyun and Cram first reported the preparation of *tert*-butylphenyl ether by treating bromobenzene with *tert*-butoxide in DMSO.[7] Bromonaphthalene cannot be used to prepare *tert*-butylnaphthyl ethers because a mixture of *tert*-butyl-1- and 2-naphthyl ethers are obtained in this reaction.[4] Fluoronaphthalene, on the other hand, reacted to yield only the one ether product.[3] Pure *tert*-butylnaphthyl ethers can also be prepared by treating the naphthyl Grignard reagent with *tert*-butyl perbenzoate.[8]

The reaction was carried out by adding the DMSO, *tert*-butyl alcohol, potassium *tert*-butoxide, and 2-fluoronaphthalene in that order to the reaction vessel at 70°

(1) This work was supported by the Research Division, Brigham Young University.

(2) National Defense Education Act Fellow, 1967–1970.

(3) R. H. Hales, J. S. Bradshaw, and D. R. Pratt, *J. Org. Chem.*, **36**, 314 (1971).

(4) J. S. Bradshaw and R. H. Hales, *ibid.*, **36**, 318 (1971).

(5) J. S. Bradshaw, J. A. South, and R. H. Hales, *ibid.*, in press.

(6) See, for example, D. M. Musser and H. Adkins, *J. Amer. Chem. Soc.*, **60**, 664 (1938).

(7) M. R. V. Sahyun and D. J. Cram, *Org. Syn.*, **45**, 89 (1965).

(8) C. Frisell and S. D. Lawesson, *Org. Syn.*, **41**, 91 (1961).

and stirring for 14 hr. These conditions gave the maximum yield of *tert*-butyl-2-naphthyl ether (38%) while keeping the yield of 2-naphthol to a minimum (27%). The naphthol is a degradation product of the *tert*-butylnaphthyl ether.[4] An excellent yield of purified *n*-butyl-2-naphthyl ether (84%) was obtained at 150° using this process.

The alkylnaphthyl sulfides are not as readily available. One preparative method is the acid-catalyzed reaction of naphthol and a mercaptan.[9] In our reaction, 2-bromonaphthalene was added to a mixture of DMSO, *n*-butyl mercaptan, and sodium methoxide and the resulting solution was refluxed for 1 hr. *n*-Butyl-2-naphthyl sulfide was obtained in a 58% yield. This reaction has been carried out on 1- and 2-fluoronaphthalene as well as 1- and 2-bromonaphthalene using both *n*-butyl and *tert*-butyl mercaptans.[5]

Experimental Section

Materials.—2-Fluoronaphthalene was obtained from P. C. R. Inc. 2-Bromonaphthalene and dimethyl sulfoxide (DMSO) were obtained from J. T. Baker Chemical Co. The DMSO was passed through silica gel and stored over Linde 4A, $^1/_{16}$-in. molecular sieves before using. Sodium methoxide (Olin Matheson Co.) and potassium *tert*-butoxide (M. S. A. Research Corp.) were kept in sealed containers. 1-Butanethiol was purchased from Aldrich Chemical Co. and stored over molecular sieves.

Preparation of *tert*-Butyl-2-naphthyl Ether.—A mixture of DMSO (140 g, 1.8 mol) and 30.5 g (0.41 mol) of *tert*-butyl alcohol was heated to 70° in a 500-ml, three-necked, round-bottom flask equipped with a magnetic stirrer, thermometer, reflux condenser, and addition funnel. Potassium *tert*-butoxide (31.0 g, 0.28 mol) was added and the mixture was stirred until all the base dissolved. 2-Fluoronaphthalene (20.0 g, 0.14 mol) dissolved in 20 g of DMSO (total DMSO in the reaction mixture = 160 g, 2.05 mol) was rapidly added and the resulting mixture was stirred at 70° for 14 hr. The reaction mixture was then added to 50 ml of ice water and extracted four times with 200-ml portions of ether. The combined ether extracts were washed with aqueous sodium hydroxide and dried over anhydrous magnesium sulfate. The filtered ether extract was distilled to give 4.67 g (23%) of starting 2-fluoronaphthalene, bp 75–90° (1 mm), and 8.2 g (38%, based on amount of starting material actually used) of *tert*-butyl-2-naphthyl ether, bp 95–105° (1 mm), n^{22}D 1.5740 (lit.[10] n^{22}D 1.5724). The infrared spectrum of this compound was the same as that previously reported.[10]

The aqueous reaction mixture was acidified to pH 1 with concentrated hydrochloric acid and extracted with ether. The ether extracted yielded 4.25 g (27%) of 2-naphthol.

Prepartion of *n*-Butyl-2-naphthyl Ether.—This reaction was carried out in the same manner as the above reaction except that potassium metal (10.1 g, 0.28 mol) was dissolved in 51 g (0.69 mol) of *n*-butyl alcohol to make the base–alcohol portion of the reaction mixture. A dark yellow solid (26.03 g) was obtained after the ether extract was evaporated. Five grams of this material was recrystallized twice from a 90% aqueous alcohol solution to yield 4.5 g of *n*-butyl-2-naphthyl ether, mp 33.5–34.5° (lit.[11] mp 33–35°). The total yield of purified ether would be 22.4 g (84%).

Preparation of *n*-Butyl-2-naphthyl Sulfide.—Twenty grams (0.096 mol) of 2-bromonaphthalene in 44 g of DMSO was added to a mixture of 70 g of DMSO, 43.6 g (0.48 mol) of 1-butanethiol, and 15.7 g (0.29 mol) of sodium methoxide at reflux temperature (110°) in the same apparatus as reported above. The reaction mixture was worked up as in the *tert*-butyl-2-naphthyl ether reaction to yield 12.12 g (58%) of *n*-butyl-2-naphthyl sulfide, bp 147–152° (1 mm), n^{25}D 1.6205 (lit.[5] n^{25}D 1.6195). The infrared spectrum for this compound was the same as that previously reported.[5]

(9) F. M. Furman, J. H. Thelin, D. W. Hein, and W. B. Hardy, *J. Amer. Chem. Soc.*, **82**, 1450 (1960).

(10) J. S. Bradshaw, N. B. Nielsen, and D. P. Rees, *J. Org. Chem.*, **33**, 259 (1968).

(11) E. Wenkert, R. D. Youssefyeh, and R. G. Lewis, *J. Amer. Chem. Soc.*, **82**, 4675 (1960).

Registry No.—*tert*-Butyl-2-naphthyl ether, 15052-11-6; *tert*-butyl alcohol, 75-65-0; 2-fluoronaphthalene, 323-09-1; *n*-butyl-2-naphthyl ether, 10484-56-7; *n*-butyl alcohol, 71-36-3; *n*-butyl-2-naphthyl sulfide, 5286-43-1; 2-bromonaphthalene, 580-13-2; 1-butanethiol, 109-79-5.

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Lead Tetraacetate Oxidation of Guanylhydrazones. A Novel Rearrangement

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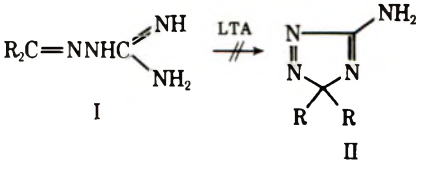
Nitrogen-containing heterocyclic compounds have been synthesized by the oxidative cyclization of ketone or aldehyde semicarbazones, acylhydrazones, *N*-alkylsemicarbazones, thiosemicarbazones, and carbohydrazones.[1]

By analogy, lead tetraacetate oxidation of a guanylhydrazone I should have led to the formation of a triazole derivative II.



I II

Addition of molar quantities of lead tetraacetate to a dichloromethane solution of acetophenone guanylhydrazone[2] resulted in 35% yield of a compound which showed a molecular ion at *m/e* 144. Increasing the quantity of lead tetraacetate to 2 equiv gave a nearly quantitative yield. The infrared spectrum of this compound showed an intense band at 2200 cm^{-1}, in accordance with the structure III shown in Scheme I. Similarly, the nmr spectrum showed only the two signals for the methyl and the phenyl groups at 2.77 and 7.72 ppm, respectively.

Treatment of this compound with dilute boiling HCl followed by extraction with chloroform gave a liquid which was shown to be acetophenone. Evaporation to dryness of the aqueous layer gave a solid which had an identical infrared spectrum with that of a sample of cyanamide which had been treated with acetophenone and hydrochloric acid as above.

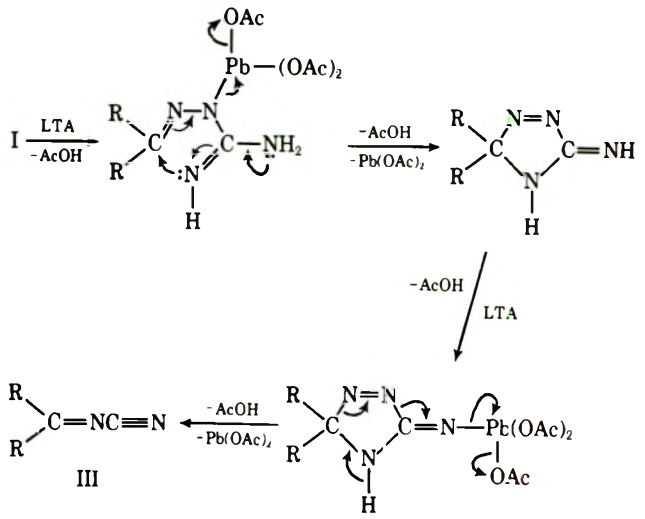
The oxidative conversion of guanylhydrazones into cyanimino derivatives is visualized as proceeding through the sequence shown in Scheme I.

(1) J. Warkentin, *Synthesis*, **1**, 279 (1970).

(2) E. Wedekind and S. Bronstein, *Justus Liebigs Ann. Chem.*, **307**, 3041 (1899).

J. Org. Chem., Vol. 37, No. 12, 1972 2053

SCHEME I



According to this mechanism under the reaction conditions used the intermediate triazole sought is unstable and is further oxidized to give a cyanimino derivative.

The results (Table I) show that starting with a guanylhydrazone and using lead tetraacetate as an oxidant one can obtain a new class of ketone derivatives.

TABLE I

SYNTHESIS OF CYANIMINO KETONES

RR'C=NC≡N

Registry no.	R	R'	Yield, %	Mp, °C
34441-01-5	Phenyl	Methyl	76	68–69[b]
34441-02-6	α-Naphthyl	Methyl	79	71–72[c]
34427-53-7	β-Naphthyl	Methyl	84	118–119[d]
34414-10-3	Phenyl	Phenyl	74	81–83[b]

[a] Satisfactory analyses (±0.2% for C and H) were reported for all compounds: Ed. [b] Recrystallized from ether–petroleum ether. [c] Recrystallized from ether. [d] Recrystallized from acetone.

Experimental Section

All melting points were taken with a Kofler hot stage apparatus and are uncorrected. Nmr spectra were determined using a Varian A-60A spectrometer. Infrared spectra were obtained from a Leitz Model III. Mass spectra were run on a Varian Model CH5 instrument.

General Procedure for the Oxidation of Guanylhydrazones.—To a solution of 0.02 mol of the guanylhydrazone in a mixture of 10 ml of glacial acetic acid and 90 ml of dichloromethane, at room temperature, was added a solution of 0.04 mol of lead tetraacetate (70% in acetic acid) in 50 ml of dichloromethane dropwise, during a period of 30 min. The mixture was allowed to stand for 1 hr. Water was added and the dichloromethane layer was separated, washed with sodium bicarbonate solution, and dried. After evaporation of the dichloromethane the residue was recrystallized from an appropriate solvent. Melting points are given in Table I.

Hydrolysis of Cyaniminoacetophenone.—Cyaniminoacetophenone (1.0 g) in 20 ml of 6 *N* HCl was refluxed for 0.5 hr. The solution was extracted with chloroform. The chloroform layer was dried and evaporated. The liquid residue was found to be identical with acetophenone. The aqueous layer was evaporated to dryness. The solid residue gave an infrared spectrum that was superimposable on that given by a sample of material obtained from the treatment of acetophenone and cyanamide hydrochloride as above.

Registry No.—Lead tetraacetate, 546-67-8.

7-Trimethylsilylcycloheptatriene

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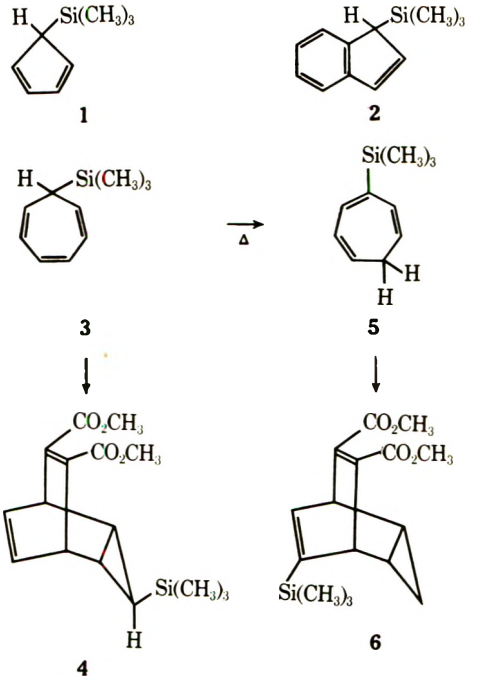
5-Trimethylsilylcyclopentadiene (**1**)[1–6] and 1-trimethylsilylindene (**2**)[7–9] show thermal [1,5] sigmatropic migrations of hydrogen and silicon. However, silicon migration occurs approximately 10^6 faster than that of hydrogen in both systems.[4,9,10] In order to test the generality of these rapid silicon migrations, we have examined 7-trimethylsilylcycloheptatriene (**3**) and have found that hydrogen migration occurs exclusive of silicon in this case.



7-Trimethylsilylcycloheptatriene can be prepared by the CuCl-catalyzed addition of trimethylsilyldiazomethane[11] to benzene. The yellow **3** was identified by elemental analysis and its pmr spectrum: ($CDCl_3$) τ 9.9 (s) [9 H, $Si(CH_3)_3$], 8.5 (t) (1 H, allylic), 4.0 (t) (2 H, vinylic), 3.8–4.2 (m) (4 H, vinylic). Reaction with dimethyl acetylenedicarboxylate gave a 1:1 adduct, assigned structure **4** on the basis of its pmr spectrum: ($CDCl_3$) τ 10.1 (s) [9 H, $Si(CH_3)_3$], 9.7 (t) (1 H, CHSi), 8.7 (m) (2 H, *tert*-cyclopropyl), 6.2 (s) (6 H, OCH_3), 5.9

(1) H. P. Fritz and C. G. Kreiter, *J. Organometal. Chem.*, **4**, 313 (1965).
(2) Y. A. Ustynyuk, A. V. Kisin, and O. E. Oksinoid, *J. Gen. Chem. USSR*, **38**, 389 (1968).
(3) A. Davison and P. E. Rakita, *Inorg. Chem.*, **9**, 289 (1970).
(4) A. J. Ashe, III, *J. Amer. Chem. Soc.*, **92**, 1233 (1970).
(5) S. McLean and G. W. B. Reed, *Can. J. Chem.*, **48**, 3110 (1970).
(6) K. W. Egger and T. L. James, *J. Organometal. Chem.*, **26**, 335 (1971).
(7) A. Davison and P. E. Rakita, *Inorg. Chem.*, **8**, 1164 (1969); *J. Organometal Chem.*, **21**, P 55 (1970); **23**, 407 (1970).
(8) R. B. Larrabee and B. F. Dowden, *Tetrahedron Lett.*, 915 (1970).
(9) A. J. Ashe, III, *ibid.*, 2105 (1970).
(10) For the rate of hydrogen migration in indene see W. R. Roth, *ibid.*, 1009 (1964).
(11) D. Seyferth, A. W. Dow, H. Menzel, and T. C. Flood, *J. Amer. Chem. Soc.*, **90**, 1080 (1968).

(m) (2 H, bridgehead position), and 3.9 (m) (2 H, vinyl). The stereochemistry has been assumed to be analogous to other cycloheptatriene–dienophile adducts.[12]

Heating **3** to 170° for 1 hr leads to irreversible changes in its pmr spectrum[13] indicating its isomerization to **5**. A new trimethylsilyl singlet at τ 9.8 and a new allylic triplet at τ 7.9 appear as well as a more complicated pattern in the vinyl region. Addition of dimethyl acetylenedicarboxylate to this mixture of **3** and **5** gave a new adduct **6** as well as **4**. The structure of **6** follows from its pmr spectrum: ($CDCl_3$) τ 9.9 (s) [10 H, Si-$(CH_3)_3$ and one *sec*-cyclopropyl], 9.5 (t) (1 H, *sec*-cyclopropyl), 8.6 (m) (2 H, *tert*-cyclopropyl), 6.2 (s) (6 H, OCH_3), 5.9 (m) (2 H, bridgehead position), 3.8 (dd) (1 H, vinyl). Qualitatively the rate of [1,5] hydrogen migration of **3** is not greatly different from that of other cycloheptatrienes.[14]

In order to detect possible silicon migration in **3**, 7-trimethylsilylcycloheptatriene-1,2,3,4,5,6-d_6 (**7**) was prepared from benzene-d_6 and trimethylsilyldiazomethane. The pmr spectrum of this material showed only a broad singlet at τ 8.5 for the unique ring proton in addition to the trimethylsilyl peak. Silicon migration would be observed by the conversion of this proton from an allylic to a vinylic position. However the only changes in the pmr spectrum[13] of **7** on heating, to 170° for 1 hr were the appearance of the new allylic proton at τ 7.9 of hexadeuterio-**5** as well as its trimethylsilyl peak. No new vinylic protons could be detected after more than half of **7** was gone, indicating that the rate of silicon migration must be at least an order of magnitude slower than that of hydrogen.

The facile migration of silicon compared to hydrogen in systems **1** and **2** coupled with its relative inertness in **3** demonstrate the different requirements for migration of the two atoms. Perhaps it is more difficult for the large trimethylsilyl to bridge the concave face of the nonplanar cycloheptatriene ring.[14,15] This steric difficulty should be minimized in the nearly planar **1** and **2**.[16]

(12) M. J. Goldstein and A. H. Gevirtz, *Tetrahedron Lett.*, 4413 (1965). A. H. Gevirtz, Ph.D. Dissertation, Cornell University, 1965; *Diss. Abstr.*, **26**, 5716 (1966); J. Bordner and G. H. Wahl, Jr., *J. Org. Chem.*, **36**, 3630 (1971).

(13) Pmr spectrum in benzene-d_6.

(14) A. P. Ter Borg, H. Kloosterziel, and N. Van Meurs, *Recl. Trav. Chim. Pays-Bas*, **82**, 717 (1963); A. P. Ter Borg and H. Kloosterziel, *ibid.*, **82**, 741 (1963).

(15) For conformational studies of 7-substituted cycloheptatrienes see H. Günther, M. Görlitz, and H.-H. Hinrichs, *Tetrahedron*, **24**, 5665 (1968).

(16) R. B. Larrabee, *J. Amer. Chem. Soc.*, **93**, 1510 (1971), has found that [1,5] metal shifts occur faster than hydrogen shifts in 7-triphenylstannylcycloheptatriene. This contrasts with **3** and is perhaps due to the known greater migratory aptitude of tin. See footnotes 1, 3, 7, and 8.

Experimental Section

General.—Glpc analyses were performed with a Varian Aerograph 90P chromatograph using a 20 ft × 0.25 in. column containing 20% Carbowax 20 M on Chromosorb W and a 5 ft × 0.25 in. column containing 20% Apiezon L on Chromosorb W. The pmr spectra were recorded using a Varian T-60 instrument. Peak positions were recorded to the nearest 0.1 ppm relative to internal TMS. Elemental analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

Trimethylsilyldiazomethane.—The procedure of Seyferth[11] was modified slightly in that product was extracted with mineral oil instead of benzene to facilitate separation by distillation. It always contained approximately 30% hexamethyldisiloxane.

7-Trimethylsilylcycloheptatriene (3).—Trimethylsilyldiazomethane (4.0 g) in 50 ml of benzene was added dropwise over 6 hr to a stirred mixture of 0.3 g of CuCl in benzene at reflux. After an additional 1 hr at reflux the mixture was filtered and solvent was removed by distillation through a 30-cm tantalum spiral column. This left 5 g of crude product, which was purified by glpc on an Apiezon L column. Besides residual solvent the major component (retention time 3 min at 40 lb He, 140°) was 7-trimethylsilylcycloheptatriene. *Anal.* Calcd for $C_{10}H_{16}Si$: C, 73.09; H, 9.89. Found: C, 73.01; H, 9.86.

Dimethyl 3-Trimethylsilyltricyclo[3.2.2.0^{2,4}]-6,8-nonadiene-6,7-dicarboxylate (4).—Trimethylsilylcycloheptatriene (0.5 g) and dimethyl acetylenedicarboxylate (0.75 g) in 0.5 ml of benzene were sealed under nitrogen in a glass tube. The mixture was heated to 160° for 0.5 hr, causing considerable darkening. Glpc on the Carbowax column showed a single component (retention time 10.5 min at 60 lb He, 240°). The material was collected. Its spectra were consistent with structure **4**. *Anal.* Calcd for $C_{16}H_{22}O_4Si$: C, 62.72; H, 7.24. Found: C, 62.51; H, 7.15.

Dimethyl 8-Trimethylsilyltricyclo[3.2.2.0^{2,4}]-6,8-nonadiene-6,7-dicarboxylate (6).—7-Trimethylsilylcycloheptatriene (0.5 g) and 0.5 ml of benzene-d_6 were sealed in an nmr tube. The tube was heated to 170° for 1 hr, at which time the nmr spectrum was recorded and showed peaks associated with **5** in addition to those of **3**. Attempted separation of this mixture on a variety of glpc columns was unsuccessful.

Excess dimethyl acetylenedicarboxylate (0.75 g) was added to the mixture and it was heated to 160° for 0.5 hr. Glpc (Carbowax, 60 lb He at 240°) showed two peaks (retention time 9.5 and 10.5 min). Both were collected and the high retention time peak was shown to be **4**. The lower retention time peak was an isomer. *Anal.* Calcd for $C_{16}H_{22}O_4Si$: C, 62.72; H, 7.24. Found: C, 62.68; H, 7.17. The pmr spectrum was consistent with structure **6**.

Pyrolysis of 7.—This material was prepared from benzene-d_6 and trimethylsilyldiazomethane in the same manner as **3**. Heating to 170° for 1 hr in benzene-d_6 gave partial conversion to hexadeuterio-**5**, although no vinyl hydrogen peaks were noted in the pmr spectrum.

Registry No.—**3**, 34542-20-6; **4**, 34542-21-7; **6**, 34578-23-9.

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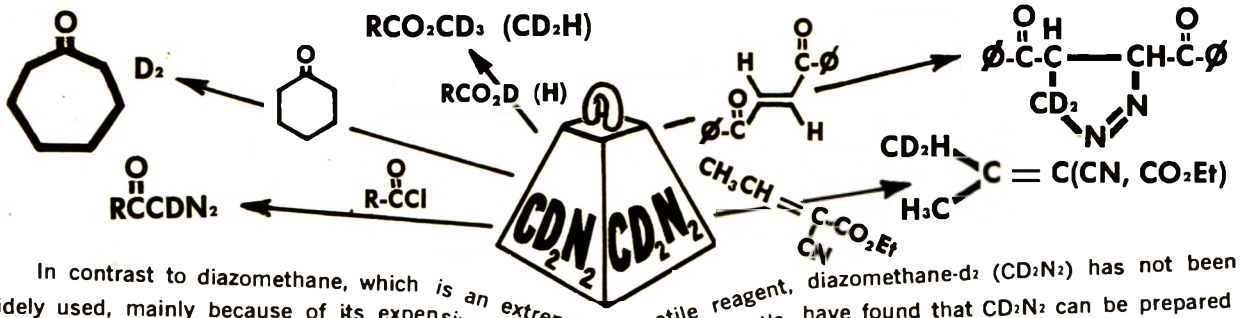

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(1) J. R. Campbell, Chemistry and Industry, (1972), in press.
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