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THE JOURNAL OF Organic Chemistry®

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Pyrido[2,3-*d*]pyrimidines. II. Synthesis of Ribonucleosides of 4-Oxo- and 2,4-Dioxopyrido[2,3-*d*]pyrimidines[1]

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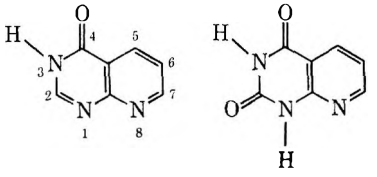
Received March 14, 1972

The syntheses of 1-β-D-ribofuranosyl-4-oxopyrido[2,3-*d*]pyrimidine and 1- and 8-β-D-ribofuranosyl-2,4-dioxopyrido[2,3-*d*]pyrimidine are described. The site of ribosylation in each case is assigned by uv and pmr comparisons with requisite *N*-methyl model compounds. The assignment of anomeric configuration is based upon pmr spectroscopy. A facile N-8 → N-1 ribosyl rearrangement is described.

Significant antitumor activity against Walker muscular carcinosarcoma in rats has recently been demonstrated for 4-oxopyrido[2,3-*d*]pyrimidine[2] (**1**, NSC 112518) and 2,4-dioxopyrido[2,3-*d*]pyrimidine[2] (**2**, NSC 112519). It was, therefore, of interest to undertake the synthesis of certain ribonucleoside derivatives of **1** and **2** as potential antitumor and antiviral agents.



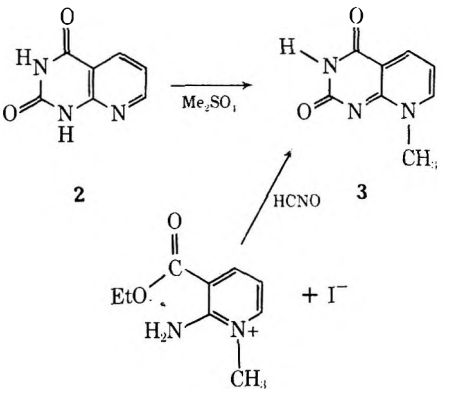
1 **2**

Despite the extensive literature describing the synthesis of pyrido[2,3-*d*]pyrimidines,[3] there are no reported examples of nucleosides of this ring system. Ribonucleosides of the related quinazoline ring system have been previously reported.[4]

There are three possible sites of N-alkylation on the pyrido[2,3-*d*]pyrimidine nucleus, namely, positions 1, 3, and 8. In a study involving the chemical synthesis of nucleosides of **1** and **2**, therefore, it was necessary to obtain model compounds in order to ascertain the position of N-ribosylation. *N*-Methyl derivatives, which have been widely used as models in the proof of site of substitution of the sugar moiety of nucleosides,[5] were chosen as the appropriate model compounds. The synthesis of ribonucleosides of **1** and **2** and the necessary *N*-methyl model compounds comprises the basis for this report.

Results and Discussion

***N*-Methyl Model Compounds.**—As noted above, three sites of N-alkylation are possible for both **1** and **2**. It was necessary, therefore, to synthesize two *N*-methyl isomers of each in order to unambiguously determine the site of N-ribosylation by physical methods. Examination of the structure of 2,4-dioxopyrido[2,3-*d*]pyrimidine (**2**) suggested that alkylation in neutral aprotic media should result in selective alkylation at N-8, since N-1 and N-3 are amide-type nitrogens –CONH– which already bear a proton. Methylation of **2** with dimethyl



2 **3** **4**

(1) (a) Paper I in this series: J. L. Shim, R. Niess, and A. D. Broom, *J. Org. Chem.*, **37**, 578 (1972). (b) Supported by Research Grant T491 from American Cancer Society, Research Grant CA 12823 from the National Cancer Institute, NIH, and Training Grant CA 5209 from the National Cancer Institute, NIH.

(2) R. K. Robins and G. H. Hitchings, *J. Amer. Chem. Soc.*, **77**, 2267 (1955).

(3) For a recent review, see W. J. Irwin and D. B. Wibberley, *Advan. Heterocycl. Chem.*, **10**, 149 (1969).

(4) (a) M. G. Stout and R. K. Robins, *J. Org. Chem.*, **33**, 1219 (1968); (b) M. G. Stout and R. K. Robins, *J. Heterocycl. Chem.*, **6**, 89 (1969).

(5) A. M. Michelson, "The Chemistry of Nucleosides and Nucleotides," Academic Press, New York, N. Y., 1963.

TABLE I

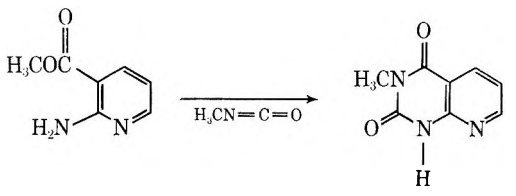
PROTON MAGNETIC RESONANCE FREQUENCIES (δ) FOR VARIOUS PYRIDO[2,3-*d*]PYRIMIDINE DERIVATIVES

Compd no.	Solvent	C-2 H	C-5 H	C-6 H	C-7 H	N-3 CH_3	N-8 CH_3	C-1′ H
1	DMSO-d_6	8.22 (s)	8.40 (d of d)	7.45 (q)	8.83 (d of d)			
2	DMSO-d_6		8.17 (d of d)	8.17 (q)	8.50 (d of d)			
2	A[a]		8.00 (d of d)	6.91 (q)	8.25 (d of d)			
3	A[a]		8.23 (d of d)	6.97 (t)	8.37 (d of d)		3.76 (s)	
5	DMSO-d_6		8.01 (d of d)	7.01 (q)	8.40 (d of d)	3.20 (s)		
5	A[a]		8.00 (d of d)	6.83 (q)	8.33 (d of d)	3.30 (s)		
6	DMSO-d_6	8.50 (s)	8.36 (m)	7.46 (q)	8.86 (d of d)	3.50 (s)		
7	DMSO-d_6	8.20 (s)	8.57 (d)	7.32 (t)	8.70 (d)		4.05 (s)	
10	DMSO-d_6		8.25 (d of d)	7.26 (m)	8.55 (d of d)			6.56 (d), $J_{1',2'}$ = 3.5 Hz
12	DMSO-d_6	8.41 (s)	8.41 (d of d)	7.46 (q)	8.83 (m)			6.03 (d), $J_{1',2'}$ = 3 Hz
14	DMSO-d_6		8.31 (d of d)	6.93 (t)	8.88 (d of d)			6.38 (s)
14	A[a]		8.21 (d of d)	6.86 (t)	8.45 (d of d)			6.30 (s)

[a] A, mixture of D_2O–DMSO-d_6 (75:25). All other spectra were run in DMSO-d_6 solution; DSS as internal reference. All spectra were obtained on a 60-MHz Jeol nmr instrument; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

sulfate in anhydrous dimethylformamide indeed gave the expected 8-methyl derivative **3**. Compound **3** was established as the 8-methyl derivative by an unambiguous synthetic procedure. Methylation of ethyl 2-aminonicotinate[6] according to Hirai[7] gave 2-amino-3-carbethoxy-1-methylpyridinium iodide (**4**). Condensation of **4** with cyanic acid gave **3**. The uv and pmr spectra of **3** prepared by either route were superimposable.

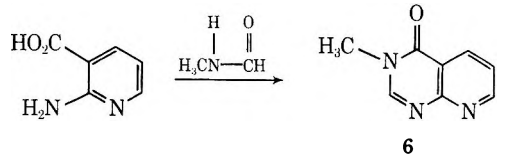
The synthesis of 3-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidine (**5**) had been previously reported by Capuano, *et al.*[8] Attempts to repeat this procedure resulted only in the recovery of starting material; the product described as melting at 226° was not obtained. However, when methyl 2-aminonicotinate was refluxed with methyl isocyanate in pyridine, a 76% yield of the desired product **5** having a melting point of 274–275°



5

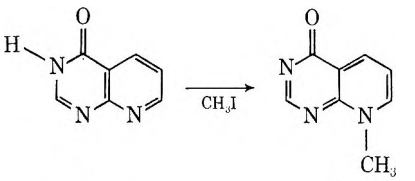
was obtained. This product gave the correct elemental analysis for **5**; the pmr spectrum showed a singlet (three protons) at δ 3.2 corresponding to the *N*-methyl group at position 3.

A somewhat similar procedure involving a high-temperature condensation of 2-aminonicotinic acid with *N*-methylformamide afforded 3-methyl-4-oxopyrido-[2,3-*d*]pyrimidine (**6**).



6

Methylation of 4-oxopyrido[2,3-*d*]pyrimidine (**1**) with methyl iodide in dimethyl sulfoxide gave only the 8-methyl derivative **7** in 57% yield plus starting material. This demonstrated that the most nucleophilic center in **1**



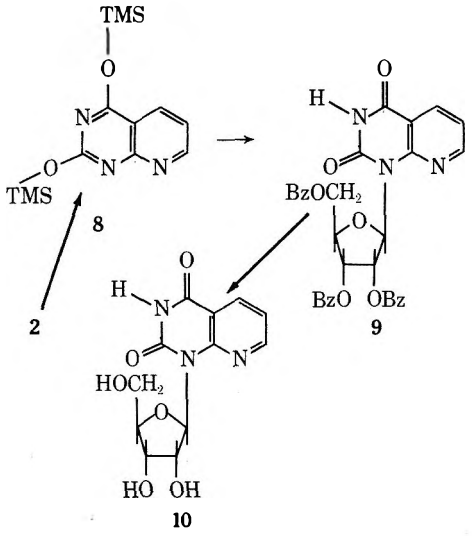
1 **7**

is N-8, at least under the conditions employed in this alkylation reaction. The assignment of the site of alkylation as N-8 rather than N-1 was based on pmr spectroscopy. It is known that N-methylation of pyridine[9] and also fused ring systems containing a pyridine ring[10] causes downfield shifts of the pyridine ring γ-position proton signals and either upfield or downfield shifts of the α-proton signals (the "α effect").[10b] Examination of the data in Table I reveals that the signal for the C-5 H (pyridine ring γ position) of **7** appears 0.17 ppm *downfield* from the corresponding signal in **1** and the C-7 H signal occurs 0.13 ppm upfield relative to that of **1**. In the case of 3-methyl-4-oxopyrido[2,3-*d*]pyrimidine (**6**) and 1-ribosyl derivative (*vide infra*), a pronounced downfield shift of the C-2 proton resonance was observed, as expected,[11] but there was essentially no change in the chemical shift of the pyridine ring proton resonances (C-5, C-6, C-7, Table I) relative to the parent compound **1**.

Nucleosides.—The use of trimethylsilyl derivatives of nitrogen heterocycles in nucleoside syntheses[12,13] circumvents difficulties associated with the low solubility and high melting point of the pyrido[2,3-*d*]pyrimidines used in this work. The present study required the attachment of a β-D-ribofuranosyl moiety to position 1 of 2,4-dioxopyrido[2,3-*d*]pyrimidine (**2**). Trimethylsilylation of **2** with hexamethyldisilazane gave 2,4-bis(trimethylsilyloxy)pyrido[2,3-*d*]pyrimidine (**8**). Integration of the pmr spectrum of **8** indicated the presence of six Si–CH_3 groups. Treatment of **8** with freshly prepared 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in dry acetonitrile gave a complex mixture from which 2,4-dioxo-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-

(6) H. H. Fox, *J. Org. Chem.*, **17**, 547 (1952).
(7) H. Hirai, *Chem. Pharm. Bull.*, **14**, 861 (1966).
(8) L. Capuano, M. Welter, and R. Zander, *Chem. Ber.*, **102**, 3698 (1969).
(9) R. J. Chuck and E. W. Randal, *J. Chem. Soc. B*, 261 (1967).
(10) (a) D. J. Blears and S. S. Danyluk, *Tetrahedron*, **23**, 2927 (1967); (b) J. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1969, p 82.
(11) A. D. Broom and R. K. Robins, *J. Org. Chem.*, **24**, 1025 (1969).
(12) M. W. Winkley and R. K. Robins, *ibid.*, **33**, 2822 (1968).
(13) L. Birkhofer, A. Ritter, and H. P. Keuhltan, *Angew. Chem.*, **75**, 209 (1963).

pyrido[2,3-*d*]pyrimidine (**9**) was isolated by a chromatographic procedure. Treatment of **9** with methanolic sodium methoxide gave 2,4-dioxo-1-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (**10**). The pre-

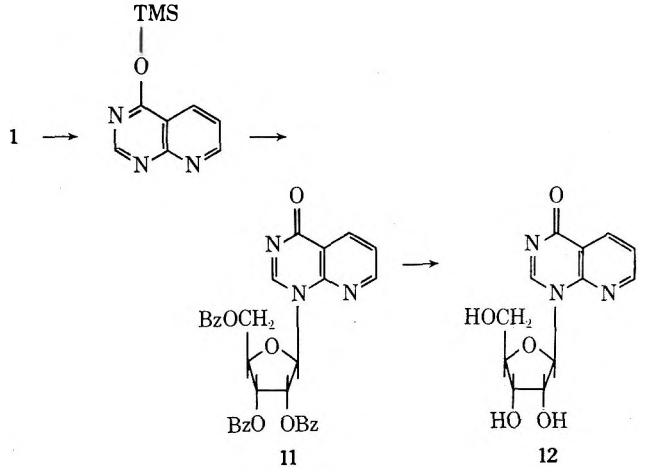


TMS = trimethylsilyl, Bz = benzoyl

dominate formation of the β anomer would be expected on the basis of previous studies in the quinazoline series[4] and of Baker's "trans rule."[14] The configurational assignment of **10** was supported by the small coupling constant of the anomeric proton ($J_{1',2'}$ = 3.5 Hz).[15]

Assignment of the site of ribosylation was made by uv comparisons with the *N*-methyl model compounds previously described. The uv spectra of 2,4-dioxo-3-methylpyrido[2,3-*d*]pyrimidine (**5**) were quite similar to those of **2** at pH 1 and 7 (Table II). At pH 11, however, a 23-nm bathochromic shift in the long wavelength absorption maximum of **5** relative to **2** was observed. Since the monoanion of each was present in this alkaline medium, this established N-3 H in compound **2** as the more acidic proton. The uv spectrum of **10** at pH 11 was dissimilar to those of **5**, **3**, and the 8-(β-D-ribofuranosyl) derivative **14** (*vide infra*), but quite similar to that of **2** (Table II). This firmly established that **10** is, in fact, the N-1-substituted nucleoside.

A similar procedure was used for the synthesis of 1-(β-D-ribofuranosyl)-4-oxopyrido[2,3-*d*]pyrimidine (**12**).



(14) B. R. Baker, *et al.*, *J. Org. Chem.*, **19**, 1786 (1954).

(15) R. U. Lemieux and D. R. Lineback, *Annu. Rev. Biochem.*, **32**, 155 (1963).

TABLE II
ULTRAVIOLET ABSORPTION DATA FOR VARIOUS PYRIDO[2,3-*d*]PYRIMIDINE DERIVATIVES

Compd no.	pH 1 λ_{max}, nm	pH 1 ϵ_{max}	pH 7 λ_{max}, nm	pH 7 ϵ_{max}	pH 11 λ_{max}, nm	pH 11 ϵ_{max}
1	270	4200	270	4,200	280	4,200
	317	7950	317	4,200	323	7,400
2	305	8000	306	8,050	263	9,150
					310	8,950
3[a]	237	5850	237	6,300	257	10,100
	311	9700	27[illegible]	11,400	356.5	8,150
			353	8,500		
5	305	6700	304	6,750	265	11,200
					333	5,150
6	270	3950	270	5,600	270	6,150
	278	3850	299	6,350	290	6,850
	320	8200	309 (s)	4,500	309 (s)	4,900
7	220	9500	247	7,200	246	8,600
	277	3300	285	1,750	284 (s)	1,750
	328	9650	360	7,750	361	8,600
10	301	6800	301	6,800	235	13,200
					261.5	3,850
					305	7,500
12	245 (s)	5500	263	5,550	269	6,100
	317	5300	300	5,000	300	5,000
			313	3,600	313	3,800
14[a]	237	6450	272	16,200	258	10,100
	306	7750	356.5	13,500	359	7,500

[a] Acidic spectra were obtained in 1*N* HCl, pH ~0.

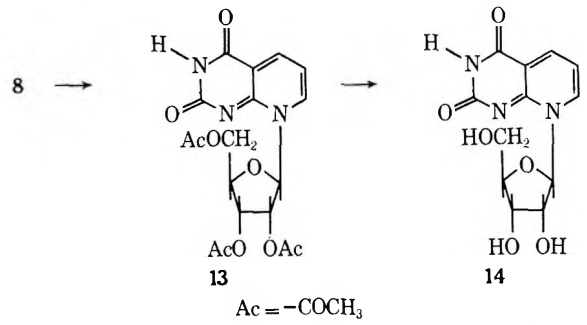
Assignment of position of ribosylation in **12** was based on uv and pmr spectrometry. The uv spectrum of **12** at pH 11 (Table II) was unlike those of 3-methyl-4-oxopyrido[2,3-*d*]pyrimidine (**6**) and the 8-methyl derivative (**7**). This confirms that **12** is the 1-ribosyl derivative. This assignment is further supported by the pmr data (Table I). As previously noted (*vide supra*) ribosylation at N-1 or methylation at N-3 leads to a downfield shift of the H-2 resonance, and alkylation at N-8 markedly alters the pyridine proton signals without changing the signal for H-2. Examination of the pmr data reveal that the spectrum of **12** is similar to that of 3-methyl-4-oxopyrido[2,3-*d*]pyrimidine (**6**) and totally unlike that of the 8-methyl derivative **7**, Since the uv data clearly eliminated 3-ribosylation, the assignment of **12** as a 1-substituted nucleoside is confirmed. A small coupling constant for the anomeric proton ($J_{1',2'}$ = 3.0 Hz) again permitted assignment of the β configuration.[15]

It was previously noted that methylation of compounds **1** and **2** in nonaqueous, essentially neutral media occurred at the most nucleophilic nonprotonated site (the N-8 position). Ribosylation of **1** and **2** under similar conditions gave, on the other hand, the 1-ribosyl derivatives. This result may be explained on the basis that bromo sugars usually contain HBr carried along in the isolation procedure. Furthermore, they are unstable, giving HBr on decomposition. The presence of HBr in solution with either **1** or **2** would result in N-protonation at position 8, thus directing alkylation with the sugar to the pyrimidine ring.

The synthesis of the 8-ribosyl derivative of **2** was achieved only by using the condensation procedure of Furukawa and Honjo.[16] A solution of **8** in dry chlorobenzene was treated with tetra-*O*-acetyl-β-D-ribofura-

(16) Y. Furukawa and M. Honjo, *Chem. Pharm. Bull.*, **16**, 1076 (1968).

nose and anhydrous aluminum chloride at room temperature to give the 8-ribosyl derivative **13**. Deblocking with methanolic ammonia gave 2,4-dioxo-8-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (**14**).



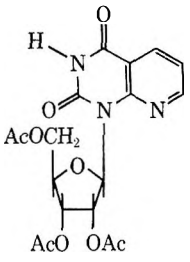
13 **14**

Ac = −COCH3

Assignment of the position of alkylation with the sugar in **14** as N-8 was based on the close similarity between the uv spectra of **14** and of 2,4-dioxo-8-methylpyrido[2,3-*d*]pyrimidine (**3**) at pH 0, 7, and 11.[17]

Further confirmation of 8-ribosylation in **14** was obtained from the pmr data (Table I). As noted earlier, the pmr signal of H-5 is the most sensitive to N-8 substitution. The signals for H-5 of both the 8-methyl (**3**) and 8-ribosyl (**14**) derivatives appear 0.2 ppm downfield from those of the parent compound **2** and the 3-methyl derivative (**5**). The β configuration was confirmed by the observation that the signal for the anomeric proton appeared as a rather broad singlet ($J_{1',2'} < 1$ Hz).[15,18]

Alteration of the reaction conditions for the preparation of **13** by adding dropwise a solution of tetra-*O*-acetyl-D-ribofuranose in chlorobenzene to a hot mixture of **8** and $AlCl_3$ in chlorobenzene gave mainly the 1-ribosyl derivative (**15**). This may be explained by



15

assuming that **15** is the more thermodynamically stable product and that a facile rearrangement from N-8 to N-1 may be taking place at the higher temperature. This was confirmed by heating for 3 min a mixture of **13**, $AlCl_3$, and chlorobenzene. A rapid rearrangement occurred to give only **15** as judged by thin layer chromatography. Analogous N-3 → N-9 alkyl and glycosyl migrations have been described for purine derivatives.[19,20]

It is of interest that, while application of the $AlCl_3$ procedure[16] for nucleoside synthesis from **2** gave the desired **13**, this and every other procedure attempted with 4-oxopyrido[2,3-*d*]pyrimidine (**1**) gave mostly the 1-ribosyl derivatives; none of the 8-ribosyl isomer was formed in any case. This may well be attributed to an extremely facile rearrangement of an 8-ribosyl to a 1-ribosyl derivative in this case. This argument receives support from the finding that, in the case of 4-oxoquinazoline, which lacks the pyridine nitrogen at N-8,[4] and 6-methylpyrimidines,[12] alkylation is directed to N-3 rather than N-1.

Experimental Section

2,4-Dioxo-8-methylpyrido[2,3-*d*]pyrimidine (3). Method A.—To a suspension of 800 mg of **2**[2] (6.12 mmol) in 25 ml of *N*,*N*-dimethylformamide was added 2.0 ml of dimethyl sulfate. The reaction mixture was heated on a steam bath for 24 hr. The clear dark red solution was poured into 600 ml of methylene chloride with continuous stirring. The yellow precipitate was filtered and washed with methylene chloride. The precipitate was suspended in acetone and neutralized with concentrated aqueous ammonium hydroxide. The precipitate was filtered, dissolved in 25 ml of boiling water, and kept at 5° for crystallization. The yellow fine powder was filtered, washed with a little cold water, and air-dried to give 550 mg (48.9%), mp >360°. *Anal.* Calcd for $C_8H_7N_3O_2$: C, 54.25; H, 3.96; N, 23.74. Found: C, 54.53; H, 4.31; N, 23.91.

Method B.—2-Amino-3-carboxyethyl-*N*-methylpyridinium iodide[7] (301 mg, 1.0 mmol) was dissolved in 15 ml of ethanol. Potassium cyanate (160 mg, 2.20 mmol) and 2.0 ml of glacial acetic acid were added, and refluxing was continued for a total of 24 hr. The precipitate was filtered, washed with ethanol, and air-dried. The solid was crystallized from water to yield 120 mg (68.5%), mp >360°. Uv and pmr spectra were identical with those of the compound prepared by method A.

2,4-Dioxo-3-methylpyrido[2,3-*d*]pyrimidine (5). Method A.—Methyl 2-aminonicotinate (1.0 g, 6.6 mmol) was dissolved in 25 ml of pyridine. Methyl isocyanate (1.0 ml) was added, and the mixture was refluxed for 16 hr. The dark red solution was evaporated to dryness. The residue was refluxed with 40.0 ml of ethanol, and the precipitate was filtered. The precipitate was crystallized from 30 ml of a methanol–H_2O mixture to yield 0.9 g (76%), mp 274–275°. A sample was dried *in vacuo* over refluxing toluene for elemental analysis. *Anal.* Calcd for $C_8H_7N_3O_2 \cdot 0.5H_2O$: C, 51.60; H, 4.31; N, 22.65. Found: C, 51.70; H, 4.31; N, 22.99.

Method B.—2,4-Dioxopyrido[2,3-*d*]pyrimidine (1.0 g, 6.2 mmol) was dissolved in 100 ml of 1 *N* aqueous NaOH. Dimethyl sulfate (882 mg, 7 mmol) was added, and the mixture was stirred at room temperature for 4 hr. Another 882-mg portion of dimethyl sulfate was added. The mixture was stirred overnight. The solution was acidified with glacial acetic acid to pH 5 and filtered. A yellow precipitate formed upon concentrating the filtrate to 60 ml. The precipitate was filtered, washed with little cold water, and crystallized from water to yield 160 mg (15%), mp 274–275°. A mixture melting point was not depressed.

3-Methyl-4-oxopyrido[2,3-*d*]pyrimidine (6).—2-Aminonicotinic acid (1.0 g, 7.25 mmol) and 2 g of *N*-methylformamide (33.6 mmol) were heated together at an oil bath temperature of 180° for 5 hr. The solution solidified on cooling, and the product was recrystallized from ethanol. The small needles were filtered, washed with a little cold ethanol, and air-dried to yield 600 mg (51.2%), mp 204–205°. *Anal.* Calcd for $C_8H_7N_3O$: C, 59.60; H, 4.35; N, 26.10. Found: C, 59.65; H, 4.64; N, 26.21.

8-Methyl-4-oxopyrido[2,3-*d*]pyrimidine (7).—To a solution of 800 mg of 4-oxopyrido[2,3-*d*]pyrimidine (5.45 mmol) dissolved in 25 ml of dry dimethyl sulfoxide was added 2.0 ml of methyl iodide. The solution was stirred at room temperature for 36 hr

(17) (a) Whereas compound **14** showed a λ_{max} at 359 nm at pH 1 or 7, the λ_{max} of **3** shifted from 353 to 311 nm upon changing the pH from 7 to 1. This difference at pH 1 was apparently due to the difference in pK_a of **3** *vs.* **14** created by the electron-withdrawing effect of the ribosyl group relative to a methyl group. By comparison with a methyl substituent, a ribosyl moiety has a net electron-withdrawing (−*I*) effect. This is demonstrable by a comparison of the greater basiciy of 9- methylhypoxanthine (pK_a = 1.86) relative to inosine (pK_a = 1.2). Adjustment of solutions of **3** and **14** to pH of about 0 resulted in the disappearance of the absorption at 350–360 nm with the concomitant appearance of a peak at 306 nm for **14** and 311 nm for **3**, supporting the assignment of N-8 substitution in **14**. (b) A. R. Katritzky, "Physical Methods in Heterocyclic Chemistry," Vol. I, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, p 100.

(18) Coupling constants of 1.0 Hz or less are unusual in the β-D-ribofuranoside series, but by no means unprecedented. See, for example, R. J. Rousseau, R. K. Robins, and L. B. Townsend, *J. Heterocycl. Chem.*, **4**, 311 (1967).

(19) M. Miyaki and B. Shimizu, *Chem. Pharm. Bull.*, **18**, 732 (1970).

(20) B. Shimizu and M. Miyaki, *ibid.*, **18**, 579 (1970).

in a stoppered flask. The dark red solution was poured into 700 ml of methylene chloride with continuous stirring. The yellow precipitate was filtered and air-dried. The precipitate was dissolved in water and neutralized with concentrated ammonium hydroxide solution to pH 7.0. Acetone was added and the clear solution was kept at 5° for crystallization. The long yellow crystals were filtered, washed with acetone, and dried to yield 650 mg (57%), mp 253–254° dec. *Anal.* Calcd for $C_8H_7N_3O$: C, 59.60; H, 4.35; N, 26.10. Found: C, 59.49; H, 4.62; N, 26.41.

General Method for the Preparation of the Trimethylsilyl Derivatives of 2,4-Dioxo- and 4-Oxopyrido[2,3-*d*]pyrimidine.—The appropriate pyrido[2,3-*d*]pyrimidine was dried by refluxing in toluene (Dean-Stark water trap), and the mixture was cooled. A few crystals of ammonium sulfate and 2.0 ml of hexamethyldisilazane for every 1 g of base were added. The mixture was refluxed for 24 hr, the solution was filtered, and the filtrate was evaporated to near dryness under reduced pressure. The residue was distilled *in vacuo* at oil bath temperature of 160–170°. The solidified distillate was collected and stored in a stoppered flask in the refrigerator for use.

2,4-Dioxo-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (9).—To a solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (obtained from 47 g of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-ribofuranose and 40 g of dry hydrobromic acid)[21] in 500 ml of dry acetonitrile, 17.0 g of molecular sieves (4A, 1/16-in. pellets) and 26.2 g of 2,4-bis(trimethylsilyloxy)pyrido[2,3-*d*]pyrimidine (85.0 mmol) were added. The flask was stoppered, and the mixture was stirred for 72 hr. The mixture was filtered, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 130 ml of ethanol and 40 ml of water and heated to reflux for 5 min. The solution was evaporated to dryness. The solid residue was triturated with 300 ml of chloroform for 2 days. The chloroform solution was filtered and evaporated to dryness to give 40 g of solid. A 5-g sample of this solid residue was dissolved in 10 ml of chloroform and applied to a column of silicAR 7 G (1 m in length and 10 cm in diameter, holding 2 lb of silicAR 7 G). The column was eluted with chloroform. The first 1300 ml of elute was discarded. The next 400 ml contained a mixture of two compounds. A third fraction (200 ml) contained only the desired compound. This fraction was evaporated to dryness, and the oily residue was crystallized from benzene–cyclohexane to yield 0.8 g (15%), mp 114°. *Anal.* Calcd for $C_{33}H_{25}N_3O_9$: C, 65.12; H, 4.12; N, 6.93. Found: C, 64.93; H, 4.28; N, 6.75.

2,4-Dioxo-1-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (10).—A 0.4-g sample of 9 was dissolved in 30 ml of methanol saturated with ammonia at 0°. The flask was sealed and kept at room temperature overnight. The solution was evaporated under reduced pressure, and the residue was crystallized from methanol to yield 150 mg (75%), mp 193–194°. *Anal.* Calcd for $C_{12}H_{13}N_3O_6$: C, 48.90; H, 4.42; N, 14.25. Found: C, 48.75; H, 4.52; N, 14.12.

4-Oxo-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (11).—To the 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide obtained from 11.5 g of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose[21] in 120 ml of dry acetonitrile, 4.9 g of 4-trimethylsilyloxypyrido[2,3-*d*]pyrimidine (22.4 mmol) suspended in 15.0 ml of acetonitrile was added with stirring. Stirring was continued overnight. The clear solution was evaporated to dryness, and the solid was dissolved in 75 ml of boiling ethanol. Distilled water (20 ml) was added, and the solution was cooled to room temperature over 4 hr and filtered to give 6.6 g, mp 190–194°. Crystallization several times from a benzene–cyclohexane mixture gave a product of mp 194–195°. *Anal.* Calcd for $C_{33}H_{25}N_3O_8$: C, 67.00; H, 4.26; N, 7.10. Found: C, 67.61; H, 4.36; N, 7.22.

4-Oxo-1-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (12).—To a solution of 0.108 g of sodium methoxide in 25 ml of methanol was added 500 mg of 11. The solid was dissolved by heating on a steam bath. The solution was left at room temperature overnight. The solvent was removed *in vacuo*, and the powder was extracted with ether and filtered. The residue was dissolved in methanol and Amberlite 120 (prewashed with methanol) added with stirring until the solution was neutral. The mixture was filtered and the filtrate was concentrated and kept at 5° overnight. The precipitate was filtered, washed with cold methanol, and air-dried to yield 0.200 g (85.5%), mp 174°. A sample was recrystallized from an isopropyl alcohol–water mixture. The crystals were dried *in vacuo*. *Anal.* Calcd for $C_{12}H_{13}N_3O_5 \cdot 0.5H_2O$: C, 50.00; H, 4.87; N, 14.6. Found: C, 49.99; H, 4.77; N, 14.53.

2,4-Dioxo-8-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (13).—2,4-Bistrimethylsilyloxypyrido[2,3-*d*]pyrimidine (3.75 g, 12.2 mmol), prepared by the general method, was added to 250 ml of dry chlorobenzene. The mixture was stirred for 3 min and 3.05 g of tetra *O*-acetyl-β-D-ribofuranose (9.6 mmol) was added. Anhydrous aluminum chloride (1.63 g, 11.2 mmol) was added gradually, and the mixture was cooled in an ice bath and neutralized with methanolic ammonia to apparent pH 7.0 (pHydrion paper). The mixture was filtered and the precipitate triturated well with 800 ml of $CHCl_3$ and filtered. The combined filtrate was evaporated under reduced pressure to a syrupy residue. The residue was dissolved in 2.0 l. of boiling diethyl ether. The solution was filtered, concentrated to 300 ml, and kept overnight. The fine yellow powder was filtered, washed with ether, and recrystallized from ethyl acetate to yield 1.20 g (30.3%), mp 99–100°. *Anal.* Calcd for $C_{18}H_{19}N_3O_9 \cdot 0.5H_2O$: C, 50.20; H, 4.66; N 9.78. Found: C, 50.45; H, 4.71; N, 9.49.

2,4-Dioxo-8-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (14).—Compound 13 (150 mg, 0.38 mmol) was dissolved in 25 ml of methanol saturated with ammonia at 0°. The flask was sealed and left at room temperature overnight. The crystals were filtered and washed with little cold methanol to yield 75 mg. Another crop was obtained from the filtrate by evaporation to dryness under reduced pressure and crystallization from a minimum volume of methanol. The precipitate was filtered to yield 90 mg (combined yield 82%), mp 235° dec. *Anal.* Calcd for $C_{12}H_{13}N_3O_6 \cdot H_2O$: C, 46.00; H, 4.80; N, 13.22. Found: C, 46.05; H, 4.75; N, 13.53.

Registry No.—**1**, 24410-19-3; **2**, 21038-66-4; **3**, 36259-09-3; **5**, 24541-54-6; **6**, 36259-11-7; **7**, 36259-12-8; **9**, 36259-13-9; **10**, 36259-14-0; **11**, 36259-15-1; **12**, 36259-16-2; **13**, 36208-02-3; **14**, 36208-03-4.

(21) W. W. Zorbach and R. S. Tipson, "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, Wiley-Interscience, New York, N. Y., 1968, p 161.

Pyrido[2,3-*d*]pyrimidines. III. Synthesis of Some 8-(β-D-Ribofuranosyl)pyrido[2,3-*d*]pyrimidines Structurally Related to the Antibiotic Sangivamycin[1]

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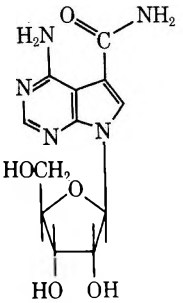
Received March 14, 1972

The chemical synthesis of a series of 6-carbethoxy- and 6-carboxamido-5-oxopyrido[2,3-*d*]pyrimidines *via* the requisite diethyl (6-pyrimidinyl)aminomethylenemalonates is described. Certain of these pyrido[2,3-*d*]pyrimidines are converted into 8-(β-D-ribofuranosyl) derivatives, which may be regarded as analogs of the antibiotic sangivamycin. A unique H–N–H geminal coupling in several 4-amino-5-oxo- and 4-amino-6-carboxamido-5-oxopyrido[2,3-*d*]pyrimidine derivatives is described.

The pyrrolo[2,3-*d*]pyrimidine nucleoside antibiotic sangivamycin (**1**) has been found to possess potent antitumor activity.[2,3] The pyrido[2,3-*d*]pyrimidine ring system may be regarded as a simple homolog of the pyrrolo[2,3-*d*]pyrimidine system. This consideration suggested the synthesis of pyrido[2,3-*d*]pyrimidine nucleoside analogs of sangivamycin (for example, **2**).



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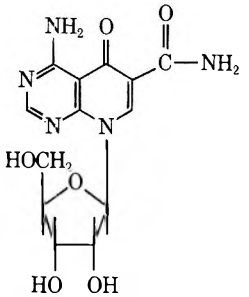

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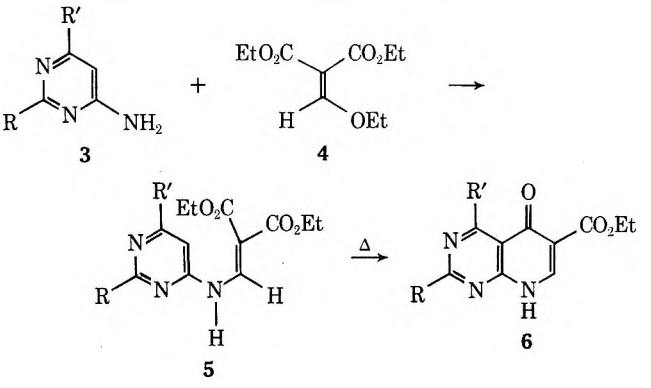
The synthesis and chemistry of the requisite pyrido[2,3-*d*]pyrimidine bases and nucleosides form the basis of this report.

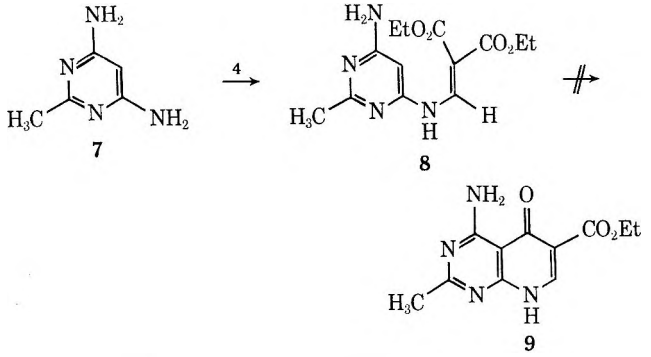
Results and Discussion

Pyrido[2,3-*d*]pyrimidine Bases.—A fundamental structural requirement for the synthesis of pyrido[2,3-*d*]pyrimidine analogs of **1** is the presence of a carboxamide function at position 6. Of the many routes available to the synthesis of the pyrido[2,3-*d*]pyrimidine system,[4] the Gould–Jacobs reaction is the method of choice for introduction of the desired functionality at C-6.[5] This reaction consists of the condensation of an appropriately substituted 6-aminopyrimidine (**3**) with diethyl ethoxymethylenemalonate (**4**) followed by thermal cyclization to the 5-oxo-6-carbethoxypyrido[2,3-*d*]pyrimidine (**6**).[6]

It has been suggested[6b] that an electron-releasing group in the pyrimidine moiety is essential to effect cyclization of the intermediate (6-pyrimidinyl)aminomethylenemalonate diester (**5**). It is, however, noteworthy that, while 4,6-diamino-2-methylpyrimidine (**7**) was condensed readily with **4** to give the intermediate **8**, repeated attempts to cyclize **8** to **9** were unsuccessful.[6]

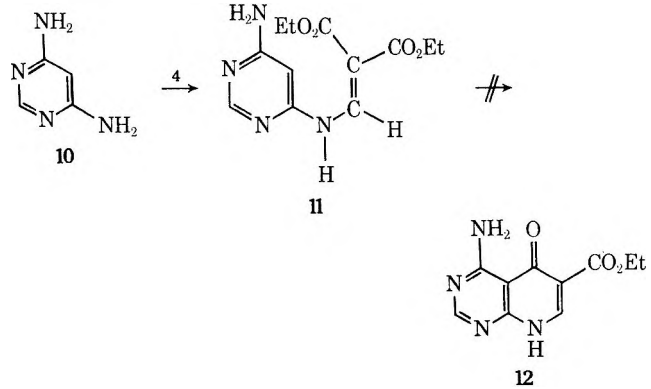


3 **4** **5** **6**



7 **8** **9**

The same situation prevailed in the reaction of 4,6-diaminopyrimidine (**10**) with **4**. The condensation product **11** was readily obtained in good yield and char-



10 **11** **12**

(1) (a) Supported by Research Grant No. CA 12823 from the National Cancer Institute, NIH. (b) Paper II in this series: B. H. Rizkalla, A. D. Broom, M. G. Stout, and R. K. Robins, *J. Org. Chem.*, **37**, 3975 (1972).

(2) J. A. Cavins, *Proc. Amer. Ass. Cancer Res.*, **7**, 12 (1966).

(3) J. A. Cavins, *et al.*, *Cancer Chemother. Rep.*, **51**, 197 (1967).

(4) For a recent review see W. J. Irwin and D. G. Wibberley, *Advan. Heterocycl. Chem.*, **10**, 149 (1969).

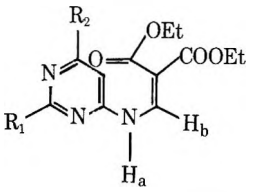
(5) L. A. Paquette, "Principles of Modern Heterocyclic Chemistry," W. A. Benjamin, New York, N. Y., 1968, p 280.

(6) (a) G. Y. Lesher and N. Y. Schodack, U. S. Patent 3,320,257 (1967); (b) S. Nishigaki, K. Ogiwara, K. Senga, S. Fukazawa, K. Aida, Y. Machica, and F. Yoneda, *Chem. Pharm. Bull.*, **18**, 1385 (1970).

acterized by elemental analysis and pmr spectra. The pmr spectrum of **11** revealed two singlets at δ 6.16 and 8.18 (Table I) corresponding to C-5 H and C-2 H, respectively, and doublets at δ 8.95 and 10.62 having the same coupling constant. Upon addition of D_2O to the solution the δ 8.95 doublet collapsed to a sharp singlet and the δ 10.62 doublet disappeared, permitting assignment of the former to the vinyl C–H and the latter to the adjacent N–H and confirming the structure of **11** as shown. Attempts to cyclize **11** to **12** under a variety of conditions failed, apparently because of a competing polymerization reaction.

TABLE I

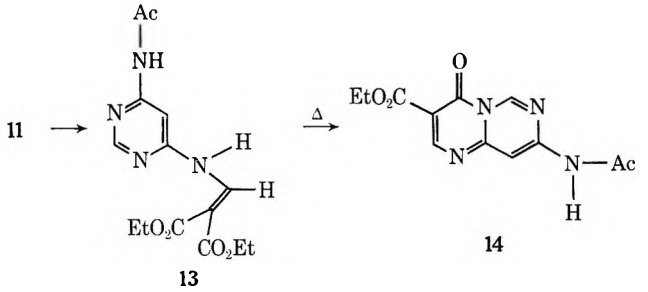
PROTON MAGNETIC RESONANCE FREQUENCIES FOR VARIOUS DIETHYL *N*-(6-PYRIMIDINYL)AMINOMETHYLENEMALONATES[a]



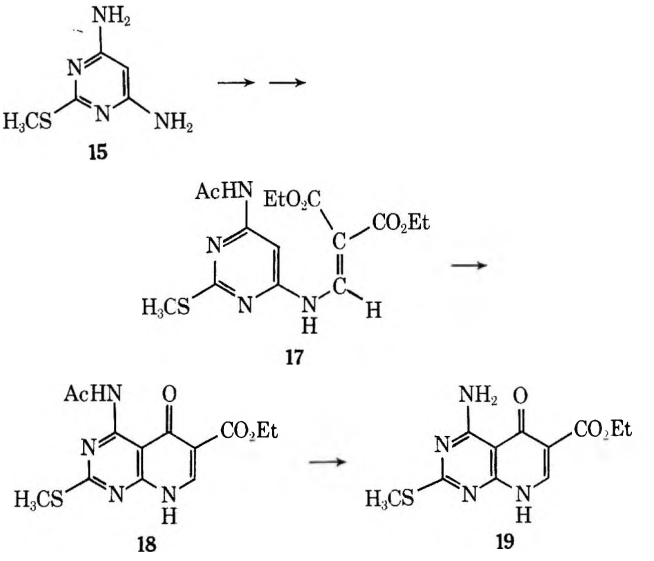
Compd no.	R_1		R_2		C-5		
	SCH_3	H	NH_2	$NHCOCH_3$	H	H_b	H_a
11		8.18 (s)	6.93 (s)		6.16 (s)	8.95 (d)	10.62 (d)
13		8.36 (s)		2.11 (s)	7.66 (s)	8.61 (d)	10.73 (d)
17	2.5 (s)			2.06 (s)	7.48 (s)	8.73 (d)	10.66 (d)
21		8.08 (s)			6.13 (s)	8.66 (d)	10.50 (d)
23	2.53 (s)				6.00 (s)	8.90 (d)	10.46 (d)

[a] All spectra run in DMSO-d_6 using DSS (2,2-dimethyl-2-silapentane sulfonate sodium salt) as internal reference.

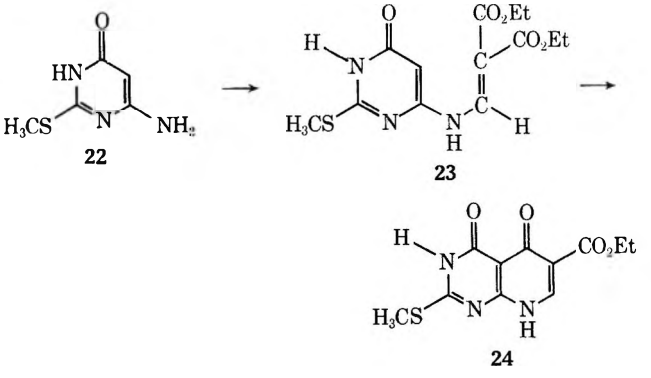
In an attempt to prevent the polymerization, **11** was N-acetylated to give **13**. Thermal cyclization of **13** gave a compound (**14**) which gave the correct elemental analysis for the *N*-acetyl derivative of **12**. The pmr spectrum of **14** revealed, however, that the product was not a pyrido[2,3-*d*]pyrimidine, but that cyclization had occurred at the pyrimidine ring nitrogen to give 8-acetamido-3-carbethoxy-4-oxopyrimido[1,6-*a*]pyrimidine (**14**). The assignment was based on the appearance of three 1-proton singlets in the pmr spectrum of **14** (not exchangeable with D_2O) at δ 8.0, 8.7, and 9.6. Only two such "aromatic" protons would be found in the *N*-acetyl derivative of **12**.



Because N-acylation markedly reduces the electron-donating capability of an amino group, a pyrimidine bearing an additional electron-releasing group, 4,6-diamino-2-methylthiopyrimidine (**15**),[7] was selected. Treatment of **15** with diethyl ethoxymethylenemalonate (**4**) gave the expected intermediate **16** which was acylated with acetic anhydride to give diethyl *N*-(4-acetamido-2-methylthio-6-pyrimidinyl)aminoethylenemalonate (**17**). It is noteworthy that, while thermal cyclization of **13** gave only the pyrimido[1,6-*a*]pyrimidine derivative in 70% yield, application of the same conditions to **17** gave only the desired 4-acetamido-6-carbethoxy-2-methylthio-5-oxopyrido[2,3-*d*]pyrimidine (**18**), also in about 70% yield. Alkaline hydrolysis of **18** in ethanolic sodium ethoxide afforded the 4-amino derivative (**19**).



Similar results were obtained in reactions leading to the 4,5-dioxopyrido[2,3-*d*]pyrimidines. Treatment of 4-amino-6-oxopyrimidine (**20**) with **4** gave the intermediate diethyl *N*-(4-oxopyrimidinyl)aminomethylenemalonate (**21**), but no conditions could be found for the cyclization of **21**. Again, however, it was found that 4-amino-2-methylthio-6-oxopyrimidine (**22**) could be readily converted into 6-carbethoxy-4,5-dioxo-2-methylthiopyrido[2,3-*d*]pyrimidine (**24**) *via* the usual intermediate (**23**). In each of these cyclization reactions the assigned structure is supported by the disappearance of the typical pyrimidine C-5 H signal in the pmr spectrum at about δ 6 together with the appearance of a new peak at about δ 8–8.5 characteristic of the α proton of a 4-pyridone type compound (C-7 H).

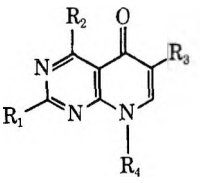


Pyrido[2,3-*d*]pyrimidine Nucleosides.—When applicable, the direct fusion of heterocyclic bases with fully acylated sugars is the most facile of the many methods

(7) D. Söll and W. Pfleiderer, *Chem. Ber.*, **96**, 2977 (1963).

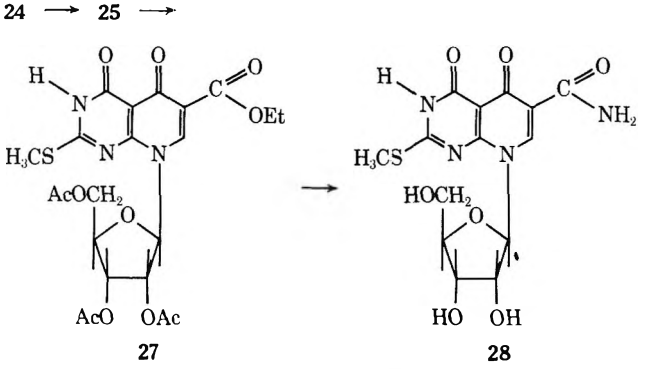
TABLE II

PROTON MAGNETIC RESONANCE FREQUENCIES (δ) FOR VARIOUS 5-OXOPYRIDO[2,3-*d*]PYRIMIDINE DERIVATIVES



Compd no.	R_1 SCH₃	R_1 H	R_2 NH₂	R_2 O‖NHCCH₃	R_3 —COOCH₂CH₃ CH₂	R_3 —COOCH₂CH₃ CH₃	R_3 —CONH₂	C-7 H	R_4 C-1′ H
2		8.21 (s)	8.83, (d), 9.43 (d) J_{H-N-H} = 4.0 Hz				7.60 (d), 8.50 (d) J_{H-N-H} = 4.4 Hz	8.91 (s)	6.38 (d) $J_{1',2'}$ = 4 Hz
18	2.5 (s)			2.5 (s)	4.15 (q)	1.28 (t)		8.16 (s)	
19	2.46 (s)		8.1 (d), 9.7 (d)		4.15 (q)	1.28 (t)		8.16 (s)	
24	2.53 (s)				4.23 (q)	1.3 (t)		8.33 (s)	
27	2.41 (s)				4.21 (m)	1.23 (t)		8.80 (s)	6.43 (d) $J_{1',2'}$ = 3 Hz
28	2.56 (s)						7.43 (br), 8.7 (br)	8.90 (s)	6.43 (d) $J_{1',2'}$ = 2.5 Hz
29	2.5 (s)			2.5 (s)	4.15 (m)	1.28 (t)		8.58 (s)	6.48 (d) $J_{1',2'}$ = 2.6 Hz
30	2.5 (s)		8.36 (d), 9.5 (d) J_{H-N-H} = 3.4 Hz				7.4 (d), 8.1 (d) J_{H-N-H} = 3.6 Hz	8.85 (s)	6.4 (d) $J_{1',2'}$ = 3 Hz

of nucleoside synthesis.[8] Because of the low solubility and high melting point of 6-carbethoxy-4,5-dioxo-2-methylthiopyrido[2,3-*d*]pyrimidine (**24**), direct fusion coupling with tetra-*O*-acetyl-D-ribofuranose is not practicable. These problems may be readily overcome, however, by trimethylsilylation of the heterocycle.[1b,9,10] Thus **24** was treated with hexamethyldisilazane in anhydrous toluene to give an uncharacterized trimethylsilyloxy derivative **25**. Compound **25** was fused with tetra-*O*-acetyl-D-ribofuranose (**26**) giving 6-carbethoxy-4,5-dioxo-2-methylthio-8-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (**27**). When **27** was subjected to the action of liquid ammonia at room temperature, the 6-carboxamido derivative of the free nucleoside (**28**) was obtained.



27 28

Proof of structure of **28** was based primarily on pmr spectrometry. It has been previously shown that substitution of an alkyl group for hydrogen on the nitrogen of a potentially tautomeric (lactam–lactim) heteroaromatic system results in a substantial downfield shift of the pmr signal for an adjacent proton.[11] A downfield shift of the C-7 H resonance of 0.57 ppm (Table II) is observed upon ribosylation of **24**, whereas the signal for the methyl protons of the 2-methylthio group remained unchanged; this permits assignment of N-8 as the site of alkylation. The uv spectrum of **28** resembles that of **24** at pH 7 (Table III), supporting the assignment of alkylation as N-8. Assignment of the anomeric configuration as β was based on the small coupling constant for H-1′ ($J_{1',2'}$ = 2.5 Hz).[12]

The synthesis of compound **2** was accomplished starting with the blocked pyrido[2,3-*d*]pyrimidine **18**. Compound **18** possessed melting point and solubility characteristics such that it was suitable for the direct fusion with tetra-*O*-acetyl-D-ribofuranose (**26**). Uncatalyzed fusion of **18** and **26** provided the fully blocked nucleoside **29** in good yield. Both the site of alkylation and the anomeric configuration of **29** were readily assigned by pmr spectroscopy in the same manner as described for nucleoside **28**. Thus alkylation with the sugar resulted in a downfield shift of 0.42 ppm for the C-7 proton resonance of **29** relative to that of the starting material **18** while the methyl proton signals of the 2-methylthio groups remained essentially unchanged. The $H_{1'},H_{2'}$ coupling constant ($J_{1',2'}$ =

(8) For a recent review see L. Goodman in "The Carbohydrates: Chemistry and Biochemistry," Vol. IIA, 2nd ed, W. Pigman and D. Horton, Ed., Academic Press, New York, N. Y., 1970, p 9.

(9) M. G. Stout and R. K. Robins, *J. Org. Chem.*, **33**, 1219 (1968).

(10) L. Birkhofer, A. Ritter, and H. P. Kuehlthan, *Angew. Chem.*, **75**, 209 (1963).

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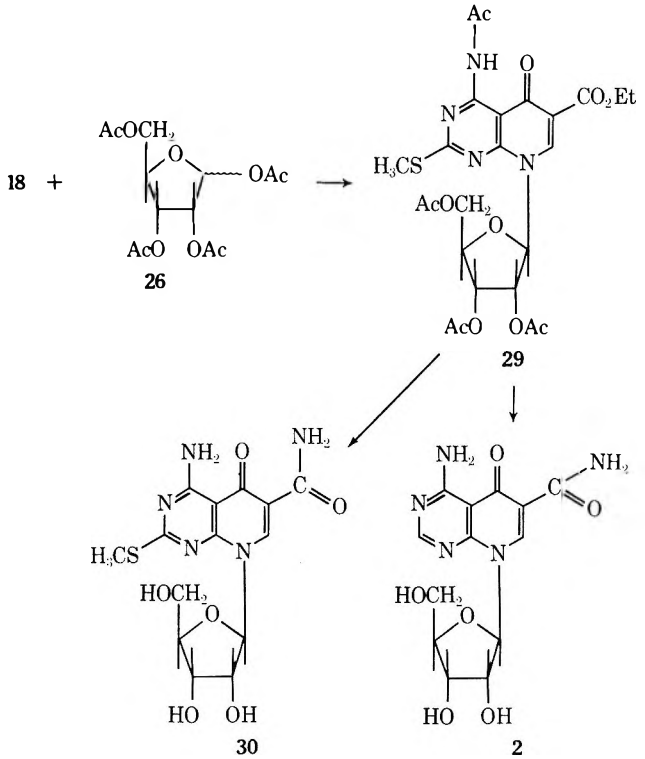
(12) R. U. Lemieux and D. R. Lineback, *Annu. Rev. Biochem.*, **32**, 155 (1963).

TABLE III
ULTRAVIOLET ABSORPTION DATA FOR VARIOUS PYRIDO[2,3-*d*]PYRIMIDINE DERIVATIVES

Compd	pH 1		pH 7		pH 11	
no.	λ_{max}, nm	ϵ	λ_{max}, nm	ϵ	λ_{max}, nm	ϵ
2	258	27,200	272	21,700	272	21,400
	294	11,250	300	15,800	300	15,900
18	272	43,100	276	40,500	262 (s)	26,700
	310 (s)	14,200	310 (s)	14,200	274 (s)	30,500
					287	33,600
					322 (s)	12,200
19	272	38,500	272	41,500	270	40,200
	294	18,400	297 (s)	14,800	318	17,200
24	267	31,500	267	37,000	267	38,750
	291	20,700	291 (s)	19,000	307	15,400
27	273	3,700	263	3,150	262 (s)	3,700
			273	3,750	272	4,000
28	273	34,400	263 (s)	25,500	263 (s)	34,000
	294	19,200	273	37,200	273	38,000
			294 (s)	17,600	301	13,300
29	276	23,000	276	23,600	275	21,800
	312	7,600	312	7,800	302	7,500
30	276	17,600	275	14,800	275	14,900
	302	39,500	302	40,500	302	42,500

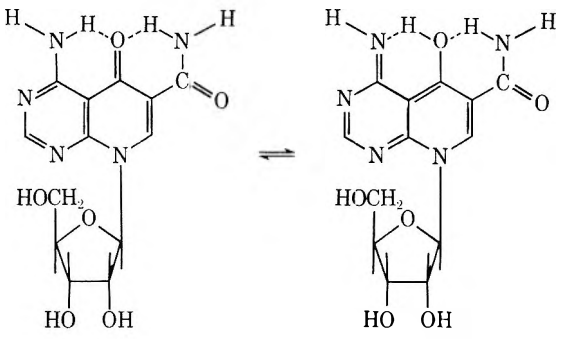
2.6 Hz) permits assignment of the β configuration to the anomeric carbon.[12]

Treatment of **29** with liquid ammonia at room temperature gave 4-amino-6-carboxamido-2-methylthio-5-oxo-8-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (**30**).



The blocked nucleoside **29** was also treated with Raney nickel followed by treatment of the product *in situ* with liquid ammonia to give the sangivamycin analog, 4-amino-6-carboxamido-5-oxo-8-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (**2**). The pmr spectrum of **2** revealed the loss of the signal due to the protons of the 2-methylthio function and the presence of two 1-proton singlets corresponding to C-2 H (δ 8.21) and C-7 H (δ 8.91).

Pmr Spectral Considerations.—The 4-amino-5-oxopyrido[2,3-*d*]pyrimidines and their ribonucleosides described above gave rise to unique and very interesting pmr spectra in DMSO-d_5 solution. The nucleoside **2** will be used for illustration. The amino group in the 4 position of **2** gave rise to two broad doublets at δ 8.83 and 9.43 (J_{H-N-H} = 4.0 Hz). The nonequivalence of the two N–H protons is not surprising; as clearly seen in structure **31a**, one of the protons may hydrogen bond



31a **31b**

intramolecularly (the chemical shifts remain unchanged upon dilution) to the 5-oxo group. Rotation about the C–N bond is slow on the pmr time scale; the downfield signal (δ 9.43) may thus be assigned to the proton which is hydrogen bonded to the 5-oxo group. Of two possible tautomers **31a** and **31b**, the former is established as the predominant form because of the observed H–N–H geminal coupling. It has been firmly established for a variety of ketamine systems involving a monoalkyl amine that H–N–C–H coupling only occurs when the hydrogen is bound to nitrogen and hydrogen bonded to oxygen as is the case with **31a**.[13] That such a geminal coupling is observed at all appears to be unique; similar amino–oxo hydrogen-bonded systems have been described,[14,15] but no geminal coupling was observed because of ^{14}N quadrupole broadening of the resonance signals of the amino protons. H–N–H geminal coupling has only been observed by application of double resonance techniques; ^{14}N heteronuclear decoupling in amides has demonstrated geminal coupling constants of about 2.4 Hz.[16] Examination of the N–H signals arising from the 6-carboxamide group in **2** revealed the same pattern of two doublets at δ 7.60 and 8.50 (J_{H-N-H} = 4.4 Hz); clearly, then, **2** exists primarily in the conformation shown in **31a**. It is presumed that geminal coupling is observed because of an increase in sp^2 character of the amino groups resulting from H-bond formation.[16]

Experimental Section[17]

Diethyl *N*-(4-Amino-6-pyrimidinyl)aminomethylenemalonate (11).—4,6-Diaminopyrimidine (1 g, 9 mmol) was heated with 1.8 g of diethyl ethoxymethylenemalonate (9 mmol) at an oil bath temperature of 165° for 20 min. The melt was cooled and dissolved in 120 ml of ethyl acetate and 20 ml of methanol by boil-

(13) R. N. Schut, W. G. Strycker, and T. M. H. Lill, *J. Org. Chem.*, **28**, 3046 (1963).
(14) G. O. Dudek and G. P. Volpp, *ibid.*, **30**, 50 (1965).
(15) R. Wasyleshen and T. Schaefer, *Can. J. Chem.*, **49**, 3575 (1971).
(16) H. Kamei, *Bull. Chem. Soc. Jap.*, **38**, 1212 (1965).
(17) Elemental analyses were performed by Heterocyclic Chemical Co., Harrisonville, Mo. Pmr spectra were run on a Jeolco C60H spectrometer at ambient temperature. Uv spectra were obtained using a Cary Model 15 spectrophotometer. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected.

ing. The solution was filtered; the filtrate was concentrated to 60 ml and kept at 5° overnight. The precipitate was filtered, washed with a little methanol and ethyl acetate, and dissolved in 60 ml of boiling methanol by adding 5 ml of ethyl acetate. The solution was treated with charcoal and filtered through a Celite pad. The filtrate was concentrated to 30 ml and kept at 5° overnight. The precipitate was filtered, washed with methanol, and dried *in vacuo* over refluxing toluene in the presence of phosphorus pentoxide to give 0.80 g (33%), mp 196–197°.

Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.70; H, 5.20; N, 20.10. Found: C, 51.50; H, 5.41; N, 20.11.

Diethyl *N*-(4-Acetamido-6-pyrimidinyl)aminomethylenemalonate (13).—A 1-g sample of **11** (3.6 mmol) was refluxed with 50 ml of acetic anhydride overnight. The acetic anhydride was removed *in vacuo*. The residue was dissolved in 60 ml of boiling ethanol, treated with charcoal, and filtered. The filtrate was concentrated to 50 ml and kept at 5° overnight. The yellowish white precipitate was filtered, washed with ethanol, and air-dried to give 0.68 g (60%), mp 204–205°.

Anal. Calcd for $C_{14}H_{18}N_4O_5$: C, 52.20; H, 5.60; N, 17.40. Found: C, 52.18; H, 5.56; N, 17.42.

8-Acetamido-3-carbethoxy-4-oxopyrimido[1,6-*a*]pyrimidine (14).—Compound **13** (1 g, 3.1 mmol) was heated in diphenyl ether at 205–210° internal temperature for 1 hr with stirring. The solution was cooled, and the brown precipitate was filtered. The precipitate was dissolved in 50 ml of a boiling chloroform–methanol mixture, treated with charcoal, and filtered. The filtrate was concentrated to 30 ml and kept at 5° overnight. The precipitate was filtered, washed with chloroform, and air-dried to give 0.60 g (70%), mp 263–264°. For analysis a sample was dried *in vacuo* over refluxing toluene in presence of phosphorus pentoxide.

Anal. Calcd for $C_{12}H_{12}N_4O_4$: C, 52.12; H, 4.35; N, 20.35. Found: C, 52.35; H, 4.25; N, 20.36.

Diethyl *N*-(2-Methylthio-4-amino-6-pyrimidinyl)aminomethylenemalonate (16).—A 6.30-g sample of 2-methylthio-4,6-diaminopyrimidine (20.0 mmol) was heated for 40 min with 4.00 g of diethyl ethoxymethylenemalonate (20 mmol) at 165°. The temperature was reduced to 135°, and heating was continued for another 60 min. The melt was cooled and dissolved in 150 ml of boiling ethanol, treated with charcoal, filtered, and concentrated to 80 ml. The solution was heated to reflux and water was added until the cloud point was reached. The solution was kept at 5° overnight. The yellowish precipitate was filtered, washed with ethanol, and air-dried to give 4.90 g (70%), mp 174–176°.

Anal. Calcd for $C_{13}H_{18}N_4O_4S$: C, 47.70; H, 5.20; N, 12.81; S, 9.8. Found: C, 47.44; H, 5.28; N, 12.43; S, 9.64.

Diethyl *N*-(4-Acetamido-2-methylthio-6-pyrimidinyl)aminomethylenemalonate (17). A 2.0-g sample of **16** (6.0 mmol) was refluxed overnight in 50 ml of acetic anhydride. The excess acetic anhydride was removed by distillation under reduced pressure. The residue was crystallized from 80 ml of an ethyl acetate–ethanol mixture (10:90). The precipitate was filtered, washed with cold ethanol, and dried over refluxing toluene in the presence of phosphorus pentoxide to give 1.5 g (68%), mp 164–164.5°.

Anal. Calcd for $C_{15}H_{20}N_4O_5S$: C, 48.90; H, 5.48; N, 15.22. Found: C, 48.81; H, 5.39; N, 15.31.

4-Acetamido-6-carbethoxy-2-methylthio-4-oxopyrido[2,3-*d*]pyrimidine (18).—A 1.3-g sample of **17** (3.70 mmol) was refluxed in 30 ml of Dowtherm A for 15 min. The solution was cooled to room temperature and diluted with 70 ml of diethyl ether. The precipitate was filtered, washed with diethyl ether, and air-dried. The residue was dissolved in 200 ml of 1,2-dimethoxyethane, treated with charcoal, and filtered. The filtrate was concentrated to 20 ml and kept at 5° overnight. The white precipitate was filtered, washed with cold 1,2-dimethoxyethane, and air-dried to yield 0.80 g (71.5%), mp 227–228°. For analysis a sample was dried over refluxing toluene in the presence of phosphorus pentoxide.

Anal. Calcd for $C_{13}H_{14}N_4O_4S$: C, 48.5; H, 4.35; N, 17.39. Found: C, 48.15; H, 4.36; N, 17.47.

4-Amino-6-carbethoxy-2-methylthio-5-oxopyrido[2,3-*d*]pyrimidine (19).—Compound **18** (1 g, 3.3 mmol) was dissolved in 150 ml of absolute ethanol. A solution of 0.2 g of metallic sodium (freshly cut) in 20 ml of absolute ethanol was added. The solution was refluxed for 20 min. The mixture was cooled and neutralized with acetic acid to pH 7.0. The solution was concentrated to about 30 ml, and the precipitate which formed was filtered, washed with ethanol, and dissolved in a hot mixture of 10 ml of water and 40 ml of ethanol. The solution was filtered hot and the filtrate left at room temperature. The precipitate was filtered, washed with ethanol, and air-dried to yield 0.80 g (86.5%), mp 274–275°. For analysis a sample was dried *in vacuo* over refluxing toluene in the presence of phosphorus pentoxide.

Anal. Calcd for $C_{11}H_{12}N_4O_3S \cdot H_2O$: C, 44.20; H, 4.70; N, 18.95. Found: C, 44.27; H, 4.66; N, 18.65.

Diethyl *N*-(4-Oxo-6-pyrimidinyl)aminomethylenemalonate (21).—Amino-6-oxopyrimidine (1.1 g, 10 mmol) and 1.97 g of diethyl ethoxymethylenemalonate (10 mmol) were refluxed in 15 ml of dimethylformamide for 9 hr. The reaction mixture was filtered. The filtrate was added to 180 ml of diethyl ether; the suspension was stirred for 1 min and filtered. The filtrate was kept at 5° overnight, and the bright yellowish orange precipitate was filtered and washed with diethyl ether to yield 0.85 g (30.5%), mp 190–191°.

Anal. Calcd for $C_{12}H_{15}N_3O_5$: C, 51.15; H, 5.35; N, 15.00. Found: C, 51.35; H, 5.37; N, 15.21.

Diethyl *N*-(2-Methylthio-4-oxo-6-pyrimidinyl)aminomethylenemalonate (23).—A 15.7-g sample of **22** (100 mmol) was heated for 1 hr with 19.8 g of diethyl ethoxymethylenemalonate (100 mmol) in a round-bottom flask immersed in an oil bath kept at 175–180°. The solid was dissolved in a boiling chloroform–methanol mixture, treated with charcoal, and filtered. The filtrate was concentrated and kept at 5° overnight. The precipitate was filtered, washed with cold methanol, and air-dried to give 20.6 g (66.7%), mp 232–234°. For analysis a sample was crystallized twice from $CHCl_3$–MeOH and dried *in vacuo*, mp 233–234°.

Anal. Calcd for $C_{13}H_{17}N_3O_5S$: C, 47.70; H, 5.20; N, 12.81; S, 9.80. Found: C, 47.44; H, 5.28; N, 12.43; S, 9.64.

6-Carbethoxy-4,5-dioxo-2-methylthiopyrido[2,3-*d*]pyrimidine (24).—Compound **23** (10 g, 32 mmol) were added to 150 ml of Dowtherm A. The mixture was heated to reflux for 20 min. The solution was cooled and the mixture treated with 300 ml of toluene and filtered. The brown precipitate was washed with toluene, dissolved in a chloroform–methanol mixture, treated with charcoal, and filtered. The solution was concentrated and kept at 5° overnight. The cream-colored precipitate was filtered, washed with methanol, and air-dried to give 6.23 g (73%), mp 269–270°. For analysis a sample was recrystallized twice from $CHCl_3$–MeOH and dried *in vacuo*, mp 270–271°.

Anal. Calcd for $C_{11}H_{11}N_3O_4S$: C, 47.01; H, 3.92; N, 14.96; S, 11.39. Found: C, 46.81; H, 4.06; N, 14.72; S, 11.19.

6-Carbethoxy-4,5-dioxo-2-methylthio-8-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (27).—A 2.3-g sample of compound **24** (8.15 mmol) was suspended in 180 ml of toluene and the mixture refluxed for 1 hr; 30 ml of toluene was distilled off. The mixture was cooled, and 4 ml of hexamethyldisilazane was added together with a few crystals of ammonium sulfate. The mixture was refluxed for 4 hr. The clear yellow solution was filtered through a sintered glass funnel. The solvent was removed *in vacuo* at bath temperature of 150°, and oil pump vacuum was applied briefly for 2 min. Five grams of tetra-*O*-acetyl-β-D-ribofuranose (15.7 mmol) was added, and the melt was stirred *in vacuo* at an oil bath temperature of 155–160° for 15 min. The vacuum was broken, and the reaction was protected from moisture with drying tube. Stirring was continued for 10 hr, vacuum being applied for 5 min every hour. The melt was dissolved in methanol, boiled for 10 min, and cooled to room temperature. The precipitate was filtered (starting material), and the filtrate was evaporated to dryness. The viscous residue was dissolved in diethyl ether, filtered, concentrated, and kept at 5° overnight. The precipitate was filtered, washed with cold ether, and air-dried to give 1.75 g, mp 147–148°. A second crop was obtained by further concentration of the filtrate and yielded 0.5 g, mp 146–147°. The total yield was 2.25 g (51%). Two further crystallizations from ether gave a product having mp 148°.

Anal. Calcd for $C_{22}H_{25}N_3O_{11}S$: C, 48.98; H, 4.67; N, 7.80, S, 5.93. Found: C, 48.95; H, 4.67; N, 7.81; S, 5.98.

6-Carboxamido-4,5-dioxo-2-methylthio-8-(β-D-ribofuranosyl)-pyrido[2,3-*d*]pyrimidine (28).—Compound **27** (539 mg, 1.0 mmol) was placed in a glass-lined bomb; 80 ml of liquid ammonia was added, and the bomb was sealed. The solution was left at room temperature for 24 hr. The liquid ammonia was allowed to evaporate. The residue was dissolved in 200 ml of hot methanol. The solution was filtered, and the filtrate was kept at 5° overnight. The white precipitate was filtered and washed with methanol to yield 340 mg (89%), mp 243°.

Anal. Calcd for $C_{14}H_{16}N_4O_7S \cdot 0.5H_2O$: C, 42.90; H, 4.10; N, 14.25. Found: C, 42.81; H, 4.04; N, 14.33.

4-Acetamido-6-carbethoxy-2-methylthio-5-oxo-8-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (29).—A 1.0-g sample of compound 18 (2.72 mmol) was mixed with 1.5 g of tetra-*O*-acetyl-β-D-ribofuranose. The mixture was fused at an oil bath temperature of 195–200° for 2.5 hr *in vacuo*. The black melt was dissolved in a minimum volume of chloroform, and the solution was filtered. The filtrate was concentrated to 5.0 ml and placed on a column packed with 50 g of silica gel in chloroform. The column was eluted with chloroform; the first 300 ml of eluent was discarded. The next 800 ml of eluent was evaporated *in vacuo* to dryness. The viscous residue was triturated with 50 ml of ether. On scratching the side wall of the beaker a white precipitate formed. The precipitate was filtered, washed with diethyl ether, and air-dried to give 0.95 g (61%), mp 106–107°. For analysis a sample was dried *in vacuo* over refluxing methanol in presence of phosphorus pentoxide.

Anal. Calcd for $C_{24}H_{28}N_4O_{11}S \cdot 0.5H_2O$: C, 49.20; H, 4.95; N, 9.55. Found: 49.09; H, 5.17; N, 9.26.

4-Amino-6-carboxamido-2-methylthio-5-oxo-8-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (30).—A 1.16-g sample of 29 (2.0 mmol) was dissolved in 80 ml of liquid ammonia in a glass-lined bomb. The bomb was sealed and left to stand at room temperature for 24 hr. The liquid ammonia was allowed to evaporate. The residue was dissolved in 200 ml of boiling methanol by the addition of water. The solution was filtered, and the filtrate was kept at 5° overnight. The white precipitate was filtered, washed with methanol, and air-dried to give 0.60 g (78%), mp 252–253°. For analysis a sample was dried *in vacuo* over refluxing toluene in the presence of phosphorus pentaoxide.

Anal. Calcd for $C_{14}H_{17}N_5O_6S \cdot H_2O$: C, 41.90; H, 4.73; N, 17.4. Found: C, 42.01; H, 5.03; N, 17.25.

4-Amino-6-carboxamido-5-oxo-8-(β-D-ribofuranosyl)pyrido-[2,3-*d*]pyrimidine (2).—A 0.58-g sample of 29 (1.0 mmol) was dissolved in 30 ml of ethanol; 2.0 g of Raney nickel (weighed wet and prewashed with distilled water followed by ethanol) was added. The mixture was refluxed for 24 hr, and 1 g more of Raney nickel (weighed wet and pretreated as above) was added. Refluxing was continued for another 4 hr. The mixture was filtered hot, and the Raney nickel was washed with 300 ml of boiling ethanol. The filtrate was evaporated to dryness. The residue was transfered to a glass-lined bomb and 80 ml of liquid ammonia was added; the bomb was sealed and left at room temperature for 24 hr. The liquid ammonia was allowed to evaporate. The residue was dissolved in a boiling mixture of 40 ml of methanol and 5 ml of water and kept at 5° overnight. The precipitate was filtered, washed with methanol, and air-dried to give 0.23 g, mp 253–254°, resolidifies (44.5% overall yield). For analysis a sample was dried *in vacuo* over refluxing toluene in the presence of phosphorus pentoxide.

Anal. Calcd for $C_{13}H_{15}N_5O_6$: C, 46.30; H, 4.46; N, 20.74. Found: C, 46.02; H, 4.35; N, 20.61.

Registry No.—**1**, 18417-89-5; **2**, 36707-00-3; **11**, 21025-64-9; **13**, 36707-40-1; **14**, 36707-41-2; **16**, 36707-42-3; **17**, 36707-43-4; **18**, 36707-44-5; **19**, 36707-45-6; **21**, 36707-46-7; **23**, 36707-47-8; **24**, 36707-48-9; **27**, 36707-01-4; **28**, 36707-02-5; **29**, 36707-03-6; **30**, 36707-04-7.

Directed Glycosylation of 8-Bromoadenine. Synthesis and Reactions of 8-Substituted 3-Glycosyladenine Derivatives

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The ratio of 3-glycosyl- *vs.* 9-glycosyladenine nucleosides using several glycosylation procedures was investigated. Treatment of the trimethylsilyl derivative of 8-bromoadenine with glycosyl halides leads to excellent yields of blocked 3-glycosyl-6-amino-8-bromopurine nucleosides. This method has been used to prepare 6-amino-8-bromo-3-β-D-ribofuranosylpurine (**6**), 3-β-D-ribofuranosyladenine (**7**), 6-amino-3-α-D-arabinofuranosyl-8-bromopurine (**10**), 3-α-D-arabinofuranosyladenine (**11**), and 3-β-D-arabinofuranosyladenine (**14**). Deamination of 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (**5**) with NOCl–pyridine in DMF and removal of the blocking groups gave improved yields of 3-β-D-ribofuranosylhypoxanthine (**16**). Similar treatment of **11** gave 3-β-D-arabinofuranosylhypoxanthine (**17**). Deamination of 6-amino-3-(2,3,5-tri-*O*-benzoyl)-8-bromopurine (**4**), using NOCl in pyridine, and subsequent debenzoylation gave 3-β-D-ribofuranosyl-8-pyridiniumhypoxanthine betaine (**19**). The reactivity of **4** toward nucleophiles was investigated. Strongly basic nucleophiles such as methoxide, benzyloxide, and hydrazine caused decomposition. Displacement was accomplished with azide ion which gave, after hydrogenation and deblocking, 6,8-diamino-3-β-D-ribofuranosylpurine (**21**).

Interest in 3-substituted purine derivatives has been stimulated by the isolation of 3-β-D-ribofuranosyluric acid and 3-(3-methyl-2-butenyl)adenine from natural sources[1-3] and by the observation of interesting biological properties[4-7] of synthetic 3-β-D-ribofuranosyladenine (**7**). Adenine has been shown to undergo preferential alkylation at the 3 position;[3,8,9] however, direct alkylation of adenine with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**1**) afforded 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (**5**) in only 26% yield with 18% of the 9 isomer.[10] Glycosylation of 6-benzamidopurine with 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride gave some 3-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)adenine (**13**) in addition to the expected 9 isomer.[11] Selective glycosylation at the 3 position has been achieved by utilizing 7-pivaloyloxymethyladenine

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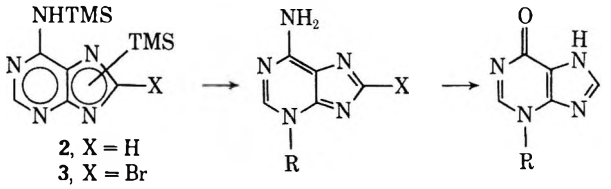


2, X = H
3, X = Br

4–14 15–17

4, X = Br; R = 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl
5, X = H; R = 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl
6, X = Br; R = β-D-ribofuranosyl
7, X = H; R = β-D-ribofuranosyl
8, X = Br; R = 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl
9, X = H; R = 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl
10, X = Br; R = α-D-arabinofuranosyl
11, X = H; R = α-D-arabinofuranosyl
12, X = Br; R = 2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl
13, X = H; R = 2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl
14, X = H; R = β-D-arabinofuranosyl
15, R = 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl
16, R = β-D-ribofuranosyl
17, R = β-D-arabinofuranosyl

followed by the sometimes difficult removal of the blocking groups.[12,13]

It was the purpose of this investigation to develop a synthetic procedure for preparing 3-glycosyladenines selectively and in good yields from readily accessible starting materials and to study their reactivity toward nucleophilic agents. Recent evidence for a 3 to 9 migration of alkyl or glycosyl substituents of purines has been presented by Shimizu and Miyaki[14-16] and the ratio of 3-substituted to 9-substituted products is thought to depend on the rate of this migration under the conditions used for alkylation.[16] The presence of a bulky substituent at the 8 position of adenine might be expected to offer steric hindrance to either direct alkylation or migration to the 9 position. Likewise an electron-withdrawing group at the 8 position might be expected to lower the electron density at the 9 position and thus slow the rate of alkylation or migration at that position. On this basis alkylation of 8-bromoadenine might be expected to give a preponderance of 3-substituted derivatives. With this in mind a study of the preparation of 3-glycosyladenines by various methods was undertaken.

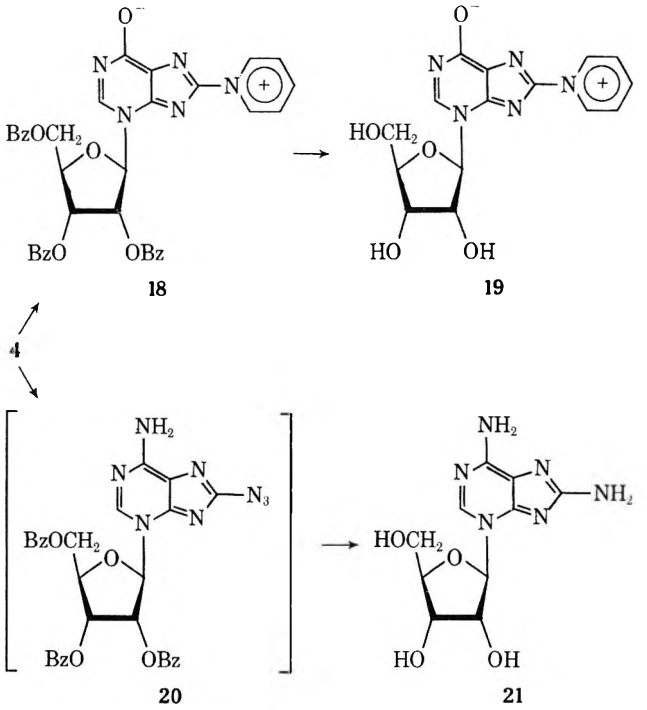
The low overall yields of nucleosides reported for direct alkylations of adenine led us at the outset to investigate the use of trimethylsilyl derivatives of adenine. Treatment of the crystalline trimethylsilyl adenine derivative (**2**) with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**1**) in acetonitrile or dichloromethane gave a poor overall yield of nucleosides and represented no improvement over previous methods. However, treatment of the crystalline trimethylsilyl-8-bromoadenine derivative (**3**) with the same glycosyl halide (**1**) in dichloromethane gave an 80% yield of crystalline 6-amino-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-8-bromopurine (**4**). This material was obtained by direct crystallization from the mixture of products. A yield of 7% of the 9 isomer could be obtained by chromatographic resolution of the crude reaction mixture. The structure of **4** was proved by hydrogenolysis to give 88% of the known[4] 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (**5**).

(12) M. Rasmussen and N. J. Leonard, *J. Amer. Chem. Soc.*, **89**, 5439 (1967).
(13) N. J. Leonard and M. Rasmussen, *J. Org. Chem.*, **33**, 2488 (1968).
(14) B. Shimizu and M. Miyaki, *Chem. Pharm. Bull.*, **18**, 579 (1970).
(15) M. Miyaki and B. Shimizu, *ibid.*, **18**, 732 (1970).
(16) M. Miyaki and B. Shimizu, *ibid.*, **18**, 1446 (1970).

Other methods of condensation gave lower total yields and greater proportions of the 9 isomer (see Table I). Fusion of **1** and **3** under reduced pressure gave results which were not so satisfactory as those from the glycosylation in acetonitrile or dichloromethane at room temperature. Condensation of the silylated 8-bromoadenine with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-α-D-ribofuranose in the presence of stannic chloride also proved inferior for the preparation of **5**. The directive effect of the 8-bromo substituent in the mercury salt procedure was also investigated. For this study 6-benzamido-8-bromopurine was prepared in poor yield by bromination of 6-benzamidopurine. The chloromercury salt was condensed with **1** in refluxing toluene to give a low yield of 3 isomer and a much higher yield of the 9 isomer.

The 3 isomer (**4**) was debenzoylated and gave a 95% yield of 6-amino-8-bromo-3-β-D-ribofuranosylpurine (**6**). Hydrogenolysis of **4** (to give **5**) followed by debenzoylation afforded known[4] 3-β-D-ribofuranosyladenine (**7**) in 61% yield from **3**.

Condensation of **3** with 2,3,5-tri-*O*-benzoyl-D-arabinofuranosyl bromide in acetonitrile gave a 73% yield of 6-amino(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl)-8-bromopurine (**8**) which was debenzoylated to give 6-amino-3-α-D-arabinofuranosyl-8-bromopurine (**10**). Hydrogenolysis of **8** (to give **9**) followed by debenzoylation gave 3-α-D-arabinofuranosyladenine (**11**). Similar treatment of **3** with 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride gave a 37% yield of 6-amino-3-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-8-bromopurine (**12**). Hydrogenolysis of **12** gave 3-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)adenine (**13**) and under more strenuous conditions 3-β-D-arabinofuranosyladenine (**14**).[11]



The deamination of **5**, followed by debenzoylation to give 3-β-D-ribofuranosylhypoxanthine (**16**), has been reported[17] using nitrosyl chloride in a mixture of pyridine and chloroform. In our hands this method

(17) R. Wolfenden, T. K. Sharpless, I. S. Ragade, and N. J. Leonard, *J. Amer. Chem. Soc.*, **88**, 185 (1966).

TABLE I

Purine base	Glycosyl Reactant	Method	Anomeric Configuration	% 3 isomer	% 9 isomer	3:9
Adenine[a]	2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl bromide	CH_3CN, reflux	β	26	18	1.4
Adenine (TMS) derivative	2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl bromide	CH_3CN, room temp	β	27	10	2.7
6-Benzamido-8-bromopurine chloromercury salt	2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl bromide	C_7H_8, reflux	β	4	39	0.1
8-Bromoadenine (TMS) derivative	2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl bromide	CH_3CN, room temp	β	80	7	10.0
8-Bromoadenine (TMS) derivative	2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl bromide	Fused, 125°	β	46	18	2.5
8-Bromoadenine (TMS) derivative	1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose	CH_3CN, $SnCl_4$[b]	β	39	20	2.0
8-Bromoadenine (TMS) derivative	2 3,5-Tri-*O*-benzoyl-α-D-arabinofuranosyl chloride	CH_3CN, room temp	β	37	4	9.2
8-Bromoadenine (TMS) derivative	2,3,5-Tri-*O*-benzoyl-D-arabinofuranosyl bromide	CH_3CN, room temp	α	73		

[a] Reference 4. [b] V. Niedballa and H. Vorbruggen, *Angew. Chem.*, 82, 449 (1970).

proved too unreliable for the preparation of **14** in large quantities. However, 5 equiv of nitrosyl chloride in DMF with 5 equiv of pyridine caused rapid deamination of **5** and afforded high yields of the blocked hypoxanthine (**15**) which was deblocked to give the aforementioned 3-β-D-ribofuranosylhypoxanthine (**16**). Similar treatment of the blocked β-D-arabino nucleoside (**13**) gave a high yield of a syrupy blocked hypoxanthine derivative. Attempts to remove the benzyl groups by catalytic hydrogenolysis met with inconsistent and unreliable results, including cleavage to hypoxanthine in some instances and in others modification of the purine nucleus presumably by ring reduction of the imidazole ring since a shift in the neutral uv from 265 to 280 nm was observed. A sample of 3-β-D-arabinofuranosylhypoxanthine (**17**) was obtained in ~30% yield by hydrogenolysis for 3 days at 30° and 3 atm of hydrogen over 10% palladium-on-carbon. In light of the difficulties in removing benzyl groups from 3-substituted hypoxanthines as reported here and by others[18] deamination of the deblocked arabinoside (**14**) was undertaken. Treatment of **14** in DMF with pyridine and a large excess of nitrosyl chloride gave a smooth conversion into **17** which was purified by chromatography on silica gel and crystallization from water.

Attempts to prepare 8-bromo-3-β-D-ribofuranosylhypoxanthine by deamination of **4** with nitrosyl chloride and pyridine in chloroform or DMF gave high yields of 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)8-pyridinium hypoxanthine betaine (**18**) which was debenzoylated in methanolic ammonia to give 3-β-D-ribofuranosyl-8-pyridinium hypoxanthine betaine (**19**). The structure of **19** was apparent from its elemental analysis and its pmr spectrum which exhibited a two-proton doublet at δ 9.75 attributable to the α-pyridinium protons and three protons in addition to H-2 centered around δ 8.4. When the reaction was repeated using nitrosyl chloride and 2,6-lutidine in DMF or chloroform, neither deamination nor displacement at C-8 to form a betaine was observed. Attempts to displace the pyridinium group from the betaine with azide ion under various conditions resulted in no reaction and treatment of **19** with hydrazine or hydrazine hydrate in alcohol led to complex mixtures of products.

The utility of 8-bromo-3-glycosyladenines as intermediates in nucleophilic displacement reactions was investigated using **4** and **6** as models. Compound **4** could be debenzoylated cleanly with methanolic ammonia to give the 8-bromo derivative **6**. The base stability of **6** contrasts with the 3-glycosyladenines previously investigated (*i.e.*, **7**) which were reported to be labile to both acid and base.[4] Attempts to displace bromide from **6** using sodium methoxide in methanol, sodium benzyloxide in benzyl alcohol, sodium hydroxide in water, or hydrazine in alcohol all led to extensive degradation including cleavage to sugar and aromatic heterocyclic derivatives. The resistance of the 8-bromo substituent of **4** and **6** to nucleophilic displacement was shown by their failure to react under conditions utilized to replace the bromo moiety from 8-bromo-9-β-D-ribofuranosyladenine reflux at alcohol temperature 4–12 hr.[19] Attempts to displace bromide from **4** with sodium acetate in DMF, acetic anhydride, or acetic acid–acetic anhydride gave no displacement under mild conditions (80°) and under more rigorous conditions (100° or greater) gave only decomposition products (glycosidic bond cleavage). However, conversion of **4** to an unstable azido derivative was accomplished using sodium azide in hexamethylphosphoric triamide at 80° for 4 days. The azide (**20**) could not be easily purified, but was hydrogenated and debenzoylated to give a 35% yield of 6,8-diamino-3-β-D-ribofuranosylpurine (**21**).

Experimental Section

General Methods.—Solutions were evaporated below 50° under diminished pressure. Melting points were determined with a Thomas-Hoover "Unimelt" apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer Model 247 spectrometer and KBr pellets. Uv spectra were recorded with a Cary Model 15 spectrometer. Optical rotations were measured in 1-dm tubes with a Perkin-Elmer Model 141 polarimeter. Nmr spectra were measured at 60 MHz with a Hitachi Perkin-Elmer R-20A nmr spectrometer (*ca.* 10% solutions measured at *ca.* 30°); tetramethylsilane (δ = 0) was used as the internal standard

(18) H. J. Thomas and J. A. Montgomery, *J. Org. Chem.*, **31**, 1413 (1966).

(19) R. E. Holmes and R. K. Robins, *J. Amer. Chem. Soc.*, **86**, 1242 (1964).

for chloroform-*d* solutions. Sodium 4,4-dimethyl-4-silapentane-1-sulfonate ($\delta = 0$) was used as the internal standard for deuterium oxide and methyl sulfoxide-d_6 solutions. Microanalytical data were obtained from Galbraith Laboratories, Inc., Knoxville, Tenn., and from M-H-W Laboratories, Garden City, Mich.

6-Amino-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-8-bromopurine (4).—8-Bromoadenine (3.2 g, 15 mmol) was refluxed in hexamethyldisilazane (15 ml) with a few crystals of ammonium sulfate until complete solution was achieved (24 hr). The excess hexamethyldisilazane was removed by distillation under diminished pressure. To the crystalline residue, 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide [from 7.0 g (14 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose] in acetonitrile (80 ml) was added, and the clear solution was kept in a sealed vessel for 20 hr. The solvent was evaporated, and the residual syrup was dissolved in chloroform–ethyl acetate (1:1, 30 ml). To the clear solution ethanol (100 ml) was added, and after a short time crystals precipitated. The mixture was kept at 0° for 12 hr and filtered to give 7.0 g (11.0 mmol, 71%) of **2a** as fine white needles. Concentration of the filtrate, storage at 4° several days, and filtration afforded an additional 1.2 g of needles. Recrystallization of the combined crops from ethanol gave pure **4** (7.6 g, 12 mmol, 80%): mp 221–222°; $[\alpha]^{25}D$ −72.1° (c 1, DMF).

Anal. Calcd for $C_{31}H_{24}BrN_5O_7$: C, 56.55; H, 3.68; N, 10.64. Found: C, 56.47; H, 3.69; N, 10.82.

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (5).—Compound **4** (3.0 g, 4.5 mmol) was dissolved in 2-methoxyethanol (100 ml), and ethanol (100 ml) was added. Concentrated NH_4OH (1 ml) and 10% palladium-on-carbon (2 g) were added, and the suspension was shaken for 2 hr under 40 psi of hydrogen. Chloroform (250 ml) was added, and the suspension was filtered through a Celite pad. The filtrate was evaporated to give a white crystalline solid which was suspended in ethanol and filtered to give **5** (1.7 g). The mother liquors afforded an additional 0.7 g of product. Crystallization of the combined crops from ethanol gave white needles: yield 2.3 g (88%); mp 238–239°; $[\alpha]^{25}D$ −63.4° (c 1, DMF) [lit.[4] mp 246–247°; $[\alpha]^{26}D$ −69° (c 0.89, DMF)].

6-Amino-8-bromo-3-β-D-ribofuranosylpurine (6).—Compound **4** (5.0 g, 7.6 mmol) was dissolved in methanol (100 ml) which had been saturated with ammonia at 0°. The solution was sealed and kept at room temperature for 4 days. The solution was evaporated to a syrup which was triturated with chloroform to give a white crystalline solid. The suspension was filtered and washed with chloroform. The solid was dissolved in water (15 ml) and methanol (15 ml) was added. This solution was seeded and allowed to crystallize overnight to yield 2.5 g (7.2 mmol, 95%): mp 185° dec; $[\alpha]^{25}D$ −63.2° (c 1, DMF); $\lambda_{max}^{pH\ 1}$ 280 nm (ε 22,500); λ_{max}^{MeOH} 286 nm (ε 17,000); $\lambda_{max}^{pH\ 11}$ 284 nm (ε 17,000); nmr (DMSO-d_6) δ 5.95 (1-proton doublet, $J_{1',2'} = 5.5$ Hz, H-1'), 8.39 (2-proton broad singlet, NH_2), 8.67 (1-proton singlet, H-2).

Anal. Calcd for $C_{10}H_{12}BrN_5O_4$ (0.5 H_2O): C, 33.84; H, 3.67; N, 19.71. Found: C, 33.76; H, 3.72; N, 19.57.

3-β-D-Ribofuranosyladenine (7).—Compound **5** (0.92 g, 1.7 mmol) was heated at reflux in a solution prepared from 30 mg of sodium in 15 ml of methanol. The starting material dissolved in 10 min, and after 15 min the product began to precipitate. After 30 min the reaction was placed in the refrigerator at 5° for 3 hr. The crystals were filtered, washed with methanol, and dried, yield 0.40 g (1.5 mmol, 87%), mp 185 (browns), 201° dec. Recrystallization from water (13 ml) gave 0.30 g of colorless needles: mp 210–211° dec; $[\alpha]^{29}D$ −98.5° (c 1, DMF); $[\alpha]^{25}D$ −29.4° (c 0.5, 0.05 *N* HCl); $\lambda_{max}^{pH\ 1}$ 274 nm (ε 17,000); λ_{max}^{MeOH} 280 nm (ε 12,000); $\lambda_{max}^{pH\ 11}$ 277 nm (ε 12,000); nmr (DMSO-d_6) δ 5.95 (1-proton doublet $J_{1',2'} = 7.0$ Hz, H-1'), 7.86, 8.62 (1-proton singlets H-8, H-2), 8.30 (2-proton broad singlet NH_2) [lit.[4] mp 210–211°, $[\alpha]^{26}D$ −35° (c 0.6, 0.05 *N* HCl)].

General Procedure for Determining Percentage Yields of Isomers of β-D-Ribofuranosyladenine Derivatives.—Trimethylsilyl derivatives were prepared from 0.50 g of purine base and 1.0 equiv of glycosyl derivative was used. Solvents were removed by evaporation under reduced pressure, and the reaction mixtures were dissolved in chloroform and washed with saturated aqueous sodium bicarbonate and water. The resultant solutions were chromatographed [$CHCl_3$–acetone (4:1)] on thick layers of silica gel to give well-resolved bands from which the isomers could be eluted (chloroform). The chloromercury procedure was carried out on 100 mg of the chloromercury salt of 6-benzamido-8-bromopurine prepared by standard procedures.[20] After the usual work-up the chloroform soluble fraction was chromatographed on silica gel plates, and the products were eluted, weighed, and then identified by debenzoylation to the known 3 and 9 isomers (results are shown in Table I).

6-Amino-3-(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl)-8-bromopurine (8).—Hydrogen bromide was bubbled through a solution of methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside (7.0 g, 15 mmol) in dichloromethane (100 ml) at 0° for 0.5 hr. The solution was kept at 0° for 1 hr and allowed to warm to ambient temperature for 15 min. The solution was evaporated and toluene was evaporated from the resulting syrup. This syrup was dissolved in acetonitrile (120 ml) and added to the trimethylsilyl derivative prepared from 8-bromoadenine (3.2 g, 15 mmol). After 24 hr white crystals were observed in the flask. The mixture was refrigerated for 24 hr, filtered, and washed with methanol to furnish 7.5 g (11 mmol, 73%) of white needles, mp 139–141°. Recrystallization from methanol gave **8** (6.5 g), mp 139–141°, $[\alpha]^{25}D$ +16.0° (c 1, $CHCl_3$).

Anal. Calcd for $C_{31}H_{24}BrN_5O_7$: C, 56.54; H, 3.67; N, 10.63; Br, 12.13. Found: C, 56.56; H, 3.67; N, 10.64; Br, 12.28.

3-(2,3,5-Tri-*O*-benzoyl-α-D-arabinofuranosyl)adenine (9).—A solution of **8** (1.6 g, 2.3 mmol) in ethanol–ethyl acetate (1:1, 150 ml) was placed in a pressure bottle with concentrated NH_4OH (1 ml) and 10% palladium-on-carbon (0.4 g). The mixture was shaken under 40 psi of hydrogen for 2 hr. The suspension was filtered and the filtrate was evaporated to a syrup, which was dissolved in benzene (40 ml) and kept at room temperature overnight to precipitate white needles, yield 1.3 g (2.2 mmol, 93%), mp 164–165°, $[\alpha]^{25}D$ +17.8° (c 1, MeOH).

Anal. Calcd for $C_{31}H_{25}N_5O_7$: C, 64.24; H, 4.34; N, 12.08. Found: C, 64.07; H, 4.29; N, 12.08.

6-Amino-3-α-D-arabinofuranosyl-8-bromopurine (10).—A solution of **8** (2.5 g, 3.8 mmol) in saturated (at 0°) methanolic ammonia (100 ml) was kept in a sealed vessel for 3 days. The solvent was evaporated to give a white crystalline mass which was washed with chloroform and filtered to give **10** as white needles, yield 1.30 g (96%). Recrystallization from 100 ml of water gave pure compound: mp 220° dec; $[\alpha]^{25}D$ +53.2° (c 0.5, DMSO); $\lambda_{max}^{pH\ 1}$ 282 nm (ε 20,500); λ_{max}^{MeOH} 285 nm (ε 14,600); $\lambda_{max}^{pH\ 11}$ 285 nm (ε 14,600); nmr (DMSO-d_6) δ 5.98 (1-proton doublet, $J_{1',2'} = 3.0$ Hz, H-1'), 8.25 (2-proton singlet, disappears on deuteration, NH_2), 8.43 (1-proton singlet, H-2).

Anal. Calcd for $C_{10}H_{12}BrN_5O_4$: C, 34.59; H, 3.20; N, 20.24. Found: C, 34.59; H, 3.36; N, 20.11.

3-α-D-Arabinofuranosyladenine (11).—To a solution of **8** (5.0 g, 7.6 mmol) in ethanol–ethyl acetate (1:1, 250 ml) was added concentrated NH_4OH (1 ml) and 10% palladium-on-carbon (2.5 g). The suspension was shaken for 2.5 hr under 40 psi of hydrogen, filtered, and evaporated to a syrup. The syrup was dissolved in methanol (125 ml), which had been saturated with ammonia at 0°, and kept in a sealed vessel for 3 days.

The solution was evaporated to a syrup and the syrup was dissolved in methanol (25 ml) from which it crystallized spontaneously. Recrystallization from aqueous methanol gave **11** as a monohydrate (1.7 g, 6.5 mmol, 85%): mp 195–196°; $[\alpha]^{25}D$ +40.8° (c 0.4, H_2O); $\lambda_{max}^{pH\ 1}$ 277 nm (ε 17,400); $\lambda_{max}^{H_2O}$ 280 nm (ε 12,500); $\lambda_{max}^{pH\ 11}$ 280 nm (ε 12,300); nmr (DMSO-d_6) δ 6.09 (after addition of D_2O, 1-proton doublet, $J_{1',2'} = 3.0$ Hz), 7.87, 8.50 (1-proton singlets, H-2 and H-8), 8.25 (2-proton broad singlet, NH_2).

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot H_2O$: C, 42.10; H, 5.30; N, 24.55. Found: C, 42.07; H, 5.15; N, 24.74.

6-Amino-3-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-8-bromopurine (12).—To the crystalline trimethylsilyl derivative prepared from 8-bromoadenine (3.00 g, 13.8 mmol) was added 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride [prepared from 9.0 g (15.6 mmol) of 2,3,5-tri-*O*-benzyl-1-*p*-nitrobenzoyl-D-arabinofuranose] in dichloromethane (210 ml). The reaction was kept at ambient temperature for 1 week, methanol (20 ml) was added, and the mixture was evaporated to a syrup. The syrup was dissolved in chloroform, washed with saturated sodium bicarbonate solution, and evaporated to give a yellow solid. This material was chromatographed on 300 g of silica gel using chloroform–acetone (7:3) as eluent, to give a syrupy mixture of 3 and 9

(20) E.M. Acton and R. H. Iwamoto in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. I, W. W. Zorbach and R. S. Tipson, Ed., Wiley, New York, N. Y., 1968, p 25.

isomers. The syrup was dissolved in ethanol, and the pure 3 isomer (12) crystallized slowly. The product was collected in five crops and recrystallized to yield 3.1 g (5.1 mmol, 37%): mp 152–154°; $[\alpha]^{25}D$ +124° (c 1.00, $CHCl_3$) {the 9 isomer could be isolated [silica gel, chloroform–acetone (4:1)] from the mother liquors by preparative layer chromatography in 4% yield}.

Anal. Calcd for $C_{31}H_{24}BrN_5O_7$: C, 60.39; H, 4.90; N, 11.35; Br, 12.96. Found: C, 60.56; H, 5.08; N, 11.25 Br, 13.01.

3-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)adenine (13).—To a solution of 12 (4.0 g, 6.5 mmol) in 2-methoxyethanol (100 ml) was added 5% palladium-on-carbon (1 g) and concentrated NH_4OH (1 ml). This mixture was shaken at room temperature under 30 psi of hydrogen for 2 hr. The suspension was filtered, and the solution was evaporated to give a white solid. The solid was triturated with hot ethyl acetate (100 ml) and filtered to remove salts. The product 13 crystallized as fluffy white needles (3.2 g, 6.0 mmol, 92%): mp 163–164°; $[\alpha]^{25}D$ +74.8° (c 1, CH_2Cl_2) [lit.[11] mp 161–163°; $[\alpha]^{31}D$ +96.0° (c 1, CH_2Cl_2)].

3-β-D-Arabinofuranosyladenine (14).—To a solution of 12 (600 mg, 0.97 mmol) in 2-methoxyethanol (100 ml) was added concentrated NH_4OH (1 ml) and 10% palladium-on-carbon (300 mg), and the solution was shaken for 24 hr at 50° under hydrogen (50 psi). The solution was filtered and evaporated to give a white solid which was crystallized from 50% aqueous methanol (40 ml) to yield 204 mg (85%): mp 232–234° dec; $[\alpha]^{25}D$ +81° (c 0.4, H_2O); $\lambda_{max}^{pH\ 1}$ 277 nm (ε 15,500); λ_{max}^{MeOH} 277 nm (ε 11,600); $\lambda_{max}^{pH\ 11}$ 278 nm (ε 11,000). The nmr spectrum of 14 was identical with that reported in the literature.[11]

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)hypoxanthine (15).—To a solution of 5 (2.0 g, 3.4 mmol) in DMF (25 ml) and pyridine (1.5 ml) at −20° was added nitrosyl chloride (1.5 g, 23 mmol) in DMF (25 ml). The solution was kept at 0° for 30 min and then poured into saturated aqueous sodium bicarbonate (50 ml). The resultant mixture was extracted with chloroform (two 100-ml portions), and the extract was evaporated to a syrup which was dissolved in methanol–ethyl acetate, (1:1, 30 ml). White crystals formed slowly to give 15 (1.5 g, 75%), mp 118–119°, $[\alpha]^{25}D$ −64.2° (c 1, $CHCl_3$).

Anal. Calcd for $C_{31}H_{24}O_8N_4$: C, 64.13; H, 4.17; N, 9.65. Found: C, 63.99; H, 4.32; N, 9.44.

3-β-D-Ribofuranosylhypoxanthine (16).—A solution of 15 (1.5 g, 2.6 mmol) in methanol (100 ml) was saturated with ammonia at −10°. The solution was sealed and kept for 3 days at room temperature. The solvent was removed, and the residue was partitioned between water (50 ml) and chloroform (50 ml). The aqueous layer was washed with chloroform (two 50-ml portions) and evaporated to a syrup. The product (16) was crystallized from 50% aqueous ethanol (25 ml) to yield 0.68 g (91%): mp 183–185°; $[\alpha]^{25}D$ −35.2° (c 1, H_2O); $\lambda_{max}^{pH\ 1}$ 253 nm (ε 11,300); λ_{max}^{MeOH} 267 nm (ε 13,900); $\lambda_{max}^{pH\ 11}$ 269 nm (ε 11,000); nmr (DMSO-d_6) δ 5.98 (1-proton doublet, $J_{1',2'}$ = 6.0 Hz, H-1'), δ 8.32, 8.67 (1-proton singlets, H-2 and H-8) (lit.[17] mp 178°).

3-β-D-Arabinofuranosylhypoxanthine (17) from Deamination of 13.—A solution of 13 (1.0 g, 1.6 mmol) in DMF (5 ml) and pyridine (1.0 ml) was cooled to 5°, and a solution of nitrosyl chloride (0.8 g) in DMF (3 ml) was added. The solution was kept at 5° for 20 min and then poured into an excess of aqueous sodium bicarbonate. The mixture was extracted with chloroform and the extract was dried [$Mg(SO_4)_2$] and evaporated to give a dark syrup. Chromatography on silica gel using chloroform–acetone (4:1) as eluent gave a homogeneous syrup (700 mg) which was used in subsequent conversions.

A portion of the above syrup (300 mg, 0.49 mmol) was dissolved in 2-methoxyethanol and 5% palladium-on-carbon (300 mg), and sodium acetate (50 mg) was added. The mixture was shaken under 40 psi of hydrogen for 72 hr. The mixture was filtered and the solution was evaporated to a white solid which was chromatographed on silica gel (20 g) using the upper phase from ethyl acetate–1-propanol–water (4:1:2) as eluent, to give 17 as a white solid which was crystallized from water: yield 50 mg (38%); mp 194–196° dec; $[\alpha]^{25}D$ +41.0° (c 1.0, H_2O); $\lambda_{max}^{pH\ 1}$ 252 nm (ε 9800); λ_{max}^{MeOH} 264 nm (ε 12,600); $\lambda_{max}^{pH\ 11}$ 268 nm (ε 9400); nmr (DMSO-d_6) δ 6.45 (1-proton doublet, $J_{1',2'}$ = 4.0 Hz, H-1'), 8.20, 8.47 (1-proton singlets, H-2 and H-8).

Anal. Calcd for $C_{10}H_{12}N_4O_5$: C, 44.78; H, 4.51; N, 20.89. Found: C, 44.63; H, 4.62; N, 20.69.

From Deamination of 14.—A suspension of 14 (1.0 g, 3.7 mmol) in DMF (10 ml) and pyridine (3 ml) was cooled to 0°, and a solution of nitrosyl chloride (2.5 g) in DMF (7 ml) was added. After 3 hr concentrated NH_4OH (10 ml) was added, and the solution was evaporated to dryness. The resultant syrup was triturated with methanol and filtered to remove salts. Silica gel (7 g) was added to the solution, and the mixture was dried under diminished pressure and applied to a column of dry silica gel (75 g). Elution with the same solvent as in the previous experiment afforded 17, yield 320 mg (32%).

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-8-pyridiniumhypoxanthine Betaine (18).—A suspension of 6-amino-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-8-bromopurine (4, 5.0 g, 7.6 mmol) in a mixture of chloroform (25 ml) and pyridine (25 ml) was stirred at 0°. Nitrosyl chloride (2 g, 40 mmol) in chloroform (25 ml) was added over 2 hr. The resulting solution was allowed to warm to room temperature, and the solution was evaporated to a dark yellow syrup. Toluene (three 25-ml portions) was evaporated from the syrup to remove pyridine, and the syrup was dissolved in ethanol. The major component, 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-8-pyridiniumhypoxanthine betaine, crystallized as yellow needles which were recrystallized from ethanol to give 4.2 g (84%) of bright yellow needles, mp 230° dec, $[\alpha]^{25}D$ −88.1° (c 1, $CHCl_3$).

Anal. Calcd for $C_{36}H_{27}N_5O_8$: C, 65.75; H, 4.14; N, 10.65. Found: C, 65.67; H, 4.34; N, 10.45.

3-(β-D-Ribofuranosyl)-8-pyridiniumhypoxanthine Betaine (19).—3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-8-pyridiniumhypoxanthine betaine (8, 1.9 g, 2.9 mmol) was suspended in 100 ml of anhydrous methanol saturated with ammonia at 0°. The mixture was stirred in a sealed vessel for 5 days. The solvent was evaporated under reduced pressure. The residue was triturated with chloroform, and the resulting insoluble yellow powder was dissolved in 35 ml of hot water. After 12 hr at room temperature crystals appeared and the suspension was cooled at 4° for 12 hr. The product (19) was collected by filtration: yield 0.85 g (85%); mp 225° dec; $[\alpha]^{25}D$ −13.9° (c 0.29, H_2O); $\lambda_{max}^{pH\ 1}$ 332 nm (ε 13,000); $\lambda_{max}^{H_2O}$ 390 nm (ε 3000); $\lambda_{max}^{pH\ 11}$ 263 nm (ε 18,500), 394 nm (17,500); nmr (DMSO-d_6) δ 5.94 (1-proton doublet, $J_{1',2'}$ = 5.7 Hz, H-1'), 8.1–8.9 (3-proton multiplet, β- and γ-pyridinium protons), 8.46 (1-proton singlet, H-2), 9.78 (2-proton doublet $J_{\alpha,\beta}$ = 5.2 Hz, α-pyridinium protons).

Anal. Calcd for $C_{15}H_{15}N_5O_5$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.96; H, 4.12; N, 20.02.

6,8-Diamino-3-β-D-ribofuranosylpurine (21).—A mixture of 4 (2.0 g, 3.0 mmol) and sodium azide (1.0 g) in hexamethylphosphoric triamide (7 ml) was stirred at 80° for 72 hr. The reaction was monitored by uv absorption change in methanol [285 (4) to 308 nm (20)]. The mixture was poured into rapidly stirred water (150 ml), and the resultant yellow precipitate was washed with water (150 ml) and partitioned between water (100 ml) and chloroform (100 ml). The chloroform layer was washed with water (3 × 50 ml) and evaporated to a powder which showed one major component on tlc and gave a strong absorption at 2061 cm^{-1} (azide). This material could not be obtained in a homogeneous form. The powder was dissolved in 2-methoxyethanol (100 ml) and shaken with 10% palladium-on-carbon (1.0 g) under 40 psi of hydrogen for 16 hr. The mixture was filtered and evaporated to a pale yellow solid which was dissolved in methanol saturated with ammonia at 0°. The solution was kept at room temperature in a sealed vessel for 3 days and then evaporated to dryness; the residue was partitioned between water (100 ml) and chloroform (100 ml). The aqueous phase was washed with chloroform (three 50-ml portions) and evaporated to give yellow solid. The solid was triturated with ethanol (two 25-ml portions) and crystallized from a small volume of water. Recrystallization from water gave 21 as colorless crystals: yield 300 mg (35%); mp 180° dec; $[\alpha]^{25}D$ −42.8° (c 0.34, H_2O); $\lambda_{max}^{pH\ 1}$ 232 nm (ε 18,900), 294 (17,700); λ_{max}^{MeOH} 232 nm (ε 15,900), 296 (15,300); $\lambda_{max}^{pH\ 11}$ 234 nm (ε 10,200), 304 (12,300); nmr (DMSO-d_6) δ 5.40 (5-proton multiplet, NH_2, OH's), 5.99 (1-proton doublet, $J_{1',2'}$ = 5.0 Hz, H-1'), 8.01 (2-proton broad singlet, NH_2), 8.69 (1-proton singlet, H-2).

Anal. Calcd for $C_{10}H_{14}O_4N_6$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.41; H, 5.08; N, 29.63.

Registry No.—**4**, 36258-93-2; **5**, 28837-63-0; **6**, 36258-95-4; **7**, 2273-78-1; **8**, 36208-01-2; **9**, 36258-97-6; **10**, 36258-98-7; **11**, 36258-99-8; **12**, 36259-00-4; **13**, 36259-01-5; **14**, 14365-78-7; **15**, 36259-03-7; **16**, 6835-54-7; **17**, 36259-05-9; **18**, 36259-06-0; **19**, 36259-07-1; **21**, 36259-08-2.

Glucosiduronates of 3α,21-Dihydroxy-5β-pregnane-11,20-dione. Synthesis of C-3, C-21, and C-3,21 Derivatives[1]

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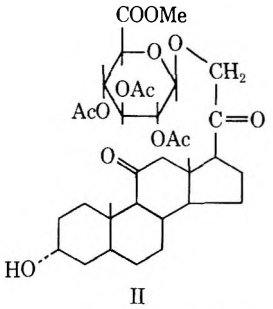
On treatment with methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-glucuronate and Ag_2CO_3, 3α,21-dihydroxy-5β-pregnane-11,20-dione (I) yielded the corresponding steroidal 21-glucosiduronate (II), the 3,21-diglucosiduronate (III), the 21-glucosiduronate 3-glucuronosyl orthoacetate (IV), and the 3-glucosiduronate (V) as methyl ester acetates. In dilute methanolic HCl, IV was converted into II. Acetyl groups were removed from II, III, and V in methanol containing a catalytic amount of NaOH, and corresponding crystalline methyl esters VI, VII, and VIII were obtained. Alkaline hydrolysis of esters VI and VII followed by acidification gave the corresponding glucosiduronic acids. The 3-glucosiduronate (V) was converted into the C-20 semicarbazone (IX) to stabilize the ketolic group during alkaline hydrolysis; alkaline cleavage of the ester groups in IX followed by hydrolysis of the semicarbazone group at pH 2.1 gave 21-hydroxy-11,20-dioxo-5β-pregnan-3α-yl β-D-glucopyranosiduronic acid in 90% yield. Treatment of the 21-acetate of I with Ag_2CO_3 in benzene gave the 3-oxo derivative of I and showed that oxidation may occur as a side reaction in the Koenigs–Knorr procedure.

One of the principal pathways of metabolism of the adrenocortical hormones in man involves reduction of the 3-oxo-Δ^4 function to the 3α-hydroxy-5β-pregnane



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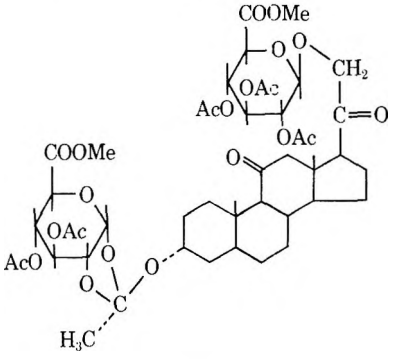

IV

structure. Subsequently, the 3α-hydroxy metabolite is joined to glucuronic acid and the conjugate is excreted in the urine. Although 3α-hydroxy-5β-pregnanes which have either a ketolic side chain or a dihydroxyacetone function at C-17 are excreted principally as the C-3 glucosiduronic acids,[2,3] small amounts of C-21 conjugates may also be present.[4,5] 3α,21-Dihydroxy-5β-pregnane-11,20-dione (1), a metabolite of corticosterone, occurs in human urine as a conjugate[6] with glucuronic acid; however, the position(s) of attachment of the conjugating group to the steroid has not been established unequivocally. In this paper we describe the synthesis of the C-3, the C-21, and the C-3,21 β-D-glucosyluronic acid derivatives of **1**.

Treatment of the 3,21-dihydroxy compound **1** with 3 equiv of methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-glucuronate (hereafter referred to as methyl acetobromoglucuronate) under conditions reported previously[7] gave a mixture which was fractionated by column chromatography to yield four substances: the C-21 glucosiduronate (**4**), the C-3,21 diglucosiduronate (**12**), the C-3 orthoacetate of the C-21 glucosiduronate (**17**), and the C-3 glucosiduronate (**18**).

The β configuration for the glucosidic linkage in compounds **4**, **12**, **17**, **18**, and **19** is suggested by the mode of synthesis,[7] by the agreement of calculated and observed molecular rotations of the compounds (Table I), and by the hydrolysis of the glucosidic linkage of the

TABLE I

MOLECULAR ROTATIONS OF CONJUGATES

Compd	Calcd, deg[a] α-Glycoside	Calcd, deg[a] β-Glycoside	Found, deg
4	+950	+244	+159
5	+1058	+352	+276
12	+1555	+143	+98
18	+950	+244	+283
19	+1027	+321	+381

[a] Values calculated as previously described.[7]

corresponding free glucosiduronic acids (**7**, **14**, and **21**) with β-glucuronidase. In addition, compounds **4** and **12** lack the nmr doublet ($\delta \cong 5.1$; $J_{1',2'} \cong 3.2$ Hz) which is characteristic[8] of acetylated α-glycosides.

The C-21 glucosiduronate (**4**) was obtained from diol **1** in yields of 32–38%. This conjugate (**4**), as well as orthoacetate **17** which is derived from it, must have the glucosiduronate function at C-21 because it (**4**) does not reduce alkaline tetrazolium blue in the manner typical of α-ketolic steroids. However, compounds **4**, **12**, and **17** give a yellow color with this reagent, a response characteristic of the C-21 glucosiduronates of 11-dehydrocorticosterone and 11-deoxycorticosterone.[9]

(1) (a) This investigation was supported in part by Research Grant AM-5452 from the National Institutes of Health, Public Health Service. (b) Part of this investigation was presented at the 51st Annual Meeting of the Federation of American Societies for Experimental Biology, Chicago, Ill., April 16–21, 1967, Abstract No. 945.

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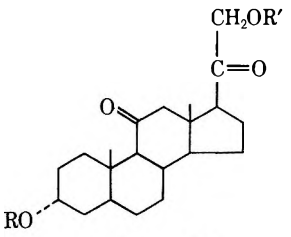
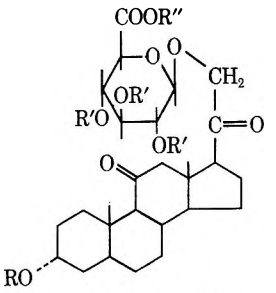
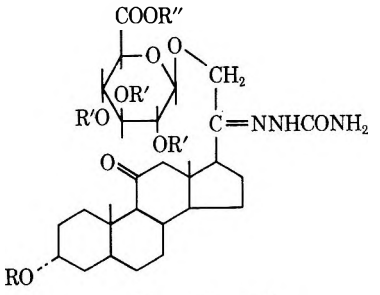


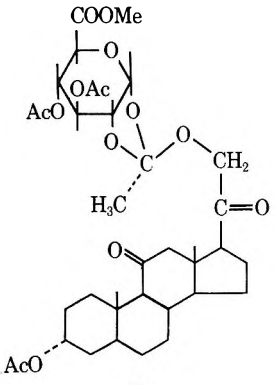
	R	R′
1	H	H
2	Ac	H
3	H	Ac



	R	R′	R″
4	H	Ac	Me
5	Ac	Ac	Me
6	H	H	Me
7	H	H	H
8	H	H	NH_4



	R	R′	R″
9	H	Ac	Me
10	Ac	Ac	Me



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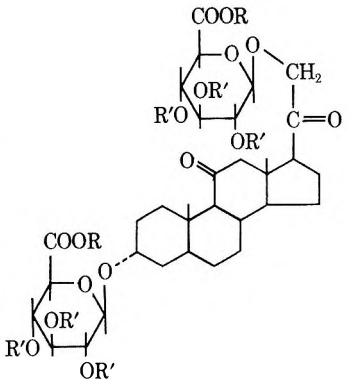
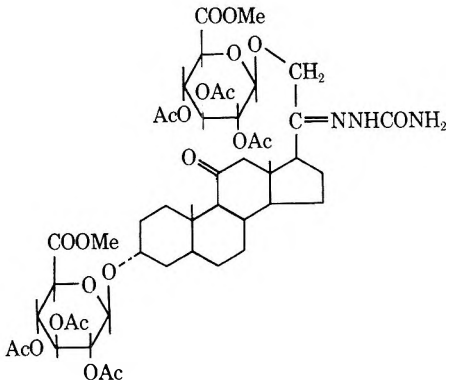


	R	R′
12	Me	Ac
13	Me	H
14	H	H
15	NH_4	H



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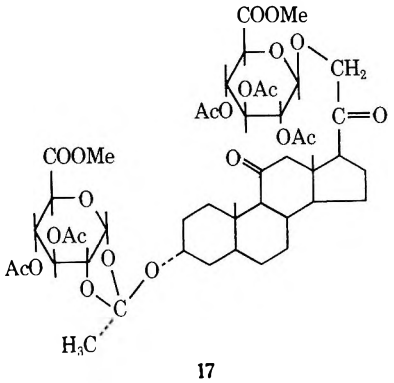

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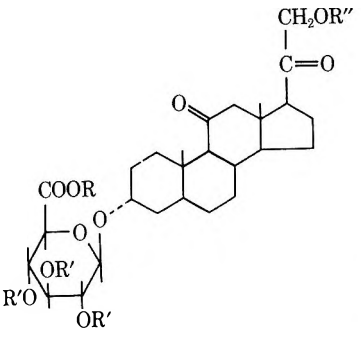
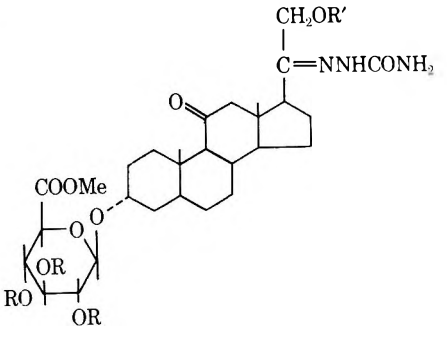
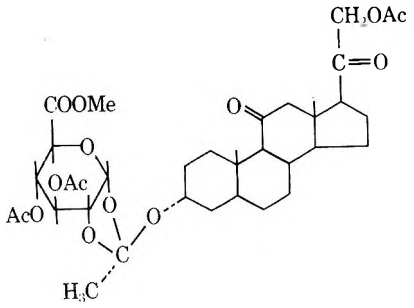


	R	R′	R″
18	Me	Ac	H
19	Me	Ac	Ac
20	Me	H	H
21	H	H	H



	R	R′
22	Ac	H
23	Ac	Ac
24	H	H



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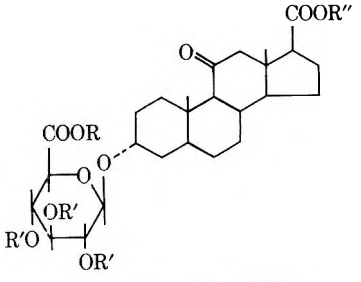

	R	R′	R″
26	H	H	H
27	Me	Ac	H
28	Me	Ac	Me

Conjugate **18**, obtained from **1** in 17% yield, has the glucosiduronate group at C-3; the substance reduces alkaline tetrazolium blue and is oxidizable by a catalytic amount of cupric acetate[10] to a product which gives a positive reaction with the Porter–Silber reagent. In addition, acetylation of **18** gave the C-21 acetate (**19**) which could be prepared in 49% yield by treatment of 21-acetoxy-3α-hydroxy-5β-pregnane-11,20-dione (**3**) with methyl acetobromoglucuronate.

Efforts to crystallize the steroidal C-3,21 diglucosiduronate (**12**) after its preparation from diol **1** or from the C-21 monoglucosiduronate (**4**) were not successful; however, the amorphous diglucosiduronate (**12**) gave a crystalline C-20 semicarbazone (**16**) in 16–18% yield from **1**. The semicarbazone could be converted to crystalline 20-oxo diglucosiduronate (**12**) by treatment[7] with pyruvic acid. Compounds **4**, **5**, **18**, **19**, and **20** also reacted with semicarbazide to give the corresponding semicarbazones which, on treatment with pyruvic acid, were converted to the 20-oxo starting materials.

The acetyl groups were removed from compounds **4**, **12**, **18**, and **19** by transesterification in methanol in the presence of dilute sodium methylate or sodium hydroxide, and the corresponding methyl esters were obtained in good yield. Removal of acetyl groups from a glucosiduronate moiety at C-3 occurs more slowly than from one at C-21.

Treatment of the C-21 glucosiduronate esters (**6** and **13**) with either ammonium hydroxide or sodium hydroxide followed by acidification gave the crystalline glucosiduronic acids (**7** and **14**). These acids were convertible back to the corresponding methyl esters (**6** and **13**) by treatment with diazomethane and to the parent dihydroxy steroid (**1**) by reaction with β-glucuronidase (Ketodase). The acetyl methyl ester glucosiduronates (**4** and **12**) were convertible to the corresponding free acids (**7** and **14**) in yields of about 80% without isolating the intermediate methyl esters.

When the acetylated glucosiduronate ester **19** was hydrolyzed with sodium hydroxide and the product was chromatographed on Celite in the presence of EDTA,[10] glucosiduronic acid **21** was obtained in 47% yield along with some etianic acid (**26**) which was formed by alkaline cleavage[11] of the ketolic side chain. In the absence of EDTA, the copper which was eluted from the Celite caused oxidation of the ketolic group, and glucosiduronic acid **21** could not be crystallized. When sodium bicarbonate was used to hydrolyze ester **20**, glucosiduronic acid **21** was obtained in 66% yield.

The structure of etianic acid **26** was demonstrated by the following transformations. Reaction of the ketolic conjugate **18** with periodate yielded acid **27**, which, on treatment with diazomethane, gave ester **28**. Similarly, the etianic acid **26** was converted into methyl ester triacetate **28** by esterification with diazomethane followed by acetylation. In addition, the 17-carboxy steroidal conjugate (**27**) could be hydrolyzed with alkali to produce **26**.

Wendler, *et al.*,[12] showed indirectly that the α-ketolic side chain of a steroid is stable toward alkali when this function is converted into a semicarbazone. We observed that, when semicarbazone **22** or **23** was treated with methanolic alkali, methyl ester semicarbazone **24** could be isolated in high yield. Reaction of this compound (**24**) with aqueous alkali followed by adjustment of the pH to 2.1 to hydrolyze the semicarbazone group gave crystalline glucosiduronic acid **21**. The yield of acid **21** from the acetate ester semicarbazone **23**, without isolation of the intermediates, was 88%. Removal of the semicarbazone function was also achieved by using the cation exchange resin, Dowex 50W-2X.

As a by-product of the Koenigs–Knorr reaction[13] orthoacetate **17** was recovered in 4% yield when dihydroxy steroid **1** was treated with methyl acetobromoglucuronate. In the preparation of diglucosiduronate **12** from monoglucosiduronate **4**, orthoacetate **17** was obtained in 9% yield. In addition to the function at C-21, this substance has a glucosyluronate group attached to the steroid at C-3 through an orthoacetate structure which involves the acetyl group at C-2 of the carbohydrate, an α linkage to C-1 of the carbohydrate, and the oxygen of the 3α-hydroxyl group of the steroid. The structure of orthoacetate **17** was suggested by its facile conversion to the C-21 glucosiduronate **4** during treatment with dilute acid,[13c] and by the analytical values for C, H, CH_3O, and CH_3CO. The structure was confirmed by the nmr spectrum,[13d,e] which has a band (δ 1.74 ppm; 3 protons) that is characteristic of the methyl group of an orthoacetate in the endo configuration relative to the carbohydrate group. This characteristic band was not present in either the C-21 glucosiduronate (**4**) or the C-3,21 diglucosiduronate (**12**).

In the preparation of the C-21 glucosiduronate (**5**) from the 21-hydroxy steroid (**2**), the corresponding steroid 21-yl glucuronylene orthoacetate (**11**) was obtained in 7% yield as a by-product. Similarly, orthoacetate **25** was obtained in 22% yield during preparation of **19**. These orthoacetates demonstrated characteristic spectral and chemical properties analogous to those of orthoacetate **17**.

Oxidation of a hydroxyl group to a ketone may occur in the Koenigs–Knorr reaction, as is shown by formation of 21-acetoxy-5β-pregnane-3,11,20-trione from **3** during the preparation of **19**. This 3,11,20-trione also was formed, and isolated in a yield of 47%, by the action of silver carbonate on the 3-hydroxy compound **3** in boiling benzene in the absence of methyl acetobromoglucuronate. It was reported[14] recently that primary and secondary alcohols are oxidized readily by silver carbonate on Celite in neutral media.

Experimental Section

Elemental analyses were carried out by Mr. Joseph F. Alicino, Metuchen, N. J.; samples were dried at 100° *in vacuo* immediately before analysis. Melting points were taken on a Fisher-Johns apparatus and are corrected. A substance synthesized by an optional procedure was identified by comparison of its melting point and ir spectrum with that of the authentic compound and by performing a mixture melting point determination. Infrared spectra were recorded with a Beckman IR-18 spectro-

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photometer; nmr measurements were made with a Varian A-60 spectrometer with deuteriochloroform as solvent and tetramethylsilane as internal standard. Rotations were taken at 26° ± 1° (*c* ~1). Evaporations were performed *in vacuo* on a rotary evaporator at a bath temperature of 40°. For column chromatography, Celite 545 was used as received from Johns-Manville and was impregnated with 40% of its weight of stationary (more dense) phase, using the solvent systems listed below. Holdback volume (HBV) represents the volume of the mobile phase retained by the packed portion of the column; the elution volume of a compound is expressed in HBV. Paper chromatography was performed as described previously;[7] Zaffaroni technique was used with systems S1–S7 and Bush technique was used for systems S8–S14. Semicarbazones were detected by viewing chromatograms over 254-mμ radiation or by treating the chromatograms with 5% ethanolic phosphomolybdic acid; other compounds were detected by treating the chromatograms with alkaline tetrazolium blue.[15] To detect acidic compounds which were not revealed by previously mentioned techniques, chromatograms were sprayed with a 0.04% solution of chlorophenol red in alcohol.[16]

Thin layer chromatography (tlc) was performed on silica gel G in 1:1 benzene–ether; compounds were detected by spraying the plates with water–sulfuric acid, 1:1, and charring.

Systems for Paper and Column Chromatography.—S1 = benzene–cyclohexane (25:75)–formamide–carbitol (1:1); S2 = benzene–cyclohexane (20:80)–formamide–carbitol (1:1); S3 = benzene–cyclohexane (25:75)–formamide; S4 = benzene–cyclohexane (50:50)–formamide; S5 = benzene–cyclohexane (75:25)–formamide; S6 = benzene–formamide; S7 = butyl acetate–formamide; mobile phase is butyl acetate saturated with formamide–water (1:1); S8 = cyclohexane–methanol–water (500:400:100); S9 = toluene–ethyl acetate–methanol–water (900:100:500:500); S10 = butyl acetate–butyl alcohol–water–acetic acid (90:10:90:10); S11 = butyl acetate–butyl alcohol–water–acetic acid (50:50:90:10); S12 = butyl acetate–butyl alcohol–water–acetic acid (25:75:90:10); S13 = butyl acetate–toluene–methanol–water–acetic acid (50:50:50:45:5); S14 = toluene–butyl acetate–methanol–water (25:75:50:50).

3α,21-Dihydroxy-5β-pregnane-11,20-dione (1).—Treatment of 1.0-mg amounts of **7**, **14**, and **21** in separate flasks with 25,000 units of β-glucuronidase (Ketodase) under conditions previously described[9] gave **1**, which was identified by its chromatographic mobility on paper in systems S6, S7, and S9, and, after acetylation, in systems S1 and S8. For a previously prepared sample[10] of **1**, $[\alpha]_D$ = +99 ± 2° ($CHCl_3$). This value is used in the calculation of M_D for compound **4** (Table I).

3α-Acetoxy-21-hydroxy-5β-pregnane-11,20-dione (2). A.—To 8.65 g (20.0 mmol) of 3α,21-diacetoxy-5β-pregnane-11,20-dione[17] in 865 ml of methanol was added 8.65 g (86 mmol) of $KHCO_3$ in 288 ml of H_2O. After 1.5 hr the solution was acidified with acetic acid, concentrated, and extracted with chloroform. The extract was washed with $NaHCO_3$ solution and water and evaporated to dryness. The residue was chromatographed in system S1 on a column containing 700 g of Celite (HBV = 3.0), and crystals (4.52 g, mp 63–64°) were obtained from benzene. When a sample was dried at 1 mm and 100°, it melted and lost 15.3% (calcd for C_6H_6, 16.7%); $[\alpha]_D$ on the dried sample = +116 ± 2° ($CHCl_3$). A sample, dried to constant weight at 60° and 1 mm, lost 12.6% (calcd for loss of $^3/_4C_6H_6$, 12.5%), and absorbance of the dried product at 255 mμ indicated 4.4% benzene (calcd for $^1/_4C_6H_6$, 4.8%): ir (KBr) 3450 (OH), 1730 (acetate C=O), 1702 (ketone C=O), and 1237 cm^{-1} (ester COC). *Anal.* Calcd for $C_{23}H_{34}O_5 \cdot {}^1/_4C_6H_6$: C, 71.76; H, 8.73. Found: C, 71.65; H, 8.74.

B. From 11.—To 100 mg of orthoacetate **11** in 10 ml of benzene was added 1.0 ml of 0.1 *N* HCl in methanol.[13c] After 10 min, the solution was washed with 1.0 *N* Na_2CO_3 and then with water until neutral and taken to dryness. The residue was chromatographed on 30 g of Celite in system S1 (HBV 3.6). Crystals (18 mg, 28%, mp 63–65°) were obtained from benzene–cyclohexane and identified as **2**.

21-Acetoxy-3α-hydroxy-5β-pregnane-11,20-dione (3). A. From 1.—A pyridinium acetate buffer was prepared by diluting 121 ml of pyridine to 500 ml with glacial acetic acid. To 14.0 g of compound **1**[10] was added 500 ml of glacial acetic acid and 500 ml of pyridinium acetate buffer at 25°. While the flask was being shaken, 100 ml of acetic anhydride was added; the mixture became homogeneous in 15 min. One hour later the mixture was worked up, and crystals (8.2 g, 52%, mp 138–141°) were obtained from ethanol. In a similar preparation in which the product was chromatographed in system S5, **3** emerged at 2.0 HBV (yield 65%, mp 142–143°), $[\alpha]_D$ +108 ± 2° ($CHCl_3$) [reported[17] mp 137–138°; $[\alpha]_D$ 109° ($CHCl_3$)].

B. From 25.—To 100 mg of orthoacetate **25** in 10 ml of benzene was added 1.0 ml of 0.1 *N* HCl in methanol. After 10 min the solution was washed twice with 1.0 *N* Na_2CO_3 and then with water until neutral and taken to dryness. Crystalline **3** (83%, mp 141–143°) was obtained from benzene–cyclohexane.

Methyl (3α-Hydroxy-11,20-dioxo-5β-pregnan-21-yl 2,3,4-Tri-*O*-acetyl-β-D-glucopyranosid)uronate (4). A. From 1.—A mixture of 348 mg (1.0 mmol) of **1** and 1.1 g (4.0 mmol) of Ag_2CO_3 in 150 ml of benzene was treated with 1.13 g (3.0 mmol) of methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-glucuronate by the general procedure described previously.[7] The product was chromatographed in solvent system S4; 9.2-ml fractions were collected. To monitor the effluent, alternate fractions were mixed with 1 ml of water and 50-μl samples of organic phase were removed, taken to dryness, and mixed with 1.0 ml of concentrated H_2SO_4. After 2 hr, the absorbance was read at 415 mμ and plotted against fraction number. Additional samples (25 μl) were removed, spotted on filter paper, and treated with alkaline tetrazolium blue. For fractions 23–37 (HBV 1.8) see **17** from **1**; for fractions 38–53 (HBV 2.6) see **16** from **1** *via* **12**; for fractions 69–94 (HBV 4.6), see **18** from **1**.

Fractions 189–259 (HBV 13.5) were combined, washed with water, and concentrated. Crystals of glucosiduronate **4** (215 mg, 32%) were obtained from ethanol: mp 108–111°; homogeneous in system S5; $[\alpha]_D$ +24 ± 2° ($CHCl_3$); ir (KBr) 3520 (OH), 1757 (ester C=O), 1705 (ketone C=O), and 1235 sh, 1215 cm^{-1} (ester COC); nmr ($CDCl_3$) δ 0.57 (C-18 CH_3), 1.15 (C-19 CH_3), 1.81 (C-3 OH?), 2.01 (two OAc), 2.08 (one OAc), 2.45 (C-12 protons), 3.75 (CH_3O of ester), and 4.50 ppm (C-21 CH_2O). *Anal.* Calcd for $C_{34}H_{48}O_{13}$: C, 61.43; H, 7.28. Found: C, 61.61; H, 7.29.

B. From 9.—Treatment of semicarbazone **9** (200 mg) in chloroform with pyruvic acid[7] gave crystals of **4**, mp 105–108°, in 79% yield.

C. From 17.—Orthoacetate **17** (30 mg) was treated as described for the preparation of **2** from **11**; crystals (4.9 mg, 24% yield, mp 103–105°) were obtained from cold ethanol and identified as glucosiduronate **4**.

Methyl (3α-Acetoxy-11,20-dioxo-5β-pregnan-21-yl 2,3,4-Tri-*O*-acetyl-β-D-glucopyranosid)uronate (5). A. From 2.—A solution of **2** (3.38 g) in benzene was treated with methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-glucuronate by the procedure described for the preparation of **4** from **1**, and the product was chromatographed on 700 g of Celite in system S1. The band eluted at 2.0 HBV contained orthoacetate **11** (see **11** from **2**). The band eluted at 3.0 HBV gave crystals of **5** from benzene–cyclohexane (1.62 g, 27%, mp 168–169°, homogeneous by tlc).

B. From 4.—Treatment of 200 mg of **4** with a mixture of 1.0 ml each of acetic anhydride and pyridine at room temperature for 3 hr followed by crystallization of the product from methanol gave homogeneous (system S5) conjugate **5** (162 mg, 76%, mp 169–170°). The pure substance had mp 170–171°; $[\alpha]_D$ +39 ± 2° ($CHCl_3$); ir (KBr) 1775, 1750 (acetate CO), 1725 (ester CO), 1702 (ketone C=O), and 1245, 1215 cm^{-1} (ester COC). *Anal.* Calcd for $C_{36}H_{50}O_{14} \cdot {}^1/_2H_2O$: C, 60.40; H, 7.32; CH_3CO, 24.06. Found: C, 60.53; H, 6.94; CH_3CO, 24.78.

Compound **5** was prepared also by acetylation of **6** and by treatment[7] of **10** with pyruvic acid.

Methyl (3α-Hydroxy-11,20-dioxo-5β-pregnan-21-yl β-D-Glucopyranosid)uronate (6). A. From 4.—To a solution of 665 mg of triacetate **4** in 40 ml of dry methanol was added 0.30 ml of 1.2 *N* sodium methylate in methanol. After 30 min a slight excess of acetic acid was added, the solution was evaporated to dryness, and crystals (393 mg, 72%, mp 203–205°; homogeneous in system S13) were obtained from cold ethanol: $[\alpha]_D$ +37 ± 2° (CH_3OH); ir (KBr) 3420, 3300 (OH), 1746 (ester C=O), and 1708 cm^{-1} (C-11 + C-20, C=O). *Anal.* Calcd for $C_{28}H_{42}O_{10} \cdot {}^1/_2H_2O$: C, 61.41; H, 7.91; CH_3O, 5.66. Found: C, 61.78; H, 7.50; CH_3O, 6.03.

B. From 7.—Treatment of acid **7** with diazomethane gave an ester (mp 202–204°) which was identical with **6**.

(15) R. Neher, "Steroid Chromatography," 2nd ed, Elsevier, New York, N. Y., 1964, p 122.

(16) M. L. Lewbart and V. R. Mattox, *J. Org. Chem.*, **28**, 1779 (1963).

(17) R. Deghenghi and C. R. Engel, *J. Amer. Chem. Soc.*, **82**, 3201 (1960).

3α-Hydroxy-11,20-dioxo-5β-pregnan-21-yl β-D-Glucopyranosiduronic Acid (7). A. From 4.—To a solution of 382 mg of triacetate **4** in 7.5 ml of chloroform and 3.75 ml of methanol was added 3.75 ml of 0.04 *N* NaOH in methanol. The mixture stood at room temperature for 45 min; then 15 ml of methanol and 7.0 ml of 1.0 *N* aqueous NaOH were added. The mixture stood at room temperature for an additional 30 min, the pH was brought to 4 with dilute H_2SO_4, and the precipitate of sodium sulfate was filtered off and washed with 10 ml of methanol; the filtrate was concentrated to about 5 ml to remove the chloroform and methanol. Water was added to a volume of 80 ml, the pH was brought to 2.1 with H_2SO_4, and the homogeneous mixture was poured onto a column containing 40 g of Amberlite XAD-2.[7,18,19] The column was washed twice with 80 ml of water and three times with 80 ml of ethanol. The ethanol eluates contained an impurity which was removed by chromatography in system S10. A band which emerged at 2.1 HBV gave crystals (241 mg, 79%) from methanol–ethyl acetate (mp 155–157.5°) which were identical with **7** prepared from **8**.

B. From 8.—A solution of ammonium salt **8** (300 mg) in 30 ml of water was adjusted to pH 3.0 with H_2SO_4 and concentrated almost to dryness. The $(NH_4)_2SO_4$ was separated by its insolubility in dry butyl alcohol, and **7** was crystallized from water and then from methanol–ethyl acetate (yield 82%, mp 157–160°): homogeneous in S10; $[\alpha]_D$ +35 ± 2° (CH_3OH); ir (KBr) 3410 (OH), 1700 cm^{-1} (C=O). *Anal.* Calcd for $C_{27}H_{40}O_{10}\cdot{}^1/_2H_2O$: C, 60.77; H, 7.75. Found: C, 60.73; H, 7.97.

Ammonium (3α-Hydroxy-11,20-dioxo-5β-pregnan-21-yl β-D-Glucopyranosid)uronate (8). A. From 6.—A solution of methyl ester **6** (1.0 mmol) in 50 ml of 1 *N* NH_4OH stood at room temperature for 30 min and was evaporated to dryness. Crystals were obtained (82%, mp 167–170° dec) from methanol–ethyl acetate: homogeneous in system S10; $[\alpha]_D$ +35 ± 2° (CH_3OH); ir (KBr) 3400–3220 (OH and NH), 1703 (C-11 + C-20, C=O), 1600 (carboxyl C=O), and 1405 cm^{-1} (COO^-). *Anal.* Calcd for $C_{27}H_{43}O_{10}N$: C, 59.87; H, 8.00. Found: C, 59.40; H, 7.60.

Compound **8** was also prepared from acid **7**.

Methyl (3α-Hydroxy-11,20-dioxo-5β-pregnan-21-yl 2,3,4-Tri-*O*-acetyl-β-D-glucopyranosid)uronate 20-Semicarbazone (9).—A solution of compound **4** (200 mg) was treated[7] with semicarbazide hydrochloride to give crystals of **9** (homogeneous in system S6; 91% yield, mp 152–153°): uv max (CH_3OH) 236 mμ (ε 12,300); ir (KBr) 3590, 3495, 3350 (OH and NH), 1758 (ester C=O), 1700 (C-11 C=O), 1690 sh (amide C=O), 1562 (amide), and 1225 sh, 1207 cm^{-1} (ester COC). *Anal.* Calcd for $C_{35}H_{51}O_{13}N_3$: N, 5.82. Found: N, 5.65.

Methyl (3α-Acetoxy-11,20-dioxo-5β-pregnan-21-yl 2,3,4-Tri-*O*-acetyl-β-D-glucopyranosid)uronate 20-Semicarbazone (10).—**10** was obtained in 94% yield from **5**: hygroscopic crystals; mp 165–167° from methanol; homogeneous in S6; uv max (CH_3OH) 236 mμ (ε 13,000); ir (KBr) 3490, 3360 (NH), 1757 (acetate C=O), 1735 sh (ester C=O), 1702 (C-11 C=O), 1690 sh (amide C=O), 1570 (amide), and 1235, 1212 cm^{-1} (ester COC). *Anal.* Calcd for $C_{37}H_{53}O_{14}N_3\cdot{}^1/_2H_2O$: C, 57.50; H, 7.01; N, 5.44. Found: C, 57.25; H, 6.61; N, 5.21.

Methyl α-D-Glucopyranosiduronate Cyclic 1,2-(Hydrogen [*S*]-Orthoacetate) 3,4-Diacetate 21-Ester with 3α,21-Dihydroxy-5β-pregnane-11,20-dione 3-Acetate (11).—Fractions 93–144 (HBV 2.0), described under **5** from **2**, were combined, washed with water, and taken to dryness. The residue was chromatographed on 300 g of Celite in system S2 (HBV 2.8) and crystals of **11** (385 mg, 6.7%) were obtained from methanol–water: homogeneous by tlc and in system S1; mp 91–94°; $[\alpha]_D$ +68 ± 2° ($CHCl_3$); ir (KBr) 1753 (acetate C=O), 1735 sh (ester C=O), 1705 (C-11 + C-20, C=O), and 1232, 1208 sh cm^{-1} (ester COC); nmr ($CDCl_3$) δ 0.58 (C-18 methyl), 1.17 (C-19 methyl), 1.75 (orthoacetate methyl, endo), 2.02 (C-3 OAc), 2.08 and 2.12 (C-4′ and C-5′ OAc), 2.47 (C-12), 3.02 [C-17 (?)], 3.78 (CH_3O of ester), 3.97 (C-21 methylene), 4.75 (C-3 proton), and 5.85 ppm (J = 5 Hz) (C-1′ proton). *Anal.* Calcd for $C_{36}H_{50}O_{14}$: C, 61.17; H, 7.13; CH_3O, 4.39; CH_3CO, 24.36. Found: C, 60.98; H, 7.31; CH_3O, 4.35; CH_3CO, 22.53.

11,20-Dioxo-5β-pregnan-3α,21-ylene Di(methyl 2,3,4-Tri-*O*-acetyl-β-D-glucopyranosiduronate) (12). A. From 13.—Acetylation of diglucosiduronate dimethyl ester **13** with 1:1 acetic anhydride–pyridine gave a product identical with ester **12** below.

B. From 16.—Semicarbazone **16** (2.08 g) was treated[7] with pyruvic acid as described previously to give **12**, which was crystallized from a mixture of ethanol–acetone–water (1.77 g, 90%, mp 125–128°): homogeneous in system S5 and by tlc; $[\alpha]_D$ +10 ± 2° ($CHCl_3$): ir (KBr) 1753 (ester C=O), 1706 (C-11 + C-20 C=O), and 1230 sh, 1210 cm^{-1} (ester COC). *Anal.* Calcd for $C_{47}H_{64}O_{22}$: C, 57.54; H, 6.58; CH_3CO, 26.32. Found: C, 57.19; H, 6.46; CH_3CO, 24.64.

Dimethyl 11,20-Dioxo-5β-pregnan-3α,21-ylene Di-β-D-glucopyranosiduronate (13). A. From 12.—Ester **13** was prepared from **12** in 86% yield as described for ester **6** from triacetate ester **4**. Crystals were obtained from a mixture of methanol and *tert*-butyl alcohol (mp 147–150°): homogeneous in S10; $[\alpha]_D$ +17 ± 2° (CH_3OH); ir (KBr) 3410 (OH), 1742 (ester C=O), and 1702 cm^{-1} (C-11 + C-20 C=O). *Anal.* Calcd for $C_{35}H_{52}O_{16}$: C, 57.68; H, 7.19. Found: C, 57.50; H, 7.61.

B. From 14.—Treatment of acid **14** with diazomethane also gave ester **13**.

11,20-Dioxo-5β-pregnan-3α,21-ylene Di(β-D-glucopyranosiduronic Acid) (14). A. From 12.—Compound **14** was prepared from diglucosiduronate **12** (0.25 mmol) as described for preparation of **7** from **4**. The residue from the Amberlite XAD-2 column contained material (chromatography system S12) which gave an atypical color (purple) with alkaline tetrazolium blue (compound **14** gave a yellow color). The residue was chromatographed on 50 g of Celite in system S11 (HBV 6.6) and the conjugate was crystallized from methanol–ethyl acetate (144 mg, 83%, mp 185° dec) and identified as **14**.

B. From 15.—A solution of ammonium salt **15** (200 mg) in water was acidified to pH 3 with H_2SO_4 and taken almost to dryness. The residue was extracted with two 100-ml portions of absolute ethanol, the solution was taken to dryness, and crystals of **14** were obtained from methanol–ethyl acetate (156 mg, 82%, mp 175° dec): homogeneous in system S11; $[\alpha]_D$ +17 ± 2° (CH_3OH); ir (KBr) 3430 (OH), 1720 sh (carboxyl C=O), and 1703 cm^{-1} (C-11 + C-20 C=O). *Anal.* Calcd for $C_{33}H_{48}O_{16}\cdot{}^1/_2H_2O$: C, 55.84; H, 6.96. Found: C, 55.77; H, 6.76.

C. From 16.—The diglucosiduronate semicarbazone **16** (1.038 g) was converted into acid **14** by the procedure used to prepare **7** from **4**, except for the following modification. The solution stood at pH 2.1 for 1 hr (in order to hydrolyze the semicarbazone) before it was poured into the column containing Amberlite XAD-2; the column was then washed with two 80-ml portions of 0.01 *N* H_2SO_4 before being washed with three 80-ml portions of water, etc. Crystals of **14** (529 mg, 75%, mp 170–174°) were obtained from methanol–ethyl acetate.

Diammonium 11,20-Dioxo-5β-pregnan-3α,21-ylene Di-β-D-Glucopyranosiduronate (15).—A solution of ester **13** (200 mg) in 20 ml of 1 *N* NH_4OH stood for 2 hr at 25° and was concentrated to dryness. Crystals (188 mg, 93%) of **15** were obtained from methanol–ethanol: mp 178–180° dec; homogeneous in system S11; $[\alpha]_D$ +10 ± 2° (CH_3OH); ir (KBr) 3400–3220 (OH and NH), 1700 (C-11 + C-20 C=O), 1600 (carboxyl C=O), and 1400 cm^{-1} (COO^-). *Anal.* Calcd for $C_{33}H_{54}O_{16}N_2\cdot H_2O$: C, 52.65; H, 7.44. Found: C, 52.66; H, 6.75.

11,20-Dioxo-5β-pregnan-3α,21-ylene Di(methyl 2,3,4-Tri-*O*-acetyl-β-D-glucopyranosiduronate) 20-Semicarbazone (16). A. From 1 *via* 12.—Fractions 38–53 (HBV 2.6), described under the preparation of **4** from **1**, were combined, washed with water, and taken to dryness. The product (**12**) would not crystallize as the ketone; it was converted[7] into semicarbazone **16** (130 mg, 13% yield from **1**, mp 174–175°), a homogeneous (system S6), hygroscopic product. When recrystallized from methanol, it had mp 179–180°; uv max (CH_3OH) 236 mμ (ε 12,800); ir (KBr) 3510, 3380 (NH), 1757 (ester C=O), 1702 (C-11 + amide, C=O), 1570 (amide), and 1230 sh, 1212 cm^{-1} (ester COC). *Anal.* Calcd for $C_{48}H_{67}O_{22}N_3\cdot{}^1/_2H_2O$: C, 55.06; H, 6.55; N, 4.02; CH_3CO, 24.67. Found: C, 54.90; H, 6.23; N, 3.78; CH_3CO, 21.83.

B. From 4 *via* 12.—Fractions corresponding to 2.6 HBV (described under preparation of **17** from **4**) were combined and converted into **16** (254 mg, 24% from **4**, mp 176–177°) as described above.

(18) This resin is very useful for separating steroidal glucosiduronic acids from inorganic acids, salts, and various other water-soluble compounds. We have employed it to separate steroidal glucosiduronic acids from ammonium sulfate, sodium sulfate, ammonium chloride, semicarbazide (after acid hydrolysis of a semicarbazone), inorganic acids in general, and debris from the effluent of a Celite column when the solvent system contained aqueous acetic acid. Also, we have used it for converting ammonium, sodium, potassium, thallium, and barium glucosiduronates into free acids.

(19) H. L. Bradlow, *Steroids*, **11**, 265 (1968).

C. From 12.—Treatment[7] of 12 (490.5 mg) with semicarbazide hydrochloride yielded a product (512 mg, 99%, mp 177–179°) identical with authentic 16.

Methyl 3α-Hydroxy-11,20-dioxo-5β-pregnan-21-yl β-D-Glucopyranosiduronate 2,3,4-Triacetate 3′-(Dihydrogen Orthoacetate) Cyclic 1,2-(*S*)-Ester with Methyl α-D-Glucopyranuronate 3,4-Diacetate (17). A. From 1.—Fractions 23–37 (HBV 1.8), obtained during preparation of 4 from 1, gave a residue which was chromatographed on 100 g of Celite in solvent system S3. The appropriate fraction (HBV 13.5) gave crystals (43 mg, 4.4%, mp 110–115°) of orthoacetate 25 from methanol–water; this product was identical with orthoacetate 25 described in the following paragraph.

B. From 4.—One millimole of 3α-hydroxy conjugate 4 was treated with 3 mmol of methyl acetobromoglucuronate as described for the preparation of 4 from 1. The product was chromatographed on 100 g of Celite (system S4). (For the substance eluted at 2.6 HBV, see 16 from 12, B.) Fractions corresponding to 1.8 HBV were combined, washed with water, and taken to dryness. The residue was rechromatographed in solvent system S3 on 100 g of Celite. The residue from the principal band (HBV 16) weighed 127 mg, a 13% yield of orthoacetate 17. Crystals (90 mg, 9.2%, mp 111–116°) from benzene–cyclohexane were homogeneous by tlc; ir (KBr) 1758 (ester C=O), 1705 (C-11 + C-20 C=O), and 1212 cm^{-1} (ester COC); nmr ($CDCl_3$) δ 0.55 (C-18 CH_3), 1.13 (C-19 CH_3), 1.74 (orthoacetate CH_3), 2.01 (two OAc groups of C-21 glucuronyl group), 2.09 (one OAc group of C-21 glucuronyl group; two OAc groups of C-3 glucuronyl function), 2.43 (probably C-12 protons), 3.75 (CH_3O of ester), and 4.50 ppm (C-21 methylene). *Anal.* Calcd for $C_{47}H_{64}O_{22}\cdot H_2O$: C, 56.50; H, 6.66; CH_3O, 6.21; CH_3CO, 25.85. Found: C, 56.40; H, 6.45; CH_3O, 7.05; CH_3CO, 24.78.

Methyl (21-Hydroxy-11,20-dioxo-5β-pregnan-3α-yl 2,3,4-Tri-*O*-acetyl-β-D-glucosid)uronate (18). A. From 1.—Fractions 69–94 (HBV 4.6), described under 4 from 1, were combined, washed with water, and freed of solvent. Crystals (113 mg, 17%, mp 113–116°), obtained from acetone–methanol–water, were homogeneous in system S5; $[\alpha]_D$ +42 ± 2° ($CHCl_3$); ir (KBr) 3490 (OH), 1755 (ester C=O), 1702 (C-11 + C-20 C=O), and 1210 cm^{-1} (ester COC). *Anal.* Calcd for $C_{34}H_{48}O_{13}\cdot{}^1/_2H_2O$: C, 60.60; H, 7.33. Found: C, 60.68; H, 7.07.

Compound 18 reduced alkaline tetrazolium blue and reacted with cupric acetate[10] to produce a product which gave a yellow color with Porter–Silber reagent.

B. From 22.—Treatment of semicarbazone 22 (20 mg) with pyruvic acid[7] produced 9 mg (49%, mp 110–113°) of 18.

Methyl (21-Acetoxy-11,20-dioxo-5β-pregnan-3α-yl 2,3,4-Tri-*O*-acetyl-β-D-glucosid)uronate (19). A. From 3.—Compound 3 (3.9 g, 10.0 mmol) was treated with methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-glucuronate as described under the preparation of 4 and the product was chromatographed in system S4. Fractions were combined to give residues designated as follows: 1.5 HBV (a mixture of glucosiduronate 19 and orthoacetate 25; see below in this paragraph); 2.2 HBV (the 3-oxo compound, 21-acetoxy-5β-pregnane-3,11,20-trione; see below). The residue designated 1.5 HBV gave crystals (3.02 g, 43% mp 106–109°) of 19 from benzene–cyclohexane: homogeneous in system S1; $[\alpha]_D$ +54 ± 2° ($CHCl_3$); nmr ($CDCl_3$) δ 0.60 (C-18 CH_3), 1.12 (C-19 CH_3), 2.02 (2′,3′,4′ OAc groups), 2.16 (C-21 OAc), 2.50 (C-12 protons), 3.5 (CH_3O of ester), and 4.55 ppm (C-21 methylene). The ir spectrum was identical with that of compound 19. (For isolation of the 3-orthoacetate 25 from the mother liquor of 19, see 25 below.)

B. From 18.—Acetylation of 18 (200 mg) followed by crystallization from methanol–water gave 19 (174 mg, 81%, mp 106–108°): $[\alpha]_D$ +54 ± 2° ($CHCl_3$); ir (KBr) 1757 (ester C=O), 1728 sh (C-20 C=O), 1707 (C-11 C=O), and 1210 cm^{-1} (ester COC). The sample for analysis was dried *in vacuo* at 78°. *Anal.* Calcd for $C_{36}H_{50}O_{14}$: C, 61.17; H, 7.13; CH_3CO, 24.36. Found: C, 60.99; H, 7.05; CH_3CO, 23.31.

Compound 19 was prepared from 20 in a similar manner and from 23 by treatment with pyruvic acid.

Methyl (21-Hydroxy-11,20-dioxo-5β-pregnan-3α-yl β-D-Glucopyranosid)uronate (20). A. From 19.—Treatment of 353 mg of compound 19 with 0.01 *N* NaOH in 15 ml of chloroform–methanol, 1:1, for 45 min followed by addition of an excess of acetic acid and 1.0 mg of EDTA, concentration *in vacuo*, and separation from ethyl acetate–cyclohexane yielded amorphous 20 which was homogeneous in system S13 (232 mg, 86%): $[\alpha]_D$ +51 ± 2° (CH_3OH); ir (KBr) 3440 (OH), 1746 (ester C=O), and 1705 cm^{-1} (C-11 + C-20 C=O). *Anal.* Calcd for $C_{28}H_{42}O_{10}\cdot H_2O$: C, 60.41; H, 7.97; CH_3O, 5.57. Found: C, 60.58; H, 7.77; CH_3O, 5.62.

B. From 21.—Esterification of acid 21 with diazomethane also gave ester 20.

21-Hydroxy-11,20-dioxo-5β-pregnan-3α-yl β-D-Glucopyranosiduronic Acid (21). A. From 19.—Compound 19 was treated as described below under procedure 1 for preparation of 21 from 23. It was not possible to obtain crystals. The product was freed of salt and inorganic acid by use[7] of Amberlite XAD-2; to the alcoholic eluate was added 2 mg of EDTA, the solution was taken to dryness, and the residue was chromatographed on 100 g of Celite (system S10). Bands emerged at 1.14 (see 26 from 19) and at 1.8 HBV. EDTA (2 mg) was added to the eluate containing the latter band, the solvent was removed, and crystals of 21 were obtained from 0.01 *N* H_2SO_4 and washed with H_2O (122 mg, 47%, mp 156–158°).

In two similar experiments on the preparation of 21 from 19 in which only 0.10 mg of EDTA was added to the alcoholic eluate from the Amberlite column and again after Celite chromatography, crystals could not be obtained. Several solvents were used during a period of 2 days. A paper chromatogram (system S10) showed that the original ketolic compound 21 (R_f 0.29) had disappeared and that a new Porter–Silber-positive[10] compound (R_f 0.70; presumably the 20-keto-21-aldehyde) had been formed.

In another experiment, the mobile phase was run through a column of Celite like that used for chromatography of 21; the fraction corresponding to the band at 1.8 HBV was collected, taken to dryness, and shown to contain (by atomic absorption) 1.5 μg of copper. To one-tenth of this residue was added 17 mg of compound 21 in 0.10 ml of methanol; after 24 hr, the solution gave a strong color with the Porter–Silber reagent. Color with the Porter–Silber reagent was not obtained when 17 mg of compound 21 was treated similarly with 0.10 mg of the residue in the presence of 0.10 mg of EDTA.

B. From 23. Procedure 1.—Semicarbazone 23 (764 mg) was treated with alkali as described under 7 from 4. Methanol[20] (10.0 ml) was added to dissolve the oil which separated when the pH was adjusted to 2.1. After 1 hr, the solution was concentrated *in vacuo* to 7 ml. Crystals, which formed slowly, were filtered, washed well with cold water, and dried at 100° (497 mg, 93%, mp 157–159°). In a second preparation the yield was 88% (mp 158–160°): homogeneous in system S10; $[\alpha]_D$ +59 ± 2° (CH_3OH); ir (KBr) 3400 (OH), 1748 sh (carboxyl C=O), and 1700 cm^{-1} (C-11 + C-20 C=O). *Anal.* Calcd for $C_{27}H_{40}O_{10}\cdot{}^1/_2H_2O$: C, 60.77; H, 7.75. Found: C, 60.76; H, 7.72.

B. From 23. Procedure 2. Ion-Exchange Column.—One millimole of 23 was treated with alkali as described in the previous paragraph and the solution was acidified with acetic acid, concentrated to dryness, and processed[7] on a column of Dowex 50W-X2 (40 g); acid 21 was obtained in 82% yield.

C. From 20.—A solution which contained 100 mg of 20 in 20 ml of 0.1 *M* $NaHCO_3$ stood at 26° for 24 hr. The pH was adjusted to 2.1 with 0.5 *M* H_2SO_4, and the solution was concentrated and cooled. Crystals of 21 (mp 157–159°) were obtained in 40% yield. By desalting the filtrate on Amberlite XAD-2 and chromatographing the steroid residue in system S10, an additional 26% of 21 was obtained.

Methyl (21-Hydroxy-11,20-dioxo-5β-pregnan-3α-yl 2,3,4-Tri-*O*-acetyl-β-D-glucosid)uronate 20-Semicarbazone (22).—22 was obtained from 18 by the procedure described in the next paragraph and crystallized from aqueous ethanol (88% yield, mp 157–159°): homogeneous in system S6; uv max (CH_3OH) 236 mμ (ε 11,800); ir (KBr) 3510, 3385 (OH and NH), 1757 (ester C=O), 1706 (C-11 C=O), 1692 (amide C=O), 1573 (amide), and 1215 cm^{-1} (ester COC). The dried product gained 4.1% in weight when exposed to the atmosphere. *Anal.* Calcd for $C_{35}H_{51}O_{13}N_3$: N, 5.82. Found: N, 5.30.

Methyl (21-Acetoxy-11,20-dioxo-5β-pregnan-3α-yl 2,3,4-Tri-*O*-acetyl-β-D-glucosid)uronate 20-Semicarbazone (23). A. From 19.—A solution of 750 mg of semicarbazide hydrochloride and 504 mg of $NaHCO_3$ in 2 ml of water was added to 695 mg of 20-oxo conjugate 19 in 20 ml of methanol. After 18 hr, crystals (709 mg, 93%, mp 178–181°) of chromatographically pure (system

(20) If the pH is adjusted to 3.0 and the solution is stirred for a few minutes, it remains homogeneous when the pH is subsequently brought to 2.1; under these conditions, addition of methanol is not necessary.

S6) semicarbazone were obtained from aqueous methanol: uv max (CH_3OH) 237 mμ (ε 12,800); ir (KBr) 3515, 3395, 3285 br (NH), 1753 (ester C=O), 1705 (C-11 + amide, C=O), 1570 (amide), and 1217 cm^{-1} (ester COC). *Anal.* Calcd for $C_{37}H_{53}O_{14}N_3 \cdot {}^1/_2H_2O$: C, 57.50; H, 7.04; N, 5.44. Found: C, 57.55; H, 6.95; N, 5.38.

B. From 22 and 24.—Acetylation of **22** and **24** in 1:1 acetic anhydride–pyridine gave **23** (mp 178–181°).

Methyl (21-Hydroxy-11,20-dioxo-5β-pregnan-3α-yl β-D-Glucopyranosid)uronate 20-Semicarbazone (24). A. From 20.—Treatment of 50 mg of ester **20** with semicarbazide hydrochloride as described under the preparation of **23** from **19** gave crystals (30.8 mg, 55% yield) of **24** from butyl acetate.

B. From 23.—To a solution of 764 mg of semicarbazone **23** in a mixture of 10 ml of chloroform and 5 ml of methanol was added 5 ml of 0.04 *N* methanolic NaOH. After 45 min, a slight excess of 1.0 *N* acetic acid in methanol was added and the solution was taken to dryness immediately to remove all acetic acid and prevent hydrolysis of the semicarbazone. Hygroscopic crystals (552 mg, 92%, mp 173° dec) were obtained from methanol–butyl acetate: homogeneous in system S14; uv max (CH_3OH) 236 mμ (ε 11,800); ir (KBr) 3500–3300 (OH and NH), 1742 (ester C=O), 1702 sh (C-11 C=O), 1680 (amide C=O), and 1565 cm^{-1} (amide). *Anal.* Calcd for $C_{29}H_{45}O_{10}N_3 \cdot {}^1/_2H_2O$: C, 57.59; H, 7.84; N, 6.95; CH_3O, 5.13. Found: C, 57.33; H, 7.64; N, 7.35; CH_3O, 5.53.

Methyl α-D-Glucopyranuronate Cyclic 1,2-(Hydrogen [*S*]-Orthoacetate) 3,4-Diacetate 3-Ester with 3α,21-Dihydroxy-5β-pregnane-11,20-dione 21-Acetate (25).—The filtrate from the crystallization of 3.02 g of compound **19** (described under **19** from **3**) was evaporated and the residue was chromatographed as described for the separation of **19** except that system S1 was used. The band at 3.1 HBV gave 1.64 g of residue which crystallized from methanol–water to yield 1.56 g (22%, mp 95–98°) of chromatographically pure (systems S1 and S4) orthoacetate **25**: $[\alpha]D$ +78 ± 2° ($CHCl_3$); ir (KBr) 1753 (ester C=O), 1708 (ketone C=O), and 1225 cm^{-1} (ester COC); nmr ($CDCl_3$) δ 0.61 (C-18 CH_3), 1.13 (C-19 CH_3), 1.75 (orthoacetate CH_3), 2.10 (3′,4′ OAc groups), 2.15 (C-21 OAc), 2.50 (C-12 protons), 3.78 (CH_3O of ester), 4.55 (C-21 methylene), and 5.81 ppm (doublet, 1-proton of glucuronyl group, $J_{1,2}$ = 5 Hz). *Anal.* Calcd for $C_{36}H_{50}O_{14}$: C, 61.17; H, 7.13; CH_3O, 4.39; CH_3CO, 24.36. Found: C, 61.31; H, 7.36; CH_3O, 4.58; CH_3CO, 22.96.

21-Acetoxy-5β-pregnane-3,11,20-trione.—Chromatography fractions 144–195 (HBV 2.2), described under **19** from **3**, afforded crystals (462 mg, 12%, mp 157–160°) from methanol; this product was identified as 21-acetoxy-5β-pregnane-3,11,20-trione[17] by comparison with an authentic sample. Paper chromatography of compound **3** (starting material in this preparation) in system S4 showed that it contained no 21-acetoxy-5β-pregnane-3,11,20-trione.

Compound **3** (781 mg, 2.0 mmol) was treated with 2.20 g (8.0 mmol) of freshly prepared silver carbonate in benzene as described for the preparation of **4** except that the methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-decxy-α-D-glucuronate was omitted. Chromatography of the product on 300 g of Celite (system S4) separated a band (HBV 2.0) which gave crystals (385 mg, 50%, mp 157–158°) of 21-acetoxy-5β-pregnane-3,11,20-trione from aqueous methanol.

17β-Carboxy-11-oxo-5β-androstan-3α-yl β-D-Glucopyranosiduronic Acid (26). A. From 19.—The residue (71 mg) from the band eluted at 1.14 HBV (described under **21** from **19**) was dissolved in the mobile phase of system S13; crystals formed (7.5 mg, 3.0%, mp 214–216° dec). The mother liquor was chromatographed on 30 g of Celite in system S13. The band eluted at 7.5 HBV yielded crystals (12.5 mg, 5.0%, mp 214–215°) of **26** (from ethanol) identical with the sample prepared in the following paragraph.

B. From 27.—Compound **27** (325 mg) was hydrolyzed by treatment with alkali as described for the preparation of **21** from **23**, procedure 1, and the solution was desalted on a column of Amberlite XAD-2. Crystals (228 mg, mp 214–215°) of chromatographically pure (system S13) **26** were obtained from ethanol: $[\alpha]D$ +43 ± 2° (CH_3OH); ir (KBr) 3380 (OH), 1763 (carboxyl C=O), 1710 sh, and 1696 cm^{-1} (C-11 C=O). *Anal.* Calcd for $C_{25}H_{38}O_{10}$: C, 61.16; H, 7.50. Found: C, 61.18; H, 7.74.

Methyl (17β-Carboxy-11-oxo-5β-androstan-3α-yl 2,3,4-Tri-*O*-acetyl-β-D-glucosid)uronate (27).—To 333 mg (0.50 mmol) of **18** in 15 ml of glacial acetic acid was added 1.54 mmol of H_5IO_6 in 70 ml of 80% acetic acid. After 15 min, water was added, the solution was extracted with ethyl acetate, and the extract was washed with water and taken to dryness. Crystals (230 mg, mp 220–222°; 61.5 mg, mp 218–220°) were obtained from ethanol. The sample for analysis melted partially at 135–140°, recrystallized spontaneously, and remelted at 220–221°: $[\alpha]D$ +41 ± 2° (CH_3OH); ir (KBr) 3320 (OH), 1756 (ester + carboxyl, C=O), 1705 (C-11 C=O), and 1212 cm^{-1} (ester COC). *Anal.* Calcd for $C_{33}H_{46}O_{13} \cdot {}^1/_2H_2O$: C, 60.08; H, 7.18; CH_3O, 4.70. Found: C, 60.35; H, 7.08; CH_3O, 4.83.

Methyl (17β-Carbomethoxy-11-oxo-5β-androstan-3α-yl 2,3,4-Tri-*O*-acetyl-β-D-glucosid)uronate (28). A. From 27.—Treatment of **27** (100 mg) in methanol with diazomethane in ether gave ester **28** (101 mg, mp 172–173°), identical with the product prepared from **26**.

B. From 26.—Treatment of 100 mg of a methanolic solution of **26** (derived from **27**) with diazomethane in ether followed by acetylation with acetic anhydride–pyridine and crystallization from ethanol gave 121 mg (92%) of chromatographically pure (tlc) ester **28** (170–171°). The analytical sample had mp 172–173°; $[\alpha]D$ +36 ± 2° (CH_3OH); ir (KBr) 1770 sh, 1755 (acetate C=O), 1740 (ester C=O), 1705 (C-11 C=O), and 1210 cm^{-1} (ester COC). *Anal.* Calcd for $C_{34}H_{48}O_{13} \cdot H_2O$: C, 59.81; H, 7.38; CH_3O, 9.09. Found: C, 60.09; H, 7.16; CH_3O, 8.99.

When dicarboxylic acid **26** (derived from **18** with alkali) was esterified with diazomethane and acetylated, **28** was obtained.

Registry No.—**1**, 566-03-0; **2**, 2631-05-2; **3**, 2526-11-6; **4**, 36707-52-5; **5**, 36707-53-6; **6**, 36707-54-7; **7**, 36707-55-8; **8**, 36707-56-9; **9**, 36707-57-0; **10**, 36763-74-3; **11**, 36763-75-4; **12**, 36707-58-1; **13**, 36707-59-2; **14**, 36707-60-5; **15**, 36707-61-6; **16**, 36707-62-7; **17**, 36707-63-8; **18**, 36707-05-8; **19**, 36707-06-9; **20**, 36707-07-0; **21**, 35105-23-8; **22**, 36707-09-2; **23**, 36707-10-5; **24**, 36707-11-6; **25**, 36707-12-7; **26**, 36707-13-8; **27**, 36707-14-9; **28**, 36707-15-0; 21-acetoxy-5β-pregnane-3,11,20-trione, 36707-16-1.

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Configurations and Conformations of Epimeric 2,5-Dimethyl-5,6-dihydro-α-pyrans

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The high-resolution nmr spectra of epimeric esters of 2,5-dimethyl-5,6-dihydro-α-pyrans were studied. Configurational and conformational assignments were made using spin–spin decoupling, variable temperature, and shift reagent techniques. In the latter case, an appreciable changing of coupling constants was observed. The 5,6-dihydro-α-pyrans seem to exist in half-chair-like conformations exclusively (at room temperature). The conformational analyses of methylodihydropyrans show that they are more similar to cyclohexene than to alkoxycyclohexenes (or unsaturated sugars). A new J_0 for the Karplus equation was calculated and applied.

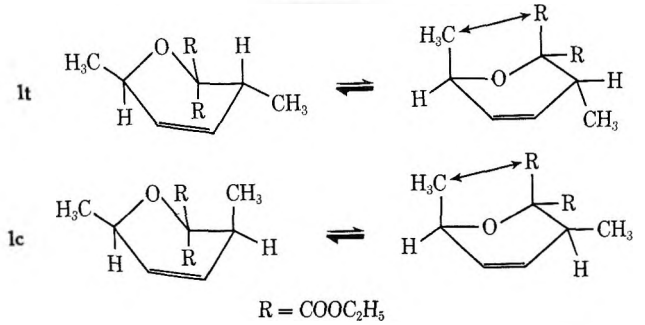
The present paper contains an analysis, by various nmr techniques, of the configurations and conformations of methylodihydropyrans, of which there have been relatively few conformational studies.[1-4]

The epimers diethyl 2β,5α-dimethyl-5,6-dihydro-α-pyrano-6,6-dicarboxylate (**1t**) and diethyl 2β,5β-dimethyl-5,6-dihydro-α-pyrano-6,6-dicarboxylate (**1c**), as well as the model compound diethyl 2β-methyl-5,6-dihydro-α-pyrano-6,6-dicarboxylate (**2**), were synthesized by the Diels–Alder reaction. The first two compounds were prepared by treating diethyl mesoxalate with *trans,cis*-2,4-hexadiene and *trans,trans*-2,4-hexadiene, respectively; the model compound was obtained by treating diethyl mesoxalate with *trans*-piperylene.[5-7]

The stereochemistries of the products obtained respect the Alder rules.

The conformations of the compounds **1t** and **1c** represent an equilibrium system (Scheme I).

SCHEME I



The equilibrium of the compound **1t** (two methyls trans) is pushed strongly to the left, the right-hand conformation being destabilized by both the 1,3-diaxial interaction and the axial positions of both methyl groups. For the compound **1c** (two methyls cis), conformational analysis shows a strong 1,3-diaxial interaction in the right-hand form which thus pushes the equilibrium to the left.

First of all, low-resolution nmr spectroscopy together with spin–spin decoupling permitted the identification of all proton signals.[8,9]

Since the 2-H of both the compounds **1t** and **1c** is partially masked by the carboxylate methylene quadruplets, our study was based on the 5-H, the observation of which is easier. For the compound **2**, the 2-H was used as a reference in view of the presence of two protons at the C-5 position.

The low-temperature nmr analysis of the compound **2** showed no coalescence in the 25 to −180° temperature range, indicating conformational homogeneity.

A coupling constant $J_{2,3}$ = 2.2 Hz was observed for the compound. On the other hand, using the Karplus equation and angles obtained from Dreiding models, this $J_{2,3}$ was calculated to be only 1.90 Hz.[11] It is this discrepancy which prompted us to introduce a modified J_0 for the Karplus equation;[9-13] a value of J_0 = 10.6 Hz was found to correlate the calculated angles and observed coupling constants, and was used in further calculations. This modified Karplus parameter is about the same as that of other authors for a similar system.[2]

The analysis of the low-temperature spectra of **1t** and **1c** (Table I) also showed the absence of coalescence in the temperature range mentioned above. Furthermore, the modified J_0 = 10.6 Hz was applied as it afforded better justification of the coupling constants found.

The dihedral angles between the protons 4-H, 5-H and 2-H, 3-H measured for the chair conformations presented were found to be about 80° for the 5-H_{ax}, C-5, C-4, 4-H (or 2-H_{ax}, C-2, C-3, 3-H) system and about 40° for the 5-H_{eq}, C-5, C-4, 4-H (or 2-H_{eq}, C-2, C-3, 3-H) system.[9,14] These values were calculated for a simple system substituted by an alkoxy group, whereas our system is one substituted by two alkyl groups. For the boat conformations, the corresponding angles are 110 and 18°, respectively.[9] The values found, using J_0 = 10.6 Hz, after the examination of the various coupling constants (see Table II, Scheme II) confirm a more folded conformation, with angle values closer to those of cyclohexene calculated by Garbisch[8,15] and Corey,[16] being about 60 and 45°, respectively, than to those of the mentioned 2-alkoxy carbohydrates.[1] Using the modified Karplus equation[9,10,17] and the measured values of the dihedral angles between 4-H

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TABLE I

PROTON CHEMICAL SHIFTS OF 1t AND 1c, WITH (δ_{SR}) AND WITHOUT (δ_0) SHIFT REAGENTS[a] ($CDCl_3$)

	1c				1t			
		δ_{SR} After addition of E-FOD[a]				δ_{SR} After addition of E-FOD[a]		
	δ_0	0.5 mol	1 mol	$\Delta\delta_{SR}$[b]	δ_0	0.5 mol	1 mol	$\Delta\delta_{SR}$[b]
H-2	4.37	5.22	6.14	1.77	4.25	4.95	6.05	1.80
H-3	5.51	5.82	6.28	0.77	5.50	5.74	6.20	0.70
H-4	5.84	6.20	6.62	0.78	5.86	6.10	6.52	0.66
H-5	3.04	3.80	4.62	1.58	3.03	3.62	4.60	1.57
H_3C-2	1.39	1.80	2.38	0.99	1.33	1.66	2.32	0.99
H_3C-5	1.02	1.42	1.90	0.88	0.99	1.38	1.82	0.83
H_3C-H_2C ax	1.27				1.17			
		1.36	1.54	0.27		1.52	1.48	0.30
eq	1.28				1.19			
H_3C-H_2C ax	4.26	4.52			4.24	4.40		
			4.78	0.51			4.70	0.45
eq	4.28	4.55			4.26	4.44		

[a] E-FOD = Eu(fod)$_3$-d_{27}. [b] Molar $\Delta\delta_{SR} = \delta_{SR} - \delta_0$.

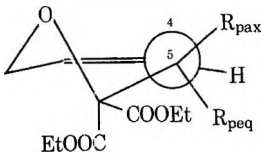
TABLE II

COUPLING CONSTANTS OF PROTONS OF 1c AND 1t (CPS)

J	1t	1c
3,4	10.15	10.35
2,5	2.45	2.0
4,5	2.70	5.25
2,3	2.20	1.40
2,4	−1.55	−1.80
3,5	−1.67	−0.74
2,CH_3-2	7.10	7.07
5,CH_3-5	7.25	6.85
CH_2,CH_3	7.15	7.02
After the Addition of 1 mol of E-FOD		
4,5	3.0 (0.3)[a]	5.85 (0.6)[a]
2,3	2.5 (0.3)[a]	1.8 (0.4)[a]

[a] Differences between $J_{2,3}$ and $J_{2,3}$ in the presence of the shift reagent.

SCHEME II



	1t	1c
R_{pax}	H	CH_3
R_{peq}	CH_3	H

and 5-H, we were able to calculate the coupling constants, which had, however, an orientational value only.

The comparison of the relative values of observed coupling constants, *i.e.*, compound **1c**, with the calculated values further establishes the existence of the product in the conformation where the 5-CH_3 is in an axial position (calcd 5.30 Hz, obsd 5.25 Hz). This places, respecting the Alder rule, the 2-CH_3 in an equatorial position.

It is not possible to apply experimental equations derived for coupling constants in a cyclohexene system in view of the fact that the presence of the oxygen atom in the cycle changes considerably and, unpredictably,[2,8,15] the coupling constant values (especially $J_{2,3}$). Nevertheless, the C-4, C-5 part of the molecule is similar to cyclohexene and therefore the application of the above-mentioned equations gives but little deviation.[1,8] Our study of the conformations of **1t** and **1c** is primarily based on $J_{4,5}$ rather than other coupling constants.

Some of the coupling constants (allylic, homoallylic) were obtained by the use of high-resolution nmr spectrometry. First of all, the homoallylic $J_{2,5}$ for the compound **1t** (2.45 Hz) was found to be larger than that for the **1c** compound (2.00 Hz). As it is, a coupling constant between two pseudoaxial protons 2-H, 5-H is predicted to be greater than the coupling between a combination of pseudoaxial and pseudoequatorial protons, this latter being larger than that between two pseudoequatorial protons.[18] For the compound **1c**, the homoallylic coupling constant calculated was $J_{2,5} = 2.0$ Hz.[12]

The allylic coupling constant on the oxygen side of the molecule is of little significance. Using Corey's values,[16] we were able to calculate the angles on the C-4, C-5 face of the molecule.

The allylic coupling, which is equally angularly dependent, calculated by Abraham's equation is in good agreement with the obtained data.[12,13]

At the outset of this analysis, we now have a more complete picture of the molecules **1t** and **1c** by evaluating the angles indicated in Tables III and IV, and by Scheme II.

TABLE III

DIHEDRAL ANGLES CALCULATED FROM J[a]

			After addition of 1 mol of E-FOD	$\Delta\phi$
H-2,C-2,C-3,H-3	1c	64°40′	61°40′	3°
	1t	63°	61°	2°
H-4,C-4,C-5,H-5	1c	39°30′	35°30′	4°
	1t	50°20′	53°30′	1°50′

[a] Karplus equation using $J_0 = 9.3$.

TABLE IV

DIHEDRAL ANGLES CALCULATED FROM J[a]

			After addition of 1 mol of E-FOD	$\Delta\phi$
H-2,C-2,C-3,H-3	1c	66°20′	64°	2°20′
	1t	61°10′	59°10′	2°
H-4,C-4,C-5,H-5	1c	43°30′	40°20′	3°10′
	1t	57°50′	56°10′	1°40′

[a] Karplus equation using modified $J_0 = 10.6$ (from product 2).

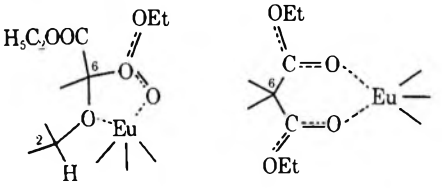
(18) D. W. Cameron, D. G. I. Kingston, N. Sheppard, and L. Todd, *J. Chem. Soc.*, 98 (1964).

The molecules show a great resemblance to Corey's propositions for cyclohexenes,[16,17] in opposition to Reeves's proposition—therefore half-chair-like conformations for a like system.[19]

The application of shift reagents such as E-DPM, P-DPM, E-FOD, and P-FOD enabled us to better identify certain protons and coupling constants, *i.e.*, 2-H (Table I). E-FOD, or Eu(fod)$_3$-d_{27} was preferred by us for use with ester-type compounds.[20] Praseodymium derivatives, in shifting signals to already occupied regions, are clearly less useful.

The addition of E-FOD (in chloroform) displaces differently relative shifts in epimers, especially for the protons 3-H and 4-H. For example, in the compound **1t,** the 3-H signal is the most displaced, whereas, in the compound **1c,** it is the 4-H signal which is the most displaced. The addition of the complexing agent displaces appreciably in decreasing order the 2-H, 5-H, and 2-CH$_3$ signals. The simplification of two ester ethyl signals (axial and equatorial) after the addition of an equimolar quantity of shift reagent was also noticed. This may indicate the formation of a complex involving both carboethoxy groups or, more probably, one of the two carboethoxy groups and the oxygen atom of the cycle. According to Buckingham and Sargeson,[21] the oxygen of the cycle must participate in the formation of such a complex [five-membered cycle, large $\Delta\delta_{SR}$(2-H)] which undoubtedly causes a greater rigidity in the molecule (Scheme III).

SCHEME III



Therefore, we are proposing the introduction of a quantity referred to earlier in Table I, that is, the molar shift reagent chemical shift, $\Delta\delta_{SR}$(molar). This would be a unit chemical shift/mole shift reagent, and could be determined for different classes of compounds such as ethers, amines, pyrans, and pyridines. This value would permit the determination of the exact influence of the soluble mole:mole complex on the conformation of a molecule in a given solvent.

Another interesting observation was that of the changing of coupling constants under the influence of shift reagent. Indeed, E-FOD in chloroformic solution changes the value of certain coupling constants, *i.e.*, by 0.6 Hz for $J_{2,3}$ of the compound **1c** and by 0.3 Hz for the same coupling in the compound **1t** (Table II). This indicates a changing of conformation in the neighborhood of the oxygen atom in the molecule. These changes, corresponding to dihedral angle variation with the overall effect of flattening the molecule, are shown in Tables III and IV. We have used both the normal Karplus J_0 (Table III) and the modified Karplus J_0 (Table IV).

The changes in coupling constants mentioned above illustrate that many conformational conclusions drawn with the help of shift reagent application must be verified, and that the technique itself must be applied with greater caution and in limited cases. In fact, it must be realized that it is the complex's coupling constants that are being measured, and not those of the original compound. Nevertheless, the application of shift reagents can become a useful method in the study of conformers or epimers.

A correct interpretation of data is difficult if the products are left in an even lightly acidic solution. The epimerization of the C-2 is observed even in chloroformic solution.

Experimental Section

The nmr spectra, in CCl_4, CS_2, or $CDCl_3$, were registered on Varian A-60, T-60, HA-100, and HR-220 MHz, as well as Bruker XL-60 and XL-90 spectrometers. Spin–spin decouplings were carried out on HA-100 and HR-220 MHz instruments; variable-temperature measurements were obtained on a Bruker XL-60 spectrometer. The shift reagent Eu(fod)$_3$-d_{27} was purchased from Merck Sharp and Dohme, Canada Ltd., and was added gradually up to equimolar quantities, in $CDCl_3$.

The compounds 1c, bp 82° (0.17 mm), 47% yield, 1t, bp 84° (0.12 mm), 34% yield, and 2, bp 79° (0.1 mm), 45% yield, were prepared by ourselves[5,7] in bomb tubes, at 120–140° for 24 hr. These were purified by vpc preparative and their purity was verified on a Varian MAT-Gnom 411 VPC-MS system.[6]

Registry No.—*cis*-**1**, 36736-30-8; *trans*-**1**, 36736-31-9; **2**, 36749-08-3.

Acknowledgments.—The authors are indebted to the National Research Council of Canada for the financial support received (Grant Number A5976), as well as to Dr. A. Zamojski (IChO, PAN) for his discussions.

(19) R. E. Reeves, *Advan. Carbohyd. Chem.*, **6**, 107 (1951); see also C. J. Bushweller and J. W. O'Neil, *Tetrahedron Lett.*, 4713 (1963).

(20) R. E. Rondeau and R. E. Sivers, *J. Amer. Chem. Soc.*, **93**, 1522 (1971).

(21) D. A. Buckingham and A. M. Sargeson, *Top. Stereochem.*, **6**, 219 (1971).

6α- and 6β-Hydroxyestriol. Synthesis, Configurational Assignments, and Spectral Properties[1]

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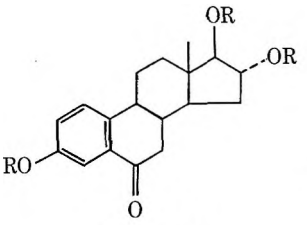
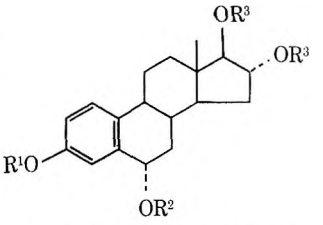
Preparation and properties of both epimers of 6-hydroxyestriol, an important metabolite in human pregnancy urine, are described. Configurational assignments are made on the basis of nmr spectral data. CD spectra for estradiol, estriol, 6-oxoestriol, 6-oxoestriol triacetate, and 6α- and 6β-hydroxyestriol are reported.

Of the two hydroxyestriols[5] present in significant amounts in human late pregnancy urine, one has been conclusively identified as 15α-hydroxyestriol.[6] The second urinary metabolite was shown to be a 6-hydroxyestriol of undefined stereochemistry.[7] A 6-hydroxyestriol had been synthesized by sodium borohydride reduction of 6-oxoestriol[8] and was designated as "6α" on the basis of a thermodynamic–steric argument advanced by Wintersteiner and Moore in the closely related case of the 6-hydroxyestradiols.[9,10] No spectral data were given for the "6α"-hydroxyestriol from borohydride reduction, or for the urinary metabolite. Identification of the latter was based on identical mobilities in a number of paper chromatographic and tlc systems and on dehydration to 6-dehydroestriol. 6β-Hydroxyestriol has not been reported or described.

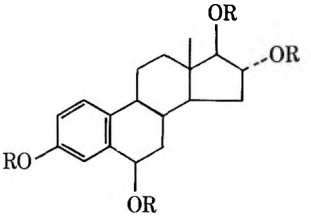
We here report the synthesis of both 6-hydroxyestriols, and assign the configurations by comparison of spectral data.



1a, R = Ac
b, R = H



2a, $R^1 = R^3 = Ac$; $R^2 = H$
b, $R^1 = R^2 = H$; $R^3 = Ac$
c, $R^1 = R^2 = R^3 = H$
d, $R^1 = R^2 = R^3 = Ac$



3a, R = H
b, R = Ac

Results and Discussion

Sodium borohydride reduction of 6-oxoestriol triacetate[8] (**1a**) at 0° gave a readily separable mixture of two acetates, later identified as 6α-hydroxyestriol 3,16,17-triacetate (**2a**) and 6α-hydroxyestriol 16,17-diacetate (**2b**). Phenolic acetates are known to be readily hydrolyzed by methanolic borohydride solutions.[11,12] In this case, while **2b** was the major product (65:35) in methanol, **2a** predominated (85:15) in ethanol. Mild alkaline hydrolysis of **2a** or **2b** gave the tetrol **2c**, whose physical constants agreed with those previously reported for "6α"-hydroxyestriol.[8]

Triacetate **1a** was hydrolyzed to the known[8] 6-oxoestriol (**1b**) which was hydrogenated over platinum to the tetrol **3a**. Tetrols **2c** and **3a** each showed a single spot on tlc but were not separable from one another in the systems used; however, mixture melting points were depressed by 20–40°. From the spectral data presented below we may conclude that, while a few per cent of the other isomer would be undetected, samples of **2c** and **3a** obtained in this manner are at least 95% configurationally pure.[12a]

We sought to establish the configurations of the tetrols **2c** and **3a** by a comparison of their C-6 proton nmr signals. The spectrum of **3a** (determined in methanol-d_4 because the tetrols are insoluble in chloroform, benzene, and acetone) showed clearly the C-17 proton signal as a doublet at 3.47 ppm and the C-16 proton signal as a multiplet at 4.07 ppm, but the C-6 proton signal at *ca.* 4.6 ppm was largely obscured by the huge CD_3OH peak. Consequently, tetraacetates **2d** and **3b** were prepared and their spectra were determined in deuteriochloroform. Both displayed identical signals for the C-17 and C-16 protons, the former a doublet at 4.98 ppm, the latter a broad unsymmetrical triplet at 5.19 ppm. The C-6 proton signals (at 6.02 ppm in both spectra), however, differed significantly. That of **2d** was a broad, poorly defined triplet (J = 8 Hz, with further splitting) while that of **3b** was a narrow doublet (J = 2.5 Hz, with further splitting). The widths at half height were, respectively, 17 and 5 Hz. Thus proof of the orientation of the C-6 proton as pseudoaxial in **2d** and pseudoequatorial in **3b** conclusively establishes the configuration of the hydroxyl group at C-6 as α (pseudoequatorial) in **2d** and β (pseu-

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(2) Department of Chemistry.

(3) Department of Obstetrics and Gynecology.

(4) Supported by NIH Grant HD-05797.

(5) Estriol is the trivial name for 1,3,5(10)-estratriene-3,16α,17β-triol.

(6) G. Zucconi, B. P. Lisboa, E. Simonitsch, L. Roth, A. A. Hagen, and E. Diczfalusy, *Acta Endocrinol.*, **56**, 413 (1967).

(7) J. Breuer, F. Breuer, H. Breuer, and R. Knuppen, *Z. Physiol. Chem.*, **346**, 279 (1966).

(8) G. F. Marrian and A. Sneddon, *Biochem. J.*, **74**, 430 (1960).

(9) Estradiol is the trivial name for 1,3,5(10)-estratriene-3,17β-diol.

(10) O. Wintersteiner and M. Moore, *J. Amer. Chem. Soc.*, **81**, 442 (1959).

(11) K. Tsuneda, K. Yasuda, and N. Yamada, Japanese Patent 20,163 (1964); *Chem. Abstr.*, **62**, 10484*h* (1965).

(12) J. S. Elce, J. G. D. Carpenter, and A. E. Kellie, *J. Chem. Soc. C*, 542 (1967).

(12a) NOTE ADDED IN PROOF.—Tetrols **2c** and **3a** are readily separable by liquid chromatography using a Waters Model ALC-202. By this method the samples were shown to be at least 99% configurationally pure. Conditions were 6 ft × 2 mm i.d. Corasil/C_{18}, 9:1 water–acetonitrile, flow rate 1.0 ml/min. Retention times of **2c** and **3a** were 11.9 and 10.3 min, respectively.

doaxial) in **3b**. Accordingly, borohydride reduction does give the thermodynamically favored product, and on catalytic hydrogenation the less sterically hindered α side of the steroid does face the catalyst.

Comparison of the acetyl methyl group resonances in the nmr spectra of tetraacetates **2d** and **3b** showed another significant difference. Singlets at 2.06 and 2.09 ppm were assigned to the C-16, C-17 acetyl groups because identical signals also appeared at these positions in the spectra of triacetate **2a** and diacetate **2b**. In the spectrum of the 6β-tetraacetate **3b** the C-6 acetyl signal was also at 2.06 ppm, resulting in a six-proton singlet.[13] The C-6 acetyl signal of **2d** was shifted downfield 7 Hz relative to that of **3b**, resulting in three three-proton singlets at 2.05, 2.09, and 2.13 ppm.

Investigation of the CD spectra of the estriol derivatives here described (Table I and Figure 1) revealed a dramatic effect due to the 6-hydroxyl substituent. Estradiol and estriol showed nearly identical spectra with two weak negative maxima at 290 and 282 (283) nm and a strong positive maximum at 230 (229) nm. The C-16 hydroxyl group is so remote as to have little effect on either the CD absorption within the ^1L_b band or within the ^1L_a band.[14] However, the effect of the 6-hydroxyl group is strong and configurationally specific on both bands. In 6α-hydroxyestriol (**2c**) the intensity of the negative maxima at 288 and 283 nm was more than doubled relative to estriol, and the ^1L_a band CD showed a strong *negative* maximum. In 6β-hydroxyestriol (**3a**) the ^1L_b band CD maxima were weakly positive and the ^1L_a band maximum was very strongly positive ([θ] +20,000 compared to [θ] +12,000 in the case of estriol). Thus, while estradiol and estriol display ^1L_b and ^1L_a Cotton effects of opposite sign, both Cotton effects are negative for **2c** and positive for **3a**.

TABLE I

SPECTRAL DATA FOR ESTRADIOL DERIVATIVES IN ABSOLUTE ETHANOL[a]

Compd	Uv maxima λ, nm	Uv maxima (ε)	CD maxima λ, nm	CD maxima ([θ])
Estradiol	287[b]	(1900)	290	(−310)
	282	(2100)	282	(−520)
	230[b]	(4800)	230	(+11,000)
	222	(7000)		
Estriol	287[b]	(1900)	290	(−540)
	282	(2100)	283	(−700)
	229[b]	(6100)	229	(+12,000)
	222	(8400)		
6-Oxoestriol triacetate (**1a**)			366	(+1500)
			352	(+4700)
			338	(+8900)
			326	(+10,000)
	298	(2300)	296	(−15,000)
	247	(11,000)	247	(−15,000)[c]
6-Oxoestriol (**1b**)	327	(3100)	345	(+23,000)[d]
			310	(−21,000)[d]
	256	(9300)	252	(−11,000)[e]
	222	(21,000)	222	(+27,000)
6α-Hydroxyestriol (**2c**)	288[b]	(1900)	288	(−1700)
	283	(2100)	283	(−1700)
	230[b]	(6000)	229	(−5200)
	222	(7700)		
6β-Hydroxyestriol (**3a**)	288[b]	(1900)	288	(+550)
	282	(2100)	280	(+620)
	228[b]	(6200)	227	(+20,000)
	222	(7500)		

[a] *c* 0.0028–0.021 g/100 ml; *l* = 1 cm; temperature, 25°. [b] Shoulder. [c] Negative minimum, $[\theta]_{268}$ −3000. [d] Reported for 6-oxoestradiol, $[\theta]_{345}^{MeOH}$ +24,982 (max), $[\theta]_{310}^{MeOH}$ −20,573 (max): R. C. Cambie, L. N. Mander, A. K. Bose, and M. S. Manhas, *Tetrahedron*, **20**, 409 (1964). Spectrum below 280 nm not described. [e] Negative minimum, $[\theta]_{275}$ −2500.

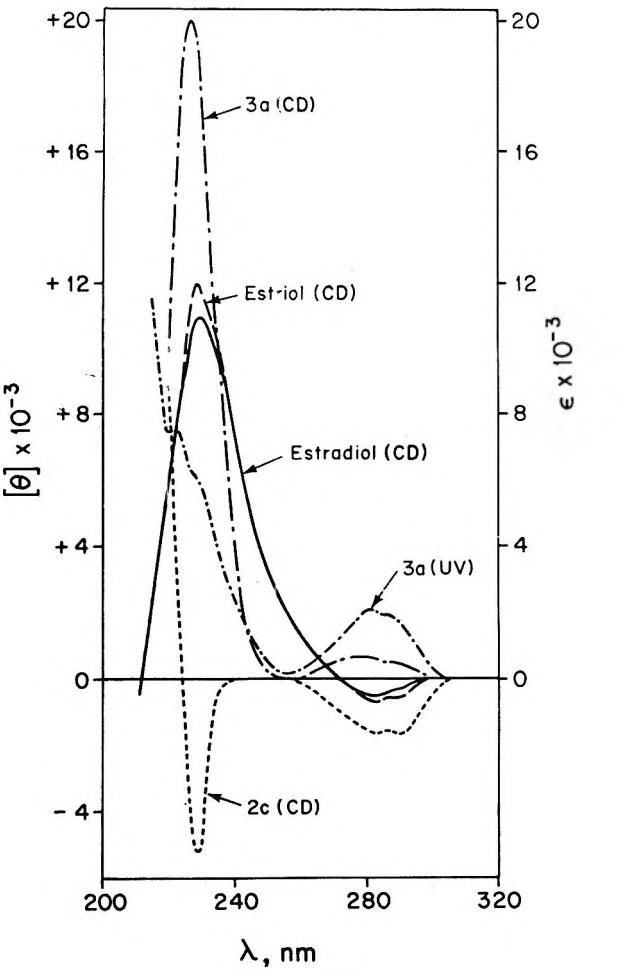

Figure 1.—Circular dichroism (CD) and ultraviolet (uv) absorption spectra of estradiol, estriol, 6α-hydroxyestriol (**2c**), and 6β-hydroxyestriol (**3a**) in absolute ethanol.

We had hoped, on the basis of the observed correlation of spectral data with configuration for the 6-hydroxyestriols, to be able to make unambiguous assignment of configuration to the 6-hydroxyestradiols.[10] Crabbé and Klyne reported[15] that the ORD spectrum of Wintersteiner's "6β"-hydroxyestradiol showed a weak negative Cotton effect (*a* −18) centered at 272 nm and a strong positive Cotton effect centered at 221 nm. This prompted us to determine the ORD spectrum of **3a**. It displayed a weak positive Cotton effect (*a* +9) centered at 280 nm (superimposed on a strongly positive background curve), in full accord with its CD spectrum. Consequently the question of configuration of the 6-hydroxyestradiols cannot be resolved without determination of the CD (or ORD) spectrum of a sample of demonstrated purity.

Regarding configurational identification of the 6-hydroxyestriol from pregnancy urine, our observation

(13) Slow scan on expanded scale revealed two singlets separated by 0.5 Hz.

(14) G. Snatzke and P. C. Ho, *Tetrahedron*, **27**, 3645 (1971).

(15) P. Crabbé and W. Klyne, *ibid.*, **23**, 3449 (1967).

that the epimers were not separable by tlc renders spectral determinations essential.[12a]

Experimental Section

Melting points were taken in open capillary tubes and are corrected. Elemental analyses were done by Galbraith Laboratories, Knoxville, Tenn. Tlc systems (silica gel HF-254) were the following: system 1, 9:1 benzene–ethyl acetate; system 2, 9:1 benzene–methanol; system 3, 4:1 benzene–methanol; system 4, 19:1 ethyl acetate–absolute ethanol. Nmr spectra were determined with a Varian XL-100-15 spectrometer and chemical shifts (δ) are reported in parts per million downfield from TMS. A Beckman IR-10 spectrophotometer was used for ir spectra, and a Cary Model 14 spectrophotometer for uv spectra. CD (in absolute ethanol) and ORD (in methanol) spectra were measured using a Cary Model 60 spectropolarimeter equipped with a CD Model 6001 accessory.

6-Oxoestriol Triacetate (1a).—To a stirred, ice-cooled solution of estriol triacetate (1.96 g, 4.73 mmol) in glacial acetic acid was added during 10 min a solution of chromium trioxide (1.45 g, 14.5 mmol) in water (1 ml) and glacial acetic acid (9 ml). The ice bath was removed and stirring was continued for 24 hr. The mixture was diluted with water (300 ml) and extracted with ether (150 ml). The ether layer was washed with water followed by small portions of 2% sodium bicarbonate until the aqueous layer had pH 8 and was pink in color, and finally was washed with water. Chromatography of the contents of the dried ($MgSO_4$) ether solution (1.85 g) on silica gel (38 g, packed in benzene and eluted with 50:1 benzene–ether) gave unchanged estriol triacetate (145 mg, 7%) (R_f 0.6, system 1) followed by crude **1a** (516 mg, oil). The yield of pure **1a** (R_f 0.25, system 1; R_f 0.9, system 2), mp 137–139°, $[\alpha]^{25}D$ −48° (*c* 0.58, absolute C_2H_5OH) [lit.[8] mp 137–139°, $[\alpha]^{16.5}D$ −41° (*c* 0.493, C_2H_5OH)], crystallized from methanol, was 312 mg (15%).

Sodium Borohydride Reductions of 6-Oxoestriol Triacetate (1a).—To a stirred, ice-cooled solution of **1a** (180 mg, 0.42 mmol) in methanol (10 ml) was added sodium borohydride (60 mg, 1.6 mmol) and the mixture was stirred for 40 min at 0°. Acetic acid was added dropwise to pH 5 (moist Hydrion paper) and the mixture was evaporated to dryness. The residue was partitioned between ethyl acetate (20 ml) and water (5 ml). The ethyl acetate was washed with small portions of 1% sodium bicarbonate until the aqueous phase had pH 8 and then twice with water. Chromatography of the dried ($MgSO_4$) product so obtained (180 mg) on silica gel (3.5 g, packed in benzene and eluted with benzene–ether mixtures gradually progressing from 50:1 to 1:1) yielded 6α-hydroxyestriol 3,16,17-triacetate (**2a**) (35%, oil) (R_f 0.7, system 2) and 6α-hydroxyestriol 16,17-diacetate (**2b**) (65%, oil) (R_f 0.35, system 2). **2b** had nmr ($CDCl_3$) δ 0.84 (s, 3, C-18 H), 2.06 (s, 3, C-16 or C-17 CH_3CO), 2.09 (s, 3, C-16 or C-17 CH_3CO), 3.78 (br s, 1, disappears with D_2O, C-6 OH), 4.76 (m, 1, C-6 H), 4.96 (d, 1, J = 6 Hz, C-17 H), 5.17 (br t, 1, C-16 H), 6.37 (br s, 1, disappears with D_2O, C-3 OH), 6.69 (q, 1, J = 3 and 9 Hz, C-2 H), and 7.06 ppm (m, 2, C-1 and C-4 H). The spectrum of **2a** was identical except for the absence of the phenolic proton at 6.37 ppm, the presence of a third CH_3CO singlet at 2.28 ppm, and the positions of the aromatic quartet (6.91 ppm) and multiplet (7.25 ppm, partially obscured by $CHCl_3$).

The reduction was carried out as described above for 1 hr using 211 mg (0.49 mmol) of **1a** and 75 mg (2 mmol) of sodium borohydride in absolute ethanol (20 ml), and was worked up in a similar manner. A similar chromatographic separation (4 g of silica gel) yielded **2a** (85%) and **2b** (15%).

6α-Hydroxyestriol (2c).—A solution of diacetate **2b** (50 mg) in 0.2 *N* 95% methanolic potassium hydroxide (1 ml) was allowed to stand for 5 hr at room temperature. Most of the solvent was removed under a stream of nitrogen, and the residue was diluted with water (1 ml) and acidified with 5% hydrochloric acid. The resulting crystalline solid was collected, washed well with water, and dried at reduced pressure. **2c** so obtained (23 mg, 59%) had mp 238–240°, $[\alpha]^{25}D$ +80° (*c* 0.547, absolute C_2H_5OH) [lit.[8] mp 242–245°, $[\alpha]^{14}D$ +84° (*c* 0.498, C_2H_5OH)], ir (KBr) 920, 1305, 1325, and 1610 cm^{-1}, and was homogeneous on tlc (R_f 0.4, systems 3 and 4).

6β-Hydroxyestriol (3a).—A trial saponification of **1a** (19 mg) in 0.5 *N* 95% methanolic potassium hydroxide (0.5 ml) at room temperature for 18 hr followed by a work-up similar to that described above for **2c** yielded pure 6-oxoestriol (**1b**) (10 mg, 77%; R_f 0.55, system 3; R_f 0.5, system 4). A sample recrystallized from methanol had mp 241–242° (lit.[8] mp 240–242°). A 115-mg sample of **1a** was similarly saponified and the resulting product was dissolved in absolute ethanol (15 ml) and hydrogenated for 9 hr over platinum (from 45 mg of platinum oxide). Tlc of the residue (68 mg, 83% from **1a**) after filtration through celite and evaporation of the solvent revealed a small amount of unchanged **1b** in addition to a major component of R_f 0.4 (systems 3 and 4). The mixture was unchanged on further hydrogenation over fresh platinum, but recrystallization from methanol yielded 40 mg (47% from **1a**) of **3a**: mp 255–260° dec; mixture with **2c**, mp 218–230° dec; $[\alpha]^{25}D$ +24° (*c* 0.536, absolute C_2H_5OH); ir (KBr) 945, 1165, 1290, 1350, 1580, and 1620 cm^{-1}; nmr (CD_3OD) δ 0.83 (s, 3, C-18 H), 3.47 (d, 1, J = 6 Hz, C-17 H), 4.07 (m, 1, C-16 H), 6.68 (q, 1, J = 3 and 9 Hz, C-2 H), 6.79 (d, 1, J = 3 Hz, C-4 H), and 7.13 ppm (d, 1, J = 9 Hz, C-1 H). Absorption at *ca.* 4.6 ppm due to the C-6 proton was largely obscured by CD_3OH.

Anal. Calcd for $C_{18}H_{24}O_4 \cdot {}^1/_2CH_3OH$: C, 69.35; H, 8.18. Found: C, 69.10; H, 7.95.

6α- and 6β-Hydroxyestriol Tetraacetates (2d and 3b).—Treatment of **2c** and **3a** with acetic anhydride in pyridine at room temperature overnight gave the respective tetraacetates **2d** and **3b** as oils (lit.[8] for **2d**, mp 159–161°) inseparable by tlc (R_f 0.3, system 1; R_f 0.95, system 2) and with essentially identical ir spectra. **2d** had nmr ($CDCl_3$) δ 0.86 (s, 3, C-18 H), 2.05 (s, 3, C-16 or C-17 CH_3CO), 2.09 (s, 3, C-16 or C-17 CH_3CO), 2.13 (s, 3, C-6 CH_3CO), 2.28 (s, 3, C-3 CH_3CO), 4.97 (d, 1, J = 6 Hz, C-17 H), 5.19 (t, 1, C-16 H), 6.02 (br t, 1, J = 8 Hz, C-6 H), and 6.96 and 7.3 ppm (two m, partially obscured by $CHCl_3$, C-1, C-2, and C-4 H). **3b** had nmr ($CDCl_3$) δ 0.90 (s, 3, C-18 H), 2.06 (s, 6, C-16 or C-17 and C-6 CH_3CO), 2.09 (s, 3, C-16 or C-17 CH_3CO), 2.26 (s, 3, C-3 CH_3CO), 4.99 (d, 1, J = 6 Hz, C-17 H), 5.19 (t, 1, C-16 H), 6.02 (d, 1, J = 2.5 Hz, C-6 H), and 7.03 and 7.3 ppm (two m, partially obscured by $CHCl_3$, C-1, C-2, and C-4 H).

Registry No.—**1a**, 36614-98-9; **1b**, 7323-86-6; **2a**, 36615-00-6; **2b**, 36615-01-7; **2c**, 7291-49-8; **2d**, 36615-03-9; **3a**, 36615-04-0; **3b**, 36615-05-1; estradiol, 50-28-2; estriol, 50-27-1.

Chemistry of Steroidal Tetrafluorocyclopropyl Enol Acetates[1]

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The chemical behavior of the α-tetrafluorocyclopropyl enol acetates **2** and **3** is reported. Treatment of these compounds with sodium hydroxide in methanol yields the rearranged cyclic product **6** as well as acyclic esters and ortho esters, depending on the reaction conditions. The structural and stereochemical assignments and spectral properties of the resulting new compounds are discussed.

Recently, a novel acyl migration was reported[2] which occurred during the course of difluorocarbene addition[3] to the ethynyl side chain of 17β-acetoxy-17α-ethynyl estratriene and androstane derivatives **1A** and **1B** (R = $COCH_3$) leading to the isomeric tetrafluorocyclopropyl enol acetates **2** and **3**. In this work we wish to report the unusual behavior of the tetrafluorocyclopropane system of adducts **2** and **3**.

To confirm that adducts **2** and **3** are indeed geometrical isomers,[2] we attempted to hydrolyze these compounds under a variety of alkaline conditions. The enol acetate moiety, however, turned out to be more resistant to alkaline treatment than the tetrafluorocyclopropyl group. As reported previously,[2] sodium hydroxide treatment of **2** and **3** in acetone, for example, gave the conjugated dienes **4** and **5**, resulting from the elimination of hydrogen fluoride (Chart I).

Hydrolysis of **2A** and **2B** with sodium hydroxide in aqueous methanol at room temperature afforded a major product **6** (*ca.* 40%), in which two of the fluorines were replaced by methoxyl groups. Two minor products, the open-chain unsaturated esters **8** (*ca.* 20%) and **9** (*ca.* 20%), were also isolated. Hydrolysis of the enol acetate **3B** under these conditions also provided compounds **6B** and **9B**, thus supporting the geometrical isomeric relationship between **2** and **3**.

The isolation of compound **8** from the hydrolyses of **2** and **4** and the absence of the geometric isomer of **8** among the hydrolysis products of **3** may indicate that the enol acetate is sterically more hindered in **2** and **4** than in **3**.

The structural assignment of the hydrolysis products **6A** and **6B** is based on the following physical and chemical evidence. The mass spectra of **6A** and **6B** (R = H) exhibited molecular ions of 434 and 440 mass units, respectively. They also showed fragment ions derived from the consecutive and combined losses of CH_3, CH_3OH, and HF, the expected cleavage products of the steroid skeletons, and weak but diagnostically significant fragment ions of *m/e* 344 and 350 ($M^+ - CH_3OCOOCH_3$), respectively. In the nmr spectra, in addition to the expected signals due to the protons on rings A and B, both compounds exhibited resonances corresponding to two nearly equivalent methoxyl groups. These results indicate that hydrolysis of the enol acetate was accompanied by the exchange of two fluorines with methoxyl groups, presumably *via* a successive elimination–addition mechanism[4] (*vide infra*).

The ^{19}F nmr spectrum of **6B** (R = *p*-BrC_6H_4CO) consists of the AB part of an ABX system with the following coupling constants: J_{AB} = 242.5 Hz, J_{AX} = 5.9 Hz, and J_{BX} = 1.6 Hz. The magnitude of J_{AB} is in good agreement with the expected value for geminal fluorines on a five-membered ring[5] while it is too high[6] for *gem*-difluorocyclopropyl derivatives.

In the low-field region of the pmr spectra both **6A** and **6B** exhibit a narrow doublet centered at 5.03 ppm (vinylic H) which is coupled (J = 1.5 Hz) to a proton which resonates in the 2.0-ppm region (C-17 H) as shown by double resonance experiments. This signal was absent in the spectrum of the hydrolysis product when **2B** (R = $COCH_3$) was treated with sodium deuterioxide in methanol-*O*-*d* yielding **7B** (R = H). This compound was shown to contain two deuteriums by mass spectrometric analysis. The AX and BX couplings in the ^{19}F nmr spectrum of **7B** (R = H) were also absent, showing only the AB pattern (J_{FF} = 245 Hz) of the geminal fluorines.

The deuteriums in **7B** (R = H) were unaffected by treatment with boiling alkaline methanol, and correspondingly no deuteriums could be incorporated onto a carbon atom in **6B** under base-catalyzed exchange conditions. This indicates the absence of any deuterium or hydrogen which is activated by enolization.

In the ir spectrum both **6A** and **6B** exhibited a strong absorption at 1660 cm^{-1} due to the double bond stretching of an enol ether moiety. Compound **6B** (R = H) was recovered unchanged when treated with sodium borohydride or lithium aluminum hydride. It is evident, therefore, that compound **6** contains no carbonyl function, which implies that the initial hydrolysis product of the enol acetate must have rearranged in forming **6**. This is further supported by the observation that **6B** (R = H) is unaffected by heating with sodium hydroxide in methanol, proving that it is not an intermediate in the formation of **8** and **9**, both of which could be derived from the expected cyclopropyl ketone.

(1) Contribution No. 387 from the Institute of Organic Chemistry, Syntex Research.

(2) E. Velarde, P. Crabbé, A. Christensen, L. Tökés, J. W. Murphy, and J. H. Fried, *Chem. Commun.*, 725 (1970).

(3) For previous parts in this series see P. Crabbé, R. Grezemkovsky, and L. H. Knox, *Bull. Soc. Chim. Fr.*, 789 (1968); P. Crabbé, P. Anderson, and E. Velarde, *J. Amer. Chem. Soc.*, **90**, 2998 (1968); P. Anderson, P. Crabbé, A. D. Cross, J. H. Fried, L. H. Knox, J. Murphy, and E. Velarde, *ibid.*, **90**, 3888 (1968); P. Crabbé, H. Carpio, and E. Velarde, *Chem. Commun.*, 1028 (1971); and ref 2.

(4) T. C. Shields and P. D. Gardner, *J. Amer. Chem. Soc.*, **89**, 5425 (1967); T. C. Shields, B. A. Loving, and P. D. Gardner, *J. Chem. Soc. D*, 556 (1967); G. Camaggi and F. Gozzo, *J. Chem. Soc. C*, 178 (1970).

(5) R. E. Banks, M. G. Barlow, R. N. Haszeldine, M. Lapin, V. Mathews, and N. I. Tucker, *ibid.*, 548 (1963).

(6) K. L. Williamson and B. A. Braman, *J. Amer. Chem. Soc.*, **89**, 6183 (1967); M. G. Barlow, R. Fields, and F. P. Temme, *J. Chem. Soc. D*, 1671 (1968).

Compound **6** is acid sensitive; it decomposes on prolonged contact with silica gel. When stored at room temperature with hydrochloric acid in dioxane, it gives in high yield a difluoro keto ester (**11**) which still contains the four-carbon side chain, a carbonyl group at C-20, and the geminal fluorines. The structural assignment of **11** is fully supported by its ir and mass spectral data, and the observed A_2X_2 pattern in both pmr and ^{19}F nmr spectra (J_{HF} = 13.8 Hz) established unequivocally the vicinal relationship between the methylene (triplet at 3.32 ppm) and the difluoromethylene groups (triplet at −105.5 ppm relative to $CFCl_3$). Compound **11B** (R = H) upon treatment with sodium hydroxide in boiling dioxane was converted into 5α-pregnan-3β-ol-20-one **13B** (R = H), presumably *via* a β-diketo intermediate (**12**), which confirmed that the fluorines in **11** are adjacent to the ester group. Similarly, base treatment of **8B** and **9B** also afforded the pregnane derivative **13B**. The similarity of the chemical shifts of the C-18 protons in **11B** (R = H, 0.60 ppm) and in **13B** (R = H, 0.59 ppm) indicates that in **11** the C-17 side chain has the β configuration.

The structure most compatible with the chemical and physical characteristics of the major hydrolysis product of **2** and **3** is the substituted butenolide dimethyl ketal **6**. The absence of any coupling between the fluorines and the C-21 vinylic proton and the observed long-range coupling between the fluorines and the C-17 proton (which is probably α, although its stereochemistry has not been established) deserves some comments however. Williamson, *et al.*,[7] have shown that vicinal H–F couplings depend on bond angle, dihedral angle, and bond length. The small vicinal H–H coupling in the –CHCH=C fragment in five-membered rings[8] and the conformational dependence of the vicinal HF coupling in 3-fluoropropenes[9] indicate that a small (if not zero) H–F coupling in **6** is to be expected. The $^4J_{H_{17}-H_{21}}$ coupling (1.5 Hz) is within the range expected for allylic H–H couplings.

Homoallylic hydrogen–fluorine couplings of the order of 2.6–2.8 Hz have been observed in 1,1,1-trifluoro-2-butene in which the coupling nuclei are freely rotating.[10] The difference in the two $^5J_{H_{17}-F}$ values is apparently an indication that the side-chain ring exists mainly in a preferential conformation due to hindered rotation around the 17–20 bond.

A mechanistic scheme for the formation of the various hydrolysis products from the tetrafluorocyclopropyl derivative **2** is outlined in Chart II. The sequence begins with hydrogen fluoride elimination (**2** → **4**) and methanol addition (**4** → **16**) steps leading to the enol acetate **16**. The intermediacy of **4** has been confirmed by its conversion into **6**, **8**, and **9** upon treatment with sodium hydroxide in aqueous methanol. Elimination of the second fluorine atom in the form of hydrogen fluoride, or fluoride ion, is enhanced by the methoxyl group in **16**. The resulting cyclopropene (**17a**) or cyclopropyl carbonium ion (**17b**) intermediate yields the dimethoxydifluorocyclopropyl enol ether **18** in presence of methanol. This dimethoxy intermediate (**18**) can either hydrolyze to the corresponding ketone (**19**) or undergo further elimination–addition reactions leading to **20** (R′ = F or OCH_3). Similar exchange of functional groups *via* elimination–addition reactions have been well documented with halogenated cyclopropyl derivatives.[4,11]

Opening of the cyclopropyl ring[11] in **19** is facilitated by both the carbonyl group and by the electron-donating geminal methoxyl groups. Reclosure through the carbonyl oxygen leads then to the ring-enlarged rearrangement product **6**. Similar rearrangements have been reported previously in the formation of substituted butenolides under strongly[12] or mildly[13] acidic and thermal[12] conditions from various carbomethoxyl group containing cyclopropenyl derivatives.

When **18** undergoes further elimination–addition reactions prior to hydrolysis of the enol acetate, the ring opening in the resulting intermediate **20** follows a different course which involves the expulsion of a fluoride (when R′ = F) or a methoxyl group (when R′ = OCH_3). Instead of reclosure of the ring, the presumed intermediate **21**[14] leads to the open-chain products **8** and **9**, or **22** and **23**, depending on the presence or absence of water in the reaction medium. In addition to **22** and **23**, other ortho esters have been detected, but owing to their instability they were not isolated. The deuterium-labeled analogs of ortho ester **23** have been isolated, however, in both geometrically isomeric forms (**14** and **15** in Chart I) from the hydrolysis of **2B** (R = $COCH_3$) with sodium deuterioxide in anhydrous methanol-*O*-*d*. One of the undeuterated geometric isomers of **23A** was also isolated from the hydrolysis of a small amount of **2A** in anhydrous methanol. The other isomer and various other esters were also detected from this small-scale reaction, but they could not be obtained in sufficient quantity and purity for analysis.

The ortho esters **14B** (R = H) and **15B** (R = H) exhibited no molecular ions in their mass spectra, only $M^+ - OCH_3$, $M^+ - CH_3OH$ and $M^+ - CH_3OD$ peaks (*m/e* 435, 434, and 433). These assignments were supported by the observed unresolved metastable peaks in the region of *m/e* 404–406. The most diagnostic features in the mass spectra of the ortho esters **14B** and **15B** were the two very intense (70–100% relative intensity) peaks at 105 and 190 mass units. These peaks are due to trimethoxycarbonium ion (*m/e* 105) and to a fragment ion which results from the cleavage of the C-17 ↔ C-20 bond (α cleavage to the carbonyl group) the charge being retained on the carbonyl side (for cleavage pattern, see compound **23** in Chart II). These peaks were at 105 and 189 mass units in the mass spectrum of the undeuterated sample **23A**.

The structure assignment of these ortho esters was further substantiated by the nine-proton singlet at 3.20 ppm for the ortho ester methyl groups and three-proton singlets at 3.91 and 3.57 ppm, respectively, for

(7) K. L. Williamson, Y.-F. Li Hsu, F. H. Hall, S. Swager, and M. S. Coulter, *J. Amer. Chem. Soc.*, **90**, 6717 (1968).

(8) A. A. Bothner-By, *Advan. Magn. Resonance*, **1**, 250 (1965).

(9) A. A. Bothner-By, S. Castellano, and H. Gunther, *J. Amer. Chem. Soc.*, **87**, 2439 (1965).

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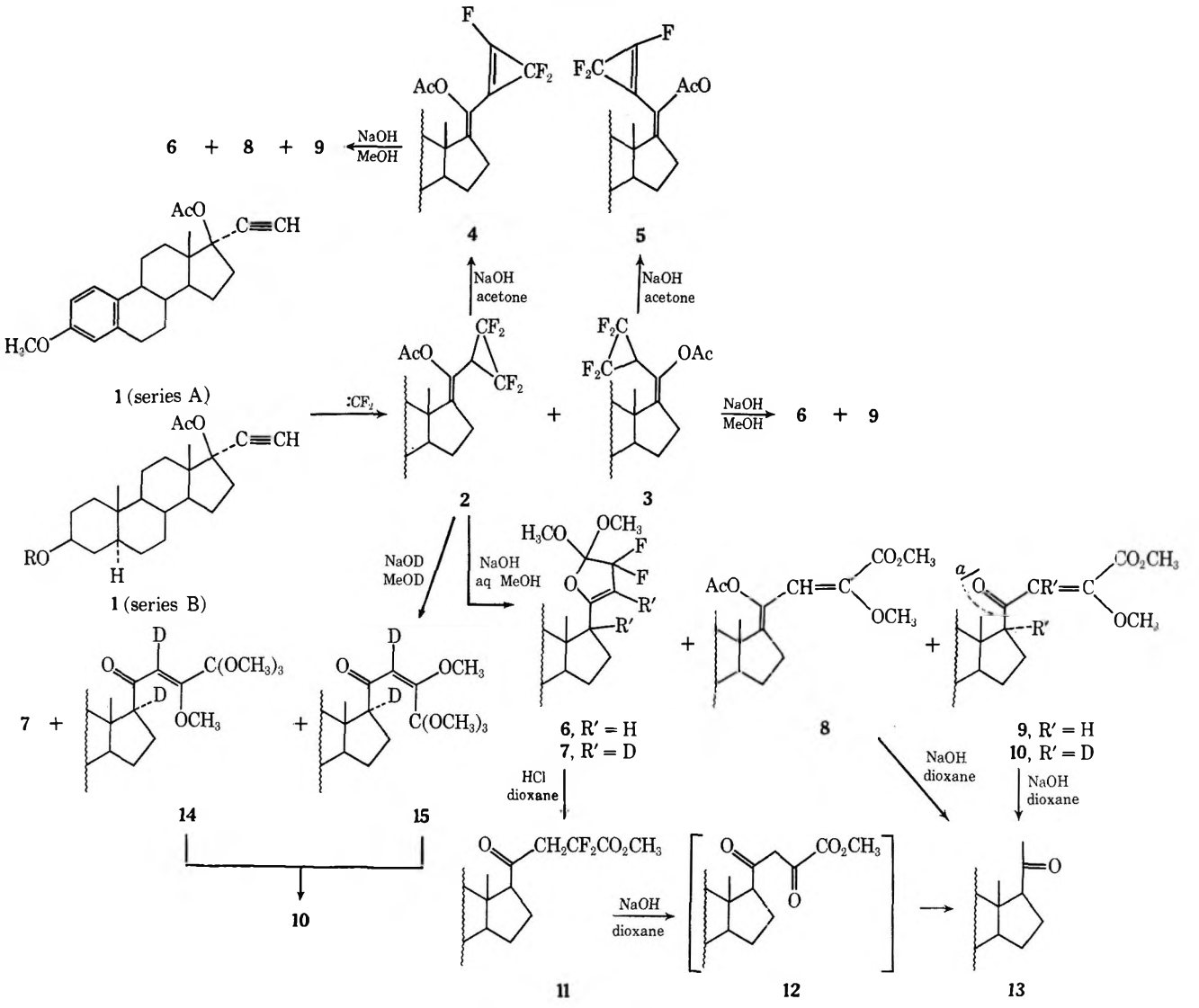
(11) U. Schöllkopf, E. Ruban, P. Tonne, and K. Riedel, *Tetrahedron Lett.*, 5077 (1970), and references cited therein.

(12) R. Breslow, R. Winter, and M. Battiste, *J. Org. Chem.*, **24**, 415 (1959).

(13) L. Schrader, *Tetrahedron Lett.*, 2993 (1971).

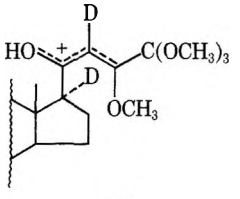
(14) *Cf.* P. v. R. Schleyer, W. F. Sliwinski, G. W. Van Dine, U. Schöllkopf, J. Paust, and K. Fellenberger, *J. Amer. Chem. Soc.*, **94**, 125 (1972); W. F. Sliwinski, T. M. Su, and P. v. R. Schleyer, *ibid.*, **94**, 133 (1972), and related papers.

CHART I



the enol ether protons in the nmr spectra of **14B** and **15B**. The virtually identical chemical shifts (0.59–0.60 ppm) of the C-18 proton resonances in **13B** (R = H), **14B** (R = H), and **15B** (R = H) indicate that the stereochemistry of the C-17 side chain in all these compounds is most probably β. The cis stereochemistry of the enol ether with respect to the carbonyl group in **14** is tentatively assigned to the isomer which shows the more deshielded (3.91 ppm) enol ether signal. On treatment with aqueous methanol both ortho esters gave the same dideuterio methyl ester **10B** (R = H) whose physical characteristics are identical with those of the hydrolysis product **9B** (R = H) with the exception of the spectral differences due to the presence of the deuteriums. This indicates that the enol ethers can undergo isomerization to the thermodynamically more stable geometric form under the hydrolysis conditions. Since the two deuteriums were retained during the conversion of both cis and trans ortho ester **14** and **15** into the methyl ester **10**, the isomerization most probably proceeds *via* an enolate ion intermediate such as **24**, formed prior to hydrolysis of the ortho ester.

The spectral data of the hydrolysis products **8** and **9** are in good agreement with their assigned structures



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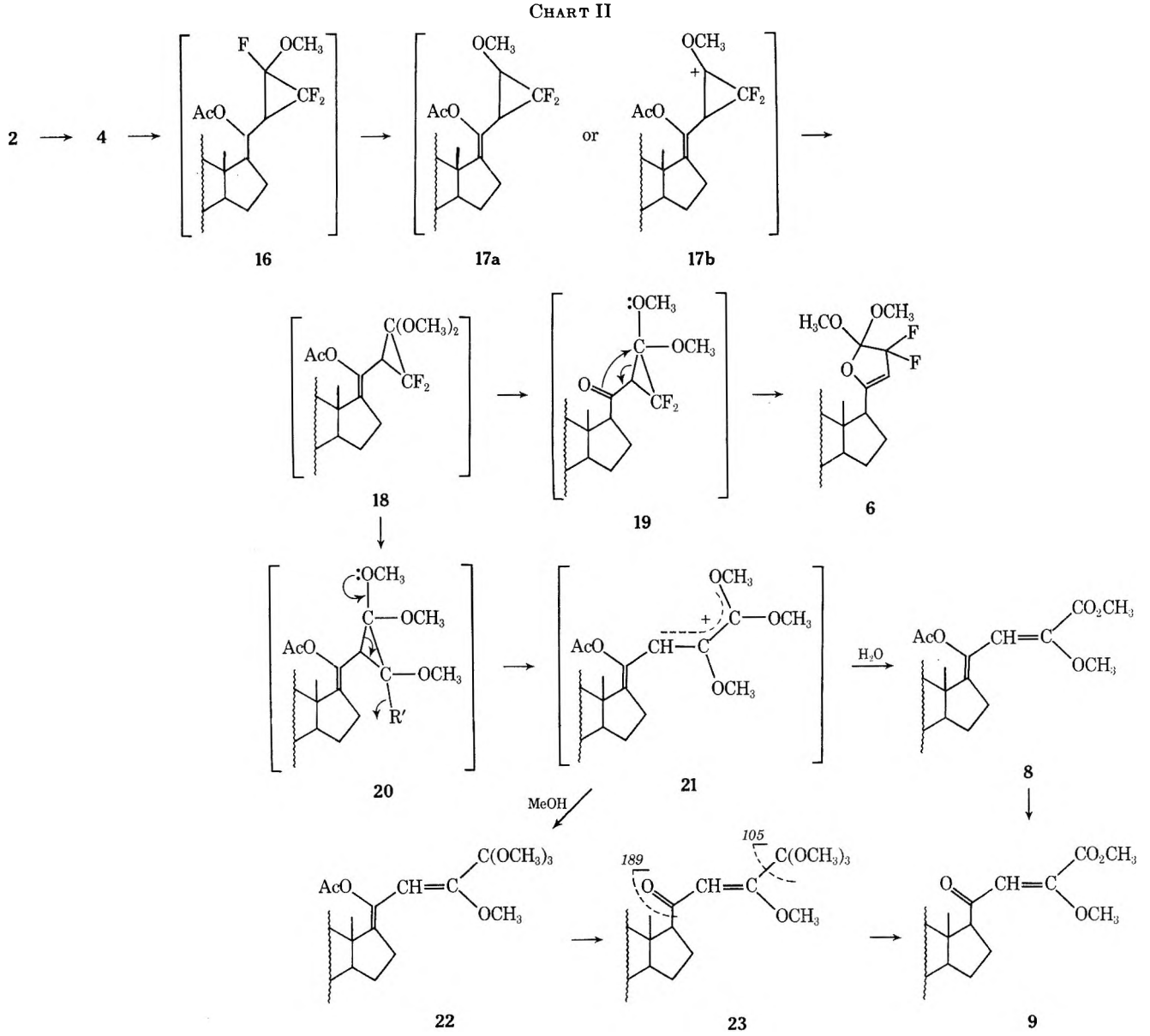
in both estratriene (**A**) and androstane (**B**) series. The C-18 proton resonance (0.59 ppm) of **9B** (R = H) is indicative of β-side-chain configuration. The stereoconfiguration of the side chain in **8** and **9** is presumably trans at the enol ether double bond, but this has not been established with certainty.[15] Conversion of both **8B** (R = H) and **9B** (R = H) into 5α-pregnan-3β-ol-20-one (**13B**, R = H) by sodium hydroxide treatment in boiling dioxane confirms the location of the methoxyl group at C-22.

(15) In certain enol ethers the stereoconfiguration can be assigned on the basis of the chemical shift of the vinylic proton by calculating the shielding effect of the substituents which were found to be additive by U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, **25**, 691 (1969), and in earlier reports cited therein. This method, however, was found to be unreliable when both methoxyl and carbonyl substituents are present on the double bond: S. W. Tobey, *J. Org. Chem.*, **34**, 1281 (1969).

CHART II



Experimental Section[16]

Hydrolysis of 2A with Sodium Hydroxide in Aqueous Methanol.—The tetrafluorocyclopropyl adduct **2A** (400 mg) was dissolved in a solution (20 ml) of 2% sodium hydroxide in *ca.* 97% methanol. The mixture was stirred for 45 min at room temperature. The product was isolated by dilution with water and extraction with ethyl acetate. The organic layer was washed, dried, filtered, and evaporated to dryness. The product was purified by preparative tlc (hexane–ethyl acetate 85:15). The least polar fraction (173 mg, 43%) gave crystalline product **6A**: mp 111°; $[\alpha]_D$ +47°; λ_{max} 278–287 nm (ϵ 1687–1585); ν_{max} 1660, 1620, 1580 cm^{-1}; nmr (T-60) ($CDCl_3$) 0.70 (18-H), 3.53 (2 OCH_3), 3.86 (3-OMe), 5.06 (vinylic H), 6.5–7.3 ppm (3 aromatic H); mass spectrum *m/e* 434 (M^+).

Anal. Calcd for $C_{25}H_{32}O_4F_2$: C, 69.08; H, 7.42. Found: C, 69.02; H, 7.63.

The two more polar fractions were tentatively identified as **9A** (90 mg, 20%; mp 85–90°; λ_{max} 262 nm (ϵ 8128); ν_{max} 1750, 1680, 1610 cm^{-1}) and **23A** (100 mg, 25%; oil; ν_{max} 1680, 1610 cm^{-1}) which were not further purified and characterized.

(16) The nmr spectra were measured on a Varian HA-100 or T-60 spectrometer using tetramethylsilane as an internal reference. Proton chemical shifts are reported on the δ scale. The ^{19}F nmr spectra were recorded by computer averaging of transients using an IBM-1800. The lock signal was provided by an external capillary of $(CF_3)_2CO \cdot 3H_2O$. $CFCl_3$ was used as an internal standard; shifts to higher field are negative. The mass spectra were recorded on an Atlas CH-4 spectrometer equipped with an EFO-4B ion source; the ionizing energy was maintained at 70 eV.

Hydrolysis of 2B with Sodium Hydroxide in Aqueous Methanol.—Adduct **2B** (R = $COCH_3$, 1.8 g) was dissolved in a solution (90 ml) of 2% sodium hydroxide in *ca.* 97% methanol. The mixture was stirred at room temperature for 45 min. The product was isolated by dilution with water and extraction with ethyl acetate. The organic layer was washed, dried, filtered, and evaporated to dryness. The product was chromatographed on Florisil (100 g). The fractions eluted with hexane–ether (9:1) afforded 650 mg (42%) of **6B** (R = H): mp 155–156°; $[\alpha]_D$ +8°; ν_{max} 1660 cm^{-1}; nmr (T-60) ($CDCl_3$) 0.66 (18-H), 0.80 (19-H), 3.5 (2 OCH_3), 5.03 ppm (vinylic H); mass spectrum *m/e* 440 (M^+).

Anal. Calcd for $C_{25}H_{36}O_4F_2$: C, 68.14; H, 8.69; F, 8.62. Found: C, 68.16; H, 8.95; F, 9.20.

The fractions eluted with ethyl acetate gave 1 g of a mixture of compounds **8B** and **9B**. These esters were purified by tlc on silica gel in hexane–ethyl acetate (4:1). The less polar fraction gave 300 mg (20%) of **9B** (R = H): mp 140–142°; $[\alpha]_D$ −113°; λ_{max} 256 nm (ϵ 11,220); ν_{max} 3450, 1760, 1695, 1600 cm^{-1}; nmr (T-60) ($CDCl_3$) 0.60 (18-H), 0.80 (19-H), 3.73 and 3.86 (2 OCH_3), 5.50 ppm (vinylic H); mass spectrum *m/e* 418 (M^+).

Anal. Calcd for $C_{25}H_{38}O_5 \cdot CH_3OH$: C, 69.31; H, 9.39. Found: C, 68.92; H, 9.34.

The more polar compound was **8B** (R = H, 400 mg, 23%): mp 174–175°; $[\alpha]_D$ +9°; λ_{max} 230–232 nm (ϵ 10,470); ν_{max} 3450, 1740, 1720, 1630 cm^{-1}; nmr ($CDCl_3$) 0.80 (19-H), 0.910 (18-H), 2.35 (20-OAc), 3.71 (OCH_3), 3.91 (=$COCH_3$), 7.27 ppm (vinylic H); mass spectrum *m/e* 460 (M^+).

Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.41; H, 8.71. Found: C, 69.98; H, 8.95.

Hydrolysis of 3B with Sodium Hydroxide in Aqueous Methanol.—Adduct **3B** (R = $COCH_3$, 130 mg) was dissolved in a solution (5 ml) of 2% sodium hydroxide in *ca.* 97% methanol. The mixture was stirred for 1 hr at room temperature. The product was isolated by dilution with water and extraction with ethyl acetate. The organic layer was washed, dried, filtered, and evaporated to dryness. The crude product was chromatographed on Florisil (5 g). In fractions eluted with hexane–ether (9:1) 45 mg (39%) of **6B** (R = H) was isolated. The residue (40 mg) from the ethyl acetate fractions was purified by tlc in hexane–ethyl acetate (4:1) yielding 18 mg (18%) of **9B** (R = H). Both of these samples were identical with those obtained from the hydrolysis of **2B**; *vide supra*.

Hydrolysis of 2A with Sodium Hydroxide in Anhydrous Methanol.—Sodium hydroxide (100 mg) and then compound **2A** (10 mg) were dissolved in anhydrous methanol (5 ml). The solution was heated gently for 1 hr; then it was diluted with ether, washed with water, and dried (Na_2SO_4), yielding a glassy mixture of products.

Plate chromatography on silica gel in ether–benzene (1:9) after two developments gave five fractions. Elution of the least polar fraction (I) gave a crystalline product (2.9 mg, 13%) which proved to be identical with **6A**. With the exception of fraction IV, all other fractions were too small in quantity and were not sufficiently pure for characterization.

Fraction IV, upon elution with ether, gave a semicrystalline ortho ester (**23A**): 3.0 mg (30%); nmr ($CDCl_3$) 0.65 (18-H), 3.23 (3 OCH_3), 3.73 (aromatic OCH_3), 3.92 (enol ether), 6.02 (vinylic H), 6.6–7.25 ppm (3 aromatic H); mass spectrum *m/e* 458 (M^+), 189 and 105 (see compound **23** in Chart II). This ortho ester was converted into the conjugated methyl ester **9A** upon storing at room temperature for 48 hr in aqueous methanol containing trace of hydrochloric acid.

Hydrolysis of 2B with Sodium Deuterioxide in Methanol-*O-d*.—Sodium (52 mg) was treated with methanol-*O-d* (2 ml) which contained deuterium oxide (0.05 ml). After cooling a methanol-*O-d* solution (3 ml) of the tetrafluorocyclopropyl enol ether **2B** (R = $COCH_3$, 24 mg) was added and the reaction mixture was stored at room temperature for 1 hr. The solution was then diluted with ether, washed with water, and dried (Na_2SO_4). Evaporation of the solvent gave a glassy residue which was chromatographed on a silica gel plate in ether–benzene (1:1).

The least polar fraction (I), which exhibited the same R_f value as **6B** (R = H), contained the dideuteriobutenolide dimethyl ketal **7B** (R = H, 3 mg, 14%): mp 157–158° (aq MeOH); pmr ($CDCl_3$) 0.64 (18-H), 0.79 (19-H), 3.47 ppm (2 OCH_3); ^{19}F nmr ($CDCl_3$ with $CFCl_3$ internal standard) −104.4 and −103.4 ppm (AB pattern, J_{FF} = 245 Hz); mass spectrum *m/e* 442 (M^+), isotope composition 2% d_0, 14% d_1, and 84% d_2.

Elution of the two more polar fractions (II and III) with ether yielded two semicrystalline isomeric ortho esters tentatively identified as **14B** and **15B**, respectively. These ortho esters were analyzed without further purification since attempted recrystallizations led to decomposition.

Ortho ester **14B** (R = H) (fraction II, 6.5 mg, 29%): nmr ($CDCl_3$) 0.60 (18-H), 0.79 (19-H), 3.20 (3 × OCH_3), 3.91 ppm (enol ether); mass spectrum *m/e* 435 (M^+ − OCH_3), 434 (M^+ − MeOH), 433 (M^+ − MeOD), 190 (70%, analogous to *m/e* 189 fragment of compound **23**, Chart II) and 105 [100%, $C^+(O\text{-}CH_3)_3$].

Ortho ester **15B** (R = H) (fraction III, 12 mg, 53%): nmr ($CDCl_3$) 0.60 (18-H), 0.78 (19-H), 3.20 (3 OCH_3), 3.57 ppm (enol ether); mass spectrum *m/e* 435 (M^+ − OCH_3), 434 (M^+ − MeOH), 433 (M^+ − MeOD), 190 (100%, analogous to *m/e* 189 fragment of compound **23**, Chart II) and 105 [83%, $C^+(OCH_3)_3$].

Both ortho esters **14B** and **15B** were dissolved in aqueous methanol (2 ml) which contained a trace of hydrochloric acid, and the solutions were stored at room temperature for 20 hr. Evaporation of the solvent under a stream of nitrogen gave the same hydrolysis product from both ortho esters which exhibited the same R_f value as **9B** (R = H). The residues were purified by chromatography on silica gel plates in ether–benzene (1:1) yielding the dideuterio ester **10B** (R = H): mp 140–142.5° (aq MeOH); nmr ($CDCl_3$) 0.595 (18-H), 0.79 (19-H), 3.71 and 3.85 ppm (2 OCH_3); mass spectrum *m/e* 420 (M^+), 144 and 116 (fragment a and a − CO as shown on compound **10**, Chart I); isotope composition 3% d_0, 15% d_1, and 82% d_2.

Hydrolysis of 4B with Sodium Hydroxide in Aqueous Methanol.—Compound **4B** (R = $COCH_3$, 10 mg) was dissolved in a solution (1 ml) of 2% sodium hydroxide in *ca.* 97% methanol. The mixture was stirred for 1 hr at room temperature. The product was isolated as described above and purified by tlc thus affording compounds **6B** (R = H), **8B** (R = H), and **9B** (R = H).

Reactions of 6B (R = H).—Compound **6B** (R = H) was recovered unchanged upon further treatment with sodium hydroxide in anhydrous or aqueous methanol at room temperature, as well as at boiling temperature.

A solution of **6B** (R = H, 10 mg) in methanol-*O-d* (5 ml) was saturated with 10% sodium deuterioxide in deuterium oxide. The solution was heated under reflux for 24 hr and then cooled, extracted with ether, washed with cold water, and dried (Na_2SO_4). The recovered crystalline product after the evaporation of the ether showed no deuterium content by mass spectrometric analysis.

Compound **6B** (R = H) was recovered unchanged when it was heated for 24 hr with sodium borohydride in isopropyl alcohol or from a 4-hr treatment with lithium aluminum hydride in boiling ether.

3β-(*p*-Bromobenzoate) Derivative of 6B (R = *p*-BrC_6H_4CO).—A solution containing **6B** (R = H, 80 mg) and *p*-bromobenzoyl chloride (100 mg) in pyridine (2 ml) was heated at 70° for 2 hr. After cooling, the mixture was poured into water, filtered, and washed to neutrality. Crystallization from methanol provided the pure sample of the *p*-bromobenzoate **6B** (R = *p*-BrC_6H_4CO): mp 175–178°; λ_{max} 244 nm (ε 19,500); ν_{max} 1600, 1650, 1720; nmr ($CDCl_3$) 0.66 (18-H), 0.86 (19-H), 3.50 (2 OCH_3), 5.83 (21-H), 7.40–8.10 ppm (aromatic H); mass spectrum *m/e* 622 (M^+).

Hydrolysis of 6B with Hydrochloric Acid.—A solution of **6B** (R = H, 155 mg) in dioxane (12 ml) and 10% hydrochloric acid (6 ml) was stirred for 4 hr at room temperature. The reaction mixture was diluted with ethyl acetate and washed with water to neutrality. Evaporation of the solvent and purification by tlc in hexane–ethyl acetate (7:3) yielded the difluoro keto ester **11B** (R = H, 108 mg, 72%): mp 165–167°; $[\alpha]D$ +87°; ν_{max} 3510, 1790, 1710 cm^{-1}; nmr ($CDCl_3$) 0.60 (18-H), 0.79 (19-H), 3.32 [t, $J_{H,F}$ = 13 Hz —C(=O)CH_2CF_2—], 3.90 ppm [—C(=O)OCH_3]; mass spectrum *m/e* 426 (M^+).

Anal. Calcd for $C_{24}H_{36}O_4F_2$: C, 67.57; H, 8.50; F, 8.91. Found: C, 67.29; H, 8.64; F, 8.14.

3β-Hydroxy-5α-pregnan-20-one (13B, R = H). Method I.—A solution of **2B** (R = $COCH_3$, 200 mg) in *ca.* 95% dioxane (20 ml) containing 5% sodium hydroxide was heated under reflux for 45 min. The product was isolated by dilution with water and extraction with ethyl acetate. The organic layer was washed, dried, filtered, and evaporated to dryness, yielding **13B** (R = H, 95 mg, 90%): mp 193–195° (lit.[17] mp 194°); $[\alpha]D$ +118°; ν_{max} 3400, 1700, 1690 cm^{-1}; nmr ($CDCl_3$) 0.59 (18-H), 0.79 (19-H), 2.08 ppm (21-H); mass spectrum *m/e* 318 (M^+).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 76.62; H, 10.07. Found: C, 76.28; H, 10.38.

Method II.—A solution of **11B** (R = H, 22 mg) in *ca.* 95% dioxane (2.5 ml) containing 5% sodium hydroxide was heated under reflux for 3 hr. The product was isolated as described above yielding **13B** (R = H, 14 mg, 87%), which was shown to be identical with an authentic sample by usual criteria.

Method III.—A mixture (40 mg) of compounds **8B** and **9B** dissolved in a 5% sodium hydroxide solution in *ca.* 95% dioxane (4 ml) was heated at reflux temperature for 10 hr. The product was isolated as usual thus affording compound **13B** (R = H, 40%), shown to be identical (mixture mp, ir, nmr, tlc) with an authentic sample.

Registry No.—**2A**, 36706-82-8; **2B**, 27741-56-6; **3B**, 27932-70-3; **4B**, 36706-85-1; **6A**, 36706-86-2; **6B**, 36706-87-3; **6B** (*p*-bromobenzoate), 36763-72-1; **7B**, 36706-88-4; **8B**, 36706-89-5; **9A**, 36706-90-8; **9B**, 36706-91-9; **10B**, 36706-92-0; **11B**, 36706-93-1; **13B**, 516-55-2; **14B**, 36706-95-3; **15B**, 36706-96-4; **23A**, 36706-97-5.

Acknowledgments.—The authors wish to thank Dr. M. Marx of this institute for his suggestion of the structure of compound **6**.

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Cyclopentylcarbene-α-*d*. Stereochemistry at the Carbene Carbon in Intramolecular Carbene and Carbenoid Insertion[1]

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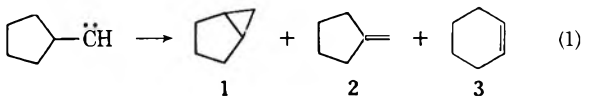
Bicyclo[3.1.0]hexane is the major product formed from cyclopentylcarbene **1**, or related carbenoids, generated by (a) the decomposition of the tosylhydrazone of cyclopentanecarboxaldehyde; (b) the action of sodium on cyclopentylmethyl chloride; (c) the reaction of cyclopentyllithium with methylene chloride; and (d) the reaction of cyclopentylmagnesium chloride with methylene chloride. Using a deuterium label in the carbene precursors, it was found that the stereochemistry of bond formation at the carbene carbon varies with carbene or carbenoid source. Observed stereochemistry is rationalized on the basis of likely transition-state geometries.

Knowledge of the stereochemistry of organic reactions often provides illuminating insight into their mechanisms. In the case of carbene insertion into a saturated C–H bond, it has been found previously that the reaction occurs with retention of configuration at the C–H bond being attacked.[2,3] In the present study, we report findings concerning another aspect of the stereochemistry of carbene or carbenoid insertion—the steric preference for formation of the new bonds to the "bivalent" carbon.

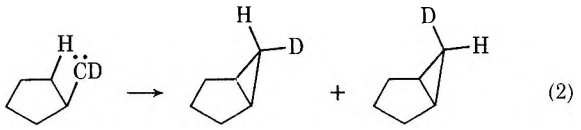
In previous work, we have found that three probably "carbene-derived" products—bicyclo[3.1.0]-hexane, methylenecyclopentane, and cyclohexene—are formed in the reaction of cyclopentylmethyl chloride with metallic sodium (eq 1).[4] In the first of these,



(1)

1 2 3

two stereochemical outcomes at the "carbene carbon" are possible: the hydrogen originally attached to this carbon may be either exo or endo in the final bicyclic product. In eq 2, this is illustrated in the instance



(2)

4 5 6

of a deuterated carbene. The relative preference for **5** *vs.* **6** may provide valuable insight into the nature of the transition state for the insertion. In this paper, we report the product distribution and stereochemical preference for several variations of "carbene-generating" reactions in the cyclopentylmethyl system.

Results

In Tables I and II, the products of a variety of "cyclopentylcarbene" reactions are summarized. Reactions studied were the decomposition of the tosylhydrazone of cyclopentanecarboxaldehyde with base under several sets of conditions, the reaction of cyclopentylmethyl chloride with sodium metal, and the reactions of cyclopentyllithium and cyclopentylmagnesium chloride with methylene chloride. Product distributions were determined by gas chromatography or nmr, and the identity of the products was confirmed by nmr spectra of the mixed or separated products. In the tosylhydrazone decomposition, the three products **1**, **2**, and **3** were detected by gas chromatography. The methylenecyclopentane fraction contained an additional alkene, most probably 1-methylcyclopentene formed by base-catalyzed isomerization. Both are included as methylenecyclopentane in Tables I and II. The methylene chloride reactions produced complex product mixtures, with the same products present in the C_6 portion. Methylcyclopentane was formed in the cyclopentylmethyl chloride[4] and cyclopentylmagnesium chloride reactions.

The deuterated carbene **4** and corresponding carbenoids were generated in similar fashion. Deuterated precursors were cyclopentanecarboxaldehyde-α-*d*, cyclopentylmethyl chloride-α,α-d_2, and methylene chloride-d_2. The stereochemistry of deuterium in products **5** and **6** was determined by nmr. From published data, it is expected that the secondary *endo*-cyclopropane proton in **5** should be at higher field than the exo hydrogen in **6**.[5] Furthermore, the cis vicinal coupling constant in cyclopropanes is expected to be somewhat larger than the trans constant.[5] Consequently, a triplet absorption at δ 0.15 ppm (J = 3.9 Hz) is assigned to the endo proton of **5** and triplet absorption at δ 0.30 ppm (J = 7.9 Hz) to the exo proton of **6**. The spectrum was determined in various cases at 100 MHz, which gave complete separation of the two triplets, or at 60 MHz, with deuterium decoupling to sharpen the overlapping absorptions.

Discussion

It may be seen from Tables I and II that the stereochemistry of deuterium in the bicyclo[3.1.0]hexane product (**1**) is highly dependent upon the carbene or carbenoid precursor. In the tosylhydrazone decompositions, which have the greatest likelihood of a free carbene intermediate,[3] there is a small but definite preference for formation of **5**, with the deuterium exo. The organometallic routes show the opposite stereo-

(1) (a) This research was supported by a grant from the Petroleum Research Fund, administered by the American Chemical Society. (b) Reported in part at the 154th National Meeting of the American Chemical Society, Miami, Fla., Sept 1967, Abstracts S-107.

(2) (a) J. A. Landgrebe and D. E. Thurman, *J. Amer. Chem. Soc.*, **91**, 1759 (1969). (b) W. Kirmse and M. Buschhoff, *Chem. Ber.*, **102**, 1098 (1969). (c) D. Seyferth and V. M. Cheng, *J. Amer. Chem. Soc.*, **93**, 4072 (1971). (d) For examples of other stereochemical outcomes, see V. Franzen and R. Edens, *Justus Liebigs Ann. Chem.*, **729**, 33 (1969).

(3) For reviews of carbene chemistry, see J. Hine, "Divalent Carbon," Ronald Press, New York, N. Y., 1964; W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964; D. Bethel, *Advan. Phys. Org. Chem.*, **7**, 153 (1969).

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TABLE I
BASIC DECOMPOSITION OF CYCLOPENTANECARBOXALDEHYDE TOSYLHYDRAZONE

Solvent	Base	Yield, % N_2	Yield, % Hydrocarbon	C_6H_{10} product distribution[a] 1	2	3	2/1	endo D/exo D (6/5)[a]
Ethylene glycol	$NaOCH_3$	86		3	15	82	(5)	
DEC[b]	$NaOCH_3$	87	10	36	18	46	0.50	
DEC[b,c]	$NaOCH_3$	82	10	36	20	44	0.56	1.05 ± 0.10[d]
DEC[b] + 1 equiv of CH_3OH	$NaOCH_3$	60	10	32	18	50	0.56	
DEC[b]	$NaOCH_3$ (6 equiv)	82	30	71	27	2	0.39	
DEC[b,c,e]	NaH	85	30	73	27	0	0.37	0.6 ± 0.10[d]
$C_{16}H_{34}$	$NaOCH_3$	70		22	15	63	0.68	
$C_{16}H_{34}$	NaH	90[f]	10	36	21	43	0.59	
$C_{16}H_{34}$	NaH	90[f]	10	36	25	39	0.69	0.85 ± 0.05
								0.95 ± 0.05
$C_{16}H_{34}$[c]	Na salt[g]	90	12	73	26	1	0.36	0.61 ± 0.05
$C_{16}H_{14}$	C_4H_9Li[h]	75	25	54	28	48	0.52	
$C_{16}H_{14}$	Li salt[i]	55	10	68	30	2	0.44	
$C_{16}H_{14}$	*j*			67	33		0.49	
NMP[c,k]	NaH	80	30	70	28	2	0.39	*l*
None	Na salt[g]	80	50	69	30	2	0.44	
None[c]	Na salt[g]	90	45	70	30		0.43	0.68 ± 0.05
None	Li salt[i]	75	42	58	39	3	0.67	
None[c]	Li salt[i]	75	35	62	35	3	0.56	0.67 ± 0.05
				56	43	1	0.77	0.68 ± 0.05

[a] Uncertainties in product distribution ±5%; uncertainties in 6/5 ratio estimated by examination of nmr tracings. [b] Diethylcarbitol. [c] Tosylhydrazone from α-*d* aldehyde. [d] Partial exchange of deuterium. [e] Solvent stored over molecular sieves; run on undried solvent sample gave ~20% cyclohexene and 6/5 ratio of 1.0. [f] Nitrogen plus hydrogen. [g] Na salt prepared with NaH in THF; THF removed under vacuum. [h] Butyllithium in hexane added to tosylhydrazone suspended in $C_{16}H_{34}$; no reaction until heating. [i] Li salt prepared with C_4H_9Li in THF; THF removed under vacuum. [j] Isolated diazo compound. [k] *N*-Methylpyrrolidone. [l] Complete exchange of *d* in **1**.

TABLE II
ORGANOMETALLIC "CYCLOPENTYLCARBENE" REACTIONS

Reactants	C_6H_{10} product distribution 1	2	3	2/1	endo D/exo D (6/5)[a]
c-$C_5H_9CH_2Cl$ + Na	74	24	2	0.32	2 ± 0.3
c-C_5H_9Li + CH_2Cl_2	60	40	0	0.67	1.8 ± 0.2
c-C_5H_9MgCl + CH_2Cl_2	50	45	5	0.9	3.6 ± 0.3

[a] Uncertainties estimated by examination of nmr tracings.

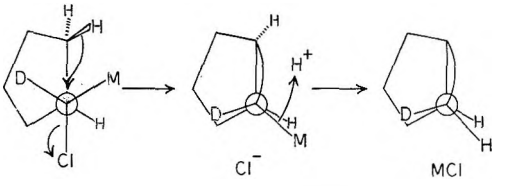

Figure 1.—Rationalization of insertion stereochemistry in cyclopentylcarbenoid insertions. Representation in two stages is for purposes of clarity.

chemical preference, most strikingly so in the magnesium case. This difference may probably be interpreted to imply that the precursor to products in all three organometallic routes is not the free carbene, but, instead, an α-halo organometallic compound, or carbenoid. Such species have been shown to be the product-determining intermediates in numerous instances of cyclopropane formation from alkenes[3,6] and are suggested in some cases of insertion into a C–H bond.[7] A less likely alternative is that carbenes are intermediates in all cases, but that different modes of generation produce the carbene in different rotational conformations. If insertion and rearrangement were to occur more rapidly than internal rotation, then different product distributions and stereochemistries could result.

Rationalizations of the product stereochemistries may be made on the basis of possible transition-state structures for insertion.

For the carbenoid intermediates in the organometallic routes, the insertion may be pictured as simultaneous nucleophilic and electrophilic substitution processes at the carbenoid carbon (see Figure 1). The nucleophilic displacement of chloride by the electrons of the C_2–H bond should occur with inversion of configuration at C_α (first stage of Figure 1). The electrophilic substitution, protolysis of the carbon–metal bond by the C_2 H proton, would be expected to occur with retention of configuration at C_α (second stage of Figure 1). Since the electron-deficient metal of most organometallic compounds is involved in solvation or aggregation, the metal would probably be the bulkiest of the groups on the carbenoid carbon, and so the conformation shown in Figure 1 should predominate. From this conformation, the insertion product, **6**, with endo deuterium should then be expected. Though the process in Figure 1 is drawn in two stages for purposes of clarity, we envision the insertion as a single step. However, the generally electrophilic nature of carbenoids suggests that in the transition state for insertion the electronic displacements represented in the

(6) (a) G. L. Closs and R. A. Moss, *J. Amer. Chem. Soc.*, **86**, 4042 (1964). (b) L. Friedman, R. J. Honour, and J. G. Berger, *ibid.*, **92**, 4640 (1970). (c) H. E. Simmons, E. P. Blanchard, and R. D. Smith, *ibid.*, **86**, 1347 (1964). (d) G. Kobrich, *Angew. Chem., Int. Ed. Engl.*, **6**, 41 (1967). (e) See also G. Kobrich, H. Buttner, and E. Wagner, *ibid.*, **9**, 169 (1970), for an alternate explanation of some results.

(7) M. J. Goldstein and W. J. Dolbier, *J. Amer. Chem. Soc.*, **87**, 2293 (1965); L. Y. Goh and S. H. Goh, *J. Organometal. Chem.*, **23**, 5 (1970).

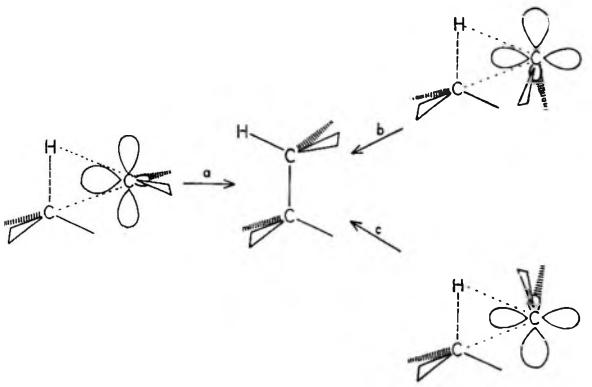

Figure 2.—Triangular "Skell-Doering" transition state for carbene insertion. Reaction paths b and c are in better accord with orbital symmetry considerations. In all cases, the reacting carbene orbitals, the CH bond, and the new C–C and C–H bonds are all coplanar.

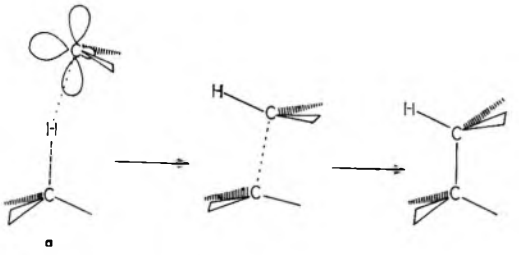

Figure 3.—Abstraction-like "Benson–Hoffman" reaction coordinate for carbene insertion. The transition state is calculated to resemble the first structure shown.[12]

first stage of Figure 1 may be more advanced than those in the second stage. Somewhat similar considerations have led to a proposed transition-state geometry for the addition of a carbenoid to a carbon–carbon double bond.[6a]

For the insertion of a free carbene into a C–H bond, the literature contains conflicting opinions. In the pioneering studies of Skell and Woodworth[8] and Doering and Prinzbach,[9] a triangular addition-like reaction path was originally presumed (interpreted as path a in Figure 2). More contemporary considerations of orbital symmetry would prefer "nonlinear cheletropic" reaction paths[10] (b and c in Figure 2). Here, the symmetry "match-ups" would be the vacant carbene p orbital with the filled CH σ orbital, and the filled carbene hybrid orbital with the σ^* orbital. The projection of the hybrid orbital points toward either the hydrogen (path b) or the carbon (path c) of the C–H bond. Benson and DeMore[11] have concluded that an alternative abstraction-like reaction coordinate is more consistent with the high efficiency of insertion reactions. Extended Hückel calculations by Dobson, Hayes, and Hoffmann[12] support this picture as the path of minimum energy. They predict the reaction path shown in Figure 3, with the transition state ap-

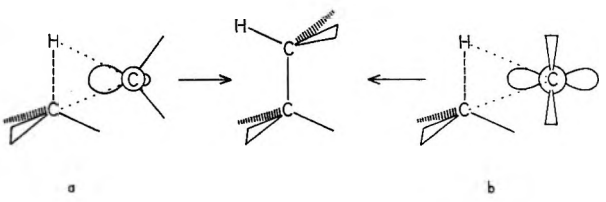

Figure 4.—Unfavorable insertion transition-state geometries. Reacting orbitals in these structures are not coplanar. The carbene p-orbital in a and hybrid orbital in b are perpendicular to the plane of the paper.

proximating the structure a. Though the reaction coordinate resembles an abstraction–recombination sequence, the calculations suggest substantial C–C bonding *before* shift of the hydrogen and transfer of electron density from the σ bond to the carbene p orbital. The energy is relatively insensitive to distortion from this geometry, and, indeed, a continuum of transition-state structures differing little in energy may be visualized between extremes pictured in Figures 2 and 3.[13] However, where the insertion is intramolecular, yielding a cyclopropane ring, the triangular *vs.* abstraction question is no longer meaningful. Normal bond lengths and angles preclude approach of the carbene along the line of the C–H bond and constrain it to a position nearer to a perpendicular from the midpoint of the C–H bond (see, for example, **4** in eq 2). Since the insertion is exothermic, the transition state probably has a similar geometry.

A significant distinction in transition-state geometries exists, however, which *does* apply to the intramolecular cyclopropane-forming insertion. In all transition-state geometries drawn in Figures 2 and 3, one feature consistently recurs: all orbitals involved in the reaction lie in one plane—the carbene p and hybrid orbitals and the C–H bonding and antibonding orbitals, as well as the orbitals of the new C–C and C–H bonds being formed. Such a geometric relationship is expected to be favorable, as it gives maximum overlap between reacting orbitals. If a cyclopropane ring is being formed by intramolecular insertion, examination of models shows that it is no longer possible to have all of the appropriate orbitals of reactant and product in the same plane. However, it is reasonable that transition states most closely approaching a coplanar arrangement of orbitals would be most favorable. Figure 4 shows two triangular transition states which lack the "coplanar orbital" geometry. To maintain the same perspective as in Figures 2 and 3, these transition states are drawn with one of the carbene orbitals (p orbital in 4a and hybrid orbital in 4b) perpendicular to the plane of the paper, in which the other orbitals lie. Because the transition states of Figure 4 lack a coplanar geometry of reacting orbitals they might be expected to be higher in energy than ones resembling Figure 2. For example, in 4a, the carbene

(8) P. S. Skell and R. C. Woodworth, *J. Amer. Chem. Soc.*, **78**, 4496 (1956).

(9) W. von E. Doering and H. Prinzbach, *Tetrahedron*, **6**, 24 (1956).

(10) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie, GmbH, Weinheim/Bergstr., 1970, pp 152–158; R. Hoffmann, *J. Amer. Chem. Soc.*, **90**, 1475 (1968); P. S. Skell and A. Y. Garner, *ibid.*, **78**, 5430 (1956).

(11) S. W. Benson, *Advan. Photochem.*, **2**, 1 (1964); W. B. DeMore and S. W. Benson, *ibid.*, **2**, 219 (1964).

(12) R. C. Dobson, D. M. Hayes, and R. Hoffmann, *J. Amer. Chem. Soc.*, **93**, 6188 (1971).

(13) Gutsche and coworkers[14] have interpreted the distribution of products in an intramolecular insertion reaction as providing a preference for the triangular transition state of Figure 2a. A product that would appear from models to result from a near-perfect Benson–Hoffmann transition state is formed in only minor amounts, while a more strained product, whose formation almost demands a perpendicular approach of the carbene to the C–H bond, is the major isomer isolated. It would appear that the symmetry-preferred reaction path of Figure 2b would be equally acceptable.

(14) C. D. Gutsche, G. L. Bachman, W. Udell, and S. Bäuerlein, *J. Amer. Chem. Soc.*, **93**, 5172 (1971); T. A. Baer and C. D. Gutsche, *ibid.*, **93**, 5180 (1971).

p orbital is orthogonal to both the C–H bonding and antibonding orbitals.

Two possibilities for a geometry leading to insertion in cyclopentylcarbene are shown in Figure 5. In both of these, the carbene carbon occupies a pseudoequatorial conformation on the cyclopentane ring. The carbene p orbital, which is not shown in these drawings, is approximately perpendicular to the plane of the paper. The two geometries differ by a 180° rotation about the ring–carbene bond. The relative orientations of the carbene carbon and the reacting C–H bond in 5a and 5b nearly resemble 2b and 4a, respectively. (In the drawings of Figure 5, the vantage point has been changed for a clearer visualization of the stereochemistry resulting upon insertion. The vantage point in Figure 5 is equivalent to a location in the plane of the paper and to the right of the drawings in Figures 2 and 4.) Insertion from the favorable geometry of Figure 5a most smoothly proceeds to product in which deuterium originally on the carbene carbon becomes exo in the bicyclic product. This is the result found experimentally. The smaller amount of product formed with endo deuterium could be formed either *via* a transition state resembling the less favorable 5b or through a transition state in which the carbene carbon is pseudoaxial on the ring.

Several somewhat less central features of the present results may also be profitably discussed.

A complicating feature in the generation of carbenes from tosylhydrazones is the competing cationic (carbonium ion) reaction of the intermediate diazo compound, favored by a proton-donating reaction medium.[15] Data in Table I suggest that reactions which are largely carbene are characterized by formation of little or no cyclohexene and a low ratio of methylenecyclopentane to bicyclohexane (2/1 < 0.5). In diethylcarbitol, sodium hydride as base appears to favor the carbene process. With sodium methoxide, methanol formed in the acid–base reaction is an effective proton donor, but a large excess of methoxide decreases proton availability.[15b] In the reactions of sodium hydride or butyllithium in hexadecane, the tosylhydrazone is relatively insoluble until high reaction temperatures are reached, so that undissociated tosylhydrazone may serve as a readily accessible proton donor. The decomposition of the dry lithium salt is somewhat anomalous, since low cyclohexene yields accompany a relatively high ratio of methylenecyclopentane to bicyclohexane. It is possible that the lithium ion may act as an electrophile, or otherwise influence the course of reaction. (It was also noted that some tetrahydrofuran, used as solvent in preparation of the tosylhydrazone salts, remained with the lithium salt, but not with the sodium salt.)

A small but real variation in the stereochemical outcome occurs in the tosylhydrazone reactions. This may result from production of bicyclohexane of different stereochemical specificity in the competing cationic reaction, or, alternatively, it may reflect a sensitivity of the carbene's reaction to its environment.

Another complication in the tosylhydrazone reactions is isotopic hydrogen exchange, shown by the presence of more complex absorption in the cyclopropane methylene region attributed to undeuterated product. In *N*-methylpyrrolidone, the bicyclohexane from deuterated tosylhydrazone was undeuterated. It is most probable that exchange of the tosylhydrazone or its salt, or of the diazo compound, had occurred, so that the stereochemical result was not affected by a selective exchange of one bicyclohexane isomer.

In the reaction of cyclopentylmethyl chloride with sodium, nmr and mass spectral analysis showed much dideuterated methylcyclopentane along with the trideuterated material expected from α elimination. This result would be consistent with competing β elimination, as would the presence of dideuterated methylenecyclopentane and an increase in the ratio of methylenecyclopentane to bicyclohexane.

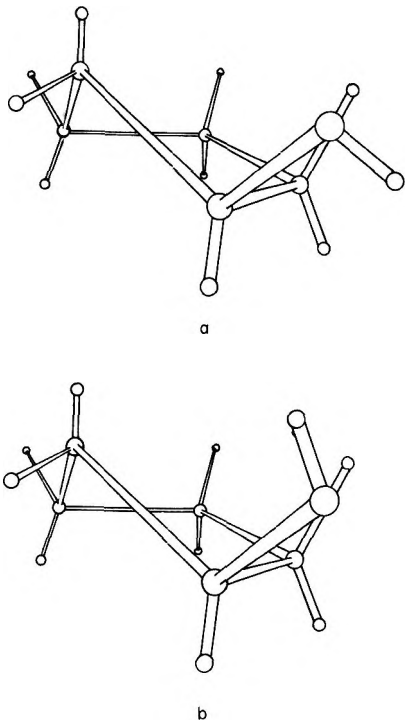

Figure 5.—Two cyclopentylcarbene conformations with the carbene carbon in pseudoequatorial position. The model in these drawings is oriented to show the carbene carbon and C–H bond as they would be seen from a vantage point in the plane of of the paper and to the right in Figures 2 and 4.

Experimental Section

Nmr spectra were run on Varian Associates HA-100 and A-60 spectrometers. Deuterium decoupling on the latter instrument was done with an Nmr Specialties heteronuclear decoupler. Ir spectra were run on Beckman IR-8 and IR-5 spectrometers. Gas chromatography was carried out on an Aerograph A90-P chromatograph. Elemental analyses were done by the Schwarzkopf Microanalytical Laboratory. Melting points and boiling points are uncorrected. Assistance of Mr. H. B. Clark in the alkyl chloride–sodium reaction is acknowledged.

Cyclopentylmethyl chloride-α,α-d_2 was prepared by a method analogous to that used previously for the preparation of isotopically normal material,[4] except that reduction of ethyl cyclopentanecarboxylate was carried out with lithium aluminum deuteride. The product chloride had bp 138–139°. The nmr spectrum showed no absorption (<2%) at δ 3.55 ppm, where the α hydrogens of the undeuterated compound absorb. Less than 5% cyclohexyl chloride was present.

Reaction of Cyclopentylmethyl Chloride-α,α-d_2 with Sodium.—This reaction was carried out in a manner similar to that described previously, using a small amount of dodecane as solvent.

(15) (a) L. Friedman and H. Shechter, *J. Amer. Chem. Soc.*, **81**, 5512 (1959). (b) R. H. Shapiro, J. H. Duncan, and J. C. Clopton, *ibid.*, **89**, 442 (1967); see also discussion and references in ref 3.

In a reaction with undeuterated chloride, gas chromatography on silicone grease yielded three fractions: (1) 61% methylcyclopentane; (2) 9% mostly methylenecyclopentane by nmr and ir (cyclohexane was found as a minor component by chromatography on tricresyl phosphate and nmr; an additional olefinic component, absorbing in the nmr at δ 5.32 ppm, not separated from methylenecyclopentane on silicone grease or tricresyl phosphate, was tentatively identified as 1-methylcyclopentene; a published spectrum of methylenecyclopentane shows the same absorption[16]); (3) 30% bicyclo[3.1.0]hexane by nmr and ir, contaminated by ~4% cyclohexane by nmr or gc on tricresyl phosphate. The deuterated chloride gave similar results, with distributions among the fractions: (1) 88%; (2) 5%; (3) 7%. The nmr spectrum of the methylcyclopentane suggested a mixture of CHD_2 and CD_3 groups, with a splitting pattern in the former consistent with $J_{HCCH} = 6.0$ Hz, $J_{HCD} = 2.0$ Hz. The mass spectrum indicated 23% trideuteration and 77% dideuteration. The mass spectrum of the methylenecyclopentane sample indicated nearly equal amounts of mono- and dideuterated material, along with smaller amounts (~10%) of tri- and undeuterated product. The nmr spectrum of the bicyclo[3.1.0]hexane fraction at 60 MHz had a multiplet absorption at δ 0.08 to 0.45 ppm. Decoupling from deuterium sharpened the spectrum sufficiently to allow interpretation as a pair of overlapping triplets at δ 0.15 ($J = 3.9$ Hz) and 0.30 ppm ($J = 7.9$ Hz). Analysis of the areas of the components of the multiplet as the A part of an AB_2 spectrum[17] yielded a ratio of the two triplets of 1.0:2.0 ($\pm$0.3). The nmr spectrum of this fraction also showed ~8% cyclohexene in the sample.

Cyclopentanecarboxaldehyde-α-d. — Cyclopentanecarbonyl chloride was prepared by addition of the acid to an excess of thionyl chloride, followed by brief heating at 100°, bp 159–160.5° (lit.[18] bp 160–162°).

Cyclopentanecarbonyl chloride (42.3 g, 0.32 mol) was added dropwise over 0.75 hr to a mixture of freshly distilled aziridine (13.7 g, 0.32 mol) and triethylamine (32.2 g, 0.32 mol) in 250 ml of benzene, maintained below −12°. The mixture was allowed to warm to room temperature and stirred for 2 hr. After filtration to remove precipitated salts, the solvent was removed, and the product distilled under vacuum, bp 45° (1 mm), yield 32.7 g (74%). Distillation of the product was necessary to separate it from a material tentatively identified as the cyclopentanecarboxamide of 2-chloroethylamine.

The aziridide of cyclopentanecarboxylic acid (16.5 g, 0.119 mol) in 100 ml of anhydrous ether was added over 30 min to 1.29 g (0.0307 mol) of lithium aluminum deuteride in 50 ml of ether, maintained below 4°. After 1 hr of stirring below 10°, an excess of 6 N sulfuric acid was added. The ether phase was washed with aqueous bicarbonate and sodium chloride and dried over sodium sulfate. The product (8.9 g, 76%) was isolated by distillation, bp 28–30° (8 mm) [lit.[19] bp 34° (10 mm)]. The product was shown by gas chromatography to be pure. The nmr spectrum showed no detectable aldehydic proton resonance; the ir had a prominent C–D stretch at 2060 and lacked bands at 2800 and 2700 cm^{-1} present in the isotopically normal compound which had been prepared similarly.

Cyclopentanecarboxaldehyde-α-d tosylhydrazone was prepared by adding the aldehyde (5.0 g, 0.0505 mol) to a solution of p-toluenesulfonylhydrazine (9.5 g, 0.051 mol) in 19 ml of methanol, containing 8 drops glacial acetic acid. The precipitate that formed was collected, washed, and dried under vacuum, mp 90–91° dec. The isotopically normal compound was prepared in similar fashion.

Anal. Calcd for $C_{13}H_{18}N_2O_2S$: C, 58.62; H, 6.81. Found: C, 58.67; H, 6.79.

Tosylhydrazone Decomposition.—Most experiments were carried out with 1-g samples of tosylhydrazone. With sodium methoxide or sodium hydride as base, the dry reactants were mixed before addition of solvent. For formation of the lithium salts, butyllithium in n-hexane was added by syringe. The reaction flask was swept with nitrogen before reaction. For preparation of the dry lithium or sodium salts, tetrahydrofuran (at 0°) was used as solvent and was removed under vacuum; the salt was dried at ~20 μ before heating either dry or as a suspension in hexadecane. The decomposition was brought about by rapid heating on a Woods metal bath to ~175°. The reaction flask was attached through a cold trap (solid CO_2–acetone) to a gas buret, with which the volume of evolved nitrogen was measured approximately ($\pm$10%). After cooling to room temperature, the remaining product was transferred to the trap under 10-mm vacuum. The product was examined by nmr and gas chromatography on a Carbowax 20M column, with an internal benzene standard. In some cases, individual product fractions were isolated and examined. The methylenecyclopentane peak from solution decompositions of the tosylhydrazone with base exhibited a shoulder, and the nmr spectrum generally showed olefinic absorption tentatively ascribed to 1-methylcyclopentene formed by base-catalyzed isomerization. This was absent from pyrolyses of dry lithium or sodium salts, from pyrolysis of the preformed salts in solution, and from the reaction in N-methylpyrrolidone.

In one case, the diazo compound was distilled at ~100 μ to a cold trap (solid CO_2–acetone) by gradual heating of the dried lithium salt to about 125°. The ir spectrum of the orange liquid showed an intense band at 2050 and a weaker band at 1632 cm^{-1}. After this stood in CCl_4 solution, a band at 1720 cm^{-1} slowly grew in intensity. On heating in hexadecane, the diazo compound evolved gas, and a small yield of volatile products could be isolated.

Reaction of Cyclopentyllithium with Methylene Chloride.—Cyclopentyllithium was prepared by addition over 2 hr of 26.1 g (0.25 mol) of cyclopentyl chloride to lithium wire (4.5 g, 0.65 g-atom) in 200 ml of pentane with vigorous stirring in a Morton flask, under argon. After settling, the clear supernatant liquid was found to be 0.71 M in base.

To a portion of the above alkyllithium solution (50 ml, 35 mmol) was added methylene chloride (1.5 g, 17.5 mmol). Cloudiness developed rapidly. After the mixture stirred overnight, titration of a sample showed consumption of 95% of the base. In a similar reaction with deuterated methylene chloride, ~70% of the base was consumed. The product was poured into water, and most of the pentane solvent was removed by careful distillation through a spinning-band column. It was possible to obtain the nmr spectrum of the secondary cyclopropane hydrogens in the residue without further separation of the mixture. The product mixture was shown by nmr to contain methylenecyclopentane and bicyclo[3.1.0]hexane in a ratio of 4:6, along with a complex mixture of higher boiling components.

Reaction of Cyclopentylmagnesium Chloride with Methylene Chloride.—A Grignard reagent was prepared from 26 g (0.25 mol) of cyclopentyl chloride and 7.0 g (0.30 g-atom) of magnesium in tetrahydrofuran. The final solution was 1.5 M by acid–base titration. A portion of this solution (40 ml, 60 mmol) was stirred with methylene chloride overnight and then heated at reflux for 2 hr. The mixture was poured over ice and extracted with ether, and the solvent was distilled on a spinning-band column. The C_6 fraction of the residue was separated by preparative gas chromatography and its nmr spectrum examined.

Registry No.—Cyclopentylcarbene-α-d, 36595-06-9; cyclopentylcarbene, 7162-01-8; cyclopentanecarboxaldehyde tosylhydrazone, 36601-82-8; cyclopentylmethyl chloride, 13988-39-1; cyclopentyllithium, 23473-12-3; cyclopentylmagnesium chloride, 32916-51-1; sodium, 7440-23-5; dichloromethane, 75-09-2; cyclopentylmethyl chloride-α,α-d_2, 36601-85-1; cyclopentanecarboxaldehyde-α-d, 36601-86-2; aziridide of cyclopentanecarboxylic acid, 36601-87-3; cyclopentanecarboxaldehyde-α-d tosylhydrazone, 36601-88-4.

(16) Nmr Spectral Data, American Petroleum Institute Research Project 44, Spectrum No. 128.

(17) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1970, pp 123–128.

(18) G. B. Payne and C. W. Smith, *J. Org. Chem.*, **22**, 1680 (1957).

(19) E. Urion, *Ann. Chim.*, [11] **1**, 5 (1934).

Stereoelectronic Effects in the Base-Catalyzed Decomposition of Stereoisomeric Norbornanediol Mesylates

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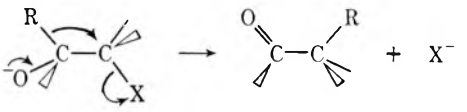
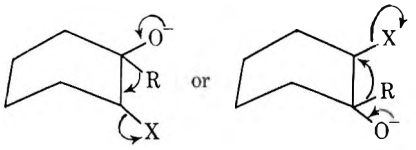
The four stereoisomeric 2-methyl-2,3-norbornanediols were prepared and the products of the decomposition of their monomesylates **12**, **17**, **20**, and **24** by sodium hydride and by potassium *tert*-butoxide were determined. **12** and **17** yielded chiefly 2-*endo*-methyl-2,3-*exo*-epoxynorbornane; **24** yielded 3-methyl-2-norbornanone; and **20** yielded either 3-methyl-2-norbornanone or 2-*exo*-methyl-2,3-*endo*-epoxynorbornane, depending on the base and solvent used. The formation of these products is interpreted in terms of solvolytic formation of the bipolar ions **15** and **23**, although concerted reaction paths, involving in one case a front-side nucleophilic displacement, are also considered.

The course of the base-catalyzed reaction of alcohols having a vicinal leaving group depends on a stereoelectronic factor. If the alcohol oxygen can be trans to the leaving group, an epoxide is formed. If, however, the stereochemistry is fixed so that the bond to the leaving group is coplanar with the bond to an alkyl or hydrogen substituent on the adjacent carbon, rearrangement to a ketone or aldehyde can occur.[2]



In all of the stereochemically defined examples reported for this rearrangement,[3] the leaving and migrating groups have been associated with a chair cyclohexane ring, and the requirement of bond coplanarity has necessarily resulted in migration of a group trans to the leaving group. In a boat cyclohexane ring, the cis vicinal substituents are coplanar, and Barton's coplanarity rule would result in migration of a group cis to the leaving group. Since such



cis migrations have not been reported, we sought for evidence of their existence by preparing the four stereoisomeric 2-methyl-2,3-norbornanediols, **4**, **5**, **8**, and **10**, and examining the base-catalyzed decomposition of their monomesylates **12**, **17**, **20**, and **24**.

The synthesis of the four diols is summarized in Chart I. Epoxidation of the acetates of 3-methylene-2-*exo*-norbornanol (**1**)[4] and of 3-methylene-2-*endo*-norbornanol[5] (**6**) gave in each case a mixture of two epoxides. Lithium aluminum hydride reduction of each of these mixtures gave a mixture of a cis and a trans diol which was separable by crystallization. The cis diol derived from **1** was identical with 2-methyl-2,3-*cis*,*exo*-norbornanediol (**4**), which has been prepared previously by hydroxylation of 2-methylnorbornene.[6] The cis diol derived from **6** was prepared independently in two steps from the adduct of cyclopentadiene and 4-methyl-1,3-dioxol-4-en-2-one, and was assigned structure **10**, it being assumed that the adduct had the endo configuration.[7]

The cis-vicinal relationship of the hydroxyl groups in diols **4** and **10** was confirmed by their reaction with periodic acid. The diols **5** and **8** did not react with periodic acid, but could be oxidized with CrO_3 to α-ketols, establishing the trans-vicinal relationship of their hydroxyl groups. The assignment of the configuration of the methyl and tertiary hydroxyl groups in the four diols rested on the assumption that the epoxides formed in greater yield from **1** and **6** were those resulting from exo attack. This assumption was verified by the alternate methods of preparation of the two cis diols.

Each of the diols could be converted to a monomesylate. The proton nmr spectra of the four mesylates provided additional evidence for the correctness of the structural and stereochemical assignments. Each had an upsplit signal for the *C*-methyl group and a downfield signal for the single proton α to the mesylate group. This latter signal appeared as a doublet, with $J = 2$ Hz for the two mesylates from **4** and **5** and $J = 5$ Hz for the mesylates from **8** and **10**. This confirmed the stereochemistry of the C-3 proton as endo in **4** and **5** and exo in **8** and **10**.[8]

Results

The results of the mesylate decompositions are summarized in Chart II. Reaction of the *cis*,*exo*-diol mesylate **12** with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol gave a 90:6:4 mixture of three products, separated gas chromatographically and identified respectively as 2-*endo*-methyl-2,3-*exo*-epoxynorbornane[9] (**14**), 3-*endo*-methyl-2-norbornanone[10] (**16**), and 3-*exo*-methyl-2-norbornanone[11] (**19**). The mixture of ketones is a result of epimerization at C-3 during the

(1) Based on work by E. K. O. in partial fulfillment of the requirements for the Ph.D. degree at Stevens Institute of Technology.

(2) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(3) G. Büchi, W. Hofheinz, and J. V. Paukstelis, *J. Amer. Chem. Soc.*, **91**, 6473 (1969); A. K. Bose and N. G. Steinberg, *J. Org. Chem.*, **36**, 2400 (1971); R. H. Starkey and W. H. Reusch, *ibid.*, **34**, 3522 (1969); D. J. Collins, J. J. Hobbs, and R. J. Rawson, *Aust. J. Chem.*, **22**, 607, 807 (1969); and references cited in these papers.

(4) H. Krieger, K. Manninen, and J. Paasivirta, *Suom. Kemistilehti B*, **39**, 8 (1966); *Chem. Abstr.*, **64**, 17441*d* (1966).

(5) W. F. Erman, *J. Org. Chem.*, **32**, 765 (1967).

(6) J. A. Berson, J. H. Hammons, A. W. McRowe, A. Remanick, and D. Houston, *J. Amer. Chem. Soc.*, **89**, 2590 (1967).

(7) M. S. Newman and R. W. Addor, *ibid.*, **77**, 3789 (1955).

(8) The vicinal coupling constant between the exo C-3 proton and the C-4 proton in norbornanes is 3–5 Hz; this coupling constant for an endo C-3 proton is 0 Hz, but the endo C-3 proton can have a long-range coupling of 1–2 Hz with the anti C-7 proton. J. Musher, *Mol. Phys.*, **6**, 93 (1963).

(9) H. C. Brown, J. H. Kawakami, and S. Ikegani, *J. Amer. Chem. Soc.*, **92**, 6914 (1970).

(10) K. Alder and A. Grell, *Chem. Ber.*, **89**, 2198 (1956).

(11) J. Wolinsky, D. R. Dimmel, and T. W. Gibson, *J. Org. Chem.*, **32**, 2087 (1967).

CHART I

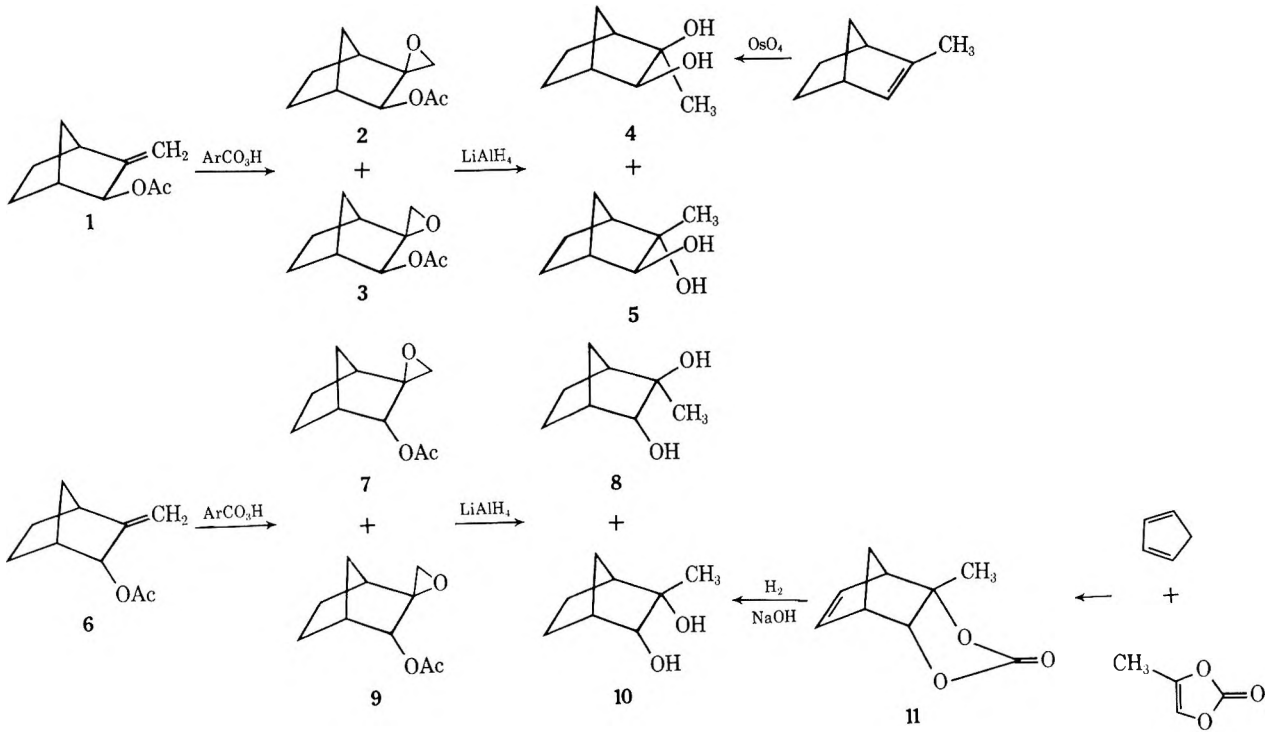
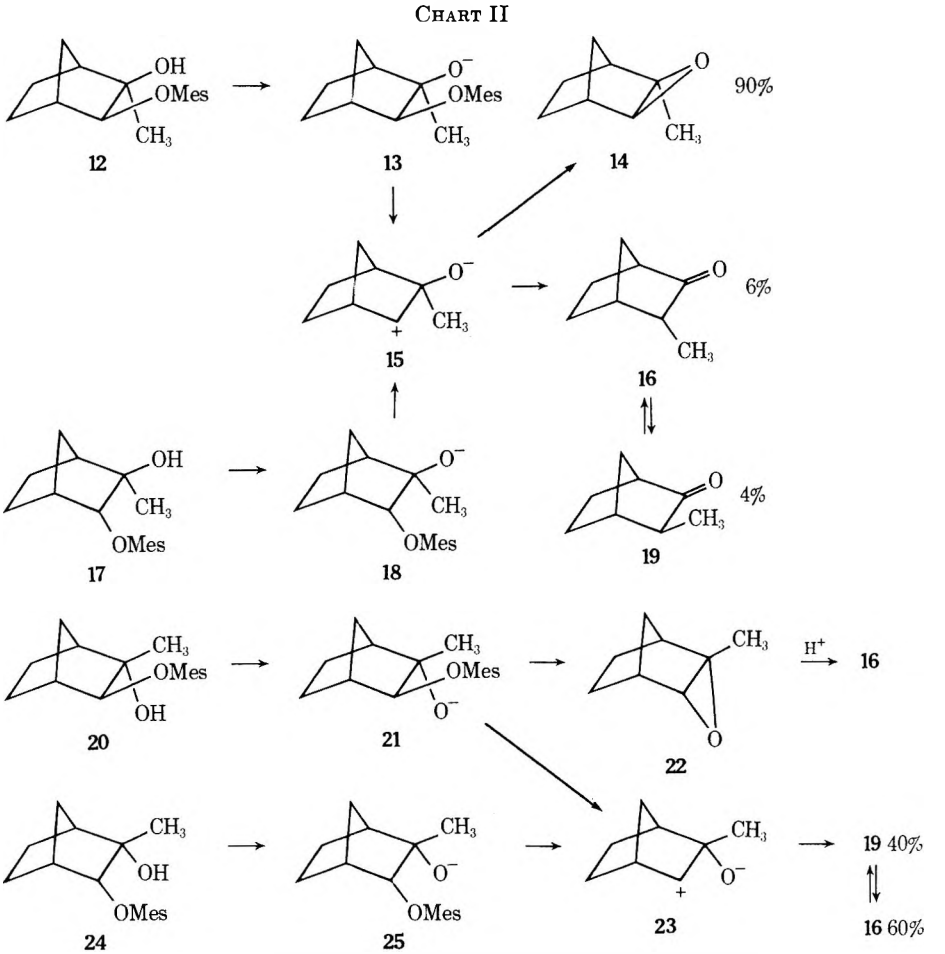


CHART II



reaction, since either **16** or **19**, when subjected to the reaction conditions, was transformed to a 60:40 mixture of the two. Hence no information is available on the stereochemistry of the ketone initially formed from **12**.

Since the formation of the exo epoxide **14** from **12** represents substitution with retention at C-3, some additional experiments were carried out aimed at clarifying the process of epoxide formation. The process does not involve nucleophilic participation by *tert*-

butoxide ion, because the same 90:6:4 mixture of **14**, **16**, and **19** was formed when mesylate **12** was treated with sodium hydride in boiling benzene. The epoxide did not result from solvolysis of the mesylate, since **12** was recovered unchanged from refluxing benzene or *tert*-butyl alcohol.[12] Finally, the tricyclanol **28** (R = CH_3) cannot be an intermediate in the process, since a synthetic sample[13] was unchanged by either potassium *tert*-butoxide or sodium hydride under the reaction conditions.

A 90:6:4 mixture of **14**, **16**, and **19** was also formed when the mesylate **17** was treated with either potassium *tert*-butoxide or sodium hydride. There was no qualitative evidence for a large difference in the rate of decomposition of **12** and **17**.

The similarity in the composition of the product mixture from the two mesylates suggests a common intermediate. We propose that this intermediate is the bipolar ion **15**, formed by solvolysis of the alkoxide ions **13** and **18**.

The reaction of the *endo,cis*-diol mesylate **24** with either potassium *tert*-butoxide or sodium hydride gave only the ketones **16** and **19** in the equilibrium 60:40 proportion. The same mixture was obtained from the reaction of mesylate **20** with sodium hydride. Again, this result can be rationalized in terms of a common intermediate, the bipolar ion **23**, which could undergo *exo*-methyl migration to **19**, followed by epimerization by excess base.

In contrast, the *endo*-methyl ketone **16** was the sole product isolated from the reaction of **20** with potassium *tert*-butoxide in *tert*-butyl alcohol. We concluded that **16** was an artifact formed during the isolation procedure, since it would have been epimerized had it been present in the reaction solution. In agreement with this reasoning, we found that a modified isolation procedure, in which precaution was taken against the presence of any acidic substances, permitted the isolation of a crude product whose nmr spectrum was consistent with the presence of the endo epoxide **22**, having an unsplit signal from a *C*-methyl group at δ 1.35 and a doublet (J = 3 Hz) from an exo C-3 proton at δ 3.15. The corresponding resonances in the exo epoxide **14** are at δ 1.35 and 2.67, the latter being an unresolved multiplet (J < 1 Hz). Addition of *p*-toluenesulfonic acid to this substance caused immediate transformation to **16**. Attempts to purify and further characterize the endo epoxide were frustrated by the extraordinary ease with which it was transformed to the *endo*-methyl ketone[14] (see Experimental Section).

If methyl migration to form **19** from **20** in the reaction with sodium hydride in benzene occurs by way of the bipolar ion **23**, then formation of the endo epoxide **22** from **20** with *tert*-butoxide ion in *tert*-butyl alcohol must be attributed to direct displacement of mesylate ion in the alkoxide **21**.

(12) The other three mesylates, **17**, **20**, and **24**, were also recovered unchanged from refluxing benzene or *tert*-butyl alcohol in the absence of base.

(13) H. Krieger, *Ann. Acad. Sci. Fenn., Ser. A*, **109**, 39 (1961); *Chem. Abstr.*, **58**, 5979*a* (1961).

(14) Indirect evidence for the instability of an *endo*-epoxynorbornane has been presented by R. M. Moriarty, *Tetrahedron Lett.*, 3715 (1969).

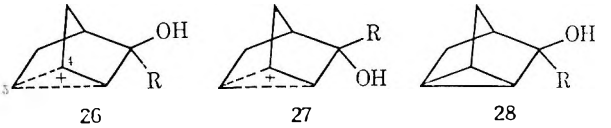
Discussion

The solvolytic formation of carbonium ion intermediates in base-catalyzed reactions in solvents as nonpolar as *tert*-butyl alcohol or benzene has little precedent, but can be attributed to electrostatic assistance to ionization by the negatively charged alkoxide oxygen. Similar electrostatic assistance has been observed in the solvolyses of 4-bromobicyclo[2.2.2]-octane-1-carboxylate,[15] 2-bromonorbornane-1-carboxylate,[16] and in substituted α-bromoacetate ions.[17] It may even be argued that the ionization is facilitated by nonpolar solvents, if the bipolar ions formed have lesser solvation requirements than do the alkoxide ions. Bordwell and Knipe report a remarkable lack of solvent dependence in the solvolysis rates of α-bromoacetate ions.[17]

The reaction paths proposed for the bipolar ions, *viz.*, collapse of **15** to epoxide and rearrangement of **23** to *exo*-methyl ketone, are in accord with expectations. Reactions involving three-membered transition states exo to the norbornyl system are facile, while those involving an endo three-membered transition state are less favored.[6,13] This difference has been explained as being due to eclipsing of the C-1 and C-4 bonds with C-2 and C-3 exo substituents caused by the endo three-ring fusion.[18]

The reactions proposed for **15** and **23** are markedly different from those reported for the hydroxynorbornyl cations **26**[19] and **27**, R = Ph.[20] The latter, formed from a variety of precursors, are interconverted by a rapid 5,4-hydride shift; the major products are the nortricyclanol **28**, R = Ph, and rearranged glycols resulting from solvent attack following the hydride shift. No rearranged ketones or epoxides were observed under reaction conditions where their formation would have been irreversible.[19,20] In our experiments, no nortricyclanol (**28**, R = CH_3) could be detected, and rapid 5,4-hydride shift could be excluded, since such a shift would interconvert **15** and **23** and would result in the same product mixture being formed from all four mesylates.

We explain this difference in reactivity by proposing that in **15** and **23** the negative charge on oxygen causes localization of the positive charge on C-3. Thus **15** and **23**, unlike **26** and **27**, are written as unbridged, classical ions. In agreement with this, we find that the solvolysis of **12** in aqueous acetone, a reaction which presumably involves the hydroxy carbonium ion **26**, R = CH_3, does not yield any epoxide or rearranged ketones.



26 27 28

(15) R. C. Fort, Jr., and P. v. R. Schleyer in "Advances in Alicyclic Chemistry," Vol. 1, H. Hart and G. J. Karabatsos, Ed., Academic Press, New York, N. Y., 1966, p 334.

(16) W. R. Vaughan, R. Caple, J. Csapilla, and P. Scheiner, *J. Amer. Chem. Soc.*, **87**, 2204 (1965).

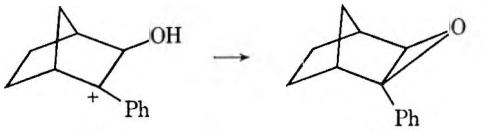
(17) F. G. Bordwell and A. C. Knipe, *J. Org. Chem.*, **35**, 2959 (1970).

(18) P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 699 (1967), and references cited therein.

(19) C. J. Collins and B. M. Benjamin, *J. Amer. Chem. Soc.*, **89**, 1652 (1967), and earlier papers cited therein.

(20) C. J. Collins, V. F. Raaen, B. M. Benjamin, and I. T. Glover, *ibid.*, **89**, 3940 (1967).

It is of interest to note that the cation **29**, tertiary at C-3 and thus classical, yields the epoxide **30** without 5,4-hydride shift or nortricyclanol formation.[21]



29 30

An alternate pathway for the formation of the exo epoxide **14** from mesylate **12** is by direct displacement, loss of mesylate ion from **13** being concerted with formation of the new C–O bond. Although this is consistent with all of our data, it does constitute a front-side nucleophilic displacement, a reaction type generally regarded as being impossible.[23] In the case of **13**, however, front-side displacement may be considerably facilitated by the circumstance that the negatively charged nucleophile is rigidly held almost within bonding distance from the substitution center. As the C-3 mesylate bond is stretched, electrostatic interaction between the negative charge on oxygen and the developing positive charge on C-3 will become increasingly important. If, at some point before the mesylate group is completely ionized, a decrease in the O^-–C-3 distance results in a net decrease in potential energy, then **15** would be bypassed as a reaction intermediate, and the ionization and displacement mechanisms would be merged.

Similar considerations apply to the formation of ketone **19** from the alkoxide ion **21**. A concerted reaction involving migration of the methyl group cis to the leaving group is a conceivable alternative to the intermediacy of **23**. Further experiments to distinguish between these alternatives are in progress.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Infracord spectrophotometer, either as thin films or as Nujol mulls. Nuclear magnetic resonance spectra were run on a Varian HA-60 spectrometer, using tetramethylsilane as internal reference. Chemical shifts are given as parts per million on the δ scale. Melting and boiling points are uncorrected. Microanalyses were performed by MHW Laboratories, Garden City, Mich.

2-*endo*-Methyl-2,3-*cis*,*exo*-norbornanediol (4).—Oxidation of 2-methyl-2-norbornene with osmium tetroxide[6] gave **4** as a waxy solid: mp 126–128° from hexane; ir (film) 3.02, 9.01 μ (OH); nmr (CCl_4) δ 4.1 (broad s, 1 H, hydroxyl proton), 3.8 (broad s, 1 H, hydroxyl proton), 3.12 (broad s, 1 H, endo C-3 proton), 2.0 (m, 2 H, C-1, C-4 protons), 1.20 (s, 3 H, C-2 methyl protons), and 0.9–1.5 (m, 6 H).

***exo*- and *endo*-Spiro[2-*exo*-norbornanol-3,2′-oxirane] Acetates (2 and 3).**—A solution of 37.6 g of 85% *m*-chloroperoxybenzoic acid in 500 ml of methylene chloride was added during 30 min to a cooled solution of 27.8 g of 3-methylene-2-*exo*-norbornanol acetate (1)[4] in 200 ml of methylene chloride. The mixture was stirred for 10 hr at room temperature and was then cooled, and the *m*-chlorobenzoic acid was removed by filtration. The filtrate was washed successively with 5% sodium sulfite and saturated sodium bicarbonate, dried ($MgSO_4$), and evaporated. Distillation of the residue gave 24.7 g (81%) of product: bp 63–68° (0.3 mm); ir (film) 5.78, 8.1 (acetate), 11.15, 11.3 μ. The nmr spectrum showed the presence of two isomers; in the more abundant, the C-2 endo proton appeared as a doublet at δ 4.58 (J = 2.5 Hz) and the oxirane protons appeared as an AB pattern at δ 2.55 and 2.90 (J_{AB} = 7 Hz); in the less abundant isomer, the corresponding resonances were at δ 4.28 (J = 2 Hz) and 2.58, 2.82 (J_{AB} = 5.5 Hz). The acetate methyl signal in both isomers appeared at δ 1.95.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.16; H, 7.83.

2-*exo*-Methyl-2-*endo*,3-*exo*-norbornanediol (5).—The mixture of **2** and **3** obtained above (24.7 g) was added dropwise with stirring to 20.0 g of lithium aluminum hydride in 650 ml of anhydrous ether at a rate which caused vigorous refluxing. After the addition was completed, the mixture was refluxed overnight. The reaction mixture was then decomposed with 10% sodium hydroxide and the ether layer was dried ($MgSO_4$) and evaporated. The residue (15.7 g) was dissolved in 300 ml of warm 9:1 hexane–ether. Cooling the solution caused the separation of 3.75 g of **5**: mp after recrystallization from ethyl acetate 124–125°; ir (mull) 3.09, 8.9, 9.6 μ (OH); nmr (acetone-d_6) δ 3.7 (d, J = 5 Hz, 1 H, C-3 hydroxyl proton), 3.38 (m, 1 H, C-3 endo proton), 2.97 (s, 1 H, C-2 hydroxyl proton), 1.7–2.2 (m, 2 H, C-1 and C-4 protons), 1.22 (s, 3 H, C-2 methyl protons), 1.0–1.5 (m, 6 H).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.60; H 10.10.

2-*endo*-Methyl-2,3-*cis*,*exo*-norbornanediol 3-Methanesulfonate (12).—The filtrate from the crystallization of **5** gave on evaporation 11.5 g of a semicrystalline mass whose infrared spectrum was identical with that of authentic **4**. This material was dissolved in cold pyridine and 12.6 g of methanesulfonyl chloride was added. The solution was stored at 5° for 24 hr and then poured into 500 ml of ice water and extracted with four 200-ml portions of ether. The ethereal layers were washed with cold dilute hydrochloric acid, dried ($MgSO_4$), and evaporated. The residue (10.5 g) was dissolved in warm 1:1 hexane–ether. Cooling gave 0.5 g of a solid methanesulfonate, mp 118–120° after recrystallization from ethyl acetate, which was tentatively identified from its nmr spectrum as the bismethanesulfonate of 3-*exo*-hydroxynorbornane-2-*exo*-methanol: nmr ($CDCl_3$) δ 4.80 (d, J = 7 Hz, 1 H, C-3 endo proton), 4.28 (d, J = 8 Hz, 2 H, C-2 methylene protons), 3.09 (s, 6 H, mesylate methyl protons), 2.3–2.6 (m, 2 H, C-1 and C-4 protons), and 1.0–1.9 (m, 7 H).

Anal. Calcd for $C_{10}H_{18}O_6S_2$: C, 40.27; H, 6.08; S, 21.46. Found: C, 40.20; H, 6.28; S, 21.27.

The filtrate from the crystallization of this substance was evaporated, and the residue (9.1 g) was recrystallized from carbon tetrachloride to give **12**: mp 60–62°; ir (mull) 3.01 (OH), 7.4, 8.65 (mesylate), 11.5 μ; nmr (CCl_4) δ 4.03 (d, J = 2 Hz, 1 H, endo C-3 proton), 3.00 (s, 3 H, mesylate methyl protons), 2.27, 2.58 (m, 2 H, C-1 and C-4 protons), 2.05 (broad s, 1 H, C-2 hydroxyl proton), 1.27 (s, 3 H, C-2 methyl protons), 1.0–1.8 (m, 6 H).

Anal. Calcd for $C_9H_{16}O_4S$: C, 49.08; H, 7.32; S, 14.53. Found: C, 48.89; H, 7.24; S, 14.42.

2-*exo*-Methyl-2-*endo*,3-*exo*-norbornanediol 3-Methanesulfonate (20).—A solution containing 2.3 g of **5** and 2.5 g of methanesulfonyl chloride in 30 ml of pyridine was stored at 5° for 24 hr. The solution was added to 200 ml of ice water and extracted with five 100-ml portions of ether. The extracts were washed with dilute hydrochloric acid and water, dried ($MgSO_4$), and evaporated, yielding **20** as a yellow oil: ir (film) 2.96 (OH), 7.6, 8.6 μ (mesylate); nmr (CCl_4) δ 4.17 (d, J = 2 Hz, endo C-3 proton), 2.97 (s, 3 H, mesylate methyl protons), 2.29, 2.02 (m, 2 H, C-1 and C-4 protons), 1.68 (broad s, 1 H, C-2 hydroxyl proton), 1.27 (s, 3 H, C-2 methyl protons), 1.1–1.8 (m, 6 H).

Anal. Calcd for $C_9H_{16}O_4S$: C, 49.08; H, 7.32; S, 14.53. Found: C, 49.20; H, 7.61; S, 14.72.

This mesylate decomposes on heating to 80° in the absence of solvent.

3-Methylene-2-*endo*-norbornanol Acetate (6).—3-Methylene-2-*endo*-norbornanol[5] (23.3 g) in 125 ml of pyridine and 50 ml of acetic anhydride was refluxed overnight. The solution was added to 1.2 l. of water and extracted with three 500-ml portions of ether. The ethereal extracts were successively washed with dilute hydrochloric acid and saturated sodium bicarbonate, dried ($MgSO_4$), and evaporated. Distillation of the residue gave 23.9 g (77%) of **6**: bp 102–103° (25 mm); ir (film) 5.77, 8.10 (acetate), 11.1 μ (=CH_2); nmr (CCl_4) δ 5.08 (m, 1 H, exo C-2 proton), 4.76, 4.71 (two d, J = 2 Hz, C-3 methylene vinyl protons), 2.48, 2.69 (m, 2 H, C-1 and C-4 protons), 1.93 (s, 3 H, acetate methyl protons), and 1.1–1.8 (m, 6 H).

(21) D. C. Kleinfelter and J. H. Long, *Tetrahedron Lett.*, 347 (1969). In more acidic media, where formation of **30** is reversible, **29** gives 3-*endo*-phenyl-2-norbornanone by successive 6,2 and *exo*-3,2-hydride shifts.[22]

(22) D. C. Kleinfelter and T. E. Dye, *J. Amer. Chem. Soc.*, **88**, 3174 (1966).

(23) J. March, "Advanced Organic Chemistry," McGraw-Hill, New York, N. Y., 1968, pp 251–255. For a recent instance where front-side nucleophilic displacement has been proposed, see T. Nishiguchi, H. Tochio, A. Nabeya, and Y. Iwakura, *J. Amer. Chem. Soc.*, **91**, 5835 (1969).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.50. Found: C, 72.36; H, 8.34.

exo- and endo-Spiro[2-endo-norbornanol-3,2′-oxirane] Acetates (7 and 9).—6 (23.9 g) was oxidized with 32.2 g of *m*-chloroperoxybenzoic acid in 500 ml of methylene chloride, using the same reaction conditions and isolation procedure used in the preparation of **2** and **3**. Distillation of the crude product gave 20.0 g of a mixture of **7** and **9**, bp 59–65° (0.2 mm), ir 5.73, 8.05 μ (acetate). In the nmr spectrum of the mixture, the more abundant isomer had signals at δ 4.70 (d, J = 5 Hz, exo C-2 proton), 2.55, 2.72 (AB quartet, J = 5.5 Hz, oxirane protons), and 1.95 (s, acetate methyl protons). The corresponding signals from the less abundant isomer were at δ 4.88 (d, J = 5 Hz), 2.57, 2.82 (AB quartet, J = 7 Hz), and 1.92 (s).

2-endo-Methyl-2-exo,3-endo-norbornanediol (8).[24]—The mixture of **7** and **9** (20.0 g) was added to 13.5 g of lithium aluminum hydride in 650 ml of anhydrous ether at a rate which caused vigorous refluxing. After addition was complete, the mixture was refluxed overnight. The mixture was then decomposed by addition of 10% sodium hydroxide and was filtered. The granular precipitate of aluminum salts was washed several times with large quantities of boiling ethyl acetate and acetone to dissolve the sparingly soluble **8**. The combined nonaqueous filtrates were dried ($MgSO_4$) and evaporated, and the residue (15.1 g) was dissolved in 50 ml of hot ethyl acetate. Cooling gave 7.1 g of **8**: mp 166–167°; ir (mull) 3.03, 8.90 μ (OH); nmr (acetone-d_6) 3.64 (q, J = 5, 7 Hz, C-3 exo proton), 2.82 (s, 1 H, C-2 hydroxyl proton), 1.6–2.3 (m, 3 H, C-1, C-4, and C-3 hydroxyl protons), 1.07 (s, 3 H, C-2 methyl proton), and 0.9–1.5 (m, 6 H).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.69; H, 10.08.

Evaporation of the filtrate from the crystallization of **8** yielded a residue whose ir spectrum indicated the presence of the cis,-endo diol **10**.

2-exo-Methylnorborn-5-ene-2,3-cis,endo-diol Cyclic Carbonate (11).—A solution of 6.0 g of freshly distilled cyclopentadiene and 9.0 g of 4-methyl-1,3-dioxol-4-en-2-one[25] in 27 g of benzene was heated in a sealed tube at 210° for 48 hr. The black mixture was distilled; redistillation of the crude product gave 6.08 g of **11**, bp 97–98° (0.1 mm). It solidified on standing, mp 64–68° after recrystallization from 3:5 hexane–ethyl acetate: ir (mull) 5.62 μ (C=O); nmr (CCl_4) δ 6.45 (m, 2 H, vinyl protons), 4.60 (d, J = 4 Hz, C-3 exo proton), 3.01, 3.26 (m, 2 H, C-1 and C-4 protons), 1.09 (s, 3 H, C-2 methyl protons), 1.3–1.9 (m, 2 H, C_7 protons).

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 7.27. Found: C, 65.15; H, 6.99.

2-exo-Methyl-2,3-cis,endo-norbornanediol (10).—**11** (3.67 g) in 125 ml of acetone was shaken with 1.0 g of Pd metal and 40 psi of hydrogen in a Paar apparatus. Filtration and evaporation gave 3.60 g of 2-*exo*-methyl-2,3-*cis*,*endo*-norbornanediol cyclic carbonate as a waxy solid, ir (mull) 5.57 μ (C=O).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.18. Found: C, 64.21; H, 7.08.

This compound was hydrolyzed overnight at room temperature with 100 ml of 5% sodium hydroxide solution. The reaction solution was extracted with four 100-ml portions of ether. Drying ($MgSO_4$) and evaporation of the extract yielded 2.8 g of **10**: mp after recrystallization from hexane 47–49.5°; ir (film) 3.03, 9.06 μ (OH); nmr (CCl_4) δ 4.17 (broad s, 1 H, C-3 hydroxyl proton), 3.71 (broad s, 1 H, C-2 hydroxyl proton) 3.40 (m, 1 H, C-3 exo proton), 2.20, 2.45 (m, 2 H, C-1 and C-4 protons), 1.19 (s, 3 H, C-2 methyl protons), 1.0–1.9 (m, 6 H).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.59; H, 9.92. Found: C, 67.77; H, 9.81.

2-endo-Methyl-2-exo,3-endo-norbornanediol 3-Methanesulfonate (17).—**8** (2.0 g) was treated with 2.0 g of methanesulfonyl chloride in 20 ml of pyridine, using reaction conditions and isolation procedure identical with those employed in the preparation of **20**. The methanesulfonate **17**, 2.18 g, was obtained as an oil: ir (film) 3.05 (OH), 7.6, 8.65 μ (mesylate); nmr (CCl_4) δ 4.53 (d, J = 5 Hz, 1 H, C-3 exo proton), 2.97 (s, 3 H, mesylate methyl protons), 2.55 and 1.88 (m, 2 H, C-1 and C-4 protons), 2.07 (s, 1 H, C-2 hydroxyl proton), 1.22 (s, 3 H, C-2 methyl protons), and 1.0–1.6 (m, 6 H).

Anal. Calcd for $C_9H_{16}O_4S$: C, 49.08; H, 7.32; S, 14.53. Found: C, 48.95; H, 7.52; S, 14.50.

2-exo-Methyl-2,3-cis,endo-norbornanediol 3-Methanesulfonate (24).—**10** (3.0 g) was treated with 3.0 g of methanesulonyl chloride, using the same reaction conditions and isolation procedure employed in the preparation of **20**. The crude mesylate was recrystallized from 2:1 CS_2–CCl_4, giving 2.1 g of **24**: mp 56–58°; ir (film) 2.92 (OH), 7.55, 8.55 μ (mesylate); nmr (CCl_4) δ 4.40 (d, J = 5 Hz, exo C-3 proton), 3.11 (s, 3 H, mesylate methyl protons), 2.53, 2.13 (m, 2 H, C-1 and C-4 protons), 1.78 (s, C-2 hydroxyl proton), 1.15 (s, 3 H, C-2 methyl protons), 1.0–1.6 (m, 6 H).

Anal. Calcd for $C_9H_{16}O_4S$: C, 49.08; H, 7.32; S, 14.53. Found: C, 48.87; H, 7.39; S, 14.38.

Reaction of Mesylates 12, 17, 20, and 24 with Potassium *tert*-Butoxide.—A solution of 1.0 g of **12** in 10 ml of *tert*-butyl alcohol was added to a solution of 0.5 g of potassium in 50 ml of *tert*-butyl alcohol. The solution was allowed to stand for 1 hr at room temperature, and then was refluxed for 2 hr. After cooling, the solution was added to 250 ml of water, and then extracted with four 100-ml portions of ether. Drying ($MgSO_4$) and evaporation of the extract yielded 0.27 g of crude product, which was analyzed by gas chromatography on a 6 ft × 1.25 in. stainless steel column packed with 10% lac on 60–80 mesh Chromosorb W, using an F & M Model 720 gas chromatograph. The reference compounds were prepared by literature procedures. Retention times are given for isothermal operation with a column temperature of 115°, an inlet temperature of 250°, and a helium flow rate of 50 ml/min: 2-*endo*-methyl-2,3-*exo*-epoxynorbornane (**14**),[9] 2.0 min; 3-methyltricyclo[2.2.1.$0^{2,6}$]heptan-3-ol (**28**, R = CH_3),[13] 3.5 min; 3-*exo*-methyl-2-norbornanone (**19**),[11] 4.5 min; and 3-*endo*-methyl-2-norbornanone (**16**),[10] 5.0 min. The crude reaction product, whose ir spectrum showed the absence of any unreacted mesylate, gave three peaks, identified by retention time as **14**, **19**, and **16**, with relative areas of 90:6:4. Their identity was confirmed by comparison of the ir spectra of the trapped peaks with those of synthetic samples.

Each of the mesylates **17**, **20**, and **24** was decomposed with potassium *tert*-butoxide, using the same reaction conditions and analysis procedure. From **17** was obtained **4**, **16**, and **19** in the proportions 90:6:4; from **24** a 60:40 mixture of **16** and **19** was obtained, and from **20** the sole product was **16**.

Reaction of the Mesylates 12, 17, 20, and 24 with Sodium Hydride.—A solution of 1.0 g of **12** in 10 ml of benzene was added to 0.25 g of sodium hydride in 100 ml of benzene. The mixture was stirred for 1 hr at room temperature followed by 2 hr of refluxing. After cooling, water was added and the mixture was stirred until all solids had dissolved. Drying ($MgSO_4$) and evaporation of the benzene layer gave 0.29 g of crude product, whose ir spectrum had no bands attributable to the starting mesylate.

Gas chromatographic analysis of the crude product showed the presence of **14**, **16**, and **19** in the proportion 90:6:4.

The mesylates **17**, **20**, and **24** were subjected to the same reaction conditions and analysis. **17** yielded a 90:6:4 mixture of **14**, **16**, and **19**. Both **20** and **24** gave a 60:40 mixture of **16** and **19**.

3-Methyltricyclo[2.2.1.$0^{2,6}$]heptan-3-ol (**28**, R = CH_3), when treated with either potassium *tert*-butoxide or sodium hydride, using the above reaction conditions and isolation procedures, gave crude product whose ir was indistinguishable from that of the starting material.

2-exo-Methyl-2,3-endo-epoxynorbornane (22).—The mesylate **20** was decomposed with potassium *tert*-butoxide in *tert*-butyl alcohol using the reaction conditions described above. Isolation of **22** was possible only when the following modifications were made in the isolation procedure. All operations were carried out in a drybox under dry N_2, all glassware was previously rinsed with NH_4OH before drying, ether was replaced by CCl_4 for extraction, solutions were dried with K_2CO_3 instead of $MgSO_4$, and evaporations were carried out at temperatures below 40°. The nmr of the crude product had peaks ascribable to **22** at δ 3.15 (d, J = 3 Hz, C-3 exo proton) and 1.35 (s, C-2 methyl protons). Addition of a crystal of *p*-toluenesulfonic acid to the nmr tube caused immediate transformation of the spectrum to that of **16**. The same transformation occurred when solutions of **22** were exposed to the laboratory air.

Solvolysis of 12 in Aqueous Acetone.—The mesylate **12** was heated in aqueous acetone, using the same reaction conditions and isolation procedure reported for the solvolysis of 2-*endo*-

(24) The preparation of **8** has been reported by A. Krieger, *Suom. Kemistilehti B*, **35**, 71 (1962); *Chem. Abstr.*, **57**, 14959 (1962). Our observations suggest that the substance isolated by Krieger was a mixture of isomeric diols.

(25) P. H. Moss, U. S. Patent 3,020,290 (Feb 6, 1962); *Chem. Abstr.*, **56**, 12904*e* (1962).

phenyl-2,3-*cis*,*exo*-norbornanediol 3-*p*-toluenesulfonate.[19] Gas chromatographic analysis of the crude product showed the presence of mesityl oxide, diacetone alcohol, and a mixture of glycols, of long retention time, which was not investigated further. No peaks due to **14**, **16**, or **19** were detectable.

Registry No.—**2**, 35623-80-4; **3**, 35623-81-5; **4**, 35623-82-6; **5**, 35623-83-7; **6**, 35623-84-8; **7**, 35623-85-9; **8**, 35623-86-0; **9**, 35623-87-1; **10**, 35623-88-2; **11**, 35623-89-3; **12**, 35623-90-6; **17**, 35623-91-7; **20**, 35623-92-8; **22**, 35623-93-9; **24**, 35623-94-0; bismethanesulfonate of 3-*exo*-hydroxynorbornane-2-*exo*-methanol, 35623-95-1; 2-*exo*-methyl-2,3-*cis*,*endo*-norbornanediol cyclic carbonate, 35623-96-2.

Structural Constraints on Electrocyclic Reactions of Unsaturated Ketenes. Synthesis and Irradiation of 2,4,4,5-Tetramethylbicyclo[4.4.0]deca-1,5-dien-3-one

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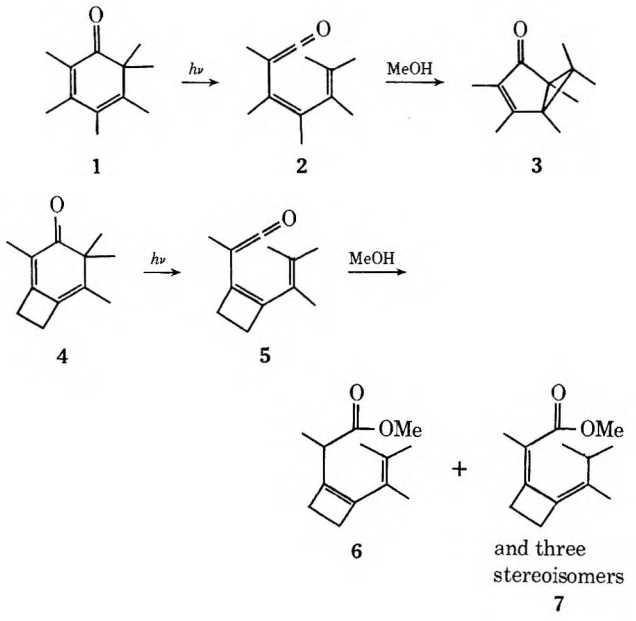
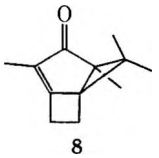
Oxidation of 5,6,7,8-tetramethyltetralin (**9**) with peroxytrifluoracetic acid–boron fluoride gave a mixture of three 2,4-cyclohexadienones (**10**, **11**, and **12**) and the 2,5-cyclohexadienone **13**, as a result of electrophilic attack at all possible ring positions. Irradiation of **13** at 2537 Å gave the expected lumiproducts **14** and **15**; similarly, irradiation of **11** and **12** at 3000 Å gave **14** and **15**, respectively. Irradiation of **10** at 3000 Å in methylene chloride or methanol gave the tetracyclic enone **26**; no methyl esters were formed. Thus the ketene **25** derived from **10** undergoes the electrocyclic reaction faster than it reacts with the nucleophile methanol; its behavior is analogous to that of **2**, not **5**.

The two ketenes formed on irradiation of the 2,4-cyclohexadienones **1** and **4**, respectively, react very differently in methanol. Ketene **2** does not react with the nucleophile to form methyl esters but cyclizes quantitatively to **3**.[1] Ketene **5**, on the other hand,

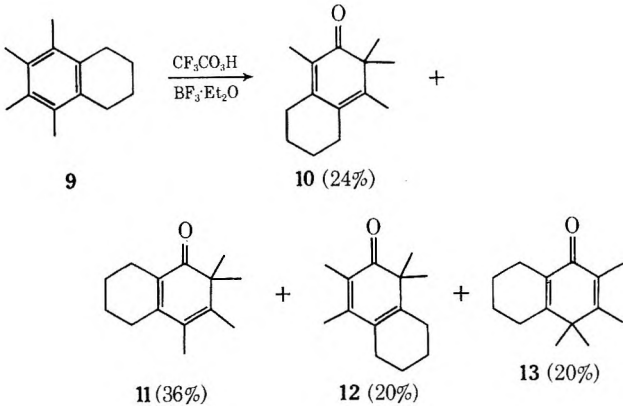


reacts with methanol to produce a mixture of esters **6** and **7**, and does not cyclize to **8**, the highly strained



analog of **3**.[2] In the present paper we explore the consequence of enlarging the four-membered ring in **5** to a six-membered ring on the behavior of the ketene toward methanol.

Oxidation of 5,6,7,8-Tetramethyltetralin.—The oxidation of highly substituted aromatic compounds with peroxytrifluoracetic acid–boron fluoride affords a useful general route to 2,4-cyclohexadienones.[3] It was anticipated that the oxidation of 5,6,7,8-tetramethyltetralin (**9**)[4] would give the desired cyclohexadienone **10**, together with other isomeric dienones. Oxidation of **9** with peroxytrifluoracetic acid–boron fluoride etherate at −10° gave an 84% yield of a mixture of isomeric dienones **10**–**13**. Unfortunately it was not



possible to obtain **10** free of contamination with **11** and **12**. However it was possible to obtain **11**, **12**, and **13** pure (by column and gas–liquid chromatography), to identify each, and to identify the photoisomerization product(s) of each. Irradiation of a mixture of **10**–**12** then permitted us to establish the photochemical behavior of **10** and to isolate its photoproduct on irradiation in methanol.

The oxidation product with the longest vpc retention time was a crystalline solid, mp 87–89°, identified as **13**. Its uv and ir spectra were characteristic of a 2,5-

(1) H. Hart, P. M. Collins, and A. J. Waring, *J. Amer. Chem. Soc.*, **88**, 1005 (1966).

(2) R. J. Bastiani and H. Hart, *J. Org. Chem.*, **37**, 2830 (1972).

(3) H. Hart, *Accounts Chem. Res.*, **4**, 337 (1971).

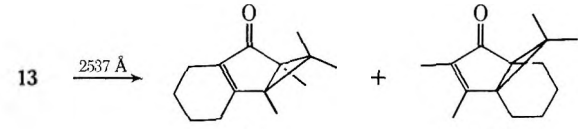
(4) B. V. Gregorovitch, C. S. Liang, D. M. Auguston, and S. F. MacDonald, *Can. J. Chem.*, **46**, 3291 (1968).

cyclohexadienone.[5] The nmr spectrum showed a *gem*-dimethyl singlet at τ 8.82, two homoallylically coupled methyl groups (τ 8.20, 8.07, J = 0.9 Hz), and two sets of four-proton multiplets at τ 7.57–7.88 and 8.25–8.55 for the methylene groups.

The remaining three dienones were fully conjugated, with λ_{max} at 329 nm characteristic of a hexaalkyl-2,4-cyclohexadienone.[5] The compound with the shortest retention time was identified as **12**. The nmr spectrum, with a singlet at τ 8.90 for the *gem*-dimethyl group, two broadened singlets at τ 8.18 and 8.03 for the allylic methyls, and two broad four-proton methylene multiplets at τ 8.12–8.53 and 7.60–7.95, was consistent with the structure but insufficient to distinguish **12** from **10** or **11**. However, when the compound was treated briefly at room temperature with CH_3OD–$NaOCH_3$, the peak for the allylic methyl at τ 8.03 disappeared. Since C-3 methyls in 2,4-cyclohexadienones exchange rapidly under these conditions whereas C-5 methyls do not,[1] the only plausible structure is **12**. Photoisomerization experiments (*vide infra*) support this assignment.

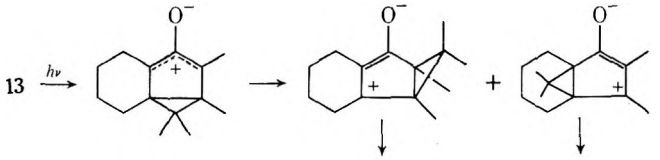
The remaining two conjugated dienones had vpc retention times which were so close that only the one with the slightly shorter retention time could be obtained pure. This turned out to have structure **11**, though its spectral properties (see Experimental Section) and the fact that it only exchanged two protons with CH_3OD–$NaOCH_3$ could not distinguish it from **10**. The structures were assigned by the following photochemical methods.

Irradiation of Dienones 11–13.—The cross-conjugated dienone **13**, on irradiation at 2537 Å in methylene chloride solution, gave complete conversion in a short time into two photoisomers, which were separated by vpc and identified as the expected[6] **14** and **15**. Both



14 15

products had ir and uv spectra characteristic of cyclopentenones. The nmr spectrum of **14** had three-proton singlets at τ 9.03, 8.90, 8.87, and 8.80, whereas the product assigned structure **15** had two sharp singlets at τ 9.07 and 8.83, and homoallylically coupled quartets at τ 8.45 and 8.10 (J = 1.0 Hz) for the allylic methyl groups. Both compounds had complex multiplets in the region τ 7.55–8.7 for the eight methylene protons. The two photoproducts presumably arise through the common intermediate **13***, which undergoes a cyclo-

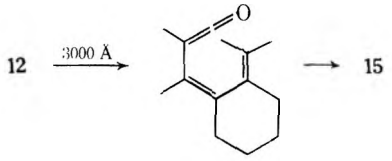


13* 14 15

propylcarbinyl rearrangement in either of the two possible directions.

(5) A. J. Waring, *Advan. Alicycl. Chem.*, **1**, 184 (1966).
(6) H. E. Zimmerman and D. I. Schuster, *J. Amer. Chem. Soc.*, **84**, 4527 (1962); H. E. Zimmerman and J. S. Swenton, *ibid.*, **89**, 906 (1967).

Consistent with the assignment based on the base-catalyzed deuterium exchange experiment (*vide supra*), dienone **12** gave, on irradiation in methylene chloride at 3000 Å, a single photoproduct identical in all respects with **15**. It presumably arises from the cyclization of ketene **16**. In an analogous fashion, irradiation of the



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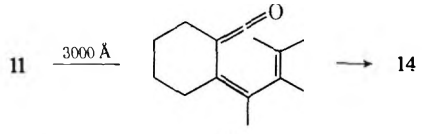
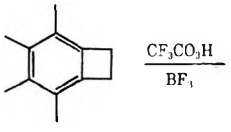
dienone with the shorter retention time (either structure **10** or **11**) gave a single photoproduct identical in all respects with **14**; it must therefore have structure **11**. By the process of elimination, the remaining conjugated dienone must be the desired **10**.

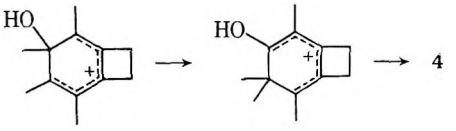


17

Comments on the Oxidation Mechanism.—Electrophilic oxidation of tetramethylbenzocyclobutene **18**

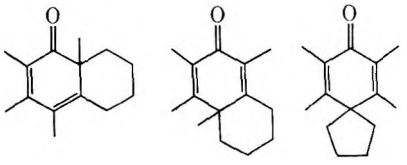


18



involves only β-type benzenonium ion intermediates, the sole monomeric product being the dienone **4**.[2] In contrast, tetramethyltetralin appears to react with the electrophile at all three positions. The products can be rationalized according to Scheme I.

Ion **9a** leads directly to **11**; apparently methyl migration occurs mainly to the adjacent methyl, rather than methylene-bearing carbon atom, since products such as **20**–**22** which could arise through the latter path

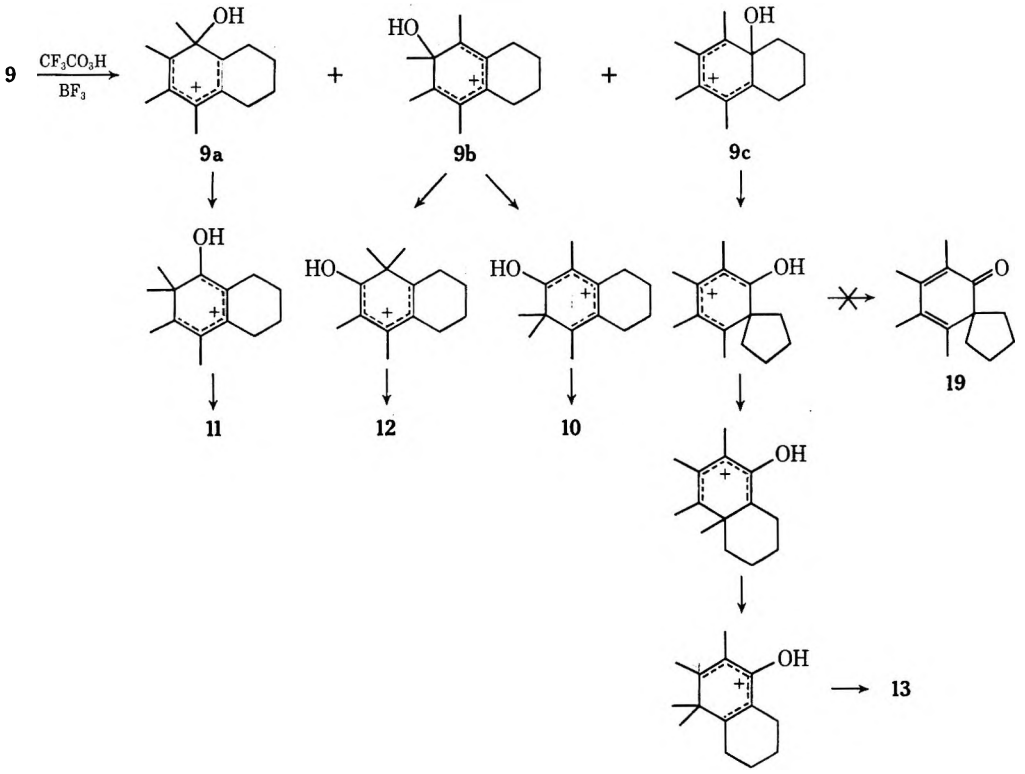


20 21 22

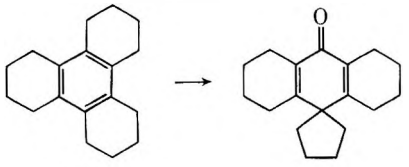
were not observed. It is possible that traces of these products escaped detection. The observed product **13** could conceivably arise from **11** through two additional methyl shifts; this route to **13** can be ruled out, since **11** was stable to the oxidizing conditions.

Ion **9b** leads to products **10** and **12** in nearly equal amounts; apparently there is no regiospecificity to the methyl migration. Product **13** is thought to arise from ion **9c**, through a sequence of three Wagner–Meerwein rearrangements. This result is exactly analogous to

SCHEME I

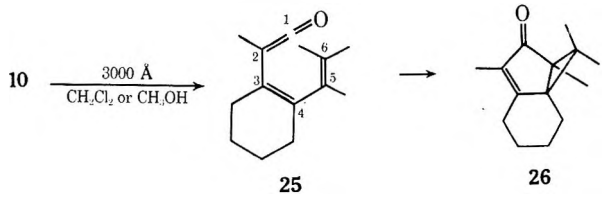


what was previously observed in the oxidation of dodecahydrotriphenylene (**23**) to **24**.[7] Spirodienones



such as **19** rearrange rapidly to 2,5-cyclohexadienones under the oxidation conditions.

Irradiation of Dienone 10.—A mixture of dienones **10**–**12** was irradiated with 3000-Å light in either methanol or methylene chloride. The same three photoproducts were observed in both solvents. Two of them were **14** and **15**, identical with the photoisomerization products of pure **11** and **12**, respectively. The third photoproduct was a colorless oil, isomeric with the starting material, to which we assign structure **26**. The ir and uv spectra were consistent with the



conjugated enone structure. The nmr methyl signals were particularly distinctive, with only one allylic methyl at τ 8.23 (br) and three sharp aliphatic singlets at τ 9.10, 9.05, and 8.92.

No esters were present in the photolysate of **10** in methanol. Thus the ketene **25** (the presumed photoproduct of **10**) reacts like **2**, not **5**, in preferring to cyclize rather than react with the nucleophile methanol. Apparently the six-membered ring in **25** does not prevent it from attaining the conformation necessary to permit overlap of the π-orbital lobes at C-4 with C-6 and C-1 with C-5 that is essential to the formation of **26**. As with **2**, the electrocyclic reaction of **25** proceeds more rapidly than attack by methanol.

Experimental Section[8]

Oxidation of 5,6,7,8-Tetramethyltetralin (9).—A solution of peroxytrifluoracetic acid was prepared from 2.28 ml (83 mmol) of 90% hydrogen peroxide and 17.7 g (83 mmol) of trifluoracetic anhydride in 24 ml of methylene chloride. The solution was maintained at 0° as it was added with stirring, over 45 min, to a solution of 10.7 g (57 mmol) of **9**[4] in 400 ml of methylene chloride which had previously been cooled to −10°. Boron fluoride etherate (25 ml of 48% $BF_3 \cdot Et_2O$) was added concurrently with the peracid. The temperature was maintained at −10° during the addition and for 2 hr of stirring thereafter. The mixture was hydrolyzed (100 ml of water), and the organic layer was washed with water (2 × 100 ml), saturated sodium bicarbonate (3 × 100 ml), 5% aqueous sodium hydroxide (3 × 100 ml), and again with water (3 × 100 ml). The dried ($MgSO_4$) organic layer was concentrated, and the residue was distilled to give a yellow oil, bp 108–114° (0.2 Torr), 9.80 g (84%). The oil was analyzed by vpc (10 ft × ¼ in., OV-25, 200°, 60 ml/min of He), which showed the presence of four major products with retention times of 20, 22.8, 24, and 28 min.

The product with a retention time of 28 min (20% of the mixture) is **3,4,5,5-tetramethylbicyclo[4.4.0]deca-1(6),3-dien-2-one (13)**: mp 87–89°; ir 1655 (s), 1625 (vs), 1600 (sh), 1475 (s), 1460 (m), 1440 (m), 1400 (s), 1380 (m), 1365 (m), 1330 (s), 1280 (s), 1220 (s), 1180 (w), 1140 (w), 1100 (m), 1000 (w), 930 (w), 890 (w) cm^{-1}; uv λ_{max} 250 nm (ϵ 12,000), 275 sh, (4500); nmr τ 8.82 (6, s, *gem*-dimethyls), 8.25–8.55 (4, m, C-8 and C-9

(7) H. Hart and D. C. Lankin, *J. Org. Chem.*, **33**, 4398 (1968).

(8) Melting points are uncorrected. Ir spectra were calibrated against polystyrene film, and tetramethylsilane was an internal reference for all nmr spectra. The ir and nmr solvent was carbon tetrachloride; the uv solvent was methanol. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

methylenes), 8.20 (3, q, J = 0.9 Hz, C-3 methyl), 8.07 (3, q, J = 0.9 Hz, C-4 methyl), 7.57–7.88 (4, m, C-7 and C-10 methylenes); m/e 204.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.08; H, 9.96.

A solution of **13** (50 mg) in 0.5 ml of 1 *M* sodium methoxide in methanol-*d*, after standing for 30 hr at room temperature, was diluted with 2 ml of carbon tetrachloride, then washed with water (3 × 5 ml). The dried organic layer ($MgSO_4$) gave, on concentration, a quantitative yield of **13**-*d*: m/e 209; nmr τ 8.82 (6, s), 8.37 (4, m), 8.20 (3, s), 7.72 (2, m).

The product with a retention time of 20 min (20% of the mixture) is **2,2,4,5-tetramethylbicyclo[4.4.0]deca-1(6),4-dien-3-one** (**12**): ir 1650 (br, vs), 1580 (s), 1470 (m), 1460 (s), 1440 (m), 1385 (s), 1360 (w), 1338 (s), 1270 (m), 1220 (m), 1060 (m), 1040 (s) cm^{-1}; uv λ_{max} 329 nm (ϵ 4600); nmr τ 8.90 (6, s, *gem*-dimethyls), 8.12–8.53 (4, m, C-8 and C-9 methylenes), 8.18 (3, br s, C-4 methyl), 8.03 (3, br s, C-5 methyl, 7.60-7.95 (4 m, C-7 and C-10 methylenes); m/e 204.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 81.78; H, 10.12.

A sample of **12** was treated at room temperature with sodium methoxide–methanol-*d* as **13** above, but exchange was complete in 1.5 hr to give **12**-d_3: m/e 207; nmr τ 8.90 (6, s), 8.37 (4, m), 8.18 (3, sharp s), 7.47–7.93 (4, m).

The product with a retention time of 22.8 min (36% of the mixture) is **3,3,4,5-tetramethylbicyclo[4.4.0]deca-1(6),4-dien-2-one** (**11**): ir 1645 (br, vs), 1580 (s), 1460 (br, s), 1400 (s), 1360 (m), 1320 (m), 1290 (m), 1280 (m), 1000 (m), 955 (m), 890 (m) cm^{-1}; uv λ_{max} 329 nm (ϵ 3000); nmr τ 8.89 (6, s, *gem*-dimethyls), 8.18 (6, s, C-4 and C-5 methyls), 8.07–8.53 (4, m, C-8 and C-9 methylenes), 7.48–7.88 (4, m, C-7 and C-10 methylenes); m/e 204.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.42; H, 9.83.

A sample of **11**, treated with sodium methoxide–methanol-*d* as **12** above, gave **11**-d_2: m/e 206; nmr τ 8.90 (6, s), 8.18 (6, s), 8.37 (4, m), 7.47–7.93 (2, m).

A sample of **11**, subjected to the procedure used to oxidize **9**, was recovered unchanged; in particular, no **13** was formed.

The product with a retention time of 24 min (*ca.* 24% of the mixture) is **2,4,4,5-tetramethylbicyclo[4.4.0]deca-1,5-dien-3-one** (**10**). This product could not be obtained pure, but was identified as a consequence of its method of synthesis and its photoisomerization to **26** (*vide infra*).

Irradiation of 13.—A solution of 100 mg of **13** in 9 ml of methylene chloride was irradiated at 2537 Å in a Rayonet reactor. The photolysis, which was monitored by vpc (5 ft × 1/4 in., SE-30, 190°, 60 ml/min He) was complete in 1.25 hr. One of the products, isolated by vpc under the above conditions, is identified as **3,4,4,5-tetramethyltricyclo[4.4.0.0^{3,5}]deca-1(6)-en-2-one** (**14**): ir 1690 (br, vs), 1640 (s), 1460 (br, s), 1430 (m), 1405–1390 (s), 1355 (w), 1310 (m), 1280 (m), 1260 (w), 1225 (m), 1190 (m), 1150 (m), 990 (m), 940 (s) cm^{-1}; uv λ_{max} 320 nm (ϵ 600), 275 (2400), 237 (7500); nmr τ 9.03, 8.90, 8.87, 8.80 (3 each, s), 7.55–8.55 (8, br m); m/e 204.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.07; H, 9.66.

The second product was thermally labile under the above vpc conditions. It was isolated by column chromatography on alumina (J. T. Baker activity 1, 80–200 mesh) and elution with hexane, then purified by vpc (2 ft × 1/4 in., 14% OV-25, 90°, 80 ml/min of He). It is assigned the structure **8,9,10,10-tetramethyltricyclo[4.3.1.0]deca-8-en-7-one** (**15**): ir 1680 (vs), 1635 (s), 1450 (s), 1385 (s), 1345 (w), 1320 (m), 1260 (m), 1190 (w), 1170 (w), 1150 (w), 1130 (w), 1100 (m), 1055 (m), 970 (m), 895 (m) cm^{-1}; uv λ_{max} 320 nm (ϵ 500), 275 (2500), 239 (4800); nmr τ 9.07, 8.83 (3 each, s, cyclopropyl methyls), 8.45 (3, q, J = 1.0 Hz, C-8 methyl), 8.10 (3, q, J = 1.0 Hz, C-9 methyl), 7.7–8.7 (8, br m); m/e 204.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.24; H, 9.89.

Irradiation of 12.—A solution of **12** (100 mg) in 9 ml of methylene chloride was irradiated at 3000 Å in a Rayonet reactor. The photolysis, which was monitored by uv, was complete in 28 hr. The sole photoproduct was **15**, identical (ir, nmr) with the same material isolated from the photolysis of **13**.

Irradiation of 11.—A solution of **11** (100 mg) in 9 ml of methylene chloride was irradiated at 3000 Å in a Rayonet reactor. The photolysis, monitored by vpc (2 ft × 1/4 in., 15% OV-25, 145°, 120 ml/min of He), was complete in 24 hr. The sole photoproduct was **14**, identical (ir, nmr) with the same material isolated from the photolysis of **13**.

Irradiation of 10.—A solution containing 300 mg of **10**, **11**, and **12** in the approximate ratio 1:1:2 in 20 ml of methylene chloride was irradiated at 3000 Å in a Rayonet reactor. The reaction, monitored by ir, was complete in 24 hr. Analysis of the photolyzate by vpc (2 ft × 1/4 in., 15% OV-25, 140°, 100 ml/min of He) showed the presence of three photoproducts. Two were identified (retention time, ir, nmr) as **14** and **15**. The third (*ca.* 25–30% of the mixture) was purified by vpc (above conditions) and identified as **2,2,3,5-tetramethyltricyclo[4.4.0.0^{1,3}]deca-5-en-4-one** (**26**): ir 1690 (s), 1625 (m), 1600 (s), 1460 (m), 1430 (m), 1380 (m), 1340 (m), 1280 (m), 1255 (s), 1200 (m), 1080 (w), 965 (m), 890 (vs) cm^{-1}; uv λ_{max} 300 nm (ϵ 1850), 231 (6250); nmr τ 9.10, 9.05, 8.92 (3 each, s, aliphatic methyls), 8.23 (3, br s, allylic methyl), 7.47–7.90 (8, br m); m/e 204.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.20; H, 9.90.

Repetition of the photolysis in methanol gave the same three products.

Registry No.—**10**, 36707-33-2; **11**, 36707-34-3; **12**, 36707-35-4; **13**, 36707-36-5; **14**, 36707-37-6; **15**, 36763-73-2; **26**, 36707-38-7.

Acknowledgment.—We express our appreciation to the National Science Foundation and the National Institutes of Health for their financial assistance.

Photorearrangement of *o*-Phenoxybenzoic Acid to Phenyl Salicylate and Related Reactions

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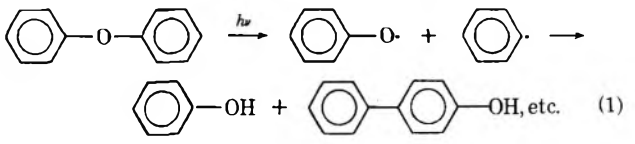
Received June 28, 1971

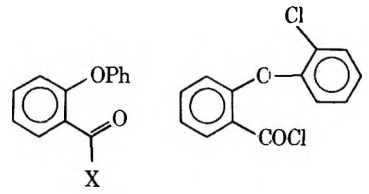
Irradiation of *o*-phenoxybenzoic acid and its derivatives with ultraviolet light yields phenyl salicylate in moderate to high yield. The reaction involves the migration of the phenyl group from the phenoxy oxygen to the acyl oxygen.

Kharasch, Stampa, and Nudenberg reported that diphenyl ether under the influence of ultraviolet light underwent cleavage and rearrangement to give phenol and hydroxybiphenyl in low efficiency and poor yields.[2] The photochemistry of diaryl ethers had been subsequently investigated in some detail, and it was suggested that the reaction proceeded *via* radical intermediates (reaction 1).[3,4] In connection with our study



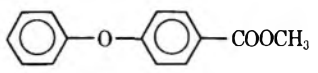
(1)

on the intramolecular photoacylation,[5] we investigated the photochemistry of *o*-phenoxybenzoic acid (**1a**, X = OH) and its derivatives. It was found that *o*-phenoxybenzoic acid undergoes a novel photorearrangement to give phenyl salicylate in excellent yield (>80%). The study was extended to the corresponding acid chloride (**1b**, X = Cl), the methyl ester (**1c**, X = OCH_3), and an *o*-chloro substituted chloride (**2**). The results obtained were compared with that obtained from the irradiation of methyl *p*-phenoxybenzoate (**3**).



1a, X = OH
b, X = Cl
c, X = OCH_3

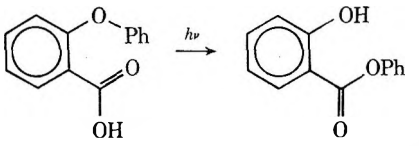
2



3

Results and Discussion

When a solution of *o*-phenoxybenzoic acid (**1a**) in benzene was irradiated through a Corex D filter (λ >280 nm), phenyl salicylate was the only product isolated (80%) together with a small amount of high molecular weight material in the acid fraction (reaction 2). However, the conversion was low (33%),



(2)

which may be attributed to the high absorbance of the product in the spectral excitation region [λ_{max} (MeOH) 308 nm (ε 4970)][6] as compared to the starting material [λ_{max} EtOH) 260 nm (ε 4500)].[7]

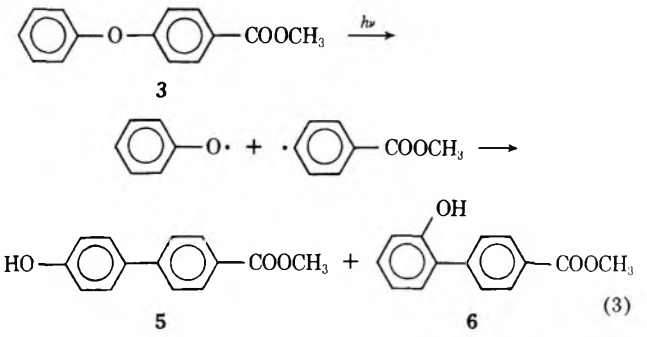
The quantum yield of this photorearrangement was determined to be 0.0014 ± 0.0002 at 313 nm with the aid of a 2-hexanone secondary actinometer.[8] Since **1a** does not exhibit appreciable emission (ϕ <0.001), there are very effective nonradiative decay processes involving the excited states of **1a**. In view of this low quantum efficiency, detailed mechanistic investigation on this process will be difficult and only qualitative measurements were made. We found that the rearrangement was retarded by *cis*-1,3-pentadiene and **1a** sensitized the geometrical isomerization of the diene, indicating that the triplet state of **1a** may participate in the photorearrangement.

Since it is well known that the esters and acyl chloride absorb at longer wavelengths than the corresponding benzoic acid,[9] the photochemistry of *o*-phenoxybenzoyl chloride (**1b**) and methyl *o*-phenoxybenzoate (**1c**) was investigated. When **1b** was prepared from **1a** and thionyl chloride, it was contaminated with small but variable amounts of xanthone and unreacted **1a**. Irradiation of the acid chloride **1b** thus prepared in benzene did lead to a higher conversion of the starting material, and phenyl salicylate was again isolated as the major product. However, the irradiation of the methyl ester **1c** yielded methyl salicylate and phenol as the major products together with a small amount of dibenzpyrone (**4**). In order to determine whether there is any solvent participation (benzene) during the irradiations or any positional rearrangement in the migrating phenyl group, the photochemistry of *o*-(*o*-chlorophenoxy)benzoyl chloride (**2**) was studied. We found that *o*-chlorophenyl salicylate was a major product, indicating that there was no solvent participation nor positional rearrangement in the migrating group during the reaction.

The photochemistry of methyl *p*-phenoxybenzoate (**3**) was then investigated in order to determine whether the photorearrangement was positional specific to the ortho-isomers. We found that the irradiation of **3** in benzene yielded methyl 4′-hydroxybiphenyl-4-carboxylate (**5**) and methyl 2′-hydroxybiphenyl-4-carboxylate

(1) National Institutes of Health Postdoctoral Fellow, 1969–1970.
(2) M. S. Kharasch, G. Stampa, and W. Nudenberg, *Science*, **116**, 309 (1952).
(3) H. J. Hageman, H. L. Louwerse, and W. J. Mijs, *Tetrahedron*, **26**, 2045 (1970).
(4) Y. Ogata, K. Takagi, and I. Ishino, *ibid.*, **26**, 2703 (1970).
(5) N. C. Yang, L. C. Lin, A. Shani, and S. S. Yang, *J. Org. Chem.*, **34**, 1845 (1969).
(6) The Sadtler Standard Ultraviolet Spectra, No. 841.
(7) O. H. Wheeler, *Can. J. Chem.*, **39**, 2603 (1961).
(8) D. R. Coulson and N. C. Yang, *J. Amer. Chem. Soc.*, **88**, 4511 (1966).
(9) The Sadtler Standard Ultraviolet Spectra, No. 252, 2, and 319.

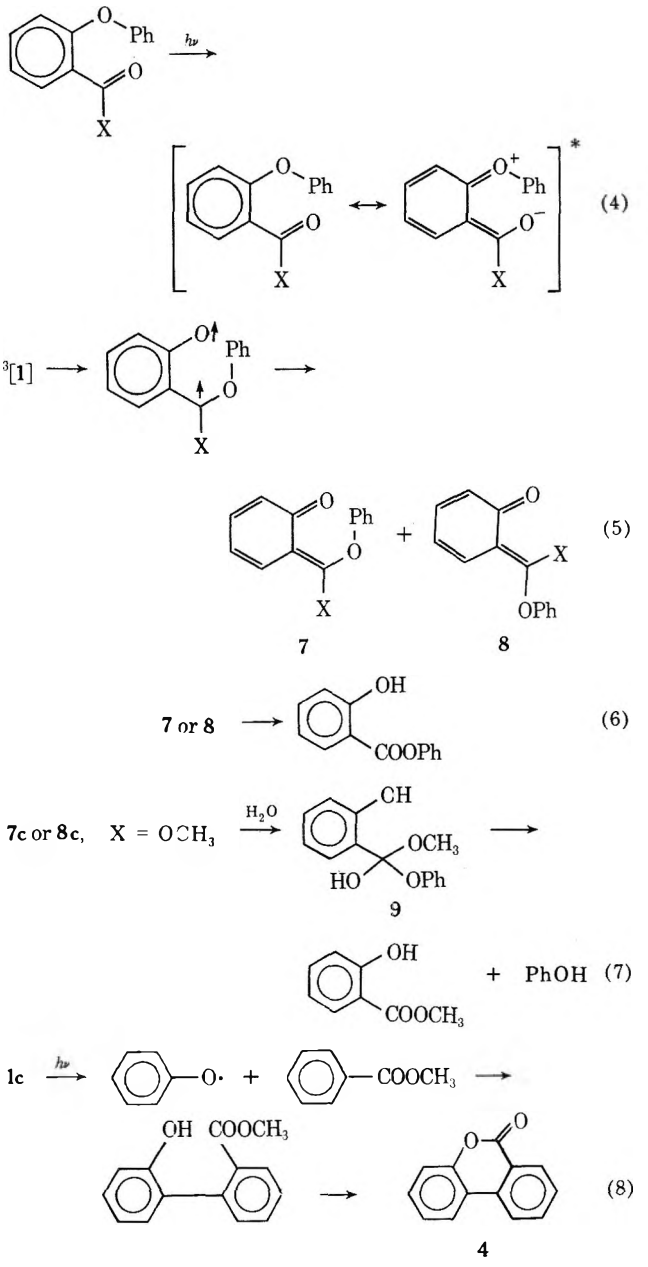
(6) among the isolated products. The photochemistry of **3** resembles that of diphenyl ether. The reaction may be rationalized to proceed *via* the cleavage of **3** to give a phenoxy radical and a substituted phenyl radical followed by the recombination of these radicals to give the products in addition to unidentified polymeric material (reaction 3). Qualitative investigation



(3)

on the effect of *cis*-1,3-pentadiene on this reaction indicated that **3** sensitized the geometrical isomerization of the diene and the diene retarded the formation of products.

The photochemistry of *o*-phenoxybenzoic acid derivatives differs from that of diphenyl ether. The derivatives rearrange or cleave in high yields to give derivatives of salicylic acid. The results imply that the *o*-acyl group may have participated in the reaction. *o*-Phenoxybenzoic acid derivatives contain an electron-donating group and an electron-withdrawing group ortho to each other. Their excited states may exhibit substantial charge transfer character which may be indicated by reaction 4.[10,11] Therefore, the migration of a phenyl group in these compounds to the acyl group is facilitated in the excited state, which may lead to an *o*-quinonemethide intermediate. If the migration takes place from the triplet state of **1**, the triplet of the *o*-quinonemethide intermediate formed may relax to either isomeric forms **7** or **8** (reaction 5). The migration of a phenyl group to an acyl oxygen had been noted previously in photochemistry,[12-14] and such a migration would not be possible in the para isomer. It is interesting to note that no xanthone was formed from **1b** under the influence of light, although its formation is rapid under the influence of heat. Since the charge transfer at excited states occurs between the functional groups, there is little delocalization into the phenoxy phenyl group and the cyclization of **1b** to xanthone is not favored at the excited state. The intermediate **7** or **8** may then be readily converted to phenyl salicylate (reaction 6). Since phenyl esters are known to be more readily hydrolyzable than methyl esters, the selective cleavage of the intermediate **9** to give methyl salicylate is expected (reaction 7).[15] The formation of dibenzpyrone (**4**) as a minor product from the irradiation of **1c** may be visualized to proceed in the manner of a conventional diaryl ether photorearrangement (reaction 1) to give methyl 2′-hydroxybiphenyl-2-carboxylate (**8**) which subsequently cyclizes to give the minor product (reaction 8).



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Although several attempts were made to trap the postulated quinonemethide intermediate (**7c** and/or **8c**) derived from methyl *o*-phenoxybenzoate (**1c**) with various olefins *in situ*, they were not successful. Olefins used included dimethyl acetylenedicarboxylate, maleic anhydride, *N*-phenylmaleimide, styrene, *cis*-1,3-pentadiene, and 1,1-diethoxyethylene. Moisture was rigorously excluded from these reactions. In the cases of maleic anhydride and *N*-phenylmaleimide, sensitized dimerization of these compounds was observed. It is probable that the quinonemethide intermediate, which contains an aryloxy and other functional groups at the methide carbon, is highly reactive toward nucleophilic agents and is rapidly consumed before they may react with olefins.

When the irradiation of *o*-phenoxybenzoyl chloride (**1b**) was carried out in the presence of an equimolar amount of *o*-phenoxybenzoic acid (**1a**), a second photoproduct, phenyl *o*-phenoxybenzoylsalicylate (**9**), was

(10) P. E. Stevenson, *J. Mol. Spectrosc.*, **15**, 220 (1965).
(11) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, New York, N. Y., 1964, p 115.
(12) H. E. Zimmermann, H. G. Dürr, R. S. Givens, and R. G. Lewis, *J. Amer. Chem. Soc.*, **89**, 1863 (1967); H. E. Zimmermann, H. G. Dürr, R. G. Lewis, and S. Bram, *ibid.*, **84**, 4149 (1962).
(13) G. W. Griffin and E. J. O'Connell, *ibid.*, **84**, 4148 (1962).
(14) H. Schmid, M. Hochweber, and H. von Halben, *Helv. Chim. Acta*, **30**, 1135 (1947).
(15) J. F. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, **86**, 837 (1964).

formed in addition to phenyl salicylate. A similar product was formed from the *o*-(*o*-chlorophenoxy)-benzoyl chloride and *o*-chlorophenoxybenzoic acid. Although **10** may be prepared by the acylation of phenyl salicylate and *o*-phenoxybenzoyl chloride in the presence of pyridine, no acylation takes place in the absence of light or pyridine. Nor is the product formed from phenyl salicylate and **1a** under the influence of light. Therefore, the product must be formed from some reactive intermediate generated from **1a** and **1b** in the presence of light.

Finally, irradiation of *o*-anisyl chloride yields no detectable change in this compound, indicating that the alkyl group does not rearrange under similar conditions.

Experimental Section

General Procedure.—The light source used was a Hanovia 450-W medium pressure mercury arc. Irradiations were carried out in an apparatus consisting of a quartz water-cooled Hanovia 5-l. flask immersion well and a Pyrex outer jacket fitted with a fritted nitrogen inlet at the bottom and septum covered inlet in the midsection for withdrawing aliquots during irradiation. Different jackets varying in capacity from 100 to 250 ml were used. The solution level was always kept above the top of the mercury arc to prevent pyrolysis. The solution was deaerated with nitrogen for 0.5 hr prior to and during the irradiation. Melting points and boiling points were uncorrected. Mass spectra were recorded with an AEI MS-9 high-resolution mass spectrometer, uv spectra with a Cary 14 spectrometer, and ir spectra with a Perkin-Elmer Infracord or a Beckman IR-7 spectrometer. Nmr spectra were obtained on a Varian A-60 or A-60A spectrometer in CCl_4 or $CDCl_3$ with TMS as an internal standard. Microanalyses were carried out by Micro-Tech, Inc., Skokie, Ill., or by Dr. A. Bernhardt, Mulheim, Germany.

***o*-Phenoxybenzoic Acid (1a).**—*o*-Phenoxybenzoic acid was prepared by a modification of the Ullmann method.[16] To a methanolic solution of sodium phenoxide, prepared by dissolving phenol (48 g) in a solution of sodium methanolate–methanol (3.6 g of sodium in 78 ml of methanol) which was concentrated under diminished pressure to a paste, the potassium salt of *o*-chlorobenzoic acid (20 g) and copper powder (0.6 g) were mixed thoroughly by shaking. The mixture was then heated on an oil bath at 180–190° for 10 min. After cooling, the reaction mixture was diluted with water (50 ml) and neutralized with 10% hydrochloric acid and then extracted with ether (50 ml × 4). The combined ethereal extract was then washed with 5% aqueous sodium bicarbonate solution (50 ml × 4). Upon acidification of the bicarbonate extract the crude acid was obtained (91% yield) and recrystallized twice (aqueous MeOH) to give 18 g of the pure acid (73%, mp 113°): ir (KBr) 3075–2880, 1685, 1240, and 1070 cm^{-1}; nmr (Me_2CO) δ 6.95–7.85 (m, 8, general aromatic H's), 8.09 (2 d, 1, J = 7.5 and 2.0 Hz, aromatic H ortho to COOH), 9.45 ppm (s, 1, COOH).

Irradiation of 1a.—A solution of *o*-phenoxybenzoic acid (1.50 g) in benzene (80 ml) was irradiated with the Hanovia 450-W arc with a Corex D filter for 16 hr. The reaction was monitored by tlc every 4 hr. The formation of phenyl salicylate was essentially constant after 12 hr. The solution was extracted with 2 × 50 ml of 5% aqueous $NaHCO_3$, washed with water, and dried. After the removal of benzene under reduced pressure a yellow oil (500 mg) was obtained which solidified upon standing and exhibited an ir spectrum virtually identical with that of phenyl salicylate.[17] Tlc analysis indicated that the compound was about 95% pure. The crude product was subjected to a short-path distillation to give phenyl salicylate (450 mg, mp 40–42°) identical in all respects with an authentic sample. Crude *o*-phenoxybenzoic acid (1.0 g) was recovered from the bicarbonate extract after acidification. The crude acid was purified by filtering a CH_2Cl_2–$CHCl_3$ solution through silica gel (40 g). From the effluent 935 mg of the acid was obtained, mp 109–111°. The yield of phenyl salicylate based on the acid reacted was over 80%.

(16) F. Ullmann and M. Zlokasoff, *Ber.*, **38**, 2112 (1905).

(17) Sadtler Standard Infrared Spectra, No. 2931.

Irradiation of o-Phenoxybenzoyl Chloride (1b).—*o*-Phenoxybenzoyl chloride was prepared by a modification of the known method.[18] *o*-Phenoxybenzoic acid (1.08 g) was treated with freshly distilled thionyl chloride (3.0 g) and heated at 58–60° for 10 min on a water bath. The excess thionyl chloride was removed under reduced pressure at 40–50°. The reaction mixture was diluted with benzene (1 ml), warmed at 50° for 2 min, and concentrated under reduced pressure at 50° to constant weight. The same process was repeated three times to remove any thionyl chloride left in the reaction mixture. The acid chloride thus prepared was dissolved in freshly distilled benzene (85 ml), and the solution was flushed with pure nitrogen for 30 min prior to the irradiation. The purity of the acid chloride was estimated by tlc of the corresponding ethyl ester. An aliquot of the acid chloride solution in benzene (1 ml) was taken and added to absolute alcohol (0.5 ml). The reaction mixture was heated at 60° for 10 min, spotted on a Kodak fluorescent silica gel strip, and developed with benzene. In comparison to authentic samples of ethyl *o*-phenoxybenzoate, xanthone, and *o*-phenoxybenzoic acid (the R_f values were 0.40, 0.23, and 0.04, respectively), the acid chloride was shown to be about 90% pure, contaminated with 5% of xanthone and 3% of the unreacted *o*-phenoxybenzoic acid.[19]

The benzene solution of the acid chloride was then irradiated with a 450-W medium-pressure mercury lamp with a Pyrex filter. Aliquots of the irradiated solution were taken from time to time, treated with absolute ethanol, and checked with tlc for new spots with a uv lamp. At the second hour, a new spot having a R_f value of 0.53 appeared. The intensity of the new spot increased while that of the ethyl *o*-phenoxybenzoate spot decreased on further irradiation. The intensity of xanthone remained essentially unchanged during the whole process of irradiation. The irradiation was stopped after 17 hr, because at this stage the intensity of the new spot was the most predominant one and the original ethyl ester spot had almost completely disappeared.

The irradiated solution was concentrated under reduced pressure at 40°, and treated with water (0.5 g) at 40–50° for 5 hr. Benzene was added to the mixture, which was then dried over sodium sulfate. The dried mixture was concentrated under reduced pressure to yield a liquid (0.95 g). A portion of *o*-phenoxybenzoic acid (160 mg) was recovered by sodium bicarbonate extraction. The liquid was chromatographed on a silica gel column (7 g) eluting first with carbon tetrachloride and then with benzene. Molecular distillation of the material isolated from the CCl_4 eluate gave phenyl salicylate (0.45 g, 57% based on acid chloride reacted), mp 40–42°, identical in all respects with an authentic sample. Xanthone (0.10 g) was isolated in 12% yield.

Methyl *o*-Phenoxybenzoate (1c).—Methyl *o*-phenoxybenzoate was prepared according to the method of Tomita and Ikawa:[20] bp 91–93° (0.04 mm); λ_{max} (EtOH) 286 nm (ε 3900) and 272 (shoulder, 2970); ir (neat) 1720 (C=O), 1240, and 1080 cm^{-1} (ArO); nmr (CCl_4) δ 3.68 (s, 3, CH_3), 6.80–7.60 (m, 8, ArH) and 7.81 ppm (2 d, 1, J = 7.5 and 2.0 Hz, ArH ortho to COOMe).

Irradiation of 1c.—A 2.307-g sample of the ester was dissolved in 250 ml of benzene, and the solution was irradiated through a Corex D insert for 18 hr. After the irradiation the solvent was removed under reduced pressure and the residue was divided into two equal fractions. One fraction was separated by preparative layer chromatography (plc) using a 20 × 100 cm plate of silica gel of *ca.* 2-mm thickness. The plate was developed five times using benzene–petroleum ether (bp 30–60°) (1:1) as the eluent. Five major zones were observed and they are listed in the order of increasing polarity. Zone 1 was identified as methyl salicylate by comparison with an authentic sample, 142 mg (59% based on reacted **1c**); zone 2 was identified as unreacted **1c**, 0.746 g (65%); zone 3 was identified as phenol, its yield could not be estimated owing to its volatility; zone 4 was identified as dibenzopyrone by comparison with an authentic sample,[21] mp 92–93°, 57 mg (15%); zone 5 was polymeric material, 160 mg.

(18) G. Lock and F. H. Kempter, *Monatsh.*, **67**, 25 (1936).

(19) The method of analysis cannot differentiate the possibilities between a mixture of acid chloride and free acid and a mixture of acid chloride and acid anhydride; the acid chloride may be about 89% pure, contaminated with 5% of xanthone and 6% of the anhydride.

(20) M. Tomita and K. Ikawa, *J. Pharm. Soc. Jap.*, **74**, 1060 (1954).

(21) N. C. Yang, A. Shani, and G. R. Lenz, *J. Amer. Chem. Soc.*, **88**, 5369 (1966).

The yield of phenol was estimated by vpc using a SF-96 column at 220° to be 89 mg (56%).

Irradiation of Methyl p-Phenoxybenzoate (3).—Methyl *p*-phenoxybenzoate (2.158 g, mp 58–60°)[22] was dissolved in 250 ml of benzene and the solution was irradiated through a Corex D filter for 20 hr. After the irradiation the solution was evaporated and triturated with ether. An amorphous tan solid (172 mg) was removed by filtration and was found to be a polymeric material and was not further characterized. The filtrate was evaporated and the residue was separated by plc using two 20 × 100 cm plates of silica gel of *ca.* 2-mm thickness. The plates were developed five times using CH_2Cl_2–benzene (2:1) as the eluent. Three minor components (<50 mg) were not characterized further. Four major fractions were isolated and they are listed according to the order of increasing polarity. Fraction 1 was identified as the starting material, 1.248 g. Fraction 2 was identified as methyl 2′-hydroxy-4-biphenylcarboxylate: 193 mg; mp 127–129° which was raised to 129–131° after one recrystallization from cyclohexane (lit.[23] mp 133–133.5°); λ_{max} 270 nm (log ϵ 4.17) and 302 (4.04); nmr ($CDCl_3$) δ 3.93 (s, 3, CH_3), 5.70 (s, broad, 1, OH), 6.80–7.45 (m, 4, ArH), and 7.85 ppm (A_2B_2 q, 4, ArH, J = 31 and 8.5 Hz); mass spectrum parent peak at *m/e* 228. Fraction 3 was identified as methyl 4′-hydroxy-4-biphenylcarboxylate: 143 mg; mp 221–223° which was raised to 224–225° after one recrystallization from benzene (lit.[24] mp 224–225°); λ_{max} 298 nm (log ϵ 4.35); nmr ($CDCl_3$–CF_3COOH) δ 4.02 (s, 3, CH_3), 7.15 (A_2B_2 q, 4, ArH, J = 25 and 9 Hz), and 7.88 ppm (A_2B_2 q, 4, ArH, J = 29 and 8 Hz); mass spectrum parent peak at *m/e* 228. Fraction 4 appeared to be the same polymeric material removed by ether trituration, 165 mg.

o-(o′-Chlorophenoxy)benzoic Acid.—*o*-(*o*′-Chlorophenoxy)benzoic acid was prepared by a modification of the Goldberg method.[25] In a 500-ml round-bottomed flask equipped with a mechanical stirrer, a mixture of *o*-chlorobenzoic acid (31.3 g), *o*-chlorophenol (28 g), K_2CO_3 (35 g), and cuprous chloride (0.2 g) was stirred with nitrobenzene (200 ml) at 160–165° for 13 hr. Having been cooled to 5°, the reaction mixture was filtered to collect the solid. The filtrate was washed with water (5 × 30 ml) and the nitrobenzene layer was discarded. The combined aqueous solution was used to dissolve the collected solid. After the removal of insoluble impurities by filtration, the filtrate was neutralized gradually with 10% HCl. At the beginning, a tar was precipitated. As the acidification continued, the precipitate deposited gradually changed from dark brown to light brown in color. At pH 5, the solution was filtered to remove the mixture of tar and precipitate. Upon further acidification of the filtrate, a white solid was collected. The solid was purified by dissolving it in 5% $NaHCO_3$ (250 ml) and washed with ether (3 × 100 ml). After aeration, the aqueous solution was neutralized with 10% HCl. The crude acid (15 g, 30%, mp 100–110°) was collected and recrystallized three times from 79% ethanol to yield 3.5 g of the product: mp 124–125°; ir (KBr) 3075–2850, 1685, 1240, and 1060 cm^{-1}; nmr (acetone) δ 6.86–7.81 (m, 7, ArH), 8.10 (2, d, 1, ArH ortho to COOH, J = 7.5 and 2 Hz), and 8.93 ppm (s, 1, COOH).

Irradiation of o-(o′-Chlorophenoxy)benzoyl Chloride.—*o*-(*o*′-Chlorophenoxy)benzoyl chloride was prepared from the acid (1.70 g) with thionyl chloride in the same way as described in the preparation of **1b**. The acid chloride prepared was analyzed by tlc to show that it contained 67% of the chloride, 31% of the acid, and only a trace of the xanthone (less than 1%).

The acid chloride thus prepared was dissolved in benzene (85 ml) and irradiated. The irradiation was continued for 20 hr, and the reaction was monitored by tlc. The mixture was worked up as in the case of *o*-phenoxybenzoyl chloride to yield a liquid crude product (1.50 g). The crude product was chromatographed on a silica gel column (20 g).

A new product was isolated from the carbon tetrachloride eluate: mp 46.5–48.5° (ethanol); R_f (silica gel–benzene) 0.53; ir (film) 3190 and 1685 cm^{-1}; nmr (CCl_4) δ 6.65–7.75 (m, 7, ArH), 8.11 (2 d, 1, J = 7.5 and 2.0 Hz, ArH ortho to COOPh), 10.32 ppm (s, 1, intramolecular H-bonded ArOH); identical with an authentic sample of *o*-chlorophenyl salicylate.[26]

The second photoproduct (0.69 g), R_f (silica gel–benzene) 0.43, was contaminated with a small amount of the xanthone. Attempted molecular distillation resulted in the sublimation of the xanthone at 140° (0.05 mm). The residue was purified through another silica gel column and a very viscous mass was thus obtained. It exhibited ir (film) 1750 cm^{-1}; nmr (CCl_4) 6.7–7.8 (m, 14, ArH), 8.16 (2 d, 1, J = 7.5 and 2.0 Hz), and 8.26 ppm (2 d, 1, J = 7.5 and 2.0 Hz). The spectroscopic properties of this product suggested that it might be *o*-chlorophenyl [*o*-(*o*′-chlorophenoxy)benzoyl]salicylate. An authentic sample was prepared in the following manner. *o*-Chlorophenoxybenzoic acid (190 mg) was treated with freshly distilled thionyl chloride at 60° for 10–20 min. The excess thionyl chloride was removed under reduced pressure at 50°. The acid chloride thus prepared was treated with *o*-chlorophenyl salicylate (190 mg) and a drop of pyridine. The mixture was heated at 60° for 10 min, cooled to room temperature, and filtered. The filtrate was evaporated and chromatographed over a column of silica gel (5 g). A small amount of *o*-chlorophenyl salicylate was recovered from the CCl_4 effluent and the desired diester (140 mg) was obtained from the benzene effluent, identical in all respects with the photoproduct.

Anal. Calcd for $C_{26}H_{16}O_5Cl_2$: C, 65.16; H, 3.36; Cl, 14.80. Found: C, 65.77; H, 3.66; Cl, 14.85.

Unreacted *o*-chlorophenoxybenzoic acid (0.5 g) was also recovered from the chromatography of the irradiation mixture from the ethyl acetate eluate.

Irradiation of a Mixture of 1a and 1b.—*o*-Phenoxybenzoyl chloride (0.46 g) was prepared from the acid (0.45 g) as before which was analyzed by tlc to be about 85% pure and contaminated with xanthone (15%). *o*-Phenoxybenzoic acid (0.46 g) was added to the acid chloride and the mixture was dissolved in 85 ml of benzene and irradiated for 7 hr. After the usual work-up, the mixture (0.85 g) was chromatographed over silica gel (10 g). Phenyl salicylate (240 mg) and xanthone (80 mg) were isolated from the CCl_4 effluent. By further elution of the column with benzene, a second photoproduct (250 mg) was isolated. The product was subjected to molecular distillation to give a viscous mass: ir (film) 1745 cm^{-1}; nmr (acetone) δ 6.85–7.90 (m, 16, ArH) and 8.29 ppm (2 d, 2, J = 7.5 and 2.0 Hz, ArH ortho to C=O); mass spectrum parent ion *m/e* 410.

Anal. Calcd for $C_{26}H_{18}O_5$: C, 76.08; H, 4.42. Found: C, 75.79; H, 4.42.

Attempted synthesis of the diester from *o*-phenoxybenzoic acid (0.38 g), thionyl chloride (1.30 g), and phenyl salicylate (0.38 g) using the method described for the *o*-chloro derivative resulted in the formation of the diester in about 20% yield. The mixture exhibited four spots on silica gel tlc developed with benzene. R_f values were 0.53, 0.36, 0.23, and 0.04, corresponding to phenyl salicylate, the diester, xanthone, and *o*-phenoxybenzoic acid. The same four spots were detected from the irradiation mixture. Authentic phenyl *o*-(*o*-phenoxybenzoyl)-salicylate was isolated by silica gel chromatography and was identical in all respects with the photoproduct.

Irradiation of a Mixture of 1a and Phenyl Salicylate.—*o*-Phenoxybenzoic acid (106 mg, 0.5 mmol) and phenyl salicylate (106 mg, 0.5 mmol) and phenyl salicylate (106 mg, 0.5 mmol) were dissolved in benzene (80 ml) and irradiated for 3 hr. The reaction was monitored by tlc, and no new product was detected.

Irradiation of o-Anisyl Chloride.—*o*-Anisyl chloride was prepared from *o*-anisic acid by the method of Billon.[27] A solution of the chloride (1.54 g) in benzene (85 ml) was irradiated through a Corex D filter for 21 hr, and no visible change was detected spectroscopically.

Quantum Yield Determination and Other Mechanistic Studies.—The quantum yield of formation of phenyl salicylate during irradiation of *o*-phenoxybenzoic acid (0.010 *M* in benzene) at 313 nm was determined with the aid of the 2-hexanone secondary actinometer and an apparatus previously described.[8] The formation of phenyl salicylate was followed by vpc using a 5 × 0.25 in. column packed with 20% SF-96 on firebrick at 200°. The rate of formation was linear with the time and the quantum yield was found to be 0.0014 ± 0.002.

The possibility of formation of a photoadduct between methyl *o*-phenoxybenzoate with olefins was investigated. The olefinic systems used included dimethyl acetylenedicarboxylate in benzene up to 3 *M*, maleic anhydride in dioxane, *N*-phenylmaleimide

(22) R. West, S. Ornstein, D. McKee, and R. Layzer, *J. Amer. Chem. Soc.*, **74**, 3960 (1952).
(23) M. Oki and H. Iwamura, *Bull. Chem. Soc. Jap.*, **34**, 1395 (1961).
(24) L. F. Fieser and C. K. Bradsher, *J. Amer. Chem. Soc.*, **58**, 1738 (1936).
(25) A. A. Goldberg and A. H. Wrapp, *J. Chem. Soc.*, 4234 (1958).
(26) N. G. Gaylord and P. M. Kamath, *Org. Syn.*, **32**, 25 (1952).
(27) P. Billon, *Justus Liebigs Ann. Chem.*, **7**, 314 (1927).

in ether, *cis*-1,3-pentadiene in benzene, styrene in benzene, and 1,1-diethoxyethylene in ether. No adduct was detected in all these systems.

The quenchings of photorearrangements of *o*-phenoxybenzoic acid (**1a**) and methyl *p*-phenoxybenzoate (**13**) in benzene by *cis*-1,3-pentadiene were also investigated. Because of their low quantum efficiencies, only qualitative investigations were carried out. Parallel irradiations through a Corex D filter were performed with solutions containing 0.015 *M* of the substrate in benzene with or without 0.5 *M* of the diene. In the case of **1a**, we found that the formation of phenyl salicylate was reduced approximately 43% and about 20% of the diene had been isomerized to the trans isomer as indicated by vpc analysis. In the case of **3**, we found that the formation of products was reduced by approximately 85% but the consumption of the substrate was increased by about threefold as indicated by both tlc and vpc analyses. In the meantime, about 15% of the diene had isomerized.

Registry No.—**1a**, 2243-42-7; phenyl salicylate, 118-55-8; *o*-(*o'*-chlorophenoxy)benzoic acid, 36809-08-2; *o*-chlorophenyl [*o*-(*o'*-chlorophenoxy)benzoyl]salicylate, 36809-09-3; phenyl *o*-phenoxybenzoylsalicylate, 36809-10-6.

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Photochemical Reductions of Unsymmetrical Benzils[1]

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Eight 4-substituted benzils have been subjected to photoreduction by 2-propanol, where one of two carbonyl groups is selectively reduced; *i.e.*, on irradiation, the corresponding benzoins and/or benzilpinacols together with 4-substituted benzoic acid derivatives were obtained. The benzoyl group substituted by a more electron-withdrawing group is preferentially reduced in the order 4-CN > 4-Cl > H > 4-Me > 4-MeO ~ 4-NMe_2. The configuration of unsymmetrical benzils in the lowest excited triplet state was also discussed by comparing their absorption and emission spectra with their photochemical reactivities.

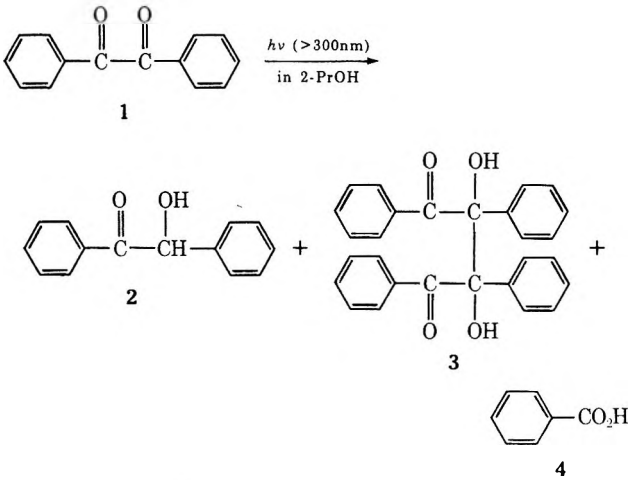
The photochemical reduction of α-dicarbonyl compounds has been an intriguing subject to a number of photochemists.[2] Some knowledge of the excited state is required to understand the photoreduction of α diketones. Reactivity might be influenced by their excited state geometries, which have been suggested to be coplanar based on absorption and emission spectra.[3] Although biacetyl is photoreduced to acetylpinacol,[4] aliphatic α diketones capable of intramolecular hydrogen abstraction through a six-membered transition state are transformed to 2-hydroxybutanones on irradiation.[5] An unsymmetrical α diketone, bornanedione, in which the carbonyl groups are essentially held in the s-cis configuration, equally yields two isomeric reduction products through a common transition state.[6]

An aromatic α diketone, benzil, is known to be twisted *ca.* 90° around its central bond at the ground state; the conjugation between two carbonyls is reduced by cross conjugation between a CO group and a phenyl group attached to the CO.[7] However, the phenyl–carbon interaction is again decreased with increasing steric hindrance at the ortho carbon of benzil. As reported by Bunbury,[8] the photoreduction of benzil by 2-propanol gives benzoin and benzilpinacol together with a small amount of decomposition products, *i.e.*, benzoic acid and benzaldehyde. Maruyama, *et al.*,[9] reported in their study on the photolyses of polymethylbenzils that ortho-substituted benzils are very photounreactive and afford low quantum yield for intersystem crossing.

The authors wish to report the photoreduction of unsymmetrical 4-substituted benzils and to correlate excited $n\pi^*$ triplet-state geometries with reductive behaviors and emission and absorption spectra.

Results and Discussion

Irradiation of benzil (**1**) in 2-propanol (~10^{-2} *M*) through a Pyrex filter under nitrogen for 12 hr results in the disappearance of benzil and the formation of a precipitate of benzilpinacol (**3**, 22.5%). The product was identified by melting point, molecular weight (420), and ir spectrum (COH). The mother liquior gave benzoin (**2**, 13.5%) and benzoic acid (**4**, 9.4%).



1 2 3 4

(1) Contribution No. 186.

(2) For a comprehensive review, see B. M. Monroe, "Advances in Photochemistry," Vol. 8, Interscience, New York, N. Y., 1971, p 77, and references cited therein.

(3) (a) T. R. Evans and P. A. Leermakers, *J. Amer. Chem. Soc.*, **89**, 4380 (1967); (b) W. G. Herkstroeter, J. Saltiel, and G. S. Hammond, *ibid.*, **85**, 482 (1963).

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(5) W. H. Urry, D. J. Trecker, and D. A. Winey, *Tetrahedron Lett.*, 609 (1962).

(6) B. M. Monroe, S. A. Weiner, and G. S. Hammond, *J. Amer. Chem. Soc.*, **90**, 1913 (1968).

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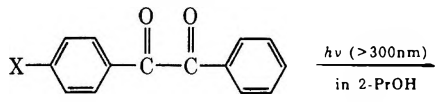
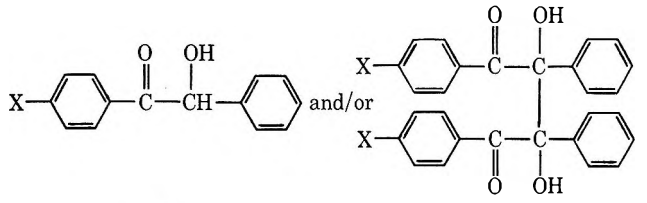
(8) D. L. Bunbury and C. T. Wang, *Can. J. Chem.*, **46**, 1473 (1968).

(9) K. Maruyama, K. Ono, and J. Osugi, *Bull. Chem. Soc. Jap.*, **45**, 847 (1972).

Photoreduction of Benzils with an Electron-Releasing Group.—Benzils with a para electron-releasing group (**5**) yield in 2-propanol on irradiation 4-substituted benzoins (**6**) and/or 4-substituted benzilpinacols (**7**) which are formed by the selective reduction at unsubstituted benzoyl.



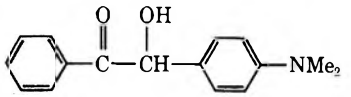
5a–c



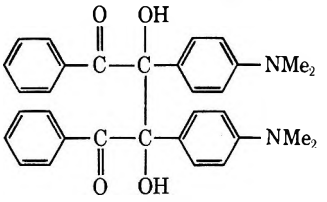
6a–c **7a–c**

a, X = NMe_2
b, X = OMe
c, X = Me

4-Dimethylaminobenzil (5a).—Diketone **5a** was photoreduced in 2-propanol until the carbonyl group disappeared. The condensed reaction mixture was separated into three components; one was 4-dimethylaminobenzoin (**6a**, 11.7%). Although the structures of the other two products are still unknown, they are not benzoin and/or benzilpinacol, which was reduced at the dimethylaminobenzoyl group in comparison with the authentic samples of **6′a** and **7′a**, respectively.

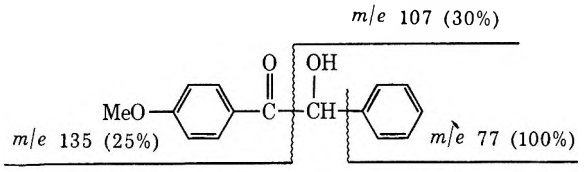


6′a



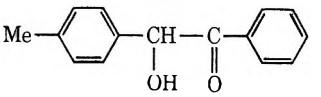
7′a

4-Methoxybenzil (5b).—Irradiation of a 2-propanol solution of **5b** for 12 hr yields 4-methoxybenzoin (**6b**, 5.5%). The ir spectrum of the product shows carbonyl stretching vibration at 1650 cm^{-1}, whereas the starting benzil exhibits two carbonyl stretching vibrations at 1670 and 1650 cm^{-1}, corresponding to benzoyl and anisoyl carbonyl stretching vibrations, respectively. Moreover, fragment ion peaks are observed at *m/e* 242 as M^+ and mainly at *m/e* 107 and 135, which are expected from the structure **6b**.



6b

4-Methylbenzil (5c).—Photoreduction of **5c** affords two products; one was 4-methylbenzoin (**6c**, 8.8%) based on its ir and uv spectra (λ_{max} 256 nm), but not **6′c** (λ_{max} 245 nm). In the mass spectral fragmenta-

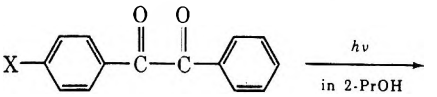


6′c

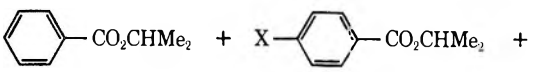
tion, the relative peak intensity of benzoyl ion to benzhydryl ions caused by the central C–C bond scission of **6c** was P_{105}/P_{107} = 2.8 in contrast to that in **6′c** of P_{119}/P_{121} = 4.

Another reduction product was **7c** (34.8%), which was confirmed by cryoscopic molecular weight, a mass spectrum similar to that of **6c**, and characteristic ir spectrum.

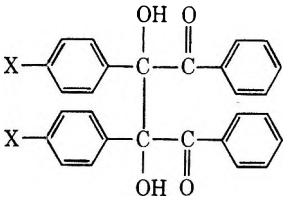
Photoreduction of Benzils with an Electron-Withdrawing Group. 4-Chlorobenzil (8a).—Diketone **8a** was almost completely photodecomposed within 6 hr. The separation of product by silica gel column gave a reduction dimer (**11a**, 51.6%) together with a little



8a, b



9a, b **10a, b**



11a, b

a, X = Cl
b, X = CN

starting material (16%), a mixture of isopropyl benzoate and 4-chlorobenzoate (**9a** + **10a**, 4.9%), and a trace of unidentified viscous oil.

Fission products **9a** and **10a** were identified by ir and nmr spectra. The structure of **11a** was determined by elemental analysis and ir and nmr spectra. Carbonyl stretching vibration of the product (**11a**) at 1670 cm^{-1} corresponds to that at 1660 cm^{-1} in the benzoyl carbonyl of **8a**, but absorption at 1650 cm^{-1} for *p*-chlorobenzoyl carbonyl disappears in **11a**. A molecular ion peak for **11a** could be detected but a trace of half value for the molecular ion peak at *m/e* 245 was observed in the mass spectrum of **11a**. Furthermore, a large difference between the relative intensity of $P_{105}(C_6H_5CO^+)/P_{106}(C_6H_5COH^+)$ = 11 and that of $P_{139+140}$(Cl-

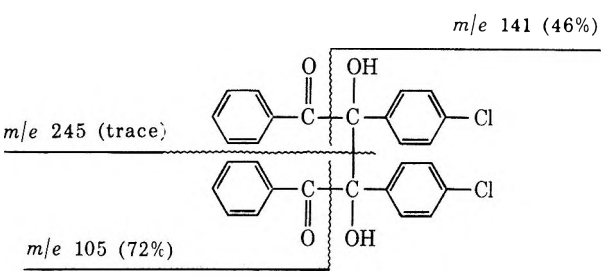


TABLE I

YIELDS FOR THE PHOTOREDUCTION OF BENZILS IN 2-PROPANOL[a]

X in 4-X-$C_6H_4C(=O)C(=O)C_6H_5$ Registry no.	X	Irradn time, hr	X and Y in 4-X-$C_6H_4C(=O)CH(OH)C_6H_4Y$-4′ Registry no.	X	Y	Yield, %	X and Y in [4-X-$C_6H_4C(=O)C(OH)C_6H_4Y$-4′]$_2$ Registry no.	X	Y	Yield, %	4-X-$C_6H_4CO_2R'$ R′ (H or 2-Pr)	Yield, %
22711-20-2	NMe_2	32	6317-85-7	NMe_2	H	11.7					...[b]	
22711-21-3	OMe	12	4254-17-5	OMe	H	5.5					...[b]	
2431-00-7	Me	28	2431-23-4	Me	H	8.8	36803-60-8	Me	H	34.8	...[b]	
134-81-6	H	12	119-53-9	H	H	13.5	36803-61-9	H	H	22.5	H	9.4
36803-53-9	Ph	98									2-Pr	*c*
22711-23-5	Cl	6					36803-62-0	H	Cl	51.6	2-Pr	4.9[c]
22711-24-6	NO_2	28										
36803-56-2	CN	4					36803-63-1	H	CN	57.0	2-Pr	4.8[c]

[a] Isolated yield was based on starting benzil used. [b] Yield was not determined. [c] A mixture of substituted and unsubstituted benzoates.

$C_6H_4CO^+)/P_{140+141}(ClC_6H_4COH^+)$ = 1.8 seems to justify the structure **11a**. Thus, the reduction occurs at the carbonyl attached to 4-chlorophenyl, giving solely dimer **11a** alone among two possible isomers.

4-Cyanobenzil (8b).—The product from irradiated **8b** in 2-propanol is a reduction dimer, 4′-cyanobenzilpinacol (**11b**, 57.0%), together with fission products, *i.e.*, a mixture of isopropyl benzoate and 4-cyanobenzoate (**9b** + **10b**, 4.8%). The dimer (mp 170–171°) was 4′-cyanobenzilpinacol (**11b**) on the basis of elemental analysis and nmr and ir spectra in which the product has one carbonyl absorption of unsubstituted benzoyl at 1680 cm^{-1} although **8b** has two carbonyl stretching vibrations at 1680 cm^{-1} for benzoyl carbonyl and 1650 cm^{-1} for 4-cyanobenzoyl. A trace of half value for the molecular ion peak was detected in the mass spectrum of **11b**, and a remarkable difference between the relative intensity of $P_{105}(PhCO^+)/P_{106}(PhCOH^+)$ = 8 and that of $P_{135}(CNC_6H_4CO^+)/[P_{131}(CNC_6H_4COH^+) + P_{104}(P_{131} - CN)]$ = 1.2 supports the structure **11b**.

4-Phenylbenzil (12).—Irradiation of **12** in 2-propanol for 98 hr afforded a solid product (mp over 300°), as well as isopropyl 4-phenylbenzoate. The former product has not yet been identified, although it has a hydroxyl group in view of its ir spectra.

The results are summarized in Table I.

Quantum Yields.—Table II lists the quantum yields for the disappearance of starting benzils. It can be seen from Tables I and II that the yield of photoproduct increases with an increase in electron-withdrawing ability of the substituent, and that the carbonyl reduction is selective, a CO group with a greater electron-withdrawing substituent being reduced exclusively, although some benzils mainly photodecompose through carbonyl–carbonyl fission.

TABLE II

QUANTUM YIELDS FOR DISAPPEARANCE OF BENZILS[c]

X in 4-X-$C_6H_4C(=O)C(=O)C_6H_5$	Solvent: 2-PrOH	Solvent: Et_2O
NMe_2	...[b]	...[b]
OMe	0.14	0.015
Me	0.076	...[b]
H	0.11	0.012[c]
Ph	0.076	0.087[c]
Cl	...[b]	0.11
NO_2	...[b]	...[b]
CN	...[b]	0.14

[a] A ferrioxalate solution was used as an actinometer. [b] Not determined. [c] Cyclohexane was used as solvent.

Absorption and Emission Spectra of Benzils.—Observed absorption and emission spectral data of these benzils are summarized in Table III. They show an $n\pi^*$ absorption maximum around 370 nm in methanol, which shifts bathochromically on lowering the solvent polarity. The absorption maximum is a broad and single one, which is expected to be due to overlapping of two possible $n\pi^*$ transitions on unsubstituted and substituted benzoyl carbonyls in a molecule. Hence, excitation energies by $n\pi^*$ transition remain at an almost equal level.

Phosphorescence spectra were also determined at 77°K in ether–isopentane–ethanol (EPA) and isopentane, but the emission spectra have little fine structure. In general, the emission is derived from the lowest excited $n\pi^*$ triplet state on the basis of solvent effect; *i.e.*, the red shift of emission was observed on changing solvent from EPA to isopentane. Observation of one emission maximum implies only one emissive triplet unsymmetrical benzil; *i.e.*, one lowest triplet $n\pi^*$ state in an unsymmetrical benzil can radiate and another higher triplet state falls to the former level only by radiationless decay.

Evans and Leermakers[3a] postulated in their phosphorescence study on benzil the coplanarity of carbonyl groups in the lowest excited triplet in spite of their twist in the ground state. The twist angle of 90° in 4-substituted benzils may also be conceivable, since the steric effect between acyl ortho hydrogen and carbonyl oxygen is not changed with para substitution.

Table III also gives energy differences ($A - P$) between the absorption maximum and phosphorescence maximum (P) (*ca.* 6000–10,000 cm^{-1}), which evaluated the energy difference between the excited singlet, formed *via* Franck–Condon transition from the ground state conformation and the emitting triplet;[3a] the value is significantly larger than the 3200-cm^{-1} splitting found for biacetyl (trans-coplanar emitting state). Accounding to Evans and Leermakers, unsymmetrical benzil as well as unsubstituted benzil may be considered to be coplanar in their excited triplet state, since the large splitting value ($A - P$) demands that there be a significant configurational change between the ground state (90° twisted) and the emitting triplet state.

Excited triplet energies were also estimated by the phosphorescence 0–0 band, and are summarized in Table III. The triplet energy tends to increase with

TABLE III

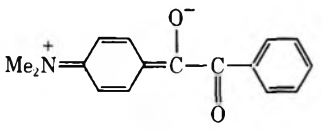
ABSORPTION AND EMISSION SPECTRA OF BENZILS[a]

X in 4-X-$C_6H_4C(=O)C(=O)C_6H_5$	Absorption λ_{max}^{MeOH}, nm (A)	Phosphorescence $\lambda_{max}^{EPA\ b}$, nm (P)	Phosphorescence $\lambda_{max}^{IP,c}$, nm	$A - P$, cm^{-1}	E_T, kcal/mol in EPA	E_T, kcal/mol in IP
NMe_2	380	538	559	7700	57.4	54.6
OMe	380	498	508	6200	62.6	58.8
Me	385	498	508	5800	61.9	60.6
H	378	495	521	6800	61.6	58.0
Ph	386	508	538	6800	60.6	55.8
Cl	387	505	530	6000		56
NO_2	380	518	535	7600	57.4	55.9
CN	340	510	545	9800		54.5
Cf. bornanedione[d]	483			2300		51.6

[a] Phosphorescence spectra were measured at 77°K. [b] EPA: ether–isopentane–ethanol (5:5:2, v/v). [c] IP: isopentane. [d] Reference 3a.

an increase in electron-releasing ability of substituent. In general, the substituent effect on $n\pi^*$ triplet energy may be rather small within the difference of 6 kcal/mol.

In view of the large uv absorption intensity around 380 nm (log ϵ 4.35), dimethylaminobenzil (**5a**) has exceptionally a charge-transfer level as the lowest triplet state in the following form (**13**).

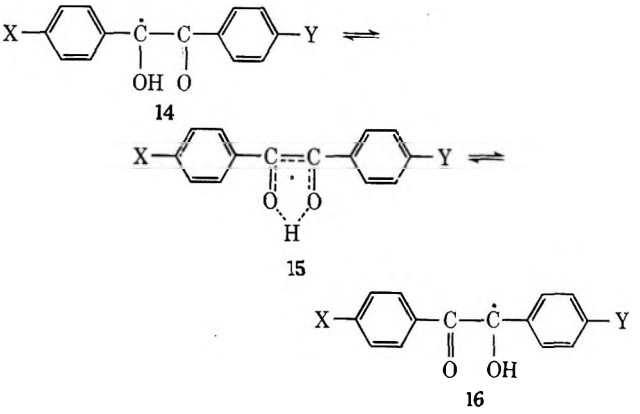


13

On addition of hydrochloric acid to **5a**, the C-T band at 358 nm disappears, and at the same time a $n\pi^*$ absorption at 370 nm appears, which is perhaps due to unsubstituted benzoyl $n\pi^*$. On the other hand, no photoreduction of 4-dimethylaminobenzophenone occurs at all, which possesses the C-T level as the lowest triplet but not the $n\pi^*$ level.[10]

Reaction Pathways.—Either of the two carbonyl group of benzils can be excited to their own $n\pi^*$ singlet state by uv light of over 300 nm. The $n\pi^*$ singlet readily cascades to the triplet. The selective photoreduction of one of two carbonyls may occur at the carbonyl of lower E_T. Though the hydrogen abstraction of the upper carbonyl triplet state competes with the decay to the lowest triplet state, the more than 100-fold difference of rate for these processes makes the latter predominate, assuming the rate for the former process[11] to be *ca.* $10^8\ M^{-1}\ sec^{-1}$ and the latter one[12a,b] to be over $10^{10}\ sec^{-1}$. The selectivity may be explained if the upper excited triplet $n\pi^*$ level is exclusively transformed to the lowest triplet $n\pi^*$ level of two carbonyls through intramolecular T–T transition followed by reduction of the two carbonyls bearing the lowest $n\pi^*$ triplet.

In order to justify the above scheme, it is necessary to assume that the carbonyl group which abstracts a hydrogen atom is the carbonyl which becomes the hydroxyl in the final product. However, biacetyl radical tautomerizes by a shift of a hydrogen atom from one oxygen to the other with a rate of *ca.* $8 \times 10^7\ sec^{-1}$ at very low $[H^+]$,[13] although no data for benzil ketyl radical are available. In contrast, the resulting benzil ketyl radicals, *e.g.*, **14** and **16**, have been reported to



14 **15** **16**

couple with a second-order rate constant of $2\text{–}4 \times 10^8\ M^{-1}\ sec^{-1}$.[11] If this estimation can be applied also to our unsymmetrical benzils, benzil ketyl radicals tautomerize faster than coupling to yield dimer when the concentration of a radical is less than $10^{-1}\ M$. The concentrations of radicals **14** and **16** in an equilibrium vary with their substituents. The orientations for the formation of the reduction dimer are determined by the following two factors: (i) the stabilities (*i.e.*, concentrations) of radicals **14** and **16**, and (ii) their reactivities for coupling.[12c] The observed substituent effect suggests that the effect depends much more on the reactivities than on the stabilities, since an electron-withdrawing group tends to increase the former but affects the latter in a complex way. Therefore, it is also probable that the resulting benzoins and/or benzilpinacols are derived from a more reactive ketyl radical substituted by an electron-withdrawing group on the basis of our observation.

However, we could not preclude that the product-determining step may be hydrogen abstraction step by the lowest $n\pi^*$ carbonyl, since kinetic data for unsymmetrical benzil ketyl radicals are unavailable at present.

Finally, it is noteworthy that no photoisomerization between 4-methylbenzoin (**6c**) and 4′-methylbenzoin (**6′c**) was observed.

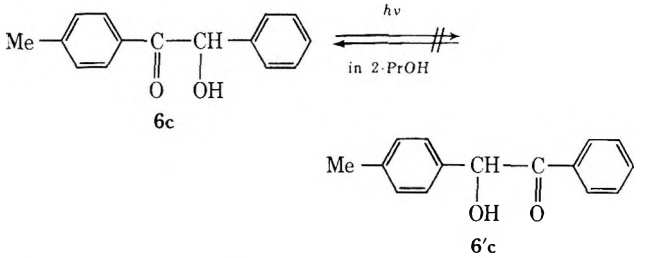
The mechanism for the formation of fission products such as benzaldehydes, benzoic acid, and benzoates is

(10) (a) G. Porter and P. Suppan, *Proc. Chem. Soc.*, 191 (1964); (b) S. G. Cohen and M. W. Siddiqui, *J. Amer. Chem. Soc.*, **86**, 5047 (1964).

(11) (a) S. A. Weiner, E. J. Hamilton, Jr., and B. M. Monroe, *ibid.*, **91**, 6350 (1969); (b) T. Fujisawa and G. S. Hammond, *ibid.*, **94**, 4175 (1972).

(12) (a) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, New York, N. Y., 1965, p 119; (b) D. O. Cowan and A. A. Baum, *J. Amer. Chem. Soc.*, **93**, 1153 (1971); (c) C. G. Swain, W. H. Stockmayer, and J. T. Clarke, *ibid.*, **72**, 5426 (1950).

(13) H. Staudinger *Ber.*, **46**, 3530 (1913).



obscure. Perhaps they are derived from benzoyl radicals *via* carbonyl–carbonyl fission in the reactive triplet.

Experimental Section

Materials.—Benzil was prepared by the oxidation of benzoin with nitric acid and recrystallized from ethanol (mp 95°): λ_{max}^{MeOH} 257 nm (log ϵ 4.33) and 378 (1.86). Dimethylaminobenzil (**5a**)[13] was prepared by the oxidation of 4-dimethylaminobenzoin with Fehling's solution (mp 115–116°): λ_{max}^{MeOH} 258 nm (log ϵ 4.15) and 358 (4.35). 4-Nitrobenzil[14] was prepared by the nitration of benzoin acetate with potassium nitrate in acetic acid and recrystallized from CCl_4 (mp 142°): λ_{max}^{MeOH} 265 nm (log ϵ 4.17). 4-Methylbenzil[15] (**5c**) was prepared by the oxidation of 4-methyldeoxybenzoin with selenium oxide and recrystallized from ethanol (mp 31°): λ_{max}^{MeOH} 264 nm (log ϵ 4.26) and 386 (1.75). 4-Phenylbenzil (**12**) was prepared by the oxidation of 4-phenyldeoxybenzoin[16] with selenium oxide and recrystallized from ethanol (mp 105°): λ_{max}^{MeOH} 255 nm (log ϵ 4.15), 300 (4.28), and 386 (1.26). 4-Methoxybenzil (**5b**)[17] was prepared by the oxidation of 4-methoxybenzoin with Fehling's solution and purified by silica gel column chromatography using petroleum ether (bp 30–60°)–ethyl acetate (7:3, v/v) as an eluent (mp 61°): λ_{max}^{MeOH} 255 nm (log ϵ 4.18), 291 (4.26), and 380 (2.08). 4-Chlorobenzil (**8a**)[18] and 4-cyanobenzil (**8b**)[18] were prepared by the decomposition of 5 *p*-chloro- and 5-*p*-cyanophenyl-2-methyl-4-phenyloxazoles with bromine in acetic acid solution, respectively, and recrystallized from aqueous EtOH: 4-chlorobenzil, mp 74–75°; λ_{max}^{EtOH} 265 nm (ϵ 22,900) and 387 (927); $\lambda_{max}^{cyclohexane}$ 266 nm (ϵ 21,600) and 405 (711); 4-cyanobenzil, mp 109–110°; λ_{max}^{EtOH} 260 nm (ϵ 21,150) and 340 (1175). Commercial cyclohexane was purified successively by washing with H_2SO_4, aqueous NaOH, and water, and then through a silica gel column followed by distillation. Ethyl ether (first grade) was purified by rectification after treatment with H_2SO_4, NaOH, and Na, bp 34.0–34.5°. Ethyl alcohol was rectified after treatment with H_2SO_4 and KOH and then through a silica gel column. Extra pure grade 2-propanol and isopentane were used without further purification. The silica gel used in the column chromatography was 100 mesh Mallinckrodt guaranteed reagent and baked at 100° for 1–2 hr before use.

Apparatus.—Melting points, measured by a Yanagimoto micro melting point apparatus, are uncorrected. Infrared spectra were measured on a Perkin-Elmer Model 337 grating infrared spectrophotometer. Ultraviolet spectra were determined on a Hitachi double-beam instrument, Model 124. Nmr spectra were determined by a Japan Electron Optic Laboratory Co., C60 HL nmr instrument. Electron impact fragmentations were carried out on a Mattauchi-Herzog type (JMS-OSG) mass spectrometer. The irradiation was carried out using a Halos 300-W high-pressure Hg lamp, which emits exclusively uv light of over 300 nm through a Pyrex filter.

Irradiation of Benzils.—The reaction vessel was a Pyrex cylindrical tube of 120 ml in which a 2-propanol solution of benzils ($\sim 10^{-2}$ *M*) was placed. The solution was flushed with nitrogen for 30 min prior to irradiation and then nitrogen flow was continued throughout the irradiation. The reaction vessel and the mercury lamp were dipped in a bath of running water at 20–30°.

Benzoin (2).—Benzil (1.94 g) dissolved in 2-propanol (1.85×10^{-2} *M*) was irradiated in the absence of oxygen. After the characteristic yellow color of benzil faded out (*ca.* 2 hr), 2-propanol was evaporated under reduced pressure. The resulting brown liquid was separated by column chromatography to yield a substance (264 mg, 13.5%), mp 137°. A mixture melting point with authentic benzoin showed no depression and its ir and uv spectra and tlc were identical with those of the authentic sample.

Benzilpinacol (3).—After removal of 2-propanol from the irradiated reaction mixture, crystals were filtered off and washed by acetone; there was obtained benzilpinacol (**3**), 439 mg (22.5%), mp 136° (lit.[8] mp 136°). The molecular weight measured by the cryoscopic method was 420 (calcd for $C_{28}H_{22}O_4$, 422); the ir peak (3400 cm^{-1}, OH) and mass spectrum, resembling that of benzoin, confirm its structure.

4-Dimethylaminobenzoin (6a).—4-Dimethylaminobenzil (1.2 g) in 2-propanol was irradiated for 32 hr until it was consumed; separation of the condensed mixture by column chromatography yielded crystals of 4-dimethylaminobenzoin (**6a**), 142 mg (12.4%), mp 157–158°. This was identified by tlc and uv and ir spectra.

Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 72.82; H, 6.31; N, 5.89.

4-Methoxybenzoin (6b).—4-Methoxybenzil (234 mg) in 2-propanol (80 ml) was irradiated for 12 hr. The first fraction eluted from a column gave the starting material (98 mg, 42%) identified by comparison of tlc, ir, and uv spectra with those of **6b**. The second fraction was 4-methoxybenzoin (13 mg, 5.5%) by tlc, ir, and uv spectra in comparison with those of the authentic 4-methoxy-[20] and 4'-methoxybenzoins.[22] Its mass spectrum exhibits a molecular ion peak at *m/e* 242, a base ion peak at *m/e* 77 (100%), and other peaks at *m/e* 107 ($PhCHOH^+$), and 135 ($CH_3C_6H_4C{=}O^+$).

4-Methylbenzoin (6c).—After the solution (1.25×10^{-2} *M*) of 4-methylbenzil (**5c**) (1.12 g) in 2-propanol was irradiated for 28 hr, the solution was concentrated to yield a brown liquid containing precipitate. The filtrate was chromatographed by silica column to afford 4-methylbenzoin (100 mg, 8.8%); its characterization was performed by the mass spectrum (molecular ion peak at *m/e* 226, 4-methylbenzoyl ion at *m/e* 119, benzhydryl ion at *m/e* 107) and by the comparison of ir and uv (λ_{max}^{MeOH} 255 nm) spectra with those of authentic 4-methyl- and 4'-methylbenzoins.[19]

4-Methylbenzilpinacol (7b).—A solid (393 mg, 34.8%) precipitated from the above irradiated mixture was 4-methylbenzilpinacol (**7b**), mp 140° dec and cryoscopic molecular weight 450 (calcd for $C_{30}H_{26}O_4$, 450). Moreover, its ir spectrum exhibits a characteristic OH absorption (3400 cm^{-1}) and the mass spectrum resembles that of 4-methylbenzoin.

4'-Chlorobenzilpinacol (11a).—4-Chlorobenzil (**8a**, 511 mg) in propanol was irradiated for 6 hr. Removal of solvent and column chromatography yielded a solid which was purified by sublimation to crystalline 4'-chlorobenzilpinacol (**11a**) (mp 119–120°), 265 mg (51.6%), nmr (DMSO-d_6) τ 2–3 (m), and $\nu_{C=O}$ 1670 and ν_{OH} 3400 cm^{-1}.

Anal. Calcd for $C_{28}H_{20}O_4Cl_2$: Cl, 14.5. Found: Cl, 15.5.

4'-Cyanobenzilpinacol (11b).—4-Cyanobenzil (473 mg) in 2-propanol (120 ml) was irradiated for 4 hr. The solvent was removed and separated by column chromatography to yield 4'-cyanobenzilpinacol (**11b**) (271 mg, 57.0%), which on sublimation had mp 170–171°; $\nu_{C=O}$ 1680, ν_{OH} 3400 cm^{-1}; nmr (DMSO-d_6) τ 2–3 (m) and nmr ($CDCl_3$) τ 2–3 (m, 9 H), 4.2 (s, 1 H).

Anal. Calcd for $C_{30}H_{20}O_4N_2$: N, 5.93. Found: N, 5.8.

Determination of Quantum Yields.—A solution (*ca.* 10^{-5} *M*) of benzils (5 ml total volume) was degassed by several freeze–thaw cycles and sealed *in vacuo* in a quartz uv cell. The cell was then irradiated through a Pyrex filter (over 300-nm light) using a Halos HIP 300-W high-pressure lamp. The disappearance of starting benzils was monitored at its $n\pi^*$ absorption maxima on the above spectrometer. Actinometries were carried out simultaneously using a ferrioxlate actinometer.

Measurement of Phosphorescence Spectra.—The phosphorescence spectra were measured by a Hitachi MPF-2A fluorescence spectrometer. All phosphorescence spectra were recorded

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as a solution of EPA (ether–isopentane–ethanol, 5:5:2 v/v) or isopentane. The solvent was checked for emission at each time. No interference due to emission of solvent was observed. The solution contains *ca.* 10^{-5} *M* solute and they formed clear glasses without micro crystals at 77°K.

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Photochemical and Thermal Reactions of Naphthoquinones and Ynamines. Formation of Intermediate Cyclobutadienes

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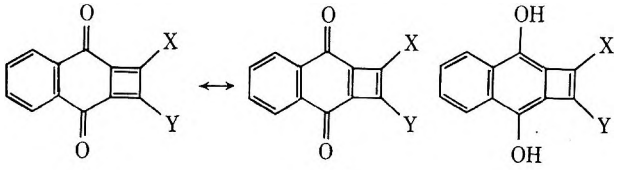
Photochemical and thermal reactions of naphthoquinones with ynamines were found to give cyclobutene, quinone methine, and naphthothiophene products. The reaction course was governed by naphthoquinone and ynamine substituents and reaction conditions. Conversions of the cyclobutenes to naphthocyclobutadienes, the corresponding naphthoquinones, and their dimerizations were studied.

The acid-promoted dimerization of ynamines to four-membered ring imonium salts and their subsequent treatment with base gave stable, tetrasubstituted cyclobutadiene compounds.[1,2] In order to study the limits of stability of these long elusive smallest cyclic polyenes, we undertook studies which should lead to the cyclobutadiene–naphthoquinone and cyclobutadiene–dihydroxynaphthalene systems A and B, in which one might expect some measurable π bond localization, depending on the substituents X and Y.

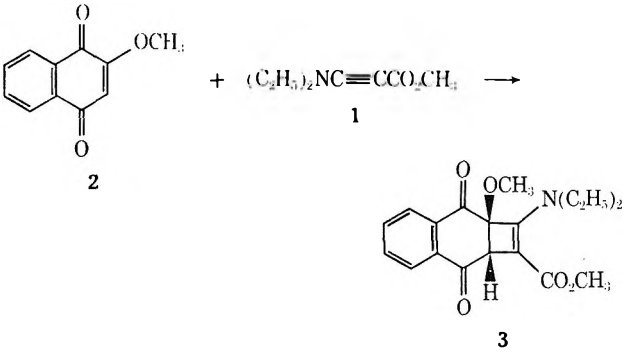


A A′ B

While enamines react with quinones, quinone imines, and naphthoquinones to form substituted hydroquinones or their corresponding derivatives,[3-8] ynamines were found to give products derived from addition to the quinone carbonyl group.[9] The formation of intermediate oxirans was again observed in the photochemical reactions of other acetylenes with naphthoquinones, but these reactions also gave fused cyclobutene products.[10-13] This paper describes studies of the photochemical and nonphotochemical reactions of naphthoquinones with ynamines and subsequent conversions designed to give A and B.

Irradiation of a solution of carbomethoxydiethylaminoacetylene (**1**) and 2-methoxynaphthoquinone (**2**) in acetonitrile through a Pyrex filter (λ >280 mμ) produced a 58% yield of the adduct **3**. Since ir, uv, and nmr spectra did not allow a rigorous exclusion of the isomeric cyclobutene product with adjacent carbomethoxy and methoxy groups (though there was no double-bond isomerization evident in our product), a single-crystal X-ray analysis was enlisted.[14] This firmly established the structure of **3**.

A uv spectrum of the reaction mixture prior to irradiation did not reveal formation of an initial complex of the reactants, and the isolated product **3** proved to be stable to further irradiation. The 1,3-photorearrangement[15] through Norrish type I cleavage, which has been observed for other naphthoquinone–acetylene adducts, would not be expected in this case, since it would lead to the cyclobutene where amine and ester group conjugation is lost. No adduct **3** was formed in acetonitrile without irradiation.



2 **1** **3**

Similarly, the cyanoynamine **4** was found to react with 2-methoxynaphthoquinone (**2**) to form the cyclobutene **5** in 70% yield. The structure of this product was suggested by a close spectroscopic correlation with **3**. (Profound differences were found in the isomeric cyclobutenes obtained in the acetoxy series, below.)

Together with the cyclobutene **5**, a quinone methine **6** was obtained in 2–5% yield. This product arises on opening of the oxirane obtained by addition of the ynamine to one of the naphthoquinone carbonyl groups.

A cyclobutene product was also formed from diethylaminophenylacetylene (**7**) and 2-methoxynaphtho-

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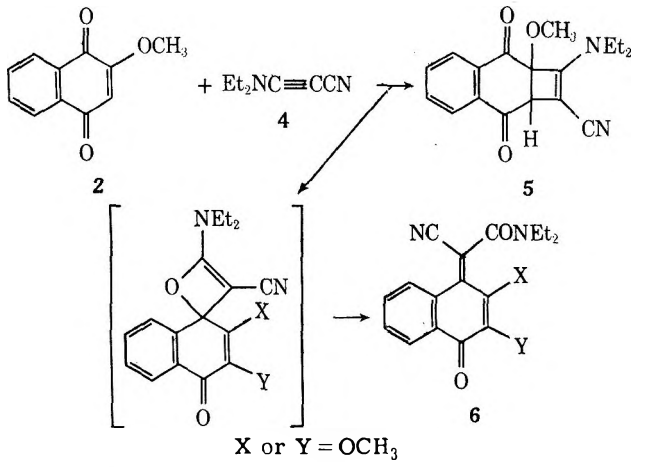
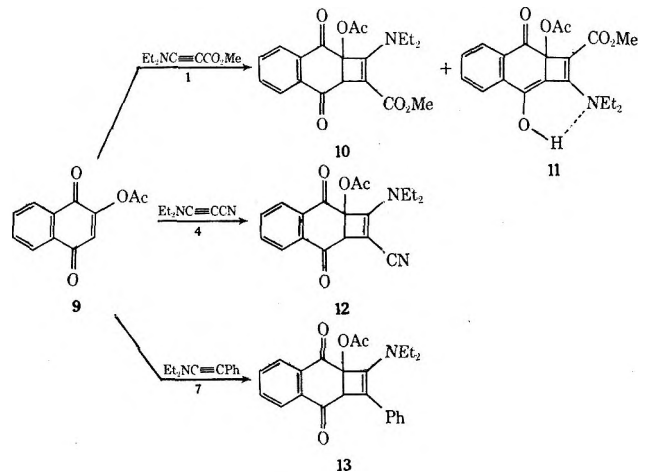


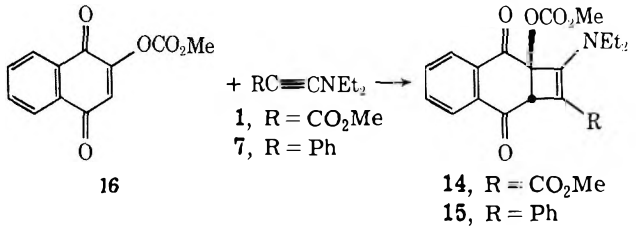
quinone (2), but this compound decomposed on purification and was not investigated further. No product could be obtained from a reaction with diethylaminomethylacetylene (8), possibly because of the increased reactivity of the unconjugated cyclobutene enamine system.

When 2-acetoxynaphthoquinone (9) was irradiated in the presence of the carbomethoxy ynamine 1, two cyclobutene products were obtained. While one showed all of the spectroscopic characteristics associated with the corresponding methoxy product 3, and could thus be assigned structure 10, the other showed one enolic hydroxyl group in nmr and ir spectra and intramolecular hydrogen bonding to nitrogen. The isomeric structure 11 was thus assigned to this compound. In addition to these products, some 20 others were formed and seen on chromatography of the reaction mixture. A large number of colored products were also obtained without irradiation in benzene or acetonitrile, but the cyclobutene compounds could not be isolated from those reactions.

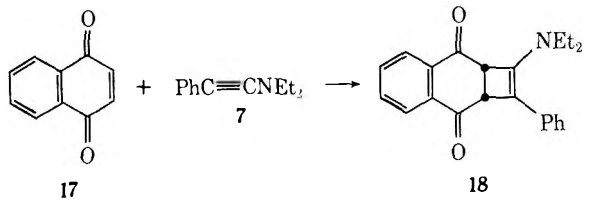
Irradiation of 2-acetoxynaphthoquinone (9) with the cyanoynamine 4 or the phenylynamine 7 led to the cyclobutene compounds 12 and 13 as well as a large number of unidentified products. Again 12 and 13 were not produced in benzene or acetonitrile without irradiation.



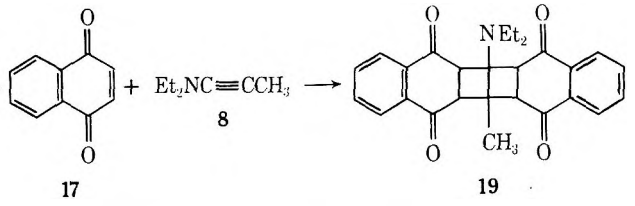
However, it was found that the cyclobutenes 14 and 15 were formed without irradiation from the methyl carbonate compound 16 and the carbomethoxy and phenyl ynamines 1 and 7. These reactions gave better yields of 14 and 15 when acetonitrile, rather than benzene, was used as solvent. No addition products of the methyl carbonate 16 could be obtained with the cyano ynamine 4 or the methyl ynamine 8, with or without irradiation.



Addition of the phenyl ynamine 7 to the unsubstituted naphthoquinone 17 and formation of the cyclobutene 18 without irradiation was also observed.[13a]



Addition of the methyl ynamine 8 to naphthoquinone (17) without irradiation led to a 1:2 adduct. In view of the known reactions of enamines with naphthoquinones, addition of a second equivalent of naphthoquinone to the initial cyclobutene is expected. While previous examples led to the formation of only one carbon–carbon bond, the formation of a second cyclobutane ring, in 19, became evident by the simplicity of the nmr spectrum, which did not allow for phenolic or benzodihydrofuranoid structures.

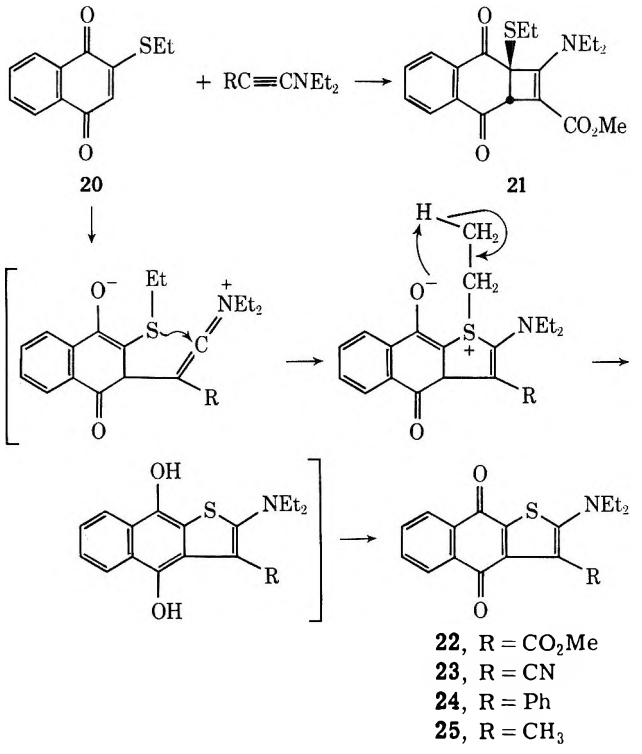


A complex product mixture resulted from irradiation of 2-ethylthionaphthoquinone (20) and the ynamine ester 1 in acetonitrile. From this mixture the cyclobutene 21 was isolated as well as the aminothiophene 22. Structural assignment of 22 was based on loss of the *S*-ethyl group, apparent in the nmr spectrum, with retention of sulfur. Extended conjugation was evident in uv and visible spectra of 22 and the molecular weight was found from the mass spectrum. These conclusions were confirmed by a single-crystal X-ray analysis of 22.[16]

The thiophene product 22 was also formed without irradiation and similar additions of the cyano, phenyl, and methyl ynamines 4, 7, and 8 led to analogous thiophene products 23, 24, and 25. A speculative mechanism for the formation of these compounds is shown. In accord with this mechanism, one observes higher yields of the thiophene products with the carbomethoxy and cyano ynamines 1 and 4 *vs.* the phenyl and methyl

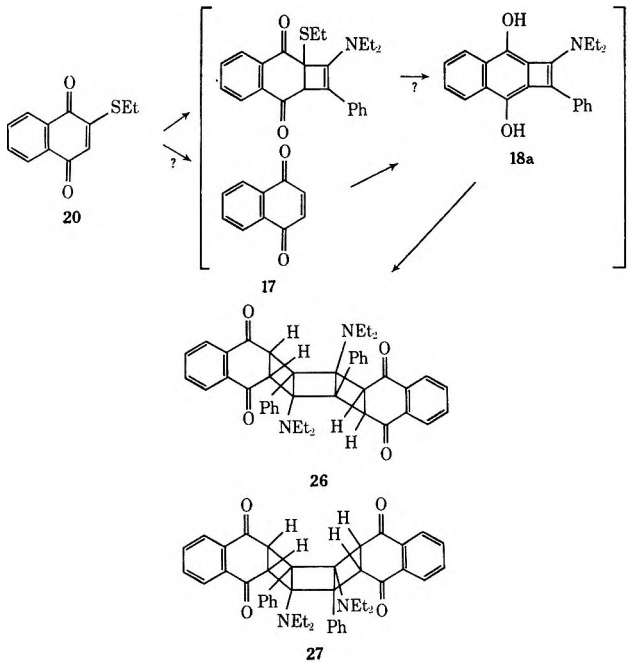
(16) We thank Drs. J. Lerbscher, C. Gibbons, and J. Trotter for their valuable cooperation. The results are to be published by the University of British Columbia group.

ynamines **7** and **8** owing to relative facility of electrophilic attack on sulfur.



22, R = CO_2Me
23, R = CN
24, R = Ph
25, R = CH_3

The last step in the proposed pathway involves oxidation of hydroquinones to the quinone products **22**–**25**. A clue to this step may be seen in the isolation of the dimeric ynamine adducts **26** and **27** on fractionation of the corresponding reaction mixture. These compounds were formed on preparative chromatography and were absent from the original reaction mixture. Dimerization may proceed through the phenolic tautomer **18a** of an initial naphthoquinone–ynamine adduct **18** lacking the sulfur substituent. Reduction of 2-ethylthionaphthoquinone (**20**) to naphthoquinone (**17**) and addition of the phenyl ynamine **7**, or reduction of a thioethylcyclobutene, would give **18** and **18a**. The dimeric compounds **26** and **27** could also be isolated from the reaction of naphthoquinone (**17**) with the phenyl ynamine **7**.

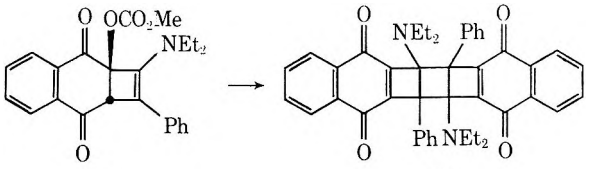


The dimeric nature of compounds **26** and **27** was evident from mass spectra. The proposed orientation and stereochemistry for **26** and **27** is tentative and based on nmr spectra which showed two pairs of methyl groups for **27** with one pair deshielded relative to the other and relative to the identical methyl groups found in **26**. This effect can be ascribed to deshielding of two ethyl groups by phenyl substituents in **27**, but alternative stereostructures with dissimilar ethyl groups are possible.

Elimination of the angular substituents in the cyclobutene products **3**, **5**, **10**–**15**, and **21** was studied next. The methoxy group was not lost under a variety of elimination conditions. Thus the cyclobutenes **3** and **5** were recovered unchanged from sodium methoxide in methanol, sodium hydride in benzene, or the cation exchange resin Rexin 101 in benzene after 18 hr at reflux. The compounds could also be recovered from *p*-toluenesulfonic acid and ethylene glycol in benzene, at reflux for 3 days, and an attempted reduction with zinc in ethanol. The thioethyl compound **21** was also stable to sodium hydride in benzene.

The acetates **10** and **11** could be recovered unchanged from attempted vapor-phase pyrolyses at 430° under vacuum. Treatment with collidine at 280° led to formation of numerous decomposition products, and reduction with zinc and acetic acid for 10 min led to loss of the methyl ester group in **10** (ester exchange) but not loss of the acetate group.

The carbonate esters **14** and **15** also proved to be stable to attempted pyrolytic cleavage below 200°, but were destroyed at higher temperatures. Elimination of the ester function from **15** with sodium hydride in refluxing benzene led to the formation of a dimeric naphthoquinone for which the head-to-tail structure **28** is suggested.



15 **28**

Present Status of This Research.—While it was possible to generate the cyclobutadienes A, A′, and B, the present examples were found to dimerize. However, the compounds studied did not have the optimum substituents X and Y for push–pull stabilization, and conditions for the final step in cyclobutadiene generation were not favorable for preservation of products with limited stability. Further studies to overcome these barriers are in progress.

Experimental Section

Irradiation of 2-Methoxy-1,4-naphthoquinone with *N*,*N*-Diethylcarbomethoxyethynylamine.—A solution of the quinone[10] (1.0 g, 5.32 mmol) and the carbomethoxy ynamine[17] (1.00 g, 6.40 mmol), in 125 ml of dry acetonitrile, was saturated with nitrogen and irradiated for 3.5 hr employing a Pyrex filter. The brown solution was vacuum evaporated to a black gum which crystallized. Chromatography of the mixture on a 1.5 × 23 cm

(17) M. E. Kuehne and P. J. Sheeran, *J. Org. Chem.*, **33**, 4406 (1968).

column of Anasil in dichloromethane gave a yellow band at the solvent front. Evaporation under vacuum and recrystallization from benzene–hexane gave 1.1 g (58%) of orange crystals (**3**): mp 120–121°; uv max (95% C_2H_5OH) 232, 270, and 288 mμ; ir (KBr) 2940, 1690, 1620, and 1450 cm^{-1}; nmr ($CDCl_3$) δ 1.10 (t, 6 H), 3.43 (s, 3 H), 3.60 (q, 4 H), 3.62 (s, 3 H), 3.98 (s, 1 H), and 7.9 (m, 4 H).

Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.64; H, 6.07; N, 4.35.

A reaction employing a filter transmitting wavelengths greater than 400 mμ, in place of the Pyrex filter, gave back predominantly starting material after 4 hr of irradiation.

Irradiation of 2-Methoxy-1,4-naphthoquinone with *N,N*-Diethylcyanoethynylamine.—A solution of 2-methoxynaphthoquinone (1.0 g, 5.32 mmol) and freshly distilled cyano ynamine[18] (1.16 g, 9.5 mmol) in 125 ml of dry acetonitrile was saturated with nitrogen. The system was irradiated for 2.75 hr using a Pyrex filter. The red solution was vacuum evaporated to a red syrup, which was chromatographed on a column of Anasil. Elution with dichloromethane gave 1.20 g (69.5%) of orange crystals (**5**) which were recrystallized from benzene–hexane: mp 139–140°; uv max (95% C_2H_5OH) 235, 263, and 305 mμ (shoulder); ir (KBr) 2965, 2930, 2190, 1690, 1650, 1590, and 1450 cm^{-1}; nmr ($CDCl_3$) δ 1.12 (t, 6 H), 3.43 (s, 3 H), 3.40 (broad q, 4 H), 3.98 (s, 1 H), and 8.0 (m, 4 H).

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.94; H, 5.95; N, 9.21.

Continued elution with ether gave a 1:1 adduct which was rechromatographed yielding 0.042 g (2.5%) of purple solid (**6**): mp 64–67°; uv max (95% C_2H_5OH) 208, 242, 248, 279, 310, and 515 mμ; ir (KBr) 2965, 2935, 2190, 1650, 1600, 1550, and 1425 cm^{-1}; nmr ($CDCl_3$) δ 1.33 (t, 6 H), 3.58 (q, 4 H), 4.20 (s, 3 H), 7.10 (s, 1 H), and 7.9 (m, 4 H).

Irradiation of 2-Methoxy-1,4-naphthoquinone with *N,N*-Diethylphenylethynylamine.—Irradiation through Pyrex, for 2.75 hr, of a solution of 2-methoxynaphthoquinone (1.00 g, 5.32 mmol) and the phenyl ynamine[19] (1.00 g, 5.79 mmol), in 125 ml of acetonitrile, yielded an orange-brown solid upon vacuum evaporation of the solvent. Chromatography on Anasil in dichloromethane gave a fast-running, yellow-orange band (however, the crystals of this compound decomposed upon recrystallization from benzene–hexane or other solvents; no stable adduct could be isolated): nmr ($CDCl_3$) δ 1.10 (split t, 6 H), 3.34 (superimposed q, five-line pattern, 4 H), 3.70 (s, 3 H), 3.86 (s, 1 H), 7.30 (s, 5 H), and 7.42 (m, 4 H).

Irradiation of 2-Acetoxy-1,4-napthoquinone with *N,N*-Diethylcarbomethoxyethynylamine.—A solution of freshly distilled ynamine (3.0 g, 0.0193 mol) and 2-acetoxynaphthoquinone (2.0 g, 9.0 mmol), in dry acetonitrile, was irradiated for 21 hr using a Corex filter. Chromatography on Anasil in toluene–ether (4:1) eluted starting quinone, followed closely by a pink fraction which crystallized upon evaporation. Recrystallization from ethyl acetate gave 0.121 g (3.5%) of **11**: mp 184.5–185.5°; uv max (95% C_2H_5OH) 214, 269, and 306 mμ, in base 246 mμ (shoulder); ir (KBr) 3450, 2910, 2740, 1760, 1660, 1620, 1590, 1575, and 1520 cm^{-1}; nmr ($CDCl_3$) δ 1.32 (t, 6 H), 2.52 (s, 3 H), 3.66 (q, 4 H), 4.00 (s, 3 H), 7.8 (m, 4 H), and 11.80 (s, 1 H).

Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.86; H, 5.68; N, 3.87.

Continued elution with ether–ethanol (10%) gave a brown gum which crystallized after continued scratching. Recrystallization from ether yielded 73 mg (2.1%) of **10**: mp 143–143.5°; uv max (95% C_2H_5OH) 227, 263, and 286 mμ; ir (KBr) 2960, 1752, 1695, 1670, 1630, 1600, and 1460 cm^{-1}; nmr (CCl_4) δ 1.10 (t, 6 H), 2.17 (s, 3 H), 3.58 (s) and 3.63 (q) (total 8 H), and 7.83 (m, 4 H).

Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.73; H, 5.64; N, 3.77.

Irradiation of 2-Acetoxy-1,4-naphthoquinone with *N,N*-Diethylcyanoethynylamine.—Irradiation of the quinone (1.25 g, 5.8 mmol) with the cyano ynamine (1.25 g, 0.010 mol), in acetonitrile through Corex optics for 19.5 hr, gave 52 mg (2.6%) of the cyclobutene **12**: mp 178°; uv max (95% C_2H_5OH) 229 and 260 mμ; ir (KBr) 2950, 2180, 1732, 1690, 1648, 1595, and 1450 cm^{-1}; nmr ($CDCl_3$) δ 1.20 (t, 6 H), 2.25 (s, 3 H), 3.50 (q, 4 H), 3.90 (s, 1 H), and 8.18 (m, 4 H).

Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.36; H, 5.49.

Chromatography of the reaction mixture on Anasil in dichloromethane and dichloromethane–ethanol (5%) recovered a large amount of starting quinone.

Irradiation of 2-Acetoxy-1,4-naphthoquinone with *N,N*-Diethylphenylethynylamine.—Irradiation of the quinone (2.00 g, 9.25 mmol) with the phenyl ynamine (1.46 g, 8.44 mmol), in acetonitrile through Corex optics for 19.5 hr, gave 41 mg (1.2%) of the cyclobutene **13**. Separation of the reaction mixture on silica gel in toluene–20% ether gave a fast-running brown oil which was rechromatographed in toluene on Anasil. The initial orange oil was crystallized from ether and hexane, yielding red diamonds of **13**: mp 163.5–164°; uv max (95% C_2H_5OH) 227, 263, and 300 mμ; ir (KBr) 1735, 1690, 1678, 1640, 1595, and 1422 cm^{-1}; nmr ($CDCl_3$) δ 0.99 (t, 6 H), 2.20 (s, 3 H), 3.30 (q, 4 H), 4.00 (s, 1 H), 7.22 (s, 5 H), and 7.85 (m, 4 H).

Anal. Calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 73.72; H, 6.21; N, 3.57.

Irradiation of 2-Ethylthio-1,4-naphthoquinone with *N,N*-Diethylcarbomethoxyethynylamine.—Irradiation of the quinone[20] (2.18 g, 10.0 mmol) and the ynamine (2.00 g, 12.9 mmol) through Corex optics for 6 hr in acetonitrile gave a sanguine solution which was vacuum evaporated and chromatographed on silica gel in dichloromethane. Starting quinone (0.445 g), a purple band, and a brown fraction were eluted (5% ethanol). Slow crystallization of the purple fraction from ethanol gave the yellow 1:1 adduct **21** and purple crystals, 0.225 g (6.5%), which were identified as the thiophene-fused naphthoquinone (**22**): mp 158–160°; uv max (95% C_2H_5OH) 241, 246, 308, and 348 mμ (shoulder); ir (KBr) 1725, 1660, 1628, 1510, 1450, 1434, 1325, 1275, and 1260 cm^{-1}; nmr ($CDCl_3$) δ 1.27 (t, 6 H), 3.48 (q, 4 H), 3.93 (s, 3 H), and 7.88 (m, 4 H); *m/e* 343.

Anal. Calcd for $C_{18}H_{17}NSO_4$: C, 62.95; H, 4.99; N, 4.08; S, 9.32. Found: C, 63.08; H, 5.14; N, 3.82; S, 9.49.

The yellow C_4 adduct **21**, which runs slightly behind the purple thiophene on tlc in benzene–dichloromethane, was isolated: 0.306 g (8.2%); mp 104.5–105.5°; uv max (95% C_2H_5OH) 231, 261, and 289 mμ; ir (KBr) 1690, 1628, 1600, and 1450 cm^{-1}; nmr ($CDCl_3$) δ 1.08 (t, 6 H), 1.28 (t, 3 H), 2.62 (q, 2 H), 3.63 (s, 3 H), 3.70 (eight-line pattern, 4 H), 3.99 (s, 1 H), and 7.85 (m, 4 H).

Anal. Calcd for $C_{20}H_{23}NSO_4$: C, 64.33; H, 6.21; N, 3.75; S, 8.57. Found: C, 64.27; H, 6.21; N, 3.58; S, 8.63.

Crystallization of the brown fraction from ethanol gave a second yellow crystalline product. Photolysis of the C_4 adduct **21** above, in acetonitrile for 2 hr through Pyrex, gave this product exclusively as seen by tlc: nmr ($CDCl_3$) δ 0.60 (t, 2 H), 1.08 (m, 6 H), 1.45 (t, 2 H), 3.3 (m, 6 H), 6.64 (s, 1 H), 7.20 (s, 4 H), and 7.68 (m, 4 H).

Reaction of 2-Ethylthio-1,4-naphthoquinone and *N,N*-Diethylcarbomethoxyethynylamine without Light.—Stirring an acetonitrile solution of the quinone (1.00 g, 4.6 mmol) and the ynamine (1.0 g, 6.45 mmol) overnight, and chromatographing the solvent-free mixture on silica gel plates in dichloromethane, yielded 99 mg (6.3%) of the thiophene adduct **22**. Tlc and spectral data match the information given previously; no C_4 adduct could be isolated.

Irradiation of 2-Ethylthio-1,4-naphthoquinone and *N,N*-Diethylphenylethynylamine.—Irradiation of a solution of the quinone (1.5 g, 6.9 mmol) and the phenyl ynamine (2.0 g, 11.6 mmol), in acetonitrile for 4.5 hr, was carried out through Vycor optics. Chromatography of the vacuum-evaporated mixture on Anasil in dichloromethane gave 0.137 g (5.5%) of the purple thiophene **24**, the C_4 adduct as a yellow gum, and 0.034 g (1.5%) of a yellow compound, at the origin, which was derived from photolysis of the C_4 adduct.

The purple thiophene **24** was separated from starting quinone by chromatographing on silica gel in petroleum ether (bp 30–60°)–benzene (60:40): mp 155–156°; uv max (95% C_2H_5OH) 227, 245, 285, 313, and 347 mμ (shoulder); ir (KBr) 1660, 1620, 1588, 1493, 1440, 1330, 1275, and 1260 cm^{-1}; nmr ($CDCl_3$) δ 1.05 (t, 6 H), 3.15 (q, 4 H), 7.39 (s, 5 H), and 7.83 (m, 4 H).

Anal. Calcd for $C_{22}H_{19}NSO_2$: C, 73.11; H, 5.30; N, 3.88; S, 8.85. Found: C, 72.90; H, 5.56; N, 3.60; S, 9.10.

The yellow C_4 adduct was identified by its nmr spectrum. However, it decomposed at a moderate rate so that its purity was always in question: ir (KBr) 1635, 1600, 1575, 1450, 1105, 760,

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752, 717, 695, and 658 cm^{-1}; nmr ($CDCl_3$) δ 1.12 (broad t, 8 H), 3.38 (borad q, 5 H), 3.72 (s, 1 H), 7.31 (s, 5 H), 7.40 (s, 3 H), 7.67 (m, 1 H), and 8.1 (m, 1 H).

The yellow crystals derived by ethanol crystallization from the origin region of the chromatograms were also prepared by photolyzing the C_4 adduct through Vycor for 2 hr in acetonitrile: mp 150–153°; uv max (95% C_2H_5OH) 220, 229 (shoulder), 256, 275, 290, 301, and 380 mμ; ir (KBr) 1628, 1590, 1570, 1530, 1515, and 1440 cm^{-1}.

Reaction of 2-Ethylthio-1,4-naphthoquinone and *N,N*-Diethylphenylethynylamine without Light (Formation of Cyclobutadienoid Dimers 26 and 27).—Stirring the quinone (1.0 g, 4.6 mmol) with the phenyl ynamine (1.0 g, 5.8 mmol), in 20 ml of acetonitrile overnight, yielded 0.079 g (4.75%) of the purple thiophene **24**, upon chromatography in dichloromethane on silica gel plates. Spectral ir and nmr matches were obtained with this adduct and the photochemical product.

Also isolated from this reaction were two isomeric compounds of lower R_f. These isomers were initially isolated as a broad band on chromatography, and were rechromatographed. This purification step resolved the mixture to a single orange band of R_f 0.5. Slow crystallization from ethanol yielded yellow and red crystals; separation with tweezers and recrystallization from ethanol yielded 119 mg (7.8%) of the red (**27**) and 131 mg (8.6%) of the yellow isomer (**26**).

Yellow isomer **26** had mp 197–198°; uv max (95% C_2H_5OH) 222, 237, 299, 307, and 352 mμ, in acid or base; ir (KBr) 1685, 1640, 1600, 1585, 1560, and 1465 cm^{-1}; nmr ($CDCl_3$) δ 1.00 (five-line pattern of two triplets, 6 H), 2.90 (q, 2 H), 3.76 (q, 2 H), 4.52 (s, 1.5 H), 7.33 (s, 5 H), and 7.67 (s, 4 H); mass spectrum *m/e* 662 and 331.

Anal. Calcd for $C_{44}H_{42}N_2O_4$: C, 79.73; H, 6.39; N, 4.23; S, 0.00. Found: C, 79.43; H, 6.24; N, 4.10; S, 0.00.

Red isomer **27** had mp 197–198°; uv max (95% C_2H_5OH) 222, 238, 297, 307, and 356 mμ, in acid or base; ir (KBr) 1680, 1640, 1600, 1585, 1560, and 1465 cm^{-1}; nmr ($CDCl_3$) δ 1.20 (q, from two triplets, 6 H), 3.10 (q, 2 H), 4.00 (m, 2 H), 4.59 (s, 1.5 H), 7.24 (s, 5 H), and 7.7 (m, 4 H); mass spectrum *m/e* 662 and 331.

Anal. Calcd for $C_{44}H_{42}N_2O_4$: C, 79.73; H, 6.39; N, 4.23; S, 0.00. Found: C, 79.70; H, 6.18; N, 4.15; S, 0.00.

Reaction of Cyclobutadienoid Dimer 27 with Sodium Hydride and Subsequently Acetic Anhydride.—Treatment of the red isomer **27** (30 mg) with washed sodium hydride, in dimethoxyethane for 6 hr, gave a deep, blue-green solution. The suspension was filtered and the blue-green color was dispelled by the addition of a few drops of acetic anhydride. The solvent was evaporated and the residue was taken up in water and extracted with ether. Drying and evaporation of the ether gave 9 mg (28%) of a white, gummy material which slowly crystallized: mp >270°; uv max (95% C_2H_5OH) 253 mμ; ir (KBr) 1720, 1640, 1555, and 1450 cm^{-1}.

Reaction of Cyclobutadienoid Dimer 26 with Sodium Hydride and Subsequently Ammonium Chloride Solution.—Treatment of a filtered solution of the blue anion, derived as above from the yellow isomer **26**, with a few drops of saturated ammonium chloride solution gave immediate discoloration. The solution was extracted with ether and evaporated to a white, amorphours gum: ir (KBr) 3300, 1665, 1640, 1590, and 1445 cm^{-1}.

Irradiation of 2-Ethylthio-1,4-naphthoquinone with *N,N*-Diethylcyanoethynylamine.—Irradiation of the quinone (1.00 g, 4.6 mmol) with the cyano ynamine (1.00 g, 8.2 mmol), in acetonitrile, was carried out through Corex. The resulting solution was vacuum evaporated and chromatographed on silica gel plates in dichloromethane. The purple thiophene **23** was isolated, 0.080 g (5.6%), and was the only identifiable product: mp 195–196°; uv max (95% C_2H_5OH) 243, 246, 307, and 333 mμ (shoulder); ir (KBr) 2210, 1668, 1640, 1592, 1528, 1468, 1455, 1332, and 1265 cm^{-1}; nmr ($CDCl_3$) δ 1.43 (t, 6 H), 3.72 (m, 4 H), and 7.89 (m, 4 H).

Anal. Calcd for $C_{17}H_{14}N_2SO_2$: C, 65.78; H, 4.55; N, 9.03; S, 10.33. Found: C, 65.63; H, 4.78; N, 8.80; S, 10.59.

Reaction of 2-Ethylthio-1,4-naphthoquinone with *N,N*-Diethylpropynylamine without Light.—Stirring a solution of 2-thioethylnaphthoquinone (1.00 g, 4.6 mmol) and the methyl ynamine[21] (1.00 g, 9.0 mmol), in acetonitrile overnight, and chromatographing the solvent-free mixture on silica gel plates, gave 41 mg (3%) of the purple thiophene **25**: uv max (95% C_2H_5OH) 242, 247, 285, 305, and 345 mμ (shoulder); ir (KBr) 1660, 1625, 1588, 1440, 1330, and 1260 cm^{-1}; nmr ($CDCl_3$) δ 1.18 (t, 6 H), 2.47 (s, 3 H), 3.25 (q, 4 H), and 7.98 (m, 4 H).

Reaction of 1,4-Naphthoquinone with *N,N*-Diethylphenylethynylamine without Light.—Vacuum evaporation of the reaction mixture of naphthoquinone (1.00 g, 6.34 mmol) with the phenyl ynamine (1.00 g, 5.8 mmol), which had been stirred in acetonitrile for 24 hr in the dark, produced a dark, amorphous solid. Chromatography on silica gel plates in dichloromethane–ethanol (1%) produced three orange bands; no naphthoquinone remained.

The region of R_f 0.6 was crystallized from ethanol, after rechromatography, and was identified as the mixture of dimeric adducts **26** and **27** previously isolated from the 2-thioethylnaphthoquinone–phenyl ynamine reaction, 26 mg (1.3%). Spectral matches (nmr, ir, and uv) and a tlc match in dichloromethane on silica gel were obtained with **26** and **27**.

A combination of naphthoquinone with the carbomethoxy ynamine gave no isolatable adducts as seen by tlc. It should be noted that difficulty was encountered in the purification of both of these reaction mixtures, since decomposition occurred rapidly while the mixtures were in solution.

Reaction of 1,4-Naphthoquinone with *N,N*-Diethylpropynylamine.—To a solution of naphthoquinone (1.00 g, 6.34 mmol), in 20 ml of acetonitrile, was added the methyl ynamine (0.98 g, 8.8 mmol). The solution was shaken without irradiation for 20 hr. Chromatography on a column of Anasil in dichloromethane, with some added ethanol, gave a yellow solid **19**, 0.105 g, which was recrystallized from ethyl acetate: mp 186–186.5° dec; uv max (95% C_2H_5OH) 240, 255, 301, and 362 mμ; ir (KBr) 1690, 1620, 1595, 1575, and 1535 cm^{-1}; nmr (DMSO) δ 0.78, 0.87 (overlapping s and t, total 8 H), 1.77 (s, 1 H), 2.48 (s, 1 H), 3.0–4.0 (m, 3.5 H), 6.10 (s, 1 H), and 7.38 (m, 7 H).

Anal. Calcd for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.90; N, 3.28. Found: C, 75.73; H, 6.11; N, 2.98.

Preparation of 2-Methylcarbono-1,4-naphthoquinone (16).—An ether solution of methyl chloroformate (4.9 g, 0.0518 mol) was added dropwise to a well-agitated solution of 2-hydroxynaphthoquinone (9.0 g, 0.0518 mol) in 4 g of pyridine and 50 ml of ether in an ice bath. The mixture was stirred overnight. Dichloromethane (150 ml) was added and the suspension was vacuum filtered. The residue was washed with small portions of dichloromethane until the washes were colorless. The orange solution was vacuum evaporated to a yellow solid, which was chromatographed on Florisil in dichloromethane, yielding 9.5 g (79%) of product **16**: mp 95°; uv max (95% C_2H_5OH) 247, 253, 262, 338, and 351 mμ; ir (KBr) 1768, 1678, 1662, 1640, 1590, and 1449 cm^{-1}; nmr ($CDCl_3$) δ 3.96 (s, 3 H), 6.83 (s, 1 H), and 7.92 (m, 4 H).

Anal. Calcd for $C_{12}H_8O_5$: C, 62.07; H, 3.47. Found: C, 62.32; H, 3.55.

Reaction of 2-Methylcarbono-1,4-naphthoquinone with *N,N*-Diethylphenylethynylamine.—Stirring a solution of the ynamine (1.00 g, 5.8 mmol) and the methylcarbonoquinone (1.00 g, 4.3 mmol), in 20 ml of acetonitrile, caused precipitation of clean, red plates after 2 hr. After 4 hr the mixture was chromatographed on Anasil in dichloromethane, yielding 1.36 g (78%) of red crystals of **16** which were recrystallized from ethyl acetate [in a second run a mixture of quinone (2.0 g) and ynamine (2.0 g) yielded 2.75 g of the adduct]: mp 173°; uv max (95% C_2H_5OH) 237, 245, 261, 301, and 345 mμ; ir (KBr) 1745, 1684, 1640, 1288, and 1250 cm^{-1}; nmr ($CDCl_3$) δ 0.98 (t, 6 H), 3.29 (q, 4 H), 3.82 (s, 3 H), 4.00 (s, 1 H), 7.21 (sharp m, 5 H), and 7.8 (m, 4 H).

Anal. Calcd for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.46. Found: C, 71.10; H, 5.81; N, 3.21.

Reaction of 2-Methylcarbono-1,4-naphthoquinone with *N,N*-Diethylcarbomethoxyethynylamine.—Stirring a solution of the ynamine (1.00 g, 6.45 mmol) and the methylcarbonoquinone (1.00 g, 4.3 mmol), in 20 ml of acetonitrile, yielded a dark solution after 6 hr. Chromatography of the mixture on Anasil in dichloromethane and recrystallization from ethyl acetate produced 0.510 g (30%) of the 1:1 adduct **14**: mp 145°; uv max (95% C_2H_5OH) 231, 264, and 287 mμ; ir (KBr) 1751, 1698, 1668, 1630, 1288, and 1258 cm^{-1}; nmr ($CDCl_3$) δ 1.12 (t, 6 H), 3.63 (s, 3 H), 3.82 (s, 3 H), 3.70 (m, 4 H), 3.89 (s, 1 H), and 7.9 (m, 4 H).

Anal. Calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62. Found: C, 62.17; H, 5.63; N, 3.46.

Elimination Conditions Employed with 2-*N,N*-Diethylamino-1-phenyl-2a,8a-dihydro-2a-methylcarbonocyclobuta[*b*]naphthalene-3,8-dione (15).—The phenyl ynamine adduct was sublimed at

(21) Purchased from Fluka A. G., Buchs, Switzerland.

165° (0.03 mm) but pyrolized at 220° (0.25 mm) to a tar and a small amount or yellow gummy material that was carbonate-free in the ir.

Stirring a sample of this compound (15) in benzene with either acid ion exchange resin or sodium hydride for 18 hr gave no reaction (tlc and ir).

Addition of 1.00 g (2.47 mmol) of the adduct 15 to a suspension of benzene-washed sodium hydride in benzene (0.5 g), and refluxing the mixture for 6 hr, produced 0.137 g (17%) of a yellow dimeric adduct (28) after chromatography on silica gel plates in dichloromethane: mp 192–193°; uv max (95% C_2H_5OH) 225, 251, 290 (shoulder), 325, and 410 mμ; ir (KBr) 1700, 1540, 1190, and 1094 cm^{-1}; nmr ($CDCl_3$) δ 0.97 (t, 6 H), 3.08 (q, 4 H), and 7.17 and 7.52 (two m, total 9.5 H).

Anal. Calcd for $(C_{22}H_{19}NO_2)_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.43; H, 5.83; N, 4.01.

Registry No.—**1**, 17691-75-7; **2**, 2348-82-5; **3**, 36623-54-8; **4**, 26391-04-8; **5**, 36623-56-0; **6**, 36623-57-1; **7**, 4231-26-9; **8**, 4231-35-0; **9**, 1785-65-5; **10**, 36623-61-7; **11**, 36674-94-9; **12**, 36623-62-8; **13**, 36623-63-9; **14**, 36674-95-0; **15**, 36623-64-0; **16**, 36674-96-1; **17**, 130-15-4; **19**, 36623-65-1; **20**, 36623-66-2; **21**, 36623-67-3; **22**, 36623-68-4; **23**, 36623-69-5; **24**, 36623-70-8; **25**, 36623-71-9; **26**, 36674-97-2; **27**, 36623-72-0; **28**, 36674-98-3.

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Deamination of Nerylamine and Geranylamine[1]

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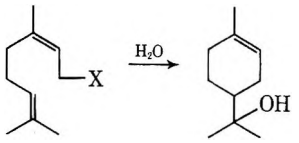
The products of deamination of nerylamine and geranylamine in water and acetic acid have been compared with the products of hydrolysis of neryl and geranyl chlorides, phosphates, and pyrophosphates. Deamination of nerylamine gives less cyclic products than hydrolysis of the neryl compounds, and deamination of geranylamine gives a much lower ratio of linalyl to geranyl products than do the corresponding hydrolyses. Alcohols as well as acetates are formed in the deamination in glacial acetic acid, and the product compositions suggest that ion pairs of the diazonium ions with hydroxide or acetate ions are reaction intermediates and that the substitution products can be formed either by ion-pair collapse or attack of an external nucleophile. Differences between the olefinic products of deamination and hydrolysis can also be explained in these terms.

The solvolysis of derivatives of nerol (I, X = OH) and geraniol (II, X = OH) have been studied extensively as models for cyclization and rearrangement in terpene biosynthesis. Neryl derivatives give largely cyclic products, *e.g.*, α-terpineol (III) and olefins



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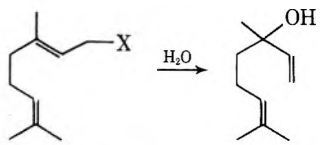
related to it, whereas geranyl derivatives give largely linalool (IV) and olefins related to it.[2–5] These results



II IV

are readily understandable in that the configuration of nerol allows a carbonium ion derived from it or its derivatives to take up a conformation which favors cyclization, whereas a carbonium ion derived from geraniol has to rotate about the 2,3 double bond before it can cyclize to terpineol.[6] Phosphates,[3,4] alcohols,[4] and chlorides,[9] have been used in these experiments, and the product compositions are relatively insensitive to the solvent composition or the nature of the leaving group.

Carbonium ions are often invoked as intermediates in deaminations by nitrous acid which can be regarded as SN1 reactions of an unstable diazonium ion, but the products of such reactions are often very different from those of solvolyses, and a number of workers have speculated on the nature of the intermediates.[10–12] Deaminations of neryl and geranylamine (I, II, X = NH_2) were therefore examined, because of the possibility that a major change in the leaving group would markedly change the products.

Experimental Section

Materials.—Nerol and geraniol were obtained from Fluka, Chemical Samples Co. or Columbia Organics. Their purities were tested by glc, and samples having >95% overall purity and <0.1% of the other geometrical isomer were used. Preparation of geranyl chloride by reaction of the alcohol with PCl_3 or $SOCl_2$ has been reported,[13] but in our hands these methods gave mix-

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tures of chlorides. We therefore used Stork's method[14] or, more often, a simpler variant of it, described here for neryl chloride. Nerol (65 mmol) was dissolved in dry pentane (250 ml) and freshly distilled mesyl chloride (130 mmol) was added slowly at −5° with stirring. Dried pyridine (130 mmol) in pentane (50 ml) was then added, and the stirred solution was allowed to come slowly to room temperature (4 hr). The pentane layer was washed with cold 5% HCl and then with saturated $NaHCO_3$ and was dried ($MgSO_4$). A colorless oil [bp 44–46° (0.5 mm), lit.[14] bp 66–69° (0.4 mm)] was obtained in 40% yield using a short-path distillation apparatus. A similar preparation of geranyl chloride on a 500-mmol scale gave geranyl chloride in 79% yield [bp 46–48° (0.5 mm), lit.[14] bp 64–65° (0.04 mm)]. The ir spectra of these chlorides showed the absence of OH groups and characteristic broad absorptions at 1750 cm^{-1} due to carbon–carbon double bond stretch.

The chemical shifts (60 MHz) of the alcohols and chlorides are given in Table I. The nmr spectra were determined using Varian

TABLE I

CHEMICAL SHIFTS[a]

Group	X = OH	X = Cl
$-CH_2X$	4.08 (4.14)	4.00 (4.02)
$=CHCH_2X$	5.42 (5.42)	5.41 (5.41)
$-CH_2CH_2$	2.10 (2.08)	2.09 (2.08)
$Me_2C=CH$	5.10 (5.15)	5.08 (5.05)
$CH_3C=CCH_2X$	1.60 (1.72)	1.75 (1.56)
$(CH_3)_2C=C$	1.72 (1.72)	1.58 (1.68)

[a] In ppm relative to TMS; the values for the geranyl derivatives are in parentheses. The boldface H' sindicate the protons examined.

A 60 or T 60 or Jeolco C-60 H nmr spectrometers. Solvolyses of these chlorides gave clean first-order kinetics for more than 3 half-lives.[9]

Attempts to prepare the amines by treating the chlorides with sodamide or with sodium azide, followed by reduction,[15,16] gave mixtures. The amines were therefore prepared from freshly prepared samples of the chlorides *via* the phthalimides which have already been reported but without full details of their preparation.[17] Geranyl chloride (390 mmol) was heated on a steam bath with potassium phthalimide (450 mmol) in dry DMF (250 ml) for 22 hr. The amide product was recrystallized twice (MeOH) and geranylphthalimide, mp 60–61.5°, was obtained in 80% yield. Its nmr spectrum (60 MHz) showed aromatic protons (4) at 7.72 ppm, vinyl protons (2) at 5.25 and 5.02 ppm, and $-CH_2NH$ protons (2) at 4.28 ppm. It was decomposed using 0.85 *M* hydrazine in refluxing ethanol (3 hr). The amine was extracted into hexane, and the solution was washed with solid $NaHCO_3$, and dried and distilled in a short-path apparatus [bp 49–52°, (0.25 mm), lit.[16] 105° (19 mm)]. The overall yield was 20% largely because of losses in crystallization of the phthalimide.

The same method was used for nerylamine, starting with 100 mmol of the chloride. Neryl phthalimide had mp 59–60.5°, and the nmr spectrum (60 MHz) showed four aromatic protons at 7.70 ppm and two vinyl protons at 5.20 ppm. Nerylamine, prepared as already described, had bp 48–50° (0.3 mm).

The phosphates and pyrophosphates of nerol and geraniol were prepared by Cramer's method,[3] with some modifications. Nerol (30 mmol) was treated with trichloroacetonitrile (62.5 mmol) in dry CH_3CN (100 ml). Di(triethyl)ammonium phosphate (60 mmol) was added over 0.5 hr with stirring; after a further 4 hr the solvent was removed *in vacuo* and the residual oil was dissolved in NH_3–EtOH. The white solid was filtered and washed with dry Me_2CO and then treated with cyclohexylamine (5 ml) in 70% aqueous MeOH (50 ml). Crystals of the dicyclohexylammonium phosphate separated on cooling and were washed with acetone and then with ether. The phosphate was recrystallized from water containing cyclohexylamine giving a 12% yield. The filtrate was treated with LiCl (100 mmol) giving the lithium salt of the pyrophosphate, which was purified by solution in water and precipitation with acetone in 12% yield.

Geranyl phosphate and pyrophosphate were prepared by this method. Hydrolysis of these esters using alkaline phosphatase from *E. coli* (Worthington) gave alcohols which were pure by glc.

Deamination.—The amines were deaminated under four sets of conditions, on a 5-mmol scale using 30 mmol of $NaNO_2$: (i) in 0.1 *M* HCl (100 ml) with $NaNO_2$ at 23° with stirring for 1 hr; (ii) in glacial HOAc (50 ml) with $NaNO_2$ at 23° with stirring for 1.5 hr; (iii) in glacial HOAc (50 ml) and 1 *M* NaOAc with $NaNO_2$ added with stirring (the mixture was left for 18 hr at 23°); (iv) in 100 ml of aqueous 1 *M* HOAc and 1 *M* NaOAc, pH 4.7 with $NaNO_2$ at 23° with stirring for 15 hr.

The products were extracted with ether after neutralization of the reaction solution by adding it slowly to aqueous $NaHCO_3$.

Hydrolyses.—The phosphates and pyrophosphates (1 mmol) were allowed to hydrolyze in stirred water (50 ml) for 30 min. The pH was adjusted using dilute HCl. The solution was extracted with pentane, and the pentane solution was washed with a $NaHCO_3$ and then dried ($MgSO_4$). The solution was concentrated using a 2-ft Vigreux column. The same general procedure was used for hydrolysis of the chlorides.

Product Analyses.—The products were analyzed by glc using a Varian Aerograph 1200 with a flame ionization detector and a Disc integrator. Tests with synthetic mixtures of the products showed that the products were stable under the reaction conditions and were not lost in the isolation, and the response of the detector was corrected for the various products.

Three columns were used for the glc analyses: (i) 24 ft × $^1/_{16}$ in. 1.5% TCEP, 1.5% Carbowax-4000 at 95° for olefins and methyl ethers and 90–150° at 4°/min for alcohols; (ii) 24 ft × $^1/_{16}$ in. 2% Carbowax-4000 at 90° for olefins and methyl ethers and 90–140° at 2°/min for alcohols; (iii) 150 ft × 0.01 in. Carbowax-4000 and 1.3–2.4 ml min^{-1} flow rate of N_2. Chromosorb G (100–120) and a flow rate of 50 ml min^{-1} was used for the packed columns.

Results

Hydrolysis Products.—The products of hydrolyses of neryl and geranyl chloride in acetone–water are very similar to those for hydrolyses of the phosphates and pyrophosphates in dilute acid (Tables II and III

TABLE II

SOLVOLYSIS PRODUCTS OF THE CHLORIDES[a]

	Neryl	Geranyl
Limonene	3 } (1)	} (4)
Terpinolene	2 }	}
Myrcene		1
Other olefins	1[b] (1[b])	1[c] (3[c])
Linalool	20 (17)	81 (70)
Nerol	2 (3)	
Geraniol		10 (16)
α-Terpineol	72 (58)	7 (6)
Total cyclization	77 (63)	7 (10)

[a] Mol % at 25° in acetone water 5:95 v/v; the values in parentheses are for acetone–water 70:30 v/v. [b] Myrcene and ocimene. [c] Largely ocimene.

TABLE III

HYDROLYSIS OF PHOSPHATES AND PYROPHOSPHATES[a]

Product	NP[b]	NPP[b]	GP[c]	GPP[b]
Acyclic olefins	Trace		1.5	Trace
Limonene	1.9	1.5		
Terpinolene	1.4	1.2		
Linalool	24.9	26.5	88.1	66.7
Nerol	2.9			0.3
Geraniol	Trace		9.8	5.3
α-Terpineol	69.0	70.2	0.6	20.7
Total cyclization	72.3	72.9	0.6	20.7

[a] At 25° in water. [b] pH 2. [c] pH 1.5.

(14) G. Stork, P. A. Grieco, and M. Gregson, *Tetrahedron Lett.*, 1393 (1969).

(15) M. S. Kharasch, W. Nudenberg, and E. K. Fields, *J. Amer. Chem. Soc.*, **66**, 1276 (1944).

(16) M. O. Forster and D. Caldwell, *J. Chem. Soc.*, **103**, 1343 (1913).

(17) R. B. Bates, R. H. Carnighan, and J. H. Schauble, *Chem. and Ind.*, 1020 (1962).

and ref 3 and 4), although we used a higher pH for hydrolyses of the phosphates and pyrophosphates and aqueous organic solvents for hydrolysis of the chlorides. The chlorides give slightly more olefinic products than the phosphates and pyrophosphates, possibly because of differences in the solvents.

Deamination.—Although similar products are obtained in the deaminations as in the solvolyses (Tables II–V and ref 3 and 4), the compositions differ.

TABLE IV

DEAMINATION OF NERYLAMINE[a]

	Solvent			
Product	H_2O	HOAc[b]	HOAc[c]	OAc⁻–HOAc[d]
Limonene	9.6	14.2	10.7	9.6
Linalyl acetate		7.1	6.3	1.7
Nerol	13.7	6.4	9.8	2.9
Neryl acetate		46.2	50.1	17.6
Geraniol	9.4	1.5	1.6	4.6
Geranyl acetate		5.6	4.5	14.9
α-Terpineol	32.5	2.8	2.5	33.9
α-Terpinyl acetate		12.8	10.9	3.2
Total cyclization	32.5	29.8	24.1	46.7

[a] At 25.0°. [b] Glacial HOAc. [c] 1 *M* NaOAc in glacial HOAc. [d] 1 *M* NaOAc + 1 *M* HOAc in water at pH 4.7.

TABLE V

DEAMINATION OF GERANYLAMINE[a]

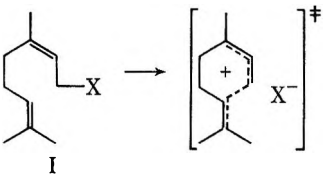
	Solvent			
Product	H_2O	HOAc[b]	HOAc[c]	OAc⁻–HOAc[d]
Acyclic olefins	4.0	2.9	7.2	5.1
Linalool	28.7	4.3	3.5	23.5
Linalyl acetate		9.7	8.6	2.8
Nerol	14.8	3.6	1.4	5.9
Neryl acetate		19.0	6.7	12.3
Geraniol	51.0	6.4	8.1	11.4
Geranyl acetate		52.9	64.2	37.9
α-Terpineol	0.6	0.3		0.7
α-Terpinyl acetate		0.6	Trace	Trace
Total cyclization	4.6	3.8	7.2	5.8

[a] At 25.0°. [b] Glacial HOAc. [c] 1 *M* NaOAc in glacial HOAc. [d] 1 *M* NaOAc + 1 *M* HOAc in water at pH 4.7.

One notable difference is that limonene (V) was the only olefin found from nerylamine, whereas only acyclic olefins were obtained from geranylamine (these acyclic olefins were myrcene and ocimene, but the glc conditions used for these particular experiments did not separate them cleanly). In addition, more olefinic products are formed in deamination than in solvolysis. Other marked differences are that cyclization is less important in deamination than in solvolysis, and that nerol and geraniol are much more evident in deaminations than in solvolyses.

Discussion

Variation of Leaving Group.—The formation of cyclic products in SN1 reactions of neryl compounds has long been recognized,[2-4] and kinetic deuterium isotope effects show that there is π participation by the isopropylidene group and allylic stabilization in transition state formation,[9] as suggested from studies of the alcohol, phosphate, and pyrophosphate reactions. Only



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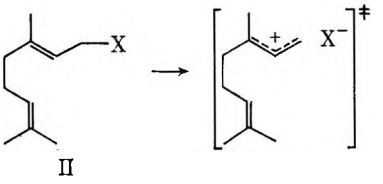
allylic stabilization is important in SN1 reactions of geranyl chloride, and the carbonium ions generated in solvolysis undergo only limited interconversion.



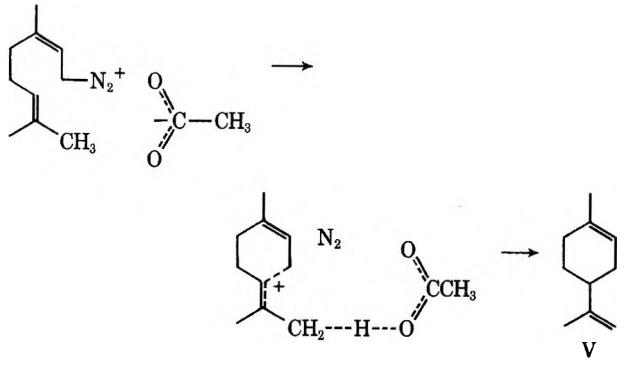
II

Deamination of aliphatic amines gives products whose composition and stereochemistry are sufficiently different from those of solvolysis products to suggest differences in the carbonium ion intermediates in the two sets of reactions.[10-12] These differences are apparent in the reactions discussed here (Tables II–V). Cyclization is less for deamination than solvolysis, probably because π participation is kinetically important in the formation of the transition state from neryl chloride or phosphate whereas loss of nitrogen from a diazonium ion requires no assistance from a neighboring group, and there is no restriction on the conformation of the reacting nerylamine or the cationic intermediates derived from it. There is much less interconversion of the geometrically isomeric neryl and geranyl compounds in solvolyses (Tables II and III and ref 3 and 4) than in deamination (Tables IV and V). This greater interconversion can be ascribed to the high energy of the cationic intermediates found in deamination.[10]

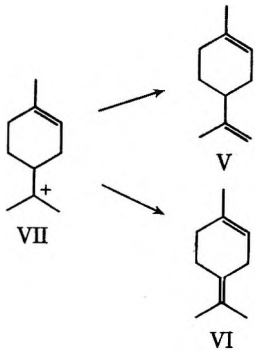
Solvolysis also differs from deamination in that its major products are tertiary alcohols (linalool or α-terpineol) or their derivatives, whereas deamination gives considerable amounts of the primary alcohols, suggesting that structural reorganization is relatively unimportant in the conversion of a diazonium ion into a carbonium ion and thence into products.

The formation of the acyclic olefins, myrcene and ocimene, by deamination of geranylamine and in solvolysis is readily understandable.[2,3] However the differences in the olefins formed by deamination of nerylamine and solvolyses of neryl chloride and phosphates are striking because, whereas deamination gives almost wholly the cyclic olefin limonene (V), solvolysis gives approximately equal amounts of limonene (V) and terpinolene (VI).[3,9] A rationalization of this behavior is that the counterion (*e.g.*, acetate) selectively deprotonates the methyl group during decomposition of the diazonium ion, as shown in Scheme I for that part of the reaction which gives elimination. Removal of a proton by the counterion also accounts for the greater proportion of elimination in deamination than in solvolysis of the chlorides or phosphates. (similar mechanisms could be written for decomposition of a covalent diazoacetate, although an ion pair is a more probable intermediate). For solvolysis of the chloride we assume that loss of the proton from the

SCHEME I

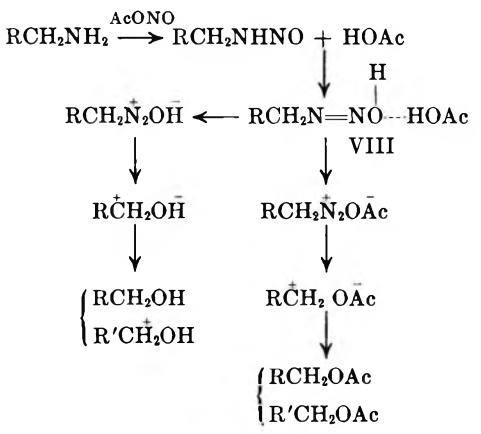


methyl group is not assisted by the leaving group, so that the terpinyl cation (VII) can give either limonene (V) or terpinolene (VI).



The substitution products of deamination can be explained by invoking ion-paired intermediates.[10-12] The formation of both alcohols (*ca.* 15%) and acetates (*ca.* 85%) even for deamination in glacial acetic acid suggests the following reactions, assuming acetyl nitrite as the most important nitrosating agent (Scheme II).

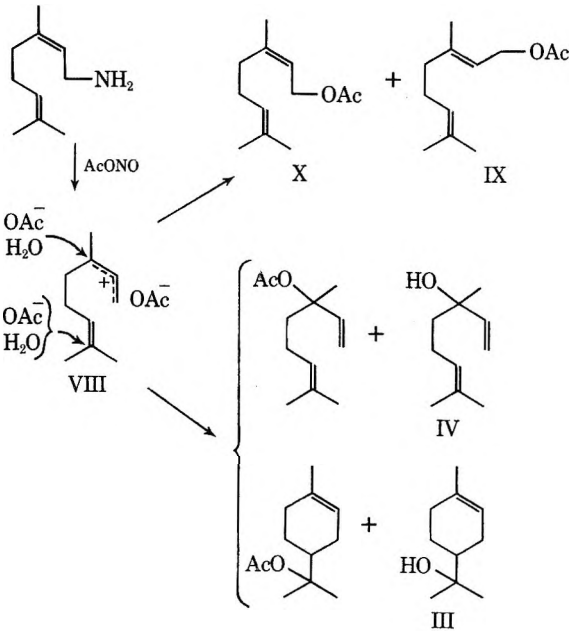
SCHEME II



For deamination in glacial acetic acid the ratio of acetate to alcohol in the products is affected little by addition of acetate ion, as predicted by Scheme II.

Deamination of nerylamine in aqueous acetate buffer (2 *M*, pH 4.7) gives an acetate to alcohol ratio of 3-6:1 for geranyl and neryl products, but one of *ca.* 0.1:1 for linalyl and terpinyl products. Both product ratios are greater than the molar ratio of 0.04:1 for acetate ion to water, as expected in view of the greater nucleophilicity of acetate ion, and these results suggest that the nitrosation gives largely a diazo compound which collapses internally *via* VIII to geranyl or neryl acetates (IX and X), but which is attacked by water or acetate ion from the bulk of the solvent to give acetate to alcohol ratios for linalool and α-terpineol which are close to the acetate ion to water ratio (Scheme III).

SCHEME III



These results can be related to the changes in alcohol to acetate ratio in the deamination of benzyl-, diphenylmethyl-, and tritylamines in nitrous acid–acetic acid, where the acetate to alcohol ratio decreases with increasing carbonium ion stability.[10] The variation of products in the deamination of 1- and 4-aminooctane can also be explained in terms of ion-pair intermediates which can decompose either by collapse of an ion pair or by attack of an external nucleophile, and where the products can be related to carbonium ion stability.[12]

The differences between the products of deamination and solvolysis in neryl and geranyl compounds are understandable in terms of the energetic carbonium ions formed in deamination which decompose with little discrimination to a variety of products, and before the counterion has time to diffuse away.

Within the accuracy of the measurements no bicyclic terpenoids have been detected as products of the solvolysis of neryl and geranyl compounds,[2-4,18] and we found none in our reactions. Their absence is understandable in terms of the reluctance of an α-terpinyl-like cation to take up a boat conformation which would be required for formation of bicyclic products. However, thermodynamic considerations suggest that such products could be derived from acyclic precursors.[19]

Registry No.—Nerylamine, 36615-19-7; geranylamine, 6246-48-6; geranylphthalimide, 36615-20-0; nerylphthalimide, 36615-21-1.

(18) C. F. Wilcox and S. S. Chibber, *J. Org. Chem.*, **27**, 2332 (1962); *cf.* R. S. Bly and H. L. Dryden, *Chem. Ind. (London)*, 1287 (1959); G. Le Ny, *C. R. Acad. Sci.*, **251**, 1526 (1960).

(19) R. M. Gascoigne, *J. Chem. Soc.*, 876 (1958).

Bufadienolides. 21. Synthesis of Cinobufagin from Bufotalin[1]

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A synthetic method was developed for transformation of bufotalin (**1a**) to cinobufagin (**5b**). The procedure was based on dehydration of bufotalin acetate (**1b**) to olefin **2** which upon treatment with hypobromous or hypoiodous acid afforded halohydrin **4**. Treatment of halohydrin **4** with either activated alumina or pyridine yielded cinobufagin acetate (**5a**). Selective acid-catalyzed hydrolysis of diacetate **5a** was employed to obtain cinobufagin (**5b**). A number of other cinobufagin derivatives were prepared including deacetylcinobufagin (**5d**) and the new bufadienolide 3-epicinobufagin (**9a**).

Cinobufagin (**5b**) and deacetylcinobufagin (**5d**) are two prominent components of the Chinese medicinal preparation Ch'an Su.[2] The structure of bufotalin (**1a**), another important toad venom constituent, has recently been reconfirmed.[3] To provide further support for the structure of cinobufagin an unequivocal transformation of bufotalin (**1a**) to cinobufagin was undertaken. The interrelationship of bufotalin with cinobufagin by synthesis was also required as part of a projected total synthesis proceeding from 14-dehydrobufalin[4] *via* bufotalin to cinobufagin.

A partial synthesis of cinobufagin (**5b**) was realized by the following route. Bufotalin (**1a**) was isolated from the toad venom preparation Ch'an Su and acetylated. Dehydration of bufotalin acetate (**1b**) was easily performed in pyridine with thionyl chloride to yield olefin **2**. Direct epoxidation of olefin **2** using *m*-chloroperbenzoic acid gave as exclusive product 14α,15α-epoxide **3**, a new isomer of cinobufagin acetate. This result was completely analogous to our earlier experience with α-epoxidation of 14-dehydrobufalin.[4] Accordingly, the halohydrin route developed for synthesis of resibufogenin[4] was applied to the problem at hand. Hypobromous acid prepared *in situ* from *N*-bromoacetamide (NBA) or *N*-bromosuccinimide (NBS) was added to 14-dehydrobufotalin acetate (**2**), and the resulting bromohydrin (**4a**) was treated with basic alumina or pyridine to afford cinobufagin acetate (**5a**). Use of *N*-iodosuccinimide (NIS) and proceeding *via* iodohydrin **4b** led to comparable yields of cinobufagin acetate. Preparation of the hypohalous acid in aqueous acetone and epoxide formation in pyridine provided approximately 80% yields of cinobufagin acetate, while preparation of the halohydrin in dioxane containing a small amount of perchloric acid and ring closure with basic alumina proved less satisfactory and led to about 30% yields of epoxide **5a**.

Selective hydrolysis of cinobufagin acetate (**5a**) to the natural product (cinobufagin, **5b**) was not easily accomplished. Mild treatment of cinobufagin acetate with basic alumina, the basic ion-exchange resin CG-400, ammonium hydroxide, or aqueous potassium bicarbonate gave almost exclusively 3β-acetoxy-16β-hydroxy-14β,15β-epoxy-5β-bufa-20,22-dienolide (**5c**) thereby illustrating sensitivity of the 16β-acetate to base. The same product (**5c**) was obtained using the enzyme Taka-diastase produced by *Aspergillus oryzae*. Fortunately, acid hydrolysis of cinobufagin acetate using Dowex-50 W-X8 gave both cinobufagin (**5b**) and deacetylcinobufagin (**5d**) accompanied by alcohol **5c**. Both cinobufagin and deacetylcinobufagin were found identical with authentic specimens isolated from Ch'an Su. The synthetic sample of cinobufagin was further characterized by preparation of 3,5-dinitrobenzoate (**5e**), cinnamate (**5f**), and succinate (**5g**) esters.

Preparation of deacetylcinobufagin was easily accomplished by hydrolysis of cinobufagin using CG-400 (OH^- form), ammonium hydroxide, Taka-diastase or Dowex-50 W-X8 (H^+ form).[5] The reverse reaction (**5d** → **5b**) was found possible using hot acetic acid, but as expected acetates **5c** and **5a** accompanied cinobufagin.

For the purpose of facilitating the possible isolation of 3-epicinobufagin (**9a**) from toad venom[6] oxidation of cinobufagin to cinobufagone (**6a**) was next viewed.[7] Oxidation of cinobufagin with chromium trioxide in acetic acid easily afforded cinobufagone (**6a**). Mild saponification of ester **6a** gave alcohol **6b**. The same product (**6b**) was prepared from deacetylcinobufagin (**5d**) by selective oxidation with chromium trioxide–pyridine or by *N*-bromoacetamide in methanol–pyridine–water. Chromic acid oxidation of either alcohol **6b** or deacetylcinobufagin provided diketone **7**. The ketone (**8**) isomeric to ketone **6a** was readily obtained by oxidizing alcohol **5c** with chromium trioxide in acetic acid.

Interpretation of the proton magnetic spectra of ketones **6**, **7**, and **8** combined with the partial synthesis of cinobufagin described herein provided further support for the structure of this substance and that of

(1) This investigation was supported by Public Health Service Research Grants CA-11451-02 and CA-10612-04 from the National Cancer Institute. We also wish to thank the National Science Foundation for Grant No. GB 4939 and GP 6979 which aided in purchase of the Varian MAT CH4B and SM1B mass spectrometers. For Bufadienolides (paper 20) and Steroids and Related Natural Products (paper 76), see Y. Kamano and G. R. Pettit, *Chem. Pharm. Bull.*, in press.

(2) A mixture corresponding to cinobufagin and cinobufotalin was isolated from toad venom by N. Kotake, *Justus Liebigs Ann. Chem.*, **465**, 11 (1928); H. Jensen and K. K. Chen, *J. Biol. Chem.*, **87**, 741 (1930); R. Tschesche and H. A. Offe, *Chem. Ber.*, **68**, 1998 (1935); and R. Tschesche and W. Haupt, *ibid.*, **70**, 43 (1937). Chromatographic resolution of the cinobufagin–cinobufotalin mixture was achieved by N. Kotake and K. Kuwada, *Nippon Kagaku Zasshi*, **58**, 838 (1937). For a summary of cinobufagin structural studies, refer to reviews by Y. Kamano, *Kagaku No Ryoiki*, **24**, 57 (1970), and R. Ode, Y. Kamano, and G. R. Pettit, "MTP International Review of Science, Organic Chemistry Series One," Vol. 8, W. D. Johns, Ed., Butterworths, London, 1972.

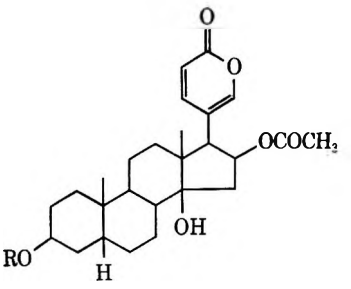
(3) G. R. Pettit, P. Brown, F. Bruschweiler, and L. E. Houghton, *Chem. Commun.*, 1566 (1970).

(4) G. R. Pettit, Y. Kamano, F. Bruschweiler, and P. Brown, *J. Org. Chem.*, **36**, 3736 (1971).

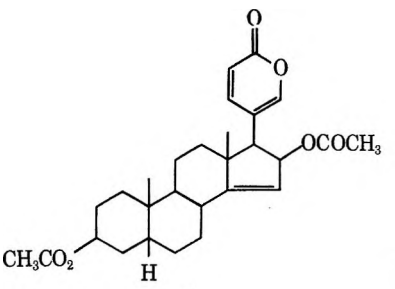
(5) Saponification of cinobufagin to desacetyl cinobufagin with aqueous potassium bicarbonate has been described by J.-T. Ruckstuhl and K. Meyer, *Helv. Chim. Acta*, **40**, 1270 (1957).

(6) Isolation of 3-epibufalin from the Japanese toad *Bufo formosus* Boulenger has been described by E. Iseli, M. Kotake, E. K. Weiss, and T. Reichstein, *ibid.*, **48**, 1093 (1965). A partial synthesis of 3-epibufalin has been summarized by C. Tamm, *ibid.*, **43**, 338 (1960).

(7) Cinobufagone (**6a**) had been previously described: N. Kotake and K. Kuwada, *Sci. Pap. Inst. Phys. Chem. Res. Tokyo*, **32**, 1 (1937); J.-P. Ruckstuhl and K. Meyer, *Helv. Chim. Acta*, **41**, 2121 (1958).



1a, R = H
b, R = $COCH_3$



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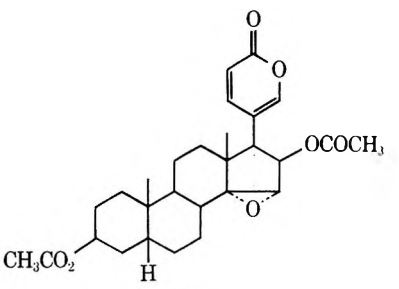

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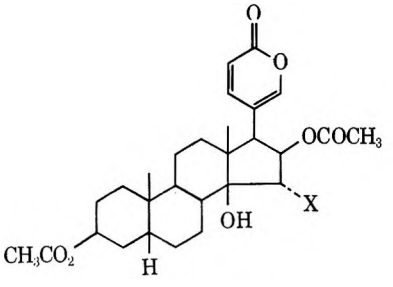
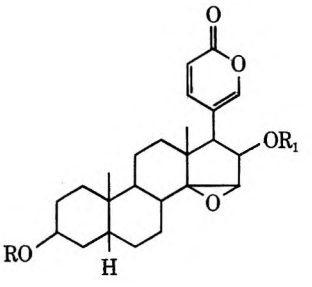
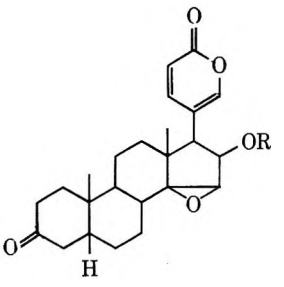


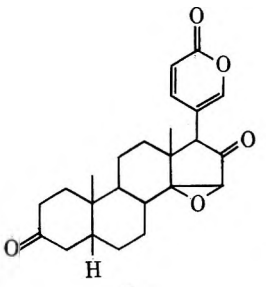
4a, X = Br
b, X = I



5a, R = R_1 = $COCH_3$
b, R = H, R_1 = $COCH_3$
c, R = $COCH_3$, R_1 = H
d, R = R_1 = H
e, R = 3,5-$(NO_2)_2C_6H_3CO$, R_1 = $COCH_3$
f, R = $C_6H_5CH{=}CHCO$, R_1 = $COCH_3$
g, R = $HO_2CCH_2CH_2CO$, R_1 = $COCH_3$



6a, R = $COCH_3$
b, R = H



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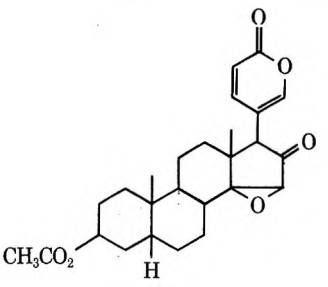

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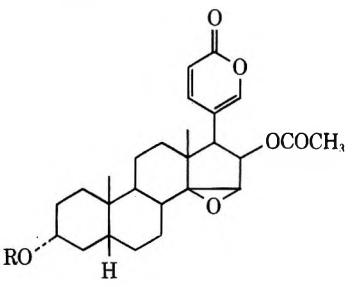

9a, R = H
b, R = $COCH_3$

bufotalin (**1a**). For example, the 17α-proton signal of ketones **7** and **8** appeared as a sharp singlet as compared to the doublet (J = 6.5 Hz) of ketone **6**, thus verifying the D-ring substitution relationships.

Reduction of cinobufagone (**6a**) with sodium borohydride provided 3-epicinobufagin (**9a**) accompanied by cinobufagin (**5b**) in a 3:1 ratio. Acetylation of the 3α-alcohol (**9a**) gave acetate **9b**, and chromic acid oxidation led to the starting ketone **6a**. The series of reactions just described and the preceding synthetic interrelationship with bufotalin served to substantiate firmly structure **5b** for cinobufagin.

Experimental Section

Bufotalin, cinobufagin, and deacetylcinobufagin were isolated from Ch'an Su. The Chinese medicinal preparation, Ch'an Su, is generally prepared from venom of local toads such as *Bufo bufo gargarizans* Cantor and *Bufo melanostrictus* Schneider and is available in the Asian market in the "disk-like" (round cake, dark brown and hard) and "thin-plate" (thin, brownish black) forms. The Japanese variety is known as Senso.

Solvents were redistilled and ligroin refers to a fraction boiling at 60–80°. The Taka-diastase (Fisher Scientific Co.) was used as received. All solvent extracts of aqueous solutions were dried over sodium sulfate and concentrated or evaporated under reduced pressure using a rotatory evaporator. Basic alumina (Merck, Rahway, "Suitable for Chromatography") and silica gel (0.05–0.20 mm, E. Merck, Darmstadt) were employed for column chromatography. Silica gel thin-layer chromatography plates were supplied by E. Merck and acetone–chloroform–*n*-hexane (3:3:4) or ethyl acetate–*n*-hexane (9:1) or methanol–ethyl acetate–*n*-hexane (1:3:4) was employed as solvent, and the plate was developed with sulfuric acid or iodine.

All analytical samples were colorless and displayed a single spot on a thin layer chromatograph. The mutual identity of specimens prepared by different procedures or with natural products was established by mixture melting point determination and infrared spectral as well as thin-layer chromatographic comparisons. Melting points were determined with a micro hot-stage apparatus (Reichert, Austria) and are uncorrected. The ultraviolet (Perkin-Elmer, Model 400, methanol solution), infrared (potassium bromide pellets, Beckman IR-12 instrument), and pmr (deuteriochloroform solution with tetramethylsilane as internal standard, Varian A-60) were recorded by Miss K. Reimer The low resolution mass spectra were obtained by Messrs. Richard Scott and Eugene Kelley using an Atlas CH-4B instrument equipped with a molecular beam type inlet system. The results of elemental microanalyses were provided by the laboratories of Dr. A. Bernhardt, 5251 Elbach über Engelskirche, Muhheim (Ruhr) West Germany.

3β-Acetoxy-14-dehydrobufotalin (3β,16β-Diacetoxy-5β-bufa-14,20,22-trienolide) (2).—To a solution of bufotalin acetate (**1b**,

289 mg) in pyridine (19 ml) was added 1.9 ml of thionyl chloride. The mixture was allowed to stand for 25 min at room temperature, poured into ice–water, and extracted with chloroform. The chloroform extract was washed with water, 2% hydrochloric acid, and water and evaporated. The product (300 mg) was chromatographed on a column of silica gel. Elution with ligroin–acetone (9:1) gave olefin **2** (122 mg), mp 178–179°, as colorless prisms from acetone–*n*-hexane. Recrystallization from the same solvent provided a pure sample melting at 204–207°: λ_{max} nm (log ϵ) 299 (3.71); ν_{max} cm^{-1} 1760, 1740 (ester CO and conjugated CO), 1660, 1550 (conjugated C=C), 1270, 1260, 1240 (ester C–O), 958, 750 (C=C); pmr δ 0.80 (3 H, s, 18-CH_3), 0.98 (3 H, s, 19-CH_3), 2.05 (3 H, s, 3-$OCOCH_3$), 2.65 (1 H, d, J = 9 Hz, 17-H), 3.37 (3 H, s, 16-$OCOCH_3$), 4.52 (1 H, d, J = 9 Hz, 16-H), 5.06 (1 H, broad s, 3-H), 5.45 (1 H, s, 15-H), 6.31 (1 H, d, J = 10 Hz, 23-H), 7.28 (1 H, d, J = 10 Hz, 22-H), 7.37 (1 H, s, 21-H); mass spectrum m/e 468 (M^+).

Anal. Calcd for $C_{28}H_{36}O_6$: C, 71.77; H, 7.74. Found: C, 71.91; H, 7.68.

3β,16β-Diacetoxy-14α,15α-epoxy-5β-bufa-20,22-dienolide (14α,15α-Epoxycinobufagin Acetate) (3).—To a solution of olefin **2** (80 mg) in 5 ml of chloroform, *m*-chloroperbenzoic acid (64 mg) was added, and the mixture was allowed to stand at room temperature for 30 min. After dilution with chloroform, the solution was poured into ice–water. The chloroform layer was washed with dilute sodium thiosulfate solution and water and concentrated to dryness. The product (80 mg) was chromatographed on a column of silica gel. Elution with ligroin–acetone (9:1) provided 14α,15α-epoxide **3** (33 mg), as a colorless amorphous solid: λ_{max} nm (log ϵ) 302 (3.69); ν_{max} cm^{-1} 1750, 1740 (ester CO and conjugated CO), 1640, 1540 (conjugated C=C), 1260–1240, 1230 (ester C–O), 950, 750 (C=C); pmr δ 0.77 (3 H, s, 18-CH_3), 1.0 (3 H, s, 19-CH_3), 2.06 (3 H, s, 3-$OCOCH_3$), 2.54 (1 H, d, J = 9.5 Hz, 17-H), 3.46 (3 H, s, 16-$OCOCH_3$), 3.72 (1 H, s, 15-H), 3.91 (1 H, d, J = 9.5 Hz, 16-H), 5.08 (1 H, broad s, 3-H), 6.30 (1 H, d, J = 10 Hz, 23-H), 7.19 (1 H, d, J = 10 Hz, 22-H), 7.26 (1 H, s, 21-H); mass spectrum m/e 484 (M^+).

Anal. Calcd for $C_{28}H_{36}O_7$: C, 69.40; H, 7.48. Found: C, 69.53; H, 7.74.

Cinobufagin Acetate (5a). Method A. Using NBA.—In a typical experiment a solution of *N*-bromoacetamide (25 mg) in acetone (0.5 ml)–water (0.5 ml) was added to a solution of olefin **2** (25 mg) in acetone (4 ml). After stirring for 30 min, the mixture was allowed to stand for 20 hr at room temperature. A solution prepared from sodium sulfite (anhydrous, 25 mg) in water (1 ml) was added, and the mixture was poured into ice–water and extracted with chloroform. Following a wash with water the chloroform extract was evaporated to dryness. The crude bromohydrin (**4a**, 22 mg) was stirred in pyridine (1 ml) for 2 hr at room temperature. The solvent was evaporated, and the product was chromatographed on a column of silica gel. Elution with ligroin–acetone (19:1) provided 20 mg (80%) of cinobufagin acetate (**5a**) as needles melting at 202–205°.

In another experiment a solution of *N*-bromoacetamide (68 mg) in dioxane (1 ml) was added to a mixture prepared from 3β,16β-diacetoxy-5β-bufa-14,20,22-trienolide (70 mg) (**2**) in dioxane (3 ml) containing 70% perchloric acid (0.02 ml). Before adding a solution prepared from sodium sulfite (70 mg) and water (1.5 ml), the mixture was stirred 90 min at room temperature. The solution was concentrated under reduced pressure to approximately one-third of the original volume, poured into ice–water with stirring, and extracted with chloroform. The chloroform extract was washed with water and evaporated to dryness. The crude bromohydrin (**4a**, 75 mg), without further purification, was chromatographed on basic alumina (3 g). The fraction (27 mg) eluted by benzene–chloroform (19:1) was crystallized from acetone to afford 15.5 mg (22%) of cinobufagin acetate (**5a**) as needles melting at 203–205°.

Method B. Using NBS.—The preceding reaction (method A, pyridine procedure) was repeated using 50 mg of olefin **2** and 50 mg of *N*-bromosuccinimide. In this example the reaction time was 18 hr (after stirring for 10 min at room temperature), and the crude yield of bromohydrin (**4a**) was 52 mg. Treatment of bromohydrin **4a** with pyridine (2 ml), chromatography of the product on a column of silica gel, and elution with ligroin–acetone (19:1) provided 41 mg (82%) of cinobufagin acetate (**5a**), mp 202–204°.

Method C. Using NIS.—When *N*-iodosuccinimide (50 mg) was substituted for NBA as described in the second part of method A, olefin **2** (50 mg) led to 46 mg of crude iodohydrin (**4b**). Conversion of the iodohydrin (25 mg) into cinobufagin acetate by the basic alumina technique resulted in a 34% yield (17 mg) of product, mp 202–203°.

The pyridine (1 ml) route with iodohydrin **4b** (25 mg) provided an 83% yield (21 mg) of product (**5a**) melting at 201–204°.

The samples of cinobufagin acetate (**5a**) prepared by methods A–C were found identical with the acetate (**5a**) prepared from natural cinobufagin (**5b**).

3β-Acetoxy-16β-hydroxy-14β,15β-epoxy-5β-bufa-20,22-dienolide (5c). Method A. Using Alumina.—The mixture prepared from cinobufagin acetate (**5a**, 20 mg) in benzene (3 ml)–ether (1.5 ml) and basic alumina (600 mg) was stirred at room temperature. After 24 hr, methanol (1 ml) was added, and stirring was continued for 18 hr. The solution obtained by filtration was concentrated, and the crude product (18 mg) was chromatographed on a column of silica gel. Elution with ligroin–acetone (9:1 and 5:1) provided 13.5 mg of 16β-alcohol **5c** as needles melting at 207–209° (from methanol).

Method B. Using Basic Ion-Exchange Resin.—The mixture prepared from cinobufagin acetate (**5a**, 20 mg), methanol (5 ml), water (0.5 ml), and 100 mg of Amberlite CG-400 (OH^- form) ion-exchange resin was stirred for 2 hr at room temperature. After filtration the solution was concentrated to afford 19 mg of crude product which was chromatographed on a column of silica gel. Elution with ligroin–acetone (9:1 and 5:1) and recrystallization from methanol provided 11 mg of 16β-alcohol **5c** as needles melting at 207–208°.

Method C. Using Ammonium Hydroxide.—To a solution of 20 mg of cinobufagin acetate (**5a**) in ethanol (6 ml)–water (1 ml), 0.1 ml of 30% ammonium hydroxide solution was added. The mixture was allowed to stand for 40 hr at room temperature and then neutralized with dilute hydrochloric acid, poured into water, and extracted with chloroform. The chloroform extract was washed with water and concentrated to dryness. The crude product (19 mg) was chromatographed on a column of silica gel and 16β-alcohol **5c** was eluted with ligroin–acetone (9:1 and 5:1) the yield after recrystallization from methanol was 15 mg as needles.

Method D. Using Taka-diastase.—A solution composed of cinobufagin acetate (**5a**, 20 mg), Taka-diastase (1 g), and methanol (10 ml)–water (5 ml), was allowed to stand for 14 days at 30°. After dilution with water, the mixture was extracted with chloroform, and the extract was washed with water and concentrated to dryness. The crude product (21 mg) was purified as described above to yield 13 mg of 16β-alcohol **5c** as needles melting at 205–208°.

Method E. Using Potassium Bicarbonate.—To a solution of cinobufagin acetate **5a** (14 mg) in methanol (3 ml), 17 mg of potassium bicarbonate in water (0.5 ml) was added. The solution was allowed to stand for 3 days at 30° and then acidified (pH 3.0) with dilute sulfuric acid. After extraction with chloroform, the extract was washed with water and concentrated to dryness. Recrystallization of the product (10 mg) from methanol provided 8 mg of 16β-alcohol **5c** as needles melting at 206–207°. Each sample of 16β-alcohol **5c** prepared by methods A–E exhibited the following physical constants: λ_{max}^{EtOH} nm (log ϵ) 298 (3.74); ν_{max} cm^{-1} 3400 (OH), 1730, 1710, 1695 (ester CO and conjugated CO), 1630, 1538 (conjugated C=C), 1260, 1245, 1230–1220 (ester C–O), 960, 840, 790, 755 (C=C); pmr δ 0.80 (3 H, s, 18-CH_3), 0.99 (3 H, s, 19-CH_3), 2.05 (3 H, s, 3-$OCOCH_3$), 2.60 (1 H, d, J = 9 Hz, 17-H), 3.07 (1 H, broad s, 3-H), 6.18 (1 H, d, J = 10.5 Hz, 23-H), 7.25 (1 H, d, J = 3 Hz, 21-H), 7.95 (1 H, dd, J = 3 and 10.5 Hz, 22-H); mass spectrum m/e 442 (M^+).

Anal. Calcd for $C_{26}H_{34}O_6$: C, 70.18; H, 7.68. Found: C, 70.56; H, 7.74.

Cinobufagin (5b).—A mixture prepared from cinobufagin acetate (**5a**, 200 mg) in ethanol (50 ml)–water (10 ml) and 2 g of the acidic ion-exchange resin Dowex 50W-X8 (H^+ form) was stirred for 40 hr at room temperature. The solution obtained by filtration was evaporated to dryness. The crude product (230 mg) was chromatographed on a column of silica gel. Elution with ligroin–acetone (19:1, 9:1, 5:1, and 3:1) provided 27 mg of **cinobufagin** (**5b**, as prisms from acetone melting at 213–215°), 20 mg of **3β-acetoxy-16β-hydroxy-14β,15β-epoxy-5β-bufa-20,22-dienolide** (**5c**, as needles from methanol melting at 206–207°), and 11 mg of **deacetylcinobufagin** (**5d**, as a colorless amorphous solid melting at 153–160°), in addition to unreacted starting material (**5a**, 120 mg).

The samples of cinobufagin (**5b**) and deacetylcinobufagin (**5d**) were found identical with natural specimens isolated from Ch'an Su. The sample of 16β-alcohol **5c** was found identical with material obtained by methods A–E, as described above.

Cinobufagin 3,5-dinitrobenzoate (**5e**) was prepared using cinobufagin (60 mg) in pyridine (1 ml), and 3,5-dinitrobenzoyl chloride (60 mg). After 18 hr at room temperature, the mixture was poured into ice–water and extracted with chloroform. The solvent extract was washed with dilute hydrochloric acid and water and concentrated to give 68 mg of crude product which was chromatographed on a column of silica gel. Recrystallization of the ligroin–acetone (9:1) fraction from acetone–methanol afforded an analytical sample (51 mg) as needles melting at 159–162°: $\lambda_{max}^{CHCl_3}$ nm (log ε) 294 (3.58); ν_{max} cm^{-1} 3100 (CH), 3040 (CH), 1760–1740, 1720 (ester CO and conjugated CO), 1630, 1600, 1500 (conjugated C=C), 1550 (conjugated C=C and C–NO_2), 1340 (C–NO_2), 1270–1260, 1240 (ester C–O and epoxy C–O), 980 (C=C), 870 (C–N), 835 (epoxy C–O), 757 (C=C); pmr δ 0.84 (3 H, s, 18-CH_3), 1.09 (3 H, s, 19-CH_3), 1.91 (3 H, s, 16-OCOCH_3), 2.84 (1 H, d, J = 9 Hz, 17-H), 3.69 (1 H, s, 15-H), 5.42 (1 H, broad s, 3-H), 5.54 (1 H, d, J = 9 Hz, 16-H), 6.22 (1 H, d, J = 11 Hz, 23-H), 7.19 (1 H, d, J = 3 Hz, 21-H), 7.94 (1 H, dd, J = 11 and 3 Hz, 22-H), 9.18 (3 H, m, aromatic protons); mass spectrum m/e 636 (M^+).

Anal. Calcd for $C_{33}H_{36}O_{11}N_2$: C, 62.24; H, 5.69; N, 4.56. Found: C, 62.47; H, 5.95; N, 4.38.

Cinobufagin cinnamate (**5f**) was obtained when cinobufagin (40 mg) in pyridine (4 ml) was treated with cinnamoyl chloride (40 mg) for 20 hr at room temperature. The product was isolated as described for 3,5-dinitrobenzoate ester **5e**, and the analytical sample was recyrstallized from methanol to afford 35 mg of ester **5f** decomposing at 250°: $\lambda_{max}^{CHCl_3}$ nm (log ε) 283 (5.88) and 302 (3.68); ν_{max} cm^{-1} 3100, 3040 (CH), 1760–1740, 1720 (ester O=C and conjugated CO), 1640, 1540 (conjugated C=C of α-pyrone ring), 1580, 1500 (conjugated C=C of phenyl group), 1270, 1240, 1220 (ester C–O and epoxy C–O), 955 (C=C), 910 (C=C), 850 (epoxy C–O), 770, 750 (C=C); pmr δ 0.82 (3 H, s, 18-CH_3), 1.02 (3 H, s, 19-CH_3), 1.89 (3 H, s, 16-OCOCH_3), 2.79 (1 H, d, J = 9.5 Hz, 17-H), 3.66 (1 H, s, 15-H), 5.22 (1 H, broad s, 3-H), 5.47 (1 H, d, J = 9.5 Hz, 16-H), 6.21 (1 H, d, J = 11 Hz, 23-H), 7.70–7.10 (about 8 H, m, 21-H and annamoyl group), 7.90 (1 H, dd, J = 11 and 3 Hz, 22-H); mass spectrum m/e 572 (M^+).

Anal. Calcd for $C_{35}H_{40}O_7$: C, 73.40; H, 7.04. Found: C, 73.11; H, 6.90.

Cinobufagin succinate (**5g**) was prepared from cinobufagin (50 mg) and succinic anhydride (100 mg) in pyridine (15 ml). The mixture was heated at reflux 2 hr, poured into ice–water, and extracted with chloroform, and the extract was washed with dilute sulfuric acid and water. Following removal of solvent, the residue (65 mg) was chromatographed on a column of silica gel. Elution with ligroin–acetone (3:1) and recrystallization from acetone provided 39 mg of needles (**5g**): mp 258–260°; λ_{max}^{ETOH} nm (log ε) 297 (3.75); ν_{max} cm^{-1} 3400–3100 (OH of COOH), 3040 (CH), 1740, 1728, 1720 (ester CO and conjugated CO), 1675 (COOH), 1620, 1540 (conjugated C=C), 1270, 1245, 1230 (ester C–O and epoxy C–O), 954 (C=C), 832 (epoxy C–O), 800, 750 (C=C); pmr (10% solution in $CDCl_3$) δ 0.82 (3 H, s, 18-CH_3), 0.97 (3 H, s, 19-CH_3), 1.89 (3 H, s, 16-OCOCH_3), 2.68 (4 H, s, CH_2CH_2), 2.81 (1 H, d, J = 9 Hz, 17-H), 3.68 (1 H, s, 15-H), 5.14 (1 H, broad s, 3-H), 5.46 (1 H, d, J = 9 Hz, 16-H), 6.20 (1 H, d, J = 11 Hz, 23-H), 7.15 (1 H, d, J = 3 Hz, 21-H), 7.90 (1 H, dd, J = 11 and 3 Hz, 22-H), 11.15 (1 H, broad peak, COOH); mass spectrum m/e 542 (M^+).

Anal. Calcd for $C_{30}H_{38}O_9$: C, 66.40; H, 7.06. Found: C, 66.24; H, 7.36.

Deacetylcinobufagin (**5d**). **Method A.**—The mixture prepared from cinobufagin (**5b**, 20 mg), benzene (3 ml), chloroform (1 ml), methanol (0.5 ml), and basic alumina was allowed to react and the product isolated as described above (method A) for preparation of 16β-alcohol **5c**. Chromatography of the crude product (17 mg) on a column of silica gel and elution with ligroin–acetone (3:1) provided 11 mg of alcohol **5d** as an amorphous solid.

In the following series of experiments alcohol **5d** was obtained from cinobufagin (**5b**) using methods B–D summarized for hydrolysis of cinobufagin acetate (**5a**) to 16β-alcohol **5c**, and elution of the silica gel column with ligroin–acetone (3:1). Cinobufagin (18 mg), in methanol (4.5 ml)–water (0.8 ml), was treated with 100 mg of CG-400 (OH^- form) to yield 9 mg of amorphous solid. The same yield was realized from cinobufagin (15 mg), ethanol (5 ml), water (0.5 ml), and 0.09 ml of 30% ammonium hydroxide solution. When a mixture of cinobufagin (30 mg), methanol (15 ml), water (7 ml), and Taka-diastase (1.5 g) was used 14 mg of amorphous deacetylcinobufagin was obtained.

Method B.—A mixture of 3β-acetoxy-16β-hydroxy-14β,15β-epoxy-5β-bufa-20,22-dienolide (**5c**, 18 mg), ethanol (5 ml), water (1 ml), and 0.2 g of Dowex 50W-X8 (H^+ form) was stirred for 40 hr at room temperature. The crude product (15 mg) was chromatographed on a column of silica gel. Elution with ligroin–acetone (5:1 and 3:1) yielded 10 mg of amorphous **5d** and 4 mg of starting material.

The specimens of deacetylcinobufagin obtained by methods A and B were found identical with the natural material isolated from Ch'an Su.

Acetylation of Deacetylcinobufagin (**5d**).—A solution of deacetylcinobufagin (**5d**, 100 mg) in glacial acetic acid (2 ml) was heated at reflux for 60 min. After evaporation of solvent the the residue was chromatographed on a column of silica gel. Elution with ligroin–acetone (19:1, 9:1, 5:1, and 3:1) provided 15 mg of **cinobufagin acetate** (**5a**, as needles melting a 202–204°), 21 mg of **cinobufagin** (**5b**, as prisms melting at 213–215°), and 27 mg of **3β-acetoxy-16β-hydroxy-14β,15β-epoxy-5β-bufa-20,22-dienolide** (**5c**, as needles melting at 206–208°), in addition to 33 mg of starting material (**5d**).

The sample of cinobufagin (**5b**) obtained in this experiment was found identical with the specimen isolated from Ch'an Su. Also, the samples of cinobufagin acetate (**5a**) and 3β-acetoxy-16β-hydroxy-14β,15β-epoxy-5β-bufa-20,22-dienolide (**5c**) were identical with the same materials prepared from natural cinobufagin.

Cinobufagone (**3-Oxocinobufagin, 6a**).—To a solution prepared from cinobufagin (**5b**, 500 mg) and glacial acetic acid (5 ml) was added with stirring chromic acid (110 mg)–acetic acid (6 ml). The oxidation was conducted at 15–18° for 4 hr. After decomposition of excess reagent with methanol (0.5 ml with stirring), the mixture was poured into ice–water and extracted with chloroform. The combined extract was washed with water and concentrated to dryness. Recrystallization of the residue (410 mg) from methanol led to 370 mg of 3-oxocinobufagin (**6a**) as needles: mp 235–236°; λ_{max}^{ETOH} nm (log ε) 297.5 (3.75); ν_{max} cm^{-1} 3040 (CH), 1740, 1725, 1700–1685 (ester, conjugated CO and ketone CO), 1635, 1540 (conjugated C=C), 1250, 1240, 1220 (ester C–O and epoxy C–O), 963 (C=C), 840 (epoxy C–O), 785, 750 (C=C); pmr δ 0.95 (3 H, s, 18-CH_3), 1.06 (3 H, s, 19-CH_3), 1.89 (3 H, s, 16-OCOCH_3), 2.82 (1 H, d, J = 9 Hz, 17-H), 3.68 (1 H, s, 15-H), 5.47 (1 H, d, J = 9 Hz, 16-H), 6.19 (1 H, d, J = 10.5 Hz, 23-H), 7.18 (1 H, d, J = 3 Hz, 21-H), 7.90 (1 H, dd, J = 10.5 and 3 Hz, 22-H); mass spectrum m/e 440 (M^+).

Anal. Calcd for $C_{26}H_{32}O_6$: C, 70.88; H, 7.32. Found: C, 70.57; H, 7.19.

3-Oxo-16β-hydroxy-14β,15β-epoxy-5β-bufa-20,22-dienolide (**6b**). **Method A. From Acetate 6a.**—The solution prepared from 3-oxocinobufagin (**6a**, 70 mg), methanol (56 ml), water (26 ml), and potassium bicarbonate (78 mg) was allowed to stand for 4 days at room temperature and then poured into ice–water. After acidification with dilute sulfuric acid and extraction with chloroform, the extract was washed with water and concentrated. The crude product (68 mg) was chromatographed on a column of silica gel and the fraction eluted with ligroin–acetone (3:1) was recrystallized from acetone to afford 44 mg of 3-oxo-16β-hydroxy-14β,15β-epoxy-5β-bufa-20,22-dienolide (**6b**) as needles, dec pt 233°.

In an analogous experiment, 3-oxocinobufagin (20 mg), ethanol (7 ml), water (1 ml), and 0.2 ml of 30% ammonium hydroxide was allowed to remain at room temperature 40 hr. Isolation of crude product (22 mg) and subsequent purification as just described gave 13 mg of recrystallized alcohol **6b**, dec pt 231–233°. The same product was obtained in 12-mg (dec pt 232–233°) yield employing 3-oxocinobufagin (20 mg), methanol (7 ml), water (0.5 ml), and 0.10 g of CG-400 (OH^- form). The reaction period in this example was 2 hr at room temperature.

Method B. From Deacetylcinobufagin (**5d**) **Using Chromic Acid–Pyridine.**—To a solution of chromic acid (15 mg) in pyridine (0.2 ml) was added (dropwise with stirring) a solution of deacetylcinobufagin (**4a**, 50 mg) in pyridine (1 ml). Stirring was continued for 8 hr and the mixture was poured into ice–water, acidified with dilute hydrochloric acid, and extracted with chloroform. The extract was washed with water and evaporated to provide 53 mg of crude product which was chromatographed on

a column of silica gel. Elution with ligroin–acetone (3:1) gave a fraction which recrystallized from acetone to yield (32 mg) of ketone **6b** as needles, dec pt 231–233°.

Method C. From Deacetylcinobufagin (5d) Using *N*-Bromoacetamide.—To a solution (at 10°) of deacetylcinobufagin (50 mg) in methanol (6 ml), pyridine (2 ml), and water (0.2 ml) was added 45 mg of *N*-bromoacetamide. The mixture was allowed to stand for 18 hr at 10–15° in the dark, poured into ice–water, and extracted with chloroform. Following washing with water, the solvent extract was concentrated to dryness, and the crude product (48 mg) was purified as described in method B to afford 41 mg of ketone **6b**, dec pt 230–232°. Each sample of ketone **6b** prepared in this series of experiments corresponded to the following data: λ_{max}^{EtOH} nm (log ϵ) 297 (3.72); ν_{max} cm^{-1} 3440 (OH), 3040 (CH), 1720, 1710, 1700 (conjugated CO and ketone CO), 1640, 1535 (conjugated C=C), 1230 (epoxy C–O), 955 (C=C), 835 (epoxy C–O), 790, 755 (C=C); pmr δ 0.84 (3 H, s, 18-CH$_3$), 1.06 (3 H, s, 19-CH$_3$), 2.63 (1 H, d, J = 9 Hz, 17-H), 3.61 (1 H, s, 15-H), 4.77 (1 H, d, J = 9 Hz, 16-H), 6.19 (1 H, d, J = 10 Hz, 23-H), 7.22 (1 H, d, J = 3 Hz, 21-H), 7.98 (1 H, dd, J = 10 and 3 Hz, 22-H); mass spectrum m/e 398 (M$^+$).

Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.33; H, 7.58. Found: C, 72.59; H, 7.42.

3,16-Dioxo-14β,15β-epoxy-5β-bufa-20,22-dienolide (7). Method A. From Alcohol 6b.—To a solution of 3-oxo-16β-hydroxybufadienolide **6b** (117 mg) in acetic acid (5 ml) was added (gradually with stirring during 4 hr at room temperature) a solution of chromium trioxide (0.05 g) in acetic acid (2 ml)–water (0.05 ml). After stirring an additional 2 hr excess chromic acid was decomposed with methanol (2 ml). The mixture was poured into ice–water and extracted with chloroform, and the extract was washed with water and concentrated to dryness. The residue (110 mg) was chromatographed on a column of silica gel and the fraction eluted by ligroin–acetone (9:1) was recrystallized from methanol–acetone to give diketone **7** (66 mg, needles, dec pt 218.5°): λ_{max} nm (log ϵ) 298 (3.73); ν_{max} cm^{-1} 3040 (CH), 1740, 1720–1700 (conjugated CO and ketone CO), 1650, 1550 (conjugated C=C), 1520 (epoxy C–O), 955 (C=C), 840 (epoxy C–O), 790, 760 (C=C); pmr δ 1.08 (3 H, s, 18-CH$_3$), 1.28 (3 H, s, 19-CH$_3$), 3.40 (1 H, s, 17-H), 3.49 (1 H, s, 15-H), 6.29 (1 H, d, J = 10 Hz, 23-H), 7.11 (1 H, dd, J = 10 and 3 Hz, 22-H), 7.26 (1 H, d, J = 3 Hz, 21-H); mass spectrum m/e 396 (M$^+$).

Anal. Calcd for $C_{24}H_{28}O_5$: C, 72.70; H, 7.12. Found: C, 72.46; H, 7.02.

Method B. From Deacetylcinobufagin (5d).—Oxidation of deacetylcinobufagin (**5d**, 40 mg) in acetic acid (3 ml) with chromium trioxide (25 mg) in acetic acid (1 ml) water (0.03 ml) was perfomed as illustrated by method A (above). Silica gel column chromatography of the crude product (42 mg) and recrystallization provided 24 mg of 3,16-diketone **7** as needles decomposing at 216–218° and identical with the sample prepared by method A.

3β-Acetoxy-16-oxo-14β,15β-epoxy-5β-bufa-20,22-dienolide (8).—A solution of 16β-alcohol **5c** (85 mg) in acetic acid (1 ml) was treated with a solution of chromium trioxide (40 mg) in acetic acid (1 ml). Stirring was continued for 1 hr at room temperature. After standing for 16 hr, methanol (0.5 ml) was added, and the mixture was poured into ice–water and extracted with chloroform. The combined extract was washed with water, and solvent was removed. Silica gel column chromatography of the crude product (88 mg), elution with ligroin–acetone (9:1), and recrystallization from acetone–methanol led to 62 mg of 3β-acetoxy-16-ketone **8** as needles: mp 226–228°; λ_{max} nm (log ϵ) 297.5 (3.72); ν_{max} cm^{-1} 3060 (CH), 1760–1720, 1700 (ester CO, conjugated CO, and ketone CO), 1643, 1542 (conjugated C=C), 1265, 1252, 1235 (ester C–O and epoxy C–O), 955 (C=C), 863 (epoxy C–O), 756 (C=C); pmr (10% solution in CDCl$_3$) δ 0.97 (3 H, s, 18-CH$_3$), 1.04 (3 H, s, 19-CH$_3$), 2.08 (3 H, s, 16-OCOCH$_3$), 2.61 (1 H, s, 17-H), 3.52 (1 H, s, 15-H), 5.08 (1, H, broad s, 3-H), 6.24 (1 H, d, J = 10 Hz, 23-H), 7.29 (1 H, d, J = 3 Hz, 21-H), 7.45 (1 H, dd, J = 10 and 3 Hz, 22-H); mass spectrum m/e 440 (M$^+$).

Anal. Calcd for $C_{26}H_{32}O_6$: C, 70.89; H, 7.23. Found: C, 71.01; H, 7.29.

3-Epicinobufagin (3α-Hydroxy-16β-acetoxy-14β,15β-epoxy-bufa-20,22-dienolide) (9a).—To a solution of 3-oxocinobufagin (**6a**, 210 mg) in dioxane (21 ml)–water (7 ml) was added a solution of sodium borohydride (200 mg) in dioxane (12 ml)–water (4 ml). The mixture was allowed to stand for 3 hr at room temperature, poured into ice–water, acidified with dilute sulfuric acid, and extracted with chloroform. The combined extract was washed with water and concentrated to dryness. Chromatography of the crude product (225 mg) on a column of silica gel and elution with ligroin–acetone (5:1) provided 60 mg of 3-epicinobufagin (**9a**), mp 137–139° (as needles from methanol), and 20 mg of cinobufagin (**5b**), mp 214–218°, which were found identical with authentic samples. In addition, 100 mg of unreacted starting material (**6a**) was recovered. The 3-epicinobufagin exhibited λ_{max} nm (log ϵ) 298 (3.74); ν_{max} cm^{-1} 3540 (OH), 3040 (CH), 1740, 1720–1700 (ester CO and conjugated CO), 1630, 1540 (conjugated C=C), 1250, 1220 (ester C–O and epoxy C–O), 957 (C=C), 833 (epoxy C–O), 785, 750 (C=C); pmr δ 0.82 (3 H, s, 18-CH$_3$), 0.97 (3 H, s, 19-CH$_3$), 2.19 (3 H, s, 16-OCOCH$_3$), 2.82 (1 H, d, J = 9 Hz, 17-H), 3.66 (2 H, broad s, 15-H and 3-H), 5.42 (1 H, d, J = 9 Hz, 16-H), 6.19 (1 H, d, J = 9.5 Hz, 23-H), 7.17 (1 H, d, J = 2.5 Hz, 21-H), 7.89 (1 H, dd, J = 9.5 and 2.5 Hz, 22-H); mass spectrum m/e 422 (M$^+$).

Anal. Calcd for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.56; H, 7.77.

A specimen of **3-epicinobufagin acetate (9b)** was prepared from 50 mg of 3-epicinobufagin (**9a**) and acetic anhydride (1 ml)–pyridine (0.7 ml). Silica gel column chromatography of the crude product (53 mg) and elution with ligroin–acetone (9:1) led to 44 mg of diacetate **9b** as an amorphous solid: λ_{max} nm (log ϵ) 298 (3.71); ν_{max} cm^{-1} 3040 (CH), 1760, 1740, 1720 (ester CO and conjugated CO), 1645, 1545 (conjugated C=C), 1250–1220 (strong peak; ester C–O and epoxy C–O), 950 (C=C), 830 (epoxy C–O), 785, 755 (C=C); pmr δ 0.82 (3 H, s, 18-CH$_3$), 0.97 (3 H, s, 19-CH$_3$), 1.91 (3 H, s, 16-OCOCH$_3$), 2.05 (3 H, s, 3-OCOCH$_3$), 2.81 (1 H, d, J = 9 Hz, 17-H), 3.67 (1 H, s, 15-H), 4.71 (1 H, broad peak, 3-H), 5.45 (1 H, d, J = 9 Hz, 16-H), 6.19 (1 H d, J = 9.5 Hz, 23-H), 7.14 (1 H, d, J = 2.5 Hz, 21-H), 7.89 (1 H, dd, J = 9.5 and 2.5 Hz, 22-H); mass spectrum m/e 484 (M$^+$).

Anal. Calcd for $C_{28}H_{36}O_7$: C, 69.40; H, 7.48. Found: C, 69.52; H, 7.47.

Oxidation of 3-Epicinobufagin (9a).—The chromic acid oxidation of 3α-alcohol **9a** (20 mg) was carried out using chromium trioxide (10 mg in acetic acid–water) as described above for preparation of ketone **6a**. Chromatographic purification afforded 13 mg of 3-oxocinobufagin (**6a**, mp 234–236°), which was found identical with the material prepared from cinobufagin.

Registry No.—**1a**, 471-95-4; **2**, 36615-06-2; **3**, 36615-07-3; **5a**, 4026-97-5; **5b**, 470-37-1; **5c**, 4026-96-4; **5d**, 4026-95-3; **5e**, 36635-92-4; **5f**, 36615-11-9; **5g**, 36615-12-0; **6a**, 6869-66-5; **6b**, 36615-14-2; **7**, 36615-15-3; **8**, 36615-16-4; **9a**, 36121-84-3; **9b**, 36615-18-6.

Thiocarbonyl Ylides. Generation, Properties, and Reactions[1]

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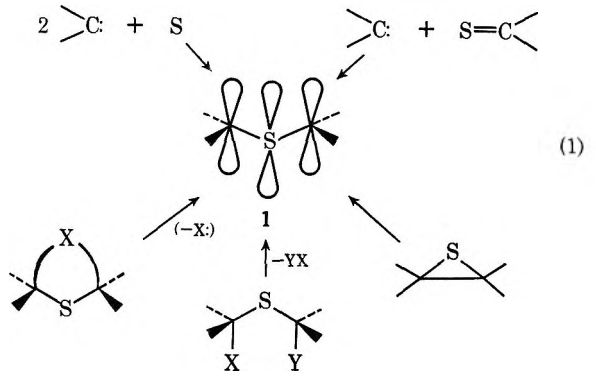
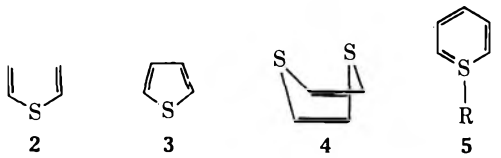
Several 2,5-dialkylsubstituted Δ^3-1,3,4-thiadiazolines have been prepared. On heating these afford unstable thiocarbonyl ylides, R_2CSCR_2, which are characterized by their tendency to yield episulfides on ring closure or cycloadducts on reaction with dipolarophiles such as dimethyl acetylenedicarboxylate or diethyl azodicarboxylate. The stereochemistry of these processes is in accord with predictions based on orbital symmetry considerations: conrotatory ring closure and retention of configuration during cycloaddition. The stereochemical behavior was established with *cis*- and *trans*-2,5-diethyl-Δ^3-1,3,4-thiadiazolines and *cis*- and *trans*-2,5-di-*tert*-butyl-Δ^3-1,3,4-thiadiazolines. Syntheses of the thiadiazolines are accomplished by (a) condensation of a carbonyl compound, hydrazine, and hydrogen sulfide to afford a 1,3,4-thiadiazolidine that is subsequently dehydrogenated; (b) addition of hydrogen sulfide to an azine followed by dehydrogenation of the 1,3,4-thiadiazolidine; (c) reaction of hydrogen sulfide with the addition products of chlorine with azines. The activation parameters for decomposition of the thiadiazolines were determined. On the basis of steric considerations, thiocarbonyl ylides are concluded to be nonplanar. Factors affecting reactivity are discussed.

The term "thiocarbonyl ylide"[3] denotes the electrically neutral entity consisting of two trivalent carbon atoms bonded to a central sulfur atom. The simplest geometrical formulation is planar **1**, which, from a pedagogical point of view, could be derived by the routes illustrated in eq 1. The components of **1**, albeit greatly



(1)

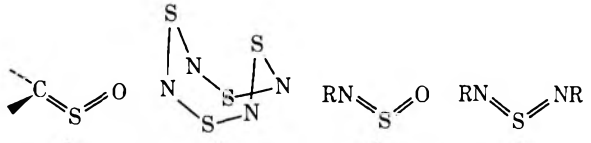
perturbed electronically and/or geometrically, are recognized in a diversity of compounds, including, for example, divinyl sulfide (**2**), thiophene (**3**), and 1,4-dithiadiene (**4**).



2 **3** **4** **5**

Our interest in generating simple examples of thiocarbonyl ylides was grounded in a variety of motives.

First, fundamental information pertinent to the long-standing question of the nature of sulfur bonding might be forthcoming. Especially the suggestion of Schomaker and Pauling[4] that in thiophene the sulfur atom may offer extra resonance possibilities by expanding its valence shell to accommodate two extra electrons has provided the impetus for numerous theoretical and experimental investigations. This question is still surrounded in controversy.[5] One notes that for thiocarbonyl ylides, like thiophene, electronic arrangements involving d-orbital participation are not mandatory; in this wise an essential difference exists with, say, thiabenzenes (**5**) wherein the illustrated resonance structure requires the accommodation of two electrons in a sulfur 3d shell.[6] Hopefully, comparison of the chemical properties of thiocarbonyl ylides with those of structurally and electronically related systems including, for example, sulfines (**6**),[7] tetrasulfur tetranitride (**7**) (the nature of the bonding here being a subject of discussion),[8] *N*-sulfinyl compounds (**8**),[9] sulfur diimides (**9**),[9] sulfur dihalides,[10] and sulfur dioxide[11,12] would shed light on the means by which bonding occurs.



6 **7** **8** **9**

Second, important stereochemical questions are associated with thiocarbonyl ylides. Presuming for the sake of argument the applicability of the planar formulation (**1**), it is readily demonstrated that the molecular orbital description of the system will qualitatively resemble that of the allyl anion. As such, highly prob-

(1) Preliminary communications: (a) R. M. Kellogg and S. Wassenaar, *Tetrahedron Lett.*, 1987 (1970); (b) R. M. Kellogg, S. Wassenaar, and J. Buter, *ibid.*, 4689 (1970).

(2) NATO Postdoctoral Fellow at the University of Groningen, 1969–1970.

(3) This name is based on the nomenclature suggested by R. Huisgen, *Angew. Chem.*, **75**, 604 (1963).

(4) V. Schomaker and L. Pauling, *J. Amer. Chem. Soc.*, **61**, 1769 (1939).

(5) See, for a theoretical discussion of the situation in thiophene, M. J. Bielefeld and D. D. Fitts, *ibid.*, **88**, 4804 (1966).

(6) C. C. Price, J. Follweiler, N. Pirelahi, and M. Siskin, *J. Org. Chem.*, **36**, 791 (1971); (b) C. C. Price, M. Siskin, and C. K. Miao, *ibid.*, **36**, 794 (1971); (c) A. G. Hortmann and R. L. Harris, *J. Amer. Chem. Soc.*, **92**, 1803 (1970).

(7) See, for example, (a) J. Strating, L. Thijs, and B. Zwanenburg, *Tetrahedron Lett.*, 65 (1966); (b) B. Zwanenburg, L. Thijs, and J. Strating, *Recl. Trav. Chim. Pays-Bas*, **86**, 577 (1967); (c) B. Zwanenburg, L. Thijs and J. Strating, *ibid.*, **90**, 614 (1971); (d) B. Zwanenburg and J. Strating, *Quart. Rep. Sulfur Chem.*, **5**, 79 (1970); (e) G. Optiz, *Angew. Chem.*, **79**, 161 (1967).

(8) (a) O. Glemser *ibid.*, **75**, 697 (1963). (b) H. G. Heal, "Inorganic Sulfur Chemistry," G. Nickless, Ed., Elsevier, New York, N. Y., 1968, p 459. (c) For a 1,3-dipolar addition of **7**, see M. R. Brinkman and C. W. Allen, *J. Amer. Chem. Soc.*, **94**, 1550 (1972).

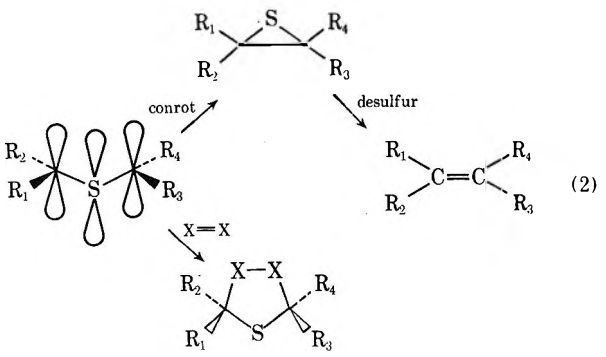
(9) W. Wucherpfennig and G. Kresze, *Tetrahedron Lett.*, 1671 (1966); (b) G. Kresze and H. Grill, *ibid.*, 4117 (1969); (c) H. Grill and G. Kresze, *ibid.*, 1427 (1970); (d) G. Kresze and W. Wucherpfennig, *Angew. Chem.*, **79**, 109 (1967), and references contained therein.

(10) For a description, see F. A. Cotton and E. Wilkinson, "Advanced Inorganic Chemistry," Interscience, New York, N. Y., 1966, pp 534–540.

(11) For early studies on the addition of sulfur dioxide to dienes, see H. J. Backer, J. Strating, and C. M. H. Kool, *Recl. Trav. Chim. Pays-Bas*, **58**, 778 (1939).

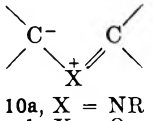
(12) For an early MO description, see (a) H. P. Koch and W. E. Moffit, *Trans. Faraday Soc.*, **47**, 7 (1951); (b) also L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, 3rd ed, Ithaca, N. Y., 1960.

able closure to isomeric episulfide (thiirane) structures is anticipated to occur with *conrotation* of the substituents (eq 2). On the other hand, thiocarbonyl



(2)

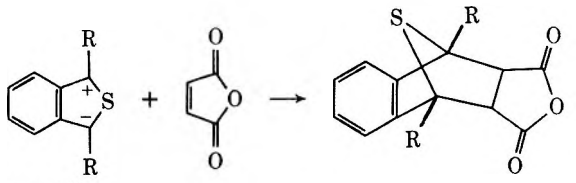
ylides obviously have 1,3-dipolar characteristics;[13] the expected cycloadditions should occur with *retention of configuration* (eq 2). These predictions, derived from conservation of orbital symmetry requirements,[14] have been amply confirmed for azomethine ylides (**10a**)[15] and carbonyl ylides (**10b**),[16] and more indirectly for the allyl anion itself.[17] We wished to test experimentally the validity of these considerations for thiocarbonyl ylides.



10a, X = NR
b, X = O

Synthetic utility proved a third motive. Successful realization of ring closure to episulfides would open a route to the possibly stereospecific syntheses of olefins (eq 2).[18] Moreover, the anticipated cycloadditions would provide routes to the synthesis of a variety of otherwise difficultly accessible heterocyclic compounds.

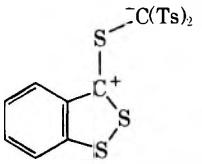
At the outset of this work, little was known about thiocarbonyl ylides. Questions of the importance of conjugation through sulfur had led to the occasional consideration of such structures.[19] The participation of this component in the cycloadditions of benzo[*c*]thiophenes (eq 3) was recognized by Pedersen.[20,21] Several



(3)

R = H[20a]
R = aryl[21]

thiophene analogs with expanded valence shells for sulfur are known[22] as well as a fascinating mesoionic structure containing the thiocarbonyl ylide system.[23] Thiocarbonyl ylide intermediates were implicated in the deprotonations of some alicyclic sulfonium salts[24] and a colored intermediate formed during low temperature irradiation of tetraphenylepisulfide might be a thiocarbonyl ylide.[25] Recently **11** was isolated as a stable substance.[26]

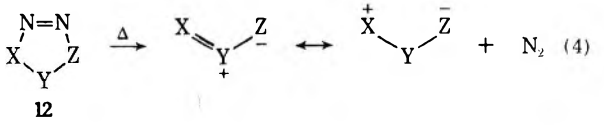


11

We report here our attempts to obtain a variety of thiocarbonyl ylides.

Results and Discussion

Synthesis of Precursors.—An ultimately successful approach to the generation of examples of **1** hinged on the assumption that elimination of nitrogen from the appropriate heterocyclic system (**12**) would lead to the thiocarbonyl ylide. Clear analogy for this assumption exists in the successful preparation of a variety of 1,3-dipolar intermediates[3] by the scheme depicted in eq 4. This generalized route also succeeds for the syn-



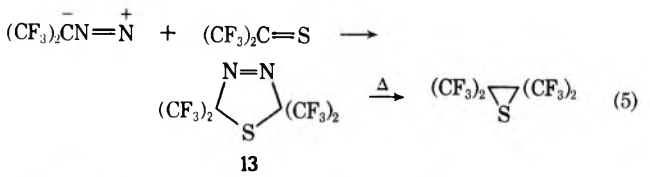
(4)

12

thesis of carbonyl ylides.[16] Obtainment of the requisite Δ^3-1,3,4-thiadiazolines (**12**, X = Z = CR_2; Y = S) seemed a synthetically reasonable goal although only concurrently with our own efforts were the first examples (**13** and **14**) of this ring system reported.[27] The 1,3-4-thiadiazoline structure was established un-

(13) R. Hoffmann, *J. Amer. Chem. Soc.*, **90**, 1475 (1968).
(14) R. B. Woodward and R. Hoffmann, *Angew. Chem.*, **81**, 797 (1969).
(15) (a) R. Huisgen, W. Scheer, and H. Huber, *J. Amer. Chem. Soc.*, **89**, 1753 (1967); (b) R. Huisgen, W. Scheer, and H. Mäder, *Angew. Chem. Int. Ed. Engl.*, **8**, 602 (1969); (c) R. Huisgen, W. Scheer, H. Mäder, and E. Brunn, *ibid.*, **8**, 604 (1969); (d) R. Huisgen and H. Mäder, *ibid.*, **8**, 604 (1969); (e) P. B. Woller and N. H. Cromwell, *J. Org. Chem.*, **35**, 888 (1970); (f) J. H. Hall and R. Huisgen, *Chem. Commun.*, 1187 (1971); (g) J. H. Hall, R. Huisgen, C. H. Ross, and W. Scheer, *ibid.*, 1188 (1971).
(16) (a) R. W. Hoffmann and H. J. Luthardt, *Chem. Ber.*, **101**, 3851, 3861 (1968); (b) P. Rajagopalan and B. G. Advani, *Tetrahedron Lett.*, 2689 (1967); (c) W. J. Linn and R. T. Benson, *J. Amer. Chem. Soc.*, **87**, 3657 (1965); (d) E. F. Ullmann and W. A. Henderson, Jr., *ibid.*, **88**, 4942 (1966); (e) P. Brown and R. C. Cookson, *Tetrahedron*, **24**, 2551 (1968); (f) T. Do-Minh, A. M. Trozzolo, and G. W. Griffin, *J. Amer. Chem. Soc.*, **92**, 1402 (1970); (g) D. R. Arnold and L. A. Karnischky, *ibid.*, **92**, 1404 (1970); (h) D. Seyferth and W. Tronich, *J. Organometal. Chem.*, **18**, P8 (1969); (i) C. W. Martin, J. A. Landgrebe, and E. Rapp, *Chem. Commun.*, 1438 (1971); (j) A. Dahmen, H. Hamberger, R. Huisgen, and V. Markowsky, *ibid.*, 1192 (1971).
(17) (a) P. Eberhard and R. Huisgen, *J. Amer. Chem. Soc.*, **94**, 1345 (1972); (b) R. Huisgen and P. Eberhard, *ibid.*, **94**, 1346 (1972).
(18) The principle of olefin synthesis by a "twofold extrusion process" has been elegantly enunciated by D. H. R. Barton and B. J. Willis, *J. Chem. Soc., Perkin Trans. I*, 305 (1972); *Chem. Commun.*, 1225 (1970). Among the compounds investigated was a thiadiazolidine (see further) that was concurrently prepared by our group.[1] We are grateful to Professor Barton for correspondence on this matter.
(19) See, for an early example, E. B. Knott, *J. Chem. Soc.*, 916 (1955).
(20) (a) C. T. Pedersen, *Acta Chem. Scand.*, **20**, 2314 (1966); (b) G. Wittig, E. Knaus, and K. Niethammer, *Justus Liebigs Ann. Chem.*, **630**, 10 (1960).
(21) R. Mayer, H. Kleinert, S. Richter, and K. Gewald, *Angew. Chem.*, **74**, 118 (1962).
(22) See, for example, (a) M. P. Cava and G. E. M. Husbands, *J. Amer. Chem. Soc.*, **91**, 3952 (1969); (b) J. D. Bower and R. H. Schlessinger, *ibid.*, **91**, 6891 (1969).
(23) H. Gotthardt and B. Christl, *Tetrahedron Lett.*, 4743, 4747, 4751 (1968).
(24) M. Takaku, S. Mitamura, and H. Nozaki, *ibid.*, 3651 (1969).
(25) R. S. Becker, R. O. Bost, J. Kolc, N. R. Bertonière, R. L. Smith, and G. W. Griffin, *J. Amer. Chem. Soc.*, **92**, 1302 (1970).
(26) S. Tamagaki and S. Oae, *Tetrahedron Lett.*, 1159 (1972).
(27) W. J. Middelton, *J. Org. Chem.*, **34**, 3201 (1969).

ambiguously by nmr spectroscopy and the expected episulfides were secured on thermolysis (eq 5 and 6).[28]



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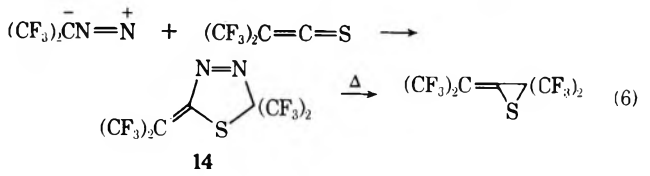
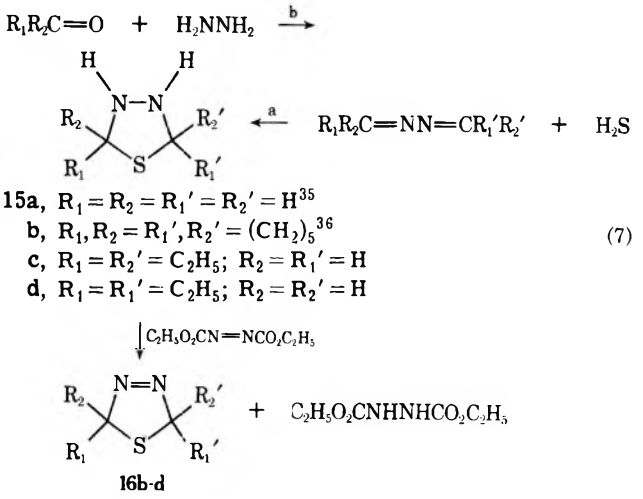


14 (6)

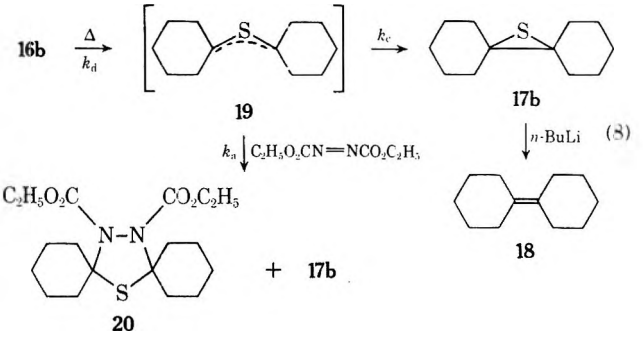
We investigated the addition of diazoalkanes to aliphatic thiocarbonyl compounds as a potential route to the desired precursors (being unaware at the time of the work of Middelton).[27,30] Although these efforts appeared to lead to partial success, we were discouraged from extensive investigation of this route owing to the difficulties, dangers, and unpleasantness associated with aliphatic diazo[32] and thiocarbonyl[33] compounds.[34] (The decision to work with aliphatically substituted derivatives was dictated by the knowledge that with the more stable aryl substituted systems only episulfide is obtained.[28,29]) A more pleasing route was the dehydrogenation of 1,3,4-thiadiazolidines (**15**), two syntheses of which had appeared in the literature (eq 7).[35,36] Neureiter[35a] had reported **15a** as the product of diazine with H_2S (route a). Earlier, Rühlmann[36] had reported some examples of a simple condensation reaction (route b), which seemed potentially amenable to considerable variation in substrate. The dehydrogenation step necessary for conversion of **15b**, chosen as a test case, to the thiadiazoline **16b** failed with heavy metal oxides, which gave only the metal sulfide. The dehydrogenation was successfully accomplished with diethyl azodicarboxylate which dehydrogenates hydrazines and other substrates presumably *via* a concerted, six-membered transition state.[37] In ether solution **15b** reacted exothermically with this reagent affording **16b** as a stable, crystalline solid. The ir (KBr) showed a strong, characteristic absorption for –N=N– at 1570 cm^{-1} and the uv in ethanol exhibited two low intensity absorptions at 289 nm (ϵ 340) and 322 (240). This type of uv absorption was found to be characteristic of most thiadiazolines.



15a, $R_1 = R_2 = R_1' = R_2' = H$[35]
b, $R_1, R_2 = R_1', R_2' = (CH_2)_5$[36]
c, $R_1 = R_2' = C_2H_5$; $R_2 = R_1' = H$
d, $R_1 = R_1' = C_2H_5$; $R_2 = R_2' = H$ (7)

16b-d

Chemical and Kinetic Evidence.—Pyrolysis of **16b** occurred smoothly either in the melt or in hydrocarbon solution beginning at about 80°. There was obtained in quantitative yield the episulfide **17b**, which, in addition to correct analytical data, afforded cyclohexylidenecyclohexane (**18**) in 77% yield on treatment with *n*-butyllithium (eq 8). Tentative evidence that



(8)

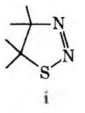
16b, on decomposition, affords an intermediate (**19**) was obtained from the observation (eq 8) that cycloadduct **20**, identified by analysis and spectroscopy, was obtained along with **17b** when **16b** was allowed to decompose in the presence of diethyl azodicarboxylate. Episulfide **17b** failed to react with this reagent eliminating this potential route to **20**.

If the scheme given in eq 8 is correct, namely that **16b** affords **19** with rate constant k_d and that **19** is partitioned between ring closure to **17b**, rate constant k_c, and that cycloaddition affords **20**, rate constant k_a, then, assuming a steady-state concentration of **19**, eq 9 may be

$$\frac{\ln \{[ADC]_0/([ADC]_0 - [20])\}}{[17b]} = \frac{k_a}{k_c} \quad (9)$$

derived where $[ADC]_{t=0}$ is the concentration of diethyl azodicarboxylate at the start of the reaction. By glpc using appropriate internal standards it was shown that

(28) Staudinger[29] had suggested that addition of a diazo compound to a thiocarbonyl compound should yield a Δ^2-1,2,3-thiadiazoline (i). Since



i

with, for example, diphenyl diazomethane and thiobenzophenone, only tetraphenyl episulfide could be isolated, the question was somewhat academic at the time. With a variety of aryl-substituted diazo compounds and thiocarbonyl compounds we observed spontaneous nitrogen elimination and episulfide formation even at −70°.

(29) H. Staudinger and J. Siegwart, *Helv. Chim. Acta*, **3**, 833 (1920).

(30) The Δ^3-1,3,4-thiadiazoline 1,1-dioxide structure is obtainable by the addition of diazo compounds to sulfur dioxide.[31] Pyrolysis of these compounds affords modest yields of the respective olefins (see also ref 18).

(31) (a) G. Hesse and E. Reichold, *Chem. Ber.*, **90**, 2106 (1957); (b) H. H. Inhoffen, R. Jonas, H. Kroesche, and U. Eder, *Justus Liebigs Ann. Chem.*, **694**, 19 (1966).

(32) G. M. Kaufman, J. A. Smith, G. G. Vander Stouw, and H. Shechter, *J. Amer. Chem. Soc.*, **87**, 935 (1965).

(33) R. Mayer, "Organosulfur Chemistry," M. J. Janssen, Ed., Interscience, New York, N. Y., 1967, pp 219–240.

(34) A. P. Krapcho, D. R. Raa, M. P. Silvon, and B. Abegaz, *J. Org. Chem.*, **36**, 3885 (1971), reported the successful isolation of 1,3,4-thiadiazolines from the reactions of diazomethane with some spiro thioketones.

(35) (a) N. Neureiter, *J. Amer. Chem. Soc.*, **81**, 2910 (1959). (b) We have repeated this work and have also identified **15a**, formed in low yield. Dehydrogenation to the desired thiadiazoline has thus far failed (T. Beetz, unpublished results).

(36) K. Rühlmann, *J. Prakt. Chem.*, [4] **8**, 285 (1959).

(37) F. Yoneda, K. Suzuki, and Y. Nitta, *J. Amer. Chem. Soc.*, **88**, 2328 (1966).

the yield of **20** plus **17b** was equal to the amount of **16b** consumed; hence $[ADC]_{t=t} = [ADC]_{t=0} - [20]$, which relationship is used to integrate the rate expression leading to eq 9. Calculated values for k_a/k_c as function of diethyl azodicarboxylate concentration are given in Table I. As can be seen the values of k_a/k_c are

TABLE I

VALUE OF k_a/k_c AS A FUNCTION OF DIETHYL AZODICARBOXYLATE CONCENTRATION

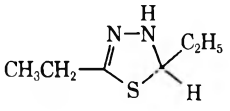
[ADC], mol/l.[a,b]	[20]/[17b]	k_a/k_c
0.103	2.32	37.7
0.129	3.06	35.9
0.161	4.10	35.2
0.204	5.13	32.4
0.249	7.33	36.2
	Av	35.5 ± 1.3

[a] Concentration of **16b** was 9.95×10^{-2} *M* for all experiments. [b] All experiments were run at 97° until **16b** was completely decomposed. Solvent was cyclohexane.

virtually invariant. A second prediction of eq 8 is that the rate constant, k_d, for decomposition of **16b** will not vary with diethyl azodicarboxylate concentration. At 97° in the absence of azodicarboxylate, $k_d = 5.36 \times 10^{-4}$ sec^{-1} for a 10^{-1} *M* solution of **16b**, whereas, with 0.204 *M* azodicarboxylate, $k_d = 5.07 \times 10^{-4}$ sec^{-1}. We submit that these product and kinetic data demonstrate the existence of an intermediate in the decomposition of **16b**, namely the thiocarbonyl ylide **19**.

Stereochemical Aspects.—With strong evidence for the existence of a thiocarbonyl ylide in hand, attention was turned to the stereochemistry of ring closure and cycloaddition. After extensive modification (Experimental Section) of the described procedure,[36] a moderate yield of **15c,d** was obtained. The isomer ratio was established by observing the resonances in the nmr spectrum for the 2,5 protons. On repeated recrystallization the major isomer, mp 70–72°, was obtained uncontaminated with the minor isomer. Unfortunately, despite the utmost care the minor isomer decomposed into azine and H_2S as soon as it was concentrated in the mother liquors.

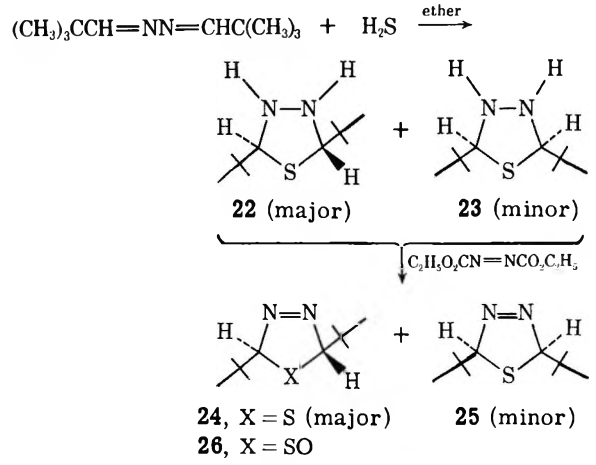
The pure isomer, mp 72°, was dehydrogenated at −10° with diethyl azodicarboxylate. Work-up was carried out at 5–10° affording material that was clearly the desired thiadiazoline **16**. The symmetry of nmr spectrum precluded structure **21**. Spontaneous evolu-



21

tion of nitrogen began at 30–35°. Dehydrogenation of a 75:25 mixture of **15c,d** afforded in a 75:25 ratio the previously obtained thiadiazoline plus a new thermally unstable isomer. Stereochemical assignments could be made at this point from the observation that the major isomer in CCl_4 solution showed in the nmr spectrum a complex multiplet at δ 5.90–6.25 for the 2,5 protons, whereas the minor isomer displayed at δ 4.0 a broadened quartet (J = 6.2 Hz) for the 2,5 protons (broad hump in benzene). The difference in chemical shift for these isomers is in complete accord with the idea that the major isomer is *trans*-**16c** (derived from **15c**) and the minor isomer is *cis*-**16d** (derived from **15d**).[38] Analyses of **16c,d** could not be obtained owing to their instability.

A second approach to obtaining disubstituted thiadiazolines suitable for resolution of stereochemical problems was investigated simultaneously. Condensation at room temperature of the azine of pivaldehyde and excess hydrogen sulfide in ether solution in a sealed tube (eq 10) led to precipitation of an unstable white



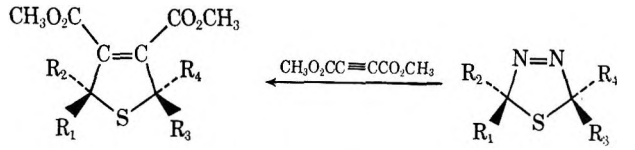
22 (major) **23** (minor) (10)

24, X = S (major) **25** (minor)
26, X = SO

solid that at −20° in $CDCl_3$ solution displayed nmr absorptions for *tert*-butyl (δ 1.01), NH (3.41), and tertiary protons (4.43) consistent with a thiadiazolidine structure (**22**). Several minor peaks remained unassigned. This material was immediately dehydrogenated with diethyl azodicarboxylate. After work-up and careful recrystallization from methanol, **24** was obtained in good yield. The structure of **24** was established by correct elemental analysis and by the nmr spectrum, which showed singlets for *tert*-butyl (δ 0.92) and the 2,5 protons (5.62). Unambiguous assignment of trans stereochemistry was obtained on oxidizing **24** to sulfoxide **26**, which showed nonequivalent *tert*-butyl (δ 1.07 and 1.40) and nonequivalent, coupled 2,5 protons (doublets, J = 1.4 Hz, at 4.05 and 5.68) consistent only with trans stereochemistry. (Despite repeated attempts a sulfoxide from **16c**, for which similar stereochemical proof would be desirable, could not be obtained.) Reexamination of the nmr spectra of freshly prepared thiadiazoline mixtures revealed, in addition to **24**, extra nmr singlets at δ 1.15 (*tert*-butyl) and 5.52 (2,5 H). These were attributed to cis isomer **25**, present in ~0.6:1 ratio with **24**. By avoiding warming, the concentration of **25** could be raised to about equal to that of **24** by crystallizing out **24**. In addition, some episulfide (see further) was present. By careful preparative layer chromatography, a pure mixture of **24** and **25** was obtained. The latter decomposes spontaneously unless kept cold. Although **25** could not be isolated free from **24**, the proposed structure was amply verified by subsequent reactions (below).

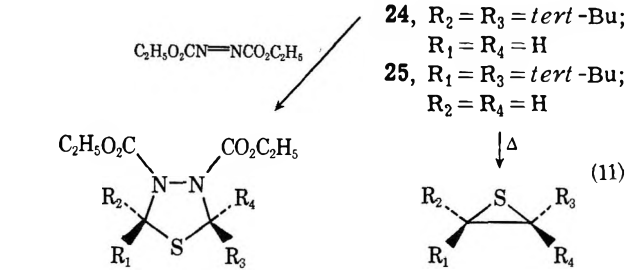
The results of the stereochemical investigations with **16c–16d** and **24–25** are summarized in eq 11. Trans isomer **16c** contaminated with <3% **16d** (nmr analysis) on pyrolysis afforded in quantitative yield a mixture consisting of 93 ± 2% **27** and 7 ± 2% **28** (glpc anal-

(38) (a) N. S. Crossley and C. Djerassi, *J. Chem. Soc.*, 1459 (1962); (b) R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **44**, 249 (1966); (c) E. L. Eliel, M. H. Gianni, T. H. Williams, and J. D. Stothers, *Tetrahedron Lett.*, 741 (1962).



31, $R_2 = R_3 = C_2H_5$; $R_1 = R_4 = H$
32, $R_1 = R_3 = C_2H_5$; $R_2 = R_4 = H$
33, $R_2 = R_3 = tert$-Bu; $R_1 = R_4 = H$

16c, $R_2 = R_3 = C_2H_5$; $R_1 = R_4 = H$
d, $R_1 = R_3 = C_2H_5$; $R_2 = R_4 = H$
24, $R_2 = R_3 = tert$-Bu; $R_1 = R_4 = H$
25, $R_1 = R_3 = tert$-Bu; $R_2 = R_4 = H$



(11)

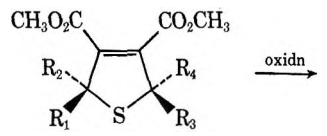
34, $R_2 = R_3 = C_2H_5$; $R_1 = R_4 = H$
35, $R_1 = R_3 = C_2H_5$; $R_2 = R_4 = H$
36, $R_2 = R_3 = tert$-Bu; $R_1 = R_4 = H$

27, $R_2 = R_3 = C_2H_5$; $R_1 = R_4 = H$
28, $R_1 = R_3 = C_2H_5$; $R_2 = R_4 = H$
29, $R_2 = R_3 = tert$-Bu; $R_1 = R_4 = H$
30, $R_1 = R_3 = tert$-Bu; $R_2 = R_4 = H$

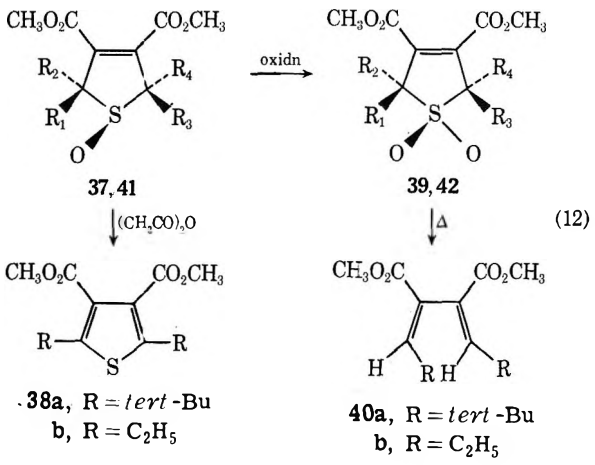
ysis). The episulfides were identified by comparison with independently synthesized samples.[39] The major product **27** is obviously that derived from predicted conrotatory ring closure (eq 2). Pyrolysis of a mixture of 80 ± 3% **16c** and 20 ± 3% **16d** afforded in quantitative yield a mixture of 69 ± 2% **27** and 31 ± 2% **28**. Using the data for pure **16c**, the ring closure of **16d** is calculated to proceed essentially 100% conrotatorily. (This obviously suggests "leakage" of the thiocarbonyl ylide derived from **16c** to disrotatory product **28**. However, the necessity of using imprecise nmr analyses to determine **16c**:**16d** ratios suggests caution in drawing conclusions.)

Far more dramatic evidence for conrotatory ring closure was obtained with **24** and **25**. Pyrolysis of repeatedly recrystallized **24** afforded in quantitative yield *exclusively* **29**,[40] the stereochemistry of which was established by desulfurization with *n*-butyllithium affording *cis*-di-*tert*-butylethylene.[41] Isomer **25**, present as a mixture with **24**, could be selectively pyrolyzed at 40° at which temperature **24** fails to decompose. There was obtained *exclusively* **30**, identified by desulfurization to *trans*-di-*tert*-butylethylene.

The cycloaddition reactions illustrated in eq 11 are within experimental error completely stereospecific. Nearly quantitative yields can usually be obtained by using 2–3-fold excesses of dipolarophile. The general principle used for stereochemical assignment of the trans cycloaddition products with dimethyl acetylenedicarboxylate is given in eq 12. Sodium metaperiodate or *m*-chloroperbenzoic acid oxidation of **33** led to sulfoxide **37** with nonequivalent *tert*-butyl groups in the



33, $R_2 = R_3 = tert$-Bu; $R_1 = R_4 = H$
31, $R_2 = R_3 = C_2H_5$; $R_1 = R_4 = H$



37, **41**

38a, R = *tert*-Bu
b, R = C_2H_5

39, **42**

40a, R = *tert*-Bu
b, R = C_2H_5

(12)

nmr spectrum. Further oxidation led to sulfone **39** in which C_2 symmetry was reestablished. Pyrolysis afforded exclusively the known[42] diene **40** by the expected disrotatory course of the retro reaction.[43,44] An analogous cycle was carried out with *trans*-**31** yielding ultimately the known[42] *Z*,*E*-diene **40b**. The sulfone **42** appears to epimerize readily. Both sulfoxides **37** and **41** could be dehydrated to the respective thiophenes **38a**,**b**.[45] Similar stereochemical proofs were carried out for **34**–**36**; these are described in the Experimental Section.

Unfortunately, **25** stubbornly refused to react with dipolarophiles. Only trans episulfide **30** was obtained on attempted reaction with dimethyl acetylenedicarboxylate or dicyanoacetylene. With diethyl azodicarboxylate some dehydrogenation to 2,5-di-*tert*-butyl-1,3,4-thiadiazole took place. Stereospecific addition could be established with **16d**, however. A 20:80 mixture of **16d** and **16c** (determined by nmr) afforded 22:78 mixture (glpc analysis) of **32** and **31**, respectively. The cis isomer **32** was isolated by preparative glpc and it was identified by its nmr spectrum, which, in addition to the expected ethyl and methoxy absorptions, showed the 2,5 tertiary protons at 0.36-ppm higher field than those of **31** as is expected for the cis configuration.[38] No further transformations were carried out with **32** owing to the extreme difficulty in obtaining pure material, caused by the ready dehydrogenation to thiophene **38b**.

The results of eq 11 demonstrate that thiocarbonyl ylides react in accord with Woodward–Hoffmann predictions, namely retention of configuration during cycloaddition ($[4_s + 2_s]$ reaction) and conrotatory ring closure, and this even in the face of serious steric interactions as illustrated with **24** where ring closure results in the energetically unfavorable cis positioning of two *tert*-butyl groups. Although the observation is qualitative, the difference in proclivity for cycloaddition of

(39) N. P. Neureiter and F. G. Bordwell, *J. Amer. Chem. Soc.*, **81**, 578 (1959).

(40) If **24** has not been recrystallized several times, small amounts of *trans*-**30** are obtained. This was apparently the cause of the formation of small amounts of this isomer reported previously.[1b]

(41) W. H. Puterbaugh and M. S. Newman, *J. Amer. Chem. Soc.*, **81**, 1611 (1959).

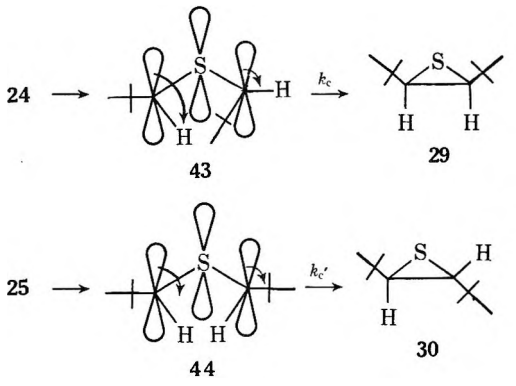
(42) R. M. Kellogg, *ibid.*, **93**, 2344 (1971).

(43) W. L. Mock, *ibid.*, **88**, 2857 (1966).

(44) S. D. McGregor and D. M. Lemal, *ibid.*, **88**, 2858 (1966).

(45) M. P. Cava and N. M. Pollack, *ibid.*, **88**, 4112 (1966).

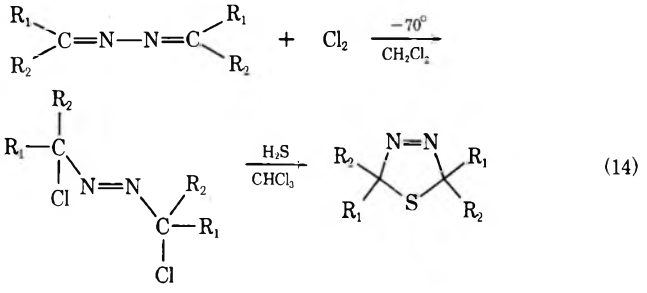
the thiocarbonyl ylides **43** and **44**, derived from **24** and **25** (eq 13), respectively, can likely be attributed to



(13)

steric effects. In **43** developing steric interactions will diminish the rate constant for ring closure, k_c, relative to k_c' for **44** (drawn in the sterically more probable "W" conformation). This will result in a longer lifetime for **43** relative to **44** allowing the former to have a greater chance of undergoing bimolecular cycloaddition, as is indeed observed.

General Synthesis of Thiadiazolines.—We next initiated a search for general syntheses of a variety of thiadiazolines. The routes proceeding through thiadiazolidines, formed either by condensation of a carbonyl component, hydrazine, and hydrogen sulfide or by addition of hydrogen sulfide to azines (eq 7) were applicable only to special cases likely owing to the instability of thiadiazolidine relative to azine and hydrogen sulfide. The most successful general method that we developed is shown in eq 14. This synthesis



(14)

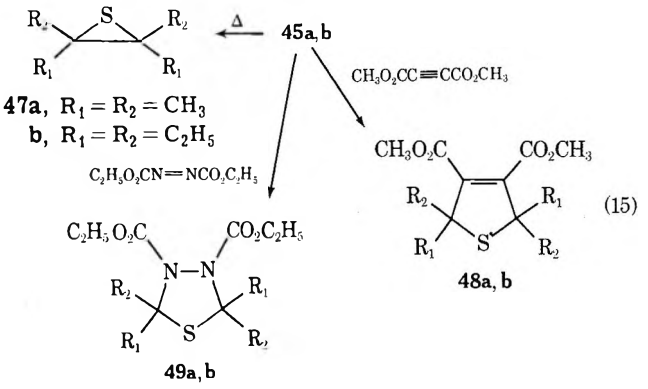
45a, $R_1 = R_2 = CH_3$
b, $R_1 = R_2 = C_2H_5$
c, $R_1 = R_2 = (CH_2)_2CH(tert\text{-}Bu)(CH_2)_2$
d, $R_1, R_2 = (CH_2)_6$
e, $R_1 = tert\text{-}Bu$; $R_2 = CH_3$

is deliberately designed to avoid the unstable thiadiazolidine stage by "oxidizing" the azine prior to ring closure. The 1,4 addition of chlorine to (chiefly aliphatic) azines is a smooth reaction[46-48] and the dichloroazoalkanes formed are extremely subject to reaction with nucleophilic species. These reactions are presumed to involve a carbonium ion intermediate (**46**).

$$R_1R_2\overset{+}{C}\text{—}N\text{=}N\text{—}C(Cl)R_1R_2$$
46

This knowledge hinted that reaction with a bidentate nucleophile might succeed since the steric constraint engendered by the trans geometry of the azo compound could be released in the intermediate carbonium ion allowing ring closure. After considerable experimentation it was found that ring closure occurred on allowing the dichloroazoalkane to react with hydrogen sulfide gas in chloroform solution. The thiadiazolines **45** were obtained in 60–100% yield. The conditions are admittedly rather bizarre for a carbonium ion reaction, and indeed another mechanism could be operative. However, success does recommend this technique. The compound **45c** was also prepared by the thiadiazolidine method similar to that in eq 7. In most cases the thiadiazolines were also oxidized to their respective sulfoxides and sulfones (Experimental Section).

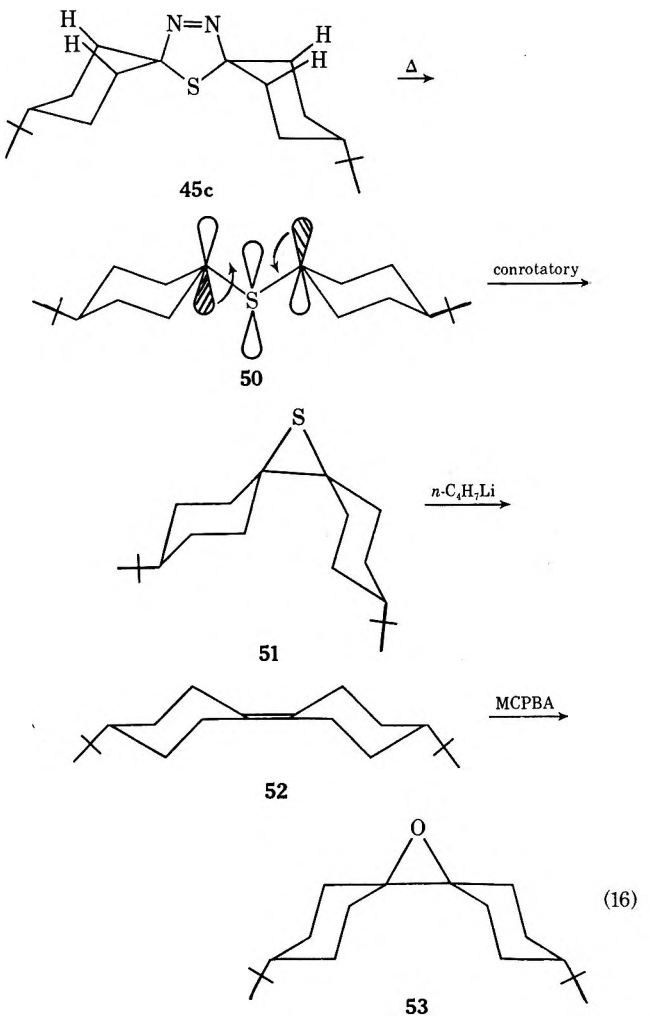
Comments on Thiadiazoline Reactions.—Several points observed in the reactions of **45a–e** deserve mention. Both **45a** and **45b** reacted as expected affording the episulfides **47a,b** on pyrolysis either neat or in methylcyclohexane. In the presence of either dimethyl acetylenedicarboxylate or diethyl azodicarboxylate the corresponding cycloadducts **48** and **49** are isolated (eq 15). The episulfides **47** can be converted to the respective olefins.[49]



(15)

Rather interesting stereochemical aspects are associated with **45c**. Its nmr spectrum displays a single absorption for the *tert*-butyl groups and in the presence of tris(dipivalomethanato)europium a broad, poorly resolved triplet corresponding to four protons is shifted downfield. This points to a symmetrical structure, and likely that with the azo bridge located equatorially, since the broad triplet probably arises from axial protons[50] and in the indicated structure (eq 16) the axial protons are indeed brought into the vicinity of where complex forming is expected. Pyrolysis of **45c** gave a single episulfide, mp 205–207°, that had nonequivalent *tert*-butyl groups (δ 0.85 and 0.90). We believe this to be **51** formed from *conrotatory* ring closure of thiocarbonyl ylide **50**. On treatment with *n*-butyllithium **51** afforded olefin **52** (equivalent *tert*-butyl groups). Epoxidation of **52** gave **53** with equivalent *tert*-butyl groups. The indicated configuration (eq 16) is based on the rather tenuous assumption that less 1,3-diaxial interaction will be involved in the indicated direction of

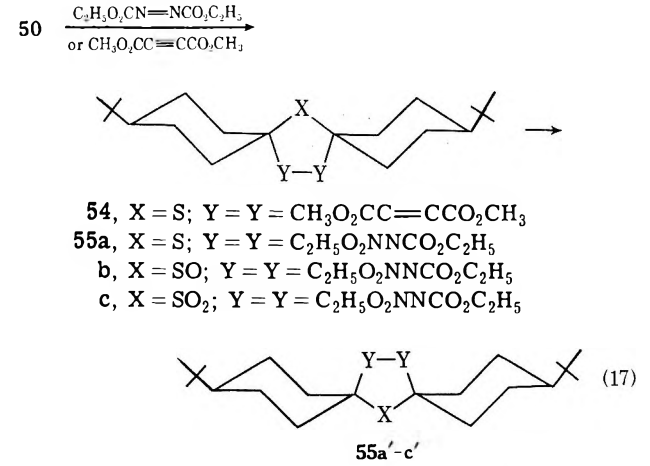
(46) S. Goldschmidt and B. Acksteiner, *Justus Liebigs Ann. Chem.*, **618**, 173 (1958).
(47) E. Benzing, *ibid.*, **631**, 1 (1960).
(48) D. S. Malament and J. M. McBride, *J. Amer. Chem. Soc.*, **92**, 4586, 4593 (1970).
(49) F. G. Bordwell, N. M. Andersen, and B. M. Pitt, *ibid.*, **76**, 1082 (1959).
(50) (a) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance," Vol. 2, Pergamon Press, Oxford, 1966, p 703; (b) P. D. Readio and P. S. Skell, *J. Org. Chem.*, **31**, 759 (1966).



(16)

attack. As expected **53** could not be converted to an episulfide on treatment with thiocyanate.

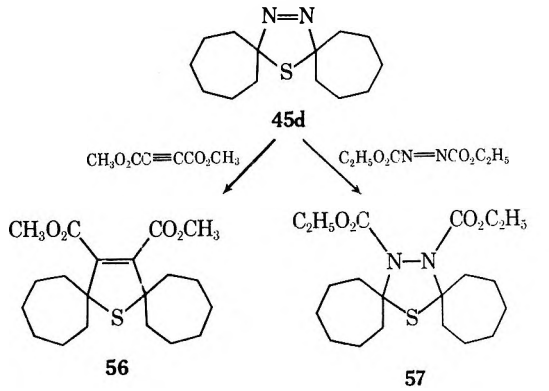
Cycloaddition of **51** to dimethyl acetylenedicarboxylate proceeded sluggishly giving in 13% yield (after extensive purification) a cycloadduct **54** (eq 17).



(17)

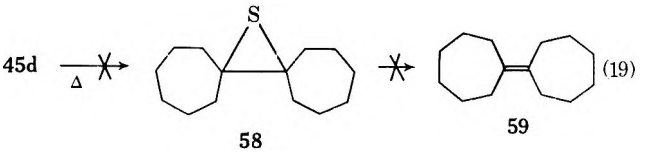
This appeared to be a single isomer as judged by the sharp melting point (133–135°) and the appearance of a single sharp absorption for the *tert*-butyl protons in the nmr spectrum (however, the methoxy absorption was suspiciously broadened). Inspection of models leads to the anticipation that the direction of approach leading to **54** involves the least steric interaction. However, reaction with diethyl azodicarboxylate led in 95% yield to an ~60:40 mixture of cycloadducts for which structures **55a** and **55a′** are suggested. That a mixture is present is indicated by overlapping quartets and triplets for the methylene and methyl resonances, respectively, in the nmr spectrum. This nonequivalence is maintained in the sulfoxides **55b** and **55b′** and the sulfones **55c** and **55c′**. Although the nmr spectra of **54** and **55a** and **55a′** were affected by europium complexes, no conclusions could be drawn.

The cycloheptyl compound **45d** underwent cycloaddition with dimethyl acetylenedicarboxylate and diethyl azodicarboxylate giving **56** and **57**, respectively (eq 18).[51] Despite repeated attempts under a wide



(18)

variety of conditions neither episulfide **58** nor cycloheptylidenecycloheptane **59** could be secured on pyrolysis of **45d** (eq 19). Only intractable materials

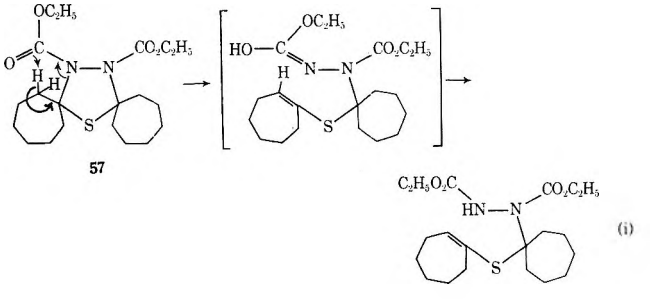


(19)

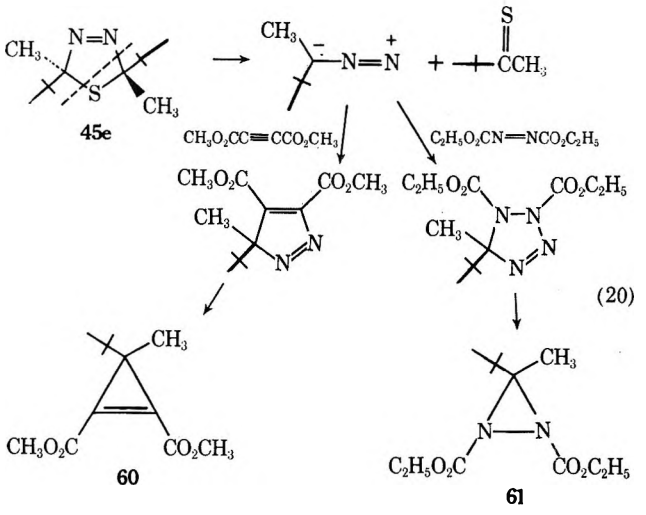
were isolated. The causes for the failure of this reaction are mysterious.

Thiadiazoline **45e** on pyrolysis under a variety of conditions gave extremely complex mixtures that may contain small amounts of olefin. Decomposition in the presence of dipolarophiles also failed to give the expected cycloadducts. Although the reactions are difficultly reproducible, low yields of compounds with nmr and mass spectra consistent with **60** and **61** were obtained from attempted cycloadditions. This might be accounted for by the route suggested in eq 20 wherein cleavage to a diazo compound and a thiocarbonyl compound occurs.

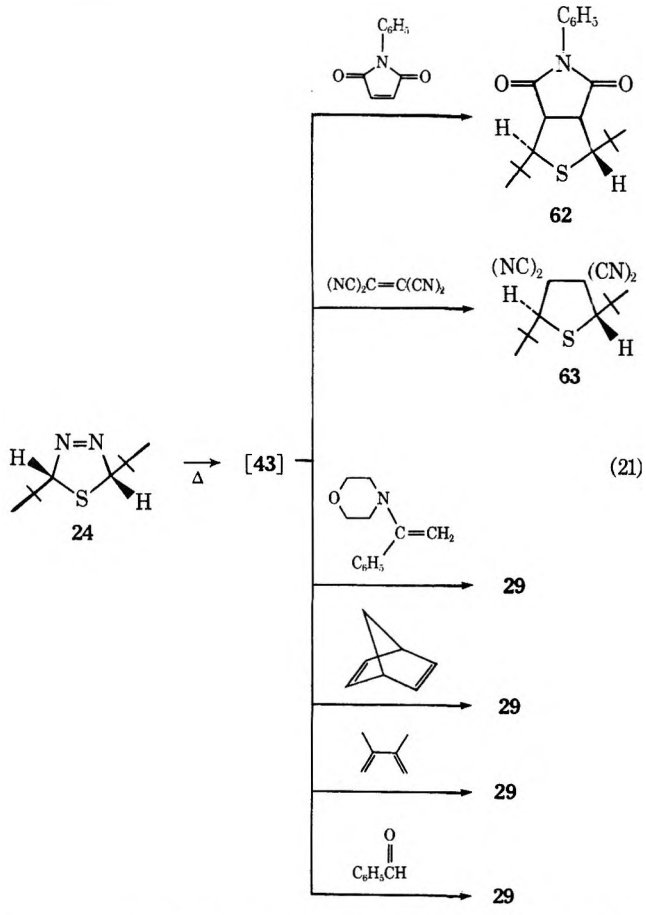
(51) On attempted distillation **57** rearranged to a isomer containing a vinylic proton, an NH group, and nonequivalent carbomethoxy groups. At the high temperature (130°) required for distillation, the rearrangement indicated in eq i may have taken place.



(i)



Cycloaddition reactions were attempted with a variety of dipolarophiles using the thiocarbonyl ylide **43** derived from **24** (eq 21). This intermediate is one of



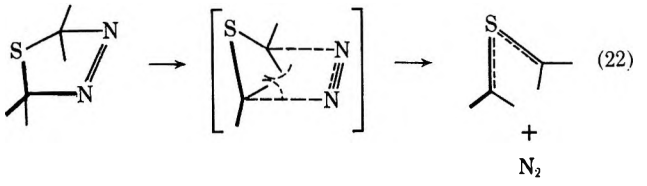
the most reactive towards cycloaddition. The cycloadducts **62** and **63** were obtained in good yield, but attempted cycloaddition with enamines, 2,3-dimethylbutadiene, norbornadiene, or benzaldehyde, led to *cis*-**29** as the exclusive product.

Kinetic Parameters for Thiadiazoline Decomposition.—In Table II the activation parameters are compiled for the decomposition of a variety of thiadiazolines. All compounds decomposed smoothly following first-order kinetics through at least two half-lives and the rate constants (checked with **16b**) were independent of concentration in the range 10^{-1}–10^{-2} M. For the compounds measured the relative rates corrected to 25° span a range of nearly 10^5 or $\sim 10^4$ if one rejects **45e** as a reference because products from its decomposition are anomalous. Obviously a variety of factors reflected in modest changes in $\Delta H^{\ddagger}$ and appreciable fluctuations in the size of $\Delta S^{\ddagger}$ cause these rather large rate variations. Comparing **45a** with 3,3,-5,5-tetramethylpyrazoline ($\Delta H^{\ddagger}_{298°}$ = 37.1 kcal/mol, $\Delta S^{\ddagger}_{250°}$ = 4.6 eu in the gas phase)[52] a lowering of $\Delta H^{\ddagger}$ by 11 kcal/mol is noted. Although hydrocarbon analogs are not known for the other isomers tabulated in Table II, roughly similar lowering of activation energies for decomposition would be expected. Two major factors are presumed operative in increasing so drastically the rate of nitrogen elimination from thiadiazolines relative to pyrazolines. First, the presence of a sulfur atom will relieve some steric interaction relative to the pyrazoline. One expects puckered conformations[53] for thiadiazolines as illustrated as in eq 22.

TABLE II
KINETIC PARAMETERS FOR THE DECOMPOSITION OF THIADIAZOLINES

Compd	$\Delta H^{\ddagger}_{298°}$, kcal/mol[a]	$\Delta S^{\ddagger}_{298°}$, eu[b]	k_{25}, sec^{-1}	Rel reactivity
45c	31.4	11.6	$8.50.10^{-9}$	73.8
45d	26.8	7.9	$3.09.10^{-6}$	26,800
45e	30.8	1.1	$1.15.10^{-10}$	1.0
45b	28.1	4.7	$5.62.10^{-8}$	489
45a	26.0	3.3	$9.3.10^{-7}$	8,080
16b	29.2	7.0	$2.82.10^{-8}$	245
15c[c]	26.9	11.1	$1.02.10^{-5}$	87,900
24	30.1	9.7	$2.82.10^{-8}$	245

[a] Maximum errors ±1.0 kcal/mol. [b] Maximum errors ±3.0 eu. [c] Determined by nmr spectroscopy.



This is well illustrated by the upfield shifts of the tertiary protons of *cis*-**25**, relative to those of *trans*-**24**, and *cis*-**16**, relative to those of *trans*-**16**, arising from the tendency of the alkyl substituents to remain equatorial forcing the axially located hydrogen atoms into the shielding region of the azo group (eq 22).[54] An increase in puckering in the transition state may involve less nonbonding interactions between the departing nitrogen and sulfur than in the pyrazolines. This may account for the troubles with **45e** where a *tert*-butyl and a methyl substituent are forced together. Second, and likely more important, sulfur substituents α to an azo functionality are known to exert a presumed resonance effect which lowers the activation energies for decomposition.[55] The thiocarbonyl ylide formed can be viewed as a stabilized 1,3 biradical[13,56] and the transition state will likely benefit from this potential stabilization. However, since stabilization is

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

(53) E. L. Eliel, "The Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, pp 248–252.

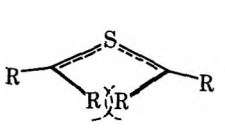
(54) J. J. Uebel and J. C. Martin, *J. Amer. Chem. Soc.*, **86**, 4618 (1964).

(55) See, for example, A. Ohne and Y. Ohnishi, *Tetrahedron Lett.*, 4405 (1969).

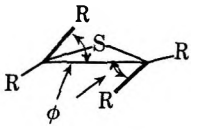
(56) (a) L. Salem, *Chem. Commun.*, 981 (1970); (b) E. F. Hayes and A. K. Q. Sin, *J. Amer. Chem. Soc.*, **93**, 2091 (1971).

gained, at least to the first approximation, by overlap of the developing carbon p orbital with the sulfur 3p orbital, the transition state will likely be a complicated conformational compromise allowing the developing p orbitals on carbon in so far possible to overlap with the sulfur 3p orbital. Although the relative rate differences among the various thiadiazolines are large, it is difficult to distinguish unambiguously a trend of steric effects that rationalizes the rates of decomposition. Similar problems attend interpretations of activation parameters for pyrazoline decomposition.[57]

The Geometry of Thiocarbonyl Ylides.—The intermediate generated on decomposition of thiadiazolines obediently behaves according to the Woodward–Hoffmann predictions for the formulation **1**. But does planar **1** represent the correct geometry for the thiocarbonyl ylide? The somewhat embarrassing answer must be *no*, at least for certain examples. Consider for example the thiocarbonyl ylide **64** (R = CH_3) derived from **45a**. The C–S–C bond angle[58,59] should not exceed 120° (measured for SO_2)[60] and will be likely closer to that in di-*p*-tolyl sulfide, 109°.[59,61] Using this bond angle and also the carbon–sulfur bond lengths for this molecule, 1.75 Å, and normal carbon–carbon and carbon–hydrogen bond lengths for **64** (R = CH_3), in a planar arrangement the closest approach of nuclear centers of hydrogens on the inner methyl groups is 0.3 Å. Presuming that this obviously untenable situation is relieved by tilting of one p orbital upward by an angle φ and the other downward also by angle φ, then, when the distance of closest approach of the two hydrogen atoms is the sum of the Van der Waals radii, $2\varphi = 92°$. This is readily determined from straightforward geometrical considerations.



64 (planar)



64 (tilted)

The tilted model is crude but the conclusion is inescapable, namely, that at least in **64** (the situation is even worse in the tetraethyl derivative) a fully planar geometry is impossible. Spreading of the C–S–C angle to even 120° helps relieve, but does not remove, steric interactions. The same problem is present even in less highly substituted intermediates such as **43** where severe *tert*-butyl–hydrogen interaction is expected in a planar conformation. If the tilted formulation of **64** is correct, the bonding likely involves some form of p–d hybridization.

(57) (a) A "recoil" effect resulting in inversion of configuration at the carbon atom is suggested to be operative at least in bicyclic compounds: E. L. Allred and R. L. Smith, *ibid.*, **91**, 6766 (1969). (b) Strong conformational preferences in the transition states for decomposition of diazabicyclo[2.1.0]pentane derivatives has been demonstrated by J. A. Berson and S. S. Olin, *ibid.*, **91**, 777 (1969).

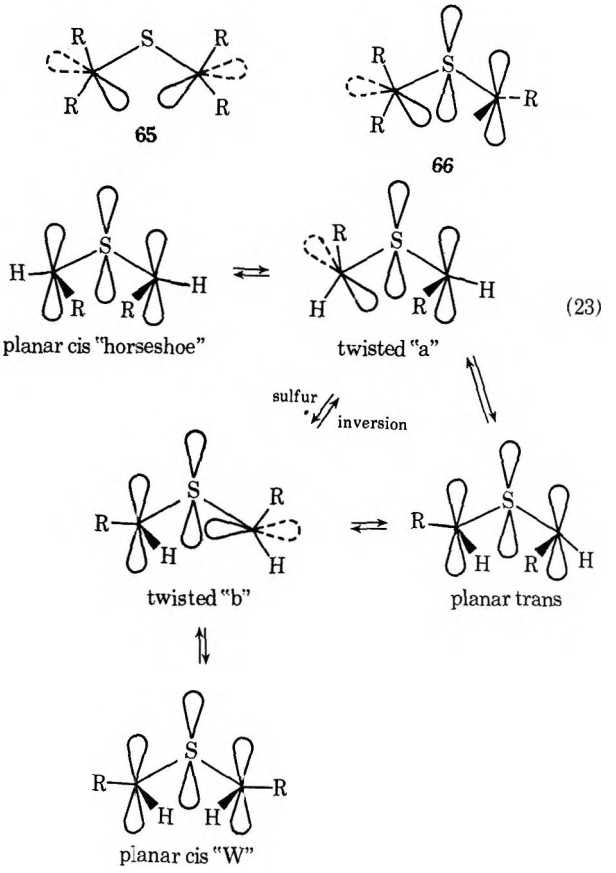
(58) That thiocarbonyl ylides should be nonlinear follows directly from application of Walsh's rules: (a) A. D. Walsh, *J. Chem. Soc.*, 2260, 2266, 2288, 2296, 2301 (1953); (b) Y. Takahata, G. W. Schnuelle, and R. G. Parr, *J. Amer. Chem. Soc.*, **93**, 784 (1971); (c) H. B. Thompson, *ibid.*, **93**, 4609 (1971).

(59) For a general review of the geometry of sulfur compounds, see S. C. Abrahams, *Quart. Rev.*, **X**, 407 (1956).

(60) M. H. Sirvetz, *J. Chem. Phys.*, **19**, 938 (1951).

(61) W. R. Blackmore and S. C. Abrahams, *Acta Crystallogr.*, **8**, 329 (1959).

Are there geometrical alternatives to a tilted model? Two conceivable possibilities are **65** and **66**. The geometry of **65** is that of an episulfide save that the C–S–C interior angle is widened. Collapse to an episulfide seems the most obvious fate of **66**.[62] The half-twisted geometry of **66** is more intriguing. But can **66** pass the crucial test of predicting conrotatory ring closure? Owing to the expectations that the C–S–C bond angle is not 180°,[58] disubstituted **66** has two forms (which is not the case in a linear allene). The *completely hypothetical* isomerization sequence of eq 23 illustrates some



(23)

geometrical relationships. The twisted "a" and "b" forms are derivable from *either* cis or trans geometrical forms; as such they bear no geometrical "memory" of their origin with respect to cis or trans (but there is memory for the type of cis). Likewise any electronic "memory" is difficult to see; formulation of ring closure as a $[2_a + 2_s]$ reaction leads to no unique stereochemical predictions. Stereospecific cycloaddition is also difficult to rationalize. Unequivocal rejection of an intermediate at this stage of knowledge is unwise, but the evidence now in hand does suggest that the tilted model **64** is a better approximation than twisted **66** (or **65**) for the thiocarbonyl ylide structure. One also notes that the di-*p*-tolyl sulfide is tilted 32–35° in the crystal structure.[59]

If thiocarbonyl ylides do not have a planar structure, is the simple Woodward–Hoffman argumentation used in the discussion invalid? Most likely not, if the tilted structure **64** provides a fair estimate of the true geometry. No obvious reason is present why a tilted

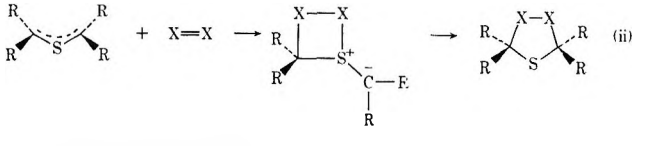
(62) See ref 13 for calculations on the trimethylene with equivalent geometry.

structure should not have roughly the same ordering of molecular orbitals as in a planar arrangement, although this conclusion has not yet been supported by calculation. But note, however, that the most dramatic tests of conrotatory ring closure are provided with the di-*tert*-butyl derivatives **43** and **44**. *Conrotatory* ring closure of **43**, for example, if in tilted conformation **64**, could involve a synchronous movement of one (inner) substituent downwards through an angle of $\sim 120° - \varphi$ and the other upward through essentially the same angle (presuming that in the episulfide the substituents make a 120° angle with the carbon–carbon bond). Steric interference will develop late in the transition state. A disrotatory motion could involve either (a) passing through a hindered planar conformation with *tert*-butyl–hydrogen interactions or (b) a movement wherein one (inner) substituent moves through an angle of $\sim 120° - \varphi$ while the other (inner) substituent moves through an angle $120° + \varphi$. The latter motion, besides being completely nonsynchronous, also involves interaction of the inner substituents. Thus, if the transition state is reached early,[63] the conrotatory motion in **43** may well be energetically more favorable *on steric grounds*, at least in the early stages of the reaction. Trans episulfide **30** is expected from **44** purely on steric arguments. With the thiocarbonyl ylides bearing ethyl groups, which are sterically less demanding than *tert*-butyl, there may well be some "leakage" of *trans*-thiocarbonyl ylide to trans episulfide **28**. The suggestion is, therefore, that there may be a built-in stereochemical bias favoring conrotatory ring closure and that this could significantly augment (or mask) any electronic effect. The high retention of configuration during cycloaddition is logical since any "leakage" would involve less likely complete cis–trans isomerization of the thiocarbonyl ylide.

A final point deals with the problems raised on comparing the chemistry of thiocarbonyl ylides with that of sulfur dioxide, sulfur diimides (**9**), *N*-sulfinyl compounds (**8**), and sulfines (**6**). Of this series only thiocarbonyl ylides isomerize to the three-membered rings (episulfides). Thiocarbonyl ylides react with good dipolarophiles yielding products derived from addition at the two carbon atoms; tetrasulfur tetranitride (**7**) behaves similarly,[8c] but sulfur dioxide adds dienes across the sulfur atom,[11,43,44] and sulfines,[7] *N*-sulfinyl compounds,[9] and sulfur diimides[9] add dienes across a carbon–sulfur or a nitrogen–sulfur bond whereas thiocarbonyl ylides (at least those prepared so far) do not react with dienes. At the present time a consistent explanation for these remarkable differences is lacking.[64] We hope in the future to contribute to the clarification of this problem.

(63) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(64) A two-step cycloaddition to the thiocarbonyl ylide first involving addition of the dipolarophile across a carbon–sulfur bond with subsequent ring expansion (eq ii) is quite unlikely since the stereospecificity of cyclo-



(ii)

addition is hard to rationalize. The type of reaction has been observed for *N*-sulfinyl compounds[9c] but only with ketenes, which are known to participate readily in [2 + 2] dimerizations.[14]

Experimental Section

All melting points were determined with calibrated thermometers on a melting point block; boiling points are uncorrected. Uv, ir, and nmr spectra were obtained on common laboratory instruments; mass spectra (also coupled with glpc) were taken on an AEI MS 9 instrument.

All chemicals cited without reference were either in stock or were prepared by well-known laboratory methods. Elemental analyses were carried out at this university. In some cases difficulty was experienced with sulfur or nitrogen determinations; in that case mass spectral determination of the molecular weight was done.

Preparation of 2,2,5,5-bis(pentamethylene)-1,3,4-Δ^3-thiadiazoline (16b) was accomplished from the analogous[1,3,4] thiadiazolidine (**15b**) prepared as described.[36] The crude thiadiazolidine was dissolved in ether and treated with an equimolar amount of diethyl azodicarboxylate, whereupon a vigorous reaction ensued. After standing overnight the reaction mixture was evaporated to dryness and the residue taken up in petroleum ether (bp 40–60°). The diethyl hydrazodicarboxylate, mp 133° (lit.[65] mp 129–131°), dissolves only slightly in hydrocarbon solvents and may be filtered off readily. The filtrate, after removal of solvent, was chromatographed over Al_2O_3 using benzene as eluent. The crude product was recrystallized from methanol giving **16b** in 54% yield (based on cyclohexanone using impure **15b**): mp 81–82° (without decomposition); ir (KBr) 1579 cm^{-1} (N=N); uv max (96% EtOH) 2890 Å (ϵ 342) and 3220 (238). Reactions using purified **15b** (involving extra loss of material) gave **16b** quantitatively.

Anal. Calcd for $C_{12}H_{20}N_2S$: C, 64.23; H, 9.00; S, 14.29; N, 12.48. Found: C, 64.15; H, 8.95; S, 14.22; N, 12.44.

Pyrolysis of 16b was carried out by refluxing a sample (500 mg, 2.23 mmol) in 100 ml of petroleum ether (bp 80–100°) for 5 hr. Removal of the solvent left virtually pure **17b** (449 mg, 2.29 mmol, 103% yield). This was recrystallized from methanol to give an analytical sample, mp 75–77°, uv max (96% EtOH) 2590 Å (ϵ 50).

Anal. Calcd for $C_{12}H_{20}S$: C, 73.39; H, 10.29; S, 16.33; mol wt, 196. Found: C, 73.24; H, 10.19; S, 16.33; mol wt (osmometry in C_6H_6), 199.9.

Desulfurization of 2,2,3,3-bis(pentamethylene)episulfide (17b) was done with a sample of **17b** (250 mg, 2.3 mmol) dissolved in 10 ml of dry ether. This was treated at room temperature with *n*-butyllithium (10 ml, 0.8 *M* in ether solution). A yellow precipitate formed during addition. After 3 hr at room temperature, water was added, and the organic layer was extracted with ether. The ether layer was washed with dilute NaOH and with water. After the mixture was dried over $MgSO_4$, there was obtained cyclohexylidenecyclohexane (**18**) (290 mg, 1.76 mmol, 77%), mp 55° (lit.[66] mp 55, 54.5–55.5°).

Cycloaddition of 16b (486 mg, 2.17 mmol) was carried out with diethyl azodicarboxylate (271 mg, 1.56 mmol) in 15 ml of petroleum ether (bp 80–100°). The solution was refluxed for 5 hr and the solvent was removed. The semisolid residue was chromatographed over 100 g of Al_2O_3 (neutral); elution with 150 ml of 10% ether–90% benzene gave **17b** (100 mg, 0.51 mmol, 23%) (a portion of the episulfide was lost during manipulation). The rest of the organic material was eluted with 100% ether giving 2,2,5,5-bis(pentamethylene)-3,4-dicarboethoxy-1,3,4-thiadiazolidine (**20**) as a clear oil (230 mg, 0.62 mmol, 40%) that solidified on standing. Three recrystallizations from methanol gave an analytical sample: mp 65–67.5°; ir (KBr) 1720 cm^{-1} (C=O); nmr (CCl_4) δ 1.23 (t, J = 7.0 Hz, 6 H, CH_3), 1.40-2.20 (complex m, 20 H, ring (CH_2)), 4.10 (q, J = 7.0 Hz, 4, OCH_2CH_3).

Anal. Calcd for $C_{18}H_{30}N_2O_4S$: C, 58.34; H, 8.10; N, 7.56; S, 8.65. Found: C, 58.02; H, 8.23; N, 7.57; S, 8.62.

Various attempts were made to obtain a cycloaddition product from **16b** and dimethyl acetylenedicarboxylate. Although nmr spectra were consistent with the formation of small amounts of adduct, the chief product was **17b** and only this product could be obtained on working up the reaction mixture.

Stability of 17b in the presence of diethyl azodicarboxylate was checked by refluxing **17b** (420 mg, 2.14 mmol) with the

(65) N. Rabjohn, *Org. Syn.*, **28**, 58 (1948).

(66) (a) R. Criegee, E. Vogel, and H. Höger, *Chem. Ber.*, **85**, 144 (1952). (b) S. D. Koch, R. M. Kliss, D. V. Lopiekes, and R. J. Wineman, *J. Org. Chem.*, **26**, 3122 (1961).

ester (270 mg, 1.55 mol) in 20 ml of petroleum ether (bp 80–100°) for 4.5 hr. The ir spectra of the sample after evaporation of the solvent showed only peaks for **17b** and azo ester. *No* absorptions for **20** were detectable.

Oxidation of 16b was carried out with 1.00 g (4.46 mmol) dissolved in 30 ml of absolute MeOH. $NaIO_4$ (1.65 g, 7.7 mmol) dissolved in H_2O was added and the reaction mixture was warmed for about 1 hr. The reaction mixture was poured into H_2O, extracted three times with $CHCl_3$, and dried over $MgSO_4$. Removal of the solvent left crude 2,2,5,5-bis(pentamethylene)-1,3,4-Δ^3-thiadiazoline *S*-oxide, mp 146–144° (980 mg, 4.08 mmol, 91%). Recrystallization from MeOH gave an analytical sample: mp 148–149.5° dec; ir (KBr) 1550 and 1535 (N=N), 1045 and 1055 cm^{-1} (S—O).

Anal. Calcd for $C_{12}H_{20}N_2OS$: C, 60.00; H, 8.33; N, 11.66; S, 13.35. Found: C, 59.62; H, 8.50; N, 11.53; S, 13.19.

The analogous sulfone has been prepared.[18]

Kinetics of 16b Decomposition.—Solutions (1.0×10^{-1} M in methyl cyclohexane) were made 0.0 to 0.25 *M* in diethyl azodicarboxylate. After mixing, a portion of the solution was sealed in heavy-walled Pyrex tubes that were then sealed in the cold. *In one case an extremely violent explosion occurred on warming to room temperature. The cause is unknown. Considerable caution in handling these compounds is strongly advised.* The samples were held at 98.0° for 7 hr, 40 min, after which time no **16b** remained. Analysis by glpc (3-ft glass SE-30, 98° for 12 min, 15°/min to 142°) established that for all samples [**17b**] + [**20**] = [**16b**]$_0$; known standards were used for calibration. Careful injection technique was required to prevent desulfurization of the episulfide even in a glass-lined injection port. The value of k_a/k_c was calculated from these data.

The rate of decomposition of **16b** at 97.0° was determined by monitoring the decrease in the uv absorption band at 327 mμ.

Synthesis of *cis,trans*-**2,5-diethyl-1,3,4-thiadiazolidines (15c,d)** was accomplished by a modified version of the described procedure.[36] In our hands no detectable amount of desired product was obtained by following the directions given. The following modification proved successful. Propionaldehyde (136 g, 2.36 moles), which had been distilled *immediately* before use, was placed in a glass Friedel–Crafts vessel with the stirring rod attached to a vibrator. This solution was cooled in a solid CO_2–acetone bath and to the *vigorously stirred* solution was added H_2S (39.7 g, 1.17 mmol) as rapidly as possible. Uptake is initially slow but, once it has begun, proceeds rapidly; care must be taken to avoid adding too much H_2S. To the cold solution was added immediately thereafter a solution of 98% hydrazine hydrate (58.5 g, 1.17 mmol) over a period of about 30 min. (Essentially the same results are obtained by condensing the desired amount of hydrogen sulfide at −70° and pressing this over into a propionaldehyde solution at −70°; hydrazine is then added.) The reaction mixture, which often became partially solid, was allowed to come to room temperature, whereupon a mixture of 200 ml of water and 200 ml of diethyl ether was added. The layers were separated and the ether layer was washed with water and dried over $MgSO_4$. Removal of the solvent left 141 g (0.965 mol, 83%) of crude white crystals. The ratio of trans to cis isomers was determined by monitoring the nmr absorptions for the tertiary protons in benzene solution: for *trans*-**15c** a triplet (J = 6.4 Hz) at δ 4.32 is seen and for the *cis*-**15d** a triplet (J = ~6.7 Hz) at 4.25 is observed.

The crude material could be purified by recrystallization from petroleum ether (bp 60–80°). The solid was dissolved in the solvent at room temperature and then chilled to about −20° to reprecipitate it. After three–four cycles, with considerable loss of material, pure **15c** was obtained: mp 70–72°;[67] nmr (C_6H_6) δ 0.90 (t, 6, J = 6.0 Hz, CH_3), 1.20–1.70 (complex m, 4, CH_2), 3.20 (br s, 2, NH), 4.32 (t, 2, J = 6.4 Hz, tertiary H). The nmr of the mother liquors was monitored after each stage in the crystallization with the thought that **15d** should be concentrated here. However, only a small amount of trans isomer and, for the rest, propionaldehyde azine, were observed. The cis isomer obviously decomposes spontaneously on attempted concentration. Moreover, mixtures of **15c,d**, after standing for ~1 week in the refrigerator, consisted only of pure **15c** and propionaldehyde azine.

Preparation of isomerically pure *trans*-**2,5-diethyl-1,3,4-Δ^3-thiadiazoline (16c)** was carried out by dehydrogenation of **15c** (900 mg, 6.15 mmol, 99% trans by nmr) in 20 ml of ether solution at −15°. A cold solution of diethyl azodicarboxylate (1.07 g, 6.15 mmol) in 10 ml of ether was added to the solution. The reaction mixture was kept in the freezer overnight after which time all color had disappeared. The reaction mixture was concentrated on the solvent stripper taking care that the temperature did not rise above ~10°. The semisolid material was taken up in 20 ml of ice-cold pentane and the diethyl hydrazodicarboxylate (995 mg, 5.66 mmol, 92% yield) was filtered off and washed with cold pentane. The pentane solution was washed with chilled $NaHSO_3$ solution to remove the last traces of azo ester and thereafter was washed with ice–water and dried over $MgSO_4$ in the cold. Removal of the solvent at low temperature left **16c** as an oil (885 mg, 6.15 mmol, 100% yield) which solidified in the freezer but became liquid at room temperature and began to evolve gas spontaneously beginning at ~30–35°. This material had nmr (C_6H_6) δ 0.83 (t, 6, J = 7.5 Hz, CH_3), 1.50–2.11 (complex m, 4, CH_2), 5.67–6.04 (complex m, 2, tertiary H). The spectrum was virtually identical in CCl_4.

The above experiment was repeated using a 75:25 mixture of **15c** and **15d**. The nmr of the dehydrogenated product showed a broad, unresolved hump for the tertiary H of the **16d** (along with the absorptions for **16c**). In CCl_4 solution, however, the tertiary protons for **16d** appeared at δ 4.00 as a slightly broadened q (J = 6.2 Hz). The absorptions from both the **16c** and **16d** disappeared completely at 50–60° in the nmr and were replaced by absorptions for the diethyl episulfides **27** and **28**, respectively.

Reaction of 16c,d with Dimethyl Acetylenedicarboxylate.—A sample of isomerically pure (99%) **15c** (3.65 g, 25 mmol) was dehydrogenated in quantitative yield to **16c**. This was dissolved in ~30 ml of ether and diethyl azodicarboxylate (8.2 g, 57.7 mmol) was added. A distillation head was fitted to the flask and, as the ether was distilled off, petroleum ether (bp 60–80°) was added from a dropping funnel. (The low solubility of dimethyl acetylenedicarboxylate in petroleum ether necessitates this procedure.) The final temperature was ~80° and this temperature was maintained for ~1 hr, after which time gas evolution, as evidenced by frothing, had ceased. The solution was concentrated and the excess ester was separated. The petroleum ether layers were combined; the solution was washed with H_2O and dried over $MgSO_4$. Removal of the solvent and distillation gave, after a forerun of residual acetylenic ester, 5.25 g (20.4 mmol, 81%) of *trans*-2,5-diethyl-3,4-dicarbomethoxy-2,5-dihydrothiophene (**31**): 100-MHz nmr (C_6D_6) δ 0.92 (t, 6, J = 7.0 Hz, CH_3), 1.52–1.90 (complex m, 4, CH_2), 3.42 (s, 6, OCH_3), 4.42–4.62 (complex m, 2, tertiary H). Rather surprisingly the tertiary proton appeared as a broad triplet when decoupled from the methylene protons; no temperature dependence of the spectrum was noted.[68]

Anal. Calcd for $C_{12}H_{18}O_4S$: C, 55.80; H, 7.02; S, 12.41. Found: C, 55.28; H, 7.11; S, 12.53.

The above experiment was repeated starting from a mixture of 20% **16d** and 80% **16c** (determined by nmr analysis directly after preparation by dehydrogenation of the respective thiadiazolidines). Reaction with dimethyl acetylenedicarboxylate gave a mixture of 22% **32** and 78% **31** [as determined by glpc (4-ft DEGS, 200°)]. The cis isomer **32** was separated by preparative glpc using a glass 4-ft DEGS column at 200° equipped with glass injection port liner and a stainless steel splitter; the gas flow was sufficient to give retention times of <4 min. If these precautions were not followed, partial to complete dehydrogenation to 2,5-diethyl-3,4-dicarbomethoxythiophene (**38b**) took place. A few milligrams of pure **32** had nmr (CAT in CCl_4) δ 0.94 (t, 6, J = 7.0 Hz, CH_3), 1.77 (center, complex m, 4, CH_2), 3.67 (s, 6, OCH_3), 4.00–4.32 (complex m, 2, tertiary H). In the unseparated mixture the tertiary protons were clearly seen in $CDCl_3$ solution as a triplet (J = 7.4 Hz further split into doublets (J = 1.8 Hz) by coupling with diastereomeric methylene protons.

Oxidation of 31 with 2 equiv of *m*-chloroperbenzoic acid afforded crude *trans*-2,5-diethyl-3,4-dicarbomethoxy-2,5-dihydrothiophene *S*-oxide (**41**): nmr (CCl_4) δ 1.11 (t, J = 7 Hz, 3, CH_3CH_2), 1.13 (t, J = 7 Hz, 3, CH_3CH_2), 1.45–2.25 (complex m, 4, CH_2CH_3), 3.70 (s, 6, OCH_3), 3.84–4.10 (complex m, 2, tertiary H). A sample of this material (1 g, 3.65 mmol) was refluxed for 1 hr in acetic anhydride. The material was poured into water and extracted with chloroform, and the chloroform extract was washed with sodium bicarbonate solution and there-

(67) The reported[36] mp of 72° was likely determined on a repeatedly recrystallized sample that was essentially pure **15c**.

(68) These spectra were run by Dr. R. A. Raphael at the University of East Anglia, England.

after with water. After drying over magnesium sulfate and removal of the chloroform there was obtained 3,4-dicarbomethoxy-2,5-diethylthiophene (**38b**, 930 mg, 100%): nmr (CCl_4) δ 1.27 (t, J = 7.0 Hz, 6, CH_3CH_2), 2.92 (q, J = 7.0 Hz, 4, CH_2-CH_3), 3.75 (s, 6, OCH_3).

Anal. Calcd for $C_{12}H_{16}O_4S$: C, 56.23; H, 6.29; S, 12.51. Found: C, 55.58; H, 6.45; S, 12.31.

Oxidation of **31** with 2 equiv. of MCPBA gave *trans*-2,5-diethyl-3,4-dicarbomethoxy-2,5-dihydrothiophene *S*-dioxide (**42**): nmr (CCl_4) δ 1.11 (t, J = 7 Hz, 6, CH_3CH_2), 1.95 (br quintet, J = ~7 Hz, CH_2CH_3), 3.84 (s, 6, OCH_3); the tertiary H's are buried under the absorption at δ 3.84. The material could not be obtained crystalline. Pyrolysis at ~250° for a few minutes afforded chiefly the known[42] diene **40b**.

Oxidation of a mixture of **31** and **32** afforded a mixture of sulfones. The cis sulfone showed a separate triplet at δ 1.08 in the nmr spectrum. Pyrolysis of this mixture afforded **40b** and chiefly *E*,*E*-diene[42] from the cis sulfone.

Cycloaddition of 16c with Diethyl Azodicarboxylate.—Isomerically pure **16c** (400 mg, 2.78 mmol) was dissolved in petroleum ether (bp 40–60°) to which azo ester (1.43 g, 8.22 mmol) was added. The solution was refluxed for 3 hr after which time nmr indicated a 100 ± 4% yield of cycloadduct. The solution was washed with $NaHSO_3$ until the color disappeared, was washed once with water and dried over $MgSO_4$. After removal of the solvent the residue was distilled to afford 720 mg (2.48 mmol, 89%) of *trans*-2,5-diethyl-3,4-dicarboethoxy-1,3,4-thiadiazolidine (**34**): bp 96–98° (0.05 mm); nmr (CCl_4) δ 1.33–1.80 (complex m, 4, CH_3CH_2), 1.20 (t, J = 7.5 Hz, 6, OCH_2CH_3), 5.49 (t, J = 6.5 Hz, 2, tertiary H).

Anal. Calcd for $C_{12}H_{22}N_2O_4S$: C, 49.63; H, 7.65; N, 9.65; S, 11.04. Found: C, 49.72; H, 7.75; N, 9.58; S, 11.07.

A sample of **34** (250 mg, 0.863 mmol) was dissolved in ~10 ml of MeOH. A solution of $NaIO_4$ (230 mg, 1.13 mmol) in a minimal amount of water was added; the resulting solution was refluxed briefly and allowed to stand overnight. Filtration afforded 167 mg (0.845 mmol, 98%) of $NaIO_3$. Water was added to the filtrate, the resulting solution was extracted with benzene, and the organic layer was dried over $MgSO_4$. Removal of the solvent left 250 mg (0.818 mmol, 97%) of the crude *trans*-2,5-diethyl-3,4-dicarboethoxy-1,3,4-thiadiazolidine *S*-oxide which was not purified further. It had ir (neat) 1720 (C=O), 1060–1075 cm^{-1} (S—O); nmr (CCl_4) δ 1.08 [t (poorly resolved), 6, J = ~7 Hz, CH_3], 1.25 (t, 3, J = 7 Hz, OCH_2CH_3), 1.28 (t, 3, J = 7 Hz, OCH_2CH_3), 1.45–2.00 (complex m, 4, CH_2), 4.17 (q, 2, J = 7 Hz, OCH_2), 4.20 (q, 2, J = 7 Hz, OCH_2), 4.82 (t, 1, J = 7.5 Hz, tertiary H), 5.21 (very br s,[69] 1, tertiary H); nmr (C_6H_6) δ 0.87–1.28 (complex set of absorptions, 14, 12 CH_3 + CH_2CH_3), 2.06 (q, 2, J = 7.5 Hz, CH_2CH_3), 4.00 (q, 2, J = 7 Hz, OCH_2), 4.05 (q, 2, J = 7 Hz, OCH_2), 4.83 (t, 1, J = 7.5 Hz, tertiary H), 5.24 (very br s, 1, tertiary H).

The above sulfoxide (100 mg, 0.327 mmol) was dissolved in $CHCl_3$ and a solution of 85% *m*-chloroperbenzoic acid (70 mg, 0.35 mmol) was added. The solution was allowed to stand overnight. Work-up afforded 100 mg (0.310 mmol, 95%) of *trans*-2,5-diethyl-3,4-dicarboethoxy-1,3,4-thiadiazolidine *S*-dioxide as an oil, which slowly crystallized. Recrystallization from a large volume of pentane gave 49.3 mg (0.531 mmol, 47%) of analytically pure sulfone: mp 75–76°; ir (KBr) 1720 (C=O), 1340 (S—O), 1110 cm^{-1} (S—O); nmr (CCl_4) δ 1.12 (t, 6, J = 7.5 Hz, CH_3), 1.34 (t, 6, J = 7.5 Hz, CH_3), 4.62 (q, 4, J = 7.0 Hz, OCH_2), 4.49 (d, 1, J = 5.5 Hz, tertiary H), 4.64 (d, 1, J = 5.5 Hz, tertiary H). The OCH_2CH_3 quartet has a half-width of 1 Hz in both CCl_4 and benzene precluding the idea of two overlapping absorption patterns; the tertiary protons apparently show up as the X portion of an ABX system.

Anal. Calcd for $C_{12}H_{22}N_2O_6S$: C, 44.70; H, 6.89; N, 8.69; S, 9.94. Found: C, 44.69; H, 6.92; N, 8.65; S, 9.94.

Pyrolysis of 16c and 16d.—A sample of **16c** of at least 97% isomeric purity (allowing for nmr error or ±3%) was allowed to decompose in refluxing petroleum ether (bp 40–60°). Analysis by nmr indicated a quantitative conversion to episulfide; this was shown to consist of 7 ± 2% *trans*-2,3-diethyl episulfide (**28**) and 93 ± 2% *cis*-2,3-diethyl episulfide (**27**) by glpc (glass 3-ft SE-30, 80°). A similar experiment with a mixture of 80 ± 3% **16c** and 20 ± 3% **16d** gave again in quantitative yield a mixture of 69 ± 2% **27** and 31 ± 2% **28**.

(69) Broadening seems to arise from conformational effects. This problem is being investigated further.

Synthesis of *trans*- and *cis*-2,3-Diethyl Episulfides.—A sample of *trans*-2,3-diethyl epoxide was prepared by treatment of *trans*-3-hexene with *m*-chloroperbenzoic acid following the normal procedure.[70] The material had bp 104–106° (atm); nmr (CCl_4) δ 0.98 (t, 6, J = 6.5 Hz, CH_3), 1.24–1.70 (complex m, 4, CH_2), 2.50 (t, 2, J = 5 Hz, 2,3 H).

Anal. Calcd for $C_6H_{12}O$: C, 71.93; H, 12.10. Found: C, 71.75; H, 12.09.

After some initial experimentation, it was found that the above epoxide could be converted to **28** only by drastically increasing the severity of the normal reaction conditions.[71] The epoxide (1.5 g, 15 mmol) was mixed with KSCN (2.0 g, 20.6 mmol) in 2 ml of H_2O and 2 ml of ethanol. Sufficient ethanol was added to give a homogenous solution. This was refluxed with stirring for 3 days and thereafter stirred at room temperature for 5 days. Work-up and distillation gave **28** (0.50 g, 4.46 mmol, 30%): bp 120–122° (atm); nmr (CCl_4) δ 1.03 (t, 6, J = 7.0 Hz, CH_3), 1.23–2.05 complex m, 4, CH_2), 2.48 (broadened t, 2, J = ~4.5 Hz, 2,3 H). The low yield was caused chiefly by difficulties in distilling **28** which foams badly.

Anal. Calcd for $C_6H_{12}S$: C, 61.99; H, 10.43; S, 27.58. Found: C, 61.65; H, 10.30; S, 26.59.

Preparation of *cis*-**27** was accomplished in a similar manner. Reaction of the disodium salt of acetylene with ethyl bromide gave diethylacetylene, which was hydrogenated over palladium on barium sulfate in pyridine solution. There was obtained *cis*-3-hexene: ir (pure) 830 cm^{-1} (cis C=C), no absorption at 970 cm^{-1}; nmr (CCl_4) δ 0.97 (t, J = 7 Hz, 6 H, CH_3), 2.0 (quintet, J = ~7 Hz, 4 H, CH_2), 5.23 (br t, J = ~7 Hz, 2 H, vinyl H). Oxidation with *m*-chloroperbenzoic acid gave *cis*-2,3-diethyl epoxide, bp 106–109° (atm), in 53% yield: ir (neat) 900 cm^{-1} (epoxide); nmr (CCl_4) δ 1.0 (t, J = 7.0 Hz, 6 H, CH_3), 1.46 (br q, J = ~7 Hz, 4 H, CH_2), 2.70 (complex m, 2 H, tertiary H).

Treatment of this epoxide in 50:50 water–methanol with excess KSCN for 3 days at 40° gave **27**, bp 138–140° (atm), in 49% yield: ir (neat) 900, 1070 cm^{-1}; nmr (CCl_4) δ 1.10 (t, J = 7 Hz, 6 H, CH_3), 1.33–1.99 (complex m, 4 H, CH_2), 2.65–2.90 (complex m, 2 H, tertiary H). This spectrum was identical with that of **27** obtained from pyrolysis of **16c**.

Anal. Calcd for $C_6H_{12}S$: C, 62.00; H, 10.41. Found: C, 62.38; H, 10.45.

The products **27** and **28** were coinjected with samples obtained from pyrolysis of **16c** and **16d**. The expected peak enhancement was seen confirming the stereochemical assignments.

Preparation of 2,5-Di-*tert*-butyl-1,3,4-Δ^3-thiadiazolines (24) and (25).—An ~5% by weight solution of pivaldehyde azine in ether was prepared. This was put in a heavy-walled tube, which was then cooled to −70°; hydrogen sulfide (excess) was condensed in the tube, which was then sealed. The tube was shaken for 32 hr at room temperature, cooled to −70° and broken. After evaporation of the hydrogen sulfide at −30°, a slight excess of diethyl azodicarboxylate was added (at −30°). The contents were well stirred and allowed to stand overnight at −30° and then for several hours at −5°. The reaction mixture was taken up in pentane and washed with aqueous sodium bisulfate until colorless. The pentane solution was then dried over $MgSO_4$. Nmr analysis of this crude product revealed it to consist of 41.5% trans isomer **24** and 25% cis isomer **25** with 21% *cis*-2,3-di-*tert*-butyl episulfide (**29**) and 12.5% *trans*-2,3-di-*tert*-butyl episulfide (**30**) (see further for assignment of nmr resonances). Trace quantities of pivaldehyde azine and 2,5-di-*tert*-butyl-1,3,4-thiadiazole were also seen. The episulfides appear to arise from routes other than through the thiadiazolines since these were stable under the careful work-up conditions. Recrystallization out of methanol gave pure **24** in ~40% yield. (In some runs the yield was as high as 70% apparently owing to the formation of less episulfide during ring closure.) This isomer has mp 62–63° dec; ir (KBr) 1585 cm^{-1} (N=N); nmr (CCl_4) δ 1.07 (s, 18, *t*-Bu), δ 5.95 (s, 2, 2,5 H).[72]

Anal. Calcd for $C_{10}H_{20}N_2S$: C, 59.95; H, 10.07; N, 13.98; S, 16.00. Found: C, 59.81; H, 10.27; S, 16.09.

(70) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., p 136.

(71) H. R. Snyder, J. M. Stewart, and J. B. Ziegler, *J. Amer. Chem. Soc.*, **69**, 2672 (1947).

(72) The position of this absorption appears to be both solvent and concentration dependent.

An acceptable nitrogen analysis could not be obtained.

The concentration of **25** [nmr (CCl_4) δ 1.15 (s, 18, *t*-Bu), 5.52 (s, 2, 2,5 H)] was equal to that of **24** in the mother liquors. Careful chromatography in the cold over silica gel allowed the isolation of a 50:50 mixture of **24** and **25**. The isomer **25** could be stored indefinitely in the cold but began to decompose at room temperature.

Oxidation of 24 to *trans*-2,5-di-*tert*-butyl-1,3,4-Δ³-thiadiazoline *S*-oxide (26) with (*m*-chloroperbenzoic acid) afforded, after recrystallization from petroleum ether (bp 40–60°), in 46% yield (quantitatively nmr but much lost in recrystallization) the solid sulfoxide **26**: mp 99–105° dec; ir (KBr) 1060 cm^{-1} (S→O); nmr (CCl_4) δ 1.07 [s, 9 H, $(CH_3)_3C$], 1.40 [s, 9 H, $(CH_3)_3C$], 4.05 [d, J = 1.4 Hz, 2(5) H], 5.68 [d, J = 1.4 Hz, 5(2) H].

Anal. Calcd for $C_{10}H_{20}N_2OS$: C, 55.50; H, 9.34; N, 12.95; S, 14.82. Found: C, 55.42; H, 9.27; N, 12.78; S, 14.73.

Attempted oxidation to the sulfone failed to afford a pure product.

Pyrolysis of 24 was carried out in refluxing methylcyclohexane for 5 hr. Removal of the solid left a liquid (100% yield determined by nmr): uv (EtOH) 2650 Å (ε 105); nmr (CCl_4) δ 1.15 [s, 18 H, $(CH_3)_3C$], 2.78 (s, 2 H, 2,3 H); mass spectrum *m/e* 172 (parent, calcd for $C_{10}H_{20}S$ 172), 140 (S), 125 (CH_3S), 115 (*t*-Bu). Distillation of the episulfide was difficult owing to severe foaming.

In a flame-dried three-necked flask swept with dry nitrogen, a solution of phenyllithium was prepared from the reaction of iodobenzene (3.2 g, 15.7 mmol) with lithium wire (203 mg, 29 mg-atoms) in ether solution. The above crude episulfide **29** (400 mg, 2.32 mmol) dissolved in ether was added to the phenyllithium solution. Turbidity developed immediately. After refluxing for ~1 hr, the solution was poured into water; the stench of phenylthiol was noted. The ether solution was washed repeatedly with $NaHCO_3$ solution and dried over $MgSO_4$. Distillation at 12 mm (very difficult owing to foaming, boiling point not measured) gave 210 mg (1.5 mmol, 65%) of a clear liquid olefin: $n^{28}D$ 1.4582 (lit.[73] $n^{20}D$ 1.4269); ir (pure) 3040 and 3060 (vinyl H), 740 cm^{-1} (cis C=C), no absorption at 970 cm^{-1} (trans C=C);[72] mass spectrum *m/e* 140 (parent, calcd for $C_{10}H_{20}$ 140, rel intensity 8), 97 (C_3H_7, 18), 83 (*t*-Bu, 72), 70 [$(CH_3)_3CCH_2$, 100];[74] nmr (CCl_4) δ 1.14 [s, 18 H, $(CH_3)_3C$], 5.13 (s, 2 H, vinyl H). These data identify the olefin as *cis*-di-*tert*-butylethylene and its precursor as *cis*-2,3-di-*tert*-butyl episulfide (**29**).

Pyrolysis of 25 was accomplished using a 50:50 mixture of **24** and **25**. At 40° **25** decomposes selectively affording a single episulfide **30** [nmr (CCl_4) δ 0.93 (s, 18, *t*-Bu), 2.52 (s, 2, 2,3 H)]. This was isolated by preparative plate chromatography over silica gel (benzene eluent). Desulfurization with phenyllithium proceeded sluggishly. Exclusively *trans*-2,3-di-*tert*-butylethylene was formed: nmr (CCl_4) δ 0.98 (s, 18, *t*-Bu), 5.40 (s, 2, vinyl H); mass spectrum *m/e* 140 (parent, rel intensity 40), 69 (100).[73,74]

Cycloadditons of 25 were attempted with two–threefold molar excesses of dicyanoacetylene and dimethyl acetylenedicarboxylate. Reactions were carried out at 40° with 50:50 mixture of **24** and **25**; **24** does not react at this temperature. Only **30** was formed. With diethyl azodicarboxylate about an equal mixture of **30** and 2,5-di-*tert*-butyl-1,3,4-thiadiazoline was obtained.

Cycloadditions of 24 were carried out with various dipolarophiles. With diethyl azodicarboxylate in methyl cyclohexane using a three-fold excess of dipolarophile there was obtained after distillation, bp 122° (0.4–0.5 mm), in 90% yield *trans*-2,5-di-*tert*-butyl-3,4-dicarboethoxy-1,3,4-thiadiazolidine (**36**): ir (pure) 1720 cm^{-1} (C=O); nmr (CCl_4) δ 0.95 [s, 18 H, $(CH_3)_3C$], 1.30 [t, J = 7.5 Hz, 6 H, CH_3CH_2O], 4.23 (q, J = 7.5 Hz, 4 H, CH_3CH_2O), 5.39 (s, 2 H, 2,5 H).

Anal. Calcd $C_{16}H_{30}N_2O_4S$: C, 55.46; H, 8.73; N, 8.08; S, 9.25. Found: C, 55.78; H, 8.72; N, 7.92; S, 9.01.

Oxidation with *m*-chloroperbenzoic acid to the sulfoxide afforded in 67% yield a white solid: mp 57–59°; ir (pure) 1740 (C=O), 1050 and 1090 cm^{-1} (S→O); nmr (CCl_4) δ 1.07 [s, 9 H, $(CH_3)_3C$], 1.20 [s, 9 H, $(CH_3)_3C$], 1.29 (t, J = 7.0 Hz, 3 H, CH_3CH_2O), 1.33 (t, J = 7.0 Hz, 3 H, CH_3CH_2O), 4.19 (q, J = 7.0 Hz, 2 H, CH_3CH_2O), 4.27 (q, J = 7.0 Hz, 2 H, CH_3CH_2O), and δ 4.78 (br s, 2 H, 2,5 H).

Anal. Calcd for $C_{16}H_{30}N_2O_5S$: C, 53.02; H, 8.34; N, 7.72; S, 8.85. Found: C, 52.67; H, 8.24; N, 7.78; S, 8.82.

Oxidation with *m*-chloroperbenzoic acid to the sulfone afforded in 96% yield a white solid: mp 64–66°; ir 1730 (C=O), 1330 cm^{-1} (S→O); nmr (CCl_4) δ 1.17 [s, 18 H, $(CH_3)_3C$], 1.34 (t, J = 7.0 Hz, 6 H, CH_3CH_2O), 4.27 (q, J = 7.0 Hz, 4 H, OCH_2CH_3), 4.50 (br s, 2 H, 2,5 H). Expansion and attenuation of the area between δ 4.0 and 4.6 by means of the CAT showed only the sharp methylene quartet (half-width 2 Hz) and the broadened singlet for the 2,5 protons.

Anal. Calcd for $C_{16}H_{30}N_2O_6S$: C, 50.77; H, 7.99; N, 7.40; S, 8.47. Found: C, 50.68; H, 7.94; N, 7.37; S, 8.33.

Reaction of **24** with dimethyl acetylenedicarboxylate yielded after purification in 67% yield *trans*-2,5-di-*tert*-butyl-3,4-dicarbomethoxy-2,5-dihydrothiophene (**33**): mp 119.5–120°; nmr (CCl_4) δ 0.95 [s, 18 H, $(CH_3)_3C$], 3.70 (s, 6 H, OCH_3), 4.30 (s, 2 H, 2,5 H).

Anal. Calcd for $C_{16}H_{26}O_4S$: C, 61.11; H, 8.34; S, 10.20. Found: C, 61.14; H, 8.21; S, 10.29.

Oxidation to *trans*-2,5-di-*tert*-butyl-3,4-dicarbomethoxy-2,5-dihydrothiophene *S*-oxide (**37**) with *m*-chloroperbenzoic acid gave in 92% yield a white solid: mp 168–169°; nmr (CCl_4) δ 1.05 [s, 9 H, $(CH_3)_3C$], 1.20 [s, 9 H, $(CH_3)_3C$], 3.63 [d, J = 1.5–2.0 Hz, 1 H, 2(5) H], 3.76 (s, 6 H, OCH_3), 3.84 [d, J = 1.5–2.0 Hz, 1 H, 5(2) H].

Anal. Calcd for $C_{16}H_{26}O_5S$: C, 58.16; H, 7.93; S, 9.70. Found: C, 57.72; H, 7.75; S, 9.54.

Treatment of **37** (1 g, 3 mmol) in refluxing acetic anhydride afforded after work-up 930 mg (100%) of 3,4-dicarbomethoxy-2,5-di-*tert* butylthiophene (**38a**): nmr (CCl_4) δ 1.42 (s, 18 H, *t*-Bu), 3.73 (s, 6 H, OCH_3)

Oxidation to the sulfone with *m*-chloroperbenzoic acid afforded in 96% yield *trans*-2,5-di-*tert*-butyl-3,4-dicarbomethoxy-2,5-dihydrothiophene *S*-dioxide (**39**): mp 185–187°; nmr (CCl_4) δ 1.09 [s, 18 H, $(CH_3)_3C$], 3.70 (s, 2 H, 2,5 H), 3.75 (s, 6 H, OCH_3).

Anal. Calcd for $C_{16}H_{26}O_6S$: C, 55.47; H, 7.57; S, 9.25. Found: C, 55.49; C, 7.69; S, 9.05.

Cycloaddition was carried out with **24** (350 mg, 1.75 mmol) with tetracyanoethylene (224 mg, 1.73 mmol). A methylcyclohexane solution was refluxed overnight. After removal of solvent the crude product was chromatographed over Al_2O_3 eluting with benzene. Recrystallization from petroleum ether (bp 40–60°) containing a trace of benzene gave 530 mg (1.73 mmol, 100%) of *trans*-2,5-di-*tert*-butyl-3,3,4,4-tetracyanosulfolane (**63**): mp 144.5–145.5°; ir (KBr) 2280 cm^{-1} (C≡N); nmr (CCl_4) δ 1.34 [s, 18 H, $(CH_3)_3C$], 3.90 (s, 2,5 H).

Anal. Calcd for $C_{16}H_{20}N_4S$: C, 63.97; H, 6.71; N, 18.64; S, 10.67. Found: C, 64.02; H, 6.81; N, 18.68; S, 10.77.

Trans stereochemistry is presumed by analogy.

Cycloadditon of **24** (350 mg, 1.75 mmol) with *N*-phenylmaleimide (303 mg, 1.75 mmol) gave, after refluxing overnight in methylcyclohexane solution, a crude, white solid (630 mg). This was recrystallized from methanol–water to afford 407 mg (1.18 mmol, 67% yield) of cycloadduct **62**: mp 151–152°; ir (KBr) 1710 cm^{-1} (1770 cm^{-1}, w) (C=O); nmr (CCl_4) δ 1.07 [s, 9 H, $(CH_3)_3C$], δ 1.18 [s, 9 H, $(CH_3)_3C$], 3.29–3.75 (m, 4 H, 2,5 H, 3,4 H), 7.16–7.50 (m, 5 H, C_6H_5).

Anal. Calcd for $C_{20}H_{27}NO_2S$: C, 69.53; H, 7.88; N, 4.05; S, 9.28. Found: C, 69.48; H, 7.92; N, 4.02; S, 9.51.

Oxidation to the sulfoxide with *m*-chloroperbenzoic acid was carried out in 95% yield affording a solid, mp 235–236°. Nmr (CCl_4) consisted of two sets of *tert*-butyl peaks, δ 1.03 and 1.40 and δ 1.23 and 1.40, in the ratio of ~2:1, likely corresponding to the ratios of isomeric sulfoxides. Complex absorptions at δ 2.63–3.93 (4 H) and 7.20–7.50 completed the spectrum.

Oxidation to the sulfone with MCPBA afforded in 55% yield a solid, mp 278–280°.

Anal. Calcd for $C_{20}H_{27}NO_4S$: C, 63.63; H, 7.21; N, 3.71; S, 8.49. Found: C, 63.59; H, 7.17; N, 3.69; S, 8.55.

When **24** was decomposed in refluxing methylcyclohexane with equivalent amounts of 3-morpholinostyrene, 2-morpholinobutene-2, bicyclo[2.2.1]hepta-2,5-diene, or 2,3-dimethylbutadiene, only **29** obtained from ring closure of the thiocarbonyl ylide could be detected. With benzaldehyde chiefly **29** was formed, although a small amount of another product may have been present.

Experiments with 29 were carried out. With diethyl azodicarboxylate in refluxing methylcyclohexane no cycloaddition

(73) A. R. Bader, R. P. Buckley, F. Leavitt, and M. Szwarc, *J. Amer. Chem. Soc.*, **79**, 5621 (1957).

(74) See, for example, P. Natalis and J. F. Franklin, *Bull. Soc. Chim. Belg.*, **75**, 328 (1966).

took place; the episulfide was quite stable. Similar results were obtained with dimethyl acetylenedicarboxylate. On irradiation in ether solution (medium pressure, Hg lamp) **30** slowly accumulated as determined by glpc. Simultaneously, considerable destruction of starting material took place.

Pyrolysis of 39 was accomplished either in the injection port of the glpc (250°) or in a Pyrex tube at ~250°. Nmr and glpc analyses established that quantitative conversion to a mixture consisting of 90% *Z,E*, 6% *E,E*-, and 4% *Z,Z*-dienes[42] had taken place.

General Procedures.—A number of the procedure are repetitious and hence are described briefly here.

A. Synthesis of Thiadiazolines from Dichloroazo Compounds.—The azine was prepared from reaction of the carbonyl component with hydrazine; it was distilled or recrystallized before use. About a 10% by weight solution of azine in methylene chloride was made and this solution was cooled to −70°. In a dimly lighted hood chlorine was passed through the solution until a yellow color persisted. The solution was warmed to 10–15° and the methylene chloride was removed on a rotatory evaporator. The crude dichloroazo compound, formed nearly quantitatively, was dissolved in chloroform or ether and put in a heavy-walled Pyrex tube; excess hydrogen sulfide was added; and the tube was sealed shut. The tube was rocked at room temperature for 1–2 days and then opened. After evaporation of the hydrogen sulfide, the crude thiadiazoline was purified by either crystallization or distillation.

B. Cycloaddition of the Thiadiazolines with Diethyl Azodicarboxylate.—The thiadiazoline (2.5 mmol) in methylcyclohexane was dropped slowly in a refluxing solution of azo ester (7.5–12.5 mmol) in methylcyclohexane, after which the reaction mixture was refluxed for another 12–24 hr. After evaporation of the solvent, cooling in ice, and dilution with diethyl ether, the resulting solution was washed with 10% Na_2SO_3 solution and water, respectively; if necessary the washings were repeated. The solution was then dried over $MgSO_4$, filtered, and evaporated, and the product was isolated by means of distillation *in vacuo* or recrystallization. In some cases column chromatography was used. The problem was to get rid of the hydrazo ester formed after extractions (washings) with Na_2SO_3 solution.

C. Cycloaddition with Dimethyl Acetylenedicarboxylate.—To a refluxing solution of acetylenic ester (10 mmol) in methylcyclohexane–benzene (10:1) was dropped slowly a solution of the thiadiazoline (5 mmol) dissolved in the same solvent mixture. Refluxing was continued for 12–24 hr. After the solvents had been removed by evaporation, *n*-heptane or *n*-pentane, in which dimethyl acetylenedicarboxylate is very insoluble, was added allowing separation of much excess ester. Sometimes it was necessary to repeat the evaporation and addition of heptane to remove the still present ester. The cycloadduct could then be isolated by distillation or recrystallization from petroleum ether (bp 40–60°). In some cases a fivefold excess of acetylenic ester was used. The chromatography was done with aid of silica gel and elution with a mixture of petroleum ether (bp 40–60°) and ether (10%); the cycloadduct was then eluted.

D. Synthesis of the Sulfoxides and the Sulfones.—The substrate (thiadiazoline, thiadiazolidine, or dihydrothiophene, 5 mmol) and *m*-chloroperbenzoic acid (5 mmol) in chloroform was stirred overnight and 0.5 hr at 40–50° thereafter. After evaporation in the cold, ether was added. The resulting ether solution was washed with 10% Na_2SO_3 solution, $NaHCO_3$ solution, and distilled water, respectively. After drying and evaporation, often recrystallization from a mixture of petroleum ether (bp 40–60°) and a little ether was sufficient to give pure sulfoxide. We also used chromatography in some cases, with a silica gel column and elution with benzene and ether respectively.

The procedure for the synthesis of the sulfones can be followed as above using 2 equiv of *m*-chloroperbenzoic acid.

Preparation of 2,2,5,5-tetramethyl-1,3,4-Δ³-thiadiazoline (45a) was carried out in 81% yield. The compound, mp 95.5–97° dec, had ir (KBr) 1580 cm^{-1} (N=N), nmr (CCl_4) δ 1.70 (s, 12 H).

Anal. Calcd for $C_6H_{12}N_2S$: C, 49.96; H, 8.39; N, 19.42; S, 22.23. Found: C, 49.84; H, 8.67; N, 19.42; S, 21.86.

Oxidation to 2,2,5,5-tetramethyl-1,3,4-Δ³-thiadiazoline *S*-dioxide gave in 53% yield white crystals: mp 72–73° dec; ir (Nujol) 1590 (N=N), 1060 cm^{-1} (S→O); nmr (CCl_4) δ 1.47 (s, 6 H), 1.70 (s, 6 H).

Anal. Calcd for $C_6H_{12}N_2OS$: C, 44.97; H, 7.55; N, 17.48; S, 20.01. Found: C, 44.90; H, 7.93; N, 17.32; S, 20.01.

Oxidation to 2,2,5,5-tetramethyl-1,3,4-Δ³-thiadiazoline *S*-dioxide gave in 51% yield a white solid: mp 112.5–114.5° dec; ir (Nujol) 1310 cm^{-1} (SO_2); nmr (CCl_4) δ 1.65 (s, 12 H).

Anal. Calcd for $C_6H_{12}N_2O_2S$: C, 40.89; H, 6.86; N, 15.90; S, 18.20. Found: C, 41.20; H, 6.91; N, 16.06; S, 18.18.

Cycloadditions of 45a were carried out with diethyl azodicarboxylate using a 1.7 excess. There was obtained in 81% crude yield 2,2,5,5-tetramethyl-3,4-dicarboethoxy-1,3,4-thiadiazolidine (**49a**) as a heavy oil: bp 85° (0.1 mm); ir (neat) 1730 cm^{-1} (C=O); nmr (CCl_4) δ 1.25 (t, J = 7.0 Hz, 6 H, OCH_2CH_3), 1.60–2.10 (br, poorly resolved d, 12 H, CH_3), 4.12 (q, J = 7.0 Hz, 4 H, OCH_2CH_3); mass spectrum m/e 290 ($C_{12}H_{22}N_2O_4S$), 217 ($CO_2C_2H_5$), 216 [$(CH_3)_2C{=}S$].

Anal. Calcd for $C_{12}H_{22}N_2O_4S$: C, 49.64; H, 7.64; N, 9.65; S, 11.03. Found: C, 49.37; H, 7.65; N, 9.26.

An acceptable sulfur analysis could not be obtained.

Oxidation to 2,2,5,5-tetramethyl-3,4-dicarboethoxy-1,3,4-thiadiazolidine *S*-dioxide was carried out (the sulfoxide could not be obtained crystalline and was not investigated further). There was obtained in 73% yield a solid: mp 41–43°; ir (Nujol) 1740 (C=O), 1350 cm^{-1} (SO_2); nmr (CCl_4) δ 1.25 (br t, J = 7.0 Hz, 6, OCH_2CH_3), 1.42–δ 1.93 (v br s, 12 H, CH_3), 4.15 (slightly br q, J = 7.0 Hz, 4 H, OCH_2CH_3).

Anal. Calcd for $C_{12}H_{22}N_2O_6S$: C, 44.71; H, 6.88; N, 8.68; S, 9.95. Found: C, 44.80; H, 6.91; N, 8.65; S, 10.22.

Cycloaddition of 45a with dimethyl acetylenedicarboxylate with 3.3-fold excess of acetylenic ester gave in 45% yield after distillation and recrystallization from pentane 2,2,5,5-tetramethyl-3,4-dicarbomethoxy-2,5-dihydrothiophene (**48a**) as a white solid: mp 80–82.5°; ir (KBr) 1740 cm^{-1} (C=O); nmr (CCl_4) δ 1.61 (s, 12 H, CH_3), 3.75 (s, 6 H, OCH_3).

Anal. Calcd for $C_{12}H_{18}O_4S$: C, 55.79; H, 7.04; S, 12.41. Found: C, 55.88; H, 7.09; S, 12.39.

Oxidation to 2,2,5,5-tetramethyl-3,4-dicarbomethoxy-2,5-dihydrothiophene *S*-oxide was accomplished by treating **48a** (3.0 g, 11.6 mmol) dissolved in methanol with sodium metaperiodate (2.8 g, 13 mmol) dissolved in water. The temperature was held at 25–40° for 4 hr. The precipitate of sodium iodate was filtered off, the methanol was evaporated down, and the resulting solution was extracted three times with 100 ml of ether. After drying there was obtained 3.05 g (11.1 mmol, 96%) of sulfoxide as a white solid: mp 73–74°; ir (Nujol) 1710 (C=O), 1030 cm^{-1} (S→O); nmr (CCl_4) δ 1.37 (s, 6 H, CH_3), 1.55 (s, 6 H, CH_3), 3.75 (s, 6 H, OCH_3).

Anal. Calcd for $C_{12}H_{18}O_5S$: C, 52.54; H, 6.62; S, 11.69. Found: C, 52.63; H, 6.67; S, 12.02.

Oxidation to the sulfone afforded in 99% yield 2,2,5,5-tetramethyl-3,4-dicarbomethoxy-2,5-dihydrothiophene *S*-dioxide: mp 104–105.5°; ir (Nujol) 1720 (C=O), 1320 cm^{-1} (SO_2); nmr (CCl_4) δ 1.51 (s, 12 H, CH_3), 3.75 (s, 6 H, OCH_3).

Anal. Calcd for $C_{12}H_{18}O_6S$: C, 49.64; C, 6.25; S, 11.05. Found: C, 49.89; H, 6.25; S, 11.06.

Pyrolysis of 45a was accomplished by carefully heating 300 mg (2.08 mmol) in a microdistillation apparatus. After nitrogen evolution had ceased the product was distilled; it became solid on standing. After one recrystallization from methanol there was obtained 207 mg (85%) of tetramethyl episulfide, mp 54–56° (lit.[75] mp 76°), nmr (CCl_4) δ 1.60.

Anal. Calcd for $C_6H_{12}S$: C, 62.00; H, 10.41; S, 27.59. Found: C, 62.05; H, 10.53; S, 27.67.

The synthesis of 2,2,5,5-tetraethyl-1,3,4-Δ³-thiadiazoline (45b) was accomplished in 86% yield: bp 60° (0.8 mm); ir (pure) 1585 cm^{-1} (N=N); nmr (CCl_4) δ 0.97 (t, J = 7.0 Hz, 12 H, CH_3), 1.67–2.34 (m, 8 H, CH_2CH_3).

Anal. Calcd for $C_{10}H_{20}N_2S$: C, 59.95; H, 10.06; S, 16.00; N, 14.00. Found: C, 59.63; H, 9.97; S, 16.12; N, 13.39.

Oxidation gave 2,2,5,5-tetraethyl-1,3,4-Δ³-thiadiazoline *S*-oxide, mp 46–48°, in 76% yield: ir (Nujol) 1585 (N=N), 1045 and 1065 cm^{-1} (S→O),

Anal. Calcd for $C_{10}H_{20}N_2OS$: C, 55.52; H, 9.32; S, 14.82; N, 12.95. Found: C, 55.53; H, 9.21; N, 12.94; S, 14.77.

Further oxidation afforded 2,2,5,5-tetraethyl-1,3,4-Δ³-thiadiazoline *S*-dioxide, mp 108–109.5°, in poor yield (not determined accurately): mass spectrum m/e 232 ($C_{10}H_{20}N_2O_2S$), 168 (SO_2), 140 ($SO_2 + N_2$).

Cycloaddition with 45b were carried out first with 1.7 mole equiv of diethyl azodicarboxylate. There was obtained 92%

(75) M. A. Youtz and P. P. Perkins, *J. Amer. Chem. Soc.*, **51**, 3508 (1929); the reason for the discrepancy in melting point is unknown.

of 2,2,5,5-tetraethyl-3,4-dicarboethoxy-1,3,4-thiadiazolidine (**49b**) as a heavy oil: bp 112° (0.125 mm); ir (neat) 1730 cm^{-1} (C=O); nmr (CCl_4) δ 1.02 (t, J = 7.0 Hz, 6 H, CH_2CH_3), 1.25 (t, J = 7.0 Hz, 6 H, OCH_2CH_3), 1.59–2.40 (m, 4, CH_2CH_3), 4.10 (q, J = 7.0 Hz, 4 H, OCH_2CH_3); mass spectrum m/e 346 ($C_{16}H_{30}N_2O_4S$), 317 (C_2H_5), 273 ($CO_2C_2H_5$).

Anal. Calcd for $C_{16}H_{30}O_4N_2S$: C, 55.46; H, 8.73; N, 8.09; S, 9.26. Found: C, 55.88; H, 8.76.

Repeated attempts to determine nitrogen and sulfur led to divergent results.

Oxidation to 2,2,5,5-tetraethyl-3,4-dicarboethoxy-1,3,4-thiadiazolidine *S*-oxide gave in 72% yield a white solid: mp 57–59°; ir (Nujol) 1740 (C=O), 1060 cm^{-1} (S→O).

Anal. Calcd for $C_{16}H_{30}O_5N_2S$: C, 53.02; H, 8.34; N, 7.73; S, 8.84. Found: C, 52.85; H, 8.23; N, 7.52; S, 9.34.

Oxidation to 2,2,5,5-tetraethyl-3,4-dicarboethoxy-1,3,4-thiadiazolidine *S*-dioxide gave in 78% yield a white solid: mp 108–109.5°; ir (Nujol) 1740 (C=O), 1390 cm^{-1} (SO_2).

Anal. Calcd for $C_{16}H_{30}O_6N_2S$: C, 50.76; H, 7.99; N, 7.40; S, 8.47. Found: C, 51.14; H, 8.04; N, 7.40; S, 8.53.

Cycloaddition of 45b with dimethyl acetylenedicarboxylate (fourfold excess) gave on distillation in 30% yield 2,2,5,5-tetramethyl-3,4-dicarbomethoxy-2,5-dihydrothiophene (**48b**), bp 110–114°, (0.25 mm), which after recrystallization from methanol had mp 40–42.5°; ir 1740 cm^{-1} (C=O); nmr (CCl_4) δ 1.00 (t, J = 6.8 Hz, 6 H, CH_2CH_3), 1.80 (q, J = 6.8 Hz, 4 H, CH_2CH_3), 3.69 (s, 6, OCH_3).

Anal. Calcd for $C_{16}H_{26}O_4S$: C, 61.10; H, 8.34; S, 10.21. Found: C, 61.07; H, 8.26; S, 10.48.

Pyrolysis of 45b was accomplished by refluxing 0.5 g (2.5 mmol) in methylcyclohexane. On removal of solvent tetraethyl episulfide remained in quantitative yield as determined by nmr. Distillation [bp ~75° (12 mm)] went with difficulty owing to foaming. The product had nmr (CCl_4) δ 1.0 (t, J = 7 Hz, 12 H, CH_3), 1.83 (q, J = 7 Hz, 8 H, CH_2).

Anal. Calcd for $C_{16}H_{30}S$: C, 69.70; H, 11.70; S, 18.60. Found: C, 69.49; H, 11.63; S, 18.69.

Synthesis of 2,2,5,5-bis[(3-*tert*-butyl)pentamethylene]-1,3,4-Δ³-thiadiazoline (45c) was accomplished in 21% yield by addition of hydrogen sulfide to the azine followed by dehydrogenation. Treatment with hydrogen sulfide of the product of addition of chlorine to the azine afforded **45c** in 80% yield. The compound had mp 126–128° dec; ir (KBr) 1590 cm^{-1} (N=N); nmr (CCl_4) δ 0.90 [s, 18 H, $(CH_3)_3C$], 1.11–2.50 (complex m, 16 H, ring CH_2). The spectrum with europium complex is described in the text.

Anal. Calcd for $C_{20}H_{36}N_2S$: C, 71.37; H, 10.79; N, 8.31; S, 9.53. Found: C, 71.42; H, 10.83; N, 8.30; S, 9.50.

The sulfoxide of **45c** was prepared in 68% yield as a solid: mp 164–166° dec; ir (Nujol) 1580 (N=N), 1040 cm^{-1} (S—O); nmr (CCl_4) δ 0.92 [s, 18 H, $(CH_3)_3C$], 1.10–2.52 (complex m, 18 H, ring CH_2).

Anal. Calcd for $C_{20}H_{36}N_2OS$: C, 68.15; H, 10.29; N, 7.95; S, 9.09. Found: C, 68.09; H, 10.29; N, 7.77; S, 9.40.

An acceptable sample of the corresponding sulfone could not be obtained.

Cycloadditions of 45c with diethyl azodicarboxylate in fourfold excess gave after work-up in 95% yield (calculated for cycloadduct) a thick syrup: ir (pure) 1720 cm^{-1} (C=O); nmr (CCl_4) δ 0.88 [s, 18 H, $(CH_3)_3C$], 1.23 (br t, J = 7.0 Hz, 6 H, OCH_2CH_3), 1.40–2.20 (complex m, 18 H, ring CH_2), 4.10 (q, J = 7.0 Hz, 2 H, OCH_2CH_3), 4.12 (q, J = 7.0 Hz, 2, OCH_2CH_3). The ratio of the δ 4.10 to 4.12 quartets is 2:1.

The basic structure 2,2,5,5-bis[(3-*tert*-butyl)pentamethylene]-3,4-dicarboethoxy-1,3,4-thiadiazolidine (**55**, **55'**) is assigned to this material. Experiments with europium shift reagent failed to produce more clearly defined spectra. Attempted distillation failed; some rearrangement of the undistilled material appeared to take place (see experiment with **57**). The mass spectrum showed the parent peak at m/e 482 (calcd for $C_{26}H_{46}N_2O_4S$ 482).

Cycloaddition of 45c with dimethyl acetylenedicarboxylate using a fourfold excess of dipolarophile afforded, after repeated recrystallizations from methanol and chromatography over Al_2O_3 to remove (**51**), in 13% yield 2,2,5,5-bis[(3-*tert*-butyl)pentamethylene]-3,4-dicarbomethoxy-2,5-dihydrothiophene (**54**): mp 131–133°; ir (KBr) 1730 cm^{-1} (C=O); nmr (CCl_4) δ 0.88 [s, 18 H, $(CH_3)_3C$], 1.10–2.10 (complex m, 18 H, ring CH_2), 3.67 (br s, 6 H, OCH_3) (experiments with europium shift reagent failed to improve the spectrum); mass spectrum m/e 450 (parent, calcd for $C_{26}H_{42}O_4S$ 450), 428 (S), 393 [$(CH_3)_3C$]. A satisfactory elemental analysis could not be obtained; the C:H ratio was correct but the S value varied badly.

Pyrolysis of 45c was carried out by heating (320 mg (0.455) mmol) in methylcyclohexane for 5 hr. Removal of the solvent and recrystallization from methanol gave 290 mg (0.94 mmol, 99%) of 2,2,3,3-bis[(3-*tert*-butyl)pentamethylene] episulfide (**51**): mp 205–207°; ir (KBr) 2950, 1440, 1360 cm^{-1}; nmr ($CDCl_3$) δ 0.85 [s, 9 H, $(CH_3)_3C$], 0.90 [s, 9 H, $(CH_3)_3C$], 1.70–2.20 (complex m, 18 H, ring CH_2).

Anal. Calcd for $C_{20}H_{36}S$: C, 77.85; H, 11.76; S, 10.39. Found: C, 77.48; H, 11.72; S, 10.28.

Desulfurization of **51** (230 mg, 0.75 mmol) with phenyllithium (procedure used for *tert*-butyl episulfides) afforded 194 mg (0.70 mmol, 93%) of 4,4'-di-*tert*-butylcyclohexylidenecyclohexane (**52**) which was sublimed (164 mg obtained) and recrystallized from methanol to afford a sample of mp 121–124°; ir (KBr) 3000, 2900, 1450, 1370 cm^{-1}; nmr (CCl_4) δ 0.85 [s, 18 H, $(CH_3)_3C$], 1.05–2.0 (complex m, 10 H, ring CH_2), 2.50–2.90 (br m, 8 H, ring CH_2).

Anal. Calcd for $C_{20}H_{36}$: C, 86.87; H, 13.13. Found: C, 86.63; H, 13.07.

A sample of **52** (84 mg, 0.302 mmol) was treated with excess (60 mg) *m*-chloroperbenzoic acid in $CHCl_3$ solution. After standing overnight the solution was worked up to afford 2,2,3,3-bis[(3-*tert*-butyl)pentamethylene] epoxide (**53**), 88 mg, 0.3 mmol, 100%), which was recrystallized from methanol: mp 158–160°; ir (Nujol) 3000, 2900, 1460, 1360, 900 cm^{-1}; nmr (CCl_4) δ 0.87 [s (very slightly broadened), 18 H, $(CH_3)_3C$], 1.17–1.70 (complex m, 18 H, ring CH_2).

Anal. Calcd for $C_{20}H_{36}O$: C, 82.12; H, 12.40. Found: C, 81.83; H, 12.44.

Attempts to convert **53** into an episulfide by treatment with KSCN in methanol–water led only to eventual decomposition of the epoxide. No trace of an episulfide could be isolated.

Synthesis of 2,2,5,5-bis(hexamethylene)-1,3,4-Δ³-thiadiazoline (45d) proceeded in 50% yield: mp 73–75° dec; ir (Nujol) 1590 cm^{-1} (N=N); nmr (CCl_4) δ 1.70 and 2.02–2.50 (br m).

Anal. Calcd for $C_{14}H_{24}N_2S$: C, 66.62; H, 9.58; N, 11.10; S, 12.70. Found: C, 66.43; H, 9.51; N, 10.94; S, 13.10.

Cycloaddition of 45d with diethyl azodicarboxylate was carried out with a threefold excess of dipolarophile. After work-up there was obtained 490 mg (1.23 mmol, 31% yield) of 2,2,5,5-bis(hexamethylene)-3,4-dicarboethoxy-1,3,4-thiadiazolidine (**57**) as a thick syrup: ir (pure) 1720 cm (C=O); nmr (CCl_4) δ 1.26 (t, J = 7.0 Hz, 6 H, OCH_2CH_3), 1.43–1.97 and 1.97–2.41 (br s, 24 H, ring CH_2), 4.11 (q, J = 7.0 Hz, 4 H, OCH_2CH_3); mass spectrum m/e 398 (parent, calcd for $C_{20}H_{34}N_2O_4S$ 398), 365 (HS), 325 ($CO_2C_2H_5$), 270 ($C_7H_{12}S$). On distillation, bp 130° (0.2–0.3 mm), a heavy liquid was obtained the nmr of which was virtually unchanged in the region of δ 0.9–2.5 except for a broadening of the methyl triplet. However, *two* quartets at δ 4.11 and 4.13 were present as well as a single vinylic proton at δ 5.74 (br t, J = 6.0 Hz). A number of changes occurred in the 650–1200-cm^{-1} region of the ir; however most significant was the appearance of an N–H absorption at 3400 cm^{-1}. The mass spectrum still showed the parent peak at m/e 398. A satisfactory elemental analysis could not be obtained.

Cycloaddition of 45d with dimethyl acetylenediacarboxylate using a 5.7-fold excess of dipolarophile gave, after distillation of unreacted ester and some unidentified material, an undistillable residue (~30–40% assuming pure cycloadduct) that slowly become crystalline on standing. After several recrystallizations from methanol sufficient material was obtained for analysis and spectral determinations. The material assigned the structure of 2,2,5,5-bis(hexamethylene)-3,4-dicarbomethoxy-2,5-dihydrothiophene (**56**) had mp 76.5–78°; ir (pure) 1710, 1740 cm^{-1} (C=O); nmr (CCl_4) δ 1.53 (br s) 1.80–2.30 (complex m, total 24 H), 3.70 (s, 6 H, OCH_3).

Anal. Calcd for $C_{20}H_{30}O_4S$: C, 65.55; H, 8.25; S, 8.75. Found: C, 65.54; H, 8.21; S, 8.70.

Pyrolysis of 45d was attempted a number of times but no well-defined product was ever isolated. Pyrolysis in methylcyclohexane gave one major and two minor products as obtained by glpc. Isolation by preparative glpc gave products with analytical data corresponding to mixture of sulfur-containing products. A small amount of cycloheptylidenecycloheptane could have been present. One product had physical properties and an analysis close to that expected for cycloheptyl thioketone. Treatment of the crude pyrolysis mixture with *n*-butyllithium gave a product (isolated by preparative glpc) which was probably *n*-butyl-

cycloheptyl sulfide. Pyrolysis of **45d** in the presence of triethyl phosphite of tris(dimethylamino)phosphine failed to give any characterizable product.

The synthesis of *trans*-2,5-di-*tert*-butyl-2,5-dimethyl-1,3,4-Δ^3-thiadiazoline (45e) was accomplished in 98% yield. The product had mp 103–105°; ir KBr) 1580 cm^{-1} (N=N); nmr (CCl_4) δ 1.07 (s, 18 H, *t*-Bu), 1.67 (s, 6 H, CH_3).

Anal. Calcd for $C_{12}H_{24}N_2S$: C, 63.10; H, 10.59; N, 12.27; S, 14.04. Found: C, 62.76; H, 10.61; N, 12.22; S, 13.95.

Oxidation with 1 equiv of *m*-chloroperbenzoic acid afforded *trans*-2,5-di-*tert*-butyl-2,5-dimethyl-1,3,4-Δ^3-thiadiazoline *S*-oxide in 73% yield: mp 102–103°; ir (KBr) 1580 (N=N, 1050 and 1080 cm^{-1} (SO); nmr (CCl_4) δ 1.01 (s, 9 H, *t*-Bu), 1.24 (s, 9 H, *t*-Bu), 1.41 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3). This spectrum is consistent only for a trans configuration of the *tert*-butyl and methyl groups, respectively.

Anal. Calcd for $C_{12}H_{24}N_2OS$: C, 58.97; H, 9.89; N, 11.46; S, 13.12. Found: C, 58.72; H, 10.06; N, 11.30; S, 13.19.

Further oxidation afforded *trans*-2,5-di-*tert*-butyl-2,5-dimethyl-1,3,4-Δ^3-thiadiazoline *S*-dioxide in 90% crude yield. After repeated recrystallization and chromatography an analytical sample was obtained: mp 78–80°; ir (KBr) 1540 (N=N?), 1380 cm^{-1} (SO_2?); nmr (CCl_4) δ 1.27 (s, 18 H, *t*-Bu), 1.58 (s, 6 H, CH_3).

Anal. Calcd for $C_{12}H_{24}N_2O_2S$: C, 55.36; H, 9.29; N, 10.75; S, 12.31. Found: C, 55.23; H, 9.18; N, 10.56. Analyses for sulfur consistently gave incorrect results.

Pyrolysis of 45e led to complex reaction mixtures that were often red colored. Usually peaks at δ 1.17 and 1.70 appeared in the nmr spectrum; these were in the ratio expected for *tert*-butyl and methyl groups, respectively. In addition extra complex absorptions in the aliphatic region were present. Attempts at desulfurization of the crude product with triethyl phosphite or *n*-butyllithium led to no conclusive result. Pyrolysis of **45e** in the presence of triethyl phosphite or tris(dimethylamino)phosphine failed to give characterizable products.

Cycloadditions with 45e—The crude products obtained from attempted cyclization had always very complex nmr spectra. The reaction with diethyl azodicarboxylate, (threefold excess) was performed by pyrolyzing the reaction mixture in methylcyclohexane in a sealed tube at 130°. Distillation afforded a modest (30%) yield of a fraction, bp 100–110° (0.25 mm), that had ir (neat) 1720 cm^{-1} (C=O); nmr (CCl_4) δ 1.18 (s, 9 H, *t*-Bu), 1.28 (t, J = 7.0 Hz, 6 H, CH_2CH_3), 1.75 (s, 3 H, CH_3), 4.18 (q, J = 7.0 Hz, 4 H, OCH_2CH_3). The parent in the mass spectrum was at m/e 258 ($C_{12}H_{22}N_2O_4$) with strong fragmentations at m/e 243, 216, 172, 171, 144, 129, 101, 69, and 57. This was thought to be **61**.

With dimethyl acetylenedicarboxylate (fourfold excess) pyrolysis in methylcyclohexane gave a complex reaction mixture that was subjected to distillation. One fraction (~20%) on redistillation afforded a single product: bp 105–110° (0.05 mm); ir (neat) 1740 cm^{-1} (C=O); nmr (CCl_4) δ 1.07 (s, 9 H, *t*-Bu), 1.68 (s, 3 H, CH_3), 3.82 (s, 6 H, OCH_3). Structure **60** was tentatively assigned to this material. Too little material remained for further investigation.

Kinetics of Decomposition of Thiadiazolines and Activation Parameters.—The thiadiazolines were made up as 10^{-2} *M* solutions in methylcyclohexane and individual samples were sealed in heavy-walled Pyrex tubes. Pyrolysis was carried out in a thermostated oil bath with ±0.1° temperature control. The rate of reaction was followed by monitoring the decrease in uv absorption at 320 mμ. Small infinity absorptions remained, apparently due to a slight amount of absorption by episulfide.

The relative instability of **16c** prevented use of the uv technique. A 0.73 *M* solution in cyclohexane was allowed to decompose in the nmr spectrometer. Disappearance of the δ 5.67–6.02 multiplet (*t*-H) was used to monitor the reactions; the high concentration was necessary to obtain reproducible results. Benzene was used as an internal standard. The temperature was determined by the ethylene glycol technique; a check was carried out every 20–30 min during the run, but no variation in temperature could be observed. An attempt to determine the activation parameters for the cis isomer **16d** failed. A cis–trans mixture was used and separate monitoring of the cis and trans tertiary protons was attempted. The cis compound appeared to decompose more slowly than the trans, but no reliable activation data could be obtained.

Registry No.—**15c,** 30465-38-4; **15d,** 30465-39-5; **16b,** 28037-21-0; **16c,** 30465-41-9; **17b,** 19566-11-1; **20,** 28037-23-2; **24,** 30465-43-1; **25,** 36614-90-1; **26,** 30465-44-2; **27,** 30465-45-3; **28,** 30465-46-4; *cis*-**32,** 30646-53-8; **33,** 30465-51-1; **34,** 28163-94-2; **36,** 36635-87-7; **36** sulfoxide, 36614-97-8; **36** sulfone, 36611-65-1; **37,** 36611-66-2; **38b,** 36614-44-5; **39,** 36611-67-3; **41,** 36635-88-8; **42,** 30465-50-0; **45a,** 36635-89-9; **45a** sulfoxide, 36614-45-6; **45a** sulfone, 36614-46-7; **45b,** 36614-47-8; **45b** sulfoxide, 36614-48-9; **45b** sulfone, 36614-49-0; **45c,** 36614-50-3; **45c** sulfoxide, 36614-51-4; **45d,** 36614-52-5; **45e,** 36635-90-2; **45e** sulfoxide, 36611-69-5; **45e** sulfone, 36611-70-8; **48a,** 36614-53-6; **48a** sulfoxide, 36614-54-7; **48a** sulfone, 36614-55-8; **48b,** 36614-56-9; **49a,** 36614-57-0; **49a** sulfone, 36614-58-1; **49b,** 36614-59-2; **49b** sulfoxide, 36614-60-5; **49b** sulfone, 36614-61-6; **51,** 36614-62-7; **52,** 36635-91-3; **53,** 36614-63-8; **54,** 36614-64-9; **55a,** 36614-77-4; **56,** 36614-78-5; **57,** 36614-79-6; **60,** 36614-80-9; **61,** 36614-81-0; **62,** 36614-82-1; **62** sulfoxide, 36614-83-2; **62** sulfone, 36614-84-3; **63,** 36611-89-9; 2,2,5,5-bis(pentamethylene)-1,3,4-Δ^3-thiadiazoline *S*-oxide, 30167-48-7; *trans*-2,5-diethyl-3,4-dicarbomethoxy-2,5-dihydrothiophene, 30465-50-0; *trans*-2,5-diethyl-3,4-dicarboethoxy-1,3,4-thiadiazoline *S*-oxide, 30504-12-2; *trans*-2,5-diethyl-3,4-dicarboethoxy-1,3,4-thiadiazolidine *S*-dioxide, 30504-13-3; *trans*-2,3-diethyl epoxide, 36611-93-5; *cis*-2,3-diethyl epoxide, 36611-94-6; tetramethyl episulfide, 36614-86-5; tetraethyl episulfide, 36614-87-6.

Acknowledgment.—Dr. T. Beetz discovered and studied the reactions of *cis*-thiadiazoline **25**; his contributions are acknowledged with pleasure. Dr. W. Prins studied the pyrolyses of some sulfones. Miss M. Noteboom and Mr. A. E. P. de Jong provided assistance at various stages of the research.

The Reaction of Acylferrocenes with Dimethyloxosulfonium Methylide and Dimethylsulfonium Methylide

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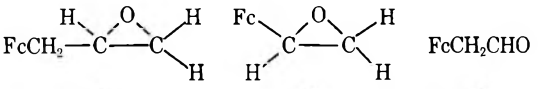
The reactions of ferrocenecarboxaldehyde, acetylferrocene, and benzoylferrocene with dimethylsulfonium methylide (4) give rise, not to the expected epoxides, but to ferrocenylacetaldehydes. Although the epoxides are presumably intermediates in these reactions, ring opening occurs in the direction giving rise to the greatest stabilization of positive charge. The reaction of acylferrocenes with dimethyloxosulfonium methylide (5) shows lower reactivity, gives products derived from the attack of both one and two molecules of the ylide, and in the case of ferrocenecarboxaldehyde gives some products not derived from intermediate epoxide formation. The reaction of 4 with acylferrocenes is of synthetic utility.

The synthesis of epoxides containing a ferrocenyl group is not straightforward, since the peroxy reagents often used in such preparations normally oxidize the iron atom to Fe(III). The base-catalyzed formation of epoxides from the corresponding chlorohydrins has been used by Japanese workers[1,2] to prepare 3-ferrocenyl-1,2-epoxypropane (1) and some related compounds, but a similar effort by German workers[3] to prepare vinylferrocene oxide (2) gave rise to a condensation product of ferrocenylacetaldehyde (3). The



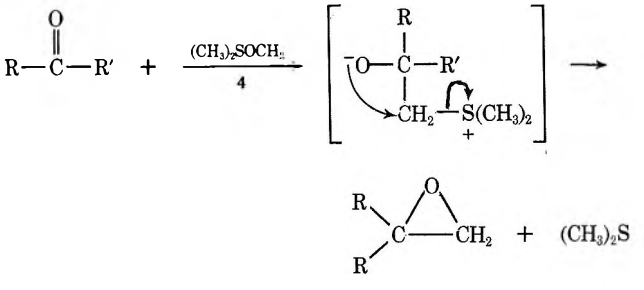
1 2 3

Fc = ferrocenyl

epoxide 2 was postulated as an intermediate, but no direct evidence for its presence was obtained.

The reagents dimethylsulfonium methylide (4)[4-6] and dimethyloxosulfonium methylide (5),[4,7] introduced by Corey and Chaykovsky, are epoxide-forming reagents but show essentially no oxidizing properties. Both have been found[4] to be of wide application in the preparation of epoxides from aldehydes and ketones; a possible mechanism for their action is given in Scheme I. We originally thought, therefore, that 1-ferrocenyl

SCHEME I

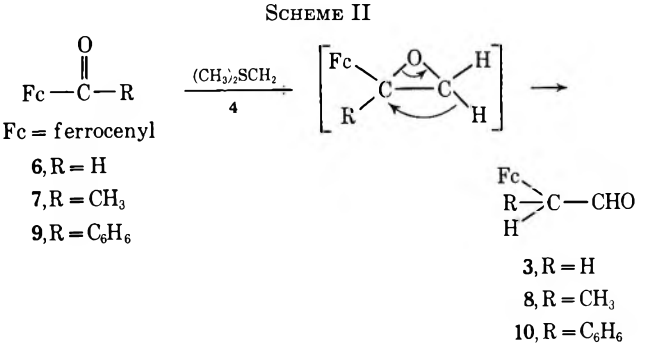


epoxides would be readily accessible through these ylides. However, when the simple acylferrocenes such as ferrocenecarboxaldehyde, acetylferrocene, and benzoylferrocene were treated with these ylides, the major products were aldehydes, the products of regiospecific epoxide ring opening. These products are shown in Table I.

For example, the reaction of 4 generated under a nitrogen atmosphere at −15° in dimethyl sulfoxide–tetrahydrofuran solution with ferrocenecarboxaldehyde gave ferrocenylacetaldehyde (3) and not vinylferrocene oxide (2) as the major product. The yield of the aldehyde was 64% and none of the ketone, which would result from the alternate direction of ring opening, was detected. Under the same conditions acetylferrocene (7) gave rise to 2-ferrocenylpropionaldehyde (8) in 70% yield. Ferrocenylphenylacetaldehyde (10) was obtained in 72% yield from benzoylferrocene, but it was observed that the aldehyde was not the initial product in this case. The aldehyde was only isolated after the extremely air- and temperature-sensitive intermediate product, having no aldehyde protons in the nmr, was allowed to stand at room temperature overnight. The latter result suggests that the epoxide in this case is somewhat stable; it seems likely therefore that even more stable 1-ferrocenyl epoxides might be prepared if appropriate substituents were introduced.

These products may be explained by assuming the intermediate formation of the epoxide, followed by regiospecific ring opening and hydride shift to give the aldehyde (Scheme II). The ring opening of epoxides

SCHEME II



Fc = ferrocenyl

6, R = H
7, R = CH_3
9, R = C_6H_6

3, R = H
8, R = CH_3
10, R = C_6H_6

in the presence of Lewis acids to give aldehydes or ketones is a well-known reaction.[7-9] The direction of ring opening in these latter cases is dictated by the

(1) K. Hata, I. Motoyama, and H. Watanabe, *Bull. Chem. Soc. Jap.*, **36**, 1698 (1963).
(2) H. Watanabe, I. Motoyama, and K. Hata, *ibid.*, **39**, 784 (1966).
(3) H. Egger and K. Schlogl, *J. Organometal. Chem.*, **2**, 398 (1964).
(4) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).
(5) E. J. Corey and M. Chaykovsky, *ibid.*, **84**, 3782 (1962).
(6) E. J. Corey and M. Chaykovsky, *Tetrahedron Lett.*, 169 (1963).
(7) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 867 (1962).
(8) E. L. Eliel and D. W. Delmonte, *ibid.*, **80**, 1744 (1958).
(9) N. L. Wendler in "Molecular Rearrangements," Part 2, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 1035.

TABLE I
PRODUCTS OF THE REACTION OF ACYLFERROCENES WITH SULFONIUM YLIDES

Ylide	Acylferrocene[a]	Product	Yield, %	Scheme
$(CH_3)_2SCH_2$ (4)	FcCHO (6)	$FcCH_2CHO$ (3)	64	II
	$FcCOCH_3$ (7)	$FcCH(CH_3)CHO$ (8)	70	II
	$FcCOC_6H_5$ (9)	$FcCH(C_6H_5)CHO$ (10)	72	II
$(CH_3)_2SOCH_2$ (5)	FcCHO (6)	$FcCH_2COCH_3$ (11)	27	II and III
		$FcCH_2\overline{CHCH_2O}$ (1)	18	I and II
		$FcCOCH_3$ (7)	1	III
	$FcCOCH_3$ (7)	$FcCH(CH_3)\overline{CHCH_2O}$ (12)	40	IV
		$FcCH(CH_3)CHO$ (8)	8	IV
	$FcCOC_6H_5$ (9)	No reaction		

[a] Fc = ferrocenyl.

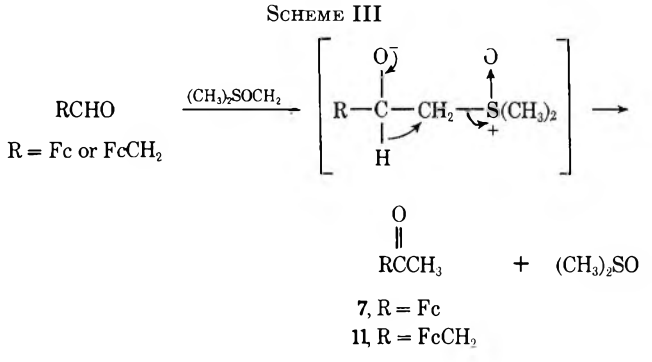
greater stability of an intermediate with positive charge delocalized from a benzyl or other stabilized carbon atom.

The reaction of the acylferrocenes with **4**, however, is conducted under rather basic conditions; the strongest acid employed throughout is water. However, the ability of the ferrocenyl group to stabilize an adjacent positive charge is much greater than that of a phenyl group,[10] and it is not surprising, therefore, that the opening of 1-ferrocenyl epoxides takes place under these very mild conditions.

The yields obtained are such that this method is of considerable utility in the synthesis of ferrocenylacetaldehyde and its derivatives. It should be noted that these products react rather rapidly with atmospheric oxygen; when stored and handled under nitrogen they are stable.

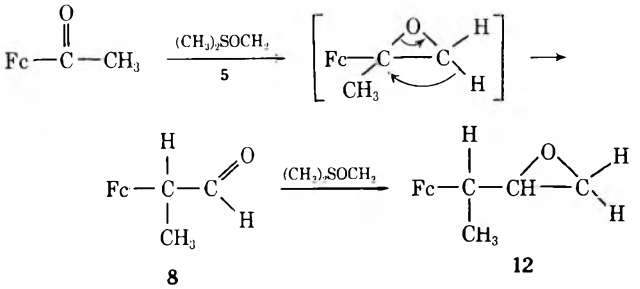
Dimethyloxosulfonium methylide (**5**) is both less reactive and less specific in its reactions with the acylferrocenes than is dimethylsulfonium methylide (**4**). In the reaction of **5** with ferrocenecarboxaldehyde, neither the epoxide **2** nor the aldehyde **3** was detected; however, 3-ferrocenyl-1,2-epoxypropane (**1**), the product resulting from the attack of two molecules of ylide on the original aldehyde, is obtained in 18% yield. The other two products are acetylferrocene (**7**), formed in 1% yield, and ferrocenylacetone (**11**), formed in 27% yield. A reasonable mechanism for the formation of the latter products is shown in Scheme III.

SCHEME III



Addition of the ylide to the aldehyde gives a zwitterionic intermediate similar to that shown in Scheme I, but in this case expulsion of the dimethyl sulfoxide molecule occurs *via* a hydride shift rather than *via* direct displacement by oxygen. The reaction of **5** with acetylferrocene gives products which can be explained by a reaction sequence involving epoxide formation, regiospecific ring opening to the aldehyde, and the formation of a second epoxide as shown in Scheme IV. The

SCHEME IV



8 **12**

products observed from this reaction are the aldehyde **8**, formed in 8% yield, and 3-ferrocenyl-1,2-epoxybutane (**12**), obtained as a mixture of diastereomers in 40% yield. Compound **12** was also synthesized by the reaction of **8** with ylide **4**.

The lower reactivity of ylide **5** as compared to ylide **4** is demonstrated by the 41% recovery of acetylferrocene in the previous reaction. Ylide **5** failed to react with benzoylferrocene significantly, even over a 2-day period. The lesser selectivity of **5** in this case may be partially attributed to its greater stability; **4** appears to decompose faster than the intermediate leading to the aldehyde products, while **5** survives long enough under the reaction conditions to react with the initial aldehyde product as it is generated.

This difference in stability of the two ylides might also be a clue as to why the reaction of ylide **5** with ferrocenecarboxaldehyde leads to ketones **7** and **11** (in addition to epoxide **1**) while the reaction of ylide **4** with ferrocenecarboxaldehyde gave only ferrocenylacetaldehyde **3** as the major product. A more complete answer to this question, however, must await further experimental evidence.

Experimental Section

Spectra were recorded using a Perkin-Elmer 337 ir spectrophotometer and a Hitachi Perkin-Elmer R-20B nmr spectrometer; tetramethylsilane was used as internal standard in the nmr work. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., or by Atlantic Microlab, Atlanta, Ga.

(10) (a) M. D. Rausch, *Can. J. Chem.*, **41**, 1289 (1963); (b) M. Cais, *Organometal. Chem. Rev.*, **1**, 435 (1966); (c) T. G. Traylor and I. C. Ware, *J. Amer. Chem. Soc.*, **89**, 2304 (1967).

Acylferrocenes were purchased or prepared by standard methods. Trimethyloxosulfonium iodide and trimethylsulfonium iodide were prepared as described by Corey and Chaykovsky.[4] Dimethyl sulfoxide (DMSO) was purified by vacuum distillation from calcium hydride; tetrahydrofuran (THF) was dried by distillation from lithium aluminum hydride under nitrogen.

Reaction of Dimethylsulfonium Methylide with Ferrocenecarboxaldehyde.—A solution of methylsulfinyl carbanion[11] (0.035 mol) in 1:1 DMSO–THF (50 ml) was cooled to −15° under a nitrogen atmosphere. To this solution was added, dropwise over 3 min, 7.0 g (0.035 mol) of trimethylsulfonium iodide dissolved in 30 ml of DMSO. After stirring for 1 min a solution of ferrocenecarboxaldehyde (1.5 g, 0.0069 mol) in THF (20 ml) was added dropwise to this ylide solution over a period of 2–3 min. The mixture was stirred at −15° for 5 min, and then allowed to warm to room temperature over 0.5 hr and poured into 300 ml of water. The resulting solution was extracted three times with 50-ml portions of diethyl ether; the combined ether portions were washed with water and dried ($MgSO_4$). Removal of the solvent gave the crude product, the components of which were separated by chromatography on silica gel with benzene as eluent.

The major product was ferrocenylacetaldehyde, formed in 64% yield: ir (neat) 1705 (C=O), 1100, and 995 cm^{-1}; nmr ($CDCl_3$) δ 3.22 (J = 3 Hz), 4.09 (s, 9), and 9.68 (t, 1, J = 3 Hz). This compound, a liquid, decomposed quantitatively in 2 days in contact with air to a brown powder, in keeping with its known behavior.[3]

A small amount of unreacted ferrocenecarboxaldehyde was recovered.

Reaction of Dimethylsulfonium Methylide with Acetylferrocene.—The reaction was run and the product was purified as described above for ferrocenecarboxaldehyde.

The major product, isolated in 70% crude yield, was 2-ferrocenylpropionaldehyde; ir (neat) 1725, 1101, and 997 cm^{-1}; nmr ($CDCl_3$) δ 1.30 (d, 3, J = 7.5 Hz), 3.19 (quartet of doublets, 1, J = 7.5 and 2.2 Hz), 4.10 (m, 9), 9.71 (d, 1, J = 2.2 Hz). *Anal.* Calcd for $C_{13}H_{14}FeO$: C, 64.49; H, 5.83; Fe, 23.07. Found: C, 64.41; H, 5.71; Fe, 22.92. This compound, a liquid, decomposed slowly in contact with air to a brown powder.

A small amount of acetylferrocene was recovered.

Reaction of Dimethylsulfonium Methylide with Benzoylferrocene.—The reaction was run as described for ferrocenecarboxaldehyde; the work-up was carried out in the absence of oxygen, with benzene used as the extracting solvent instead of ether.

An nmr of the initial product showed multiplets at δ 1.6, 2.2, 4.1, and 7.3, but no absorption in the region δ 9–11. Several attempts to purify this product always led to either complete decomposition or to the isolation of a small amount of the major product described below.

After standing overnight at room temperature, a 72% crude yield of ferrocenylphenylacetaldehyde was obtained. This product was sublimed at 140° (0.25 mm): nmr (CCl_4) δ 4.1 (m, 9), 4.41 (d, 1, J = 4.2 Hz), 7.2 (m, 5), and 9.74 (d, 1, J = 4.2 Hz); ir (neat) 1725 (aldehyde C=O), 1101, and 994 cm^{-1}. *Anal.* Calcd for $C_{18}H_{16}FeO$: C, 71.08; H, 5.30; Fe, 18.36. Found: C, 67.80; H, 5.13; Fe, 17.50. This compound decomposes quickly on exposure to air, which probably accounts for the low elemental analysis.

Reaction of Dimethyloxosulfonium Methylide with Ferrocenecarboxaldehyde.—Sodium hydride (1.4 g, 0.035 mol of 58% mineral oil dispersion) was washed three times with hexane and dried under vacuum. To this was added 7.6 g (0.035 mol) of trimethyloxosulfonium iodide and 50 ml of DMSO. After 30 min, sufficient time to generate the ylide, the temperature was raised to 55° and the dropwise addition of ferrocenecarboxaldehyde was carried out over a period of 1.5 hr. After an additional 30 min of stirring, followed by cooling, the reaction mixture was poured into water (300 ml) and the resulting solution was extracted three times with ether. The combined ether washings were washed with water, dried ($MgSO_4$), and evaporated to give the crude product. Products of the reaction were separated by column chromatography on silica gel, with benzene as the eluent.

The liquid compound 3-ferrocenyl-1,2-epoxypropane was formed in 18% yield, as calculated from the nmr of the crude material: ir (neat) 1257, 1102, and 997 cm^{-1}; nmr ($CDCl_3$) δ 2.55 (m, 4), 3.05 (m, 1), and 4.10 (m, 9). *Anal.* Calcd for $C_{13}H_{14}FeO$: C, 64.49; H, 5.83; Fe, 23.07. Found: C, 64.68; H, 6.00; Fe, 22.92.

The ir spectrum of ferrocenylacetone showed peaks at 1705, 1103, and 998 cm^{-1}; nmr δ 2.04 (s, 3), 3.37 (s, 2), and 4.11 (s, 9). *Anal.* Calcd for $C_{13}H_{14}FeO$: C, 64.49; H, 5.83; Fe, 23.07. Found: C, 61.43; H, 5.46; Fe, 20.84. The yield was 27%; the product, a liquid, decomposed in contact with air in 2 days to a brown solid. This sensitivity to air probably accounts for the low elemental analysis.

Acetylferrocene, obtained in 1% yield, was identified by the comparison of the ir and nmr spectra with those of an authentic sample. Vacuum sublimation gave purified material, mp 83° (lit.[12] mp 85–86°).

No ferrocenecarboxaldehyde was recovered.

Reaction of Dimethyloxosulfonium Methylide and Acetylferrocene.—The reaction was carried out as described for ferrocenecarboxaldehyde, above.

The yield of 2-ferrocenylpropionaldehyde was 8%; the compound was characterized by comparison of its ir and nmr spectra with those of authentic samples.

The ir spectrum of 3-ferrocenyl-1,2-epoxybutane, obtained as a liquid mixture of diastereomers, showed peaks at 1256, 1102, and 995 cm^{-1}; nmr δ 1.30 (overlapping doublets, 3), 2.1–3.1 (m, 4), 4.01 (m, 9). *Anal.* Calcd for $C_{14}H_{16}FeO$: C, 65.64; H, 6.29; Fe, 21.83. Found: C, 65.85; H, 6.39; Fe, 21.66. The spectra of the product thus obtained were identical with those obtained from this product as prepared by another method). The crude yield was 40%.

The recovery of acetylferrocene was 41%.

Attempted Reaction of Benzoylferrocene and Dimethyloxosulfonium Methylide.—When reaction was attempted under the conditions used for ferrocenecarboxaldehyde and acetylferrocene above the recovery of benzoylferrocene was quantitative. If reaction was continued for 2 days a small amount of an apparently polymeric product was obtained.

3-Ferrocenyl-1,2-epoxybutane.—A sample of 2-ferrocenylpropionaldehyde was prepared by the reaction of acetylferrocene and dimethylsulfonium methylide, as above. A second ylide solution was prepared, and the 2-ferrocenylpropionaldehyde was added to it in the usual manner. The product, identified by comparison of its ir and nmr spectra with those of an authentic sample, was 3-ferrocenyl-1,2-epoxybutane, bp 144–154° (3.5 mm). The yield was 30%, based on acetylferrocene.

Registry No.—**1**, 1298-50-6; **3**, 36731-63-2; **4**, 6814-64-8; **5**, 5367-24-8; **6**, 12093-10-6; **7**, 1271-55-2; **8**, 36731-64-3; **9**, 1272-44-2; **10**, 36731-65-4; **11**, 12215-52-0; **12**, 36731-67-6.

Acknowledgment.—The authors wish to thank Professor Robert H. Garner of this department for many helpful discussions relating to this work. The financial support of this work by the National Aeronautics and Space Administration, Grant No. NGL-01-002-064, is gratefully acknowledged.

(11) F. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 866 (1962).

(12) P. J. Graham, R. V. Lindsey, G. W. Parshall, M. L. Patterson, and G. M. Whitman, *ibid.* **79**, 3416 (1957).

Ferrocenobenzosemiquinones

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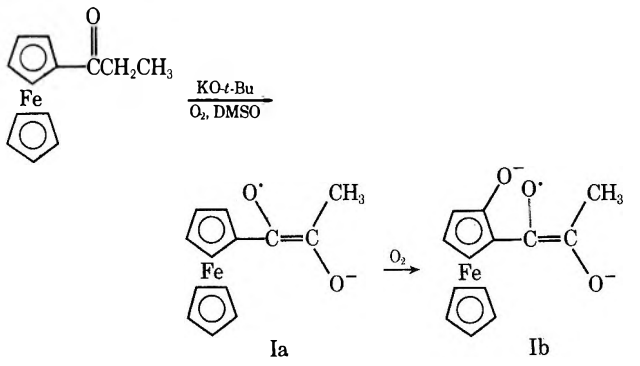
Received April 10, 1972

Novel paramagnetic ligands are observed by esr spectroscopy. These paramagnetic ligands are discussed in terms of oxidation chemistry and electron spin delocalization. Electron spin density is experimentally demonstrated to be on the metal by observation of $Mn^{5/2}$ splitting of 5.63 G. The role of charge separation in electron spin delocalization is briefly discussed.

The preparation of paramagnetic metallocenes *via* Scheme I has been previously reported.[1] Ia and Ib

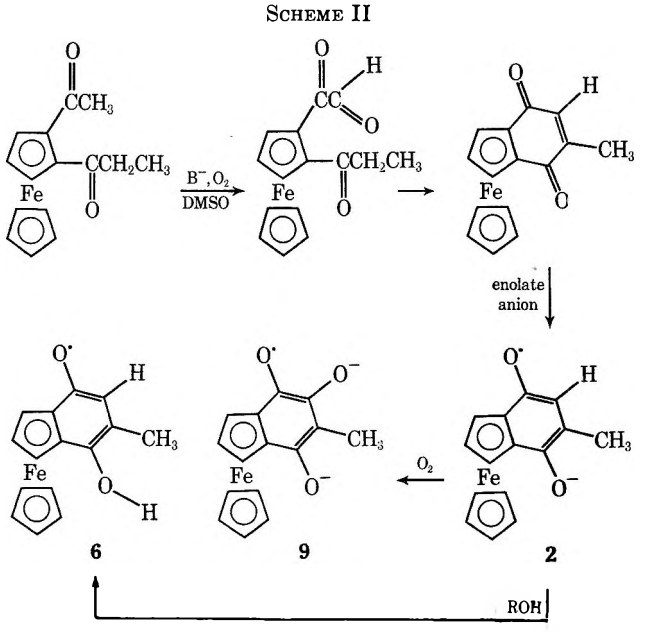
SCHEME I



were observed by electron spin resonance spectroscopy and these species were discussed in terms of electron spin delocalization and oxidation chemistry.

Using the reaction conditions in Scheme I, we have observed that 1,2-ferrocenyl diketones condense upon initial oxidation to form the corresponding quinones according to Scheme II.

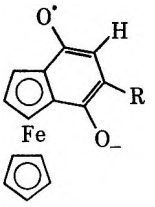
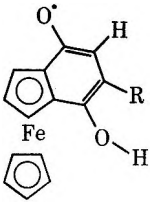
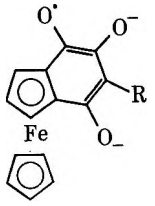
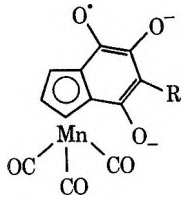
SCHEME II



Entries 1–10 of Table I provide proof of the reaction sequence shown in Scheme II. Examples 1 and 8 were produced by independent means. 1 was produced by reduction of the corresponding quinone and by oxidation of 1,2-diacetylferrocene (Scheme III). Figure 1 shows the esr spectrum of 1. Entry 8 was produced by overoxidation of 1 and by oxidation of 1,2-(α-ketotetramethylene)ferrocene (Scheme IV). Figure 2 shows the esr spectrum of 8. Figure 3 shows the esr spectrum resulting from the oxidation of 1-acetyl-2-

(1) J. J. McDonnell and D. J. Pochopien, *J. Org. Chem.*, **36**, 2092 (1971).

TABLE I

Compd	R	H_a	Fc ring	g
				
1[a]	H	4.05 (2 H)	0.43 (2 H)	
2	CH_3	3.47 (4 H)	0.43 (2 H)	2.00792
3	CH_2CH_3	3.54 (1 H), 2.45 (2 H)	0.43 (2 H)	2.00791
4	$CH(CH_3)_2$	3.35 (1 H), 1.67 (1 H)	0.74 (2 H)	2.00790
				
5	H	3.97 (1 H), 3.52 (1 H)	1.15 (1 H), 0.35 (2 H)	2.00785
6	CH_3	4.25 (1 H), 3.3 (3 H)	1.1 (1 H), 0.35 (2 H)	2.00785
7	CH_2CH_3	4.32 (1 H), 2.45 (2 H)	1.1 (1 H), 0.35 (2 H)	2.00785
				
8[b]	H	4.65 (1 H)	0.35 (2 H)	
9	CH_3	4.48 (3 H)	0.35 (2 H)	
10	CH_2CH_3	4.30 (2 H)	0.35 (2 H)	
				
			Cy ring	
11[c]	H	4.15 (1 H) 5.63 ($Mn^{5/2}$)	0.675 (2 H)	2.00492

[a] Produced by electrolytic reduction of the quinone and by the oxidation of 1,2-diacetylferrocene. [b] Produced by oxidation of 1,2-(α-ketotetramethylene)ferrocene and overoxidation of 1. [c] Produced by oxidation of 1,2-(α-ketotetramethylene)cyclopentadienylmanganese tricarbonyl. Prepared by method of M. Cais, and A. Modiano, *Chem. Ind. (London)*, 202 (1960).

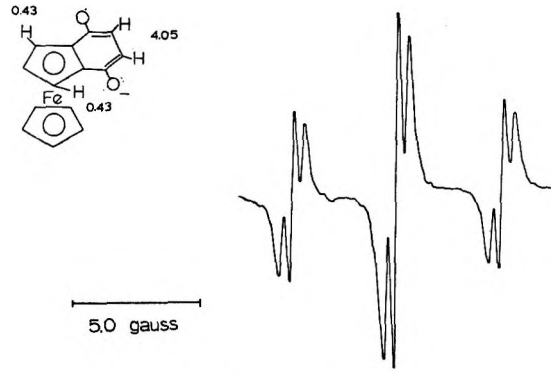


Figure 1.

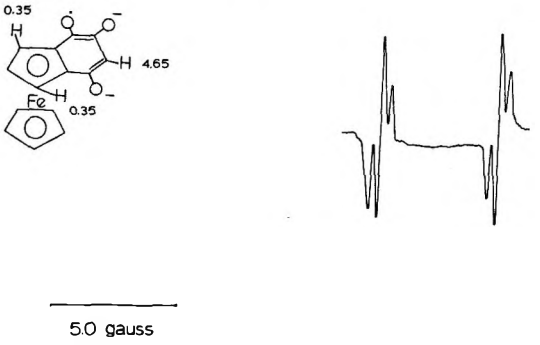


Figure 2.

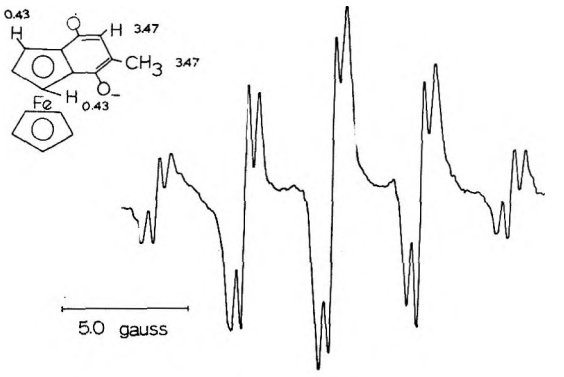


Figure 3.

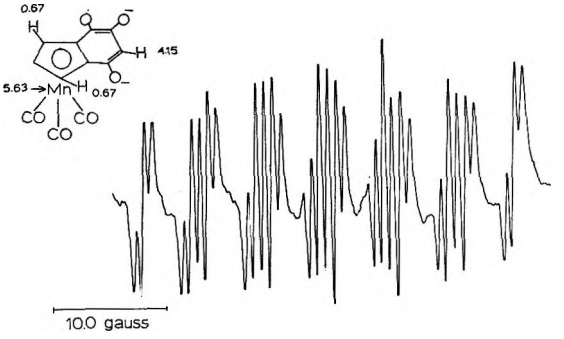
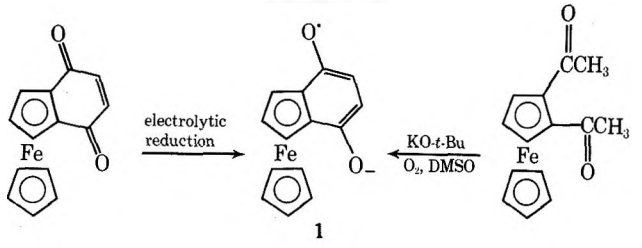
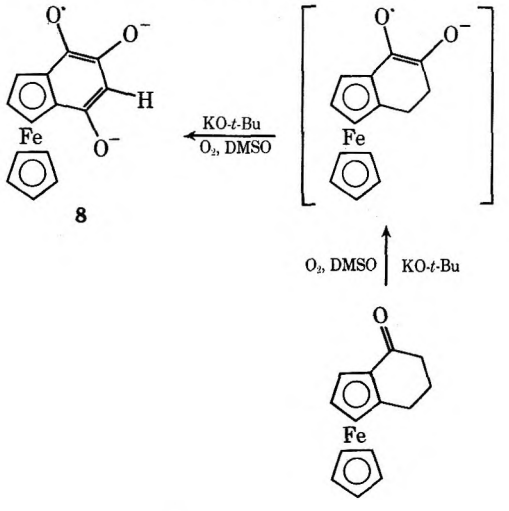


Figure 4.

SCHEME III



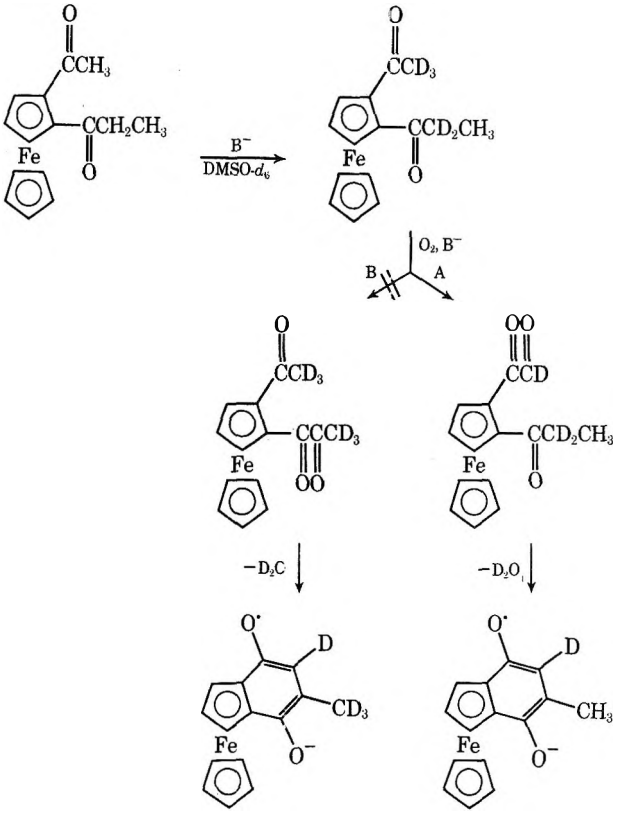
SCHEME IV



propionylferrocene. This spectrum requires the assignment of hyperfine splitting constants as shown. **5–7** were produced by simply adding *tert*-butyl alcohol to entries **1–3**.

When oxidation in Scheme II is conducted in DMSO-d_6 an esr spectrum is observed which is consistant with the replacement of a hydrogen splitting of 3.47 G with a deuterium splitting of 0.53 G (Figure 3B). This would seem to require that the quinone is formed *via* initial oxidation of the acetyl group in Scheme Va. In Scheme Vb, the initial oxidation of the propionyl group would replace four large hydrogen splittings with deuterium. The latter is not observed.

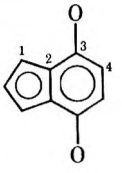
SCHEME V



Entry **11** in Table I makes it clear that some electron density resides on the metal atom. Figure 4 shows the high resolution esr spectrum of **11** and the analysis of this spectrum requires the hyperfine splitting of a $Mn^{5/2}$ nucleus of 5.63 G. The spectra of **8** and **11** show approximately equal spin distribution in the ligand. However, the g value in **8** is higher than that in **11**. It is interesting to observe that **8**, the ferrocene analog, has a higher g value than 2-hydroxy-1,4-naphthaquinone (g 2.00403)[2] and **11**, the cyclopentadienylmanganese tricarbonyl analog, has a g value much closer to that of the corresponding 2-hydroxy-1,4-naphthaquinone. g values are controlled by a delicate balance of several factors—λ coefficient of the HOMO, spin density distribution, and the spin–orbit coupling coefficient of the atoms containing free electron density.[3] The higher spin–orbit coupling constant of Fe^{2+} (400 cm^{-1}) *vs.* 305 cm^{-1} [4] for Mn^{+} is qualitatively in the right direction for the observed g value change.[5]

Hückel and Hückel–McLachlan calculations[6] using a large variety of coulombic integrals for oxygen and carbon atoms as well as various bond integrals for C–C and C–O bonds in the ligand π system do not agree with the experimental spin densities. Chart I shows

CHART I[a]

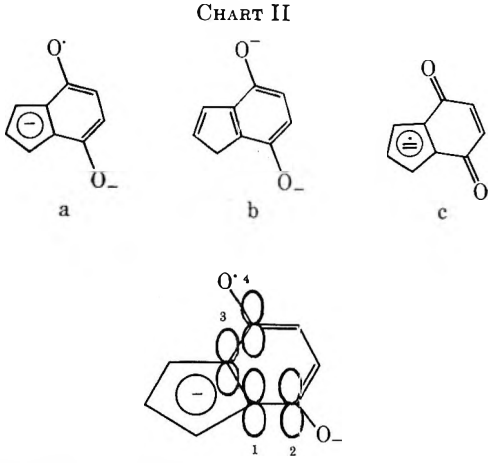


Exptl spin densities, ρ	Calcd spin densities, ρ
0.0186 (1)	0.284 (1)
0.174 (4)	0.112 (4)

[a] $\alpha_0 = \alpha_c + 5h$, $Q = -23$, $A_H = Q\rho$.

the results of a typical calculation. In these systems charge separation undoubtedly plays an important role in electron spin delocalization in the ligand.[7] For example, of the resonance structures (a, b, and c) shown in Chart II, a may well be the most favored on the basis of change separation. This is especially true

CHART II



when the coulombic interaction of the metal ion is considered. a places very little free electron density into the carbon skeleton of the five-membered ring as observed by experiment. Electron spin density could be placed on the metal by direct interaction with the p orbital of carbon atoms in the 1 and 2 position. We are in the process of developing a complete theoretical treatment in this regard.

Experimental Section

General Procedure for Electrolytic Reductions.—Radical anions were generated in a slightly modified Varian electrolytic cell; the part extending into the microwave cavity was of the flat cell type. The cell was evacuated and flushed with nitrogen several times before use. Mercury, serving as the cathode material, was filled into the cell until it reached the flat part of the cell. The solution of the substrate to be reduced was then added and the cell closed under nitrogen. Reduction was accomplished with a Heath-Kit power supply.

The solvent employed in the reductions was DMF which had been refluxed and distilled over CaH_2 in a nitrogen atmosphere. The electrolyte, tetraethylammonium perchlorate, was dried under vacuum over P_2O_5. In all cases, the solution was 0.1 M in the electrolyte and 1×10^{-3} M in the substrate. Concentrations of substrate which were greater than 1×10^{-3} M resulted in the broadening of the esr spectrum.

The radical could be regenerated several times from the same solution if the solution was shaken so as to replenish the concentration of substrate near the cathode.

General Procedure for the Preparation of Semiquinones.—The cyclization of 1,2-diacylferrocenes was achieved under conditions similar to the formation of the semidione radical anions. To 15 mg of the ferrocenyl derivative in one half of an H-cell was added 0.9 cc of dry DMSO; to a 3–4 molar excess of potassium *tert*-butoxide in the other half of the H-cell was added 0.9 cc of dry DMSO. After both of the solutions were thoroughly degassed with N_2 (5 min), the sealed H-cell was inverted and the solutions were thoroughly mixed; 2 cc of air were injected into the H-cell through a serum cap by means of a syringe. An additional needle placed through a serum cap on the other half of the H-cell allowed the air to be added without a pressure buildup. The semiquinone was then formed by shaking the contents of the cell.

Further oxidation of the semiquinone was achieved by the subsequent addition of small amounts of oxygen to the H-cell. The addition of excessive amounts of oxygen, however, resulted in the disappearance of the signal.

Protonation of the semiquinone was achieved by using a DMSO solution containing 20% *t*-BuOH in place of the dry DMSO.

Ferrocobenzoquinone was prepared by a modification of the procedure of Rinehardt.[8] To 5.0 g of 1,2-(α-ketotetramethylene)-ferrocene in 200 ml of $CHCl_3$ was added 200 g of activated MnO_2 and the mixture was stirred in the dark for 20 hr. The slurry was filtered through Celite and the MnO_2 was washed with ether until the washings were colorless. The solvent was removed under reduced pressure and the residue was taken up in 25 ml of ether to which was added 150 ml of hexane. The ether was removed under reduced pressure and the violet quinone extracted with H_2O leaving an orange hexane layer. The quinone was extracted from the salted aqueous layer with ether. The layers were separated and the organic layer was dried ($MgSO_4$). Recrystallization from ether–hexane produced 2.3 g (43.9%) of **24**: mp 152° (lit.[9] 150–151.5°); nmr ($CDCl_3$) δ 4.33 (s, 5, Fc), 5.12 (t, 1, Fc), 5.41 (d, 2, Fc), 6.69 (s, 2, Qu).

Preparation of Ketonic Precursors. 1,2-α-Ketotetramethyleneferrocene was prepared according to the method of Rinehardt:[10] mp 85° (lit.[10] mp 85.4–85.7°); nmr ($CDCl_3$) δ 2.35 (m, 6, CH_2-CH_2), 4.18 (s, 5, Fc), 4.48 (d, 2, Fc), 4.84 (t, 1, Fc).

1,2-Diacetylferrocene was prepared according to the procedure of Rosenblum and Woodward[11] in 1.9% yield: mp 105° (lit.[11] mp 106–107°); nmr ($CDCl_3$) δ 2.50 (s, 6, $COCH_3$), 4.28 (s, 5, Fc), 4.62 (t, 1, Fc), 4.88 (d, 2, Fc).

(2) T. C. Hollocher, N. Tooney, and R. Adman, *Nature*, **197**, 74 (1963).
(3) A. J. Stone, *Mol. Phys.*, **6**, 509 (1963).
(4) T. M. Dunn, *Trans. Faraday Soc.*, 1441 (1961).
(5) H. M. McConnell and R. T. Robertson, *J. Phys. Chem.*, **61**, 1018 (1957).
(6) A. D. McLachlan, *Mol. Phys.*, **3**, 233 (1960).
(7) Hückel–McLachlen calculations are not well designed to accommodate charge separation.
(8) K. L. Rinehardt, A. F. Ellis, C. J. Michejda, and P. A. Kittle, *J. Amer. Chem. Soc.*, **82**, 4112 (1962).
(9) R. A. Johnson and H. C. Murray, *J. Chem. Soc. D*, 989 (1971).
(10) K. L. Rinehardt and A. J. Cury, *J. Amer. Chem. Soc.*, **79**, 3290 (1957).
(11) M. Rosenblum and R. B. Woodward, *ibid.*, **80**, 5443 (1958).

1-Acetyl-2-propionylferrocene was prepared as we previously reported:[1] mp 46°; nmr ($CDCl_3$) δ 1.17 (t, 3, CH_2CH_3), 2.47 (s, 3, $COCH_3$), 2.86 (m, 2, CH_2CH_3), 4.25 (s, 5, Fc), 4.58 (t, 1, Fc), 4.88 (d, 2, Fc).

1-Acetyl-2-butyrylferrocene.—To 15.0 g (0.1128 mol) of $AlCl_3$ in 100 ml of CH_2Cl_2 was added 9.4 g (0.0412 mol) of acetylferrocene and 12.0 g (0.0760 mol) of butyric anhydride in 250 ml of dry ($MgSO_4$) CH_2Cl_2 dropwise with stirring under N_2. After 4 hr the solution was cooled to 5° and hydrolyzed, and the layers were separated. The combined organic layer and ethereal wash of the aqueous layer were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The red oil which remained was chromatographed on silica gel. Elution with 25% ether in hexane produced three bands. The first band (orange) contained a trace of acetylferrocene. The second band (orange) contained 0.23 g (1.87%) of desired compound: mp 103–103.5°; nmr ($CDCl_3$) δ 1.0 (t, 3, CH_2CH_3), 1.74 (m, 2, CH_2CH_3), 2.48 (s, 3, $COCH_3$), 2.81 (t, 2, $COCH_2$), 4.27 (s, 5, Fc), 4.61 (t, 1, Fc), 4.89 (d, 2, Fc). The third band (red) contained 8.65 g (70.3%) of 1-acetyl-1′-butyrylferrocene: mp 54°; nmr ($CDCl_3$) δ 1.01 (t, 3, CH_2CH_3), 1.72 (m, 2, CH_2CH_3), 2.34 (s, 3, $COCH_3$), 2.65 (t, 2, $COCH_2$), 4.48 (t, 4, Fc), 4.74 (m, 4, Fc.)

Anal. Calcd for $C_{16}H_{18}O_2Fe$: C, 64.45; H, 6.08. Found: C, 64.32; H, 6.12. *Anal.* Calcd for $C_{16}H_{18}O_2Fe$: C, 64.45; H, 6.08. Found: C, 64.37; H, 6.04.

1-Acetyl-2-(3-methyl)butyrylferrocene.—To 16.0 g (0.120) mol) of $AlCl_3$ in 150 ml of CH_2Cl_2 was added 12.0 g (0.0996 mol) of 3-methylbutyryl chloride and 10.0 g (0.0438 mol) of acetylferrocene in 250 ml of dry CH_2Cl_2 dropwise with stirring under N_2. After 5 hr the solution was cooled to 6° and hydrolyzed, and the layers were separated. The organic layer was washed with 2 *M* Na_2CO_3 solution. The combined organic layer and ethereal wash of the aqueous layer were dried ($MgSO_4$) and the solvent was under reduced pressure. The red oil which remained was chromatographed on silica gel. Elution with 10% ether in hexane produced five bands. The first band (yellow) and the second band (orange) contained traces of some material which was not characterized. The third band (red) contained 0.90 g (9%) of starting material. The fourth band (red) contained 0.86 g (6.29%) of **27**: mp 59–60°; nmr ($CDCl_3$) δ 1.00 [d, 6, $CH(CH_3)_2$], 2.28 (m, 1, CH), 2.49 (s, 3, $COCH_3$), 2.72 (d, 2, $COCH_2$) 4.28 (s, 5, Fc), 4.62 (t, 1, Fc), 4.90 (d, 2, Fc). The fifth band (red) contained 9.85 g (72.0%) of 1-acetyl-1′-(3-methyl)butyrylferrocene: mp 76–77°; nmr ($CDCl_3$) δ 1.01 [d, 6, $CH(CH_3)_2$], 2.28 (m, 1, CH), 2.35 (s, 3, $COCH_3$), 2.55 (d, 2, $COCH_2$), 4.51 (t, 4, Fc), 4.78 (t, 4, Fc).

Anal. Calcd for $C_{17}H_{20}O_2Fe$: C, 65.40; H, 6.46. Found: C, 65.61; H, 6.48. *Anal.* Calcd for $C_{17}H_{20}O_2Fe$: C, 65.40; H, 6.46. Found: C, 65.48; H, 6.40.

Registry No.—**1**, 12766-52-8; **2**, 12766-58-4; **3**, 12766-62-0; **4**, 12766-65-3; **5**, 12766-54-0; **6**, 12766-59-5; **7**, 12766-63-1; **8**, 12766-51-7; **9**, 12766-57-3; **10**, 12766-61-9; **11**, 12766-50-6; ferrocobenzoquinone, 12766-53-9; 1,2-α-ketotetramethyleneferrocene, 12766-55-1; 1,2-diacetylferrocene, 12766-56-2; 1-acetyl-2-propionylferrocene, 12766-60-8; 1-acetyl-2-butyrylferrocene, 12766-64-2; 1-acetyl-2-(3-methyl)butyrylferrocene, 12766-66-4.

Competitive Metal Hydride Reductions of β-Phorone with Cyclic Ketones

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Received July 5, 1972

Competitive reductions with lithium aluminum tri-*tert*-butoxyhydride of β-phorone, a nonconjugated enone, and a number of cyclic saturated ketones and conjugated enones having varied steric environments were studied. The nonconjugated enone was found to be less reactive than cyclic saturated ketones, but more reactive than the conjugated enones. Steric and torsional factors are involved, but apparently not in a major way, in determining relative reactivities in these experiments.

The greater reactivity toward metal hydride reduction of cyclic saturated ketones as compared with cyclic conjugated enones has been recognized, and selective reductions have been successfully carried out with steroids. For example, reduction of androst-4-ene-3,17-dione (**1**) with lithium aluminum tri-*tert*-butoxyhydride (LATH)[2] occurred at C-17 in preference to reduction at C-3.[3] A similar result with the same substrate was obtained with sodium borohydride in methanol, giving 17β-hydroxyandrost-4-en-3-one.[4] With six-membered ring ketones, similar large reactivity differences were encountered in intermolecular competition studies with lithium aluminum hydride and LATH.[5] The α,β-unsaturated ketones were consistently less reactive than their saturated competitors, even when steric or torsional[6] factors would have disfavored the latter. A similar observation was made in the reduction of the steroid prednisone-BMD with LATH.[7] The strongly hindered C-11 carbonyl group was reduced in preference to the conjugated carbonyl group at C-3. The greater selectivity of LATH over $LiAlH_4$ was also noted.[5,8]

A consideration of the steric and torsional factors conceivably involved in the reduction of various cyclohexanones and conjugated cyclohexenones led to the conclusion that these factors could not explain the observed reactivity differences between the two types of substrates, and an explanation was suggested in which the major factor was the stability of the conjugated enone system.[5] If the reduced reactivity of conjugated enones is due to the intrinsic stability of the conjugated π system, then there should be a marked difference in reactivity between conjugated and nonconjugated enones, with the latter being the more reactive.

This paper reports the results of competitive LATH reductions of the nonconjugated ketone 3,5,5-trimethylcyclohex-3-enone (β-phorone, **2**) with saturated and conjugated enone systems of varying steric com-

(1) Undergraduate research participant, 1971–1972.

(2) Lithium aluminum tri-*tert*-butoxyhydride is also commonly called lithium tri-*tert*-butoxyaluminohydride. However, we now prefer the former name because of its similarity to the name lithium aluminum hydride.

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(4) J. K. Norymberski and G. F. Woods, *Chem. Ind. (London)*, 518 (1954).

(5) H. Haubenstock, *J. Org. Chem.*, **37**, 656 (1972).

(6) (a) M. Chérest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2199 (1968); M. Chérest and H. Felkin, *ibid.*, 2205 (1968). (b) For a recent and thorough discussion of stereochemical factors involved in metal hydride reductions of alkylcyclohexanones, see E. L. Eliel and Y. Senda, *Tetrahedron*, **26**, 2411 (1970).

(7) J. A. Zderic and J. Iriarte, *J. Org. Chem.*, **27**, 1756 (1962).

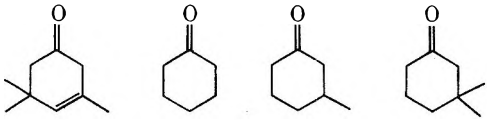
(8) H. Haubenstock and E. L. Eliel, *J. Amer. Chem. Soc.*, **84**, 2363 (1962).

TABLE I
COMPETITIVE REDUCTIONS OF KETONE PAIRS WITH LATH

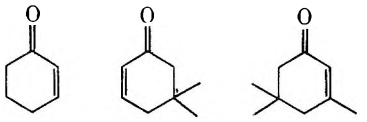
Entry	Ketone pair (mol)	Mol of LATH	Reduction, %	Ketone composition[a] of product Calcd, %	Found, %
1	2[b] (0.030), 3[c] (0.030)	0.015[d]	2 (0);[e] 3 (43)	3 36	39
2	2[f] (0.025), 4[g] (0.031)	0.015[d]	2 (0); 4 (40, 41[h,i])	4 38	39, 40[h]
3	2[j] (0.012), 5[k] (0.013)	0.0066[l]	2 (13); 5 (29)	5 45	47
4	2[j] (0.029), 6[c] (0.030)	0.0149[d]	2 (28); 6 (17)	6 53	52
5	2[m] (0.026), 7[g] (0.028)	0.0149[d]	2 (38); 7 (3)	7 58	56

[a] Ketone composition is normalized to 100%. [b] 2 was 99% pure. [c] Ketones were dissolved in 70 ml of THF. [d] In 50 ml of THF. [e] Trace quantities of alcohol product were neglected. [f] 2 was 82% pure. [g] Ketones in 75 ml of THF. [h] Analysis of hydrogenated product. [i] *cis*- and *trans*-3-methylcyclohexanol peaks overlap. [j] 2 was 95% pure. [k] Ketones in 30 ml of THF. [l] In 22 ml of THF. [m] 2 was 87% pure.

plexities. In these experiments, 2 competed for a limited quantity of LATH added inversely to 2 and one of the other ketone substrates 3 to 7 in tetrahydrofuran (THF) solution.



2 3 4 5



6 7 8

The results obtained from these experiments are summarized in Table I.

Results and Discussion

The extent of reduction for each competitive ketone pair is listed in Table I. A few pertinent comments are necessary before discussing the data. β-Phorone (2) isomerizes slowly to isophorone (8), even when kept refrigerated. It was therefore necessary to analyze 2 at the time the competition experiment was carried out. The purity of 2 used in each experiment is recorded in Table I, and the remaining material in each case is isophorone. This did not cause any serious difficulty, since the purities of 2 were usually quite good, and also because 8 is reduced by LATH extremely slowly. Note that the moles of 2 in each entry are the corrected values. In Table I, the normalized per cent of remaining unreacted ketone (3 to 7) is listed for each entry. For example, in entry 1 the product contained 39% 3 and 61% unreacted 2. Actually, in these reductions unreacted 2 was partially or completely isomerized to 8 during alkaline hydrolysis. In the calculations, account was taken of the amount of 8 present in the original reaction mixture. The unreacted ketone composition is an important analytical check for each experiment. The calculated values are based on the extent of reduction of each ketone pair, and it can be seen from Table I that the calculated and found ketone composition values are in excellent agreement in all cases. Sensitivity factors derived from standard mixtures were used in these glpc analyses and were calculated as previously described.[5]

In the experiment using ketone 4 (entry 2, Table I) two experimental variations from the normal runs were made. An aliquot was removed from the reaction mixture 26 min after addition of the LATH. This was analyzed in addition to the major portion of the product, which was hydrolyzed 200 min after LATH addition. The results were identical in both cases (40% reduction of 4), showing that, after reaction was complete, no further change in product composition occurred. Secondly, part of the reaction product was hydrogenated over 0.2 g of 10% palladium on carbon. Analysis of the hydrogenated product gave identical results with that of the nonhydrogenated product.

The data in Table I point to three basic conclusions. First, the conjugated enones studied, 6 and 7, are less reactive than the nonconjugated ketone 2, as seen from entries 4 and 5, Table I. Second, the C=C double bond in 2 does lower the reactivity of 2 relative to the saturated ketones 3, 4, and 5 (entries 1, 2, and 3, Table I). Third, steric or torsional factors are involved in comparisons of reactivity among the cyclohexanones.[6b] Thus, while 2 could not compete with ketones 3 and 4 (entries 1 and 2), introduction of the second methyl group in ketone 5 lowered its reactivity to the extent that 13% reduction of 2 was observed (entry 3, Table I). It should be noted that in ketone 5 one methyl group must be in an axial position in the chair form.[9] Similarly, while ketone 6 was reduced to an extent of 17%, ketone 7 was only 3% reduced, owing to the effect of the added methyl group.

It is rather striking that the conjugated enone 6, without alkyl substituents, is less reactive than β-phorone, with three alkyl substituents. This not only demonstrates the relative unimportance of steric and torsional constraints brought about by the alkyl groups in 2, but emphasizes the role of conjugation in affecting reactivity. When steric factors were made approximately equivalent (entry 5, Table I), the conjugated enone 7 could not compete with the nonconjugated enone 2.

One factor reducing reactivity in the *conjugated* enone system is a generally lower ground-state energy.[10] However, kinetic studies will have to be carried out in order to evaluate transition-state energy differences for these substrates. While transition states in metal hydride reductions have been assumed to be "reactant-like,"[6a] we cannot as yet define transition-state energy

(9) For a discussion of steric approach control and rate data on attack of substituted cyclohexanones from the equatorial and axial positions, see ref 6b.

(10) See, for example, K. G. Lewis and G. J. Williams, *Tetrahedron Lett.*, 4573 (1965).

differences for these intermolecular competition reactions.[11]

β-Phorone is less reactive than the saturated ketones **3**, **4**, and **5**. A comparison between **2** and **5** is the most instructive, since they both contain geminal methyl groups. If the conformation of **2** is taken as a half-chair, with carbons 2, 3, 4, and 5 coplanar, it appears from an inspection of Dreiding models that steric hindrance to axial attack due to the methyl group is certainly no worse than analogous hydride attack on ketone **5**. Equatorial attack on **2** may involve a somewhat greater extent of eclipsing with an adjacent hydrogen than similar attack on **5**, but it is difficult to draw a definite conclusion about this from the models, which are obviously approximations. Compound **2** in a boat form would minimize steric effects arising from interactions with methyl groups.

We draw the tentative conclusion that the difference in reactivity between **2** and the saturated ketone **5** is not due to steric or torsional effects primarily, but rather to an electronic effect of the C=C double bond.[12]

Control Experiments.—The fact that unreacted **2** was partially or completely converted to **8** raised the possibility that **2** was rapidly converted to **8**, which is known to undergo very slow reduction by LATH.[5] This was shown not to be the case when **2** was readily reduced by LATH at room temperature.

In another experiment, **2** was stirred in THF overnight. The solution was divided in half, and one portion was concentrated in the same manner as in the competition experiments. Analysis (glpc) showed that no isomerization occurred. The other half was treated with aqueous alkali and analysis showed that **2** had completely isomerized to **8**. Therefore unreacted **2** in the reductions isomerized to **8** during hydrolysis. Reduction of conjugated enones to saturated ketones was not encountered as a problem, as expected.[13]

Experimental Section

β-Phorone (**2**)[14] was prepared by fractional distillation of isophorone at atmospheric pressure through a helix-packed column.[15] A small pellet of sodium hydroxide was added, and the reflux ratio was maintained at about 30:1. The best sample of **2** had bp 170°, n^{23}D 1.4620 (lit.[16] n^{20}D 1.4626). Analysis by glpc using an 8-ft 10% silicone rubber SE-30 acid-washed and silanized column at 110° showed a purity of 99.1% with 0.9% isophorone (**8**). Convenient analyses of **2** were also obtained with a 5-ft 10% diethylene glycol succinate column, acid-washed and silanized, at 135°. The carbonyl stretching absorption of **2** (*ca.* 1704–1709 cm^{-1}) is readily distinguished from that of **8** (1664 cm^{-1}); nmr spectrum of **2**, δ 1.04 (6 H), 1.73 (3 H), 2.25 (2 H), 2.67 (2 H), 5.50 (1 H).

In the preparation of **2**, water sometimes codistilled with the product. This was apparently due to condensation side reactions of isophorone. In these cases **2** was dried (Na_2SO_4) and stored in a refrigerator.

Ketones **3** and **4** were commercial materials which were distilled, **6** was obtained from Aldrich Chemical Co., **7** was prepared by the $LiAlH_4$ reduction of 3-isobutoxy-5,5-dimethylcyclohex-2-enone,[17] and **5** was prepared from **7** by hydrogenation over 5% Pd/C in absolute ethanol, bp 68.5–70° (15 mm), n^{23}D 1.4435.

As a reference compound, 3,5,5-trimethylcyclohex-3-en-1-ol was prepared from **2** by reduction with $LiAlH_4$ using alkaline hydrolysis; the product had bp 68° (2.5 mm), n^{25}D 1.4704 [lit.[16] bp 71–73° (3 mm), n^{20}D 1.4737], crystallized when refrigerated but melted at room temperature. 5,5-Dimethylcyclohex-2-en-1-ol was prepared from **7** by $LiAlH_4$ reduction, bp 84–85° (15 mm), n^{25}D 1.4660. The product was contaminated with some starting ketone, but was satisfactory as a standard for glpc analysis.

Gas chromatographic analyses were carried out with a Hewlett-Packard 5750 gas chromatograph. Columns used were a 10-ft 10% Carbowax 20M acid-washed and silanized column, and a 5-ft 10% diethylene glycol succinate acid-washed and silanized column. Nmr analysis was done with a JEOL MH-100 instrument. THF was dried and distilled from $LiAlH_4$.

Competition Reduction of 2 and 3.—This reduction is described in some detail as a typical example. A solution of **2** (4.1555 g, 0.030 mol, 99% by glpc analysis) and **3** (2.9471 g, 0.030 mol, distilled and stored over anhydrous Na_2SO_4) was dissolved in 70 ml of THF and placed in a 250-ml Ace reactor equipped with a stirrer, condenser, and addition funnel. A solution of LATH (3.8 g, 0.015 mol) in 50 ml of THF was added dropwise to the rapidly stirred solution. Stirring was continued for several hours and the reaction mixture was kept overnight (about 15 hr). The reaction mixture was then cooled and hydrolyzed with water and 15% sodium hydroxide,[18] and dried ($MgSO_4$). The filtered solution was concentrated by fractional distillation through a 12-in. helix-packed column (oil bath, maximum bath temperature 102°), bp 63.5–66.5°. The concentrated residue was analyzed by glpc.

Registry No.—**2**, 471-01-2; **3**, 108-94-1; **4**, 591-24-2; **5**, 2979-19-3; **6**, 930-68-7; **7**, 4694-17-1; LATH, 17476-04-9.

(11) For a discussion of the stereochemical course of hydride reductions of conjugated enones, see T. Toromanoff in "Topics in Stereochemistry," Vol. 2, N. L. Allinger and E. L. Eliel, Ed., Interscience, New York, N. Y., 1967.

(12) The effect of "remote" unsaturation on carbonyl groups has been observed before. For example, the carbonyl group of Δ^3-cyclohexenic aldehydes is much less active than that of cyclohexanic aldehydes. See G. P. Kugatova-Shemyakina and Y. A. Ovchinnikov, *Tetrahedron*, **18**, 697 (1962). A similar explanation to the one given by these authors is conceivable, which would amount to a form of homoconjugation of the two double bonds.

(13) M. R. Johnson and B. Rickborn, *J. Org. Chem.*, **35**, 1041 (1970).

(14) M. S. Kharasch and P. O. Tawney, *J. Amer. Chem. Soc.*, **63**, 2308 (1941); **67**, 128 (1945).

(15) This distillation method, which displaces the equilibrium between **2** and **8**, was suggested by Dr. W. Wellman, Esso Research and Engineering Co., Linden, N. J. For an alternate method of preparation see J. Meinwald and L. Hendry, *J. Org. Chem.*, **36**, 1446 (1971).

(16) R. Bonnett, A. K. Mallams, A. A. Spark, J. L. Tee, B. C. L. Weedon, and A. McCormick, *J. Chem. Soc. C*, 429 (1969).

(17) H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **33**, 956 (1968).

(18) See L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 584.

Halomethyl Metal Compounds. LX. Phenyl(trifluoromethyl)mercury: a Useful Difluorocarbene Transfer Agent[1]

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The reaction of phenyl(trifluoromethyl)mercury and 3 molar equiv of anhydrous sodium iodide in benzene medium in the presence of olefins serves excellently in the synthesis of *gem*-difluorocyclopropanes. High product yields are obtained in reaction times of about 15 hr at 80–85°. Since $PhHgCF_3$ is now relatively easily prepared, this represents a very useful new CF_2 transfer system. Phenyl(trifluoromethyl)mercury, which does not release CF_2 at 140°, reacts with triorganotin halides to give R_3SnCF_3 compounds and phenylmercuric halide. When this reaction is carried out at 130° in the presence of cyclooctene, 9,9-difluorobicyclo[6.1.0]nonane is formed in moderate yield.

There are many compounds whose thermolysis or photolysis produces difluorocarbene.[2] The reagent most utilized in synthetic applications is $CClF_2CO_2^-Na^+$, which undergoes decarboxylation and loss of chloride ion in diglyme solution at 125–140°. Other CF_2 precursors are less practical, either because they are difficult to prepare, not readily available, hazardous to handle, or too stable for application at the usual temperatures (25–150°) of organic synthesis. Among the CF_2 generators studied have been some trifluoromethyl metal compounds, including trimethyl(trifluoromethyl)tin,[3] trifluoromethylgermanium triiodide,[4] trifluoromethyliron tetracarbonyl iodide,[5] and tris(trifluoromethyl)difluorophosphorane.[6] More recently, trifluoromethyltrifluorosilane has been added to this list.[7] Clark and Willis,[3] the original discoverers of the CF_2 transfer capability of trimethyl(trifluoromethyl)tin, only carried out its thermolysis at 150° in the presence of tetrafluoroethylene (a reaction which gave a quantitative yield of hexafluorocyclopropane), but Cullen and his coworkers have used this reagent to add CF_2 to various fluorinated olefins and acetylenes containing group IV and group V organometallic substituents[8] and to insert CF_2 into the Sn–H bond of trimethyltin hydride.[9] In an earlier investigation, we showed that the action of sodium iodide in 1,2-dimethoxyethane (DME) at 80–85° leads to release of CF_2 as shown in eq 1. When this reaction was carried

$$Me_3SnCF_3 + Na^+I^- \longrightarrow Me_3SnI + Na^+CF_3^- \longrightarrow NaF + CF_2 \quad (1)$$

out in the presence of olefins, *gem*-difluorocyclopropanes were produced in yields ranging from moderate to excellent, depending on the nature of the olefin.[10] This is one of the mildest procedures for the generation of difluorocarbene in solution, but a drawback to the more general application of our reagent system in synthesis was the fact that trimethyl(trifluoromethyl)tin is neither commercially available nor readily prepared from commercially available materials. Its synthesis is based on trimethyltin chloride and the expensive iodotrifluoromethane (eq 2, 3).[3,11] Furthermore, once

$$2Me_3SnCl \xrightarrow{Na} Me_3Sn\text{–}SnMe_3 \quad (2)$$

$$Me_3Sn\text{–}SnMe_3 + CF_3I \xrightarrow{\text{sealed tube, uv}} Me_3SnCF_3 + Me_3SnI \quad (3)$$

prepared, Me_3SnCF_3 must be handled with suitable precautions, since it is unstable to atmospheric moisture. The CF_3 metal derivatives are even less practical. These considerations led us to devote some attention to the possible application of trifluoromethyl mercury compounds as CF_2 precursors. In view of the successful development of phenyl(trihalomethyl)mercury compounds such as $PhHgCCl_3$, $PhHgCCl_2Br$, $PhHgCClBr_2$, $PhHgCBr_3$,[12] $PhHgCCl_2F$,[1,13] $PhHgCCl_2I$,[14] $PhHgCClBrI$,[15] and $PhHgCBr_2F$[15] as dihalocarbene transfer agents, the organomercurial of choice for the purposes of the present study was phenyl(trifluoromethyl)mercury, a compound still unknown at the outset of this investigation. Strong support for this intended investigation also was provided by the fact that, for the trichloromethyl and bromodichloromethyl systems, the respective $PhHgCX_3$ compound was quite more reactive in CX_2 transfer chemistry than was the analogous Me_3SnCX_3 compound.[16]

In previous papers of this series we have described routes to phenyl(trifluoromethyl)mercury.[17,18] Its prep-

(1) Part LIX: D. Seyferth and G. J. Murphy, *J. Organometal. Chem.*, in press.

(2) (a) W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, New York, N. Y., 1969, pp 237–271; (b) W. Kirmse, "Carbene Chemistry," 2nd ed, Academic Press, New York, N. Y., 1971.

(3) H. C. Clark and C. J. Willis, *J. Amer. Chem. Soc.*, **82**, 1888 (1960).

(4) H. C. Clark and C. J. Willis, *ibid.*, **84**, 898 (1962).

(5) R. B. King, S. L. Stafford, P. M. Treichel, and F. G. A. Stone, *ibid.*, **83**, 3604 (1961).

(6) W. Mahler, *ibid.*, **84**, 4600 (1962); *Inorg. Chem.*, **2**, 230 (1963).

(7) K. G. Sharp and T. D. Coyle, *J. Fluorine Chem.*, **1**, 249 (1971).

(8) (a) W. R. Cullen and W. R. Leeder, *Inorg. Chem.*, **5**, 1004 (1966); (b) W. R. Cullen and M. C. Waldman, *Inorg. Nucl. Chem. Lett.*, **4**, 205 (1968); (c) W. R. Cullen and M. C. Waldman, *Can. J. Chem.*, **47**, 3093 (1969); (d) W. R. Cullen and M. C. Waldman, *Inorg. Nucl. Chem. Lett.*, **6**, 205 (1969); (e) W. R. Cullen and M. C. Waldman, *J. Fluorine Chem.*, **1**, 151 (1971).

(9) W. R. Cullen, J. R. Sams, and M. C. Waldman, *Inorg. Chem.*, **9**, 1682 (1970).

(10) (a) D. Seyferth, J. Y.-P. Mui, M. E. Gordon, and J. M. Burlitch, *J. Amer. Chem. Soc.*, **87**, 681 (1965); (b) D. Seyferth, H. Dertouzos, R. Suzuki, and J. Y.-P. Mui, *J. Org. Chem.*, **32**, 2980 (1967).

(11) H. D. Kaesz, J. R. Phillips, and F. G. A. Stone, *J. Amer. Chem. Soc.*, **82**, 6228 (1960).

(12) D. Seyferth 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).

(13) D. Seyferth and K. V. Darragh, *J. Org. Chem.*, **35**, 1297 (1970).

(14) D. Seyferth and C. K. Haas *J. Organometal. Chem.*, **30**, C38 (1971).

(15) D. Seyferth, C. K. Haas, and S. P. Hopper, *ibid.* **33**, C1 (1971).

(16) D. Seyferth and F. M. Armbrecht, Jr., *J. Amer. Chem. Soc.*, **91**, 2616 (1969).

(17) D. Seyferth and S. P. Hopper, *J. Organometal. Chem.*, in press.

(18) D. Seyferth, S. P. Hopper, and G. J. Murphy, *ibid.*, in press.

aration can be effected most simply and cheaply by the sequence shown in eq 4–7. In the present report we

$$HgO + 2CF_3CO_2H \longrightarrow Hg(O_2CCF_3)_2 + H_2O \quad (4)$$

$$Hg(O_2CCF_3)_2 \xrightarrow{300^\circ} CF_3HgO_2CCF_3 + CO_2 \quad (5)$$

$$CF_3HgO_2CCF_3 + Ph_2Hg \longrightarrow PhHgCF_3 + PhHgO_2CCF_3 \quad (6)$$

$$PhHgO_2CCF_3 + NH_4^+Cl^- \xrightarrow{H_2O} PhHgCl\downarrow + NH_4^+O_2CCF_3^- \quad (7)$$

describe the application of $PhHgCF_3$ as a very useful CF_2 reagent.

Results and Discussion

All of the phenyl(trihalomethyl)mercury compounds mentioned above undergo thermal dihalocarbene extrusion in the temperature range 25–80°. Rate measurements and the fact that $PhHgCCl_2F$ eliminated phenylmercuric chloride exclusively established the sequence PhHgI > PhHgBr > PhHgCl > PhHgF for the ease of α elimination of phenylmercuric halide from phenyl(trihalomethyl)mercurials. It might therefore have been expected that the rate of CF_2 extrusion from $PhHgCF_3$ at 80° would be very slow. In actual fact, this reaction did not appear to take place at all. Phenyl(trifluoromethyl)mercury remained undecomposed after it had been heated in cyclooctene at reflux (140°) for 10 days.

This unexpected lack of reactivity of $PhHgCF_3$ on being heated in the presence of an olefin, however, did not preclude its use as a CF_2 transfer agent. The sodium iodide procedure, which had been applied to good advantage to the generation of CF_2 from trimethyl(trifluoromethyl)tin (eq 1), had been developed first to facilitate CCl_2 release from $PhHgCCl_3$.[10a,19] Thus we expected that sodium iodide would react with phenyl(trifluoromethyl)mercury to give CF_2 *via* intermediate CF_3^-. Further experiments showed this to be the case.

In previous applications of the sodium iodide procedure to dihalocarbene generation,[10,19] we found that the reactions proceeded best when DME, in which sodium iodide is soluble, was used as reaction medium. In contrast, the $PhHgCF_3$/NaI/olefin reactions did not require DME as solvent and, in fact, they proceeded readily in dry benzene medium in which sodium iodide is not soluble to an appreciable extent. In the CF_2 transfer reactions as developed, 1 molar equiv of $PhHgCF_3$ was allowed to react with 3 molar equiv of anhydrous sodium iodide in the presence of 3 molar equiv of the olefin in benzene solution at reflux. The progress of the reactions was followed by thin layer chromatographic (tlc) monitoring of the consumption of $PhHgCF_3$; reaction times of 15–20 hr (at 80°) appeared to be required. Alternatively, the reaction could be carried out in the absence of an inert diluent, using the olefin itself as reaction medium. The CF_2 transfer reactions thus were quite simple to carry out, and subsequent work-up of the reaction mixtures proceeded without difficulty. Filtration removed phenylmercuric iodide and the sodium salts (NaI and NaF) and the product *gem*-difluorocyclopropane in the filtrate could be isolated by distillation or by gas chromatography. That DME is not required as reaction medium and that benzene may be used in its place was surprising. The enhanced Lewis acidity of the mercury atom in $PhHgCF_3$ (compared to $PhHgCCl_3$) owing to the highly electronegative[20] CF_3 substituent probably is an important factor which results in this observation. In any case, the ability to use the easily purified benzene in place of DME, which is relatively difficult to maintain pure, represents a substantial improvement in procedure.

The reactions carried out with the $PhHgCF_3$/NaI reagent are summarized in Table I. The yields of the desired *gem*-difluorocyclopropane in general were quite good. It is not surprising that the more electrophilic olefins (acrylonitrile, the vinylsilanes) gave lower product yields. We note that the reactions with *cis*- and *trans*-3-hexene were stereospecific, in agreement with previous findings of Mitsch[21] on difluorocyclopropanation of *cis*- and *trans*-2-butene using difluorodiazirine as CF_2 source. The absence of a CF_3^- adduct in the case of vinyl acetate and of CH insertion of CF_2 in the case of 2,5-dihydrofuran found in these reactions of $PhHgCF_3$/NaI are observations already made and commented on previously in our study of the Me_3SnCF_3/NaI system.[10b] No CF_3^- adduct was formed in the reaction of $PhHgCF_3$/NaI with acrylonitrile, in contrast to the formation of $CCl_3CH_2CH_2CN$ in the reaction of $PhHgCCl_3$/NaI with this olefin.[19]

Some compounds which normally are reasonably good carbenophiles in the case of CCl_2 or CClF did not react with the $PhHgCF_3$/NaI reagent. Among these were cumene, thiobenzophenone, *sym*-dichlorotetrafluoroacetone, diethyl azodicarboxylate, and $PhN{=}CCl_2$. For example, the $PhHgCCl_2F$/NaI reagent was found to convert $PhN{=}CCl_2$ to 1-phenyl-2-fluoro-2,3,3-trichloroaziridine in 70% yield,[1] but $PhN{=}CCl_2$ was recovered unchanged after the $PhHgCF_3$/NaI reaction had been carried out in its presence.

An alternate but rather less useful procedure for releasing CF_2 from phenyl(trifluoromethyl)mercury is based on the well-known ability of organomercurials to undergo alkyl(or aryl)-for-halogen exchange with halides of other metals.[22] Thus $PhHgCF_3$, which, as mentioned already, does not react with cyclooctene at 140° during a 10-day reaction time, was found to transfer CF_2 to this olefin under these conditions, giving 9,9-difluorobicyclo[6.1.0]nonane in 56% yield when 3 molar equiv of tri-*n*-butyltin bromide was present in the reaction mixture. Tri-*n*-butyltin chloride was equally effective, triphenyltin bromide less so. Although a halogen exchange between $PhHgCF_3$ and n-Bu_3SnBr, to give $PhHgCF_2Br$ and n-Bu_3SnF, might be considered a possible rationalization of these results, experiments with trimethyltin bromide suggested that the actual reaction course is that shown in eq 8 and 9. Such exchange (eq 8) was demonstrated in a reaction in which $PhHgCF_3$ and 3 molar equiv of trimethyltin bromide were heated in chlorobenzene for 4 days at 130°. At the end of this time, both

(19) D. Seyferth, M. E. Gordon, J. Y.-P. Mui, and J. M. Burlitch, *J. Amer. Chem. Soc.*, **89**, 959 (1967).

(20) (a) J. J. Lagowski, *Quart. Rev., Chem. Soc.*, **13**, 233 (1959); (b) J. E. Huheey, *J. Phys. Chem.*, **68**, 3073 (1964).

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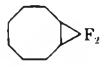
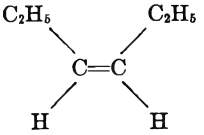
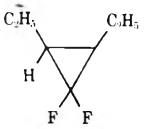
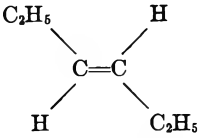
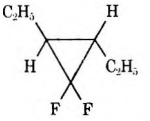
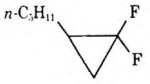
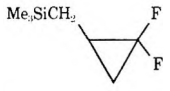
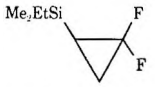
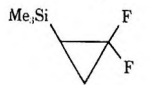
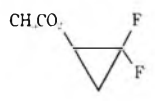
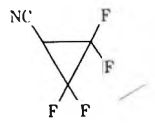
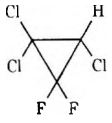
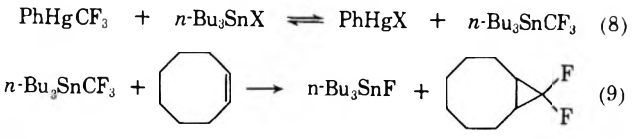
TABLE I
REACTIONS OF THE $PhHgCF_3$/NaI REAGENT WITH OLEFINS

Olefin	Registry no.	Product	(% yield)	Registry no.
	110-83-8		(83)	
	931-88-4		(83)	36601-95-3
	7642-09-3		(93)	36601-96-4
	13269-52-8		(94)	36597-13-4
n-$C_5H_{11}CH{=}CH_2$	592-76-7		(70)	
$Me_3SiCH_2CH{=}CH_2$	762-72-1		(100)	
$Me_2EtSiCH{=}CH_2$	18163-06-9		(44)	
$Me_3SiCH{=}CH_2$	754-05-2		(53)	19097-34-8
	1708-29-8		(67)	
$CH_3CO_2CH{=}CH_2$	108-05-4		(84)	
$CH_2{=}CHCN$	75-05-8		(26)	36597-03-2
$CCl_2{=}CHCl$	79-01-6		(72)	36597-04-3



PhHgBr and the known Me_3SnCF_3 could be isolated and identified. Such exchange reactions generally are equilibrium processes, and this is true also in the present case. A reaction of equimolar amounts of Me_3SnCF_3 and phenylmercuric bromide in chlorobenzene at 130° for 3 days gave some $PhHgCF_3$ and trimethyltin bromide.

Finally, a discussion of other CF_3Hg compounds as CF_2 sources is appropriate, although $PhHgCF_3$ remains the reagent of choice. In our synthesis of $PhHgCF_3$, the compound $CF_3HgO_2CCF_3$ was an intermediate (eq 5 and 6), and CF_3HgCl, CF_3HgBr, and CF_3HgI also were prepared during the course of this study. An assessment of their possible utility as CF_2 transfer agents was of interest. Of these four CF_3HgX compounds, only CF_3HgI served satisfactorily. Its reaction with 3 molar equiv of sodium iodide in the presence of cyclohexene in benzene at reflux proceeded with precipitation of red mercuric iodide and gave 7,7-difluoronorcarane in 88% yield. A similar reaction carried out in the presence of allyltrimethylsilane gave 1,1-difluoro-2-(trimethylsilylmethyl)cyclopropane in 78% yield. However, trifluoromethylmercuric iodide

is light sensitive and not very stable to storage at room temperature. Also, it is rather volatile and thus $PhHgCF_3$ is, in our opinion, a clearly superior CF_2 reagent.

No *gem*-difluorocyclopropane was formed when $CF_3HgO_2CCF_3$ and an excess of sodium iodide and olefin were heated in refluxing benzene, but addition of DME to dissolve the sodium iodide did lead to formation of the desired products, albeit in low yield. Thus a reaction of trifluoromethylmercuric trifluoroacetate with 3 molar equiv of NaI in the presence of allyltrimethylsilane in DME at reflux gave the expected cyclopropane product in 24% yield. The $CF_3HgO_2CCF_3$/NaI reaction carried out in DME in the presence of cyclohexene resulted in formation of 7,7-difluoronorcarane, but only in 16% yield.

The reaction of trifluoromethylmercuric chloride with sodium iodide in DME in the presence of cyclohexene gave only a trace amount of 7,7-difluoronorcarane during a 24-hr reflux period. Initially, a white solid was deposited. Gradually this solid dissolved and was replaced by a greenish, oily lower layer. At the end of the heating period a two-layer system was present. The upper layer was light yellow, while the lower layer was green-gray. A trap-to-trap distillation *in vacuo* gave a clear, colorless distillate which contained only a trace amount of the desired norcarane derivative. Similar behavior was observed with trifluoromethylmercuric bromide. The results with CF_3HgCl and CF_3HgBr were unexpected in view of the successful reactions with CF_3HgI. It had been expected that both would react with iodide ion to give CF_3HgI, analogous to known RHgX + NaI reactions,[23] and that the latter would then give CF_2 on further reaction with sodium iodide.

This unexpected behavior of CF_3HgCl and CF_3HgBr may find an explanation in the ability of RHgX compounds to form anionic complexes of type $[RHgX_2]^-$ and $[RHgX_3]^{2-}$. In particular, evidence for such complexes already has been cited by Emeléus and Lagowski in the case of the trifluoromethylmercuric halides.[24] Conductometric titrations of CF_3HgBr with potassium iodide gave evidence for formation of the species CF_3HgBrI^- and $CF_3HgBrI_2^{2-}$, with KBr, for $CF_3HgBr_3^{2-}$, and salts of the $CF_3HgI_3^{2-}$ anion with $Cd(en)_2^{2+}$, $Cu(en)_2^{2+}$ and $Ni(en)_2^{2+}$ counterions were isolated.[24]

In view of this previous work, it is then not too surprising that CF_3HgCl and CF_3HgBr do not transfer CF_2 on being treated with an excess of sodium iodide. What is surprising is the successful CF_2 transfer chemistry of CF_3HgI under similar conditions. One may assume that kinetic factors (*i.e.*, those which lead to CF_3^- displacement with CF_3HgI and very likely stable anionic complex formation with CF_3HgCl and CF_3HgBr) play an important role in these reactions with iodide ion. This question should receive further experimental attention.

Conclusion

This investigation has shown $PhHgCF_3$ to be an excellent CF_2 precursor. It is a stable, crystalline solid which is easily prepared and which releases CF_2 under mild, nonbasic reaction conditions to give, on reaction with olefins, *gem*-difluorocyclopropanes in high yield. Its availability should facilitate further development of the chemistry of difluorocarbene.

Experimental Section

General Comments.—All reactions were carried out in flame-dried glassware in an atomosphere of prepurified nitrogen. The "standard" apparatus consisted of a three-necked, round-bottomed flask of appropriate size equipped with a stirrer (magnetic or motor driven), a reflux condenser topped with a nitrogen inlet tube, and, when required, pressure-equalizing addition funnel and/or a thermometer. Infrared spectra were recorded using Perkin-Elmer 237B, 257, or 457A grating infrared spectrophotometers, ^1H nmr spectra using a Varian Associates T60 spectrometer. Unless otherwise specified, carbon tetrachloride was used as solvent. Chemical shifts are reported in parts per million downfield from TMS. Gas chromatography was used extensively in the analysis of reaction mixtures, determination of product yields, and isolation of samples of products. The sodium iodide used was pulverized and dried for 18–24 hr at 150° (0.1 mm). Benzene, toluene, and chlorobenzene were distilled from appropriate drying agents. The progress of the reactions was monitored by thin layer chromatographic analysis for starting mercurial.[12]

The preparation of phenyl(trifluoromethyl)mercury has been described.[17,18] A variation of the second procedure,[18] developed by Mr. G. J. Murphy, however, is preferable since it is more direct and is described in detail.[25]

A 200-ml, three-necked flask equipped with a magnetic stirring assembly, a pressure-equalizing addition funnel, and a reflux condenser topped with a nitrogen inlet tube was charged with 21.1 g (55.0 mmol) of $CF_3HgO_2CCF_3$,[18] 19.4 g (54.8 mmol) of diphenylmercury, and 100 ml of dry benzene. The resulting solution was stirred and heated at reflux for 1 hr. Subsequently, 50 ml of saturated aqueous ammonium chloride was added. A large amount of white solid was formed at the layer interface. The reaction mixture was cooled and filtered to remove 19.4 g of white powder, mp 255–258° (mostly PhHgCl). The organic layer was dried and evaporated at reduced pressure to give white crystalline solid. Recrystallization of the latter from hexane gave 13.85 g (73%) of $PhHgCF_3$, mp 141–143°.

General Procedure for $PhHgCF_3$/NaI/Olefin Reactions.—The standard apparatus was charged (under nitrogen) with 1 molar equiv of phenyl(trifluoromethyl)mercury, 2.5–3.0 molar equiv of well-dried sodium iodide, and 3.0 molar equiv of the dried olefin. An appropriate amount (about 15-20 ml per 10 mmol of $PhHgCF_3$) of benzene was distilled directly into the reaction flask from sodium benzophenone ketyl. The reaction mixture then was stirred and heated at reflux under nitrogen for 12–18 hr (except as noted). The reaction mixture was allowed to cool to room temperature, and the solids (PhHgI, NaF, and unreacted NaI) were filtered. The filtrate was trap to trap distilled at reduced pressure into a receiver at −78 to −196°. The distillate was analyzed by glc and samples for spectroscopic, physical, and analytical characterization were isolated by glc. Details of specific reactions follow.

Glc analysis of reaction mixtures was accomplished using a 6-ft commercial aluminum 20% Dow Corning DC 200 silicone oil on Chromosorb W column. Many of the *gem*-difluorocyclopropanes reported here had been prepared during the course of our earlier study of the Me_3SnCF_3/NaI system,[10b] and spectra and in some cases authentic samples were available for comparison.

Cyclohexene (15.8 mmol), $PhHgCF_3$ (5.5 mmol), and NaI (12.5 mmol) in 30 ml of benzene at reflux for 15 hr gave 7,7-difluoronorcarane[10b] in 83% yield. The solids were Soxhlet extracted with benzene to give 1.95 g (70%) of slightly impure PhHgI, mp 274–278°. A reaction of 5.0 mmol of $PhHgCF_3$, 12.5 mmol of NaI, and 10 ml of cyclohexene (no benzene), 15 hr at reflux, gave 7,7-difluoronorcarane in 81% yield.

Cyclooctene (60 mmol), $PhHgCF_3$ (20 mmol), and NaI (50 mmol) in 50 ml of benzene at reflux for 15 hr gave 9,9-difluorobicyclo[6.1.0]nonane, $n^{25}D$ 1.4338, in 83% yield.

Anal. Calcd for $C_9H_{14}F_2$: C, 67.47; H, 8.81. Found: C, 67.56; H, 8.80.

(23) D. Seyferth and R. H. Towe, *Inorg. Chem.*, **1**, 185 (1962).

(24) H. J. Emeléus and J. J. Lagowski, *J. Chem. Soc.*, 1497 (1959).

(25) Added in proof, November 1972.

Ir (liquid film): 3010 (m), 2920 (s), 2860 (s), 2790 (w), 1480 (s), 1455 (s), 1450 (s), 1375 (w), 1370 (m), 1350 (m), 1335 (m), 1305 (s), 1290 (s), 1265 (s), 1225 (s), 1210 (s), 1145 (m), 1175–1165 (s), 1085 (m), 1075 (w), 1040 (m), 1025 (m), 1005 (s), 965 (s), 955 (s), 885 (w), 865 (s), 845 (m), 805 (m), 775 (m), 750 (m), 675 (m), 645 cm^{-1} (m).

cis-**3-Hexene** (60 mmol) (Chemical Samples Co., 98% isomerically pure), $PhHgCF_3$ (20 mmol), and NaI (50 mmol) in 50 ml of benzene at reflux for 15 hr gave 1,1-difluoro-*cis*-2,3-diethylcyclopropane, $n^{25}D$ 1.3270, in 93% yield.

Anal. Calcd for $C_7H_{12}F_2$: C, 62.67; H, 9.02. Found: C, 62.57; H, 9.20. The glc retention time, 15.5 min, on a 20% SE-30 on Chromosorb W column at 57° and 15 psi helium (MIT isothermal unit) was different from that of the difluorocyclopropane derived from *trans*-3-hexene, 12.8 min.

Ir (liquid film): 3020 (m), 2980 (s), 2940 (s), 2880 (s), 2740 (m), 1480 (s), 1470 (s), 1380 (m), 1365 (m), 1340 (m), 1290 (s), 1270 (s), 1200 (s), 1160 (m), 1140 (m), 1110 (m), 1085 (m), 1040 (m), 1020 (m), 1000 (m), 990 (m), 960 (m), 940 (s), 900 (s), 820 (s), 790 (s), 750 (m), 700 (s), 680 (m), 640 cm^{-1} (m).

trans-**3-Hexene** (60 mmol) (Chemical Samples Co., 98% isomerically pure), $PhHgCF_3$ (20 mmol), and NaI (50 mmol) in 50 ml of benzene at 60–70° for 48 hr gave 1,1-difluoro-*trans*-2,3-diethylcyclopropane, $n^{25}D$ 1.3670, in 94% yield.

Anal. Calcd for $C_7H_{12}F_2$: C, 62.67; H, 9.02. Found: C, 62.82; H, 9.00.

Ir (liquid film): 3150 (w), 3080 (s), 3040 (s), 2980 (s), 2740 (m), 1480 (s), 1460 (s), 1380 (m), 1360 (m), 1340 (m), 1260 (s), 1200 (s), 1150 (m), 1100 (w), 1085 (w), 1050 (m), 1020 (w), 1000 (w), 960 (m), 875 (s), 790 (s), 785 (s), 770 (m), 715 (s), 680 (s), 670 (s), 650 cm^{-1} (s).

1-Heptene (15 mmol) (Chemical Samples Co.), $PhHgCF_3$ (5 mmol), and NaI (12.5 mmol) in 30 ml of benzene at reflux for 15 hr gave 1,1-difluoro-2-*n*-amylcyclopropane, $n^{25}D$ 1.3820 (lit.[10b] $n^{25}D$ 1.3813), in 70% yield.

Allyltrimethylsilane (20 mmol), $PhHgCF_3$ (7.5 mmol), and NaI (18.7 mmol) in 40 ml of benzene at reflux for 15 hr gave 1,1-difluoro-2-(trimethylsilylmethyl)cyclopropane, $n^{25}D$ 1.3910 (lit.[10b] $n^{25}D$ 1.3899), in 100% yield.

Vinyldimethylethylsilane (60 mmol), $PhHgCF_3$ (20 mmol), and NaI (50 mmol) in 50 ml of benzene at reflux for 15 hr gave 1,1-difluoro-2-(dimethylethylsilyl)cyclopropane, $n^{25}D$ 1.3960 (lit.[10b] $n^{25}D$ 1.3962), in 44% yield.

Vinyltrimethylsilane (30 mmol), $PhHgCF_3$ (12 mmol), and NaI (30 mmol) in 30 ml of chlorobenzene at 60° for 48 hr and 90° for 12 hr gave 1,1-difluoro-2-(trimethylsilyl)cyclopropane, $n^{25}D$ 1.3822, in 53% yield.

Anal. Calcd for $C_6H_{12}F_2Si$: C, 47.96; H, 8.05. Found: C, 48.11; H, 8.13.

Ir (liquid film): 3020 (w), 2960 (s), 2900 (m), 1460 (s), 1455 (s), 1365 (s), 1255 (s), 1180 (s), 1085 (s), 1040 (s), 1020 (s), 960 (m), 950 (m), 910 (s), 890 (s), 860–840 (s), 760 (m), 710 (m), 670 cm^{-1} (m). Nmr: δ 0.17 (s, 9 H, Me_3Si) and 1.0 ppm (m, 3 H, cyclopropyl H).

2,5-Dihydrofuran (30 mmol), $PhHgCF_3$ (10 mmol), and NaI (30 mmol) in 30 ml of benzene at 70° for 48 hr gave 3-oxa-6,6-difluorobicyclo[3.1.0]hexane, $n^{25}D$ 1.3944 (lit.[10b] $n^{25}D$ 1.3942), in 67% yield.

Vinyl acetate (30 mmol), $PhHgCF_3$ (10 mmol), and NaI (30 mmol) in 30 ml of benzene ar reflux for 15 hr gave 1,1-difluoro-2-acetoxycyclopropane in 84% yield. No other product was detected in the gas chromatogram.

Acrylonitrile (30 mmol), $PhHgCF_3$ (10 mmol), and NaI (30 mmol) in 30 ml of toluene (benzene interfered in product isolation) at 90° for 20 hr gave 1,1-difluoro-2-cyanocyclopropane, $n^{25}D$ 1.3710, in 26% yield.

Anal. Calcd for $C_4H_3NF_2$: C, 46.61; H, 3.00. Found: C, 46.47; H 3.48.

Ir (liquid film): 3110 (m), 3055 (m), 3020 (m), 2265 (s), 1470 (s), 1385 (s), 1310 (s), 1240 (vs), 1100 (w), 1080 (m), 1055 (m), 1000 (s), 950 (s), 915 (m), 820 (w), 725 (m), 650 cm^{-1} (m).

Trichloroethylene (40 ml, used as solvent), $PhHgCF_3$ (20 mmol), and NaI (50 mmol) at reflux for 15 hr gave 2,2-difluoro-1,1,3-trichlorocyclopropane, $n^{25}D$ 1.4227, in 72% yield.

Anal. Calcd for $C_3HCl_3F_2$: C, 19.86; H, 0.56. Found: C, 19.76; H, 0.62.

Ir (liquid film): 3045 (m), 1420 (s), 1400 (m), 1275 (s), 1200 (s), 1045 (s), 1035 (s), 990 (s), 905 (s), 860 (s), 810 (s), 740 (w), 690 cm^{-1} (s).

^1H nmr: δ 3.79 ppm [d, J(HF cis) = 11 Hz]. ^{19}F nmr (in CCl_4, downfield from 1,1,2,2-tetrafluoro-3,3,4,4-tetrachlorocyclobutane): δ 18.1 [d, J(FF) = 157 Hz] and 29.7 ppm [d, J(FF) = 157 Hz].

Reaction of Phenyl(trifluoromethyl)mercury with Cyclooctene in the Presence of Tri-*n*-butyltin Bromide.—The standard apparatus was charged with 4.15 g (12 mmol) of the mercurial, 13.3 g (36 mmol) of tri-*n*-butyltin bromide [prepared by reaction of bis(tri-*n*-butyltin) oxide and hydrobromic acid], and 20 ml of dry cyclooctene. The reaction mixture was heated at reflux, with stirring, under nitrogen for 7 days, until tlc indicated that the mercury reagent had been consumed. The very viscous reaction mixture was filtered from 6.80 g of solid, which was washed with benzene. The filtrate was poured into 50 ml of 10% potassium fluoride in 1:1 water–ethanol and then 100 ml of benzene was added. The mixture was shaken vigorously. The resulting gelatinous mass of solid was rendered filterable through the addition of 50 ml of acetone and further shaking. Filtration gave 8.60 g of tri-*n*-butyltin fluoride. The filtrate was dried and concentrated by distillation at atmospheric pressure. The residue was trap-to-trap distilled at 0.05 mm. Glc analysis of the filtrate showed the presence of 9,9-difluorobicyclo[6.1.0]nonane in 56% yield. An isolated sample had $n^{25}D$ 1.4339 and an ir spectrum which was identical with that of an authentic sample.

A similar reaction carried out with 10 mmol of $PhHgCF_3$, 30 mmol of tri-*n*-butyltin chloride (M & T Chemicals, Inc.), and 25 ml of cyclooctene (reflux for 12 days) gave 9,9-difluorobicyclo[6.1.0]nonane in 55% yield. This product was obtained in 37% yield when 12 mmol of $PhHgCF_3$, 36 mmol of triphenyltin bromide, and 20 ml of cyclooctene were heated at reflux under nitrogen for 10 days.

When 5 mmol (1.73 g) of $PhHgCF_3$ in 25 ml of cyclooctene was heated at reflux under nitrogen for 10 days, no 9,9-difluorobicyclo[6.1.0]nonane was produced. Trap-to-trap distillation of the solution at 0.05 mm left a residue of 1.81 g of solid, mp 137–142°. Recrystallization from 3:1 hexane–chloroform gave 1.05 g of pure $PhHgCF_3$, mp 140–142°. Glc examination of the distillate showed the expected product to be absent.

Reaction of Phenyl(trifluoromethyl)mercury with Trimethyltin Bromide.—A solution of 20 mmol of $PhHgCF_3$ and 60 mmol of trimethyltin bromide in 20 ml of dry chlorobenzene was heated under nitrogen at 130° for 4 days with stirring. Filtration removed 1.7 g of crude PhHgBr, which was purified by recrystallization from benzene to give material with mp 276–280°. The filtrate was trap to trap distilled at 0.05 mm, leaving a 0.1-g residue of $PhHgCF_3$ (identified by tlc). Examination of the distillate by glc (20% SE-30 on Chromosorb P at 110°) showed the presence of trimethyl(trifluoromethyl)tin. A sample was isolated by glc; its glc retention time and ir spectrum were in excellent agreement with those of authentic material.[10b]

A similar reaction was carried out between 10 mmol each of trimethyl(trifluoromethyl)tin and phenylmercuric bromide in 25 ml of chlorobenzene at 130° for 3 days. Filtration was followed by trap-to-trap distillation of the filtrate at 0.05 mm. The pot residue was crystallized from hexane to give a small amount of $PhHgCF_3$ (mp 140.5–144° and ir spectrum). Glc examination of the distillate showed trimethyltin bromide to be present (glc retention time, peak enhancement, and ir spectrum of an isolated sample).

Reactions of CF_3HgX Compounds with Sodium Iodide in the Presence of Olefins. A. Trifluoromethylmercuric Iodide.—The procedure described for $PhHgCF_3$/NaI/olefin reactions was used in the reaction of 10 mmol of trifluoromethylmercuric iodide,[18] 30 mmol of sodium iodide, and 30 mmol of cyclohexene in 40 ml of benzene for 20 hr at reflux. During the course of the reaction, red mercuric iodide precipitated. The pink solids (8.05 g) were filtered and the filtrate was trap to trap distilled. Glc analysis established the presence of 7,7-difluoronorcarane in 88% yield. An isolated sample had $n^{25}D$ 1.4130 and an ir spectrum which agreed with that of an authentic sample.

A similar reaction of 9.7 mmol of CF_3HgI and 30 mmol of NaI in 30 ml of benzene in the presence of 30 mmol of allyltrimethylsilane for 20 hr at reflux gave 1,1-difluoro-2-(trimethylsilylmethyl)cyclopropane, $n^{25}D$ 1.3890, in 78% yield.

B. Trifluoromethylmercuric Trifluoroacetate.—The same procedure was used in a reaction of 10 mmol of $CF_3HgO_2CCF_3$[18] and 40 mmol of NaI in the presence of 30 mmol of cyclohexene in a solvent mixture of 30 ml of benzene and 20 ml of DME (distilled successively from potassium and from lithium aluminum hydride). The NaI dissolved in DME was added dropwise to

the hot mercurial/olefin/benzene solution over 30 min, and the reaction mixture was heated at reflux for an additional 2 hr. At the end of this time tlc showed that none of the starting mercury reagent was present. The cooled reaction mixture (a three-layer system) was trap to trap distilled. Glc analysis of the distillate showed the presence of 7,7-difluoronorcarane in 16% yield.

A similar reaction carried out in benzene at reflux (no DME) for 20 hr gave none of the expected norcarane derivative.

The reaction of 10 mmol of $CF_3HgO_2CCF_3$ and 40 mmol of NaI in the presence of 30 ml of allyltrimethylsilane in 20 ml of benzene and 20 ml of DME, carried out using the procedure described above, gave 1,1-difluoro-2-(trimethylsilylmethyl)cyclopropane in 24% yield.

C. Trifluoromethylmercuric Chloride.—A solution of 30 mmol of NaI in 20 ml of dry DME was added over a 30-min period to a stirred and heated solution of 5 mmol of CF_3HgCl[18] and 30 mmol of cyclohexene in 10 ml of benzene. A white solid deposited as the NaI was added. This became gradually green and oily as the addition progressed and finally went into solution. The reaction was heated at reflux for 1 hr and then was cooled to room temperature. A two-layer system resulted. The upper light yellow layer contained no 7,7-difluoronorcarane (by glc). Trap-to-trap distillation at 0.05 mm gave a water-white distillate which was shown by glc to contain only trace amounts of 7,7-difluoronorcarane. None of this product was present in a similar reaction mixture in which the solvent contained no DME.

Very similar behavior was observed with trifluoromethylmercuric bromide.[18]

Registry No.—Phenyl(trifluoromethyl)mercury, 24925-18-6; sodium iodide, 7681-82-5; trifluoromethylmercuric iodide, 421-11-4; trifluoromethylmercuric trifluoroacetate, 675-25-2; trifluoromethylmercuric chloride, 421-10-3; phenylmercuric iodide, 823-04-1.

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Synthesis of (Fluoren-9-ylidene)(dibenzo[*a*,*d*]cyclohepten-5-ylidene)methane. Allenes as Ground-State Carbenes. I[1]

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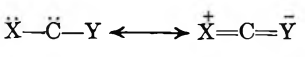
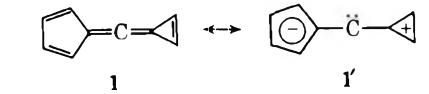
The first representative of a novel class of allenes (**3**) was synthesized by dehydrogenation of the dihydro precursor **9**, the latter compound being formed by the reaction of the phosphonium ylide **8** with the aldehyde **7**. Interest in the allene was based on the possibility that polarization of the cumulene linkage, resulting from the special properties of the end groups, would impart divalent character to the central carbon. Spectroscopic data on the allene indicated that this expectation was only minimally realized in this tetraannelated representative.

Hine[2] has suggested that a stable carbene might be formed if the electron-deficient carbon is attached to an electron donor and an electron acceptor.



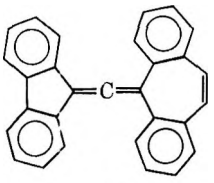
Using what might be considered an inversion of this concept, it occurred to us that allenes, appropriately substituted, might exhibit divalent character in the ground state. Two prototypical allenes (**1** and **2**) exemplify this concept.



1 **1′**

2 **2′**

Neither **1** nor **2**, which are obviously closely related to the calicenes,[3] nor any of their derivatives are known compounds. In order, then, to examine the feasibility of this concept, the synthesis of the tetraannelated derivative, (fluoren-9-ylidene)(dibenzo[*a*,*d*]cyclohepten-5-ylidene)methane (**3**), was undertaken. The representative **3** of this novel class of allenes was chosen as the initial goal because of the added stability that annelation should impart to such a system and because of the commercial availability of certain suitable starting materials.



3

Results and Discussion

The synthesis of **3** was accomplished using the reaction sequence shown in Scheme I.

Synthesis of **9** was straightforward and proceeded in good yield. Reaction of **9** with DDQ in benzene provided a soluble fraction consisting of the allene and unreacted **9** and an insoluble fraction consisting of the hydroquinone and the tropylium salt **13**. Based on the analogy of the reaction of tropylidene itself with DDQ,[4] it was initially assumed that the structure of the salt was **11**. However, treatment of the salt with a variety of bases failed to convert it to the allene. Furthermore, the elemental analysis correlates substantially better with structure **13** than with **11**.

The allene is a colorless solid, mp 242°, and its structure was established by several lines of evidence. Thus, the elemental analysis, molecular weight deter-

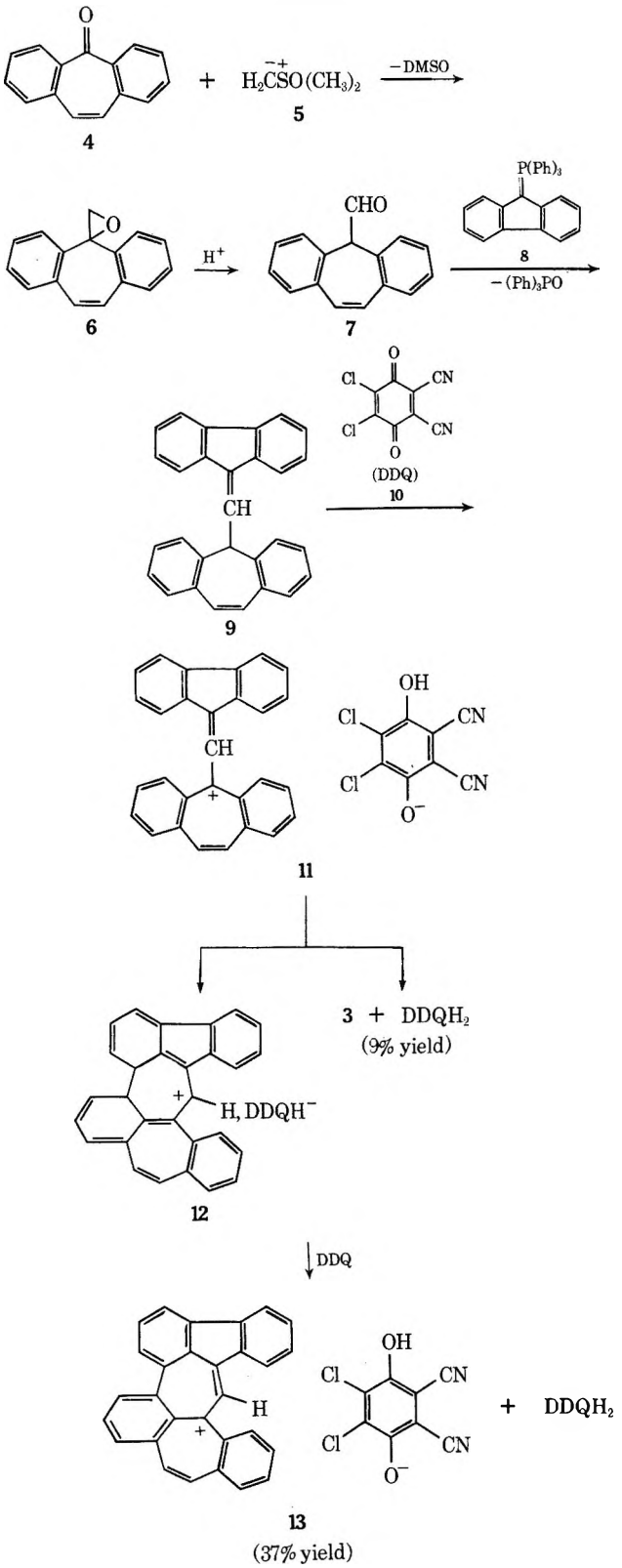
(1) This work was supported by The Petroleum Research Fund, administered by The American Chemical Society, Grant 1339-G1.

(2) J. S. Hine, "Divalent Carbon," Ronald Press, New York, N. Y., 1964, p 170.

(3) G. M. Badger, "Aromatic Character and Aromaticity," Cambridge University Press, Cambridge, England, 1969, p 76.

(4) D. H. Reid, M. Frazer, B. B. Molloy, H. A. S. Payne, and R. G. Sutherland, *Tetrahedron Lett.*, 530 (1961).

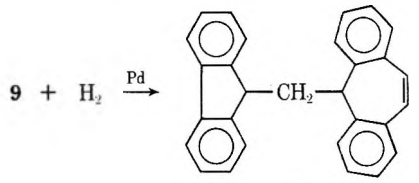
SCHEME I



mination, and mass spectrum were all consistent with the molecular formula $C_{29}H_{18}$. The infrared spectrum, in addition to bands characteristic of ortho-disubstituted benzene, exhibited a band of medium intensity at 1933 cm^{-1}, consistent with the presence of an allene group. The nmr spectrum showed the correct proton ratio and the ultraviolet spectrum was similar to that of a model allene, 2-(fluoren-9-ylidene)-1,1-diphenylethene.[5]

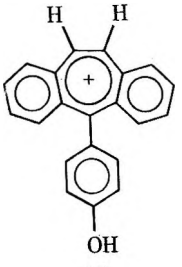
(5) H. Fischer and H. Fischer, *Chem. Ber.*, **97**, 2978 (1964).

The allene appears to be indefinitely stable in the solid state, although solutions of **3** yellow on standing, presumably to give oxidation products. Attempts to reduce the allene by catalytic hydrogenation failed. The precursor **9** readily absorbs 1 equiv of hydrogen to give (fluoren-9-yl)(5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)-methane (**14**). Hydrogenation of **3** to **14** would have



provided a rigorous proof of structure. Chemical reduction of **3** using $NaBH_4$, $LiAlH_4$, or Na/EtOH occurs rapidly but gives a variety of products, none of which is either **9** or **14**.

Having secured the allene **3**, it was of considerable interest to determine the electron distribution in its ground state, *i.e.*, to determine to what extent, if any, the dipolar carbene form contributes to the ground state of **3**. The simplest probe for this purpose appears to be the chemical shift of the protons of the seven-membered ring. Any development of positive charge in this ring should cause the protons in question to be deshielded compared to those in uncharged systems. Thus, in the charged model compound **15** the



chemical shift of the protons on the seven-membered ring is reported to be 535 Hz.[6] In the uncharged model compound, 5-methylene-5*H*-dibenzo[*a*,*d*]cycloheptene, the chemical shift of these protons is 403 Hz. In the allene **3** the chemical shift is observed at 408 Hz. It would appear then that, based on the nmr analysis, the carbene resonance form makes at best a meager contribution to the ground state of **3**. Further support for this conclusion is found in the fact that the ultraviolet spectrum of **3** is insensitive to solvent polarity, methanol and cyclohexane solutions of **3** having identical spectra.

The absence of significant carbene character in **3**, while disappointing, was not altogether unexpected, for, although the annelation of the central rings by four benzene rings can be expected to stabilize the system, a counter effect, the tendency to suppress the development of aromatic character in the central rings through bond localization, will reduce the contribution from the polar carbene form.[7] With this in mind the nonannelated representatives **1** and **2** remain attractive candidates for synthesis.

(6) B. Foehlisch, *Justus Liebigs Ann. Chem.*, **721**, 52 (1969).

(7) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, p 109.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer Infracord, Model 137; uv spectra on a Cary 14 spectrophotometer; and nmr spectra on a Varian Associates A-60 instrument, chemical shifts relative to tetramethylsilane.

5-Methylene-5*H*-dibenzo[*a*,*d*]cycloheptene-5,12-oxide (6).—The epoxide **6** was prepared by a modification of the Corey–Chaykovsky reaction.[8] A stirred solution of trimethyloxosulfonium iodide (1.76 g, 8 mmol) in 10 ml of dry dimethyl sulfoxide (DMSO) at 10° under nitrogen was treated with 5 ml of 1.6 *M* *n*-butyllithium in hexane (Foote Mineral Co.). After 10 min, 5*H*-dibenzo[*a*,*d*]cycloheptene-5-one (1.03 g, 5 mmol, Aldrich Chemical Co.) in 10 ml of dry DMSO was added in one portion. The mixture was warmed to 50–55° and stirred for 3 hr, then cooled and diluted with water (50 ml) and 1:1 benzene–hexane (50 ml). The organic layer was separated, washed five times with water, dried ($MgSO_4$), and filtered. Evaporation of the filtrate gave the crude epoxide **6** as a pale yellow oil (1.01 g) which crystallized on cooling. Recrystallization from benzene–hexane gave the pure epoxide (0.88 g, 86%) as colorless prisms: mp 92–93°; uv (EtOH) 221 nm (ϵ 25,000) and 228 (14,000); ir (KBr) 6.75, 7.64, 9.85, 10.81, 11.21, 11.65, 12.43, 12.70, 13.02, 13.15, 13.40, and 13.92 μ; nmr ($CDCl_3$) 7.2–7.8 (m, 8, aromatic), 7.0 (s, 2, seven-membered ring), and 2.67 ppm (s, 2, CH_2).

Anal. Calcd for $C_{16}H_{12}O$: C, 87.24; H, 5.49. Found: C, 86.97; H, 5.46.

The epoxide decomposes at room temperature but is stable at freezer temperature. The crude epoxide was found to be suitable for conversion to the aldehyde **7**.

5*H*-Dibenzo[*a*,*d*]cycloheptene-5-carboxaldehyde (7).—A solution of crude **6** (2.0 g) and *p*-toluenesulfonic acid (150 mg) in dry benzene (100 ml) was refluxed for 5 hr under nitrogen. The cooled solution was washed successively with bicarbonate and water, dried ($MgSO_4$), and filtered. Evaporation of the filtrate provided a yellow solid which was recrystallized from benzene–hexane to give the aldehyde **7** as colorless needles (1.0 g), mp 109–111° (lit.[9] mp 112–114°).

(Fluoren-9-ylidene)(5*H*-dibenzo[*a*,*d*]cycloheptene-5-yl)methane (9).—Fluoren-9-ylidene triphenylphosphorane (**8**) (9.0 g), prepared by the method of Pinck and Hilbert,[10] was combined with the aldehyde **7** (4.66 g) in benzene (40 ml) in a sealed tube and heated at 100° for 20 hr. The tube was cooled and opened, and the benzene was evaporated. The yellow, oily residue was chromatographed on a 5 × 100 cm column of silica gel using benzene (4 l.) as the eluent. Evaporation of the eluent provided a yellow solid (6.56 g), uniform by tlc, which was recrystallized from benzene–hexane to give **9** as very pale yellow prisms (5.11 g, 66%): mp 157–159°; uv (EtOH) 220 nm (ϵ 59,000), 245 (37,300), 255 (52,400), 280 (31,100), 298 (25,900), and 313 (21,900); ir (KBr) 6.77, 6.95, 12.60, 12.82, 12.99, 13.10, 13.49, 13.55, and 13.85 μ; nmr ($CDCl_3$) 7.1–8.2 (m, 19) and 5.67 ppm (d, J = 10.5 Hz, 1, methine H of the seven-membered ring).

Anal. Calcd for $C_{29}H_{20}$: C, 94.54; H, 5.46. Found: C, 94.29; H, 5.54.

Hydrogenation of 9 to (Fluoren-9-yl)(5*H*-dibenzo[*a*,*d*]cycloheptene-5-yl)methane (14).—A mixture of **9** (189 mg, 0.5 mmol), absolute EtOH (35 ml), and 10% Pd/C (23 mg) was treated with hydrogen at atmospheric pressure and room temperature. Hydrogen uptake (0.5 mmol) was complete after 90 min. The catalyst was filtered (Celite) and evaporation of the filtrate gave a white, crystalline solid which was recrystallized from EtOH (30 ml) to give **14** (80 mg, 42%) as colorless needles: mp 147–150°; uv (EtOH) 266 nm (ϵ 22,300), 290 (16,400), and 300 (16,900); ir (KBr) 6.73, 6.93, 10.66, 12.50, 13.09, 13.50, 13.70, and 13.81 μ; nmr ($CDCl_3$) 6.75–7.85 (m, 18), 3.98 (t, J = 7.5 Hz, 1, methine H of the fluorenyl group), 3.66 (t, J = 5.0 Hz, 1, methine H of the seven-membered ring), and 2.59–2.41 ppm (doublet of doublets, J = 5.0 Hz, 2, CH_2). The hydrogenation equivalent and nmr spectrum indicate that the endocyclic double bond of the seven-membered ring was not reduced.

Anal. Calcd for $C_{29}H_{22}$: C, 94.01; H, 5.99. Found: C, 94.06; H, 5.94.

Reaction of 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) with 9. Formation of the Allene 3 and the Tropylium Quinolate Salt 13.—To a refluxing solution of **9** (368 mg, 1 mmol) in benzene (10 ml) was added a solution of DDQ (Aldrich Chemical Co., 250 mg, 1.1 mmol) in benzene (10 ml) over a 2-min period. A copious precipitate formed during the addition and after an additional 5 min the mixture was cooled and the precipitate was filtered. The precipitate was labeled fraction A and the filtrate fraction B.

Fraction A. Isolation of the Salt 13.—This fraction consisted of a mixture of the hydroquinone (146 mg) and the salt **13** (162 mg). Washing the precipitate with MeOH (20 ml) selectively dissolved the hydroquinone and left the insoluble salt **13** as glistening gold platelets: mp 280° dec (blackens without melting on continued heating); ir (KBr) 3.00 (–OH), 4.49 (–CN), 7.00, 7.12, 7.54, 7.72, 7.91, 8.27, 8.49, 10.02, 10.74, 12.27, and 13.32 μ; uv (dioxane) 225 nm (ϵ 75,900), 268 sh (41,700), 314 (15,800), 327 (17,000), 342 (12,600), and 360 (9330).

Anal. Calcd for $C_{37}H_{18}Cl_2N_2O_2$: C, 74.87; H, 3.06; Cl, 11.95; N, 4.72. Found: C, 74.84; H, 3.08; Cl, 12.44; N, 5.07.

Fraction B. Isolation of the Allene 3.—The filtrate was evaporated to dryness and the residue was chromatographed on a thick layer of silica gel G using 50% benzene in hexane as the eluent. The uppermost band was eluted and recrystallized from benzene–hexane to give the allene **3** as colorless needles (32 mg, 9%): mp 242–245° dec; ir (KBr) 5.17 (C=C=C), 6.67, 6.85, 12.28, 12.69, 12.91, and 13.37 μ; uv (cyclohexane) 227 nm (ϵ 83,200), 246 (57,500), 255 (64,600), 279 sh (39,800), 287 (45,700), 302 (41,700), 315 (43,700); the uv spectrum is identical in MeOH; nmr ($CDCl_3$) 7.00–8.17 (m, 16, aromatic), 6.82 ppm (s, 2, seven-membered ring H); mass spectrum molecular ion *m/e* 366 (base peak; calcd for $C_{29}H_{18}$, 366); mol wt (osmometric in benzene), found 351.

Anal. Calcd for $C_{29}H_{18}$: C, 95.05; H, 4.95. Found: C, 94.74; H, 4.68.

Registry No.—**3**, 36146-49-3; **6**, 16036-73-0; **9**, 36146-51-7; **13**, 36079-64-8; **14**, 36079-65-9.

(8) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1358 (1965).

(9) S. J. Cristol and L. K. Bly, *ibid.*, **82**, 6155 (1960).

(10) L. A. Pinck and G. A. Hilbert, *ibid.*, **69**, 723 (1947).

Electrophilic Halogenation of 8-Methoxyquinoline[1]

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Electrophilic halogenation of 8-methoxyquinoline with elemental halogen and *N*-halosuccinimide was studied and compared with that of 8-quinolinol. Monochlorination and monobromination took place in the 5 position under acidic and neutral conditions, whereas iodination took place in the 7 position. This paralleled the results with 8-quinolinol. Under basic conditions, 8-methoxyquinoline remained unhalogenated, whereas 8-quinolinol formed 7-chloro, 7-bromo, and 5-iodo derivatives with the respective halogenating agents. The inactivity of 8-methoxyquinoline to halogenation in strongly basic media is attributed to the absence of an anionic form of the compound. The importance of the anionic form of 8-quinolinol for electrophilic chlorination and bromination in the 7 position and iodination in the 5 position was established.

Recent studies of the electrophilic halogenation of 8-quinolinol and its bischelate with copper(II) revealed that, although chelation does not alter the electrophilic positions, it does influence the orientation of the incoming halogen.[2,3] Other factors which influence orientation in electrophilic monohalogenation are the prototropic form of the substrate, the nature of the halogenating agent, and the solvent employed.[4] It should also be mentioned that chlorination and bromination, under acidic conditions, favor the 5 position, and in basic media the 7 position is favored. Iodination is characterized by the reverse orientation and may take place by a different mechanism.[4]

Since the prototropic form of the substrate strongly influences the orientation of the incoming halogen in electrophilic substitution of 8-quinolinol, it is of interest to examine the electrophilic halogenation of 8-methoxyquinoline, which can form cationic and neutral species but no anions. Halogenations using *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), *N*-iodosuccinimide, chlorine, bromine, and iodine were carried out in 93% sulfuric acid, glacial acetic acid, chloroform, pyridine, diethylamine, and 10% sodium hydroxide. The reactions were carried out at ambient temperatures for 3 hr with the *N*-halosuccinimides and elemental halogens and also at 40–60° with the *N*-halosuccinimides. The molar ratios of halogenating agent to substrate were 1:1, 2:1, and 3:1, and the reaction mixtures were assayed by gas chromatography. A second portion of mixture was gas chromatographed after treatment with *N,O*-bis(trimethylsilyl)acetamide to detect demethylated compounds, when present. The rationale for this approach has been previously developed.[2-4]

The results obtained are summarized in Table I. A cursory examination of the data indicates that, on monohalogenation, chlorine and bromine were oriented to the 5 position and iodine to the 7 position. No 7-monochloro- or 7-monobromo-8-methoxyquinoline was detected under any of the conditions of halogenation employed, with the following three exceptions. When 8-methoxyquinoline was treated with 3 equiv of NCS in 93% sulfuric acid at 40–60°, 2% 7-chloro-8-methoxyquinoline was formed. Upon replacing the sulfuric acid with acetic acid and keeping the remaining conditions the same, only a trace of 7-chloro-8-methoxyquinoline was detected. When the chlorination was carried out in pyridine with 1 equiv of chlorine to 1 equiv of 8-methoxyquinoline, 3% 7-chloro-8-methoxyquinoline was produced. On the other hand, upon iodination under the same conditions as employed for chlorination and bromination, only 7-iodo-8-methoxyquinoline was found. It should also be noted that no halogenation occurred in solvents that were considerably more basic than the substrate, 8-methoxyquinoline. Thus it can be concluded that, on monohalogenation of 8-quinolinol in strong base, the orientation of chloro and bromo substituents to the 7 position and iodo to the 5 position is due to the influence of the anionic form of the substrate. Where the substrate cannot form an anion, as in 8-methoxyquinoline, no halogenation takes place under any of the strongly basic conditions studied. Polyhalogenation was also observed, but this occurred only under acidic and neutral conditions.

Where direct comparisons of the halogenation of 8-quinolinol[3,4] with 8-methoxyquinoline can be made, the rate of halogenation of 8-quinolinol is greater than or equal to that for the methoxyquinoline under comparable conditions; however, the purity of the halogenomethoxy compounds was usually greater owing to the fact that only one monohalogenated isomer formed, and that dihalogenation did not occur until the monohalogenation reaction went to completion. Iodination of 8-methoxyquinoline with elemental iodine did not take place under any of the conditions employed. These results did not parallel those observed for 8-quinolinol.[3,4]

When the ratio of chlorine to 8-methoxyquinoline in 93% sulfuric acid was greater than 1:1, an unknown product was detected of which the retention time of the trimethylsilyl derivative was between that of 8-methoxyquinoline and 5-chloro-8-methoxyquinoline. It was not further characterized. The bromination of 1 equiv of 8-methoxyquinoline with 2 and 3 equiv of NBS in 93% sulfuric acid was also complicated by the appearance of side products. In the reaction of 1 equiv of 8-methoxyquinoline with 2 equiv of NBS in 93% sulfuric acid at ambient temperatures, 10% 5-bromo-8-methoxyquinoline, 30% 5,7-dibromo-8-methoxyquinoline, 45% 5-bromo-8-quinolinol, and 15% 5,7-dibromo-8-quinolinol were formed. The same re-

(1) This work was supported in part by the U. S. Public Health Service, Grant No. AI-05808.

(2) H. Gershon, M. W. McNeil, and A. T. Grefig, *J. Org. Chem.*, **34**, 3268 (1969).

(3) H. Gershon and M. W. McNeil, *ibid.*, **35**, 3993 (1970).

(4) H. Gershon, M. W. McNeil, and S. G. Schulman, *ibid.*, **36**, 1616 (1971).

action in the presence of 3 equiv of NBS yielded 57% 5,7-dibromo-8-methoxyquinoline, 11% 5-bromo-8-quinolinol, 22% 5,7-dibromo-8-quinolinol, and 7 and 11% of two uncharacterized hydroxyquinolines. When the temperature was kept at 40–60° using 2 equiv of NBS, the resulting mixture was composed of 6% 5-bromo-8-methoxyquinoline, 63% 5,7-dibromo-8-methoxyquinoline, 15% 5-bromo-8-quinolinol, and 16% 5,7-dibromo-8-quinolinol. At the same temperature, when 3 equiv of NBS was used, the products consisted of 57% 5,7-dibromo-8-methxyquinoline, 39% 5,7-dibromo-8-quinolinol, and 4% 5,6,7-tribromo-8-quinolinol.

To determine whether the demethylated products resulted from the conditions of the work-up of the sulfuric acid solutions, 5-bromo- and 5,7-dibromo-8-methoxyquinolines were treated in 93% sulfuric acid, in the absence of NBS, in the same manner as in a bromination reaction. Only starting materials were detected, and the mechanism of the demethylation reaction is not clear.

On comparing chlorine with NCS and bromine with NBS as halogenating agents in reactions with 8-methoxyquinoline, the elemental halogen reacted more rapidly and was more controllable than the *N*-halosuccinimides, as evidenced by the greater yields of products and fewer by-products. Increasing the reaction temperature increased the reaction rates, as expected. In addition, products were formed in certain instances which were not found when ambient temperatures were employed. The explanation of the greater reactivity of chlorine and bromine as compared with NCS and NBS may reside in the fact that chlorination and bromination with the elemental halogen are accompanied by the release of equivalent amounts of hydrogen halides. This aids in protonating the quinolines to enhance reactivity and control orientation, and may be especially significant where weakly acidic and weakly basic solvents as well as aprotic solvents are employed.

A striking difference between 8-quinolinol and 8-methoxyquinoline is the failure of 8-methoxyquinoline to form appreciable quantities of 7-chlorinated and 7-brominated derivatives with 1 equiv of halogenating agent per 1 equiv of substrate, even in solvents in which the neutral and protonated species derived from 8-quinolinol are halogenated in the 7 as well as in the 5 positions. This observation can be explained on the basis of the difference in hydrogen bonding properties between the 8-hydroxy and 8-methoxy compounds. In 8-quinolinol, the greatest amount of 7-chlorination and 7-bromination occurs in those species in which the amount of electronic charge released to the 7 position from the hydroxyl group is greatest. In the anions, the electron density is obviously substantial, and chlorination and bromination occur at these sites almost exclusively. However, in the neutral species derived from 8-quinolinol, substantial 7-halogenation also occurs, with the greatest ratio of 7-halogeno to 5-halogeno compound occurring in the most basic solvent, diethylamine, which is also the best hydrogen-bond acceptor. The lowest ratio of 7-halogenation to 5-halogenation occurs in the poorest hydrogen bond acceptor, chloroform. Even in the protonated species, some 7-halogenation occurs in acetic acid in which the carbonyl oxygen atom is a fair hydrogen bond acceptor, but in sulfuric acid, which is an extremely poor hydrogen bond acceptor solvent, no 7-chlorination or 7-bromination takes place. Apparently, there is a good degree of correlation between the degree of removal of the proton from the phenolic oxygen atom and the yield of 7-chlorinated and 7-brominated products. The effect of replacement of the phenolic proton of 8-quinolinol by a methyl group, as in 8-methoxyquinoline, is not only to prevent dissociation from the phenolic site, but also to eliminate hydrogen bonding of the phenolic proton with the solvent. Thus, the neutral 8-methoxyquinoline molecule does not have the appreciable excess π charge density at the 7 position which occurs in 8-quinolinol in hydrogen bond acceptor solvents, and electrophilic chlorination and bromination are directed exclusively to the 5 position. The lack of reactivity of 8-methoxyquinoline in the most basic solvents, aqueous NaOH and diethylamine, relative to that in pyridine and chloroform, is possibly due to the loss of hydrogen bonding with the by-product succinimide or hydrogen halide of the heterocyclic nitrogen. This hydrogen bonding interaction introduces positive charge into the quinoline ring, much the same as protonation does, and favors halogenation at the 5 position. In strongly basic, high-dielectric solvents, the hydrogen halide or succinimide formed as a result of the reaction is not constrained to the site of the heterocyclic nitrogen and probably reacts preferentially with the solvent.

It can be concluded that the single most important factor which influences electrophilic halogenation of both 8-quinolinol and its methyl ether is the prototropic form of the substrate. Both hydrogen bonding and dielectric properties of the solvent are of consequence in the orientation of chlorine and bromine, as a result of electrophilic halogenation of 8-quinolinol.

Experimental Section[5]

Halogenation of 8-Methoxyquinoline in Different Solvents with Elemental Halogen and *N*-Halosuccinimide.—8-Methoxyquinoline was halogenated in the same manner as described for 8-quinolinol in ref 3.

7-Chloro-8-methoxyquinoline.—To a solution of sodium (0.69 g, 0.03 g-atom) in 30 ml of mehanol was added 7-chloro-8-quinolinol[2] (5.4 g, 0.03 mol). Methyl iodide (5.7 g, 0.04 mol) was added dropwise with stirring at room temperature. Upon completion of addition of the methyl iodide, the temperature was raised slowly to 40–45° and stirring was continued overnight. The temperature was brought to boiling for 1 hr, after which the methanol was removed by flash evaporation, and the residue was dissolved in a mixture of chloroform and H_2O. After removal of the aqueous layer, the chloroform solution was washed three times with 5% aqueous KOH followed by H_2O until the washings were no longer alkaline. The chloroform was evaporated, and the residue was steam distilled. The product (3.0 g, 52%) was obtained by filtration and drying at 60° overnight, mp 73–75°. An analytical sample was crystallized from aqueous ethanol, mp 75°.

(5) Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Gas chromatography was performed on a Varian Aerograph Model 1200 gas chromatograph with a flame ionization detector to which was attached a Varian Aerograph Model 20 recorder. All of the compounds in this study (Table I) were separated on a 1% Apiezon L column under the conditions described previously.[2] Silylations were carried out according to the procedure of Klebe, *et al.*[6] 8-Methoxyquinoline and its 5-chloro, 5-bromo, 5-iodo, 5,7-dichloro, 5,7-dibromo, and 5,7-diiodo analogs were prepared by the method of Gershon and Parmegiani.[7]

(6) J. F. Klebe, H. Finkbeiner, and D. M. White, *J. Amer. Chem. Soc.*, **88**, 3390 (1966).

(7) H. Gershon and R. Parmegiani, *Contrib. Boyce Thompson Inst.*, **24**, 33 (1968).

TABLE I

ELECTROPHILIC HALOGENATION OF 8-METHOXYQUINOLINE WITH *N*-HALOSUCCINIMIDE AND WITH ELEMENTAL HALOGEN IN DIFFERENT SOLVENTS AT AMBIENT TEMPERATURES AND AT 40–60°[a]

Halogenating medium	Molecular ratio of halogen/substrate	Temp, °C	Products, %							
			N-Chlorosuccinimide				Chlorine			
			8-MeOx[b]	5-Cl-8-MeOx	7-Cl-8-MeOx	5,7-Cl_2-8-MeOx	8-MeOx	5-Cl-8-MeOx	7-Cl-8-MeOx	5,7-Cl_2-8-MeOx
H_2SO_4, 93%	1	Ambient	83	17	0	0	3	97	0	0
	2	Ambient	0	96	0	4	0	10	0	90[d]
	3	Ambient	0	90	0	10	0	0	0	95[e]
	1	40–60	0	100	0	0				
	2	40–60	0	80	0	20				
	3	40–60	0	33	2	65				
Acetic acid, glacial	1	Ambient	100	0	0	0	1	99	0	0
	2	Ambient	100	0	0	0	0	100	0	0
	3	Ambient	100	0	0	0	0	100	0	0
	1	40–60	100	Trace[c]	0	0				
	2	40–60	0	100	0	Trace				
	3	40–60	0	45	Trace	55				
Chloroform	1	Ambient	100	0	0	0	75	25	0	0
	2	Ambient	100	0	0	0	72	28	0	0
	3	Ambient	100	0	0	0	65	35	0	0
	1	40–60	100	0	0	0				
	2	40–60	77	23	0	0				
	3	40–60	65	35	0	0				
Pyridine	1	Ambient	100	0	0	0	0	97	3	Trace
	2	Ambient	100	0	0	0	0	27	0	73
	3	Ambient	100	0	0	0	0	0	0	100
	1	40–60	95	5	0	0				
	2	40–60	Trace	100	0	0				
	3	40–60	0	95	0	5				
Diethylamine	1	Ambient	100	0	0	0	100	0	0	0
	2	Ambient	100	0	0	0	100	0	0	0
	3	Ambient	100	0	0	0	100	0	0	0
	1	40–60	100	0	0	0				
	2	40–60	100	0	0	0				
	3	40–60	100	0	0	0				
NaOH, 10%	1	Ambient	100	0	0	0	100	0	0	0
	2	Ambient	100	0	0	0	100	0	0	0
	3	Ambient	100	0	0	0	100	0	0	0
	1	40–60	100	0	0	0				
	2	40–60	100	0	0	0				
	3	40–60	100	0	0	0				
			N-Bromosuccinimide				Bromine			
			8-MeOx	5-Br-8-MeOx	7-Br-8-MeOx	5,7-Br-8-MeOx	8-MeOx	5-Br-8-MeOx	7-Br-8-MeOx	5,7-Br_2-8-MeOx
H_2SO_4, 93%	1	Ambient	Trace	100	0	0	0	100	0	0
	2	Ambient	0	10	0	30[f]	0	100	0	0
	3	Ambient	0	0	0	57[g]	0	100	0	0
	1	40–60	0	100	0	0				
	2	40–60	0	6	0	63[h]				
	3	40–60	0	0	0	57[i]				
Acetic acid, glacial	1	Ambient	12	88	0	0	5	95	0	0
	2	Ambient	0	100	0	0	0	100	0	0
	3	Ambient	0	100	0	0	0	100	0	0
	1	40–60	9	91	0	0				
	2	40–60	0	90	0	10				
	3	40–60	0	10	0	90				
Chloroform	1	Ambient	100	0	0	0	0	100	0	0
	2	Ambient	0	100	0	0	0	100	0	0
	3	Ambient	0	100	0	0	0	100	0	0
	1	40–60	36	64	0	0				
	2	40–60	0	100	0	0				
	3	40–60	0	100	0	0				
Pyridine	1	Ambient	85	15	0	0	0	100	0	0
	2	Ambient	10	90	0	0	0	100	0	0
	3	Ambient	0	100	0	0	0	100	0	Trace

TABLE I
(*Continued*)

Halogenating medium	Molecular ratio of halogen/substrate		Products, %: *N*-Bromosuccinimide 8-MeOx	5-Br-8-MeOx	7-Br-8-MeOx	5,7-Br-8-MeOx	Bromine 8-MeOx	5-Br-8-MeOx	7-Br-8-MeOx	5,7-Br_2-8-MeOx
Pyridine	1	40–60	85	15	0	0				
	2	40–60	0	100	0	0				
	3	40–60	0	100	0	0				
Diethylamine	1	Ambient	100	0	0	0	100	0	0	0
	2	Ambient	100	0	0	0	100	0	0	0
	3	Ambient	100	0	0	0	100	0	0	0
	1	40–60	100	0	0	0				
	2	40–60	100	0	0	0				
	3	40–60	100	0	0	0				
NaOH, 10%	1	Ambient	100	0	0	0	100	0	0	0
	2	Ambient	100	0	0	0	100	0	0	0
	3	Ambient	100	0	0		100	0	0	0
	1	40–60	100	0	0	0				
	2	40–60	100	0	0	0				
	3	40–60	100	0	0	0				
			N-Iodosuccinimide 8-MeOx	5-I-8-MeOx	7-I-8-MeOx	5,7-I_2-6-MeOx	Iodine 8-MeOx	5-I-8-MeOx	7-I-8-MeOx	5,7-I_2-8-MeOx
H_2SO_4, 93%	1	Ambient	2	0	98	0	100	0	0	0
	2	Ambient	0	0	65	35	100	0	0	0
	3	Ambient	0	0	20	80	100	0	0	0
	1	40–60	0	0	100	0				
	2	40–60	0	0	40	60				
	3	40–60	0	0	5	95				
Acetic acid, glacial	1	Ambient	40	0	60	0	100	0	0	0
	2	Ambient	0	0	100	0	100	0	0	0
	3	Ambient	0	0	100	0	100	0	0	0
	1	40–60	17	0	83	0				
	2	40–60	Trace	0	100	0				
	3	40–60	0	0	100	0				
Chloroform	1	Ambient	100	0	0	0	100	0	0	0
	2	Ambient	100	0	0	0	100	0	0	0
	3	Ambient	100	0	0	0	100	0	0	0
	1	40–60	100	0	0	0				
	2	40–60	70	0	30	0				
	3	40–60	65	0	35	0				
Pyridine	1	Ambient	100	0	0	0	100	0	0	0
	2	Ambient	100	0	0	0	100	0	0	0
	3	Ambient	100	0	0	0	100	0	0	0
	1	40–60	100	0	0	0				
	2	40–60	100	0	0	0				
	3	40–60	100	0	0	0				
Diethylamine	1	Ambient	100	0	0	0	100	0	0	0
	2	Ambient	100	0	0	0	100	0	0	0
	3	Ambient	100	0	0	0	100	0	0	0
	1	40–60	100	0	0	0				
	2	40–60	100	0	0	0				
	3	40–60	100	0	0	0				
NaOH, 10%	1	Ambient	100	0	0	0	100	0	0	0
	2	Ambient	100	0	0	0	100	0	0	0
	3	Ambient	100	0	0	0	100	0	0	0
	1	40–60	100	0	0	0				
	2	40–60	100	0	0	0				
	3	40–60	100	0	0	0				

[a] All results are the average of three runs with an average deviation of ±10%. [b] 8-MeOx = 8-methoxyquinoline. [c] <1%. [d] Trace of unknown compound, the trimethylsilyl derivative of which had a retention time between that of 8-methoxyquinoline and 5-chloro-8-methoxyquinoline. [e] The unknown compound of *d* was 5% of the total. [f] The mixture also contained 45% 5-bromo-8-quinolinol and 15% 5,7-dibromo-8-quinolinol. [g] The mixture also contained 7% of an unknown compound, the trimethylsilyl derivative of which had a retention time shorter than that of the trimethylsilyl derivative of 8-quinolinol; 11% 5-bromo-8-quinolinol; 3% of a second unknown compound, the trimethylsilyl derivative of which had a retention time between that of the trimethylsilyl derivative of 5-bromo-8-quinolinol and 5,7-dibromo-8-methoxyquinoline; and 22% 5,7-dibromo-8-quinolinol. [h] The mixture also contained 15% 5-bromo-8-quinolinol and 16% 5,7-dibromo-8-quinolinol. [i] The mixture also contained 39% 5,7-dibromo-8-quinolinol and 4% 5,6,7-tribromo-8-quinolinol.

Anal. Calcd for $C_{10}H_8ClNO$: C, 62.03; H, 4.16; Cl, 18.31; N, 7.23. Found: C, 62.11; H, 4.19; Cl, 18.31; N, 7.40.

7-Bromo-8-methoxyquinoline was prepared in 56% yield in the same manner as the chloro analog, mp 79.5–80.5°. The analytical sample (aqueous ethanol) melted at 80–81°.

Anal. Calcd for $C_{10}H_8BrNO$: C, 50.45; H, 3.39; Br, 33.56; N, 5.88. Found: C, 50.45; H, 3.38; Br, 33.57; N, 5.83.

7-Iodo-8-methoxyquinoline was prepared in 88% yield in the same manner as the chloro analog, mp 112–113°. The analytical sample (aqueous ethanol) melted at 113°.

Anal. Calcd for $C_{10}H_8INO$: C, 42.13; H, 2.85; I, 44.52; N, 4.91. Found: C, 42.34; H, 2.79; I, 44.24; N, 5.07.

2-Acetamido-4-bromophenyl Acetate.—A mixture of 2-acetamidophenyl acetate[8] (32.7 g, 0.3 mol), NBS (53.4 g, 0.3 mol), and 1000 ml of chloroform was heated under reflux with stirring until a clear solution was formed. After cooling, the chloroform solution was washed several times with a dilute $NaHSO_3$ solution, and the chloroform was removed by flash evaporation. The product (31.5 g, 56%) was recrystallized from benzene twice and melted at 148–150°.[9]

Anal. Calcd for $C_{10}H_{10}BrNO_3$: C, 44.14; H, 3.70; Br, 29.37; N, 5.15. Found: C, 44.02; H, 3.75; Br, 29.31; N, 5.22.

6-Bromo-8-quinolinol.—A mixture of 2-acetamido-4-bromophenyl acetate (39 g, 0.14 mol), 30 ml of concentrated sulfuric acid, arsenic oxide (30 g, 0.13 mol), and glycerol (50 g, 0.54 mol) was heated under reflux for 3 hr. After cooling, it was diluted with H_2O and adjusted to pH 6 with concentrated NH_4OH. The suspension was steam distilled and yielded 10.5 g (33%) of product, mp 143–145° (lit.[10a] mp 138–139°).

5,6,7-Tribromo-8-quinolinol.—6-Bromo-8-quinolinol (2.24 g, 0.01 mol) was dissolved in 50 ml of acetic acid. A solution of 3.3 g (0.02 mol) of bromine in 25 ml of acetic acid was added dropwise with stirring. The reaction was complete when the color of the bromine persisted for 10 min. The solution was poured into 1000 ml of H_2O, decolorized with $NaHSO_3$, and brought to pH 7 with Na_2CO_3, and $NaHCO_3$. The product was removed by filtration and washed with H_2O. A yield of 3.5 g (92%) of compound, mp 182–185°, was obtained. Recrystallization from aqueous alcohol raised the melting point to 188–190° (lit.[10b] mp 192°).

Registry No.—8-Methoxyquinoline, 938-33-0; 7-chloro-8-methoxyquinoline, 36748-98-8; 7-bromo-8-methoxyquinoline, 36748-99-9; 7-iodo-8-methoxyquinoline, 36749-00-5; 2-acetamido-4-bromophenyl acetate, 36749-01-6; *N*-chlorosuccinimide, 128-09-6; *N*-bromosuccinimide, 128-08-5; *N*-iodosuccinimide, 516-12-1; 5-Cl-8-MeOx, 17012-44-1; 5,7-Cl_2-8-MeOx, 17012-48-5; 5-Br-8-MeOx, 10522-47-1; 5,7-Br_2-8-MeOx, 17012-49-6; 5-I-8-MeOx, 17012-46-3; 5,7-I_2-8-MeOx, 17012-50-9.

(8) W. Theilacker, *Chem. Ber.*, **71**, 2065 (1938).

(9) R. K. Smalley and H. Suschitzky, *J. Chem. Soc.*, 5571 (1963). This compound was mentioned but not characterized.

(10) (a) A. R. Pinnington, Ph.D. Thesis, Oxford, 1954, in R. G. W. Hollingshead, "Oxine and Its Derivatives," Vol. III, Butterworths, London, 1956, p 674; (b) p 751.

The Electrophilic Addition of Bromine to *cis*- and *trans*-1,2-Dimethylcyclopropane

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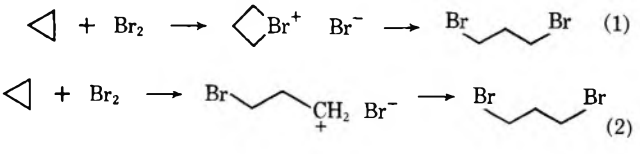
Under polar conditions, the major pathway for bromination of both *cis*- and *trans*-1,2-dimethylcyclopropane opens the less substituted carbon–carbon bond nonstereospecifically. Addition to the more substituted bond, also nonstereospecific, occurs to the extent of about 8% in both cases. A major component of the cis, but not the trans, reaction mixture is the hydride-shift product, 1,2-dibromo-2-methylbutane. The intermediates responsible for product formation are best described as nonbridged, secondary carbonium ions, because of the nonstereospecific nature of the reaction. The distribution of products is discussed in terms of steric and stereoelectronic effects.

Stereochemistry[2,3] and regiochemistry[4] have only recently been brought to bear on the mechanistic problems offered by the addition of electrophiles to cyclopropane rings. The bulk of the work to date has consisted in the addition of electrophiles to polycyclic compounds that contain a three-membered ring, and examination of the diastereomeric products in order to deduce the stereochemistry of the reaction. No single preferred stereochemical path has emerged from these studies, although individual cases have been thoroughly examined. No simple monocyclic cyclopropane has yet been studied with the view of determining the stereochemistry of the reaction.[5] To this end, we have studied the bromination of *cis*- and *trans*-1,2-dimethylcyclopropane. The products of this reaction offer a simple handle on the stereochemistry of the halogen addition. This study supplies the cyclopropane analog of the bromination of *cis*- and *trans*-2-butene. Conformational constraints on the conceivable acyclic carbonium ion intermediates produced from these monocyclic systems are much less important than those on the ions produced from the previously studied polycyclic compounds,[2,3] since the residual rings present in these latter ions prohibit free rotation. The structure of the monocyclic systems therefore has little bias on the stereochemical outcome. Furthermore, the availability of both the cis and the trans isomers enables the reaction to be studied from two diastereomeric directions. Such a comparison is not possible in polycyclic systems without using trans-fused rings.

The primary objective of these stereochemical studies is to distinguish between mechanistic pathways that involve cyclic bromonium ions (eq 1, analogous to



(1) This work was supported by the Petroleum Research Fund, administered by the American Chemical Society (Grant 2970-AC4,5) and by the National Science Foundation (Grant GP-22942).

(2) S. J. Cristol, W. Y. Lim, and A. R. Dahl, *J. Amer. Chem. Soc.*, **92**, 4013 (1970); S. J. Cristol, J. K. Harrington, T. C. Morrill, and B. E. Greenwald, *J. Org. Chem.*, **36**, 2773 (1971), and references cited therein.

(3) J. B. Lambert, R. D. H. Black, J. H. Shaw, and J. J. Papay, *J. Org. Chem.*, **35**, 3214 (1970), and references cited therein.

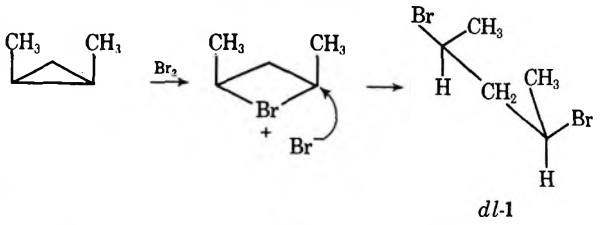
(4) N. C. Deno and W. E. Billups, *Chem. Commun.*, 1387 (1970).

(5) Since the preparation of this manuscript, the addition of bromine to the 1,2-diphenylcyclopropanes has been described; see R. T. LaLonde, P. B. Ferrara, and A. D. Debboli, Jr., *J. Org. Chem.*, **37**, 1094 (1972).

bromination of ethylenes) and pathways that involve open-chain carbonium ions (eq 2). Protonated cyclopropane rings, which are related to the bridged bromonium ion of eq 2, have been implicated in the addition of HX to the parent unsubstituted system[6a] and to some substituted cyclopropanes.[4,6b] Exclusively open-chain carbonium ions, however, have been indicated in the bromination of bicyclo[3.1.0]hexane.[3] Scheme I illus-

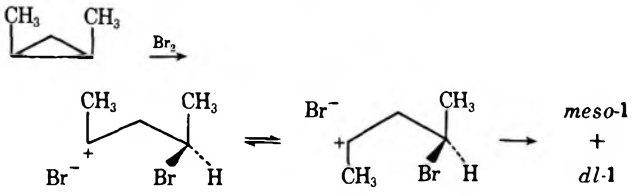
Scheme I

1,2 bond scission, bromonium ion



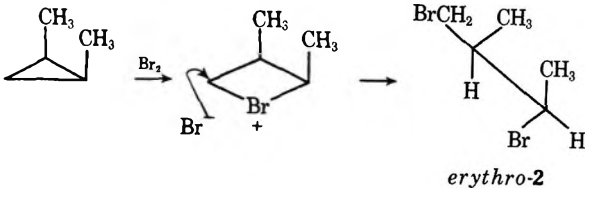
dl-1

1,2 bond scission, carbonium ion



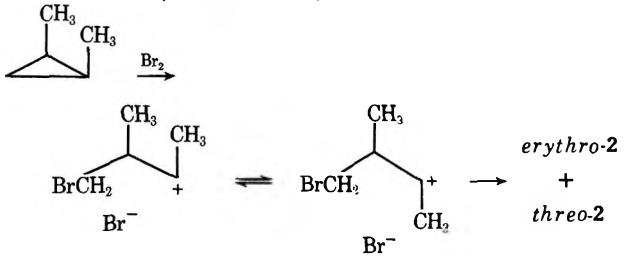
meso-1 + *dl*-1

2,3 bond scission, bromonium ion



erythro-2

2,3 bond scission, carbonium ion



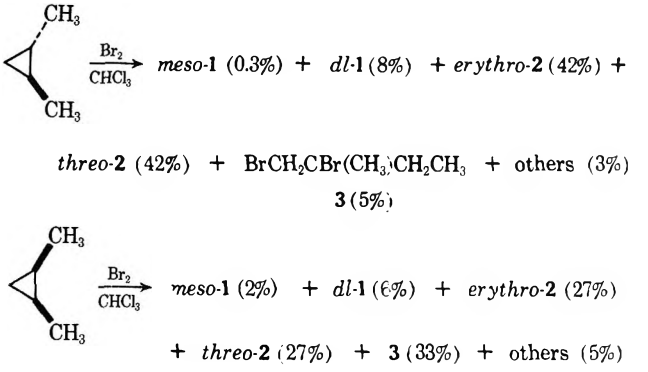
erythro-2 + *threo*-2

trates the various reaction pathways for the addition of bromine to *cis*-1,2-dimethylcyclopropane. Electrophilic addition can occur on either the more substituted 1,2 bond or on the less substituted 2,3 bond. According to the bromonium ion mechanism,[7] the cis compound would give entirely *dl*-2,4-dibromopentane (*dl*-1) from 1,2 bond scission and entirely *erythro*-1,3-dibromo-2-methylbutane (*erythro*-2) from 2,3 bond scission (Scheme I). The trans compound, on the other hand, would give *meso*-1 and *threo*-2 by these routes, respectively. According to the open-chain carbonium ion mechanism, with free rotation about carbon–carbon bonds, the cis compound would give both *meso*- and *dl*-1 from 1,2 bond scission and both *erythro*- and *threo*-2 from 2,3 bond scission. The trans compound would give a similar mixture. The procedure we followed in this study was to allow the substrates to react with bromine under polar conditions, to identify the products, and to draw mechanistic conclusions from comparisons with the expectations illustrated in Scheme I.

Results

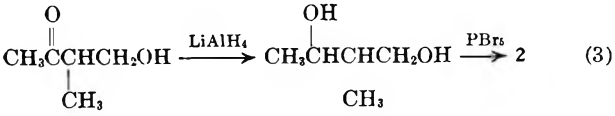
The polar addition of molecular bromine to the dimethylcyclopropanes was carried out at −60° in chloroform with the exclusion of light. The reaction mixtures were concentrated and the excess bromine was removed without altering the product composition (see Experimental Section). Each component of the reaction mixture was collected and compared with authentic material that had been independently synthesized. The product distributions, rounded off to the nearest percentage point, are given in Scheme II as the mean

Scheme II



of 25 measurements on a total of three independent brominations. The mean deviation is roughly 3–5% of each given value.

An authentic sample of 1,2-dibromo-2-methylbutane (**3**) was readily prepared by the addition of bromine to 2-methyl-1-butene. The major product, 1,3-dibromo-2-methylbutane (**2**), was obtained as a 50:50 mixture of erythro and threo stereoisomers by the method of eq 3. No attempt was made to identify the isomers

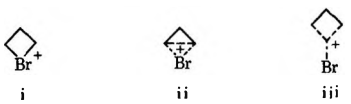


(3)

separately, because the reaction mixtures contained nearly equal amounts of each. The minor product, 2,4-dibromopentane (**1**), was obtained by bromination of the corresponding diol. Since the product mixtures from the halogenations of the dimethylcyclopropanes contained unequal amounts of the stereoisomeric meso and *dl* forms of **1**, an unambiguous isomeric assignment was necessary. The protons on the 3 carbon are chemically nonequivalent in the meso form (the AB portion of an ABX_2 spectrum), whereas those in the *dl* form are

(6) (a) C. J. Collins, *Chem. Rev.*, **69**, 543 (1969); (b) J. Mockus, Ph.D. Dissertation, Pennsylvania State University, 1971.

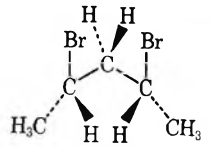
(7) We have chosen to represent the bromonium ions by structure i, although ii and iii are legitimate alternative representations. The differences have been discussed elsewhere.[8]



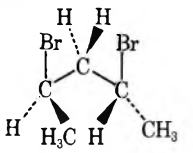
i ii iii

(8) G. A. Olah, J. M. Bollinger, Y. K. Mo, and J. M. Brinich, *J. Amer. Chem. Soc.*, **94**, 1164 (1972).

chemically equivalent (the AA′ portion of an AA′XX′ spectrum). The complexity of the 3-proton resonance



meso-1



dl-1

therefore serves as an indicator of the isomeric identity. The spectra of the 2,4-dichloropentanes have been fully analyzed in this manner.[9] Our spectra of the dibromopentanes closely resembled those of the dichloropentanes; so a parallel assignment could be made. The *dl*/meso product distributions given in Scheme II follow from the AB pattern for the 3-protons in the meso isomer and the AA′ pattern (not A_2) for the 3-protons in the *dl* isomer. Over 95% of the product mixture has therefore been identified. The remaining 3–5% was present as several short retention time products.

Discussion

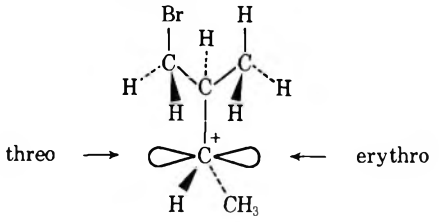
Three conclusions may be drawn from the observed product distributions. (1) Both the major (2) and minor (1) "1,3"-dibromides are formed in a nonstereospecific fashion from both the cis and the trans substrates. (2) The major path of ring opening involves scission of the less substituted carbon–carbon bond. (3) The major difference between the cis and trans reaction product mixtures is the large amount of 1,2-dibromide observed in the former case. In the folllowing discussion, we will endeavor to draw mechanistic conclusions from these three observations.

Stereochemistry.—The bromonium ion mechanism (Scheme I) requires that the cis substrate form exclusively *dl*-1 and *erythro*-2, and that the trans substrate form *meso*-1 and *threo*-2. In fact, both *cis*- and *trans*-1,2-dimethylcyclopropane form similar mixtures of 1 (with a large predominance of the *dl* form) and of 2 (with almost equal amounts of the diastereomers). These observations are consistent with the open carbonium ion mechanism, and rule cut the bromonium ion mechanism in the product-forming step. The question as to whether a bromonium ion precedes the open carbonium ion will be discussed later.

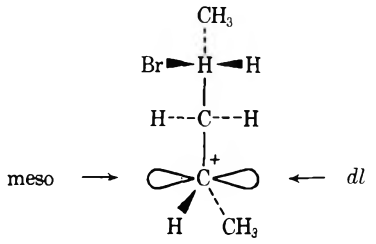
The *dl*/meso and erythro/threo ratios may be explained if it is assumed that the first-formed open carbonium ion from either the cis or the trans starting materials proceeds rapidly to the most stable conformational form. Scheme III depicts the most stable conformational form for both 2,3 and 1,2 bond scission. In the best conformer obtained by scission of the less substituted (2,3) bond, the two faces of the carbonium ion experience approximately equivalent amounts of steric crowding. The bromide ion may therefore enter equally well from either direction to form similar amounts of the erythro and threo products. In the best conformer formed from scission of the more substituted (1,2) bond, the bromine atom shields the face that would produce the meso product. As a result, there is a predominance of *dl*-1. This latter conclusion is based on the assumption that the nonbonded interactions of the bromine atom are less than those of the methyl

SCHEME III

2,3 bond scission



1,2-bond scission



group. If the reverse were true, the methyl group would shield the side of the carbonium ion that produces the *dl* isomer, and the meso form would predominate. The larger size of the methyl group has been well documented in both cyclohexyl and acyclic systems (*cf.* the *A* value of 1.8 for methyl *vs.* 0.5 for bromine).

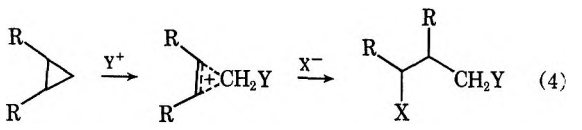
Regiochemistry.—The addition of electrophiles to substituted cyclopropane rings has a regiochemical complication not present in additions to substituted ethylenes. According to the Markovnikov rule for addition to unsymmetrically substituted double bonds, the electrophile adds to the less substituted carbon atom to form the more stable carbonium ion. Cyclopropane rings substituted at only one carbon atom would follow a similar rule. Electrophilic addition to cyclopropane rings with two substituted carbon atoms, however, can occur by two distinct modes to produce a secondary carbonium ion, as illustrated in Scheme I for the present system (1,2 and 2,3 bond scission). Ring opening of the 1,2-dimethylcyclopropanes occurs predominantly by cleavage of the less substituted (2,3) cyclopropane bond. Deno and Mockus[6] have also observed that addition of HX usually occurs between the most and the least substituted bond in cyclopropanes bearing several alkyl substituents.

Three explanations for the observed regiochemistry in the electrophilic ring-opening of disubstituted cyclopropanes are possible. (1) For steric reasons, the electrophile always attacks the least substituted carbon atom, by analogy with nucleophilic opening of substituted epoxides. Such steric effects have been established in the electrophilic cleavage of organomercurials.[10] Attack at the least substituted atom would result in cleavage of the bond to the most substituted neighbor in order to produce the most stable carbonium ion. Without knowing the stereochemistry of the initial addition,[2] we cannot assess this possibility. (2) Addition might be favored at the less substituted ring atom because this atom in fact is more nucleophilic. In order for the more substituted atom to be less nucleophilic, the methyl groups would have to be electron withdrawing. Again, this explanation cannot be tested

(9) P. E. McMahon and W. C. Tincher, *J. Mol. Spectrosc.*, **15**, 180 (1965).

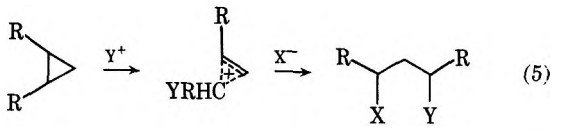
(10) F. R. Jensen and B. Rickborn, "Electrophilic Substitution of Organomercurials," McGraw-Hill, New York, N. Y., 1968, Chapters 3 and 4.

by the present experiments. (3) Mockus[6b] has suggested that the observed orientation of HX addition arises because it produces the most stable corner-protonated carbonium ion (Y = H in eq 4). Initial



(4)

addition to either of the more substituted carbon atoms, it is suggested,[6b] would produce a less stable corner-protonated species (eq 5). If the corner-

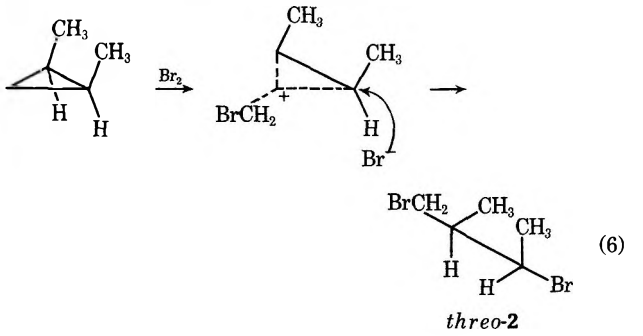


(5)

protonated ions in eq 4 and 5, however, are written with three-center bonds like that in structure iii of ref 7, there is no obvious advantage of one over the other; **4** contains a methyl and two secondary centers, **5** one

4 **5**

secondary and two primary centers. We therefore do not believe that the observed regiochemistry can be offered as evidence for corner-halogenated intermediates. Corner-halogenated ions can be firmly rejected as the product-forming intermediate. The observed regiochemistry requires that the initial attack of halogen occur at the least substituted position. The resulting species should decompose stereospecifically, with the cis starting material giving *threo*-**2**, and the trans giving *erythro*-**2** (eq 6). The observed nonstereospecificity of the reaction rules out such a process.

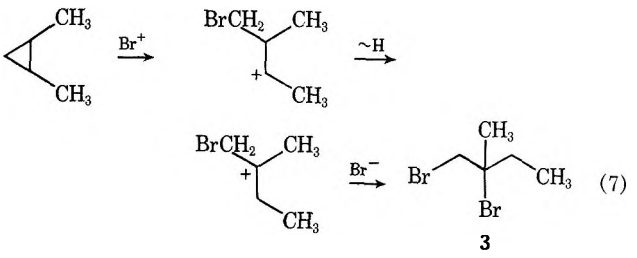


(6)

threo-**2**

Addition of bromine to bicyclo[3.1.0]hexane occurs with predominant opening of the more substituted carbon–carbon bond,[3] in contrast to these monocyclic systems. It may be that an additional effect that can alter the regiochemistry is present in polycyclic systems containing strained single bonds. In monocyclic systems, we favor either the steric or electronic effects described above, although no decision can be made until more subtle stereochemical experiments are performed.

Hydride Shift.—The final point that warrants consideration is the relative amount of the 1,2-dibromide (**3**) found in the cis and trans reaction mixtures. Whereas the cis compound produces 33% of this material on bromination, the trans compound produces only 5%. Because the 1,2 compound is formed at the expense of 1,3-dibromo-2-methylbutane (**2**), rather than of 2,4-dibromopentane (**1**), it is presumed to be a by-product of the 2,3-bond scission path (Scheme I). A simple mechanism for its production involves a hydride shift from the first-formed carbonium ion (eq 7). The

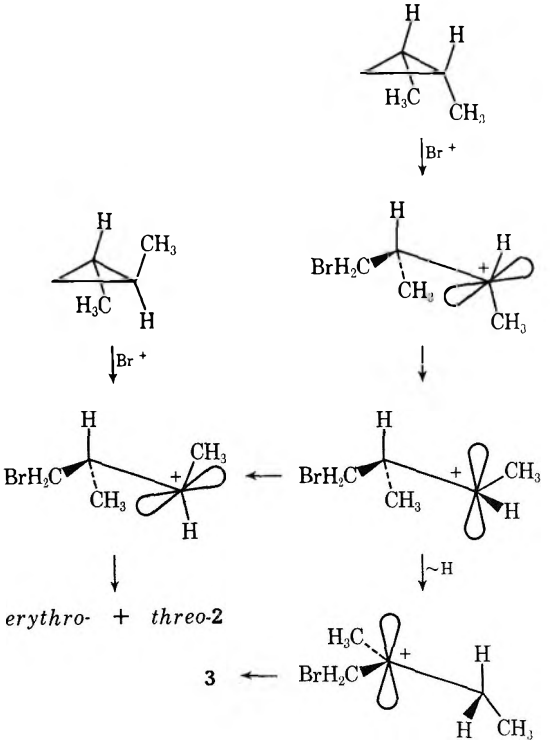


(7)

3

question remains as to why the hydride shift occurs more easily in the carbonium ion formed from the cis compound than that from the trans compound. Halogenation of the trans compound produces a carbonium ion that is very close to the most stable conformation depicted in Scheme III. The hydride shift must occur when the carbon–hydrogen bond is parallel to the empty p lobe. The carbonium ion that is initially formed from the trans compound would have to be converted into a much less favorable conformation in order to permit the hydride shift (Scheme IV). The

Scheme IV



cis compound, on the other hand, produces a carbonium ion that must undergo rotation about the bond connecting the methyl-substituted carbon atoms before achieving the most stable conformation. As it undergoes this rotation, the ion passes through the geometry that is most favorable for the hydride shift (Scheme IV). Therefore, part of the first-formed cis carbonium ion is shunted to the more stable tertiary carbonium ion by a hydride shift (eq 7) before it can achieve the best conformation that eventually would lead to the erythro/

threo mixture of compound 2. The argument illustrated in Scheme IV is not dependent on the stereochemistry of the initial electrophilic addition.

Summary.—*cis*- and *trans*-1,2-dimethylcyclopropane add bromine under polar conditions to form a mixture of 2,4-dibromopentane (1), 1,3-dibromo-2-methylbutane (2), and 1,2-dibromo-2-methylbutane (3). The major product (2) is formed in a 1:1 mixture of the erythro and threo isomers, and the minor product (1) is formed with an excess of *dl* over meso for both the cis and trans starting materials. The nonstercospecificity of the reaction precludes bridged bromonium ions from being the product-forming intermediate. The erythro/threo and *dl*/meso ratios can be readily explained in terms of steric effects on the approach of the nucleophile to the intermediate open carbonium ion. The preference for 2,3 ring scission over 1,2 ring scission is not fully explained, but can arise from steric or electronic effects during the initial electrophilic attack. The significant amount of hydride-shift product found in the cis, but not the trans, reaction mixture arises because the initially formed open carbonium ion in the cis case must rotate through a conformation favorable to hydride shift before it arrives at the conformationally more stable form that gives the 1,3 products. The initially formed ion from the trans compound is already very close to the stablest (product-forming) conformation.

Although our results require open carbonium ions as the product-forming intermediates, we cannot exclude an initial formation of edge- or corner-brominated ions that rapidly decompose to the open carbonium ions. Under conditions favorable to long-lived cations, Olah and coworkers[8] attempted to generate trimethylene halonium ions, analogous to those depicted in Scheme I, from a variety of precursors. In no case were they successful. Four-membered bromonium ions as a class therefore appear to be unstable and might have eluded our experiment. The SbF_5–FSO_3H–SO_2 experiments, however, cannot be brought directly into the context of our experiments, since the 1,3-type products, such as those observed by us, are also not stable in superacid media. Thus 2,4-dibromopentane was observed by Olah, *et al.*, to rearrange to a 1,4 product.[8] It therefore does not follow that because trimethylene bromonium ions are unstable under highly acidic conditions that they would also be unstable under our conditions and therefore be possible initial intermediates. Nonetheless, the early stages of the reaction coordinate of this reaction, particularly the stereochemistry of the initial bromination, merit further investigation.

Experimental Section

Nmr measurements were made on Varian Models T-60 and A-60 spectrometers. Infrared spectra were recorded on a Beckman IR-5 spectrophotometer. Gas chromatographic analyses and separations were carried out on F & M Model 700 instruments, using a 0.25 in. × 6 ft column containing 10% Carbowax 20M on Chromosorb W 60–80.

Brominations.—The reaction was carried out in a dark room with illumination exclusively by a red light. The appropriate 1,2-dimethylcyclopropane (1.4 g, 0.015 mol, Chemical Samples Co.) and 25 ml of $CHCl_3$ were placed in an aluminum foil wrapped 100-ml round-bottomed flask and cooled to −78° with Dry Ice–acetone. A solution of bromine (3.2 g, 0.02 mol) in 25 ml of $CHCl_3$ was placed in a 20-mm test tube with a break seal at the bottom and likewise cooled to −78°. The temperature was allowed to equilibrate to −60°, at which temperature the Br_2–$CHCl_3$ solution was frozen. The test tube was removed from its bath and wiped clean, and the glass seal was broken over the dimethylcyclopropane solution. The bromine solution dropped in slowly as the $CHCl_3$ melted. The reaction occurred rapidly and smoothly. After addition was complete, the flask was warmed first to −30°, then to room temperature. Vpc traces during this procedure showed that the reaction mixture did not change with time. The crude mixture was washed with 10 × 100 ml of H_2O to remove any excess Br_2. The solution was dried overnight ($MgSO_4$), filtered, and stripped of solvent under aspirator pressure. The residue was used directly for analysis and collection of components. The products were stable to reaction conditions.

2,3-Dibromopentane (1) was prepared by treatment of 2,4-pentanediol (Aldrich Chemical Co.) with PBr_5 according to the procedure of Pritchard and Vollmer.[11]

1,3-Dibromo-3-methylbutane (2).—4-Hydroxy-3-methyl-2-butanone (Aldrich Chemical Co.) was reduced with $LiAlH_4$ by standard procedures, and the resulting 2-methyl-1,3-butanediol was treated with PBr_5 to give a 1:1 mixture of the erythro and threo isomers of 2, as judged by vpc and nmr analysis.

1,2-Dibromo-2-methylbutane (3) was prepared by treatment of 2-methyl-1-butene (Analabs, Inc.) with Br_2 in $CHCl_3$ at 0°.

Registry No.—*cis*-1,2-Dimethylcyclopropane, 930-18-7; *trans*-1,2-dimethylcyclopropane, 2402-06-4.

(11) J. G. Pritchard and R. L. Vollmer, *J. Org. Chem.*, **28**, 1545 (1963).

Solvolysis of Cyclopropyl Halides. III. 2,3-Diphenylcyclopropyl Chlorides[1]

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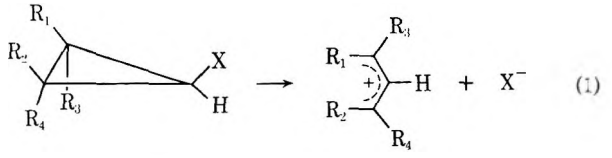
Received June 2, 1972

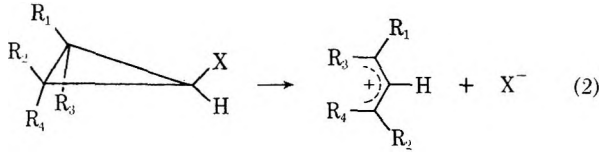
The isomeric 2,3-diphenylcyclopropyl chlorides were prepared by the addition of dichlorocarbene to *cis*- and *trans*-stilbene followed by controlled potential electrolytic reduction. Solvolysis of *cis*-2,*cis*-3-diphenylcyclopropyl chloride, *trans*-2,*trans*-3-diphenylcyclopropyl chloride, and *cis*-2,*trans*-3-diphenylcyclopropyl chloride in acetic acid afforded as the sole product α-phenylcinnamyl acetate. The kinetic data are considered in terms of the two alternate disrotatory modes of ring opening in solvolysis.

The solvolyses of cyclopropyl derivatives proceed with concerted ring opening to form allylic products in most cases.[3] The process has been characterized as an electrocyclic transformation, the stereochemistry of which is governed by orbital symmetry considerations proposed by Woodward and Hoffmann.[4] Both kinetic[5-7] and product[8] studies are in support of this proposal. The ring-opening process involves cleavage of the 2,3 bond with rotation about the 1,2 and 1,3 bonds to bring the substituents into a coplanar configuration. The predicted stereochemistry involves a disrotatory ring opening with the substituents cis to the leaving group rotating inwardly and the substituents trans to the leaving group rotating outwardly as shown in eq 1.



(1)

Based on a consideration of steric effects in the transition state of the ring-opening process it has been suggested[5] that under certain circumstances, the disrotatory mode of ring opening may proceed with the opposite rotations, as shown in eq 2. This alternate mode of disrotatory opening has been proposed for the solvolysis of *cis*-2-phenylcyclopropyl chloride.[5]



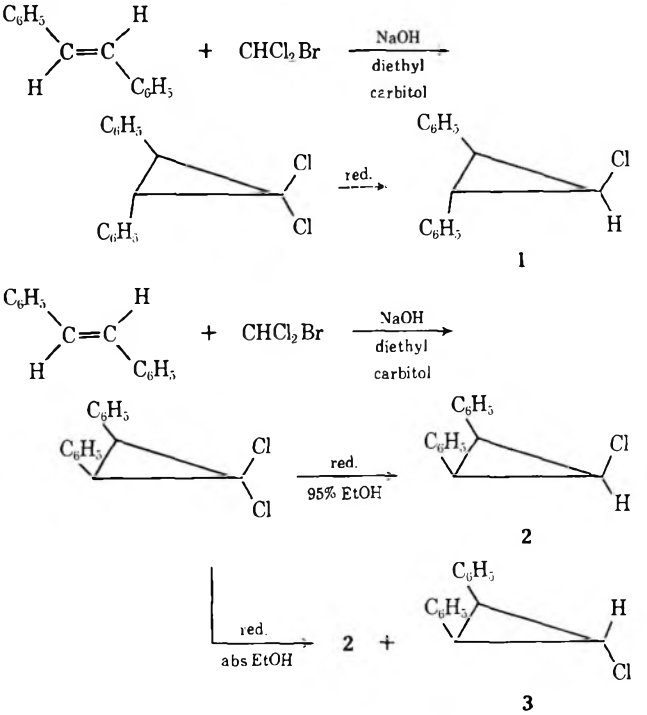
(2)

The isomeric 2,3-diphenylcyclopropyl chlorides have been prepared in order to establish the mode of ring opening in the presence of very large steric and conjugative effects.

Results

The isomeric diphenylcyclopropyl chlorides were prepared by the addition of dichlorocarbene to *cis*- or *trans*-stilbene followed by controlled-potential electrolysis of the intermediate cyclopropyl dichloride. The carbene addition to the deactivated double bond of stilbene was accomplished by generation of dichlorocarbene from the haloform and sodium hydroxide in diethylcarbitol.[9] The partial reduction of the cyclopropyl dichlorides to the monochlorides was best accomplished by controlled-potential electrolysis[10] at a massive mercury electrode in ethanol with tetraethylammonium bromide as the supporting electrolyte.

1,1-Dichloro-*trans*-2,3-diphenylcyclopropane on reduction afforded *cis*-2,*trans*-3-diphenylcyclopropyl chloride (**1**). 1,1-Dichloro-*cis*-2,3-diphenylcyclopropane on reduction in 95% ethanol afforded *cis*-2,*cis*-3-diphenylcyclopropyl chloride (**2**), whereas on reduction in ab-



1 **2** **3**

(1) Presented in part: J. W. Hausser and J. T. Uchic, Abstracts, Central Regional Meeting of the American Chemical Society, Columbus, Ohio, June 1970, p 49.

(2) Taken from the Ph.D. Thesis of J. T. Uchic, Duquesne University, 1970.

(3) J. D. Roberts and V. C. Chambers, *J. Amer. Chem. Soc.*, **73**, 5034 (1951).

(4) R. B. Woodward and R. Hoffmann, *ibid.*, **87**, 395 (1965); see also R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970.

(5) J. W. Hausser and N. J. Pinkowski, *J. Amer. Chem. Soc.*, **89**, 6981 (1967); J. W. Hausser and M. J. Grubber, *J. Org. Chem.*, **37**, 2648 (1972).

(6) C. H. DePuy, L. G. Schnack, J. W. Hausser, and W. Wiedemann, *J. Amer. Chem. Soc.*, **87**, 4006 (1965); C. H. DePuy, L. G. Schnack, and J. W. Hausser, *ibid.*, **88**, 3343 (1966); U. Schollkopf, *Angew. Chem., Int. Ed. Engl.*, **7**, 588 (1968); J. A. Langrebe and L. W. Becker, *J. Org. Chem.*, **33**, 1173 (1968); W. E. Parham and K. S. Yong, *ibid.*, **35**, 683 (1970); W. M. Hospool, R. G. Sutherland, and B. J. Thompson, *J. Chem. Soc. C*, 1554 (1971).

(7) P. v. R. Schleyer, G. W. Van Dine, U. Schöllkopf, and J. Paust. *J. Amer. Chem. Soc.*, **88**, 2868 (1966); P. v. R. Schleyer, Abstracts, 20th National Organic Symposium of the American Chemical Society, Burlington, Vt., June 1967, p 8; P. v. R. Schleyer, W. F. Sliwinski, G. W. Van Dine, U. Schollkopf, J. Paust, and K. Fellenberger, *J. Amer. Chem. Soc.*, **94**, 125 (1972); W. F. Sliwinski, T. M. Su, and P. v. R. Schleyer, *ibid.*, **94**, 133 (1972).

(8) P. v. R. Schleyer, T. M. Su, M. Saunders, and J. C. Rosenfeld, *J. Amer. Chem. Soc.*, **91**, 5174 (1969).

(9) G. C. Robinson, *Tetrahedron Lett.*, 1749 (1965).

(10) L. Meites, *Anal. Chem.*, **27**, 1116 (1955).

TABLE I

SOLVOLYSES OF THE ISOMERIC 2,3-DIPHENYLCYCLOPROPYL CHLORIDES IN ACETIC ACID[a]

Compd	Temp, °C	k_1, sec^{-1}	k_{rel}	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, eu
cis-2,*cis*-3-Diphenyl-	95.2	$3.59 \pm 0.08 \times 10^{-6}$	1.0	31.2	+0.8
cyclopropyl Chloride	110.1	$2.01 \pm 0.01 \times 10^{-5}$			
(2)	125.3	$9.68 \pm 0.09 \times 10^{-5}$			
trans-2,*trans*-3-Diphenyl-	40.0	$3.64 \pm 0.02 \times 10^{-5}$			
cyclopropyl Chloride	50.1	$1.23 \pm 0.02 \times 10^{-4}$			
(3)	65.1	$6.25 \pm 0.06 \times 10^{-4}$			
	95.2[b]	1.15 ± 10^{-2}	3200	23.1	−5.1
cis-2,*trans*-3-Diphenyl-	65.1	$9.20 \pm 0.06 \times 10^{-6}$			
cyclopropyl Chloride	80.4	$5.16 \pm 0.08 \times 10^{-5}$			
(1)	95.2	$2.46 \pm 0.04 \times 10^{-4}$	69	26.3	−4.1

[a] Anhydrous acetic acid with 0.04 *M* sodium acetate. [b] Extrapolated value.

solute ethanol it afforded a mixture of **2** and *trans*-2,-*trans*-3-diphenylcyclopropyl chloride (**3**).

Partial separation of **2** and **3** is possible by column chromatography. From the nmr spectrum and thin layer chromatography the only contaminant in **3** was shown to be the isomer **2**. The labile character of **3** required the utilization of freshly prepared material for the kinetic experiments. The other isomers, **1** and **2**, are stable and do not require special precautions.

The stereochemical assignments for **1–3** are based primarily on the assignment of chemical shifts and coupling constants in their nmr spectra.[11] The assignments were also consistent with the expected product distributions from the reduction.[12]

The product of solvolyses of **1–3** in acetic acid was shown to be the thermodynamically favored *trans*-α-phenylcinnamyl acetate (**4**) in all cases.[13] The starting chlorides **1–3** were recovered from the solvolysis mixture and were shown to be unchanged.

The kinetics of solvolysis of **1–3** were followed by formation of **4** as seen in the ultraviolet spectrum of the reaction mixture. The kinetics of the solvolysis of the samples of **3** containing the isomer **2** could be followed owing to the large difference in rates of **2** and **3**. The kinetics in all cases are first order in the chloride. The first-order rate constants and the activation parameters are presented in Table I.

Discussion

The relative rates presented in Table I are consistent with a disrotatory ring-opening process. Compound **3** in the disrotatory opening has both phenyl groups moving outwardly and away from each other. Compound **3** would be expected to have the fastest rate of solvolysis. Compound **1** in a disrotatory ring opening necessarily has one phenyl group moving inwardly and one phenyl group moving outwardly. The steric effect experienced by the phenyl group moving inwardly would prevent the phenyl group from assuming complete coplanarity,[14] resulting in less stabilization of the developing cation and a slower rate of solvolysis than compound **3**.

(11) J. D. Graham and M. T. Rogers, *J. Amer. Chem. Soc.*, **84**, 2249 (1962); G. L. Closs, R. A. Moss, and J. J. Coyle, *ibid.*, **84**, 4985 (1962); D. J. Patel, M. E. H. Howden, and J. D. Roberts, *ibid.*, **85**, 3218 (1963).

(12) A. J. Fry and R. H. Moore, *J. Org. Chem.*, **33**, 1283 (1968).

(13) The predicted allylic products would be expected to isomerize to the trans isomer under the reaction conditions. See V. Buss, R. Gleiter, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **93**, 3927 (1971), and references cited therein.

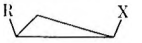
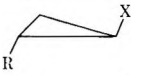
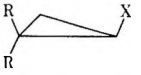
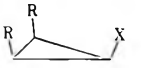
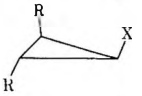
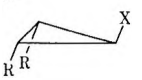
(14) A. F. Hegarty and J. E. Dubois, *Tetrahedron Lett.*, 4839 (1968); J. E. Dubois and A. F. Hegarty, *J. Chem. Soc. B*, 638 (1969).

Compound **2** in the predicted mode of disrotatory opening (eq 1) would experience severe steric compression owing to the rotation of both phenyl groups inwardly and toward each other. The rate of solvolysis of **2** by this mode must necessarily be very slow. It is for this compound that the alternate mode of ring opening would seem to have an advantage.

Additional insight into the mode of disrotatory opening for compound **2** can be gained from a consideration of the relative rates of the complete series of phenyl-substituted cyclopropyl chlorides and methyl-substituted cyclopropyl tosylates shown in Table II.

TABLE II

RELATIVE RATES OF SOLVOLYSIS OF SUBSTITUTED CYCLOPROPYL DERIVATIVES IN ACETIC ACID

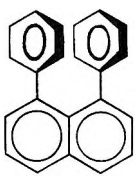
Compd	Relative rate[a] (R = C_6H_5; X = Cl)	Relative rate[b] (R = CH_3; X = OTs)
	10^{-4} [c]	0.18
	1.0[d]	1.0
	4[d]	24
	6[d]	75
	145	0.39
	10,000	81
	465,000	6700

[a] At 95°. [b] From ref 7. [c] Estimated from the rate of the tosylate given in ref 3. [d] Extrapolated from the data given in ref 5.

If the predicted mode of disrotatory ring opening (eq 1) is assumed to be operative in all cases, it would seem that compound **2** is solvolyzing much faster than expected. While **2** is slower than **1** and **3**, it is faster than the monophenyl-substituted cyclopropyl chlorides and 2,2-diphenylcyclopropyl chloride. If the corresponding *cis*-2,*cis*-3-dimethylcyclopropyl tosylate in the series of methyl-substituted cyclopropyl tosylates reported by Schleyer[7,8] is compared to **2** in the phenyl-substituted cyclopropyl chloride series, an apparent discrepancy is observed. *cis*-2,*cis*-3-Dimethylcyclopropyl tosylate shows a very minor acceleration over

the unsubstituted parent compound, suggesting that the steric effect of the methyl groups virtually cancels the inductive stabilization, whereas **2** shows a very large acceleration in spite of the substantial steric and inductive effects.

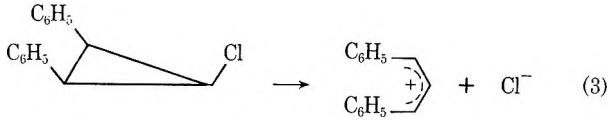
An estimate of the magnitude of the steric effect in the solvolysis of **2** can be made by a consideration of model compounds. The phenyl groups in 1,8-diphenylnaphthalene (**5**) are forced out of conjugation



5

with the naphthalene ring and assume a conformation parallel to each other.[15] The substitution on one of the phenyl groups in **5** allows resolution of optical isomers. The rate of racemization is related to the barrier for just one phenyl group to become coplanar with the naphthalene ring. The calculated barrier is 16 kcal/mol.

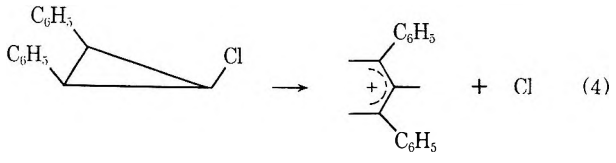
The transition state for solvolysis of **2** by the predicted mode (eq 3) of ring opening would involve ap-



(3)

proach to the same configurational requirements as **5**. While the geometry of the cation in eq 3 is not rigid as is **5**, there still should be an appreciable loss in conjugative stabilization in the transition state owing to the crowding of the phenyl groups, and in fact an inductive destabilization should result. The fact that **2** solvolyzes faster than monophenylcyclopropyl chlorides and even 2,2-diphenylcyclopropyl chloride calls into question this mode of ring opening for **2**. If the normal mode of ring opening is operative (eq 1), the acceleration must come from a very large strain in the ground state to compensate for the high strain in the transition state.

The alternate mode of disrotatory ring opening (eq 2) suggested as a possibility for *cis*-2-phenylcyclopropyl chloride appears to be the most reasonable proposal to account for the unexpectedly fast rate of solvolysis of **2**. By this mode, shown in eq 4, it is possible to generate a



(4)

degree of stability through conjugative overlap of the phenyl groups with the developing cation as the phenyl groups move outwardly and away from each other. While the favored mode (eq 1) is operative in most cases, the resulting loss of phenyl conjugation in **2**, and possibly *cis*-2-phenylcyclopropyl chloride, should make the less favored alternate mode (eq 2) more competitive. This alternate mode allows a gain in conjugation to offset the energy sacrificed in going to this mode.

The analogous methyl-substituted cyclopropyl derivatives studied by Schleyer[7,8] clearly follow the normal mode (eq 1) in all cases. This difference may lie in the fact that while the methyl group has a large steric effect, it lacks the coplanarity demand required by the phenyl group for stabilization. If the allylic cations that are kinetically formed in the solvolyses are stable at low temperatures in strong acid media it should be possible to decide on the mode of ring opening.

Experimental Section

General.—All melting points are corrected. The microanalyses were performed by Dr. Alfred Bernhardt, Max Planck Institute, Mulheim (Ruhr), Germany, and Crobaugh Laboratories, Cleveland, Ohio. Infrared spectra were recorded on a Beckman IR-20 spectrophotometer using the potassium bromide pellet technique. The ultraviolet spectra were recorded on a Cary Model 14 recording spectrophotometer. For the kinetic runs, a Beckman DU spectrophotometer was employed for absorbance measurements at 253 nm. The nuclear magnetic resonance spectra were obtained with a Varian Model A-60 spectrometer. Chemical shifts in carbon tetrachloride solution are expressed in parts per million (δ) from an internal tetramethylsilane standard.

1,1-Dichloro-*trans*-2,3-diphenylcyclopropane.—In a 100-ml flask was placed a mixture of *trans*-stilbene (0.10 mol, 18.0 g), 25 ml of diethylcarbitol, and sodium hydroxide pellets (0.40 mol, 16.0 g). The contents were vigorously stirred while the bath was heated. When the temperature approached 50°, bromodichloromethane[16] (0.15 mol, 24.6 g) was added in one portion. After 1 hr, the bath reached a maximum temperature of 79°, and then slowly dropped to 74° at the end of the 3.3-hr reaction period. The reaction mixture was poured into water, acidified with dilute hydrochloric acid, and extracted into ether (600 ml). The ether layer was washed with a dilute sodium bicarbonate solution and water, dried ($MgSO_4$), and concentrated. The diethylcarbitol was removed at 65–75° (1 mm) and the unreacted stilbene was removed at 100° (0.1 mm). The residue was transferred to a molecular still and the dichlorocyclopropane was collected as a yellow, viscous liquid, bp 85–90° (0.05–0.01 mm). Redistillation gave 13.7 g (52%) of the desired product as a viscous liquid. Crystallization could be effected from 95% ethanol, and several recrystallizations afforded a white solid: mp 39–41° (lit.[17] mp 39–40.5°); uv max (95% C_2H_5OH) 22 nm (ϵ 17,520), 254 (435), 260 (494), and 264 (382); ir (KBr) 703 (vs), 769 (s), 873 (s), and 1040 cm^{-1} (w); nmr (CCl_4) δ 3.10 (s, 2) and 7.25 ppm (s, 10).

1,1-Dichloro-*cis*-2,3-diphenylcyclopropane.—To a one-neck, 200-ml flask was added 50 ml of diethylcarbitol and sodium hydroxide pellets (0.4 mol, 16.0 g). The reaction mixture was heated to 50° and a mixture of *cis*-stilbene (0.11 mol, 20.0 g) and bromodichloromethane (0.20 mol, 32.8 g) was added in one portion. After 35 min the bath reached a maximum temperature of 80°, and the bath temperature dropped to near 50° at the end of the 2-hr reaction period. The reaction mixture was worked up in essentially the same manner as for the preparation of 1,1-dichloro-*trans*-2,3-diphenylcyclopropane. The product fraction (5.5 g, 19%) was collected at 60–70° (0.1 mm). Crystallization could be effected from 95% ethanol. Several recrystallizations from 95% ethanol gave analytically pure material: mp 56–57°; uv max (95% C_2H_5OH) 225 nm (ϵ 11,580), 253 (450), 259 (476), 262 (470), 265 (385), 267 (shoulder, 325), and 272 (shoulder, 183); ir (KBr) 708 (vs), 730 (m), 762 (s), 771 (s), 819 (vs), 1043 (m), and 1052 cm^{-1} (m); nmr (CCl_4) δ 3.16 (s, 2) and 6.77–7.25 (m, 10).

Anal. Calcd for $C_{15}H_{12}Cl_2$: C, 68.46; H, 4.60. Found: 68.20; H, 4.86.

Controlled-Potential Electrolyses.—Controlled-potential electrolysis experiments were carried out in a double-diaphraghm cell described by Meites.[10] The anode was a strip of bare silver

(15) H. O. House, W. J. Campbell, and M. Gall, *J. Org. Chem.*, **35**, 1815 (1970).

(16) M. S. Kharasch, B. M. Kuderna, and W. Urry, *ibid.*, **13**, 895 (1948).

(17) D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Yick-Pui Mui, H. D. Simmons, Jr., A. J. H. Treiber, and S. R. Dowd, *J. Amer. Chem. Soc.*, **87**, 4259 (1965).

wire 30–40 in. in length, while the cathode was a massive pool of metallic mercury. The reference electrode was an 8-in. length of bare silver wire isolated from the sample compartment by placing it in an immersion tube which contained the ethanolic solution of the electrolyte.

cis-2,*trans*-3-Diphenylcyclopropyl Chloride (1).—Into the electrolysis vessel was added a 0.13 *M* solution of tetraethylammonium bromide in 95% ethanol. A 1.0-g sample of 1,1-dichloro-*trans*-2,3-diphenylcyclopropane was added and the electrolysis was carried out at −1.65 to −2.0 V *vs.* the silver wire reference. When the current reading dropped to 1–2 mA, the electrolysis was stopped. The catholyte was removed and poured into water (500 ml), and the solution was refrigerated overnight. A white solid was obtained which was filtered, washed with water, and air dried to give 0.8 g (92%) of the monochlorocyclopropane, mp 62.5–63.5°. Recrystallization from 95% ethanol gave an analytical sample: mp 63–64°; uv max (95% C_2H_5OH) 222 nm (ϵ 19,440), 260 (697), 266 (681), and 273 (438); ir (KBr) 704 (s), 750 (s), 764 (s), and 1015 cm^{-1} (w); nmr (CCl_4) δ 2.61 (apparent d, 2), 3.40 (doublet of doublets, 1), and 7.0–7.28 ppm (m, 10).

Anal. Calcd for $C_{15}H_{13}Cl$: C, 78.77; H, 5.73; Cl, 15.50. Found: C, 78.86; H, 5.78; Cl, 15.47.

cis-2,*cis*-3-Diphenylcyclopropyl Chloride (2).—The reduction of a 1.0-g sample of 1,1-dichloro-*cis*-2,3-diphenylcyclopropane was performed in the electrolysis cell. The solution of tetraethylammonium bromide in 95% ethanol was approximately 0.1 *M*. The reduction was carried out at −1.65 to −2.0 V *vs.* the silver wire reference. The catholyte was poured into 600 ml of water and refrigerated overnight. Filtration gave a solid material which was washed with water and air dried to afford 0.7 g (80%) of product. Recrystallization from 95% ethanol gave 0.5 g of colorless crystals, mp 69–71°. An analytical sample was obtained by vacuum sublimation: mp 71–72°; uv max (95% C_2H_5OH) 220 nm (shoulder, ϵ 13,690), 255 (433), 261 (473), 265 (shoulder, 392), and 272 (shoulder, 191); ir (KBr) 694 (s), 711 (vs), 728 (s), 778 (s), 788 (s), and 1030 cm^{-1} (w); nmr (CCl_4) δ 2.43 (d, J = 7.5 Hz, 2), 3.60 (t, J = 7.5 Hz, 1), and 6.8–7.17 ppm (m, 10).

Anal. Calcd for $C_{15}H_{13}Cl$: C, 78.77; H, 5.73; Cl, 15.50. Found: C, 78.64; H, 5.86; Cl, 15.43.

trans-2,*trans*-3-Diphenylcyclopropyl Chloride (3).—A 0.7-g sample of 1,1-dichloro-*cis*-2,3-diphenylcyclopropane was reduced in the electrolysis vessel using absolute ethanol as the solvent at −1.65 to −1.9 V *vs.* the silver wire reference. The reaction period was about 2 hr. The catholyte was poured into water and extracted with ether. The ether layer was washed several times with water, dried ($MgSO_4$), and concentrated to a viscous oil consisting of a 1:3 mixture of 1-chloro-*trans*-2,*trans*-3-diphenylcyclopropane (3) and 1-chloro-*cis*-2,*cis*-3-diphenylcyclopropane (2) as determined by nmr.

Reduction of two 1-g samples of 1,1-dichloro-*cis*-2,3-diphenylcyclopropane in absolute ethanol followed by refrigeration of the oily mixtures gave, after filtration, 1.2 g of solid, mp 66–70°. On extraction of the filtrates with ether, 0.5 g of an oily material was obtained. Chromatography of the oil on neutral alumina, using low-boiling petroleum ether as the eluent, afforded about 0.1 g of liquid shown by nmr to be 1-chloro-*trans*-2,*trans*-3-diphenylcyclopropane: nmr (CCl_4) δ 2.81 (d, J = 4.5 Hz), 3.71 (t, J = 4.5 Hz), and 6.73–7.45 ppm (m).

Kinetics of 1 and 2.—A 0.020 *M* solution of the cyclopropyl chloride in acetic acid (0.040 *M* in sodium acetate) was prepared. Samples of 1.5–2.0 ml were sealed in ampoules and placed in the bath controlled to ±0.1°. The ampoules were removed and a 1-ml portion was diluted to 50 ml with 95% ethanol. A 1-ml portion of each initially diluted sample was further diluted with 9 ml of 95% ethanol and the absorbance was read at 253 nm. Since the cyclopropyl chlorides had a small absorbance at 253 nm, standard curves were necessary. Two infinity determinations were taken after 10 half-lives for each run.

Kinetics of Solvolysis of 3.—Since an isomerically pure sample of 1-chloro-*trans*-2,*trans*-3-diphenylcyclopropane was not practically obtainable, the solvolyses were performed using a mixture of 1-chloro-*cis*-2,*cis*-3- and 1-chloro-*trans*-2,*trans*,3-diphenylcyclopropane. A 0.014–0.040-g sample was dissolved in 2 ml of acetic acid (0.040 *M* in sodium acetate). About 1.0–1.5 ml of the solution was injected into a 2-ml vial capped with a rubber septum. A 50-μl Hamilton syringe was used to remove samples. At the start of a run, two 30-μl portions of the solvolysis mixture were diluted to 25 ml with 95% ethanol and the absorbance was read at 253 nm. Samples of 30 μl were removed at appropriate intervals, diluted, and read. Several infinity determinations were taken after 8 half-lives for each run.

Registry No.—1, 36611-95-7; 2, 36611-96-8; 3, 36611-97-9; 1,1-dichloro-*cis*-2,3-diphenylcyclopropane, 36611-98-0.

Acknowledgment.—This work was supported in part by the National Aeronautics and Space Administration.

Methylation of α-Chloro Ketones *via* Halohydrin Formation and Rearrangement

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A new procedure for the stereoselective introduction of an angular methyl group in two systems (1-decalone and perhydro-1-indanone) is outlined. Two monocyclic systems, cyclohexanone and 2-methylcyclohexanone, were also methylated. The sequence of reactions by which the angular methyl group was stereoselectively introduced entailed the following: the preparation of the α-chloro ketone with sulfuryl chloride, followed by its conversion to the halohydrin with methyllithium, and, lastly, transformation to the magnesium salt of the halohydrin (isopropylmagnesium bromide) followed by decomposition resulting in the production of the methylated ketone. The reaction is discussed from the synthetic and mechanistic viewpoints. The noteworthy disadvantage of the sequence is that the *trans*-methyl (angular methyl) isomers cannot be prepared; *only* the pure cis isomers can be obtained.

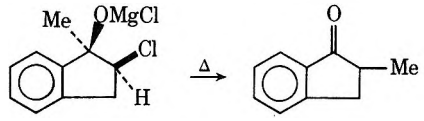
One of the more intriguing, challenging and seemingly endless areas of research in organic chemistry involves uncovering diverse approaches for the introduction of an angular methyl group into steroids and steroid-like systems. Still more challenging is to effect the *stereoselective* introduction of the angular methyl group into the system. To recount all the many excellent and efficacious methods and ingenious assaults at the problem is beyond the purpose and scope of this manuscript; suffice to mention some salient and excellent leading references.[2]

The rearrangement of the magnesium salts of halohydrins to ketones has long been known and its application to the synthesis of α-alkyl- and α-aryl-sub-

(1) From the Ph.D. Dissertation of A. C. Vitale, Adelphi University, 1970.

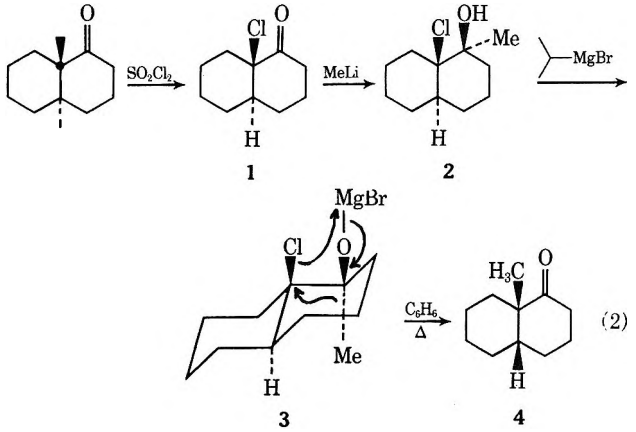
(2) R. P. Linstead, *Annu. Rep. Chem. Soc.*, **33**, 312 (1936); H. D. Springall, *ibid.*, **36**, 286 (1939); H. Wynberg, *Chem. Rev.*, **60**, 178 (1960); R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615 (1962); R. E. Ireland, D. R. Marshall, and J. W. Tilley, *J. Amer. Chem. Soc.*, **92**, 4754 (1970).

stituted ketones has also been well established.[3] More recently[4] the reaction was applied to effect various ring enlargements and it has offered a simple, new procedure. Geissman and Akawie[3] extensively studied the reaction producing ketones *via* the decomposition of the magnesium salts of halohydrins and observed that primary halides do not rearrange unless a good migrating group is involved and that secondary and tertiary halides do undergo reaction independent of the nature of the migrating group. More importantly, their stereochemical studies convincingly demonstrated that the halo and hydroxyl groups must be cis (or must attain the cis alignment in nonrigid systems) to effect the rearrangement. The trans isomer leads to extensive decomposition. Thus the results preclude an epoxide rationale for the rearrangement and leave as plausible a pinacol-type mechanism with the magnesium atom functioning as the electrophile (eq 1). In a preliminary



(1)

communication[5] the first application of the aforementioned reaction to a *stereoselective* introduction of an angular methyl group into *trans*-1-decalone was described. The sequence entailed the treatment of *trans*-1-decalone with sulfuryl chloride to yield a mixture of *cis*- and *trans*-9-chloro-1-decalone from which by a previously described procedure[6] *trans*-9-chloro-1-decalone (**1**) was isolated (10% yield). The compound **1** was then treated with methyllithium, whose expected approach to the carbonyl carbon from the least hindered side (opposite the chloro group) should produce the halohydrin **2** with the prescribed geometry necessary for the rearrangement (chloro and hydroxyl groups cis) (eq 2). Finally, the conversion of the crude halo-



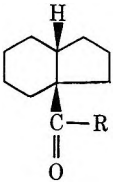
(2)

hydrin **2** to its magnesium salt **3** followed by its decomposition in refluxing benzene solution produced *only* *cis*-9-methyl-1-decalone (**4**) (58% yield based on **1**).

This manuscript presents the results of further studies of the rearrangement with the decalone system and with other simple systems.

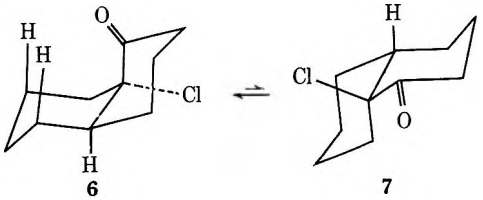
A procedural improvisation for the production of **4** entailed the direct decomposition of the intermediate lithium salt of the halohydrin **2**. The latter thus avoids the additional effort and time involved in the isolation of the halohydrin **2** and its subsequent conversion to the magnesium salt as previously reported.[5] Undoubtedly, the success of the reaction can be attributed to the known fact that the lithium ion possesses a coordination number of four,[7] thereby rendering it with electrophilic properties similar to those of the magnesium ion (coordination number four also).

Many varied attempts to separate the *cis*- from the *trans*-9-chloro-1-decalone were fruitless. Others similarly reported that their efforts were unrewarded.[6] However, after the removal of some of the pure **1** by fractional crystallization the residue composition, after its distillation, consists of approximately equal amounts of the cis and trans isomers.[6] It was therefore decided to ascertain the product(s) of the rearrangement from the *cis*-9-chloro-1-decalone utilizing the mixture of stereoisomers. Accordingly, the mixture of *cis*- and *trans*-9-chloro-1-decalone was treated with methyllithium, resulting in a stereoisomeric mixture of halohydrins which was subsequently converted to the magnesium salt with isopropylmagnesium bromide. The latter was decomposed in refluxing benzene to yield the expected **4** and methyl *cis*-hexahydroindan-3*a*-yl ketone (**5a**) both in 25% yield. The structural assignment for **5a** was based upon its conversion to, and com-



5a, R = CH_3
b, R = OH
c, R = NH_2

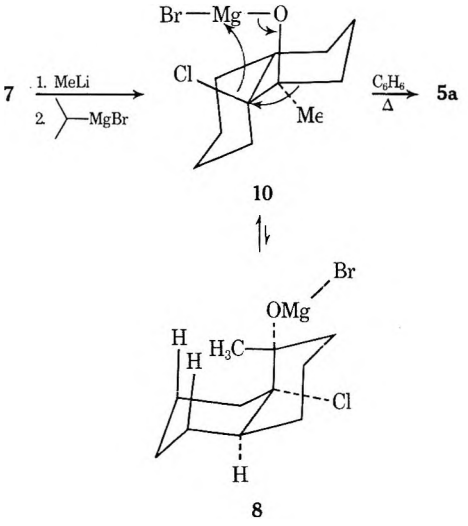
parison with an authentic sample of, the cis amide **5c**. Since pure *trans*-9-chloro-1-decalone (**1**) gave only the *cis*-9-methyl-1-decalone (**4**), it can be safely assumed that the reaction of *cis*-9-chloro-1-decalone was solely responsible for the production of **5a**. For *cis*-9-chloro-1-decalone two conformations **6** and **7** are possible.[8,9]



An examination of molecular models clearly revealed that the axial approach of methyllithium to the carbonyl carbon in **6** (side opposite the chloro group) is blocked by the two axial hydrogens shown. Thus, if formed, the cis chlorohydrin molecule (–OH and –Cl cis) will exist overwhelmingly in conformation **10**, not **8**. The latter **8** is a necessary precursor for the formation of *trans*-9-methyl-1-decalone (**9**). The conspicu-

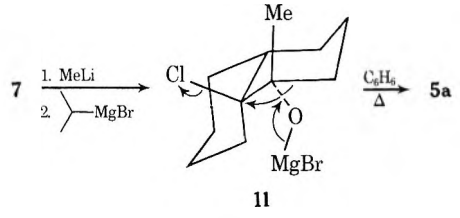
(3) M. Tiffeneau and B. Tchoubar, *C. R. Acad. Sci.*, **198**, 941 (1934); T. A. Geissman and R. I. Akawie, *J. Amer. Chem. Soc.*, **73**, 1993 (1951); A. S. Hussey and R. R. Herr, *J. Org. Chem.*, **24**, 843 (1959).
(4) A. J. Sisti, *ibid.*, **35**, 2670 (1970), and references cited therein.
(5) A. J. Sisti and A. C. Vitale, *Tetrahedron Lett.*, 2269 (1969).
(6) H. O. House and G. A. Frank, *J. Org. Chem.*, **30**, 2948 (1965).
(7) P. J. Durrant and B. Durrant, "Introduction to Advanced Inorganic Chemistry," Wiley, New York, N. Y., 1962, p 400.
(8) H. E. Zimmerman and A. Mais, *J. Amer. Chem. Soc.*, **81**, 3644 (1959).
(9) E. J. Corey, *ibid.*, **75**, 2301 (1953).

ous lack of production of **9** offered the experimental verification for the conformational preference of **10** over conformer **8**. The alternative approach of methyllithium to the carbonyl carbon in **6** is precluded as a result of the hindrance furnished by the chloro group. With regard to the conformer **7**, inspection of molecular models revealed that the approach of methyllithium to the carbonyl carbon from the equatorial side will result in the production of the halohydrin **10**, which when converted to its magnesium salt and decomposed would yield **5a** (eq 3). Alternatively, the preferred



(3)

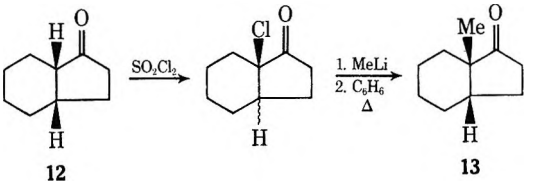
axial approach of methyllithium (conformer **7**) would yield the halohydrin **11**, whose geometry (–OH and –Cl trans) is apparently unfavorable to rearrangement. However, Geissman and Akawie[3] have demonstrated that in the cyclohexyl system a trans diequatorial alignment does not prevent the pinacol-type rearrangement, undoubtedly due to the proximity of the involved equatorial groups. Thus, the magnesium salt of the halohydrin **11** was also expected to yield **5a** as depicted (eq 4).



(4)

Therefore, it may be concluded that the rearrangement of the magnesium salts of the chlorohydrins arising from the addition of methyllithium to *cis*-9-chloro-1-decalone can produce *only* methyl *cis*-hexahydroindan-3*a*-yl ketone (**5a**) and that the lack of production of *trans*-9-methyl-1-decalone (**9**) is reasonably ascribed to the free-energy difference between conformers **8** and **10**.

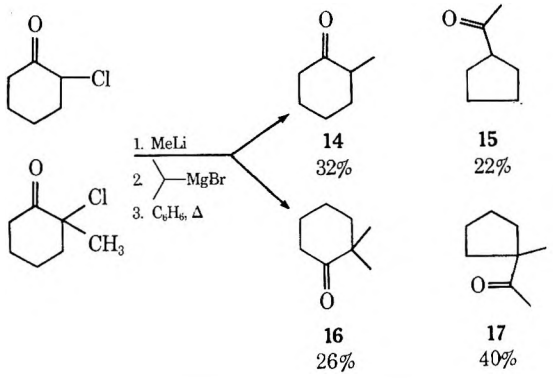
The stereoselective introduction of an angular methyl group was next attempted on the *cis*-perhydro-1-indanone (**12**) system. The ketone **12** reacted with sulfuryl chloride to yield presumably a mixture of *cis*- and *trans*-8-chlorohydrindan-1-one (cis isomer should be preferred[10]). After treatment of the chloro ketone with methyllithium at low temperatures the reaction mixture was refluxed in benzene and produced *cis*-8-methylhydrindan-1-one (**13**) in 5% yield. A large amount of nondistillable polymeric material remained after the removal of **13** (eq 5). The structural assign-



(5)

ment for **13** was based upon infrared and nmr spectra and by its conversion to a known derivative. The angularly methylated product **13** must be produced from the reaction of *trans*-8-chlorohydrindan-1-one. The approach of the methyllithium to the carbonyl carbon in the latter compound will be from the least hindered side, opposite the chloro group, resulting in the production of the lithium salt of the halohydrin with the prescribed geometry necessary for the rearrangement to occur (–OLi and –Cl cis). Thus the rearrangement will result in the production of **13**. A possible rationale for the poor yield obtained of **13** may be due to the deviation from a coplanar arrangement of the migrating methyl and departing chloro groups in the five-membered ring. This deviation should result in a relatively unfavorable energy of activation and thereby cause the poor yield of the rearrangement product. Noteworthy are the results of Mitchovitch,[11] who reported poor yields of 2-methyl- and 2-phenylcyclopentanone when 2-chlorocyclopentanone was treated with methylmagnesium and phenylmagnesium bromides followed by rearrangement of the respective magnesium salts of the resultant halohydrins. The poor results reported may also be attributed to the deviation from a coplanar arrangement of the migrating methyl (or phenyl) and departing chloro groups. No rearrangement products were isolated from the reaction of methyllithium with the cis chloro ketone.

The application of the new synthetic sequence for methylation was concluded with cyclohexanone and 2-methylcyclohexanone, the results of which are presented (eq 6).



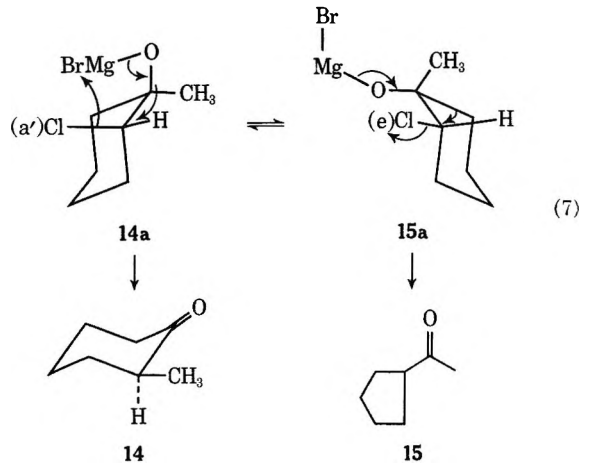
(6)

The approach of the reagent, methyllithium, to the carbonyl carbon in 2-chlorocyclohexanone should be from the side opposite the chloro group; thus one should obtain the cis halohydrin (hydroxyl and chloro groups cis) whose composition should be a mixture of two conformational isomers **14a** and **15a**. The two conformational isomers, when converted to their mag-

(10) D. W. Mathieson, *J. Chem. Soc.*, 3248 (1953).

(11) V. Mitkovitch, *C. R. Acad. Sci.*, **200**, 1601 (1935).

nesium salts and subsequently decomposed, should produce, respectively, **14** and **15** (eq 7). The pref-



(7)

erential production of **14** over **15** may be attributed to the higher relative energy level for the transition state for the formation of **15** compared to **14**. The latter may be associated with a *six-membered ring* going to a *five-membered ring*. It should be noted that the trans halohydrin (approach of methyllithium from the same side as the chloro group) can only give **15**. Vavon[12] and Tiffeneau[13] previously reported results slightly different from our own; namely, the former reported 2 parts of **14** and 1 part of **15** and the latter "mostly" **14** and a "small amount" of **15**. The discrepancies are undoubtedly attributed to the different analytical methods employed (vpc by us and separation by semicarbazones by them).[14]

When the sequence was conducted with 2-chloro-2-methylcyclohexanone (eq 6) the results favored, in this instance, the ring contraction product **17** over the product resulting from methyl migration **16**. A rationale here without definitive stereochemical information would be doubtful and therefore will be omitted at this point.

Experimental Section

General.—Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected, as are the boiling points. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Ir, uv, and nmr spectra were determined with a Perkin-Elmer Model 257 spectrophotometer, a Perkin-Elmer Model 202 ultraviolet–visible spectrophotometer, and a Varian A-60 nuclear magnetic resonance instrument, respectively. Analytical vpc analyses were performed with an F & M Scientific Model 720 dual column programmed temperature instrument and preparative vpc separations were performed with an F & M Scientific Model 776 Prepmaster Jr. A Nester/Faust Manufacturing Corp. annular teflon spinning band distillation column was used for all spinning band distillations.

9-Chloro-*trans*-1-decalone (1) was prepared according to the procedure of House,[6] mp 39–40° (lit.[6] mp 40–41°).

***cis*-9-Chloro-1-methyl-*trans*-1-decalol** (2).—Under a nitrogen atmosphere 19.0 ml of 2.05 *M* methyllithium (Alfa Inorganics, Inc.) in ether (0.031 mol + 25% excess) was added dropwise to a stirred solution of 5.8 g (0.031 mol) of **1** in 75 ml of anhydrous ether at Dry Ice–acetone temperature. The resulting mixture was stirred for 1.5 hr at Dry Ice–acetone temperature and then for 2 hr at −5°. Hydrolysis was achieved with a saturated solution of ammonium chloride and the resulting halohydrin **2** was taken up in ether, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a clear yellow oil: nmr (CCl_4) τ 8.72 (s, 3 H, $-CH_3$); ir (film) 3350 and 3460 cm^{-1} (–OH); an instantaneous precipitate with alcoholic silver nitrate.

***cis*-9-Methyl-1-decalone** (4).—A solution of 6.1 g (0.030 mol) of the crude halohydrin **2** in 100 ml of anhydrous benzene was stirred under a nitrogen atmosphere and immersed in an ice bath until the benzene solution was partially crystallized. To this partially crystallized solution 23.2 ml (0.030 mol) of 1.30 *N* isopropylmagnesium bromide[15] was added dropwise so that the temperature of the reaction vessel did not exceed room temperature. After the addition the reaction mixture was refluxed for 2 hr, then hydrolyzed with a saturated ammonium chloride solution, and the organic layer was separated, dried ($MgSO_4$), and filtered. After the removal of solvent under reduced pressure, the residue was distilled on the spinning band column. The distillate contained 2.9 g (0.018 mol) (58%) of **4**: bp 50–52° (0.3 mm) [lit.[16] bp 100° (7–8 mm)]; identification by vpc (TCEP 4-ft column, 175°) and ir, each of which gave a perfect comparison with an authentic sample;[17] nmr (CCl_4) τ 8.85 (s, 3 H, $-CH_3$); 2,4-dinitrophenylhydrazone mp 163–164° (lit.[16] mp 164–165°), and the oxime mp 109–110° (lit.[15] mp 109–110°).

In another run 23.7 ml (0.052 mol) of 2.30 *M* methyllithium was added dropwise to a stirred solution of 9.72 g (0.052 mol) of **1** in 125 ml of anhydrous ether, at Dry Ice–acetone temperature under a nitrogen atmosphere. The mixture was stirred for 1.5 hr at Dry Ice–acetone temperature and then for 2 hr at −5°. The temperature of the reaction mixture was brought slowly to room temperature and the ether was removed by distillation simultaneously with the addition of anhydrous benzene and finally refluxed for 3 hr. The reaction mixture was worked up as above and after distillation on the spinning band column there was obtained 5.4 g (0.032 mol) (62%) of **4**, bp 50–52° (0.3 mm) [lit.[16] bp 100° (7–8 mm)].

Methyl *cis*-Hexahydroindan-3*a*-yl Ketone (**5a**).—Into a flask was placed 18.7 g (0.10 mol) of an approximately equal mixture of *cis*- and *trans*-9-chloro-1-decalone[6] in 100 ml of anhydrous ether to which was added 54.4 ml of 2.30 *M* methyllithium (0.100 mol + 25% excess) in ether as described above for the preparation of **2**. The resulting 20 g of crude halohydrin was dissolved in 300 ml of anhydrous benzene and was treated with 80 ml of 1.25 *M* isopropylmagnesium bromide[15] as previously described above for the preparation of **4**. The residue was distilled on a spinning band column and afforded a first fraction containing 4.2 g (0.025 mol) (25%) of **5a** as a colorless liquid, bp 38° (0.04 mm), followed by a second fraction of 4.0 g (0.024 mol) (24%) of **4**, bp 42° (0.03 mm) [lit.[16] bp 100° (7–8 mm)].

Compound **5a** gave ir (film) 1690 cm^{-1} (C=O); nmr (CCl_4) τ 7.90 (s, 3 H, $COCH_3$); 2,4-dinitrophenylhydrazone (EtOH) mp 134–135°.

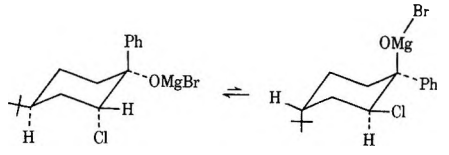
Anal. Calcd for $C_{17}H_{22}N_4O_4$: C, 58.95; H, 6.40; N, 16.17. Found: C, 59.13; H, 6.49; N, 16.26.

A haloform reaction[18] converted **5a** to *cis*-hexahydroindan-8-carboxylic acid, mp 42–43° (lit.[19] mp 43.5–44.5°); the acid was

(12) G. Vavon and A. Perlin-Borrel, *Bull. Soc. Chim. Fr.*, **51**, 994 (1932).

(13) M. Tiffeneau and B. Tchoubar, *C. R. Acad. Sci.*, **199**, 360 (1934).

(14) It is noteworthy to mention that recent work [F. G. Bordwell and K. C. Yee, *J. Amer. Chem. Soc.*, **92**, 5933 (1970)] tends to substantiate the rationale presented in eq 7. The reaction product of *trans*-4-*tert*-butyl-2-chlorocyclohexanone with phenylmagnesium bromide produced the magnesium salt of 4*e*-*tert*-butyl-2*a*-chloro-1*a*-phenylcyclohexan-1*e*-ol, which upon decomposition in refluxing xylene produced *no ring contraction product* but mostly *cis*-4*e*-*tert*-butyl-2*e*-phenylcyclohexanone. The presence of the *tert*-butyl group provides the free energy difference between the two conformers, so that the molecule exists overwhelmingly with the *tert*-butyl



group in the equatorial position. Thus the production of the ring contraction product was essentially precluded.

(15) The isopropylmagnesium bromide was prepared and titrated according to the procedure of Gilman [H. Gilman and E. Zolliner, *J. Amer. Chem. Soc.*, **51**, 1576 (1929)].

(16) W. S. Johnson, *ibid.*, **65**, 1317 (1943).

(17) Dr. W. S. Johnson graciously supplied the authentic sample containing 85% *cis*- and 15% *trans*-9-methyl-1-decalone.

(18) L. T. Sandborn and E. W. Bousquet, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 526.

(19) W. G. Dauben, J. W. McFarland, and J. B. Rogan, *J. Org. Chem.*, **26**, 297 (1961).

converted to the amide **5c** *via* the acid chloride. The *cis*-hexahydroindan-8-carboxylamide (**5c**), mp 109–110° (lit.[19] mp 109–110°), showed no depression in melting point when admixed with an authentic sample.[20]

cis-**Perhydro-1-indanone** (**12**).—The compound was prepared by the procedure described by Johnson[21] and Mathieson:[10] bp 64–65° (3.5 mm) [lit.[10] bp 72–73° (6 mm)]; ir (film) 1731 cm^{-1} (C=O); nmr (CCl_4) τ 7.7–8.0 (m, $CHCOCH_2$).

8-Chlorohydrindan-1-one.—A solution of 29 g (0.209 mol) of **12** in 160 ml of carbon tetrachloride was maintained at 19–24° while a solution of 19.7 ml (0.245 mol) of sulfuryl chloride in 85 ml of carbon tetrachloride was added dropwise with stirring over a 2-hr period. The resulting solution was stirred for 3 hr at 24° and then washed successively with water, aqueous sodium bicarbonate, and aqueous sodium chloride. The organic solution was then dried ($MgSO_4$) and the solvent was removed under vacuum. Distillation with a 10-in. Vigreux column gave a fraction of 28.4 g (0.165 mol) (79%) of 8-chlorohydrindan-1-one (presumably a cis–trans mixture): bp 62° (0.8 mm); ir (film) 1753 (C=O), 757 cm^{-1} (CCl); nmr (CCl_4) τ 7.5–7.8 (m, $COCH_2$); positive and instantaneous alcoholic silver nitrate test.

Anal. Calcd for $C_9H_{13}ClO$: C, 62.60; H, 7.54. Found: C, 62.40; H, 7.60.

cis-**8-Methylhydrindan-1-one** (**13**).—Under a nitrogen atmosphere 36.2 ml (0.0870 mol) of 2.40 *M* methyllithium in ether was added dropwise to a stirred solution of 15 g (0.0870 mol) of 8-chlorohydrindan-1-one in 200 ml of anhydrous ether at Dry Ice–acetone temperature. The resulting mixture was stirred for 1.5 hr at the latter temperature and then for 2 hr at −5°. The reaction mixture was allowed to come to room temperature and was stirred for 2 hr. The ether was removed by distillation while anhydrous benzene was simultaneously added. After the benzene reaction mixture was refluxed for 3 hr, the reaction product was worked up as described above, yielding a clear yellow, very viscous oil. Distillation with a 10-in. Vigreux column produced 0.55 g (0.0040 mol) (5%) of **13**: bp 42° (0.8 mm) [lit.[22] bp 106 (20 mm)]; ir (film) 1726 cm^{-1} (C=O); nmr (CCl_4) τ 9.0 (s, 3 H, $-CH_3$); 2,4-dinitrophenylhydrazone mp 140–141° (lit.[22] mp 140.5–141°). The residue, 12 g, was a nondistillable solid polymeric material.

2-Chloro-2-methylcyclohexanone was prepared according to the procedure described by Warnhoff,[23] bp 90–92° (25 mm) [lit.[23] bp 94–96° (27 mm)].

cis-**2-Chloro-1,2-dimethylcyclohexanol** was prepared using 15 g (0.10 mol) of 2-chloro-2-methylcyclohexanone in 100 ml of anhydrous ether and 59.6 ml of 2.05 *M* methyllithium according to the procedure for the preparation of the halohydrin **2**. After the work-up, 16 g of crude halohydrin was recovered: ir (film) 3560 and 3470 cm^{-1} (–OH); an instantaneous white precipitate with alcoholic silver nitrate.

2,2-Dimethylcyclohexanone (**16**) **and 1-Acetyl-1-methylcyclopentane** (**17**).—To a solution of 16 g of the previously prepared crude halohydrin in 300 ml of anhydrous benzene was added, dropwise, 80 ml (0.10 mol) of 1.25 *M* isopropylmagnesium bromide[15] according to the procedure described above for the preparation of **4**. After decomposition the product was distilled on a 10-in. Vigreux column, yielding 13 g (0.066 mol) (66%) of a colorless oil, bp 68–69° (33 mm), consisting of a mixture of two parts of **16** to three parts of **17** as analyzed by vpc (20% TCEP on Chromosorb P, 4 ft × 0.25 in. column, 100°). The isomeric ketones **16** and **17** were satisfactorily separated by preparative vpc (20% Carbowax on 60–80 mesh Chromosorb W acid-washed, 80 × 0.75 in. column, 80°).

Compound **17** was identified by vpc (TCEP, 4 ft × 0.25 in. column, 100°) and ir, each of which gave a perfect comparison with an authentic sample.[24] The semicarbazone of **17** was also prepared, mp 140–141° (lit.[25] mp 140–141°).

Compound **16** was identified by its 2,4-dinitrophenylhydrazone, mp 140–141° (lit.[26] mp 140–142°), and its semicarbazone mp, 198–199° (lit.[27] mp 199–200°).

cis-**2-Chloro-1-methylcyclohexanol** was prepared using 13.3 g (0.100 mol) of 2-chlorocyclohexanone (Aldrich Chemical Co.) in 200 ml of anhydrous ether and 55 ml of 2.3 *M* methyllithium in ether according to the above procedure for the preparation of the halohydrin **2**. After work-up 14.4 g of crude halohydrin was recovered, ir (film) 3560 and 3480 cm^{-1} (–OH) and an instantaneous precipitate with alcoholic silver nitrate.

2-Methylcyclohexanone (**14**) **and Acetylcyclopentane** (**15**).—To a solution of 14.4 g of the prevously prepared crude halohydrin in 300 ml of anhydrous benzene, 80 ml of 1.25 *M* isopropylmagnesium bromide[15] was added dropwise according to the above described procedure for the preparation of **4**. The residue was distilled on a 10-in. Vigreux column to give 6.1 g (0.054 mol) (54%) of a colorless liquid, bp 45–50° (8 mm). It consisted of three parts of **14** to two parts of **15** as analyzed by vpc (20% TCEP on Chromosorb P, 4 ft × 0.25 in. column, 100°). The isomeric ketones **14** nd **15** were successfully separated by preparative vpc (20% Carbowax on 60–80 mesh Chromosorb W acid washed, 80 × 0.75 in. column, 80°).

Compound **14** was identified by vpc (TCEP 4 ft × 0.25 in. column, 100°) and ir, each of which gave a perfect comparison with an authentic sample (Aldrich Chemical Co.).

Compound **15** was identified by ir (film) 1715 cm^{-1} (C=O); nmr (CCl_4) τ 7.97 (s, 3 H, $COCH_3$); semicarbazone mp 143–144° (lit.[27] mp 145°) and 2,4-dinitrophenylhydrazone mp 124–125° (lit.[28] mp 127°).

Registry No.—**2**, 23472-37-9; **4**, 770-62-7; **5a**, 36444-55-0; **5a** 2,4-DNP, 36744-51-1; **12**, 2826-65-5; **13**, 13025-91-7; **14**, 583-60-8; **15**, 6004-60-0; **16**, 1193-47-1; **17**, 13388-93-7; *cis*-8-chlorohydrindan-1-one, 36744-54-4; *trans*-8-chlorohydrindan-1-one, 36744-55-5; *cis*-2-chloro-1,2-dimethylcyclohexanol, 36744-56-6; *cis*-2-chloro-1-methylcyclohexanol, 19324-75-7.

(20) We are grateful to Dr. W. G. Dauben for supplying a sample of **5c**.

(21) W. S. Johnson, C. E. Davis, and G. Stork, *J. Amer. Chem. Soc.*, **70**, 3022 (1948).

(22) W. S. Johnson, *ibid.*, **66**, 215 (1944).

(23) E. W. Warnhoff, D. G. Martin, and W. S. Warnhoff, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 162.

(24) An expression of thanks to Dr. H. Hart for supplying a sample of **17**.

(25) W. Huckel and U. Worffel, *Chem. Ber.*, **88**, 338 (1955).

(26) P. S. Adamson, A. M. Marlow, and J. L. Simonsen, *J. Chem. Soc.*, 774 (1938).

(27) L. J. Goldsworthy, *ibid.*, 378 (1934).

(28) C. D. Nenitzescu and E. Cioranescu, *Chem. Ber.*, **69**, 1820 (1936)

The Schmidt and Beckmann Reactions of α-Trisubstituted Ketones and Ketoximes. The Synthesis of Isotopically Labeled Aniline[1]

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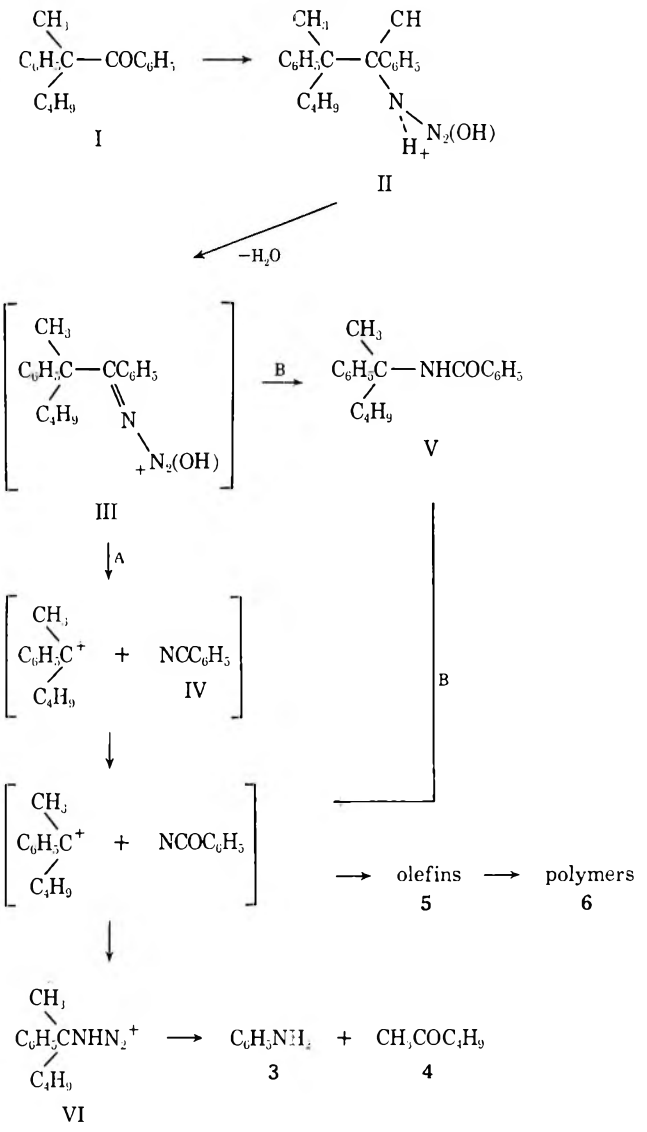
Similarities in the behavior of α-trisubstituted aralkyl ketones and ketoximes were observed during the Schmidt reaction and Beckmann rearrangement in polyphosphoric acid. Both reactions involve fragmentation to carbonium ion and nitrile or amide. The carbonium ion will react with azide to yield an aralkyl azide which rearranges to form aniline. The mechanism is discussed.

Our interest in the Beckmann and Schmidt reaction had as its focal point the behavior of α-trisubstituted aralkyl ketones and ketoximes under rearrangement conditions, particularly those considered strongly acidic such as polyphosphoric acid. Only a limited number of examples of α-trisubstituted aralkyl ketoxime systems have been examined in the case of the Beckmann rearrangement.[4,5] No studies of the Schmidt reaction of aralkyl ketones have been reported in this medium. Both reactions have certain similarities provided that they are compared on common grounds, *i.e.*, analogous ketone and ketoxime structures under the same reaction conditions.

Results and Discussion

Our previous report[6] described the fate of α-aralkyl substituted carboxylic acid under Schmidt reaction conditions. The reaction products obtained when 3-phenyl-3-methylheptanone-2 (**2**) was treated with sodium azide in polyphosphoric acid at 50° for 8 hr were almost identical with those obtained by the Schmidt reaction of 2-phenyl-2-methylhexanoic acid,[6] namely, aniline (**3**), 2-hexanone (**4**), olefins (**5**), and polymer[6] (**6**), as well as 25% of the recovered ketone. Similarly 2-methyl-2-phenylhexophenone (I) under the identical conditions gave aniline (**3**), 2-hexanone (**4**), olefins (**5**), polymer (**6**), starting ketone, and benzamide. Since both starting ketones could be recovered unchanged after being heated at 50° in polyphosphoric acid for 8 hr and since benzamide was isolated on attempted Schmidt reaction, it would appear that the observed fragmentation could have occurred by either of two pathways (Chart I). If we postulate that hydrazoic acid adds to the protonated carbonyl followed by dehydration to an iminodiazonium ion, III, as proposed by Smith[7] and confirmed in spiro ketone systems,[8] then, under the reaction conditions, the iminodiazonium ion, III, would be expected to lose nitrogen to form the nitrile, IV, and carbonium ion as proposed by Conley and Nowak[8] (Chart I, pathway A). If generalized, this postulate can be correlated to both the abnormal Schmidt and Beckmann reactions. The nitrile was then hydrolyzed to amide and the carbonium ion was attacked by azide ion to form the tertiary aralkyl azide VI, which rearranged to aniline and ketone. On the other hand, if we consider that the rearrangement has occurred simultaneously with the loss of nitrogen (Chart I, pathway B), then the resulting secondary amide V could undergo cleavage to a carbonium ion and benzamide. The aniline produced could be accounted for by the same aralkyl azide intermediate VI as previously proposed for α-trisubstituted acids.[6]

CHART I



In order to test the two mechanistic pathways, each of the secondary amides was subjected to hot poly-

(1) Presented in part at the First Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1966.

(2) (a) Abstracted in part from the Ph.D. Thesis of R. M. Palmere, Seton Hall University, 1966. To whom inquiries should be addressed c/o FMC Corp., Princeton, N. J. 08540. (b) Wright State University, Dayton, Ohio 45431.

(3) VA Hospital and University of Pennsylvania School of Dental Medicine, Philadelphia, Pa. 19104.

(4) T. T. Conley and T. M. Tencza, *Tetrahedron Lett.*, **No. 26**, 1781 (1963).

(5) R. T. Conley, *J. Org. Chem.*, **28**, 278 (1963).

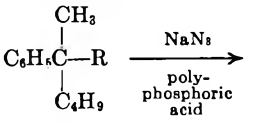
(6) R. M. Palmere and R. T. Conley, *ibid.*, **35**, 2703 (1970).

(7) P. A. S. Smith, *J. Amer. Chem. Soc.*, **70**, 320 (1948).

(8) R. T. Conley and B. E. Nowak, *J. Org. Chem.*, **26**, 692 (1961).

TABLE I

REACTIONS OF α-TRISUBSTITUTED ARALKYL COMPOUNDS WITH SODIUM AZIDE AT 50°



Registry no.	R	Sodium azide, equiv	Unreacted material, %	Olefin, %	Polymer, %	Aniline, %
	COOH[a]	None	None	10.8	79.7	None
	COOH	1[b]	0.01	6.3	34.6	57.7[c]
36789-50-1	$COCH_3$	None	98.6	None	None	None
	$COCH_3$	1	25.0	7.0	26.0	40.8
36789-51-2	COC_6H_5	None	98.9	None	None	None
	COC_6H_5	1	58.0	8.0	5.0	24.3
20826-78-2	$NHCOCH_3$	1	None	13.6	75.7	10.7
36789-53-4	$NHCOC_6H_5$	1	None	8.2	70.1	8.0
36789-54-5	$HON{=}CCH_3$	None	None	98.3	1.2	None
		1	None	1.0	51.0	54.0[d]
36789-55-6	$HON{=}CC_6H_5$	None	None	17.7	82.5	None[e]
		1[f]	None	6.0	46.4	40.0[g,h]

[a] Reference 6. [b] Isotopically labeled ^{15}N sodium azide. [c] Contained 47.345 atom % ^{15}N greater than the theoretical naturally occurring ^{15}N. [d] Isolated as aniline hydrochloride. [e] 72.4% benzamide isolated. [f] Isotopically labeled ^{15}N sodium azide. [g] Contained 46.790 atom % ^{15}N greater than the theoretical naturally occurring ^{15}N. [h] 81.6% benzamide isolated.

phosphoric acid and sodium azide. When 2-acetamido-2-phenylhexane was heated at 50° with 1 molar equiv of sodium azide for 8 hr, none of the amide was isolated. The products of the reaction were aniline (11%), *trans*-2-phenyl-2-hexane, and polymer. Although acetamide should have been found,[9] no isolation attempt was made. On the other hand, when 2-benzamido-2-phenylhexane was subjected to the identical conditions, the reaction products were aniline (8%), 2-hexanone, *trans*-2-phenyl-2-hexene, polymer, and benzamide. Since the yields of aniline were only 11 and 8% obtained from the amides as compared with 40 and 24% obtained from the ketones, we can consider any product due to amide cleavage of secondary importance. Therefore, it appears that the operating mechanism parallels that proposed by Hill and Conley[10] for fragmentation in the Beckmann rearrangement of ketoximes but that the reaction is complicated by the aralkyl azide formed (VI).

The ketoximes of **1** and **2** were subjected to Beckmann rearrangement conditions using a variety of catalysts and solvents; however, only fragmentation products were isolated. When 3-phenyl-3-methylheptanone-2 oxime was treated with polyphosphoric acid, either at room temperature for 2 hr or at 110° for 10 min, the three isomeric olefins (2-phenyl-1-hexene, *trans*-2-phenyl-2-hexene, and *cis*-2-phenyl-2-hexene) and polymer were isolated. If 1 molar equiv of sodium azide is added to the reaction in polyphosphoric acid, at 50° for 8 hr, then aniline (54%), 2-hexanone, *trans*-2-phenyl-2-hexene, and polymer are the products. The reactions performed in polyphosphoric acid are summarized in Table I.

Theoretically, the sum of olefin, polymer, and aniline in the tables should total 100% and the amount of 2-hexanone should equal the amount of aniline. The discrepancies result from analysis by two distinct procedures, determination of aniline by hydrochloride formation and the other products by vpc.

Since Hill, Conley, and Chortyk[11,12] have shown in their crossover experiment that the amide product of the Beckmann rearrangement of 3-phenyl-3-methylbutanone-2 does undergo fragmentation and recombination in polyphosphoric acid, it would appear (despite the low yields observed) that the butyl chain in the ketones here investigated sterically interferes with the recombination process. The recombination of fragments did not occur in our case since the expected amide undergoes fragmentation under these conditions.

Furthermore, when 2-methyl-2-phenylhexaphenone oxime was allowed to react with polyphosphoric acid containing 1 molar equiv of sodium azide at 50° for 8 hr, aniline (40%), *trans*-2-phenyl-2-hexene, polymer, and benzamide (80%) were found. Thus, the amount of aniline formed indicates that cleavage of oxime to carbonium ion and nitrile is the major course of reaction.

Since the results of both the Schmidt and Beckmann reactions in polyphosphoric acid are consistent with a common mechanism, *i.e.*, essentially fragmentation being the underlying course of reaction, it was reasonable to assume that isotopically labeled aniline or amides could be prepared by this method. Both 2-phenyl-2-methylhexanoic acid and 2-methyl-2-phenylhexaphenone oxime were treated with polyphosphoric acid and 1 molar equiv of sodium azide containing ^{15}N. The results of these studies are summarized in Table I. The degree of incorporation of the ^{15}N into aniline from 2-phenyl-2-methylhexanoic acid as well as from phenyl ketoxime was determined by mass spectrometry. The results described in Table I suggests that the method could be used for ^{15}N aniline derivatives in general. Furthermore, the benzamide isolated from the reaction of 2-methyl-2-phenylhexaphenone oxime and ^{15}N sodium azide contained 0.1718 atom % more than theoretical naturally occurring ^{15}N, indicating that a very small portion of the oxime must have hydrolyzed to ketone during reaction. Therefore, if ^{15}N sodium azide were treated directly with the ketone, isotopically labeled benzamide would have been formed.

Experimental Section

Melting and boiling points are uncorrected. Infrared spectra were obtained with a Beckman IR-10 grating spectrophotometer

(9) A. G. Mohan and R. T. Conley, *J. Org. Chem.*, **34**, 3529 (1969).
(10) R. K. Hill and R. T. Conley, *J. Amer. Chem. Soc.*, **82**, 645 (1960).
(11) R. T. Conley, *J. Org. Chem.*, **28**, 278 (1963).
(12) R. K. Hill, R. T. Conley, and O. T. Chortyk, *J. Amer. Chem. Soc.*, **87**, 5646 (1965).

and were consistent with the structure. Vpc was performed on an F & M Model 720 gas chromatograph as follows: 6 ft × 0.25 in. in 10% silicone gum nitrile on Chromosorb P, programmed from 60 to 220° at 20°/min with a helium flow rate of 60 cm³/min, 185° isothermal.

2-Phenyl-2-methylhexanoic Acid.—The acid was prepared in 89% yield as previously described,[6] bp 154–156° (4 mm)

3-Phenyl-3-methylheptanone-2.—An ethereal solution of 0.7 *M* methyllithium (85 ml) was added slowly over a 1.5-hr period to a solution of 6.0 g (0.029 mol) of 2-methyl-2-phenylhexanoic acid in 150 ml of anhydrous ether cooled in an ice bath. The red solution was stirred for an additional 30 min and quenched with 100 ml of water, and the ethereal layer was separated. The aqueous portion was extracted twice with 100-ml portions of ether. The ethereal portions were combined, washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to give 4.5 g (80%) of 3-phenyl-3-methylheptanone-2. The crude ketone was distilled to give 4.28 g, bp 124–126° (3.5 mm).

Vpc (20 ft, 30% SE-30) analysis indicated 98% purity. An analytical sample was trapped.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.81. Found: C, 82.18; H, 9.77.

3-Phenyl-3-methylheptanone-2 oxime (7.0 g) was prepared by literature procedure[13,14] and after three recrystallizations gave 5.42 g of 3-phenyl-3-methylheptanone-2 oxime, mp 66.5–67.5°.

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.50; H, 9.70; N, 6.30.

The 2,4-dinitrophenylhydrazone was prepared as described by Schriner, Fuson, and Curtin.[13] After four recrystallizations from dilute alcohol, the purified derivative had mp 126–128°.

Anal. Calcd for $C_{20}H_{24}N_4O_4$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.48; H, 6.31; N, 14.33.

2-Methyl-2-phenylhexaphenone.—Oxalyl chloride (12.7 g, 0.10 mol) was added to a solution of 2-phenyl-2-methylhexanoic acid in 50 ml of dry benzene and refluxed for 2 hr. The excess oxalyl chloride was distilled at atmospheric pressure, during which time portions of dry benzene were added to the flask until the temperature of the distillate reached 78°. The acid chloride was not purified further but rather was cooled in an ice bath and treated drop by drop with an ethereal solution of phenylmagnesium bromide prepared from 9.4 g (0.060 mol) of bromobenzene, 1.5 g (0.060 g-atom) of magnesium turnings, and 70 ml of anhydrous ether.

The Gilman test for Grignards was positive after 10 min at room temperature. The solution after refluxing for 15 min gave a positive Gilman test.

The ether was removed by distillation at atmospheric pressure, refluxed at 70° for 1 hr, and stirred overnight at room temperature. The mixture was then treated with ice followed by 100 ml of saturated ammonium chloride solution, and the organic phase was separated. The aqueous portion was extracted with ether. The ethereal portions were combined, washed with water, and dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. Distillation of the oily product gave 5.4 g of 2-methyl-2-phenylhexaphenone, bp 130–132° (0.1 mm) [lit.[14] bp 150–152° (0.5 mm)], $n^{20}D$ 1.5578.

The 2-methyl-2-phenylhexaphenone oxime was prepared by a literature procedure[13] and crystallized from ethanol–water, mp 72–76°. Three recrystallizations from dilute ethanol gave 0.488 g of 2-methyl-2-phenylhexaphenone oxime, mp 128–129°.

Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.97. Found: C, 81.00; H, 8.23; N, 4.83.

The 2,4-dinitrophenylhydrazone of 2-methyl-2-phenylhexaphenone was prepared by the procedure described by Schriner, Fuson, and Curtin[13] and after three recrystallizations from dilute ethanol had mp 155–157°.

Anal. Calcd for $C_{24}H_{26}N_4O_4$: C, 71.62; H, 6.51; N, 13.91. Found: C, 71.42; H, 6.53; N, 14.16.

The 2-acetamido-2-phenylhexane, mp 110–111°, and the 2-benzamido-2-phenylhexane, mp 146–147°, were prepared as previously described.[6]

Schmidt Reactions of Ketones.—Essentially the same procedure as described for the Schmidt reaction of acids[6] was used for the attempted rearrangement of 2-methyl-2-phenylhexaphenone and 3-phenyl-3-methylheptanone-2.

2-Methyl-2-phenylhexaphenone.—Sodium azide (0.65 g, 0.01 mol) was added to 2.67 g (0.01 mol) of 2-methyl-2-phenylhexaphenone in 50 g of polyphosphoric acid at 50° and stirred for 8 hr. The flask was filled with crushed ice. The cold aqueous mixture was extracted three times with 50-ml portions of methylene chloride, which was subsequently washed with water and dried over anhydrous magnesium sulfate and the solvent was evaporated at reduced pressure. The residual oil was diluted with ether to give 240 mg of benzamide, mp 124° (lit.[13,14] mp 128°), identified by comparison of the infrared and mixture melting point with those of an authentic sample. The aqueous polyphosphoric acid was basified with solid sodium hydroxide and ice maintaining a temperature below 25° and was extracted with three 50-ml portions of methylene chloride. The methylene chloride was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed at reduced pressure. Dilution with ether gave an additional 244 mg of benzamide. The ethereal mother liquors were examined by vpc (Silicone Gum Nitrile) analysis indicating four components.

The first component had a retention time of 3.2 min (7.76%) and was identified as *trans*-2-phenyl-2-hexene by its retention time.

The second component had a retention of time 3.8 min (24.3%) and was identified as aniline by isolation and derivatization to aniline hydrochloride.

The third component had a retention time of 5.8 min (58.0%) and was identified as 2-methyl-2-phenylhexaphenone by peak enhancement and comparison of its complete infrared spectrum with the spectrum of an authentic sample.

The fourth component had retention times of 8.1, 8.3, and 9.1 min (5.0% total) and was identified as polymeric material by retention time and infrared comparison with a sample as previously described.[6]

3-Phenyl-3-methylheptanone-2.—A mixture of 1.63 g (0.008 mol) of 3-phenyl-3-methylheptanone-2 in 38 g of polyphosphoric acid at 50° was treated with 0.560 g (0.008 mol) of sodium azide as previously described for 8 hr. Vpc (silicone gum nitrile) analysis showed five components.

The **first component** had a retention time of 1.2 min (29.3%) and was identified as hexanone-2 by its retention time.

The **second component** had a retention time of 3.2 min (8.3%) and was identified as *trans*-2-phenyl-2-hexene by its retention time.

The **third component** had a retention time of 3.8 min (40.8%) and was identified as aniline by its retention time and peak enhancement.

The **fourth component** had a retention time of 6.2 min (24.7%) and was identified as 3-phenyl-3-methylheptanone-2 by peak enhancement and comparison of its complete infrared spectrum with the spectrum of an authentic sample.

The **fifth component** had retention times of 8.1, 8.3, and 9.1 min (26.0% total) and was identified as polymeric products based on its retention time.

Without Sodium Azide.—When each of the ketones above was heated at 50° in polyphosphoric acid for 8 hr, the ketones were recovered unchanged in almost quantitative amounts.

Registry No.—3-Phenyl-3-methylheptanone dinitrophenylhydrazone, 36789-56-7; 2-methyl-2-phenylhexaphenone dinitrophenylhydrazone, 36789-57-8.

(13) R. L. Schriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, N. Y., 1956, p 316.

(14) J. B. Conant and G. H. Carlson, *J. Amer. Chem. Soc.*, **54**, 4048 (1932).

Convenient Synthetic Routes to the 5,6-Trimethylenenorbornanones

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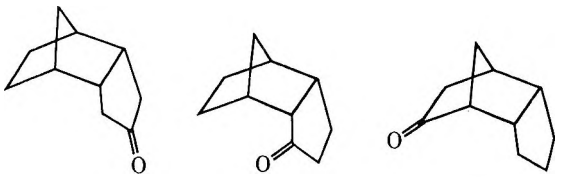
Received May 15, 1972

Convenient synthetic routes to the *endo*-5,6-trimethylenenorbornanones, the 8- (II), 9- (I), and 2- (III) ketones, were explored. The selective hydrogenation of *endo*-dicyclopentadiene over nickel boride affords pure *endo*-5,6-trimethylene-8-norbornene. Hydroboration of this olefin, followed by chromic acid oxidation, yields a mixture of I and II, which can be cleanly separated by taking advantage of the finding that I selectively forms a bisulfite addition complex. Oxymercuration–demercuration of *endo*-dicyclopentadiene led to essentially pure 2-alcohol product, the 8- and 9-alcohol products being absent. Hydrogenation of this alcohol, followed by oxidation, gives pure III.

As a part of our studies of the stereoselectivities involved in the reactions of rigid bicyclic and related compounds, we undertook to examine the *endo*-5,6-trimethylenenorbornane system.[3] For this purpose we required relatively large quantities of *endo*-5,6-trimethylene-9-norbornanone (I), *endo*-5,6-trimethylene-8-norbornanone (II), and *endo*-5,6-trimethylene-2-norbornanone (III).[4]



I II III

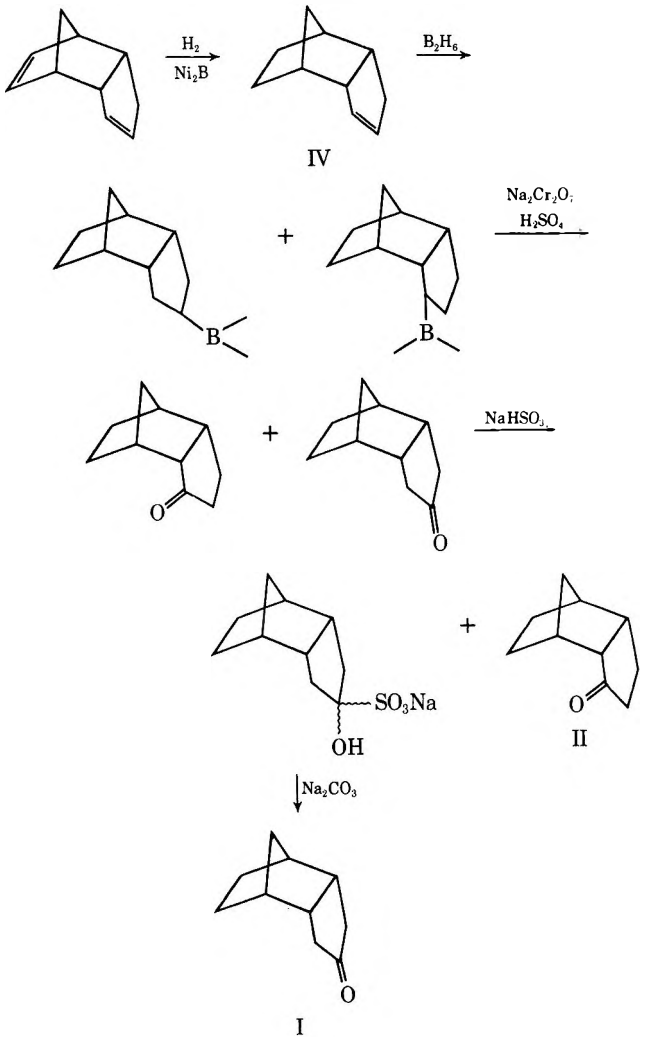
On examining the literature, we found that the synthetic procedures for these ketones are not really satisfactory. The described procedure for I required a number of steps and the yield was not specified.[5] Similarly, the previous methods for preparation of II[6] and III[6,7] involved a number of steps and/or gave poor yields of products of varying purities. Consequently, it was decided to explore more convenient routes to these ketones.

Results and Discussion

endo-5,6-Trimethylene-8-norbornanone (II) and the 9 derivative (I) were prepared by the procedure shown in Scheme I.

Selective hydrogenation of *endo*-dicyclopentadiene in a Brown□ hydrogenator[8] using nickel boride[9,10] as catalyst gave a 90% yield of *endo*-5,6-trimethylene-8-norbornene (IV) of 98.5% purity. Hydroboration[11] of IV followed by chromic acid oxidation of the alkyl boron compounds[12] yielded a 40:60 mixture of I and II. It was found that I quantitatively forms an insoluble bisulfite addition complex, while II is completely unreactive toward sodium bisulfite. The failure of II to form a bisulfite addition complex is probably the result of interference by the endo-3-hydrogen. This is analogous to the behavior of certain steroid ketones, where the angular methyl group also can prevent the formation of bisulfite addition complexes.[13] Similarly, 2,2,4-trimethylcyclopentanone fails to form a bisulfite

SCHEME I



(1) Postdoctorate research associate, 1963–1965.

(2) National Science Foundation Cooperative Fellow, 1965–1967.

(3) H. C. Brown, I. Rothberg, P. v. R. Schleyer, M. M. Donaldson, and J. J. Harper, *Proc. Nat. Acad. Sci. U. S.*, **56**, 1653 (1966); H. C. Brown, I. Rothberg, and D. L. Vander Jagt, *J. Amer. Chem. Soc.*, **89**, 6380 (1967); H. C. Brown, W. J. Hammar, J. H. Kawakami, I. Rothberg, and D. L. Vander Jagt, *ibid.*, **89**, 6381 (1967); H. C. Brown and D. L. Vander Jagt, *ibid.*, **91**, 6850 (1969).

(4) The nomenclature used for this ring system is that used by P. v. R. Schleyer and M. M. Donaldson, *ibid.*, **82**, 4645 (1960).

(5) K. Alder, F. H. Flock, A. Hausweiler, and R. Reefer, *Ber.*, **87**, 1752 (1954).

(6) (a) J. Pirsch, *ibid.*, **67**, 1115 (1935); (b) K. Alder and G. Stein, *Justus Liebigs Ann. Chem.*, **504**, 205 (1933); (c) M. M. Donaldson, Ph.D. Thesis, Princeton University, 1958.

(7) (a) H. Wieland and F. Bergel, *Justus Liebigs Ann. Chem.*, **446**, 13 (1926); (b) S. J. Cristol, W. Steifert, and S. B. Soloway, *J. Amer. Chem. Soc.*, **82**, 235 (1960).

(8) C. A. Brown and H. C. Brown, *J. Org. Chem.*, **31**, 3989 (1966).

(9) H. C. Brown and C. A. Brown, *J. Amer. Chem. Soc.*, **85**, 1004 (1963).

(10) The remarkable effectiveness of this catalyst in performing selective hydrogenation of norbornene double bonds was recently reported: C. A. Brown, *Chem. Commun.*, 952 (1969).

(11) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).

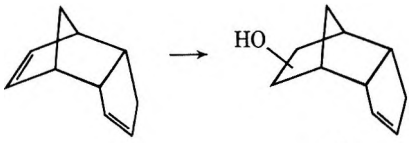
(12) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2951 (1961).

(13) R. L. Clark, *J. Org. Chem.*, **28**, 2626 (1963).

addition complex because of steric repulsions.[14] I and II, thus separated, were found to be better than 98% pure.

In our search for methods of separation of the 8- and 9-ketones, one other facet of investigation appears to be of interest. Owing to the differences in the steric environment of the 8 and 9 positions, it appeared possible that partial oxidation of a mixture of exo-8- and exo-9-alcohols might provide a means of separation through selective oxidation of one isomer. The relative rate of oxidation of the 9-alcohol to the 8-alcohol turned out to be 2.1, which is apparently too small to serve the present purpose. The observation that the oxidation of the exo-9-alcohol is significantly faster than that of the more hindered exo-8-alcohol is puzzling in view of the fact that the more strained alcohols generally undergo more rapid oxidation.[15]

The first step of the synthesis of *endo*-5,6-trimethylene-2-norbornanone (III) involves the conversion of *endo*-dicyclopentadiene to a mixture of 8,9-dehydro and 9,10-dehydro derivatives of *endo*-5,6-trimethylene-*exo*-2-norbornanol (V).

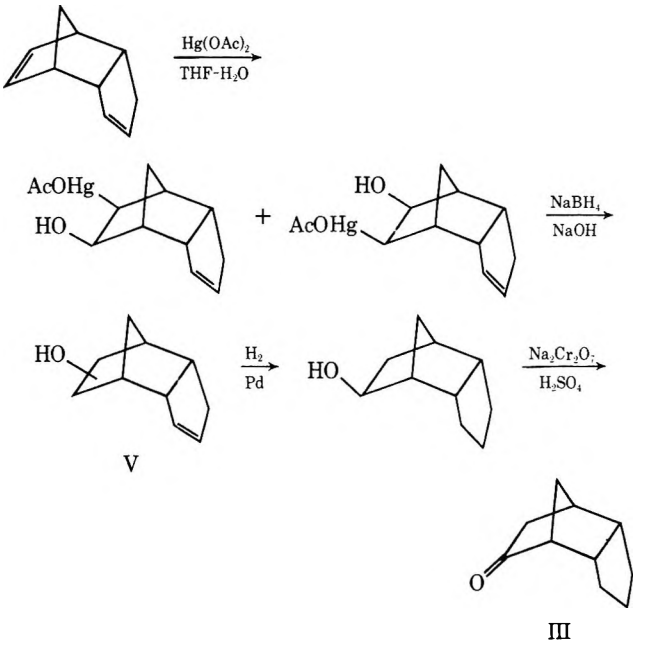


V

We initially utilized hydroboration to achieve this monohydration. However, this reaction was not selective, the product being 37% V and 63% of 8- and 9-hydroxy derivatives. Nevertheless we could quantitatively isolate V from this mixture by extracting ether solutions of the 8- and 9-alcohols with aqueous silver nitrate solution. It was found that *endo*-5,6-trimethylene-2-norbornen-*exo*-8-ol or the 9 derivative readily forms a silver ion complex, while V is essentially unreactive toward silver ion.[16]

It was later found that the above conversion can be carried out cleanly with both high stereospecificity and high yield by means of oxymercuration–demercuration.[19] Treatment of *endo*-dicyclopentadiene with mercuric acetate followed by reduction gave pure V in 89% yield.

Hydrogenation of V was performed according to the previously described procedure using a Brown□ apparatus[8] to obtain *endo*-5,6-trimethylene-*exo*-2-norbornanol in 94% yield. This alcohol was then oxidized utilizing the modified procedure developed in this laboratory[20] to obtain a high yield of pure *endo*-5,6-trimethylene-2-norbornanone (III). The synthetic route to III is summarized below.



Experimental Section

Glpc Analyses.—All analyses were carried out on a Perkin-Elmer Model 226 with use of a 150 ft × 0.01 in. Golay column coated with Carbowax 20M or UCON LB550X.

***endo*-5,6-Trimethylene-8-norbornene (IV).**—Purified *endo*-dicyclopentadiene (407 g, 3.08 mol) was dissolved in ethanol and submitted to selective hydrogenation in a Brown□ hydrogenator[8] using nickel boride as catalyst.[9,10] After the theoretical amount of hydrogen had been taken up, 200 ml of acetone and 2 g of carbon (Dacro K-B) were added to the reaction mixture and suction filtered through Celite. The solvent was removed and the residue was distilled at atmospheric pressure, bp 178–180°, mp 48.5–50° (lit.[21] mp 50–51°), yield 370 g (90%). Analysis on Ucon LB550X showed 98.5% purity.

***endo*-5,6-Trimethylene-9-norbornanone (I) and *endo*-5,6-Trimethylene-8-norbornanone (II).**—To a well-stirred suspension of 17.0 g (0.450 mol) of sodium borohydride in 500 ml of tetrahydrofuran (THF) containing 134 g (1.0 mol) of *endo*-trimethylene-8-norbornene was added 85.2 g (0.60 mol) of boron trifluoride etherate dissolved in 100 ml of THF over a period of 1 hr under a nitrogen atmosphere. The reaction mixtue was stirred for an additional 2 hr at room temperature and then the excess hydride was decomposed by careful addition of water. A chromic acid solution, prepared from 220 g (0.738 mol) of sodium dichromate dihydrate and 165 ml (2.948 mol) of 96% sulfuric acid and diluted to 1000 ml with water, was added to the stirred solution over a period of 2 hr while the temperature was maintained at 15–20°. The reaction mixture was stirred vigorously for an additional 2 hr at room temperature, and the aqueous phase was separated and washed with two 200-ml portions of ethyl ether. The combined ethereal solution was extracted with three 100-ml portions of saturated sodium carbonate, dried over magnesium sulfate, and condensed to *ca.* 200 ml. Analysis on Carbowax 20M showed the presence of 60% II and 40% I. To this solution 200 ml of ether and 300 ml of saturated aqueous sodium bisulfite were added and the mixture was stirred for 48 hr. Analysis showed that the ethereal solution contained II and I in a ratio of 97:3. The mixture was filtered and the precipitate was washed well with ethyl ether, the washings being added to the filtrate. The ethereal layer of this filtrate was separated, dried over magnesium sulfate, and distilled, affording 52 g (35%) of *endo*-5,6-trimethylene-8-norbornanone (II), bp 132–134° (17

(14) F. G. Gault and J. E. Germain, *Bull. Soc. Chim. Fr.*, 1365 (1959).

(15) For kinetic studies of oxidation of norbornyl and related alcohols, see I. Rothberg and R. V. Russo, *J. Org. Chem.*, **32**, 2003 (1967); I. Rothberg, *Chem. Commun.*, 268 (1968).

(16) The equilibrium constant for the silver ion complex formation of the 8- and 9-alcohols in the present system, $K = [\text{complex}]_{H_2O}/[Ag^+]_{H_2O}[\text{Olefin}]_{\text{ether}}$ was found to be 10 l./mol at 25°. Previous studies in this area showed that norbornene forms a silver ion complex more readily than cyclopentene, but the difference was found to be small.[17] The difference observed for the compounds under consideration is large enough to enable a quantitative separation. This may be due either to changes in structural variations, such as changes in bond angles caused by the introduction of the trimethylene bridge[18] or to differences in solubility in the aqueous phase.

(17) J. G. Traynham and M. F. Sehnert, *J. Amer. Chem. Soc.*, **78**, 4024 (1956); J. G. Traynham and J. R. Olechowski, *ibid.*, **81**, 571 (1959).

(18) It is known that introduction of substituents induces distortion of the norbornane structure: C. Altona and M. Sundaralingam, *ibid.*, **92**, 1995 (1970).

(19) H. C. Brown and P. Geoghegan, *ibid.*, **89**, 1522 (1967).

(20) H. C. Brown, C. P. Garg, and K.-T. Liu, *J. Org. Chem.*, **36**, 387 (1971); H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).

(21) K. Alder and G. Stein, *Justus Liebigs Ann. Chem.*, **485**, 223 (1931).

mm), mp 94–97°. Analysis showed 95% purity, 2% being I and 3% lower boiling unidentified materials. Recrystallization from pentane gave mp 98–99° (lit.[7a] mp 101°), semicarbazone mp 200–201° (lit.[7a] mp 200°). The precipitate, which had been set aside, was added to a mixture of 300 ml of saturated aqueous sodium carbonate and 200 ml of ethyl ether and stirred vigorously until solution had occurred. The ether layer was separated and the aqueous carbonate layer was extracted with two 50-ml ether portions. The ether portions were combined, dried over magnesium sulfate, and distilled to yield 42 g (28%) of *endo*-5,6-trimethylene-9-norbornanone (I), bp 132–134° (20 mm), mp 105–105.5°, semicarbazone mp 214–215°, dibenzylidene derivative mp 191–191.5° (lit.[5] semicarbazone mp 215°, dibenzylidene derivative mp 191°). *Anal.* Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.16; H, 9.57.

Relative Rates of Oxidation of *endo*-5,6-Trimethylene-*exo*-9-norbornanol and the Exo-8 Isomer.—A mixture of alcohols consisting of 9.75 mmol of *endo*-5,6-trimethylene-*exo*-9-norbornanol and 15.25 mmol of *endo*-5,6-trimethylene-*exo*-8-norbornanol, obtained by hydroboration of *endo*-5,6-trimethylene-8-norbornene, was treated wth 50% of the theoretical amount of chromic acid using the previously described procedure.[20] At the end of the reaction glpc analysis revealed that there remained 3.85 mmol of the 9-alcohol and 9.90 mmol of the 8-alcohol. According to the given procedure,[22] the rate of oxidation of the 9-alcohol relative to that of the 8 isomer was calculated to be 2.1.

8,9-Dehydro- and 9,10-Dehydro-*endo*-5,6-trimethylene-*exo*-2-norbornanol (V). Method A. Hydroboration of *endo*-Dicyclopentadiene.—To a well-stirred solution containing 198 g (1.5 mol) of *endo*-dicyclopentadiene in 250 ml of THF was added under a nitrogen atmosphere 167 ml (1 mol of hydride) of 1 *M* diborane solution in THF. The solution was allowed to become hot owing to an exothermic reaction. After addition was complete, the reaction mixture was stirred for 3 hr, and then 150 ml of 3 *N* sodium hydroxide was added, followed by the slow addition of 150 ml of 30% hydrogen peroxide, and stirred for 8 hr. The THF layer was salted out by adding potassium carbonate and separated. The aqueous phase was extracted with ether and the combined solution was dried over magnesium sulfate before the solvent was distilled off. The residue was distilled to give 72 g (0.55 mol) of the starting material, bp 70–75° (18 mm), 96 g (0.64 mol) of a mixture of monoalcohols, bp 124–130° (15 mm), and higher boiling diols. Analysis of the monoalcohol showed the presence of 37% 2-alcohol (V). A 1 *M* ether solution of this mixture of monoalcohols was extracted three times with a 1 *M* silver nitrate solution using $^2/_3$ the volume of silver nitrate each time as the total volume of ether solution. The aqueous portions were extracted once with ether and then back extracted once with silver nitrate solution. The combined ether solution was washed once with water and then dried over magnesium sulfate. The ether was distilled off at a reduced pressure to give a quantitative recovery of V.

Method B. Oxymercuration–Demercuration[19] of *endo*-Dicyclopentadiene.—Mercuric acetate (63.7 g, 0.2 mol) was dissolved in 200 ml of water and 200 ml of THF, and to the resulting yellow solution was added with stirring 26.4 g (0.2 mol) of *endo*-dicyclopentadiene. After the yellow color disappeared the mixture was stirred for an additional 10 min and cooled to *ca.* −10°. To this solution was added successively 200 ml of cold 3 *N* sodium hydroxide solution and 200 ml of cold basic sodium borohydride solution (0.5 *M* in borohydride and 3 *N* in sodium hydroxide). The mixture was stirred until mercury settled and the aqueous layer was separated and extracted with hexane. The combined organic solution was dried over magnesium sulfate and the solvent was removed under a reduced pressure. Analysis showed the presence of 91% alcohol and 9% acetate. The residue was then treated with lithium aluminum hydride in THF in order to reduce the small amount of acetate and, at the same time, to reduce any residual mercurial products which were found to interfere with the catalytic hydrogenation. The final product was isolated in the usual manner. Analysis showed that the reaction proceeded to the extent of 89.5%, the product being practically pure 2-alcohol (V).

***endo*-5,6-Trimethylene-*exo*-2-norbornanol.**—The mixture of 8,9-dehydro- and 9,10-dehydro-*endo*-5,6-trimethylene-*exo*-2-norbornanol (V) was reduced according to the previous procedure.[8] The product was recrystallized from pentane, mp 81.5–82.0° (lit.[7b] mp 80.5–81.5°).

***endo*-5,6-Trimethylene-2-norbornanone (III).**—*endo*-5,6-Trimethylene-*exo*-2-norbornanol was oxidized with use of the modified procedure developed in this laboratory.[20] The crude product, obtained in 95% yield, was essentially free of the starting material as shown by glpc analysis. The product was purified by sublimation, mp 102–104° (lit.[7b] mp 97–103°).

Registry No.—I, 19138-60-4; 8,9-dehydro-V, 36807-74-6; 9,10-dehydro-V, 36807-75-7; *endo*-dicyclopentadiene, 1755-01-7.

(22) R. Stewart, "Oxidation Mechanisms," W. A. Benjamin, New York N. Y., 1964, p 39.

Effects of Substituents on the Rates of Disproportionation of Substituted Phenylglyoxals in Alkaline Solution[1a,b]

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A series of meta- or para-substituted phenylglyoxals, including H, *p*-CH_3, *p*-OCH_3, *p*-Br, *p*-Cl, *p*-phenyl, *m*-OCH_3, *p*-NO_2, and *p*-OH, were examined for linear free energy relationships between chemical reactivity and substituent constants, and between chemical reactivity and carbonyl stretching frequencies of the ketone and aldehyde carbonyls. At pH 12, the hydroxide ion catalyzed disproportionation of the phenylglyoxals into the corresponding mandelic acids follows the Hammett relationship with ρ 2.0, indicative of a transition state stabilized by electron-withdrawing groups. These rates of disproportionation also correlate quite well with the carbonyl stretching frequencies of the ketone carbonyls, both for the hydrated and the anhydrous phenylglyoxals. The aldehyde carbonyl stretching frequencies are essentially independent of ring substituents, $\nu_{C=O}$ 1727 ± 2 cm^{-1}. The disproportionation of α-keto aldehydes is known to involve intramolecular hydride migration. The results of the present study suggest that hydride migration is the rate-determining step in the disproportionation of this series of substituted phenylglyoxals.

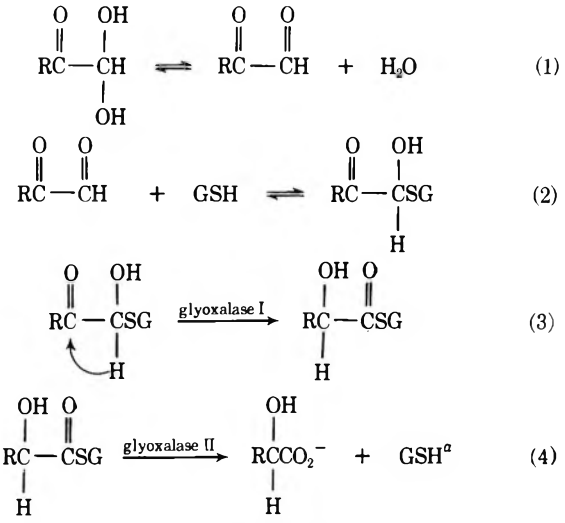
The glyoxalase system is composed of two enzymes: glyoxalase I, which utilizes glutathione (GSH) as coenzyme and catalyzes the disproportionation of methylglyoxal into the thiol ester of lactic acid and GSH, and glyoxalase II, which hydrolyzes this thiol ester to regenerate GSH and liberate lactic acid.[2,3] Scheme I

(1) (a) This work was supported by U. S. Public Health Service, National Cancer Institute (1RO1 CA 11850-01), and U. S. Atomic Energy Commission under Sandia Corporation Contract 51-1985. An equipment grant from Research Corporation is also gratefully acknowledged. (b) A preliminary report of this work was presented at the Southwest Regional Meeting of the American Chemical Society, San Antonio, Tex., Dec 1971. (c) Address correspondence to this author at the Department of Biochemistry, University of New Mexico School of Medicine, Albuquerque, N. M. 87106.

(2) E. Racker, *J. Biol. Chem.*, **190**, 685 (1951).

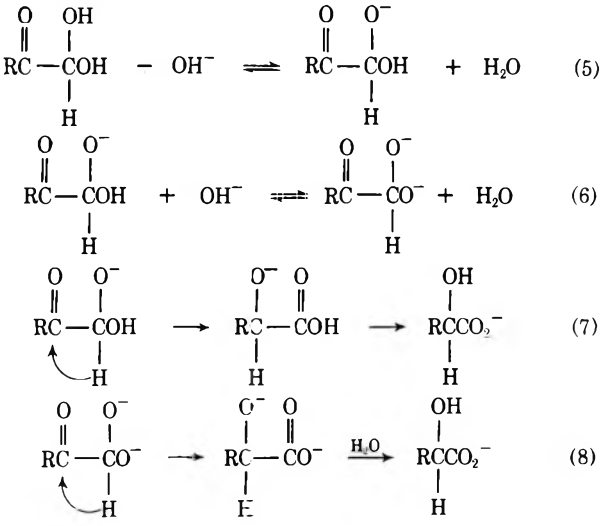
(3) Review article on glutathione and the glyoxalase system: W. E. Knox in "The Enzymes," Vol. 2, P. D. Boyer, H. Lardy, and K. Myrback, Ed., Academic Press, New York, N. Y., 1960, p 253.

SCHEME I



[a] GSH = γ-L-glutamyl-L-cysteinylglycine.

SCHEME II



summarizes the reactions of the glyoxalase system. Reactions 1 and 2 of Scheme I are preenzymic reactions to form a hemimercaptal, which is the actual enzyme substrate.[4,5] The net reaction in the glyoxalase system is the conversion of an α-keto aldehyde into an α-hydroxycarboxylic acid. This is analogous to an intramolecular Cannizzaro reaction involving hydride migration from the aldehydic group to the α carbon. The glyoxalase I reaction (reaction 3 of Scheme I) is known to occur without solvent exchange of the aldehydic hydrogen,[6,7] as in the Cannizzaro reaction. The importance of the glyoxalase system is not yet clear. It is ubiquitous in nature, and there have been suggestions that the system may play an important role in the regulation of cell growth.[8] The general ability of methylglyoxal and other α-keto aldehydes to inhibit the growth of both bacteria and mammalian cells is well established[9,10] and has resulted in the specific suggestion that the glyoxalase system may function in a regulatory capacity by monitoring intracellular methylglyoxal (or other α-keto aldehydes) concentrations.[11]

The disproportionation of α-keto aldehydes in alkaline solution is also an intramolecular Cannizzaro reaction. This reaction has been studied extensively, especially for phenylglyoxal,[12-14] and also involves migration of the aldehydic hydrogen without exchange with solvent.[13] Furthermore, Hine and Koser[14] have established that the disproportionation of phenylglyoxal involves intramolecular hydride migration as the rate-determining step. A summary of their proposed reaction sequence is given in Scheme II. Comparison of the two reaction schemes shows the formal similarity between the enzyme-catalyzed reaction (3) and the hydroxide-catalyzed reactions (7 and 8).

We have examined the effects of substituents on the hydroxide-catalyzed disproportionation of a series of substituted phenylglyoxals in order to (1) test whether reactions 7 and 8 involve rate-determining hydride migration for a broad series of meta or para substituents; (2) examine this reaction for linear free energy relationships between reactivity and substituent constants; (3) attempt to explain the observed reactivity by analyzing the carbonyl stretching frequencies of the aldehyde and ketone carbonyls; (4) obtain an understanding of reactions 7 and 8 as models for the glyoxalase I reaction. We recently observed that the glyoxalase I catalyzed disproportionation of substituted phenylglyoxals is insensitive to ring substituents.[15] This raises the question of whether reaction 3 involves rate-determining hydride migration or whether hydride migration simply shows a very small substituent effect. Reactions 7 and 8 thus become critical models for reaction 3.

Results and Discussion

The rates of disproportionation of a series of substituted phenylglyoxal hydrates, including H, *p*-CH_3, *p*-OCH_3, *p*-Br, *p*-Cl, *p*-phenyl, *m*-OCH_3, and *p*-NO_2, were measured at pH 12 by following the changes in the uv absorbances at the λ_{max} of the hydrates. *p*-Hydroxyphenylglyoxal was also examined. This member of the series disproportionated slowly at pH 12 and, consequently, was examined at higher pH. The *p*-OCH_3 derivative was also examined at this higher pH (*ca.* 0.1 *M* NaOH solution) and the factor $k_{p\text{-}OCH_3}/k_{p\text{-}O^-} = 39$ was assumed valid at pH 12. The *p*-OH derivative exists as the *p*-O^- anion at high pH. The pseudo-first-order rate constants obtained and the wavelengths employed are listed in Table I. There is a 3600-fold range in rate constants between the *p*-NO_2 and *p*-O^- derivatives, indicative of transition-state stabilization by electron-withdrawing groups. Figure 1 shows a Hammett plot of log *k* *vs.* σ_x[16] for this series of com-

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(16) σ Values taken from J. Hine, "Physical Organic Chemistry," 2nd ed., McGraw-Hill, New York, N. Y., 1962, p 87.

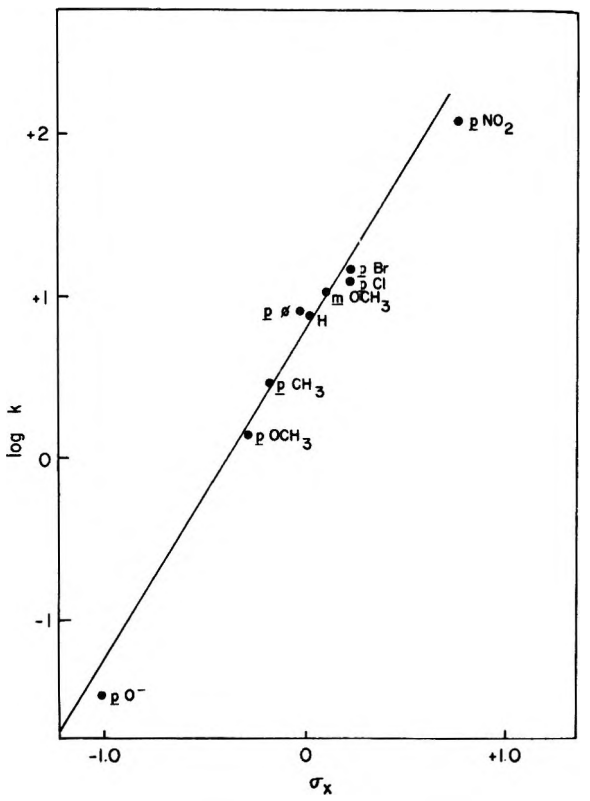

Figure 1.—Hammett plot of log k, the rate constants for the disproportionation of the substituted phenylglyoxals, pH 12, *vs.* σ_x. Slope, ρ, is 2.0.

TABLE I

RATE CONSTANTS FOR THE DISPROPORTIONATION OF SUBSTITUTED PHENYLGLYOXALS, pH 12, 25°[a]

Registry no.	x	k, 10^{-4} sec^{-1}	log k	σ_x[c]	λ, nm[d]
1074-12-0	H	7.60 ± 0.13	0.881	0.0	251
1075-47-4	*p*-CH_3	3.05 ± 0.05	0.484	−0.170	263
1076-95-5	*p*-OCH_3	1.37 ± 0.04	0.137	−0.268	287
5195-29-9	*p*-Br	13.9 ± 0.1	1.143	+0.232	264
4998-15-6	*p*-Cl	12.2 ± 0.3	1.086	+0.227	260
4974-58-7	*p*-Ph	7.91 ± 0.08	0.898	−0.01	292
32025-65-3	*m*-OCH_3	10.1 ± 0.1	1.004	+0.115	255
4974-57-6	*p*-NO_2	125 ± 5	2.097	+0.778	268
24685-80-5	*p*-O^-	0.035[b]	−1.46	−1.00	284

[a] Rates measured spectrophotometrically in phosphate buffer, μ 0.6. [b] *p*-OH phenylglyoxal exists as the *p*-O^- derivative at high pH. Since this substituted phenylglyoxal is quite stable at pH 12, it was disproportionated at higher pH along with the *p*-OCH_3 compound, and the factor *p*-OCH_3/*p*-O^- = 39 was assumed applicable at pH 12. [c] Values for σ_x obtained from ref 16. [d] λ_{max} values of the substituted phenylglyoxal hydrates, pH 7. The rates of disproportionation were monitored at these wavelengths.

pounds. A fairly good linear free energy relationship is observed. The slope, ρ, is 2.0, comparable in size and magnitude to the OH^--catalyzed hydrolysis of substituted methyl benzoates.[17] The linear relationship over this wide range of substituents suggests a common mechanism for this series of disproportionations.

In their study on the mechanism of disproportionation of phenylglyoxal hydrate, Hine and Koser[14] reported that the rate-determining step is the intramolecular hydride migration (reaction 7 or 8 of Scheme II) and that reaction 8 predominates at hydroxide concentrations above 3 mM. At pH 12, both the mono- and dianion should contribute to the observed rate with the majority of reaction occurring *via* the dianion. The existence of a linear relationship for the entire series of substituted phenylglyoxals examined in the present study at pH 12 can be explained if reaction 8 involving the dianion species is the major reaction taking place for all of the substituted phenylglyoxals examined. However, this would require that the acidities of the hydrates (*i.e.*, reactions 5 and 6 of Scheme II) show little or no sensitivity to substituents, so that at pH 12 the reactions primarily are the disproportionations of the dianions. Alternatively, the acidities of the hydrates could be sensitive to substituents, but reactions 7 and 8 could have identical sensitivities to substituents. This alternative seems unlikely. To examine whether the acidities of the hydrates are insensitive to substituents, the carbonyl stretching frequencies of the substituted phenylglyoxals were determined for the ketones in the hydrated compounds and for both the aldehydes and the ketones in the unhydrated compounds. The values are listed in Table II. The aldehyde carbonyl stretching

TABLE II

INFRARED CARBONYL STRETCHING FREQUENCIES OF THE KETONE AND ALDEHYDE CARBONYLS OF SUBSTITUTED PHENYLGLYOXALS AND THEIR HYDRATES

	$\nu_{C=O}$, cm^{-1}		
Substituent	Ketone	Aldehyde	Ketone (hydrated series)
H	1676	1727	1699
p-CH_3	1674	1726	1688
p-OCH_3	1666	1728	1681
p-Br	1680	1729	1695
p-Cl	1679	1729	1695
p-Ph	1673	1726	1694
m-OCH_3	1674	1726	1693
p-NO_2	1688	1729	1708
p-OH	1664	1728	1681

frequency is 1727 ± 2 cm^{-1}, totally insensitive to ring substituents, while the ketone carbonyls are quite sensitive to ring substituents, both for the hydrates and the unhydrated phenylglyoxals. If one assumes that the carbonyl stretching frequency reflects sensitivity to nucleophilic addition, one might expect that the extent of hydration of the aldehyde in aqueous solution and the pK_a values of the hydrates will be similar for this entire series of phenylglyoxals. This would help explain the linear relationship observed in the rates of disproportionation at pH 12. This conclusion that the chemistry at the aldehyde group is insensitive to substituents agrees with earlier observations that the rates of addition of glutathione to the aldehyde groups of substituted phenylglyoxals (reaction 2, Scheme I) and the dissociation constants of the resulting hemimercaptals are insensitive to ring substituents.[15]

If hydride migration is rate determining, and if the ketone carbonyl stretching frequencies reflect the influence of the ring substituents, linear relationships might be expected in plots of log k *vs.* $\nu_{C=O}$. Figures 2 and 3 show plots of log k *vs.* the ketone carbonyl stretching frequencies of the hydrates and the unhydrated phenylglyoxals, respectively. Fairly good

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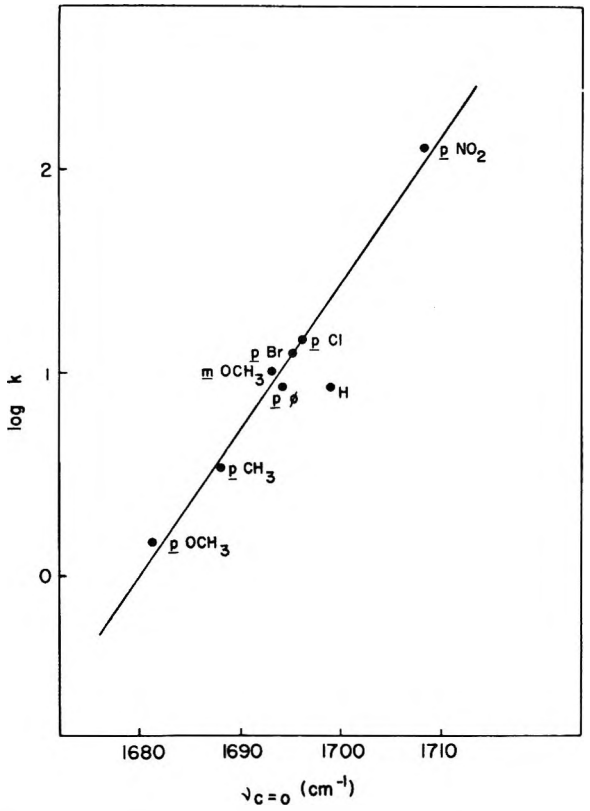

Figure 2.—Plot of log k, the rate constants for the disproportionation of the substituted phenylglyoxals, pH 12, *vs.* the ketone carbonyl stretching frequencies of the hydrated phenylglyoxals.

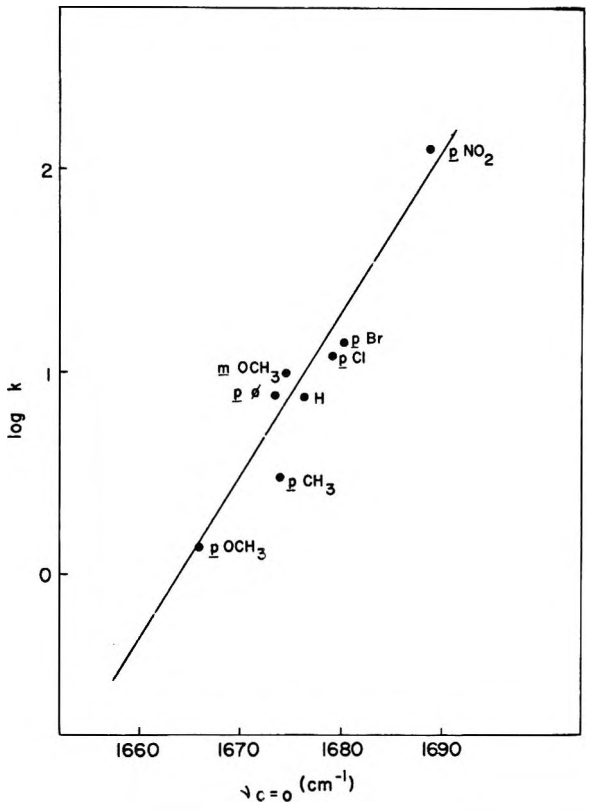

Figure 3.—Plot of log k, the rate constants for the disproportionation of the substituted phenylglyoxals, pH 12, *vs.* the ketone carbonyl stretching frequencies of the anhydrous phenylglyoxals.

linear free energy relationships are observed in both cases. The sensitivity of the reaction is about one log unit of k for a $\Delta\nu_{C=O}$ of 13 cm^{-1}. These results agree with the general conclusion that the carbonyl stretching frequency can be a good indicator of chemical reactivity. Previous studies have shown that ketone carbonyl stretching frequencies can also be good models for predicting reactivities of ester solvolyses proceeding by carbonium ion intermediates.[18,19]

The usefulness of reaction 7 and 8 as models for the glyoxalase I reaction (reaction 3, Scheme I) is limited. The high sensitivity of the OH^--catalyzed disproportionation of substituted phenylglyoxals to substituents compared to the lack of sensitivity[15] in the glyoxalase I reaction suggests that hydride migration may not be the rate-determining step in the enzyme reaction.

Experimental Section

The substituted phenylglyoxals used in this study were synthesized by the following general procedures.

Procedure A.[20]—A substituted acetophenone as a 1–2 M solution in dioxane containing an equivalent amount of selenous acid was refluxed for 4 hr. The mixture was concentrated by rotary evaporation, and the residue was vacuum distilled. The resulting oil was added to hot water to form the crystalline substituted phenylglyoxal hydrate, which was recrystallized from a mixture of chloroform and acetone.

Procedure B.[21]—A slurry of a substituted phenacyl bromide in acetonitrile was treated with a slight excess of $AgNO_3$. The resulting mixture was stirred for 24–48 hr at room temperature and filtered, and the solvent was removed by rotary evaporation. The residue (a phenacyl nitrate) was dissolved in diethyl ether and washed with water. After drying over $MgSO_4$, the solvent was removed, and the residue was added to dimethyl sulfoxide containing about 1% sodium acetate. The mixture was stirred at room temperature for 30 min and then was poured into ice–water saturated with NaCl. The resulting mixture was extracted with diethyl ether, washed with water, and dried over $MgSO_4$, and then the solvent was evaporated off. The resulting substituted phenylglyoxal hydrate was recrystallized as in procedure A.

The substituted phenylglyoxal hydrates prepared by either procedure were colorless solids except for the p-NO_2 derivative, which did not form a crystalline hydrate. The melting points, however, were observed to be somewhat variable during the recrystallization procedures. This presumably is a reflection of the extent of hydration and has also been observed by others.[14] All of the substituted phenylglyoxals were converted into the dioxime derivatives for elemental analysis. The data for characterization of the series of phenylglyoxals are given in Table III.

Rates of Disproportionation.—Phosphate buffers, pH 12, μ 0.6, were prepared by adding KOH to solutions of Na_2HPO_4 in distilled, deionized water. The ionic strength was due entirely to the buffer species. The pH measurements were made on a Sargent Welch Model DR pH meter with a glass electrode. Reaction rates were monitored at the λ_{max} values of the substituted phenylglyoxals obtained from uv spectra recorded in pH 7 phosphate buffer using a Cary 15 recording spectrophotometer. In all cases, the substituted phenylglyoxals have molar extinction coefficients of *ca.* 10^4 M^{-1} cm^{-1} at the λ_{max} whereas the substituted mandelate products show low absorption at these wavelengths. The reaction rates were measured on a Gilford 222 recording spectrophotometer employing Beckman DU optics. The temperature was controlled (±0.2°) with a circulating water bath. First-order rate constants were obtained from computer-calculated least squares slopes of plots of log absorbance change *vs.* time. Correlation coefficients were generally better than 0.999. Reactions were initiated by addition of small quantities (10-20 μl) of 1:1 ethanol-H_2O stock solution of the substituted phenylglyoxals. These small quantities were placed on the end of a flattened stirring rod and introduced directly into the spectrophotometer cell containing 3.0 ml of temperature-equilibrated buffer. The ethanol was generally useful for preparing stock

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TABLE III
CHARACTERIZATION OF SUBSTITUTED PHENYLGLYOXALS

Substituent	Synthetic procedure	Mp of hydrate, °C	Mp of dioxime, °C	Elemental analysis of dioxime, % C	H	N
H	A	76-77	174-176	58.53	4.91	17.06 calcd
				58.70	5.10	17.04 obsd
p-CH_3	A	98-99	166.5-168.2	60.67	5.66	15.96
				60.81	5.63	15.87
p-OCH_3	B	126-127.5	152-153	55.67	5.19	14.43
				55.85	5.14	14.26
p-Br	B	133.5-134.9	167.5-168.5	39.53	2.90	11.52
				39.74	3.14	11.39
p-Cl	B	120-122	159-160	48.38	3.55	14.10
				48.28	3.73	14.33
p-Ph	B	116-118	216-218	69.99	5.03	11.66
				70.02	4.94	11.59
m-OCH_3	B	77-78.5	163.5-164.8	55.67	5.19	14.43
				55.73	5.10	14.55
p-NO_2	A	13[illegible]-132 (3 mm)[a]	186-188	45.94	3.37	20.09
				45.92	3.54	20.40
p-OH	A	86.5-87.5	190-193	53.33	4.48	15.55
				53.15	4.73	15.86

[a] Boiling point of *p*-NO_2 derivative.

solutions of convenient concentrations. Use of stock solutions without ethanol gave the same rate data. The initial concentrations of substituted phenylglyoxals in the reaction cell were generally *ca.* 10^{-4} *M*.

Carbonyl Stretching Frequencies.—The ketone and aldehyde carbonyl stretching frequencies were measured on a Perkin-Elmer 621 recording spectrophotometer using very slow scan rates and expanded scales. Generally, the range 1800–1600 cm^{-1} was scanned over a 1-hr period, and a polystyrene standard was added to the cell holder immediately after the carbonyl band was passed in order to accurately locate the carbonyl stretching frequency. This procedure gave values reproducible to ± 1.5 cm^{-1}.

The ketone carbonyl stretching frequencies of the substituted phenylglyoxal hydrates were measured in Nujol mulls. The ketone and aldehyde carbonyl stretching frequencies of the unhydrated compounds were determined in dilute acetonitrile solutions. Although carbonyl frequencies are generally measured in carbon tetrachloride solutions, it was found that the unhydrated phenylglyoxals in carbon tetrachloride rapidly deteriorate, presumably by polymerization. Only a trace of water is required to initiate polymerization. Acetonitrile solutions were sufficiently stable to allow slow scanning rates to be used. The anhydrous solutions were prepared by warming acetonitrile solutions of the hydrates over molecular sieves, with repeated transfers to fresh molecular sieves.

Dehydrogenation of α-(Phenylthio)cyclohexanone Accompanying Oxime Formation

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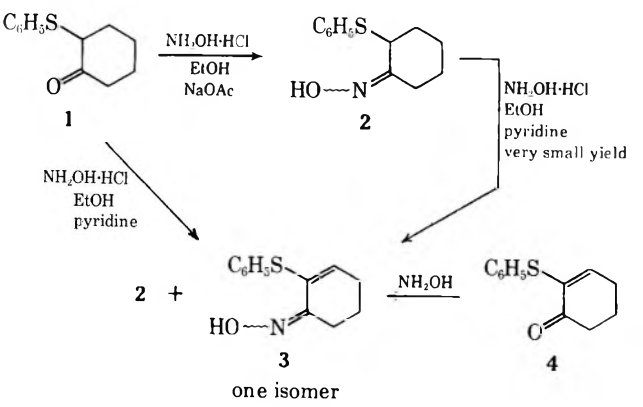
Treatment of **1** with hydroxylamine hydrochloride in ethanol–pyridine gave **3**. Compound **3** is the product of a novel oxidation–reduction reaction in the course of which a new carbon–carbon double bond is introduced.

In the course of the reaction of 2-(phenylthio)cyclohexanone (**1**) with hydroxylamine hydrochloride we have made the following observations. When the reaction was run with ethanol as the solvent and sodium acetate as the base the expected product, oxime **2**, was obtained as a mixture of *Z* and *E* isomers. On the other hand, with ethanol as the solvent and pyridine as the base, oxime **2** was obtained accompanied by an additional product **3**, clearly a result of an oxidation–reduction process. Treatment of oxime **2** under the conditions for the conversion of **1** to **3** produced very little of **3**. The resulting mixture was subjected to gc and mass spectral analysis of the TMS derivatives (*cf.* Experimental Section) and it was shown that less than 5% of **3** was produced by this route.



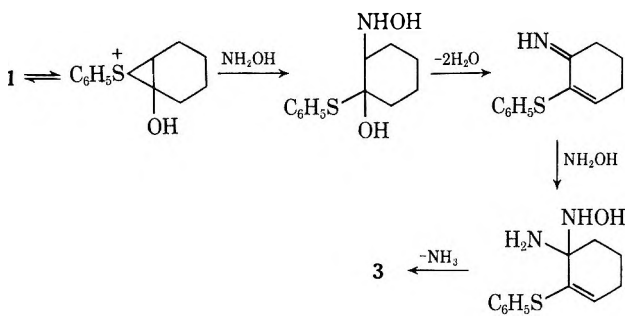
The structure of **3** was supported by (a) the nmr spectrum, which was compatible with the presence of one vinyl proton adjacent to a methylene group, and (b) the mass spectrum, which showed a molecular ion at *m/e* 219. The TMS derivative of **3** showed a molecular ion at *m/e* 291, which clearly indicated that **3** is a dehydro derivative of **2**. When the mass spectra of **2** and **3** were compared it was realized that the loss of the radical $C_6H_5S\cdot$ from the molecular ion leads to the most intense ion *m/e* 112 ($M^+ - C_6H_5S\cdot$) in the case of **2**. This loss is a minor process in the case of **3**; the intensity of the *m/e* 110 ion ($M^+ - C_6H_5S\cdot$) was less than 8% of the base peak. This observation

confirms the proposal that the C_6H_5S in **3** is attached to a C=C bond. The mass spectra of the TMS derivatives of **2** and **3** show a similar behavior: an intense ion at *m/e* 184 (293 − $C_6H_5S\cdot$) in the case of 2-TMS, and a very weak ion at *m/e* 182 (291 − $C_6H_5S\cdot$) in the case of 3-TMS.

The structure of **3** was unequivocally established by synthesis from the 2-(phenylthio)-2-cyclohexenone (**4**).[1]

We propose the following mechanism for the conversion of **1** to **3** (Scheme I).

SCHEME I

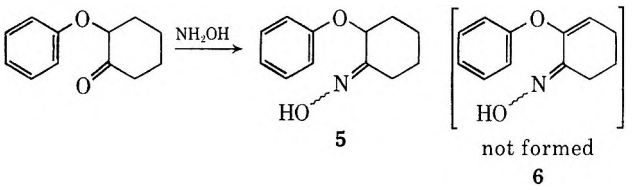


The overall reaction can be summarized as

$$1 + 2NH_2OH \longrightarrow 3 + NH_3 + 2H_2O$$

Alternative mechanisms, which proceed *via* the initial formation of oxime **2**, do not play a major role because we have demonstrated that oxime **2** produces very little of **3** when subjected to the conditions used for the conversion of **1** to **3**.

Participation of sulfur in the proposed mechanism shown in Scheme I is supported by the fact that in the following reaction the formation of **6** was not observed and only the expected oxime **5** was obtained.



Experimental Section

Melting points were taken in a capillary tube and are uncorrected. Uv spectra were determined in 95% EtOH using a Cary Model 14 spectrophotometer. Ir spectra were determined in Nujol using a Perkin-Elmer Model 421 recording spectrophotometer. Nmr spectra were recorded on a Varian Model A-60A; chemical shifts were recorded in parts per million downfield from Me_4Si; $CDCl_3$ was used as a solvent. Mass spectra were recorded using an LKB-9000 gc–mass spectral unit. The silica gel used for chromatography was obtained from E. Merck A. G., Darmstadt, Germany.

2-(Phenylthio)cyclohexanone (*Z*)- [and (*E*)-] Oxime (2). Reaction of 2-(Phenylthio)cyclohexanone (1) with Hydroxylamine HCl and NaOAc in Ethanol.—A solution of 2-thiophenylcyclohexanone[2] (5 g, 0.0243 mol) in 70 ml of ethanol was added to a solution of hydroxylamine hydrochloride (3.5 g, 0.0486 mol) and sodium acetate (6 g, 0.0729 mol) in 20 ml of water. The mixture was stirred for 20 hr and then concentrated *in vacuo* at 32° to a small volume. Ether and H_2O were added, the aqueous layer was extracted once with ether, and the combined ether solution was washed with H_2O and saturated salt solution, dried ($MgSO_4$), and evaporated.[3] Crystallization from ether–petroleum ether (bp 30–60°) gave 2.7 g of the *Z*–*E* mixture of oxime **2** melting at 74–80°: uv sh 213 nm (ε 11,650); λ_{max} 256 (4350); ir 3280 (OH); 1660 (C=N), 1585, 1480 (C=C), 1025 (NO), 980, 970, 925, 895, 885, aromatic 750, 705, 695 cm^{-1}; nmr showed a ratio of *ca.* 14% (*Z*)-oxime and 86% (*E*)-oxime based on the –SCH– positions at δ 5.1 and 4.0, respectively; mass spectrum *m/e* 221 (M^+), 204 (M^+ − OH), 112 (M^+ − SC_6H_5), 110 ($C_6H_5SH^+$)

Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33; S, 14.49. Found: C, 65.38; H, 6.95; N, 6.17; S, 14.55.

The filtrate was evaporated to give 3.1 g of an oil. Ir, uv, mass spectrum, and nmr were identical with those of the above solid.

In another seemingly identical experiment nmr showed 100% (*E*)-oxime, indicating ready equilibration of the (*Z*)- and (*E*)-oxime mixture.

2-(Phenylthio)-2-cyclohexenone Oxime (3). A. Reaction of 2-(Phenylthio)cyclohexanone (1) with Hydroxylamine HCl in Ethanol and Pyridine.—A mixture of 2-thiophenylcyclohexanone (10 g, 0.0485 mol), hydroxylamine hydrochloride (10 g, 0.144 mol), 10 ml (0.127 mol) of pyridine, and 80 ml of ethanol was refluxed for 17 hr, evaporated at 50° *in vacuo*, and worked up as usual.[3] The residue (10.3 g) was crystallized from ether–petroleum ether to give 2.8 g of crude **3**: mp 111–115°, raised to 133–134° on recrystallization from methanol; uv λ_{max} 217 nm (ε 16,100), sh 233 (13,300), 280 (3050); ir 3230 (OH), 1655 (weak, broad, C=N/C=C), 1625, 1595, 1580, 1570; 1000, 960 (NO); aromatic 760, 740, 710, 700 cm^{-1}; nmr (100 MHz) δ 9.94 (s, 1, OH), 7.35 (m, 5, aromatic H), 6.10 (t, 1, vinyl H, *J* = 4.8 Hz), 2.75 (t, 2, CH_2C=N, *J* = 6.0 Hz), 2.21 (q, 2, SC=$CHCH_2$), 1.74 (quintet, 2, $CH_2CH_2CH_2$, *J* = 6 Hz); mass spectrum 219 (M^+), 202 (M^+ − OH).

Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39; S, 14.62. Found: C, 65.50; H, 5.89; N, 6.32; S, 14.63.

The yield of **3** was improved to 27% when the original crude reaction product was chromatographed on silica gel (1:100) using 30% EtOAc–cyclohexane as the eluent.

When the above experiment was repeated using 10 g (0.0485 mol) of **1**, 33.3 g (0.485 mol) of hydroxylamine hydrochloride, 33.3 ml (0.411 mol) of pyridine, and 240 ml of ethanol, analysis of the product on the LKB-9000 showed compound **1**, 1.74%; diphenyl disulfide, 5.96%; compound **2**, 78.96% (±2%); and compound **3**, 13.33%.

B. Reaction of 2-(Phenylthio)-2-cyclohexenone (4) with Hydroxylamine.—A mixture of **4**[4] (0.15 g, 0.74 mmol), hydroxylamine hydrochloride (0.15 g), 0.15 ml of pyridine, and 2 ml of ethanol was refluxed for 22 hr, evaporated, and worked up as usual[3] to give 0.119 g of crude **3**. Analysis on the LKB-9000 showed diphenyl disulfide, 1.3% (M^+ 218); compound **3**, 96.88% (M^+ 219); unknown impurity, 1.8% (M^+ 281). Crystallization from methanol gave pure **3**, mp 136–137°, which was identical with the sample obtained previously as shown by tlc (silica gel, 20% ethyl acetate–cyclohexane), ir, uv, and nmr.

Reaction of 2 with Hydroxylamine HCl in Ethanol and Pyridine.—A mixture of **2** (0.5 g),[4] hydroxylamine hydrochloride (0.5 g), 0.5 ml of pyridine, and 4 ml of ethanol was refluxed for 17.5 hr. It was evaporated *in vacuo* and worked up as usual[3] to give 0.4 g of a yellow oil which solidified on standing.

Nmr showed a ratio of *ca.* 25% (*Z*)-oxime and 75% (*E*)-oxime **2** based on the –SCH positions at δ 5.10 and 4.0, respectively. No vinyl hydrogen was detectable by nmr.

Some of this material (*ca.* 10 mg) was dissolved in chloroform and treated with 100 μl of Regisil RC-2.[5] The resulting TMS–ether mixture was analyzed on the LKB-9000 mass spectrometer using a 6-ft, 3.8% UC-N-98 column on Diatoport S (80–100 mesh) at 200°. The mixture contained five components which were identified by their mass spectra. The composition was as follows: compound **1**, 0.95% (M^+ 206); diphenyl disulfide, 3.17% (M^+ 218); compound (*Z*)-**2**, 4.6% (M^+ 293); compound (*E*)-**2**, 86.9% (M^+ 293); compound **3**, 4.36% (M^+ 291).

Reaction of 2-Phenoxycyclohexanone with Hydroxylamine HCl

(1) T. Mukaiyama, T. Adachi, and T. Kumamoto, *Bull. Chem. Soc. Jap.*, **44**, 3155 (1971). We thank Professor T. Mukaiyama of the Tokyo Institute of Technology, Tokyo, Japan, for a generous sample of 2-(phenylthio)-2-cyclohexenone.

(2) F. Winternitz, N. J. Antia, M. Tumlirova, and R. Lachazette, *Bull. Soc. Chim. Fr.*, 1817 (1956).

(3) This work-up was employed in subsequent experiments, but the ether extract was first washed with 10% aqueous hydrochloric acid solution.

(4) *Ca.* 100% (*E*)-oxime by nmr; gc–mass spectral analysis of the TMS derivative showed no **3** present.

(5) Purchased from Regis, 99% bissilyltrifluoroacetamide (BSTFA) and 1% trimethylchlorosilane.

in Ethanol and Pyridine. 2-Phenoxycyclohexanone (*Z*)- [and (*E*)-] Oxime (5).[2]—A mixture of 2-phenoxycyclohexanone[2] (10, g, 0.0525 mol), hydroxylamine hydrochloride (10 g, 0.144 mol), 10 ml of pyridine, and 80 ml of ethanol was refluxed for 17 hr and worked up as usual.[3] The crude product (10.43 g) showed a ratio of *ca.* 25% (*Z*)-oxime and 75% (*E*)-oxime 5 based on the -OCH- positions at δ 5.70 and 4.82, respectively. No vinyl hydrogen was detectable by nmr. The mass spectrum showed a molecular ion at *m/e* 205 and a peak at 203 (*ca.* 2%) which can be due either to M − 2 ion, or less likely, to a dehydro compound. The above oxime mixture showed the same nmr and mass spectra after distillation at 0.05 mm (bp 145–155°).

Registry No.—**1**, 27920-40-7; (*Z*)-**2**, 36540-08-6; (*E*)-**2**, 36540-09-7; **3**, 36540-10-0; (*Z*)-**5**, 36540-11-1; (*E*)-**5**, 36540-12-2.

The Reactivity of Diazo Ketones. II.[1] Reaction of α-Diazo Ketones with Sulfur Dioxide

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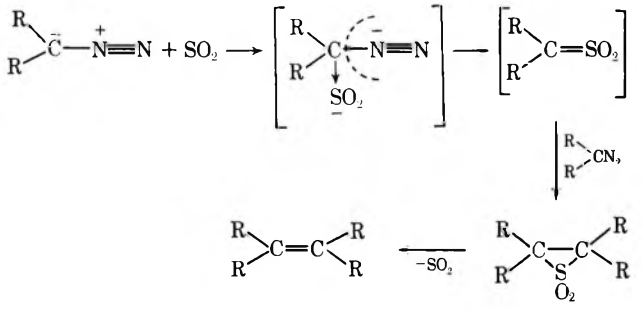
Received March 10, 1972

Reactions of some α-diazo ketones with sulfur dioxide were carried out by means of pyrolysis or photolysis. The reactions appeared to proceed *via* a free ketocarbene and a remarkable substituent effect was observed. Diazo ketones of the type $PhCN_2COR$ (R = Ph, Me) gave six-membered cyclic sulfones and sultones, while diazo ketones of the type RCN_2COPh (R = H, Me) gave products resulting from a 1,2-hydrogen shift or a 1,3-dipolar addition reaction of the ketocarbene intermediate. The mechanism of these reactions and the radical reactivity of the PhCCOR type ketocarbenes are discussed in this report.

A number of reactions of sulfur dioxide with diazo alkanes have been reported.[2,3] These reactions proceed readily at low temperature to form either stable or transient episulfones, followed by evolution of sulfur dioxide to give olefins. The proposed mechanism is as follows (Scheme I).

SCHEME I

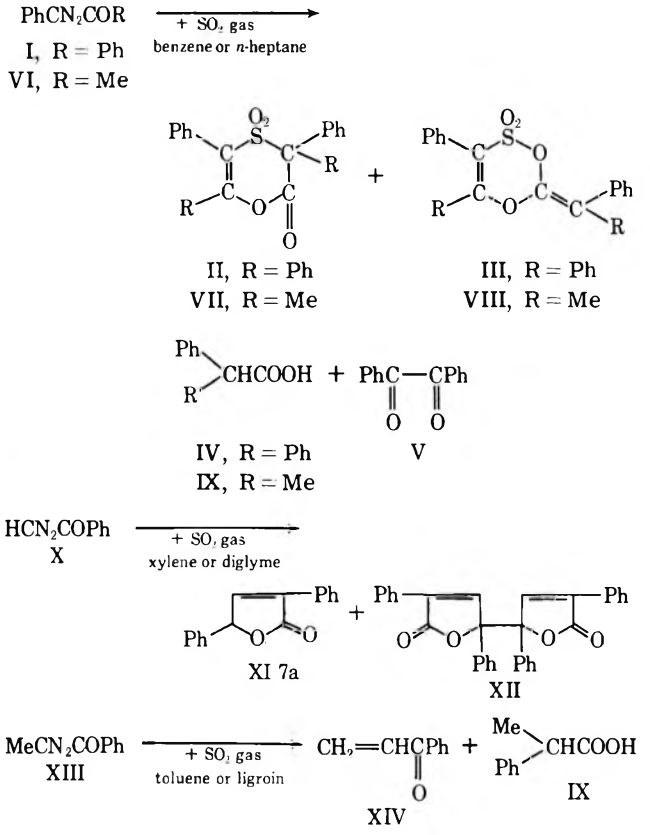
REACTION OF DIAZO ALKANE WITH SO_2



In a preceding communication,[1] we reported that the reaction of azibenzil (I) with sulfur dioxide did not proceed at room temperature, but proceeded at elevated temperature or by means of photolysis to give the cyclic sulfone II and sultone III,[4] instead of the expected episulfone or olefin (Scheme II). In order to obtain further information on the scope and mechanism of this reaction, the reactions of several α-diazo ketones with sulfur dioxide were investigated.

SCHEME II

THERMAL REACTIONS OF α-DIAZO KETONES WITH SO_2



These reactions proceeded only under conditions of pyrolysis or irradiation, and gave products which were different from those expected by analogy to the reaction of diazo alkanes with sulfur dioxide. Moreover, a significant substituent effect was observed; diazo ketones of structure A gave six-membered cyclic sulfones and sultones, while those of structure B gave no such sulfones or sultones, but rather products in which sulfur dioxide was not incorporated.

$C_6H_5CN_2COR$	$RCN_2COC_6H_5$
A, R = C_6H_5, CH_3	B, R = H, CH_3

(1) T. Nagai, M. Tanaka, and N. Tokura, *Tetrahedron Lett.*, 6293 (1968).

(2) (a) H. Staudinger and F. Pfenninger, *Chem. Ber.*, **49**, 1941 (1916); (b) H. Kloosterziel and H. J. Backer, *Recl. Trav. Chim. Pays-Bas*, **71**, 1235 (1952); (c) G. Hesse and E. Reichold, *Ber.*, **90**, 2106 (1957); (d) G. Opitz and K. Fischer, *Angew. Chem.*, **77**, 41 (1965).

(3) (a) L. V. Vargha and E. Kovacs, *Chem. Ber.*, **75**, 794 (1942); (b) G. Hesse, E. Reichold, and S. Majmudar, *ibid.*, **90**, 2106 (1957); (c) G. Hesse and S. Majmudar, *ibid.*, **93**, 1129 (1960).

(4) In the previous communication,[1] four-membered cyclic structures were postulated for the cyclic sulfone and sultone. Storthers, Danks, and King have proposed six-membered ring sulfone and sultone from the analysis of ^{13}C nmr spectra of the two compounds [*Tetrahedron Lett.*, 2551 (1971)]. Recently, the X-ray analyses of these compounds made by the present authors have also supported the six-membered sulfone. The details of the result are to be published shortly [N. Yasuoka, N. Kasai, M. Tanaka, T. Nagai, and N. Tokura, *Acta Crystallogr.*, No. 12 (1972)].

Results and Discussion

As described above, the reactions of α-diazo ketones ($R_1CN_2COR_2$) with sulfur dioxide did not proceed at room temperature, but the reaction could be made to occur at elevated temperature or by means of irradiation. Results of the thermal reactions are shown in Scheme II and Table I. The identification of these

TABLE I

THERMAL REACTION[a] OF $R_1CN_2COR_2$ WITH SO_2

R_1	R_2	Solvent	Temp, °C	Products (yield, mol %)[b]
Ph	Ph	Benzene	70	II (44), III (7), IV (23), V (23)
		n-Heptane	80	II (42.8), III (6.1), IV (20)
H	Ph	Xylene	130	XI (8.5), XII (72)
		Diglyme	140	XI (8), XII (76)
Me	Ph	Toluene	110	XIV (60), IX (trace)
		Ligroin	115	XIV (57), IX (trace)
Ph	Me	Benzene	60	VII (49), VIII (5), IX (17)
		n-Heptane	70	VII (47), VIII (6), IX (15)

[a] Reaction time 4.5 hr. [b] The yields are in mole per cent based on unrecovered starting material for IV, V, IX, and XIV, based on 0.5 mol of unrecovered starting material for II, III, VII, VIII, and XI, and based on 0.25 mol of unrecovered starting material for XII.

sulfones (II, VII) and sultones (III, VIII) was based on the ir, uv, nmr, and mass spectra and elementary analysis as described in the Experimental Section. Moreover, X-ray analysis[4] of the sulfone II indicated the presence of a six-membered ring.

These sulfones (II, VII) and sultones (III, VIII) have the structure expected from a [4 + 2][5a] cycloaddition of a keto sulfene with a ketene. Attempts to isolate cycloadducts of sulfenes and ketenes have not yet been successful.[5b] The present result might be the first observation[1,4] of the cycloaddition of sulfene to ketene.

The neat decomposition of II at 280° afforded tetraphenylethylene (XV) with evolution of sulfur dioxide gas. Basic hydrolysis of II and VII yielded quantitatively the related sulfones (XVI, XVII) and carboxylic acids (XIX, XX) (Scheme III).

The thermal reactions shown in Scheme II were carried out around the corresponding decomposition points of the diazo ketones. Benzene, toluene, or xylene were used as solvents. Also, the reactions were carried out in *n*-heptane, diglyme, or ligroin, but no appreciable solvent effect was observed (Table I). On the other hand, the substituent attached to the diazo carbon atom exerted a significant influence on the course of these reactions. In this case, however, it was not clear whether the substituent or the difference in the reaction temperature was responsible for the difference in the course of these reactions. In order to make this point clear, the photolysis of these diazo ketones was carried out under as similar conditions as possible, *i.e.*, in liquid sulfur dioxide at a low temperature (0–10°). The results are shown in Table II.

The results of photolysis closely resembled those of the thermal reactions, revealing an interesting sub-

SCHEME III

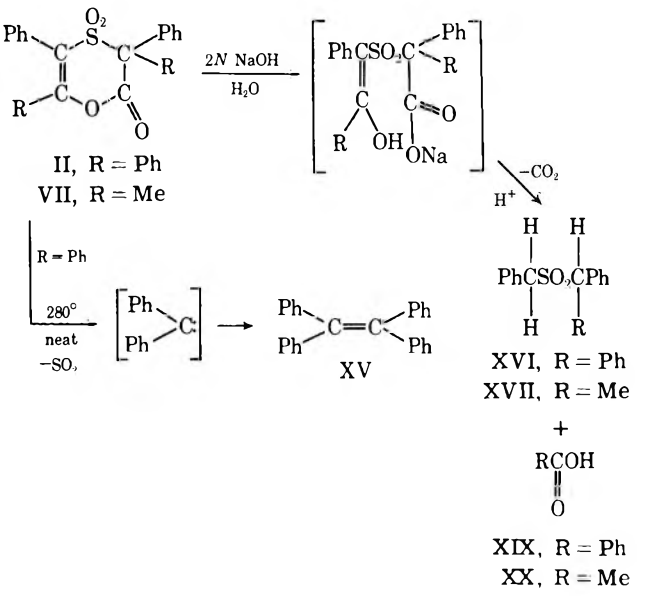


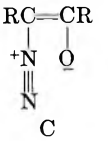
TABLE II

PHOTOLYSIS[a] OF $R_1CN_2COR_2$ IN LIQUID SO_2

R_1	R_2	Time, hr	Products (yield, mol %)[b]
Ph	Ph	6	II (35), III (17), IV (14)
H	Ph	8	XII (82), XI (trace)
Me	Ph	9	XIV (60), IX (trace)
Ph	Me	4	VII (54), VIII (11), IX (5)

[a] The irradiation was undertaken by using a 300-W high-pressure mercury lamp in a Pyrex tube at 0–10°. [b] See Table I, footnote *b*.

stituent effect; namely, $PhCN_2COR$ (R = Ph, Me) type diazo ketones gave six-membered cyclic sulfones (II, VII) and sultones (III, VIII), possibly *via* a free ketocarbene. By contrast, RCN_2COPh (R = H, Me) type diazo ketones yielded no sulfone or sultone, but gave products resulting from a 1,2-hydrogen shift[6] or a 1,3-dipolar cycloaddition[7] of the ketocarbene intermediates (Scheme II). It has been proposed[8] that the reactions of diazo alkanes with sulfur dioxide proceed by an electrophilic attack of sulfur dioxide on the diazo carbon atom, the evolution of N_2 occurring concertedly. In these reactions, such a substituent effect as observed here has not been found. Thus, both diazoethane and diphenyldiazomethane give similar products. It seems that with α-diazo ketones such a reaction as observed in diazo alkanes does not occur, since the electron density on the diazo carbon atom is too small for electrophilic attack by sulfur dioxide, owing to the conjugation with the carbonyl group (structure C).[7d]



major contribution

(5) (a) Fusco and coworkers have reported a [4 + 2] cycloaddition dimer of ketosulfene: *Gazz. Chim. Ital.*, **95**, 774 (1965). (b) W. E. Truce, J. J. Breiter, D. J. Abraham, and J. R. Norell, *J. Amer. Chem. Soc.*, **84**, 3030 (1962).

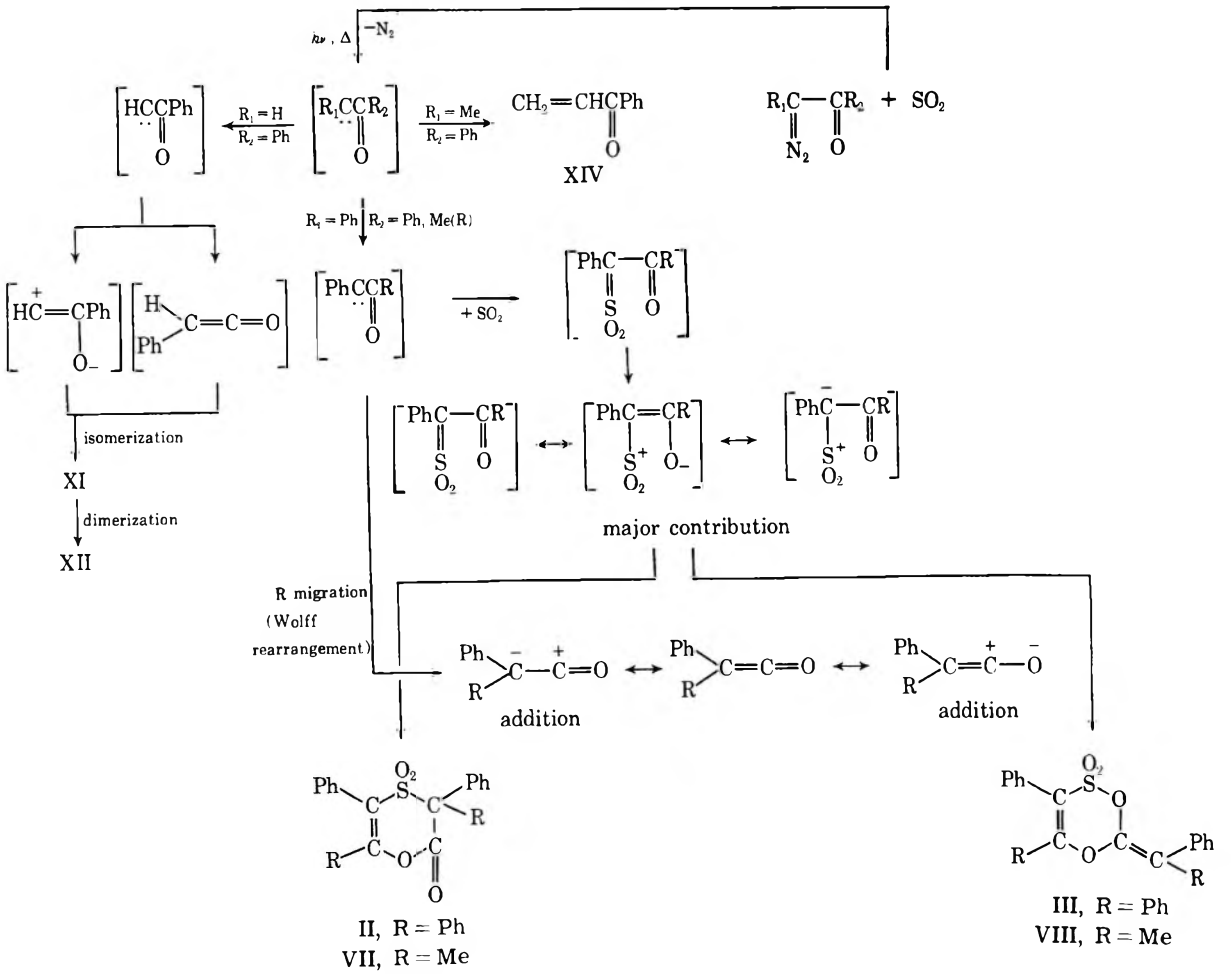
(6) (a) G. Baddeley, G. Holt, and J. Kenner, *Nature (London)*, **163**, 776 (1949); (b) V. Franzen, *Justus Liebigs Ann. Chem.*, **602**, 199 (1957).

(7) (a) D. Yates and T. J. Clark, *Tetrahedron Lett.*, 435 (1961); (b) R. Huisgen, G. Binsch, H. Konig, and H. J. Sturm, *Angew. Chem.*, **73**, 368 (1961); (c) G. Binsch, *ibid.*, **75**, 634 (1963); (d) W. Kirmse and L. Horner, *Justus Liebigs Ann. Chem.*, **625**, 34 (1959).

(8) G. Opitz, *Angew. Chem.*, **79**, 161 (1967).

SCHEME IV

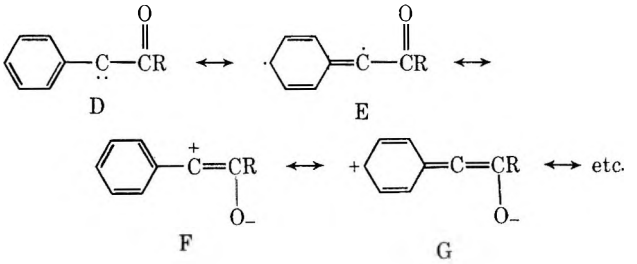
REACTION OF $R_1CN_2COR_2$ WITH SO_2



Since the diazo ketones were stable in liquid sulfur dioxide at 0–10° overnight, but decomposed under irradiation, the evolution of N_2 may occur in the first step to produce the ketocarbene as an intermediate. Thus, a ketocarbene and subsequently a ketosulfene may reasonably be postulated as the intermediate for the formation of the six-membered cyclic sulfones and sultones. The substituent effect may be explained in the following way. Ketocarbenes of the type PhCCOR (R = Ph, Me) (probably the triplet state) react with sulfur dioxide in competition with the Wolff rearrangement,[9] while RCCOPh (R = Me, H) type ketocarbenes (probably the singlet state) do not react with sulfur dioxide but undergo intramoleculr reactions such as 1,2-hydrogen shift or 1,3-dipolar reaction (Scheme IV).

As for the formation of ketosulfene from the reaction of the ketocarbene with sulfur dioxide, either a radical or a nucleophilic reaction is conceivable, although the ketocarbene may also be electrophilic because of the electron-withdrawing carbonyl group.[10]

It has been reported that carbenes can be stabilized by resonance with the phenyl ring[11] (eq 1).



(1)

At the present stage of our research, it seems plausible that the resonance form D or E of the PhCCOR type ketocarbene as shown in eq 1 above reacts with sulfur dioxide, for sulfur dioxide is known to react electrophilically and radically, but not nucleophilically.

Experimental Section

Materials.—Azibenzil (I), mp 78° (lit.[12] mp 78°), and phenylacetyldiazomethane (VI), mp 59–60° (lit.[12] mp 59–60°), were prepared by diazo transfer reactions from the related ketones.

(9) (a) L. Wolff, *Justus Liebigs Ann. Chem.*, **325**, 129 (1902); (b) L. Wolff, *ibid.*, **394**, 23 (1912); (c) G. Schroeter, *Ber. Deut. Chem. Ges.*, **42**, 3356 (1909).

(10) When the carbenes have such electron-withdrawing groups as carbonyl, sulfonyl, and ester groups, they are known to be strongly electrophilic. (a) W. Ando, T. Yagihara, S. Tozune, and T. Migita, *J. Amer. Chem. Soc.*, **91**, 2786 (1969); (b) J. Diekmann, *J. Org. Chem.*, **30**, 2272 (1965).

(11) The resonance of divalent carbon with the phenyl ring was proposed; see (a) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, p 214; (b) R. W. Murray and A. M. Trozzolo, *J. Org. Chem.*, **26**, 3109 (1961).

(12) M. Regitz, *Chem. Ber.*, **98**, 1210 (1965).

Diazoacetophenone (X), mp 48–50° (lit.[13] mp 49–50°), and methylbenzoyldiazomethane (XIII),[13] which is the liquid diazo compound recrystallized[14] from ether at −70°, were obtained by the reaction of benzoyl chloride with related diazo alkanes.

Thermal Reactions of α-Diazo Ketones with Sulfur Dioxide. A. The Reaction of Azibenzil (I) with Sulfur Dioxide Gas.—Sulfur dioxide gas (200 g) was introduced into a benzene solution (85 ml of benzene) of azibenzil (8.5 g, 0.038 mol) for 4.5 hr at refluxing temperature (78°). The products were separated by chromatography using silica gel as the adsorbent. Elution with petroleum ether (bp 40–60°), benzene, chloroform, and ether gave the products, benzil (V), 3,3,5,6-tetraphenyl-2,3-dihydro-1,4-oxathiin-2-one 4,4-dioxide (II), 2-diphenylmethylene-5,6-diphenyl-1,3,4-dioxathiin 4,4-dioxide (III), and diphenylacetic acid (IV), successively.

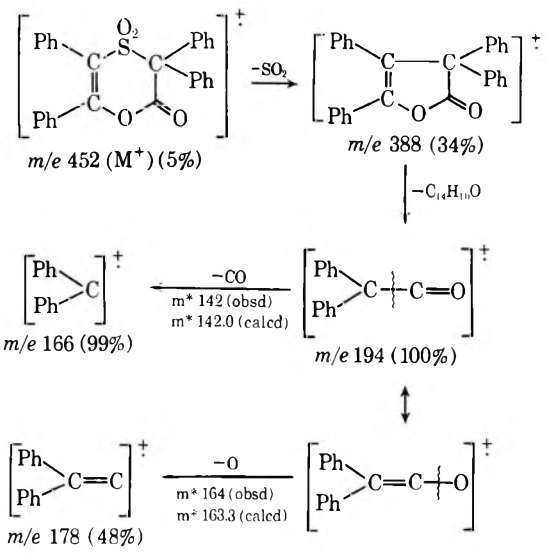
The yield was shown in Table I. Compounds IV and V were identified by infrared spectral comparison and mixture melting point, 148° and 95°, respectively, with the samples (lit. mp of IV, 148°;[15a] mp of V, 95°[15b]).

3,3,5,6-Tetraphenyl-2,3-dihydro-1,4-oxathiin-2-one 4,4-dioxide (II) was recrystallized from benzene: mp 232–233° dec; ir C=O stretching bands at 1785 ($\nu_{C=O}$ of ester group) and 1605 ($\nu_{C=C}$) and sulfone stretching bands at 1350 (ν as SO_2) and 1140 cm^{-1} (ν s SO_2); nmr ($CDCl_3$) τ 2.5–3.0 ppm (m, Ph).

The uv absorption spectrum of II in a tetrahydrofuran solution has the maximum at 292 nm (ε 1.01 × 10^4) indicating the *cis*-stilbene moiety.

Anal. Calcd for $C_{28}H_{20}SO_4$: C, 74.33; H, 4.46; S, 7.07. Found: C, 74.32; H, 4.41; S, 7.07. The mass spectrum of II was explained as shown in Scheme V.

SCHEME V



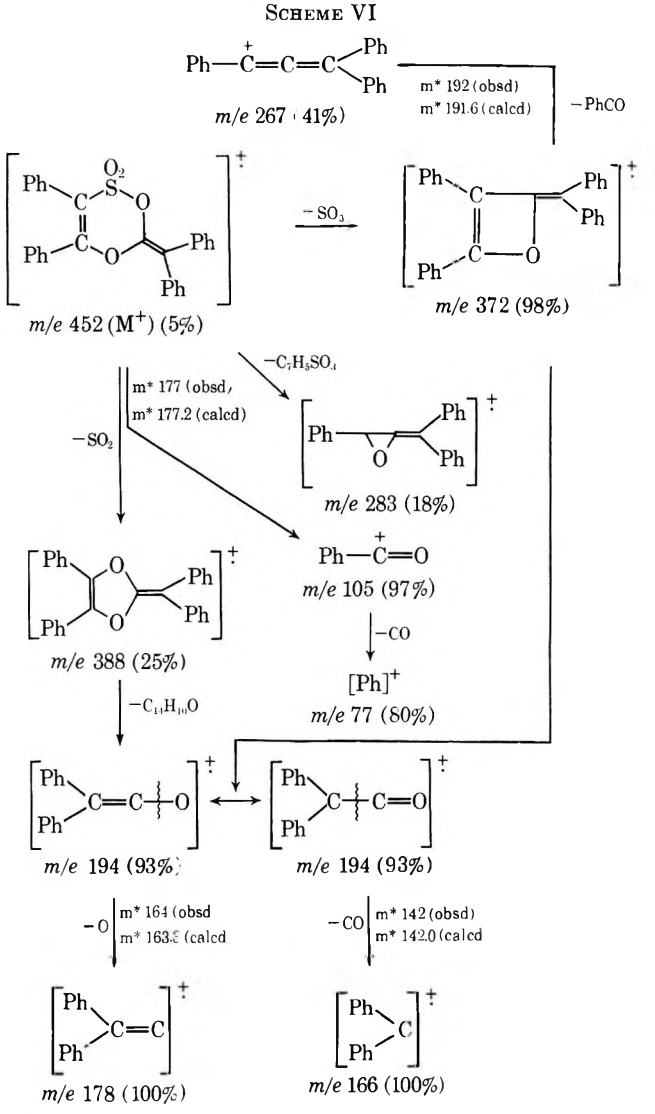
2-Diphenylmethylene-5,6-diphenyl-1,3,4-dioxathiin 4,4-dioxide (III), was recrystallized from ether: mp 173–174° dec; ir 1605 ($\nu_{C=C}$), 1350 (ν as SO_2), and 1130 cm^{-1} (ν s SO_2); nmr ($CDCl_3$) 2.6–3.0 ppm (m, Ph).

Anal. Calcd for $C_{28}H_{20}SO_4$: C, 74.33; H, 4.46. Found: C, 74.11; H, 4.78. The mass spectrum of III is shown in Scheme VI.

The thermal reaction using *n*-heptane instead of benzene as solvent was carried out under the same conditions as described above.

B. The Reaction of Diazoacetophenone (X) with Sulfur Dioxide Gas.—Into a xylene solution (73 ml of xylene) of diazoacetophenone (7.3 g, 0.05 mol), sulfur dioxide gas (200 g) was passed for 4.5 hr at 140°. No specific absorption of sulfone was shown in the ir spectrum of the reaction mixture. The products were separated by chromatography on silica gel. Elution with benzene and ether gave successively the corresponding butenolide XI, mp 107–108°, and the dimer XII, mp 288–289°, in the yields

SCHEME VI



which are shown in Table I. These products were identified by infrared spectral comparison and the mixture melting points, 106–108 and 287–289°, respectively, with the authentic samples (lit. mp of XI, 107–108°; XII, 288–289°).[7a]

The reaction also was done in a diglyme solvent under the conditions described above.

C. The Reaction of Methylbenzoyldiazomethane (XIII) with Sulfur Dioxide Gas.—Sulfur dioxide gas (200 g) was passed into a toluene solution (64 ml of toluene) of methylbenzoyldiazomethane (6.4 g, 0.04 mol) for 4.5 hr at 110–115°. Absorption of a sulfone group was absent in the ir spectrum of the reaction mixture. The products were separated by chromatography on silica gel. Elution with benzene and ether successively gave vinyl phenyl ketone (XIV), and 2-phenylpropionic acid (IX) was obtained in the yield as shown in Table I. XIV was identified by infrared spectral and boiling point comparison with the authentic sample,[6b] bp 115° (18 mm) [lit. bp 115° (18 mm)]. 2-Phenylpropionic acid, obtained after hydrolysis, was identified by the mixture melting point (264–267°) with the sample[16] (lit. mp 265–268°). The reaction using ligroin instead of toluene as solvent was carried out under the same conditions as described above.

D. The Reaction of Phenylacetyldiazomethane (VI) with Sulfur Dioxide Gas.—To a benzene solution (70 ml of benzene) of phenylacetyldiazomethane (3.2 g, 0.02 mol), sulfur dioxide gas (200 g) was introduced at 70° for 4.5 hr. Separation of the reaction mixture by chromatography on silica gel was carried out. Elution with benzene, chloroform, and ether gave successively 3,6-dimethyl-3,5-diphenyl-2,3-dihydro-1,4-oxathiin-2-one 4,4-dioxide (VII), 6-methyl-5-phenyl-2-(1-phenylethylidene)-1,3,4-dioxathiin 4,4-dioxide (VIII), and 2-phenylpropionic acid (IX),

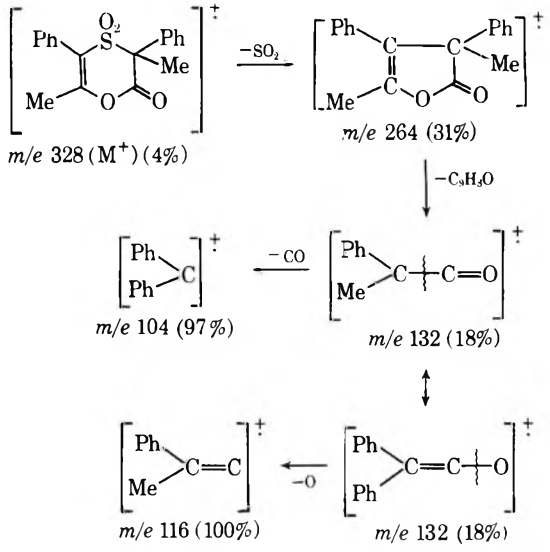
(13) F. Arndt and B. Eistert, *Chem. Ber.*, **68**, 200 (1935).
(14) M. Regitz, *Angew. Chem.*, **79**, 733 (1967).
(15) (a) R. Adams and C. S. Marvel, *Org. Syn.*, **1**, 25 (1921); (b) C. S. Marvel, F. D. Hager, and E. C. Caudle, *ibid.*, **3**, 45 (1923).
(16) W. Johnson, *J. Amer. Chem. Soc.*, **24**, 686 (1902).

in the yield as shown in Table I. IX was identified by infrared spectral comparison and the mixture melting point (264–267°) with the sample[16] (lit. mp 265–268°).

3,6-Dimethyl-3,5-diphenyl-2,3-dihydro-1,4-oxathiin-2-one 4,4-dioxide (VII) was recrystallized from benzene: mp 117–118° dec; ir 1790 ($\nu_{C=O}$ of ester group), 1650 ($\nu_{C=C}$), and sulfone stretching bands at 1320 (ν as SO_2) and 1140 cm^{-1} (ν s SO_2); nmr ($CDCl_3$) 2.55–3.25 (10 H, m, Ph), 7.95 (3 H, s, CH_3), 8.10 (3 H, s, CH_3).

Anal. Calcd for $C_{18}H_{16}O_4S$: C, 65.85; H, 4.88; S, 9.76. Found: C, 65.80; H, 4.82; S, 10.12. The mass spectrum of VII was explained as shown in Scheme VII.

SCHEME VII



6-Methyl-5-phenyl-2-(1-phenylethylene)-1,3,4-dioxathiin 4,4-dioxide (VIII)[17] was recrystallized from ether: mp 129° dec; ir 1650 ($\nu_{C=C}$), 1340 (ν a s, SO_2), and 1160 cm^{-1} (ν s, SO_2); nmr ($CDCl_3$) τ 2.55–2.80 (10 H, m, Ph), 7.85 (3 H, s, CH_3), 8.10 ppm (3 H, s, CH_3).

Anal. Calcd for $C_{18}H_{16}O_4S$: C, 65.85; H, 4.88; S, 9.76. Found: C, 65.82; H, 4.85; S, 9.95.

The mass spectrum of VIII obtained is explicable as shown in Scheme VIII.

The ^{13}C spectrum of VIII contains no signals around 190–235 ppm (corresponding to carbonyl carbons),[4,18] but three signals at δ 148, 157, and 159 ppm over the range 140–240 ppm from TMS, indicating the six-membered ring of VIII.

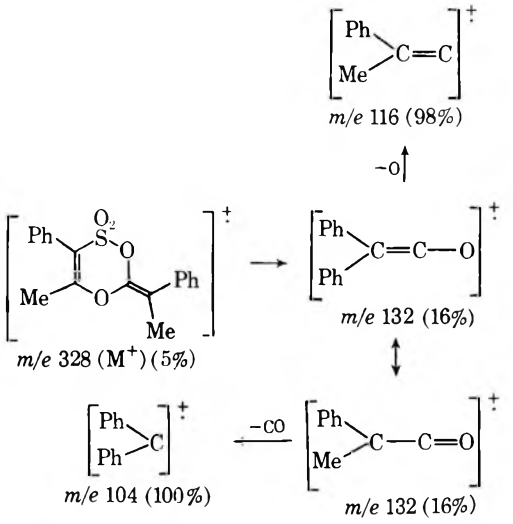
E. Derivatives of Cyclic Sulfones II and VII.—Two derivatives of II were obtained by neat thermal decomposition and basic hydrolysis. The neat thermal decomposition of II at 280° for 4 hr gave the tetraphenylethylene XV (yield 35%). XV was identified by infrared spectral comparsion and mixture melting point, 232–233°, with an authentic sample (lit.[19] mp 234°).

(17) At present, there is no evidence to indicate whether VIII is the cis or trans isomer.

(18) E. W. Randall, *Curr. Awareness*, **26**, 371 (1971).

(19) C. E. Coffey, *J. Amer. Chem. Soc.*, **83**, 1623 (1961).

SCHEME VIII



The basic hydrolysis of II, under 2 *N* sodium hydroxide in 1:1 water–dioxane for 4 hr at 60°, yielded quantitatively diphenylmethyl benzyl sulfone (XVI), mp 157–158° dec, and benzoic acid (XIX). The identification of the sulfone was made by the following manner: ir 1310 (ν as SO_2) and 1130 cm^{-1} (ν s SO_2); nmr 2.4–2.9 (15 H, m, Ph), 4.85 (1 H, s, CH), and 5.85 ppm (2 H, CH_2). The mass spectrum was also in good agreement with the structure of the sulfone, *m/e* 258 ($M^+ - SO_2$), major peaks at *m/e* 167 [$(C_6H_5)_2CH^+$] and 91 ($C_7H_7^+$).

Anal. Calcd for $C_{20}H_{18}SO_2$: C, 74.53; H, 5.59; S, 9.95; Found: C, 74.52; H, 5.56; S, 10.28.

Benzoic acid (XIX) was identified by mixture melting point with the authentic sample.

The hydrolysis of VII with sodium hydroxide in 1:1 water–dioxane at 60° for 4 hr yields quantitative moles of α-phenethyl benzyl sulfone (XVII), mp 101° dec. This identification was made by the following manner: ir 1310 (ν as SO_2) and 1130 cm^{-1} (ν s SO_2); nmr ($CDCl_3$) τ 2.60–2.75 (10 H, m, Ph), 5.85 (1 H, q, CH), 6.00 (2 H, s, CH_2), 8.25 ppm (3 H, d, CH_3).

Anal. Calcd for $C_{15}H_{16}SO_2$: C, 69.23; H, 6.15; S, 12.29. Found: C, 69.25; H, 6.18; S, 12.32.

Photolysis of α-Diazo Ketones in Liquid Sulfur Dioxide.—Four α-diazo ketones as described in the thermal reaction were used. The α-diazo ketones (0.01 mol) were dissolved in liquid sulfur dioxide (32 g, 0.5 mol) in a Pyrex tube, which was irradiated by a high-pressure mercury lamp at 0–10°. The irradiation was stopped with disappearance of the absorption in the ir caused by the diazo group. The products were separated by silica gel chromatography in yields given in Table II. These products were identified by infrared spectral comparison and mixture melting point with samples previously prepared.

Apparatus.—Ir spectra were taken on a Hitachi EPI-S2 type infrared spectrometer. Nmr spectra were obtained with a JNM3H-60 spectrometer. Mass spectra were run on a Hitachi VD-10001-A spectrometer.

Registry No.—I, 3469-17-8; II, 33250-43-0; III, 33250-42-9; IV, 3893-35-4; VII, 36611-84-4; VIII, 36611-85-5; X, 3282-32-4; XIII, 31164-01-9; XVI, 21711-81-9; XVII, 36611-88-8; sulfur dioxide, 7446-09-5.

Benzodiazepines. VIII.[1] Diborane Reduction of Benzodiazepin-2-ones

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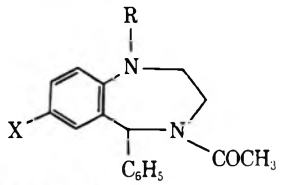
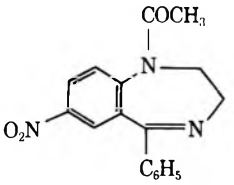
The reduction of 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones **1** with diborane gives the corresponding dihydro- or tetrahydrobenzodiazepines **2** or **3**, depending on molecular structures or reaction conditions. This reduction can also be carried out conveniently by using the sodium borohydride–boron trifluoride etherate reagent. This method is especially suitable for nitro-substituted benzodiazepinone and 1-alkyl-substituted benzodiazepinone derivatives where lithium aluminum hydride causes side reactions.

Diborane has been shown to be an effective reducing agent for the selective reduction of an amide carbonyl group in the presence of a nitro, ester, carbamate, or halogen group.[2] In connection with synthetic routes to 2,3-dihydrobenzodiazepines **2**, we have examined the diborane reduction of 1,3-dihydrobenzodiazepin-2-ones **1** in which both amide and C=N double bond groups are present. Feuer and coworkers have reported that the C=N double bonds of alkyl and α-monoaryl oximes are readily reduced with diborane at 25°, while diaryl ketoximes such as benzophenone oxime, in which the C=N double bond system is analogous to that of **1**, are not reduced even after 12 hr at 66°.[3]

As shown in Table I, the reduction of **1** with diborane gave the corresponding dihydro- or tetrahydrobenzodiazepines **2** or **3**, depending on molecular structures or reaction conditions. The product ratios obtained in the reductions were determined by nmr spectroscopy. In these reductions similar results were realized either in treating **1** with 1 *M* solution of diborane in tetrahydrofuran or in adding **1** to the reagent, conveniently prepared by the treatment of boron trifluoride etherate with sodium borohydride in tetrahydrofuran. In preliminary experiments with **1a** it was found necessary to use temperatures below 5° and a large excess of the reagent to obtain a maximum yield of **2a** (Table I). Dihydrobenzodiazepine (**2a**) was isolated by extraction of the crude acetylation mixture with 0.1 *N* hydrochloric acid after acetylation of the contaminating tetrahydrobenzodiazepine (**3a**) to the less basic 4-acetyl derivative (**4a**). Complete reduction of **1a** to **3a** was achieved by refluxing with a larger excess of diborane in tetrahydrofuran for 7.5 hr.



4a, X = Cl; R = CH_3
d, X = NO_2; R = $COCH_3$



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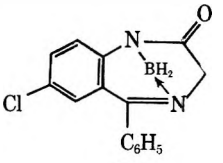
Reduction of 1-unsubstituted benzodiazepin-2-one **1b** gave **2b** and **3b** in a ratio of 1:2 even under conditions favoring selective reduction to **2b**. The lower ratio of **2b** to **3b** is perhaps best explained by assuming an initial reaction of the amide hydrogen in **1b** and diborane[2a,4] to give an amidoborane intermediate such as **6**. The



6

C=N double bond in this intermediate **6** would be readily reduced because the positive charge on C-5 would be increased resulting from coordination of N-4 with the boron atom in the molecule. A similar explanation has been proposed by Kornet and coworkers[2b] to explain the lack of selectivity in the diborane reduction of N-monosubstituted amido ester, methyl hippurate.

In contrast to the present procedure, Sternbach and coworkers[5a] have shown that reduction of **1a** with lithium aluminum hydride gives, as the only isolable product, **3a** in 20% yield, whereas reduction of **1b**[5b] gives **2b** in 71% yield. Recently, Steinman[6] has reported the selective reduction of **1a** with lithium aluminum hydride at 0° to give 7-chloro-2,3-dihydro-2-hydroxy-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (**7**) in 40% yield. We repeated his procedure and found that the formation of **7** was nearly quantitative as the primary reaction at −50° and a further reaction took place at room temperature to give an insoluble dimer (**8**)[7,8] as the major product without observable forma-

(1) Paper VII: S. Inaba, K. Ishizumi, T. Okamoto, and H. Yamamoto, *Chem. Pharm. Bull.*, **20**, 1628 (1972).

(2) (a) H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, **86**, 3566 (1964); (b) M. J. Kornet, P. A. Thio, and S. I. Tan, *J. Org. Chem.*, **33**, 3637 (1968); (c) W. V. Curran and R. B. Angier, *ibid.*, **31**, 3867 (1966); (d) E. R. Bissell and M. Finger, *ibid.*, **24**, 1256 (1959); (e) Z. B. Papanastassiou and R. J. Bruni, *ibid.*, **29**, 2870 (1964); (f) G. R. Pettit, S. K. Gupta, and P. A. Whitehouse, *J. Med. Chem.*, **10**, 692 (1967).

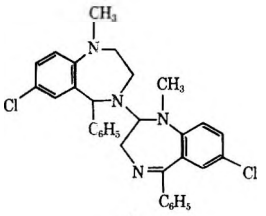
(3) (a) H. Feuer, B. F. Vincent, Jr., and R. S. Bartlett, *J. Org. Chem.*, **30**, 2877 (1965); (b) H. Feuer and D. M. Braunstein, *ibid.*, **34**, 1817 (1969).

(4) H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **82**, 681 (1960).

(5) (a) L. H. Sternbach, E. Reeder, and G. A. Archer, *J. Org. Chem.*, **28**, 2456 (1963); (b) T. S. Sulkowski and S. J. Childress, *ibid.*, **28**, 2150 (1963).

(6) M. Steinman, German Patent 1,958,742 (1970); *Chem. Abstr.*, **73**, 66637b (1970).

(7) The compound **8** was a dimer of the same empirical formula as **2a**. The mass spectrum of **8** showed the molecular ion (M^+) at *m/e* 540 and was similar to that of **7** in the region below *m/e* 286. The ir spectrum indicated a band at 1595 cm^{-1} (C=N) and nothing corresponding to NH or OH group. Attempted reduction of **8** with lithium aluminum hydride in refluxing tetrahydrofuran and acetylation with acetic anhydride in pyridine gave only starting material. However, oxidation with chromic acid in acetic acid at 50° led to the isolation of the known 6-chloro-1,2-dihydro-1-methyl-4-phenylquinazolin-2-one (A)[8b] in 40% yield. Under same conditions **3a** gave A in about 20% yield, whereas **2a** and **7** gave **1a** in nearly quantitative yield. For the oxidation of benzodiazepines **2a** and **3a**, see ref 8. Therefore, the structure **3a** appeared to be contained in **8**. From these facts we considered structure **8** to be most likely of several possible structures.

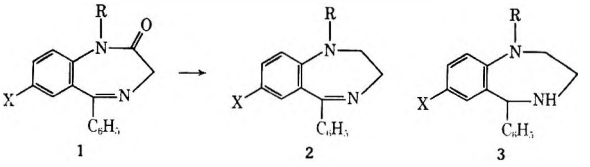


8

(8) (a) R. I. Fryer, G. A. Archer, B. Brust, W. Zally, and L. H. Sternbach, *J. Org. Chem.* **30**, 1308 (1965); (b) A. M. Felix, J. V. Earley, R. I. Fryer, and L. H. Sternbach, *J. Heterocycl. Chem.*, **5**, 731 (1968).

TABLE I

REDUCTION OF DIHYDROBENZODIAZEPIN-2-ONES WITH DIBORANE



1 2 3

Compd[a]	X	R	Reducing agent	Mole ratio, B_2H_6/compd	Temp, °C	Time, hr	Product ratio,[b] 2:3	Yield, % 2	Yield, % 3
1a	Cl	CH_3	$NaBH_4$-BF_3	8[c]	−15	22	86:14	75	11[d]
1a	Cl	CH_3	$NaBH_4$-BF_3	8[c]	0	3.5	86:14	75	
1a	Cl	CH_3	$NaBH_4$-BF_3	6[c]	5	4	86:14	70	
1a	Cl	CH_3	$NaBH_4$-BF_3	4[c]	10	3.5	76:24[e]		
1a	Cl	CH_3	B_2H_6	6	−10	2	87:13	62[f]	
1a	Cl	CH_3	B_2H_6	10	Reflux	7.5			95
1b	Cl	H	B_2H_6	4	−14	2.5	33:67	26[g]	47[h]
1b	Cl	H	$NaBH_4$-BF_3	8[c]	Reflux[i]	3			77
1c	NO_2	CH_3	B_2H_6	6	−8	1.8		77[f]	*j*
1c	NO_2	CH_3	NaBH -BF_3	8[c]	Reflux[i]	2			83[k]
1d	NO_2	H	B_2H_6	4	−13	3	71:29	39[l]	21[m]
1d	NO_2	H	$NaBH_4$-BF_3	8[c]	Reflux[i]	2			65

[a] 5 mmol. [b] Determined by nmr analysis. [c] Calculated assuming that the diborane is quantitatively generated in accordance with the amount of sodium borohydride used. [d] Isolated as the acetyl derivative **4a**. [e] Tlc analysis showed a small amount of starting material remaining in the mixture. [f] Purified by recrystallization. [g] Crystallized from pentane–ether. [h] Isolated as the hydrochloride by treatment of the filtrate with ethanolic hydrogen chloride. [i] Before refluxing, the reaction temperature was maintained at 25° with a reaction time of 2–3 hr. [j] Tlc analysis of the mother liquor indicated the presence of a small amount of the tetrahydro derivative **3c**. [k] Isolated as the hydrochloride. [l] Isolated as the acetyl derivative **5** which was reconverted into **2d** in 87% yield on heating with 1 *N* sodium hydroxide solution in methanol. [m] Isolated as the diacetyl derivative **4d**.

tion of **2a** and **3a**. Consequently, the present procedure is particularly useful for the preparation of 1-alkyl-substituted dihydrobenzodiazepines such as **2a**,[9] which cannot be obtained in a satisfactory yield by N-methylation of **2b** under ordinary conditions.[1,5a,10]

A further advantage is that the mildness of the reagent makes possible the presence of a variety of other substituents less susceptible to the reducing action of the reagent. Thus, under mild conditions 1-methyl-7-nitrobenzodiazepinone **1c** was reduced almost exclusively to the corresponding dihydrobenzodiazepine **2c**, and the 1-unsubstituted derivative **1d** to a 71:29 mixture of **2d** and **3d**. The reduction products **2d** and **3d** were converted into the 1-acetyl and 1,4-diacetyl derivatives **5** and **4d**, respectively, by treatment with acetic anhydride. The basic compound **5** was separated from **4d** by extraction of the crude acetylation mixture with dilute hydrochloric acid and reconverted into **2d** by hydrolysis with base.

The reduction of **1c** and **1d** proceeded with higher degree of selectivity than of the corresponding chloro derivatives **1a** and **1b**. This is, presumably, due to the effect of the strongly electron-withdrawing nitro group which decreases the basicity of N-4 making it less susceptible to the diborane attack.

More vigorous treatment of **1c** and **1d** led to the complete reduction to the respective tetrahydro derivatives **3c** and **3d**.

(9) An indirect reductive synthesis for **2a**, involving conversion of **1a** into the corresponding 2-thione derivative, followed by Raney nickel desulfurization, has been reported: G. A. Archer and L. H. Sternbach, *J. Org. Chem.*, **29**, 231 (1964).

(10) In contrast, the corresponding 2-one derivative **1a** is readily prepared by N-methylation of **1b**: L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *ibid.*, **27**, 3788 (1962).

Experimental Section

Infrared spectra were measured on a Hitachi Model EPI-G3 spectrophotometer and nmr spectra on a Varian T-60 instrument using tetramethylsilane as an internal standard. Mass spectra were taken on a Shimadzu LKB instrument with the direct sample inlet system and ionizing potential at 70 eV. All melting points were determined in open capillary tubes and are uncorrected.

General Procedures.—Each of the reduction reactions was carried out in a dry 100-ml three-necked flask, equipped with a magnetic stirrer, thermometer, and condenser. The 1 *M* solution of diborane in tetrahydrofuran (THF) was prepared as described by Brown.[11] The sodium borohydride–boron trifluoride etherate reagent was prepared by adding 15% excess boron trifluoride etherate to sodium borohydride in THF, in accordance with the equation $3NaBH_4 + 4BF_3 \cdot OEt_2 \rightarrow 2B_2H_6 + 3NaBF_4$. The reduction products were extracted with ether or chloroform. The drying agent used for organic solutions was anhydrous sodium sulfate.

7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (2a). A. By Sodium Borohydride–Boron Trifluoride Etherate Reduction of 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (1a).—The following procedures are representative of the reduction with sodium borohydride–boron trifluoride etherate. To a stirred suspension of 2.28 g (60 mmol) of pulverized sodium borohydride in 35 ml of THF was added dropwise a solution of 13.0 g (92 mmol) of boron trifluoride etherate in 10 ml of THF below 10°. The mixture was stirred at room temperature for 1 hr. To the resulting reagent (40 mmol as diborane) was added a solution of 1.43 g (5 mmol) of **1a** in 10 ml of THF over a period of 5 min at −15 to −12.5°. Stirring was continued for 22 hr at −15°, and the reaction mixture was cautiously poured into 100 ml of ice–water. The mixture was acidified with 20 ml of concentrated hydrochloric acid, refluxed for 30 min, and cooled. The resulting red solution was made basic with aqueous ammonia. The THF layer was separated, and the aqueous layer was extracted with ether. The organic layers were combined, washed with water, dried, and

(11) H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **81**, 6428 (1959).

evaporated. The oily residue (1.4 g) was shown by nmr in CCl_4 to be composed of **2a** (86%) and **3a** (14%). This mixture was dissolved in 5 ml of acetic anhydride and stirred at room temperature for 4 hr. The resulting solution was diluted with 30 ml of ice–water, made basic with aqueous ammonia, and then extracted with ether. The ether extracts were combined and reextracted with 0.1 *N* hydrochloric acid. The acidic solution was then made basic with aqueous ammonia and extracted with ether. The ether extracts were combined, dried, and evaporated. The oily residue was crystallized from hexane to give 1.02 g (75%) of **2a**, mp 99.5–101.0°.

The ether layer which had been separated from the acidic layer was washed with water, dried, and evaporated. The residue (243 mg) was chromatographed over 15 g of silica gel with ethyl acetate. Evaporation of homogeneous fractions and crystallization of the residue from pentane gave 172 mg (10.9%) of **4a**, mp 98.5–102.5°.

This product was shown to be identical with a sample prepared by treatment of **3a** with acetic anhydride.

When the above acetylation of the crude mixture was carried out at 5–10° using 1 ml of acetic anhydride in 10 ml of toluene, similar results were obtained.

B. By Diborane Reduction of 1a.—The following procedures are representative of the reduction with diborane. Compound **1a** (1.43 g, 5 mmol) was added in one portion to a stirred solution of 30 ml of 1 *M* diborane in THF cooled to −15°. After further stirring at −10° for 2 hr, the reaction mixture was cautiously poured into 100 ml of ice–water, acidified with 20 ml of concentrated hydrochloric acid, and refluxed for 1 hr. The resulting red solution was cooled and made basic with aqueous ammonia. The THF layer was separated, and the aqueous layer was extracted with ether. The organic layers were combined, washed with water, dried, and evaporated. The residue (1.35 g) was analyzed by nmr as a 87:13 mixture of **2a** and **3a**. Recrystallization of the crude product from hexane gave 0.70 g of **2a**, mp 99.5–101.0°. A second crop (0.14 g) was obtained from the mother liquor. Total yield was 0.84 g (62%).

7-Chloro-2,3-dihydro-2-hydroxy-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (7).—To a well-stirred suspension of 0.46 g of lithium aluminum hydride in 20 ml of THF was added a solution of 2.85 g of **1a** in 15 ml of THF over a period of 38 min at −50°. The mixture was stirred at −52 to −40° for 4 hr. The excess of lithium aluminum hydride was decomposed by cautious addition of 5 ml of water followed by 20 ml of saturated aqueous sodium chloride. The THF layer was separated, and the aqueous layer was extracted with ether. The organic layers were combined, dried, and evaporated to give 2.80 g (97.5%) of **7**, mp 138–145°. An analytical sample was obtained as colorless plates after recrystallization from ether: mp 148–151° (lit.[6] mp 120–122°, 125–126°, 136–138°); ir (Nujol) 3080 (OH), 1610 cm^{-1} (C=N); mass spectrum *m/e* 286 (M^+), 268 (M − H_2O), 257 (M − CHO), 241, 228.

Anal. Calcd for $C_{16}H_{15}ClN_2O$: C, 67.02; H, 5.27; Cl, 12.36; N, 9.77. Found: C, 66.97; H, 5.24; Cl, 12.57; N, 9.50.

When reduction was carried out using the same conditions (reverse addition at 0°) as described in the literature,[6] the crude **7** was obtained in 80% yield, mp 128–134° dec (lit.[6] mp 125–126°).

Reduction of 1a with Lithium Aluminum Hydride at Room Temperature.—Compound **1a** (2.85 g) was treated with 0.76 g of lithium aluminum hydride at −50° as described above. Conversion into **7** was nearly complete in 6.5 hr as indicated by tlc analysis (silica gel, ethyl acetate). The temperature was, then, allowed to rise to room temperature within 1.5 hr. After stirring for 1 hr, the reaction mixture was cooled to −50° and worked up as described above to give 3.55 g of an amorphous solid. Crystallization from ether afforded 0.63 g (23.3%) of the dimer **8**, mp 265–267° dec. An analytical sample was obtained as colorless prisms after recrystallization from THF, mp 281.5–285° dec.

TABLE II

MELTING POINTS AND CHARACTERIZATIONS OF BENZODIAZEPINES[a]

Compd	Mp, °C	Recrystn solvent	Lit. mp, °C
2a[b]	100–101	Hexane	102–103[c]
3a	66–68	Pentane	60–62[d]
4a	104.5–106.5	Ligroin–pentane	106–108[e]
2b[b]	173–173.5	EtOH	173–173.5[c]
3b HCl	253.5–254 dec	EtOH	259–260[d]
2c	185.5–186.5	*i*-PrOH	187–188[f]
3c[g]	96–99	*i*-PrOH	
3c HCl	295–297 dec	EtOH	
2d[b]	210–211	MeOH	209–211[c]
3d[h]	237–240	EtOH	
4d[i]	170	*i*-PrOH	
5[j]	160–160.5	*i*-PrOH	

[a] Satisfactory analytical data (±0.4% for C, H, N, and Cl) were reported for all new compounds listed in the table: Ed. [b] The product was identified with an authentic sample[1] by comparison of the ir and nmr spectra. [c] Reference 1. [d] Reference 5a. [e] R. I. Fryer and L. H. Sternbach, U. S. Patent 3,625,957 (1971). [f] L. H. Sternbach, G. A. Archer, and E. Reeder, *J. Org. Chem.*, **28**, 3013 (1963). [g] Ir (Nujol) 3310 cm^{-1} (NH); nmr ($CDCl_3$) δ 2.22 (s, 1, NH), 3.04 (s, 3, CH_3), 2.80–3.55 (m, 4, CH_2CH_2), 5.30 (s, 1, CH). [h] Ir (Nujol) 3325, 3230 cm^{-1} (NH); nmr (C_5D_5N) δ 2.96–3.40 (m, 4, CH_2 and 2 NH), 3.84 (m, 2, CH_2), 5.40 (s, 1, CH). [i] Ir (Nujol) 1634, 1648 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.60 and 1.88 (3, CH_3), 2.25 (s, 3, CH_3), 2.80–4.70 (m, 4, CH_2CH_2), 6.20 (s, 1, CH). [j] Ir (Nujol) 1650 cm^{-1} (CO); nmr ($CDCl_3$) δ 2.00 (s, 3, CH_3), 3.00–5.30 (m, 4, CH_2CH_2).

Anal. Calcd for $C_{32}H_{30}Cl_2N_4$: C, 70.98; H, 5.58; Cl, 13.09; N, 10.35. Found: C, 71.00; H, 5.65; Cl, 12.92; N, 10.34.

An examination of the ether filtrate by tlc indicated the presence of other, unidentified products, but none of these corresponded to authentic samples of **2a** and **3a**.

1-Acetyl-2,3-dihydro-7-nitro-5-phenyl-1*H*-1,4-benzodiazepine (5) and 1,4-Diacetyl-7-nitro-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (4d).—Compound **1d** (1.41 g, 5 mmol) was treated with 20 ml of a 1 *M* solution of diborane in THF at −13° for 3 hr. The reaction product (1.25 g) was shown by nmr (C_5D_5N) to be composed of **2d** (71%) and **3d** (29%). This crude mixture (0.95 g) was suspended in 8 ml of acetic anhydride and heated under reflux for 3 hr. The reaction mixture was cooled, diluted with 20 ml of ice–water, made basic with aqueous ammonia, and extracted with chloroform. The chloroform layer was extracted with 1.2 *N* hydrochloric acid. The acidic solution was then made basic with aqueous ammonia and extracted with ethyl acetate. The ethyl acetate solution was washed with water, dried, and evaporated. Recrystallization of the residue from isopropyl alcohol gave 0.46 g (39.1%) of **5**, mp 158.5–160°.

The chloroform layer that separated from the acidic layer was washed with water, dried, and evaporated. The residue, dissolved in a small volume of ethyl acetate, was placed on a column of 30 g of silica gel. Elution with ethyl acetate and recrystallization from isopropyl alcohol gave 0.28 g (20.8%) of **4d**, mp 169–170°.

See Table II for characterizations of benzodiazepines.

Registry No.—**1a**, 439-14-5; **1b**, 1088-11-5; **1c**, 2011-67-8; **1d**, 146-22-5; **2a**, 2898-12-6; **2a** dimer, 36493-03-5; **2b**, 1694-78-6; **2c**, 2898-19-3; **2d**, 2898-03-5; **3a**, 4257-07-6; **3b**, 10456-83-4; **3b** HCl, 2890-23-5; **3c**, 36508-54-0; **3c** HCl, 36508-55-1; **3d**, 36508-56-2; **4a**, 21647-87-0; **4d**, 36508-58-4; **5**, 36508-59-5; **7**, 28739-21-1; diborane, 19287-45-7.

Organic Ions in the Gas Phase. XXVI. Decomposition of 1,3,5-Trinitrobenzene under Electron Impact

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Metastable scanning of 23 fragment ions in the mass spectrum of 1,3,5-trinitrobenzene yielded 96 metastable peaks. Coupled with precise-mass measurement on selected peaks, this approach defines the underlying chemistry in considerable detail. Primary loss of NO_2 seems to play a central role in the network of competing and consecutive reactions, and may well be the rate-controlling step for a large part of it, releasing vibrational energy to drive further decomposition steps.

The mass spectrum of an organic compound is a representation of the products of ionization/dissociation of isolated gaseous molecules by electron impact, sampled a few microseconds after impact.[1,2] Deducing a molecular structure from mass spectral data thus consists in principle of defining the products and reactions involved and thence reconstructing the molecule on paper. With the growing realization that this chemistry often closely parallels that induced by heat, light, and ionizing radiation[1,3-5] and can therefore help both to rationalize and to guide exploratory work in these other contexts, the mechanistic interpretation of mass spectra has taken on added interest. Metastable peaks, which stem from ion decompositions in flight following acceleration[6] and have long been recognized as a valuable source of information in correlating mass spectra with molecular structures,[7-9] have become increasingly useful in this process as a result of recently developed instrumental techniques.[8,9] Several operating modes for double-focusing instruments have been described that defocus the ion beams giving normal peaks in a mass spectrum, and greatly increase the collection efficiency of those giving metastable peaks. The limit of detection for metastable peaks has thus been lowered to 2 to 5 $\times 10^{-8}$ of total ion yield,[9,10] estimated to be sufficient to detect metastable peaks for any breakdown path of the molecular ion.[10] For example, such "metastable scanning" produced 110, 60, 40, 30, and 25 metastable peaks, respectively, in the spectra of *n*-heptane, *n*-hexane, *n*-pentane, *n*-butane, and propane.[11] Similarly large numbers of metastable peaks have been found by metastable scanning of *n*-butane,[12] *n*-decane,[13] benzene,[14] vinyl fluoride[15] and other fluoroethylenes,[16] several C_2–C_7 nonaromatic hydrocarbons,[10] nitromethane,[17] and 4-nonanone.[18]

Following up our long-standing interest in nitroarenes,[3,5] we have studied the decomposition of 1,3,5-trinitrobenzene (TNB) under electron impact, placing particular emphasis on metastable scanning as an experimental approach.

Experimental Section

The 1,3,5-trinitrobenzene was Eastman reagent grade. Its melting point, 122°, was not changed by recrystallization from water.

The conventional 70-eV spectrum was measured on a CEC Model 21-103 mass spectrometer with the inlet system and ionization chamber both at 250°. Metastable scanning was done on a CEC Model 21-110 double-focusing instrument, following previously described procedures.[14,15,18,19] Briefly, after focusing on a selected fragment ion, the electric-sector voltage is decoupled from the ion-accelerating voltage and the latter is scanned to increasing values. This procedure defocuses the ions that produce normal peaks in the conventional spectrum, and it successively focuses the fragment ions arising *via* metastable transitions of various contributing precursors in the first field-free region. The mass of a precursor ion is calculated by multiplying the mass of the selected fragment ion by the ratio of the accelerating voltages associated with the metastable peak and the normal peak. Measurement of the accelerating voltages corresponding to the centers of the broad metastable peaks is facilitated in our system by use of a fast digital voltmeter, the output of which is recorded by one of the galvanometers in the oscillograph. Precise masses of selected peaks were also measured on the 21-110, by matching against appropriate perfluoroalkane reference peaks.

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Results and Discussion

The 70-eV spectrum of TNB obtained on the 21-103 is shown in Table I, where intensity is expressed as

TABLE I
SPECTRUM (70 eV) OF 1,3,5-TRINITROBENZENE

M/z	%Σ26	M/z	%Σ26
26	0.20	73	1.03
27	0.31	73.0 (m)	0.08
28	1.05	74	10.3
29	0.22	75	19.0
30	28.3	76	1.47
31	0.11	77	0.22
32	0.07	78	0.06
36	0.08	79	0.19
37	1.10	80	0.06
38	1.63	81	0.03
39	0.29	86	0.06
40	0.04	87	0.17
41	0.08	88	0.19
42	0.03	89	0.08
43	0.04	90	0.13
44	0.76	91	2.82
45	0.04	92	0.26
46	1.22	93	0.07
48	0.06	104	0.08
49	0.29	105	0.07
50	0.80	107	0.04
51	0.55	120	4.25
52	0.17	121	0.38
53	0.22	122	0.04
54	0.03	137	0.53
55	0.05	138	0.04
60	0.10	151	0.07
61	0.98	167	1.80
62	2.28	168	0.14
63	3.06	169	0.02
64	0.46	183	0.13
65	0.10	197	0.49
66	0.10	198	0.03
67	0.04	213	9.83
68	0.02	214	0.77
69	0.04	215	0.14
72	0.04		
72.0 (m)[a]	0.01		

[a] m denotes metastable peak.

per cent of total ion intensity from mass 26 to 215. It includes but two metastable peaks: 72.0 ($74^+ \rightarrow 73^+ + 1$), 73.0 ($75^+ \rightarrow 74^+ + 1$). Four additional metastable peaks were detected in a conventional 70-eV spectrum recorded on the 21-110: 45.6 ($120^+ \rightarrow 74^+ + 46$), 74.0 ($76^+ \rightarrow 75^+ + 1$), 75.0 ($77^+ \rightarrow 76^+ + 1$), 112.3 ($167^+ \rightarrow 137^+ + 30$).

Table II shows the parent–daughter pairs found by metastable scanning of the 23 fragment ions judged critical to understanding the decomposition chemistry. Of the 96 peaks detected, 5 are attributed to decompositions of naturally occurring heavy-isotopic ions, leaving 91 defined segments of decomposition paths. The peak heights shown are only crude measures of relative probabilities of the transitions, perhaps no better than an order of magnitude.[18] Nonetheless, the intensity ratio of the two metastable peaks that were also observed in the 21-103 spectrum is identical with that in the latter spectrum. If the proportionality holds approximately for all the peaks listed in Table II, the lower limit of detection by metastable scanning of the 21-110, scaled to the two metastable peaks observed in the 21-103 spectrum, was about 2×10^{-7} of total ion yield.

Four precursor ions—masses 181, 153, 135, and 106—were identified whose normal peaks were absent from the conventional 21-103 spectrum; they were detected, however, in the conventional spectrum measured on the 21-110 by virtue of the higher sensitivity employed. A few other cases have been reported of similar identification of a precursor ion for which the conventional spectrum contained no normal peak.[18,20]

A different problem occurs in the search for precursors of relatively low mass daughter ions, where the mass range that can be scanned is limited by the normal 21-110 instrumentation.[18] Thus, no precursors of NO^+ were detected in the accessible mass range of 30 to 64. Metastable peaks corresponding to formation of NO^+ directly from the molecular ions have been found in the conventional spectra of five other nitroarenes.[21] Likewise in TNB, NO^- may well be formed directly from the molecular ion, in a process complementary to the well-known primary loss of neutral NO from nitroarenes.

Even a cursory examination of Table II reveals many transitions that doubtless involve more than one step. For many years, a metastable peak was widely assumed always to denote a single reaction step. Such an assumption is not justified by the early work,[6,22] which explicitly recognized that the decay process need only be completed while the moving ions are in the field-free region, and is not restricted to one step; even so, in the cases studied there[6] and in the vast majority of conventionally recorded metastable peaks reported since, the neutral products are most likely single particles. A metastable peak corresponding to a process $m_1^+ \rightarrow m_2^+ + n$ establishes only that an ion having mass m_1 at the point of entry into the field-free region of the flight path breaks down in that region to produce an ion of mass m_2. The mass difference n corresponds to the one or more neutral products formed before the ionic product emerges from the field-free region. Breakdown to yield more than one neutral product may occur in a concerted fashion, as assumed by some workers,[23] but concertedness is not demanded by the experimental data, and such data are today usually interpreted in terms of series of successive reaction steps.[10,15,22,24,25] For our system, TNB in the CEC Model 21-110 instrument, the estimated time spent in transit through the field-free region is 3 to 10 μsec; the time elapsed from

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TABLE II
PARENT-DAUGHTER PAIRS FOUND BY METASTABLE SCANNING

Mass of fragment ion scanned	Mass of precursor	Approximate peak height, arbitrary units
30[a]	None	
46[b]	151	tr[c]
	167	tr
62[b]	63	25
	89	6[d]
	90	4[d]
	120	13
	137	tr
	167	tr
63[b]	64	16
	91	16
	121[e]	1
	137	tr
	167	tr
	183	tr
64[b]	92	11
	107	tr
	120	tr[d]
	121	tr[d]
	135[f]	tr[d]
	137	tr[d]
	151	tr
	167	1
	183	tr
65	66	3
	67	3
	92	2
	107	tr
	121	tr
	137	tr
	151	tr
	167	2
	213	tr
73	74	103
	120	0.4
	167	tr
	213	tr
74	75	800
	120	142
	167	1
	213	5
75	76	80
	121	33
	151	tr
	167	1
	197	tr
	213	14
76	77	11
	104	5
	121	1
	151	1
	167	3
	213	tr
77	78	8
	105	5
	120	2[d]
	121	2[d]
	135[f]	1
	151	3
	167	2
	213	tr
90	91	7
91	106[f]	3
	137	104
	167	4
	183	tr
	213	1
92	120	2[d]
	121	4[d]
	138[e]	20
	151	1
	167	2
	184[e]	tr
	214[e]	tr
104	121	3
	151	1
	167	2
107	137	3
	153[f]	0.2
	167	tr
	183	tr
	213	tr
120	151	tr
	167	20
	213	10
121	167	10
	214[e]	1
137	167	130
	183	4
	213	1
151	181[f]	1
	197	1
	213	tr
167	197	4
	213	10
183	213	2
197	213	tr

[a] The scan did not extend above mass 64 because of instrumental limitations. [b] The scan did not extend above mass 190 because of instrumental limitations. [c] tr denotes ≤1, where noise level precludes a more explicit value. [d] The peak profile and width suggest a pair of overlapping peaks. [e] The precursor and product are apparently heavy-isotopic ions. [f] The indicated precursor mass was not detected in the conventional spectrum, shown in Table I.

the moment of electron impact to entry into the field-free region would be about the same as in other instruments, of the order of 1 μsec.[6,26] The time scale is clearly sufficient to allow multistep processes.

The data in Table II, interpreted to allow a parent-daughter relationship to encompass multistep as well as one-step processes, were assembled into a decomposition scheme that should be a valid representation of the chemistry underlying the mass spectrum shown in Table I. In constructing such a scheme for TNB, the masses of neutral products pretty well define their elemental compositions (Table III). Most of these species occur commonly as neutral products in the mass spectra of nitroarenes.[3,21]

TABLE III

Mass	Assigned composition	Mass	Assigned composition
1	H	31	HNO
16	O	43	HNCO
17	OH	46	NO_2
27	HCN	47	HNO_2
28	CO	71	HC_2NO_2
30	NO		(Nitroacetylene)

With the help of these neutrals, one can assign elemental compositions to successive ionic products. In a few cases, attempts to do so led to inconsistencies. (a) The formula assigned to the ion of mass 106 is $C_6H_2O_2^+$, leaving no way to lose 15 u to go to mass 91. (b) The ion of mass 89 appears as a precursor of mass 62, implying loss of HCN. We were unable to construct a plausible path to a nitrogen-containing ion of mass 89. (c) The formula assigned to the ion of mass 107 is $C_6H_3O_2^+$, leaving no plausible path for the loss of 43 u to go to mass 64, or of 42 u to go to mass 65.

In the hope of resolving these inconsistencies and also of establishing the identities and relative abundances of isobaric products where the preliminary decomposition scheme suggested two species of a given nominal mass, we measured the precise masses of selected peaks. The resulting assignments, from which naturally occurring heavy-isotopic species have been omitted, are listed in Table IV. Among the ions so found are several containing more hydrogen atoms than the original TNB

(26) S. Meyerson, *Appl. Spectrosc.*, **22**, 30 (1968).

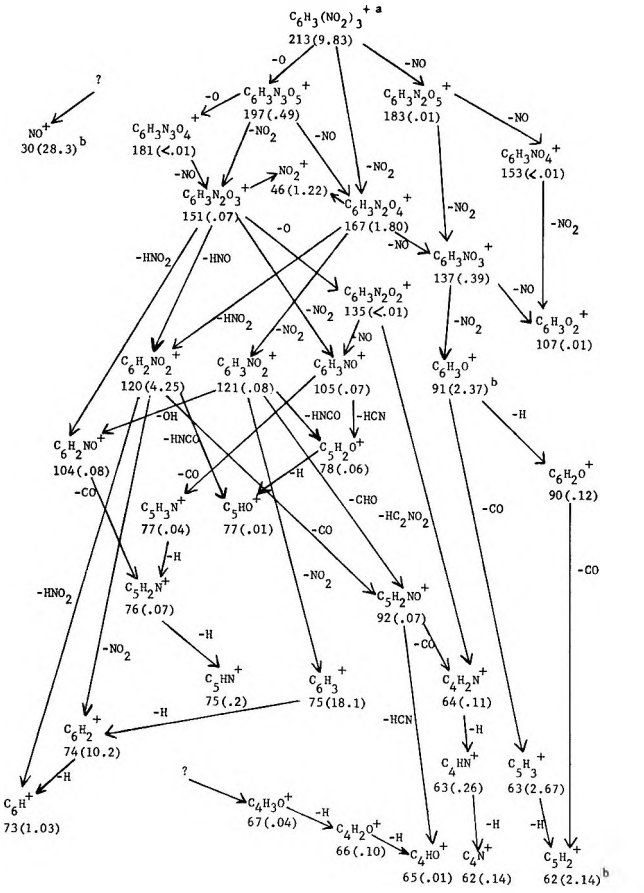

Figure 1.—Partial decomposition scheme for 1,3,5-trinitrobenzene: (a) the numbers below each ion formula give the nominal mass and, in parentheses, the relative intensity on the scale of the spectrum in Table I; (b) includes unknown contributions from dinitroaniline.

TABLE IV
IONIC SPECIES INFERRED FROM PRECISE-MASS MEASUREMENTS

Nominal mass	Species	% of intensity at nominal mass	Nominal mass	Species	% of intensity at nominal mass
62	C_4N^+	6	77	C_5HO^+	8
	$C_5H_2^+$	94		$C_5H_3N^+$	31
63	C_4HN^+	9		$C_6H_5^+$	61
	$C_5H_3^+$	91	89	$C_6H_3N^+$	100
64	$C_4H_2N^+$	35	90	$C_6H_2O^+$	94
	$C_5H_4^+$	65		$C_6H_4N^+$	6
65	C_4HO^+	7	91	$C_6H_3O^+$	84
	$C_4H_3N^+$	69		$C_6H_5N^+$	16
	$C_5H_5^+$	24	107	$C_6H_3O_2^+$	29
74	$C_6H_2^+$	100		$C_6H_5NO^+$	71
75	C_5HN^+	1	137	$C_6H_3NO_3^+$	74
	$C_6H_3^+$	99		$C_6H_5N_2O_2^+$	26
76	$C_5H_2N^+$	27	183	$C_6H_3N_2O_5^+$	6
	$C_6H_4^+$	73		$C_6H_5N_3O_4^+$	94

molecule and therefore not derivable from it. We were able to resolve the discrepancies by assuming that the anomalous data stem from a dinitroaniline impurity in the trinitrobenzene. The techniques that we employed are thus able to detect and characterize a low-level impurity whose contributions to the conventional spectrum are totally obscured by the main component. The finding for dinitroaniline is especially plausible in view of the evidence for inadvertent catalytic reduction of nitroarenes[27] and of nitromethane[17] to amines in the ionization chamber of the mass spectrometer.

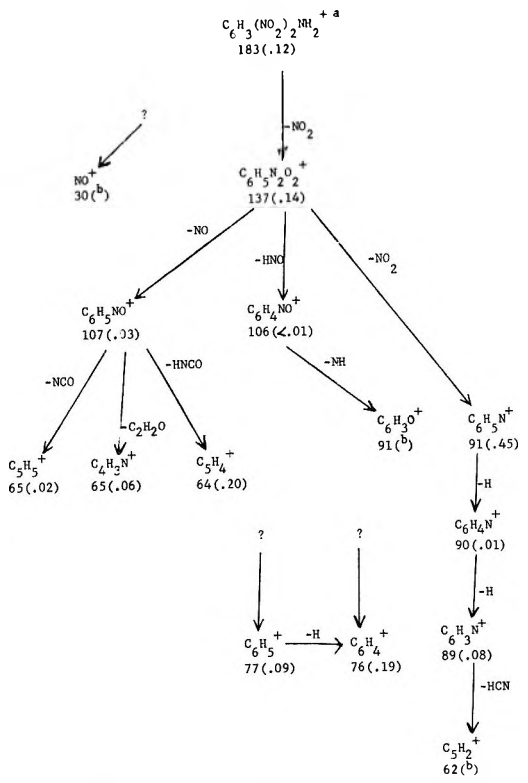

Figure 2.—Partial decomposition scheme for 3,5-dinitroaniline (in 1,3,5-trinitrobenzene): (a) the numbers below each ion formula give the nominal mass and, in parentheses, the relative intensity on the scale of the spectrum in Table I; (b) included in the intensities shown for trinitrobenzene (Figure 1).

All the available data are collected and summarized in Figures 1 and 2, partial decomposition schemes for TNB and the postulated 3,5-dinitroaniline, respectively. Below each ion formula are the nominal mass and, in parentheses, the relative intensity on the scale of the spectrum in Table I. Approximate corrections for heavy-isotopic contributions were made to the intensities listed in Table I, and the corrected values were pro-rated among isobaric components in accord with the distributions listed in Table IV. Of the total ion intensity in the spectrum in Table I, the species depicted in Figure 1 comprise 84.4% and those in Figure 2, 1.4%, although some ion origins, shown as question marks, remain unsettled. About 4.3% is attributed to heavy-isotopic contributions, and the remaining 9.9% is distributed among 34 peaks not studied in this work.

The dinitroaniline scheme includes reactions yielding neutral products of two masses in addition to those found in TNB (mass, assigned composition): 15, NH; 42, NCO or C_2H_2O (hydroxyacetylene or its tautomer, ketene).

The extent of the detail with which the complex network of competing and consecutive reactions is defined by metastable scanning supports the view that metastable peaks can thus be detected for nearly every con-

(27) J. H. Beynon, J. A. Hopkinson, and G. R. Lester, *Int. J. Mass Spectrom. Ion Phys.* **2**, 291 (1969).

tributing reaction step. The frequency of peaks corresponding to multistep sequences and the length of many of the sequences are unusual. Several such sequences (eq 1–6) comprise four and even five steps.

$$C_6H_3N_3O_6^+ \xrightarrow[213]{} C_6H_3N_2O_4^+ \xrightarrow[167]{} C_6H_3NO_2^+ \xrightarrow[121]{} C_5H_2O^+ \xrightarrow[78]{} C_5HO^+ \xrightarrow[77]{} \quad (1)$$

$$C_6H_3N_3O_6^+ \xrightarrow[213]{} C_6H_3N_2O_4^+ \xrightarrow[167]{} C_6H_3NO_2^+ \xrightarrow[121]{} C_6H_2NO^+ \xrightarrow[104]{} C_5H_2N^+ \xrightarrow[76]{} C_5HN^+ \xrightarrow[75]{} \quad (2)$$

$$C_6H_3N_3O_6^+ \xrightarrow[213]{} C_6H_3N_3O_5^+ \xrightarrow[197]{} C_6H_3N_2O_3^+ \xrightarrow[151]{} C_6H_2NO^+ \xrightarrow[104]{} C_5H_2N^+ \xrightarrow[76]{} C_5HN^+ \xrightarrow[75]{} \quad (3)$$

$$C_6H_3N_3O_6^+ \xrightarrow[213]{} C_6H_3N_2O_4^+ \xrightarrow[167]{} C_6H_2NO_2^+ \xrightarrow[120]{} C_6H_2^+ \xrightarrow[74]{} C_6H^+ \xrightarrow[73]{} \quad (4)$$

$$C_6H_3N_3O_6^+ \xrightarrow[213]{} C_6H_3N_2O_4^+ \xrightarrow[167]{} C_6H_3NO_2^+ \xrightarrow[121]{} C_5H_2NO^+ \xrightarrow[92]{} C_4HO^+ \xrightarrow[65]{} \quad (5)$$

$$C_6H_3N_2O_4^+ \xrightarrow[167]{} C_6H_3NO_3^+ \xrightarrow[137]{} \begin{cases} C_6H_2O^+ \\ 90 \end{cases} \begin{cases} C_6H_3O^+ \\ 91 \end{cases} \begin{cases} C_5H_2^+ \\ 62 \end{cases} \begin{cases} C_5H_3^+ \\ 63 \end{cases} \quad (6)$$

Strikingly, the molecular ion of mass 213 was detected as a precursor of every fragment ion scanned for it except those of masses 90, 92, 104, and 121. Likewise, the $[M^+ - NO_2]$ ion at mass 167 was detected as a precursor of every lower mass fragment ion scanned for it except those of masses 90 and 151. Thus, a substantial number of M^+ and $[M^+ - NO_2]$ ions, still intact upon entering the field-free region, about 1 μsec after electron impact, break down to give essentially all the observed products during the subsequent 3 to 10 μsec spent in this region. The low reaction rates associated with metastable transitions imply that the decomposing ions contain very little vibrational energy beyond that needed to drive the transition. Primary decomposition products that arise under these conditions and then proceed through one to four additional reaction steps must somehow have acquired the energy needed to drive the secondary and subsequent steps.[10,25,28] Such energy is most likely released early in a reaction sequence, not as translational energy, but rather as vibrational energy and perhaps as electronic excitation capable of undergoing internal conversion to vibrational energy. Previous electron-impact studies in our laboratories have led us to propose that decomposition/rearrangement processes release internal energy in a form available to drive further decomposition.[29] The seemingly crucial role performed by $C_6H_3N_2O_4^+$ in the overall decomposition of TNB makes the loss of NO_2 a prime candidate for consideration as a major source of excitational energy in the sense discussed here.

In effect, we are postulating that primary loss of NO_2 is the rate-controlling step for a large part of the chemistry occurring in the wake of electron impact on an isolated TNB molecule. This view accords well with the evidently central role of primary NO_2 loss in the mass spectra of other nitroarenes,[3,5,21,30] and it probably applies equally to pyrolysis of nitroarenes.[5,31] Specifically in the case of TNB, the postulate that this primary reaction proceeds *via* a high-energy transition state is supported by the great difficulty of nitrating *m*-dinitrobenzene;[32] by the thermal stability of TNB at temperatures as high as 260°, where it is reported to undergo no detectable decomposition after 3 days;[33] and by its great explosive power once it is detonated, exceeding that of trinitrotoluene.[32] Homolytic cleavage of a series of tetranitrobiphenyls into NO_2 and the complementary radical has been proposed as a first step in thermal decomposition of these compounds.[34] Similar loss of NO_2 may be the unidentified first-order primary reaction suggested, on the basis of thermodynamic data, as common to trinitrotoluene and other explosives containing nitro groups.[35]

Attempts to define the thermal reactions that are important in the early stages of explosions are hampered by severe experimental difficulties.[33–37] A few other workers have already suggested that the decomposition reactions of explosives under electron impact in the mass spectrometer may closely parallel those in the early stages of explosions, and therefore that mass spectra can furnish helpful guidance in the study of such processes,[38] as in that of thermal reactions of organic compounds generally. Our findings on TNB prompt us to agree with this view. We suggest that, with a little latitude in the use of the term, the breakdown of TNB in the mass spectrometer may profitably be viewed as an "explosion" in a system whose dimensions are those of a single molecule.

Registry No.—1,3,5-Trinitrobenzene, 99-35-4.

(28) U. Löhle and C. Ottinger, 17th Annual Conference on Mass Spectrometry and Allied Topics, Dallas, Texas, 1969.

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Reactions of Nitrosobenzene, *o*-Nitrosotoluene, and Pyridine *N*-Oxide with Phosphorus Pentachloride

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The products of the reaction of phosphrous pentachloride with nitrosobenzene (1), *o*-nitrosotoluene (2), and pyridine *N*-oxide (3) were identified by vpc with known samples. In all three compounds, phosphorus pentachloride deoxygenated the nitrogen and formed chlorinated aniline, toluidine, and pyridine products, respectively, in the anhydrous solvent methylene chloride.

This study investigated the products of the reaction of phosphorus pentachloride with nitrosobenzene (**1**), *o*-nitrosotoluene (**2**), and pyridine *N*-oxide (**3**) in the solvent methylene chloride. The purpose of the investigation was to ascertain whether the tetrachlorophosphonium cation (PCl_4^+) would deoxygenate the nitrogen and chlorinate the ring. As expected, the oxygen from the nitroso group was removed to form phosphoryl chloride along with the hydrochloride salts of the chlorinated aromatic amines. Nitrosobenzene has been deoxygenated previously with triethyl phosphite. Bunyan and Cadogan[1] converted nitrosobenzene into azoxybenzene which subsequently can be converted into azobenzene with excess reagent.[2]

In the reaction with pyridine *N*-oxide, the phosphorus pentachloride would not react at the refluxing temperature of methylene chloride. Previously, Murakami and Matsumura[3] had treated pyridine *N*-oxide with solid phosphorus pentachloride at 140° to form 4-chloropyridine. Consequently, the reactants were placed in a sealed Pyrex tube and heated to 130° for 90 min. The solution turned a light brownish black, but no black-tarry residue remained as was the case with the nitroso compounds.

When phosphorus pentachloride dissolves in methylene chloride, the molecular ions, $(PCl_4^+)(PCl_6^-)$, are formed in equilibrium with molecular phosphorus pentachloride. This is substantiated from our experiments with 9-xanthone and 9-thioxanthone which immediately formed brilliant yellow and red complex ions, respectively, with the $(PCl_4^+)(PCl_6^-)$ molecular ions from phosphorus pentachloride.[4] Therefore, when nitroso compounds are added to a methylene chloride solution of phosphorus pentachloride, the initial reaction is undoubtedly the electrophilic attack of the tetrachlorophosphonium cation, (PCl_4^+), onto the negative end of the oxygen–nitrogen dipole of the nitroso group with the subsequent loss of a chloride ion.

The chlorination of the aromatic ring, as revealed from Table I, is probably an intermolecular chlorination. If intramolecular chlorination were occurring, one would expect the ratio of ortho/para isomers to be greater than 1; however, for both compounds **1** and **2** the ortho/para ratios were much less than 1 with values of 0.65 and 0.024, respectively.

TABLE I

REACTIONS OF PHOSPHORUS PENTACHLORIDE WITH NITROSOBENZENE, *o*-NITROSOTOLUENE, AND PYRIDINE *N*-OXIDE

Product	Yield, %
Nitrosobenzene: $POCl_3$, 61.2%	
Aniline	3.5
4-Chloroaniline	20.0
2,4-Dichloroaniline	18.5
2-Chloroaniline	13.0
2,4,6-Trichloroaniline	2.2
Total	57.2
o-Nitrosotoluene: $POCl_3$, 68.1%	
o-Toluidine	0.8
4-Chloro-*o*-toluidine	20.8
2,4-Dichloro-*o*-toluidine	18.7
2-Chloro-*o*-toluidine	0.5
Total	40.8
Pyridine *N*-Oxide: $POCl_3$, 55.0%	
Pyridine	65.4
2-Chloropyridine	10.2
3-Chloropyridine	10.2
4-Chloropyridine	1.9
Total	87.7

The actual species responsible for chlorination was not definitely established in this study. However, the additional experiments performed with chlorine, phosphorus trichloride, and phosphoryl chloride eliminated some of the possible precursors to chlorination. Phosphorus trichloride and phosphoryl chloride have previously been reported to chlorinate aromatic rings simultaneously with their ability to deoxygenate such compounds as pyridine *N*-oxide,[5] substituted pyridine *N*-oxides,[5,6] quinoline *N*-oxides,[5] lutidine *N*-oxides,[7] picoline *N*-oxides,[7] and pyrazine *N*-oxides.[8] Consequently, we treated compound **2** with excess quantities

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of both phosphorus trichloride and phosphoryl chloride, and the results are shown in Table II. Yields were

TABLE II
REACTION OF *o*-NITROSOTOLUENE WITH PHOSPHORYL CHLORIDE AND PHOSPHORUS TRICHLORIDE

Product	Yield, % $POCl_3$	Yield, % PCl_3
o-Toluidine	0.2	5.9
2-Chloro-*o*-toluidine	0.3	1.0
4-Chloro-*o*-toluidine	4.1	3.2
2,4-Dichloro-*o*-toluidine	4.2	1.1
Total	8.8	11.2

considerably lower than with phosphorus pentachloride, but both compounds deoxygenated and chlorinated compound 2 with no trace of starting material remaining. However, considerable quantities of a black intractable residue resulted. These data, in conjunction with data from Table I, suggest that phosphorus pentachloride is responsible for the major portion of the deoxygenation and chlorination reactions.

An Orton rearrangement[9,10] also could explain the isomer distribution, especially so, if an *N*-chloro intermediate existed in the medium. The *N*-chloroacetanilide rearrangement was proved to be an intermolecular chlorination with molecular chlorine as the chlorinating agent. To rule out the molecular chlorine possibility, we treated *o*-nitrosotoluene with phosphorus pentachloride in the presence of equal molar quantities of acetanilide. Acetanilide was recovered unchanged with no trace of 4-chloroacetanilide present.

Since deoxygenation of nitroso compounds generates nitrenes,[1,11] the gas chromatograms from the nitrosobenzene reaction products were examined for the presence of azobenzene. No trace was found, but this was not expected since the nitroso solutions were highly acidic from the excess hydrogen chloride generated in the reactions. In the case of pyridine *N*-oxide, the reaction temperature was 130°. Since phosphorus pentachloride can dissociate into phosphorus trichloride and chlorine at 130°,[12] it was necessary to investigate the reaction of molecular chlorine with pyridine in the presence of phosphoryl chloride. Since the formation of pyridine from pyridine *N*-oxide with either phosphorus trichloride or phosphoryl chloride had been reported previously,[5,6,13] it was possible for both products, pyridine and the chloropyridines, to be produced from the reaction and decomposition products of phosphorus pentachloride. To prove that the chloropyridines did not result from either the molecular chlorine or the phosphoryl chloride reacting with pyridine, a sealed tube reaction was run at 130° with pyridine, phosphoryl chloride, and excess chlorine in methylene chloride. Under these conditions, no chloropyridines were formed.

If one examines Table I, a striking difference exists between the products for pyridine *N*-oxide and the nitroso compounds. The phosphoryl chloride yield is 28% less than the total yield of pyridine products. In addition the chlorinated pyridines are 66% less than the yield of pyridine, and the ortho/para ratio is 5.4. Undoubtedly, phosphoryl chloride and phosphorus trichloride play a significant role in the deoxygenation and chlorination since these compounds have already been shown to deoxygenate and chlorinate pyridine *N*-oxide.[5,6]

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Experimental Section

Nitrosobenzene–PCl_5.—A 25-ml solution of methylene chloride containing 0.990 g (0.00935 mol) of nitrosobenzene (Aldrich Chemical Co.) was added dropwise to a 25-ml solution of methylene chloride containing 1.90 g (0.00913 mol) of sublimed reagent grade phosphorus pentachloride (Allied Chemical Co). The reaction was exothermic (+11°), and the solution turned a brownish black. After all the nitrosobenzene was added, the solution was cooled in an ice bath and rotary evaporated under vacuum (0.5 Torr). The last traces of distillate were removed from a steam bath. The distillate was collected in a Dry Ice trap for immediate vpc analysis. The residue was made basic with 5% sodium hydroxide and steam-distilled which left a black tarry residue in the steam distillation flask. The distillate was extracted with ether and dried over anhydrous magnesium sulfate prior to vpc analysis. If the reaction mixture was allowed to reflux before rotary evaporation, the yields would be reduced approximately 50%. This was also noted for *o*-nitrosotoluene.

***o*-Nitrosotoluene–PCl_5.**—A 20-ml solution of methylene chloride containing 1.00 g (0.00827 mol) of *o*-nitrosotoluene (Aldrich Chemical Co.) was added dropwise to an ice-cooled solution of 20 ml of methylene chloride containing 1.94 g (0.00932 mol) of reagent grade (Allied Chemical Co.) phosphorus pentachloride. The separation of products was performed in the exact manner as given above for nitrosobenzene.

Pyridine *N*-Oxide–PCl_5.—A 20-ml solution of methylene chloride containing 0.880 g (0.00925 mol) of pyridine *N*-oxide (Aldrich Chemical Co.) and 1.93 g (0.00925 mol) of reagent grade phosphorus pentachloride (Allied Chemical Co.) reacted in a sealed Pyrex tube at 130° for 90 min. The products were separated and analyzed exactly as for the nitroso compounds.

Pyridine–Chlorine–Phosphoryl Chloride.—A 20-ml solution of methylene chloride containing 2.3 g (0.029 mol) of chlorine (Matheson Coleman and Bell), 0.48 g (0.0059 mol) of pyridine (Baker Reagent Grade), and 0.92 g (0.0060 mol) of reagent grade phosphoryl chloride (Matheson Coleman and Bell) reacted in a sealed Pyrex tube at 130° for 90 min. Products were separated and analyzed in the identical manner as for pyridine *N*-oxide.

***o*-Nitrosotoluene–Acetanilide–PCl_5.**—A 20-ml solution of methylene chloride containing 1.00 g (0.00827 mol) of *o*-nitrosotoluene (Aldrich Chemical Co.) and 1.13 g (0.00832 mol) of acetanilide (Eastman White Label) was added to a 20-ml solution of methylene chloride containing 1.71 g (0.00823 mol) of reagent grade phosphorus pentachloride (Allied Chemical Co.). The reaction temperature and color were similar to the *o*-nitrosotoluene–PCl_5 reaction. After the addition, the reaction mixture was added to approximately 30 ml of water, and the aqueous layer was separated and extracted with two 30-ml ether fractions. The combined organic fractions were dried over anhydrous potassium carbonate and concentrated to 3 ml for vpc analysis.

***o*-Nitrosotoluene–$POCl_3$.**—A 20-ml solution of methylene chloride containing 1.00 g (0.00827 mol) of *o*-nitrosotoluene (Aldrich Chemical Co.) was added dropwise at room temperature to a 20-ml solution of methylene chloride containing 1.89 g (0.0346 mol) of phosphoryl chloride (Matheson Coleman and Bell reagent grade). After stirring for 30 min, the solvent was removed by rotary evaporation, and 100 ml of water was added to the residue. The water layer was extracted with three 25-ml portions of ether which was dried over anhydrous potassium carbonate prior to vpc analysis.

***o*-Nitrosotoluene–PCl_3.**—This reaction was run and analyzed in same manner as the above reaction with phosphoryl chloride.

Solvent.—Reagent grade methylene chloride (Mallinckrodt Chemical Co.) was dried over phosphorus pentoxide and distilled prior to use.

Vpc Analysis.—Phosphoryl chloride was analyzed on a 6 ft × 1/4 in. column containing 10% OV-17 (50% phenyl silicone) substrate at 100°. Benzene was used as the internal standard for the quantitative determinations. The nitrosobenzene

products were analyzed on an 8 ft × 1/4 in. 3% SE-30 column at 120°. Calibration curves with areas of known chlorinated anilines were used to determine per cent yield. The chloropyridines were analyzed on an 8 ft × 1/4 in. column containing 3% Carbowax 20M and 5% KOH at 100°. Morpholine was used as the internal standard for quantitative measurements. For the chloro-*o*-toluidines a 6 ft × 1/8 in. column containing 10% Carbowax 1540 (polyethylene glycol) and 5% KOH at 200° was used. Quantitative measurements were made with aniline as the internal standard. Acetanilide and 4-chloroacetanilide were analyzed on a 6-ft 3% SE-30 column at 170°.

Only two compounds were not commercially available for vpc identification: 2,4-dichloro-6-methylaniline (mp 183–185° of acetanilide derivative, lit.[14] 186°) and 4-chloroacetanilide (mp 177–179°, lit.[15] 179°). The 2,4-dichloro-6-methylaniline was prepared from 4-chloro-2-methylaniline (Aldrich Chemical Co.) by chlorinating the acetanilide derivative.[16]

(14) *Beilstein*, 4th ed, **12**, 837.

(15) "Handbook of Chemistry and Physics," R. C. Weast, Ed., 48th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1966, p C-78.

Registry No.—**1**, 586-96-9; **2**, 611-23-4; **3**, 694-59-7; phosphorus pentachloride, 10026-13-8; phosphoryl chloride, 10025-87-3; phosphorus trichloride, 7719-12-2.

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(16) R. M. Roberts, J. C. Gilbert, L. R. Rodewald, and A. S. Wingrove, "An Introduction to Modern Experimental Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1969, p 294.

A Nuclear Magnetic Resonance Study of Some Nitrogen-15 Substituted Azo Heterocycles

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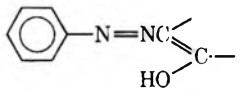
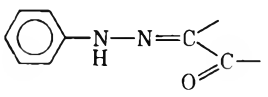
Six ^{15}N-substituted azo heterocycles have been prepared and their tautomeric structures studied by means of nmr spectroscopy. A phenylazo-3-pyrazolone and a phenylazo-4-pyrazolone exist in the azo form in $CDCl_3$, DMSO, and C_5H_5N. Phenylazothioindoxyl and the phenylazo derivative of diphenyloarbituric acid exist predominantly in the phenylhydrazone form in DMSO at room temperature. The phenylazo derivatives of coumaran-2-one and 4-hydroxycoumarin exhibit phenylhydrazone geometric isomerism in DMSO and $CHCl_3$, respectively.

The determination of the structure of azo heterocycles by the usual spectroscopic techniques is often plagued by the ambiguities inherent in peak assignment. In an attempt to eliminate these ambiguities in our own investigations, we have prepared and studied the ^{15}N isotopomers of six heterocycles containing the structural feature A or B.



A

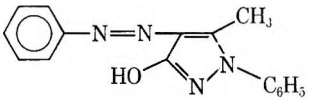


B

Each of the compounds can exist in at least two different tautomeric forms; all but the above two forms can be eliminated by conventional techniques.

The ^{15}N isotopomers were prepared by diazotization of ^{15}N-aniline and coupling to the appropriate heterocycle. The probability of isotopic scrambling under the conditions used (*vide infra*) has been shown to be very low and the heterocycles can therefore be safely assumed to carry the ^{15}N attached to the benzene ring.[1] Since the ^{15}N isotope has a spin quantum number of 1/2, the NH proton resonance of form B would be a low-field doublet with coupling constant of 90–100 Hz. The OH proton resonance of A will be, of course, a low-field singlet. If the compound exists as a mixture of A and B and if the proton exchanges intermolecularly between the ^{15}N of B and the oxygen of A or between two molecules of B, the shape of the peak(s) will depend upon the rate of exchange. If the exchange is fast and intramolecular, the shape depends upon the coupling constant in pure B and the composition of the mixture.[2]

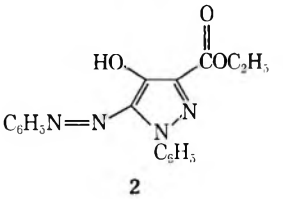
The nmr spectrum of 5-methyl-4-phenylazo-1-phenyl-3-pyrazolone (**1**), whose structure has previously been



1

determined to be the azo form shown (and for which no simple hydrazone tautomeric structure can be written),[3] showed the expected singlet for the acidic proton in both the ^{14}N and ^{15}N derivatives in $CDCl_3$ from 38 to −51°, in DMSO at 38°, and in pyridine at 38 to −23°. The chemical shifts of all compounds are listed in Table I.

The acidic proton resonance for 3-carboethoxy-1-phenyl-5-phenylazo-4-pyrazolone (**2**) in all three solvents was a singlet, an observation which could be interpreted as indicative of only the azo form or of rapid intermolecular exchange. The similarity of chemical shifts and peak shapes to those of **1** favors the



2

(1) A. K. Bose and I. Kugajevsky, *J. Amer. Chem. Soc.*, **88**, 2325 (1966).

(2) G. O. Dudek and E. P. Dudek, *ibid.*, **86**, 4283 (1964).

(3) F. A. Snavely and C. H. Yoder, *J. Org. Chem.*, **33**, 513 (1968).

TABLE I

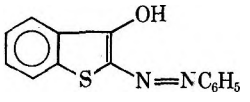
CHEMICAL SHIFTS OF ^{15}N DERIVATIVES

	$CDCl_3$[a]			DMSO-d_6[a]			C_5H_5N-d_5[a]		
Compd	δ, ppm	m,[b] J,[c] $W_{1/2}$[d]	Temp, °C	δ, ppm	m,[b] J,[c] $W_{1/2}$[d]	Temp, °C	δ, ppm	m,[b] J,[c] $W_{1/2}$[d]	Temp, °C
1	9.4[e]	bs (16)	38	10.4[e]	bs (20)	38	10.3[e]	bs (20)	38
	10.3[e]	bs (18)	−51				11.4[e]	bs (30)	−23
2	9.5[e]	bs (12)	38	9.8[e]	bs (30)	38	10.1[e]	ss (8)	38
	10.4[e]	bs (18)	−51				10.8[e]	bs (14)	−21
3				11.0[g]	vbd	18	10.9[e]	vbs (30)	−38
				10.9[f]	bs (30)	38			
				10.7[e]	bs (16)	84			
4				14.1[g,h]	d, 95 (8)	35	14.7[f]	bs (40)	38
				14[d]	vbs (90)	133			
5				12.1[g]	d, 97 (2)		12.4[g]	d, 97 (4)	35–70
						27–40			
				11.0[g]	d, 97 (6)				
				12.0[g]	bd (8)				
						80			
				10.9[f]	bd (20)				
6	14.2[g]	d, 95 (3)		14.0[e]	bs (20)		13[e]	vbs (70)	38
			38			38			
	16.4[g]	d, 93 (2)		15.6[g]	d, 97 (16)				

[a] All solutions 5%, except 1 and 2 in $CDCl_3$ and 3 and 4 in DMSO, which were 10%. [b] ss, sharp singlet; bs, broad singlet; vbs, very broad singlet; d, doublet; bd, broad doublet; vbd, very broad doublet. [c] ±1 Hz. [d] Half height width of peak in hertz given in parentheses. [e] Analogous absorption in ^{14}N derivative has the same shape. [f] Analogous peak in ^{14}N derivative is significantly sharper. [g] ^{14}N derivative has singlet(s) at center of ^{15}N doublet(s). [h] In ^{15}N at 77°, d, 92; 93°, d, 83; 103°, d, 79.

former interpretation, which is in agreement with earlier work.[3]

The room-temperature spectrum of the ^{15}N derivative of 2-phenylazothianapthen-3-one (**3**) in DMSO

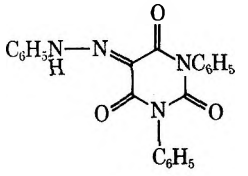


3

shows a broad singlet for the acidic proton resonance, which is considerably broader than the singlet exhibited by the ^{14}N derivative. As the temperature is decreased, the broad ^{15}N singlet degenerates to a broad doublet, while an increase in temperature sharpens the singlet until, at 84°, it is identical in shape with that of the ^{14}N derivative. This behavior is indicative of a temperature-dependent exchange process. Such a process could involve intermolecular exchange between two hydrazone forms, or inter- or intramolecular exchange between a hydrazone and an azo form. The existence of a tautomeric equilibrium for **3** in relatively nonpolar solvents is supported by its visible spectrum (in $CHCl_3$), which contains two peaks at 380 and 499 nm. If the exchange is between two tautomeric forms, the rate of the exchange and the composition of the equilibrium mixture should be affected by a change in temperature. As the composition of the azo–hydrazone mixture changes, a change in chemical shift should occur (unless the NH and OH shifts of forms A and B are identical). The data of Table I indicate that the chemical shift of the acidic proton of **3** is temperature dependent, but changes in intermolecular association could also produce such a change.

In pyridine from 0 to 38° the spectra of both the ^{14}N and ^{15}N derivatives of **3** contain a broad singlet for the low-field proton. This could be interpreted as either rapid intermolecular (hydrazone–hydrazone or hydrazone–azo) exchange or as a shift to the azo form. The latter interpretation is in agreement with earlier conclusions for azo-5-pyrazolones.[4]

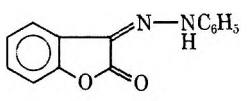
The nmr spectrum of the ^{15}N derivative of 1,3-diphenyl-4-phenylazobarbituric acid (**4**) contains a



4

doublet centered at 14.3 ppm, whose separation (J = 95.6 Hz) remains unchanged from 35 to 65°. At higher temperatures the doublet begins to coalesce until at 133° only a broad singlet remains. In pyridine, the ^{15}N derivative displays a singlet for the acidic proton, which is considerably broader than the ^{14}N singlet. These observations are amenable to the same interpretations discussed for **3**.

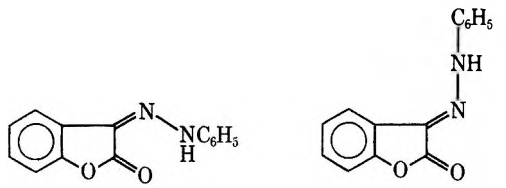
The nmr spectrum of the ^{14}N derivative of 3-phenylazocoumaran-2-one (**5**) contains two low-field singlets



5

at 11.1 and 12.1 ppm with approximately equal areas. The ^{15}N derivative shows two doublets centered at the same positions and with the same areas. The simplest explanation for this observation appears to be the presence of *two* phenylhydrazone forms, presumably the syn and anti isomers shown below. This same type of nmr pattern for an ^{15}N-acetoacetaldehyde phenylhydrazone has been previously attributed to geometrical

(4) G. J. Lestina and T. H. Regan, *J. Org. Chem.*, **34**, 1685 (1969).



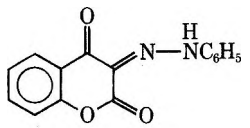
syn anti

isomerism.[5] The lower field resonance can probably be assigned to the NH proton of the intramolecularly hydrogen bonded syn form.

As the temperature is increased the low-field doublet broadens slightly and the higher field doublet coalesces (at about 120°) to a single broad peak. Apparently the syn form is stabilized by hydrogen bonding, but the anti form undergoes exchange (either with the azo form or with itself).

The low-field pattern for the ^{14}N derivative of **5** in pyridine consists of a singlet, while the ^{15}N derivative shows a doublet (J = 98 Hz), evidence for only one phenylhydrazone form in this solvent.

The nmr spectrum of 3-phenylazo-4-hydroxycoumarin (**6**) in $CDCl_3$ exhibits the same low-field pattern



6

as **5**: two doublets in the ^{15}N derivative, and two singlets in the ^{14}N with integrated ratios of 5:1 (lower field to higher field). Geometrical isomerism in the phenylhydrazone form appears again to be the most reasonable explanation. In DMSO, the low-field spectrum shows a doublet and a broad singlet; in pyridine, only a singlet appears. The explanation above applied to **5** at higher temperatures in DMSO and in pyridine would appear to hold for **6** in these solvents.

A comparison of the tautomeric forms of the above azo derivatives, and those studied previously in this laboratory (1,2-diphenyl-4-phenylazo-3,5-pyrazolidinedione,[3] 3-methyl-1-phenyl-4-phenylazo-5-pyrazolone,[3] and 3-methyl-4-phenylazo-5-isoxazolone[6]), with the structures of the heterocycles themselves[7] (*e.g.*, 3-methyl-1-phenyl-5-pyrazolone) shows that, with the probable exception of **6**, the structure of the heterocycle and its azo derivative at room temperature in relatively nonpolar solvents are the same with respect to enolization at the carbon β to the phenylazo group. In other words, if the azo derivative exists in form A (hydroxyazo) under these conditions, the heterocycle also exists in the hydroxy form. The generality of this observation remains to be determined.

Experimental Section

The ^{15}N derivatives were prepared by diazotization of 99% isotopically enriched ^{15}N-aniline at 0° and coupling to the appropriate heterocycle. The melting points of ^{15}N derivatives were identical to within ± 1° with their ^{14}N homologs and were in agreement with literature values (**1**,[8] **2**,[3] **3**,[9] **4**,[10] **5**,[11] **6**[12]).

Nmr spectra were obtained on a Varian A-60D spectrometer. Deuterated solvents were dried over molecular sieves. Integrated areas were in good agreement with the theoretical values.

Registry No.—**1**, 15095-26-8; **2**, 15096-02-3; **3**, 36540-15-5; **4**, 36540-16-6; (*Z*)-**5**, 36540-17-7; (*E*)-**5**, 36540-18-8; **6**, 36540-19-9.

Acknowledgment.—The authors are indebted to the Camille and Henry Dreyfus Foundation for partial support of this work.

(5) C. Reichardt and W. Grahn, *Tetrahedron*, **27**, 3745 (1971).

(6) F. A. Snavely and C. H. Yoder, *J. Inorg. Nucl. Chem.*, **33**, 2699 (1971).

(7) For 3-pyrazolones see A. R. Katritsky and F. W. Maine, *Tetrahedron*, **20**, 315 (1964); for 4-pyrazolones see M. J. Nye and W. P. Tang, *ibid.*, **28**, 455 (1972); for 5-pyrazolones and isoxazolones see A. R. Katritsky and F. W. Maine, *ibid.*, **20**, 299 (1964) and A. R. Katritsky, S. Økase, and A. J. Boulton, *ibid.*, **18**, 777 (1962); for others see A. R. Katritsky and A. P. Ambler in "Physical Methods in Heterocyclic Chemistry," Vol. II, A. R. Katritsky," Ed., Academic Press, New York, N. Y., 1963; A. R. Katritsky and J. W. Lagowsk. in "Advances in Heterocyclic Chemistry," Vol. 2, A. R. Katritsky, Ed., Academic Press, New York, N. Y., 1963.

(8) F. A. Snavely, D. A. Sweigart, C. H. Yoder, and A. Terzis, *Inorg. Chem.*, **6**, 1831 (1967)

(9) K. Auwers and K. Müller, *Justus Liebigs Ann. Chem.* **381**, 276 (1911).

(10) M. A. Whitely, *J. Chem. Soc.*, **91**, 1330 (1907).

(11) K. Fries and W. Pfoffendorf, *Chem. Ber.*, **45**, 154 (1912).

(12) C. F. Huebner and K. P. Link, *J. Amer. Chem. Soc.*, **67**, 99 (1945).

Studies in Nonbridgehead Fused Nitrogen Heterocycles. Fused 1,2,3-Triazoles

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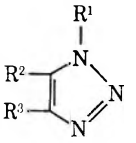
1-Benzyl-4,5-diamino-1,2,3-triazole (**5**) was prepared by the Curtius rearrangement of 5-amino-1-benzyl-1,2,3-triazole-4-carboxylic acid hydrazide (**2**). The diamine **5** was readily condensed with α-diketones, affording the 5,6-substituted 1,2,3-triazolo[4,5-*b*]pyrazines (**6**–**9**). If the condensation was carried out with ethyl acetoacetate and the intermediate crotonate **10** was refluxed with sodium ethoxide, 4*H*,6*H*-1-benzyl-7-methyl-1,2,3-triazolo-[5,4-*b*][1,4]diazepin-5-one (**11**) resulted as a mixture of tautomers. Acetylation of **5** produced 4-acetamido-5-amino-1-benzyl-1,2,3-triazole (**13**) or 4,5-diacetamido-1-benzyl-1,2,3-triazole (**15**) depending upon the reaction conditions employed. The enhanced reactivity of the 4-amino group of **5** was demonstrated by the unambiguous synthesis of 5-acetamido-1-benzyl-1,2,3-triazole (**14**).

In a search for novel nitrogen heterocycles which might possess insect chemosterilizing properties, suitably substituted 1,2,3-triazoles appeared to be attractive candidates for elaboration into fused derivatives. Some early work by Thiele[1] with 4,5-diamino-2-phenyl-1,2,3-triazole provided interesting but insufficient background material. In addition, two other factors influenced our decision: the 1,2,3-triazole ring had been shown to occur in nature[2] as 8-azaguanine, and, although considerable attention had been directed toward the thermal homolytic ring cleavage,[3,4] and acid-catalyzed heterolytic ring scission[5-7] of these compounds, to our knowledge no one had investigated the possibility of photochemical[8] ring fission of fused 1,2,3-triazoles.

Based on the antimetabolic activity reported for 8-azaguanine[9] and on the somewhat tenuous empirical relationship that exists between chemosterilants and antimetabolites, it was anticipated that some interesting fused heterocycles could be prepared from the previously unknown 1-benzyl-4,5-diamino-1,2,3-triazole. In addition, such compounds would have the potential for rapid photolytic decomposition, making them short lived. The results reported below indicate our progress toward these goals.

Results and Discussion

The condensation of benzyl azide with ethyl cyanoacetate in the presence of 1 equiv of sodium ethoxide afforded ethyl 5-amino-1-benzyl-1,2,3-triazole-4-carboxylate (**1**) under conditions that were modified slightly from those reported in the literature (see Experimental Section).[10] Likewise, 5-amino-1-benzyl-1,2,3-triazole-4-carboxamide (**1a**) resulted when benzyl azide was condensed with cyanoacetamide. The condensation of benzyl azide with acetylenedicarboxylic acid and with dimethyl acetylenedicarboxylate gave 1-benzyl-1,2,3-triazole-4,5-dicarboxylic acid (**1b**)[11] and its dimethyl ester (**1c**),[12] respectively, in excellent yield.



1, $R^1 = C_6H_5CH_2$; $R^2 = NH_2$; $R^3 = CO_2C_2H_5$
1a, $R^1 = C_6H_5CH_2$; $R^2 = NH_2$; $R^3 = CONH_2$
1b, $R^1 = C_6H_5CH_2$; $R^2 = R^3 = CO_2H$
1c, $R^1 = C_6H_5CH_2$; $R^2 = R^3 = CO_2CH_3$
1d, $R^1 = C_6H_5CH_2$; $R^2 = R^3 = CONHNH_2$

When compound **1a** was heated with sodium hypobromite in aqueous base under conditions used to effect the Hofmann rearrangement, no reaction occurred. Also, the diamide resulting from the treatment of compound **1c** with alcoholic ammonia failed to undergo the Hofmann rearrangement. This apparent lack of reactivity is most likely the result of the insolubility of the two compounds in the aqueous or methanolic base employed in the reaction. The dicarboxylic acid **1b** was decomposed to tars when treated with sodium azide in sulfuric acid (98%) in an attempt to bring about the Schmidt rearrangement. The dimethyl ester **1c** could be readily converted to the dihydrazide **1d** with hydrazine hydrate. However, when the dihydrazide **1d** was subjected to the Curtius rearrangement, no identifiable carbamates were isolated. This result verifies some earlier work reported by Curtius.[11] Finally, when compound **1** was treated with hydrazine hydrate at reflux and the resulting hydrazide (**2**) was treated with nitrous acid at 0°, an off-white precipitate (**3**) could be isolated. The formation of the heterocyclic acyl azide function was confirmed by the presence of a band at 2200 cm^{-1} in the infrared spectrum. The acyl azide **3** was stable at room temperature in the presence of air for many months, but it did explode when heated at 150°. When compound **3** was dissolved in absolute ethanol and refluxed, the evolution of a colorless, odorless gas presumed to be nitrogen was noted and the product of the Curtius rearrangement, ethyl 5-amino-1-benzyl-1,2,3-triazole-4-carbamate (**4**), was isolated in yields varying from 50 to 80%. The carbamate was readily identified from its infrared spectrum, which showed the NH_2 and NH stretching bands at 3300 and 3150 cm^{-1}, respectively. The carbonyl stretching absorption at

(1) J. Thiele and K. Schleussner, *Justus Liebigs Ann. Chem.*, **295**, 129 (1897).

(2) K. Anzai and S. Suzuki, *J. Antibiot., Ser. A*, **14**, 253 (1961); K. Anzai, J. Nagatsu, and S. Suzuki, *ibid.*, 340 (1961); *Chem. Abstr.*, **56**, 8849, 10677 (1962).

(3) W. D. Crow and C. Wentrup, *Tetrahedron Lett.*, 6149 (1968).

(4) D. J. Anderson, T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *Chem. Commun.*, 1518 (1971).

(5) J. H. Boyer and L. T. Wolford, *J. Amer. Chem. Soc.*, **80**, 2741 (1958).

(6) G. Tennant, *J. Chem. Soc. C*, 2290 (1966).

(7) G. Tennant, *ibid.*, 1279, 2658 (1967).

(8) R. Valvarajan and J. H. Boyer, *J. Heterocycl. Chem.*, **9**, 87 (1972), recently reported the photodegradation of 4-phenyl- and 4,5-diphenyl-1,2,3-triazoles, but did not investigate any fused ring triazoles.

(9) R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole, and J. R. Vaughan, Jr., *J. Amer. Chem. Soc.*, **67**, 290 (1945).

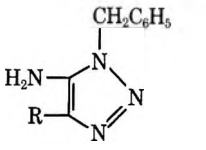
(10) J. R. E. Hoover and A. R. Day, *J. Amer. Chem. Soc.*, **78**, 5832 (1956).

(11) T. Curtius and K. Raschig, *J. Prakt. Chem.*, **125**, 466 (1930).

(12) J. C. Sheehan and C. A. Robinson, *J. Amer. Chem. Soc.*, **73**, 1207 (1951).

1680 cm^{-1} was also in agreement with that expected for a carbamate.

Attempts to hydrolyze the carbamate **4** in acid using a sealed tube[13] were completely unsuccessful, producing dark-colored solutions which did not afford any recognizable organic materials. This result is in agreement with that of Albert and Tratt,[14] who reported a similar degradataion of 5-amino-1-benzyl-1,2,3-triazole-4-carboxamide. When the carbamate was refluxed in aqueous sodium hydroxide,[15] it was smoothly cleaved to 1-benzyl-4,5-diamino-1,2,3-triazole (**5**). Compound **5** was identified by its infrared spectrum, in which the NH_2 stretching and bending frequencies occurred at 3300, 3150, and 1600 cm^{-1}, respectively. The pmr spectrum indicated the presence of four hydrogens attached to nitrogen at δ 3.10, all four being exchanged upon treatment with D_2O. The presence of methylene protons of the benzyl group at δ 5.35 and of the aromatic protons in a multiplet centered at δ 7.30 suggested the presence of the intact 1,2,3-triazole nucleus.



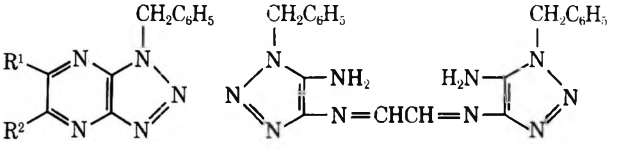
2, R = $CONHNH_2$
3, R = CON_3
4, R = $NHCO_2C_2H_5$
5, R = NH_2
5a, R = $N{=}CHC_6H_5$

The diamine **5** was moderately water soluble and formed a monopicrate when treated with 1 equiv of picric acid. It also formed the mono-*N*-benzylidene derivative **5a** when treated with an excess of benzaldehyde. The structure of **5a** was established by infrared and pmr spectral data (see Experimental Section). A complete discussion of the enhanced reactivity of one amino group when compared to the other will be discussed below.

1-Benzyl-4,5-diamino-1,2,3-triazole (**5**) was treated with an aqueous solution of glyoxal, sodium bisulfite, and a catalytic amount of hydrochloric acid and formed a mixture of two products. 1-Benzyl-1,2,3-triazolo-[4,5-*b*]pyrazine (**6**) was separated from the mixture as a methylene chloride soluble fraction and its structure was confirmed by its proton magnetic resonance spectrum, which contained two doublets at δ 8.74 and 8.65 (J = 1.5 Hz). This coupling is in excellent agreement with the reported ortho coupling constant for the pyrazine ring.[16] The remaining resonances in the spectrum were readily assigned. The paramagnetic shift (δ 5.92 *vs.* 5.35 in compound **5**) of the methylene protons indicates that an appreciable ring current exists in the fused system above that present in the 1,2,3-triazole nucleus alone. This effect is present in all fused rings examined.

In addition to **6**, a methylene chloride insoluble material was isolated (**6a**). The infrared spectrum of **6a** showed the characteristic NH_2 stretching and bending frequencies at 3300, 3150, and 1590 cm^{-1}. The pmr spectrum exhibited a singlet at δ 8.65 integrating for two protons and a broad singlet at 6.30. The latter was exchangeable in D_2O and integrated for four protons. The data are consistent with a structure such as **6a**, the result of an intermolecular condensation between one molecule of glyoxal and two of the diamine. The structure was confirmed when treatment at room temperature with aqueous hydrochloric acid produced a mixture of **5** and **6**. The formation of **6a** could never be completely eliminated, but the yield could be significantly reduced by adding the glyoxal–bisulfite solution dropwise to a solution of **5**.

Similarly, 1-benzyl-5,6-diphenyl-1,2,3-triazolo[4,5-*b*]-pyrazine (**7**) and 1-benzyl-5,6-dimethyl-1,2,3-triazolo[4,5-*b*]pyrazine (**8**) were prepared by condensing benzil or butane-2,3-dione with compound **5**. In the latter case, a yield approaching quantitative was realized. Both compounds **7** and **8** were characterized by means of their spectral data.



6, $R^1 = R^2 = H$
7, $R^1 = R^2 = C_6H_5$
8, $R^1 = R^2 = CH_3$
9a, $R^1 = CH_3$; $R^2 = H$
9b, $R^1 = H$; $R^2 = CH_3$

6a

Compound **8** was refluxed in aqueous hydrochloric acid for 5 hr and recovered unchanged in quantitative yield, indicating the resistance of the 1,2,3-triazolo-[4,5-*b*]pyrazine ring to acid hydrolysis. The ultraviolet absorption maxima measured in 50% aqueous ethanol for compound **6** were completely unaffected by either acid or base, indicating that covalent hydration is extremely unlikely in this ring system.[17] Covalent hydration has been implicated as the driving force in the acid hydrolysis of 8-azapurines.[18] In addition, compound **8** was unaffected by aqueous base and by nucleophiles such as hydrazine hydrate. Hydrazine hydrate has caused the cleavage of the pyrazine ring of some pteridines.[19]

When the diamino-1,2,3-triazole **5** was treated with pyruvic aldehyde, a single condensation product was isolated. The structure assigned (**9a** or **9b**) was based upon the pmr spectrum, in which the pyrazine ring proton appeared at δ 8.56 as a singlet and the methyl group appeared at 2.76, also a singlet. Differentiation by spectral means between **9a** and **9b** was impossible and the absolute structure remains in doubt.

When the 5,6-dimethyl derivative **8** was treated with sodium in liquid ammonia, a technique which has been used successfully to remove the 1-benzyl group,[10] it failed to effect debenzylation. A second attempt to

(13) P. A. S. Smith in "Organic Reactions," Vol. III, Wiley, New York, N. Y., 1946, p 380.
(14) A. Albert and K. Tratt, *J. Chem. Soc. C*, 344 (1968).
(15) G. B. Jambuserwala, S. Holt, and F. A. Mason, *J. Chem. Soc.*, 373 (1931).
(16) M. H. Palmer, "Heterocyclic Compounds," St. Martins Press, New York, N. Y., 1967, p 68.
(17) See ref 14. Albert reported a bathochromic shift of 33 nm upon addition of acid when measuring the uv spectra of some 8-azapurines in aqueous ethanol. This shift can be attributed to the loss of double-bond character *via* covalent hydration.
(18) A. Albert, *J. Chem. Soc. C*, 2379 (1969).
(19) J. Clark and G. Neath, *ibid.*, 1112 (1966).

remove the 1-benzyl group with hydrogen, palladium on charcoal, and magnesium oxide in ethanol[14] also failed to bring about debenzylation of compound **8**. These results were rather unexpected, since the isomeric 1,2,3-triazolo[4,5-*d*]pyrimidine nucleus undergoes ready debenzylation,[14,20] as does the parent 1,2,3-triazole ring.

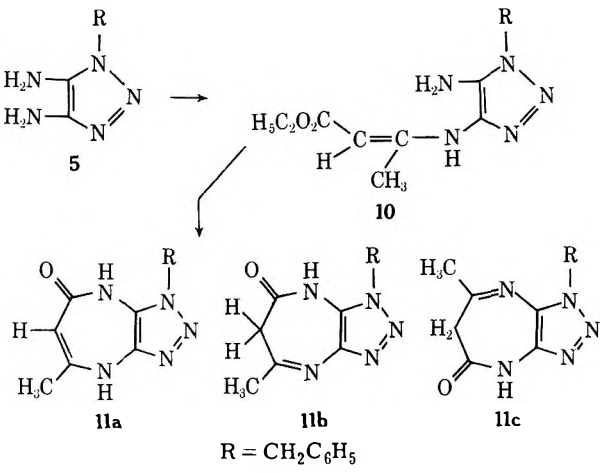
When attempts were made to extend the condensation discussed above to α-keto acids or α-keto esters such as glyoxylic acid or diethyl mesoxylate, no ring-closed products were isolated. In both cases, complex mixtures which did not lend themselves to common separation techniques were observed by tlc.

The addition of **5** to ethyl acetoacetate at 60° afforded compound **10**, which was identified by its infrared and pmr spectra. Ring closure of **10** with sodium ethoxide gave a material whose infrared spectrum contained carbonyl bands at 1700 and 1620 cm^{-1}. Heating the crude product in benzene produced a soluble and an insoluble fraction. The infrared spectrum of the insoluble fraction contained a single carbonyl band at 1620 cm^{-1}. Structures such as **11b** or **11c**, based on the findings of Israel and coworkers[21] for similar systems, would be consistent with that carbonyl absorption. The pmr spectrum contained, among other resonances, a two-proton singlet at δ 3.30, also consistent with **11b** or **11c** (the olefinic proton in **10** appeared at δ 4.75). Structure **11c** is considered unlikely in light of the enhanced reactivity of the 4-amino group (*vide infra*).[22]

The infrared spectrum of the benzene-soluble fraction contained carbonyl bands at 1700 and 1620 cm^{-1}. Israel and coworkers[21] have assigned structures such as **11a** to compounds having the 1700-cm^{-1} carbonyl absorption. Attempts to detect **11a** by pmr were unsuccessful and experiments, such as vacuum sublimation, designed to isolate pure **11a** also failed. (See Scheme I.)

Compound **5** could be monoacetylated yielding compound **12** when treated with acetic anhydride for short periods of time at room temperature. If the acetylation was accomplished at reflux, or at room temperature for longer periods of time, a diacetyl derivative **15** could be isolated. The structure of compound **12** was established by spectral means and the diacetyl product **15** was similarly identified. The presence of two acetyl methyl groups at δ 2.25 and 2.08 were invaluable in the structural assignment of **15**. Structure **15** rather than **15a** is proposed since the carbonyl band at 1660 cm^{-1} is much lower than the

SCHEME I



carbonyl frequencies reported by Sutherland and Tennant[25] for ring nitrogen acetylated 1,2,3-triazoles. Also, these workers observed ring nitrogen acetyl methyl resonances at approximately δ 2.8, much more deshielded than the methyl resonances observed[22] for **12** and **15**.

The final proof of the structure of the monoacetylated derivative **12** was obtained as follows. **12** was diazotized in the presence of sodium fluoroborate, and the diazonium fluoroborate salt was isolated. Without further characterization the diazonium salt was dissolved in methanol and treated with an excess of sodium borohydride.[26] This procedure effected smooth displacement of the diazonium group, yielding 4-acetamido-1-benzyl-1,2,3-triazole (**13**). The loss of the amino group was demonstrated by the presence of a single absorption at 3180 cm^{-1} in the infrared spectrum of **13** (secondary amide). In addition, the 5 proton was clearly visible at δ 8.02 in the proton magnetic resonance spectrum. In order to demonstrate unequivocally that acetylation had occurred on the 4-amino group and not on the 5-amino group, 5-acetamido-1-benzyl-1,2,3-triazole was prepared by the following route. Benzyl azide was condensed with cyanoacetic acid, affording 5-amino-1-benzyl-1,2,3-triazole-4-carboxylic acid (**16**) in the same fashion as described previously. The carboxylic acid was readily decarboxylated in refluxing dimethyl aniline,[10] giving 5-amino-1-benzyl-1,2,3-triazole in respectable yield. Acetylation with acetic anhydride in the presence of a small amount of sulfuric acid[25] afforded 5-acetamido-1-benzyl-1,2,3-triazole (**14**) in low yield. Compound **14** was different in all respects from **13**. The Experimental Section contains the spectral data for the two isomers and the reactions are summarized in Scheme II.

The facile acetylation with acetic anhydride thwarted attempts to prepare the imidazolo[4,5-*d*]-1,2,3-triazole ring system with either acetic anhydride or acetic anhydride–ortho esters. In fact, heating **5** with ortho esters (triethyl orthoformate) for 24 hr followed by addition of acetic anhydride produced **13** in excellent yield.

Experimental Section

The pmr spectra were determined on a Varian HA-100 spectrophotometer; infrared spectra were measured on a Perkin-

(20) G. Nübel and W. Pfleiderer, *Chem. Ber.*, **98**, 1060 (1965).

(21) M. Israel, L. C. Jones, and E. J. Modest, *J. Heterocycl. Chem.*, **4**, 659 (1967).

(22) Albert[23] has recently reported a somewhat more facile Dimroth rearrangement in base of 4-amino-3-benzyl 5-substituted 1,2,3-triazoles than had previously been noted or expected for the bulky benzyl group. However, 4-amino-3-benzyl-1,2,3-triazole-5-carboxamide does not undergo the rearrangement when heated to 180° in alcoholic ammonia.[24] It appears that the rearrangement is quite sensitive to both heat and base and not well understood when a benzyl substituent is present. The chemical shifts for the methylene protons of the benzyl group in **10** and **11** are in good agreement with Albert's[22] values for triazole ring substitution. Furthermore, he noted an upfield shift of the methylene protons and coupling between the NH and CH_2 when the benzyl group rearranged to the adjacent exocyclic amino group. No such shift or coupling was observed for **11**. With that data in hand, we believe that the Dimroth rearrangement plays an insignificant role in this reaction. Likewise, the same argument, based upon spectral evidence, can be advanced for the acid-catalyzed condensation of **5** with the α-diketones and the reaction of **5** with acetic anhydride.

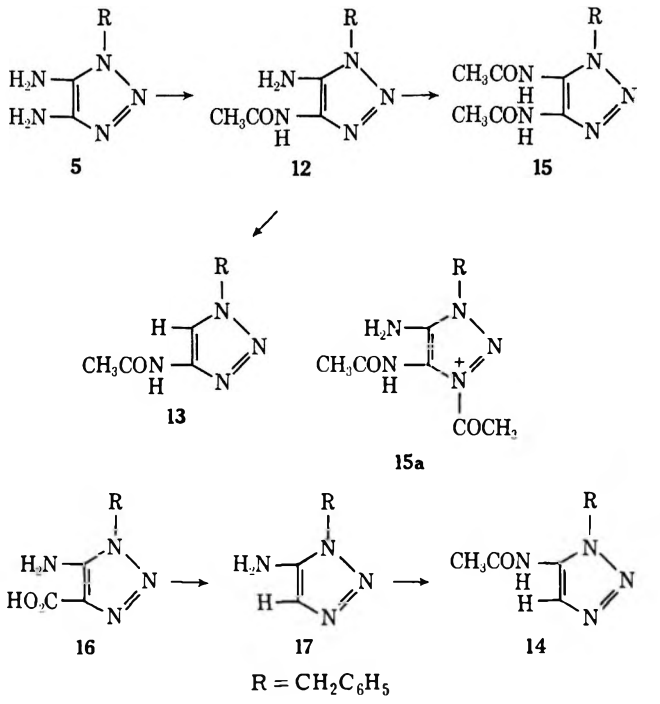
(23) A. Albert, *J. Chem. Soc. C*, 230 (1970).

(24) A. Albert, *ibid.*, 152 (1969).

(25) D. R. Sutherland and G. Tennant, *ibid.*, 706 (1971).

(26) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **83**, 1251 (1961).

SCHEME II



Elmer 137 Infracord spectrophotometer. All melting points are uncorrected and were taken on a Thomas-Hoover melting point apparatus. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. 46226.

Ethyl 5-Amino-1-benzyl-1,2,3-triazole-4-carboxylate (1).—To a solution of 11.0 g (0.5 mol) of sodium in 250 ml of absolute ethanol was added 56.5 g (0.5 mol) of ethyl cyanoacetate and 61.3 g (0.5 mol) of benzyl azide.[27] A white precipitate formed immediately and gradually dissolved during the course of 1 hr. The yellow solution which resulted was poured into 2 l. of ice–water and the crude yellow precipitate was collected. Recrystallization from ethanol afforded colorless needles: mp 153–154° (lit.[10] mp 154°); ir (KBr) 3400, 3250, 3100, 1700, 1620, 1500, 1200, 730 cm^{-1}.

5-Amino-1-benzyl-1,2,3-triazole-4-carboxylic Acid Hydrazide (2).—A mixture of 45.0 g (0.2 mol) of 1 and 200 ml of 85% hydrazine hydrate was refluxed for 1.5 hr. The pale yellow solution was cooled and the colorless plates were collected, mp 196–198° (lit.[10] mp 195°).

5-Amino-1-benzyl-1,2,3-triazole-4-carbonyl Azide (3).—A solution of 15.0 g (0.07 mol) of 2 in 200 ml of 10% hydrochloric acid was cooled to 5°. A solution of 4.5 g (0.07 mol) of sodium nitrite in water was added dropwise. The white precipitate that formed immediately became yellow with time and was collected. The precipitate was washed with cold ether and was recrystallized by dissolving in acetone and precipitating with hexane. This treatment gave 16.4 g (74%) of white, irregular prisms: mp 150° dec; ir (KBr) 3300, 3200, 2200, 1650, 1620, 1200, 980 cm^{-1}.

Ethyl 5-Amino-1-benzyl-1,2,3-triazole-4-carbamate (4).—A mixture of 6.0 g (0.04 mol) of 3 and 100 ml of absolute ethanol was refluxed for 20 hr. The darkened solution was cooled to room temperature and the off-white, irregular prisms that formed were collected. Crystallization from ethanol gave 5.40 g (52%) of 4: mp 206° dec; ir (KBr) 3300, 3150, 1680, 1600, 1260, 700 cm^{-1}; pmr (DMSO-d_6) δ 7.37–7.14 (m, 5, aromatic), 5.33 (s, 2, $BzCH_2$), 4.10 (q, J = 6 Hz, CH_2 ethyl), 1.20 (t, J = 6 Hz, CH_3 ethyl).

Anal. Calcd for $C_{12}H_{15}N_5O_2$: C, 55.16; H, 5.79; N, 26.81. Found: C, 54.81; H, 5.54; N, 26.81.

1-Benzyl-4,5-diamino-1,2,3-triazole (5).—A mixture of 1.0 g (0.004 mol) of 4, 2 ml of ethanol, and 15 ml of 1 N sodium hydroxide was refluxed for 3 hr. The yellow solution was extracted with 4 × 50 ml of methylene chloride. The methylene chloride was dried over magnesium sulfate and finally evaporated to dryness *in vacuo*. Crystallization from benzene gave 0.4 g (55%) of 5: mp 115°; ir (KBr) 3350, 3150, 1640, 1600, 1400, 740 cm^{-1}; pmr ($CDCl_3$) δ 7.36–7.18 (m, 5, aromatic), 5.35 (s, 2, $BzCH_2$), 3.08 (broad s, 4, NH_2).

Anal. Monopicrate, calcd for $C_{16}H_{14}N_8O_7$: C, 42.96; H, 3.58; N, 26.73. Found: C, 42.90; H, 3.56; N, 26.72.

5-Amino-1-benzyl-4-(*N*-benzylidene)-1,2,3-triazole (5a).—To a solution of 5 (0.85 g, 0.004 mol) in ethanol was added 1.25 g of benzaldehyde. The yellow precipitate (1.1 g, mp 177°) was collected. The material was recrystallized twice from benzene: mp 178°; pmr (acetone-d_6) δ 9.08 (s, 1, C_6H_5CH), 8.00–7.20 (series of three complex multiplets, 10, aromatic), 5.47 (s, 2, $BzCH_2$), 5.27 (broad s, 2, NH_2).

Anal. Calcd for $C_{16}H_{15}N_5$: C, 69.30; H, 5.45; N, 25.25. Found: C, 69.25; H, 5.55; N, 25.28.

1-Benzyl-1,2,3-triazolo[4,5-*b*]pyrazine (6).—A solution of 0.31 g of 40% glyoxal and 1.04 g (0.01 mol) of sodium bisulfite was added to a solution of 1.0 g (0.005 mol) of 5 in water. The orange precipitate that formed did not dissolve when warmed to 80°. The somewhat oily precipitate was collected and air dried. The precipitate was treated with hot methylene chloride and the bright yellow insoluble fraction (6a) was set aside. The methylene chloride solution was evaporated *in vacuo* until a viscous syrup remained. Upon cooling, the syrup deposited 0.55 g of crystals. These crystals were chromatographed on silica gel (100 g, ethyl acetate) and the first fraction afforded 0.3 g of buff prisms. Final purification by means of vacuum sublimation gave colorless microprisms of 6: mp 91.5°; ir (KBr) 1500, 1440, 1240, 1180, 950, 745, 700 cm^{-1}; pmr ($CDCl_3$) δ 8.75–8.65 (d, J = 1 Hz, total area 2, pyrazine ring protons), 7.55–7.22 (m, 5, aromatic), 5.92 (s, 2, $BzCH_2$).

Anal. Calcd for $C_{11}H_9N_5$: C, 62.54; H, 4.29; N, 33.16. Found: C, 62.53; H, 4.30; N, 33.16.

The yellow, irregular prisms were identified as 6a on the basis of the following spectral data: ir (KBr) 3300, 3150, 1630, 1590, 1500, 1310, 1210, 1000, 800, 690 cm^{-1}; pmr (DMSO-d_6) δ 8.65 (s, 2, N=CHCH=N), 7.40–7.20 (m, 10, aromatic), 6.30 (broad s, 4, NH_2), 5.40 (s, 4, $BzCH_2$).

1-Benzyl-5,6-diphenyl-1,2,3-triazolo[4,5-*b*]pyrazine (7).—To a solution of 1.5 g (0.008 mol) of 5 and 1.65 g (0.009 mol) of benzil in ethanol was added 3 drops of concentrated HCl. After refluxing for 5 hr the solution had become dark red. Concentration *in vacuo* gave a red oil which was chromatographed on 100 g of silica gel, using ethyl acetate as eluting solvent. The first fraction was identified as unreacted benzil and the second fraction was evaporated to dryness *in vacuo*. Two recrystallizations from methanol gave 0.5 g (33%) of 7: mp 110°; ir (KBr) 3000, 1440, 1340, 1180, 1120, 755, 700 cm^{-1}; pmr ($CDCl_3$) δ 7.60–7.10 (m, 15, aromatic), 5.94 (s, 2, $BzCH_2$).

Anal. Calcd for $C_{23}H_{17}N_5$: C, 76.01; H, 4.72; N, 19.27. Found: C, 75.90; H, 4.89; N, 19.38.

1-Benzyl-5,6-dimethyl-1,2,3-triazolo[4,5-*b*]pyrazine (8).—To a solution of 3.0 g (0.03 mol) of butane-2,3-dione and 1.0 g (0.005 mol) of 5 in 50% aqueous ethanol was added 3 drops of concentrated HCl. After refluxing for 2 hr and concentrating *in vacuo*, cooling the oil afforded 1.1 g of crude 8. Recrystallization from 50% aqueous methanol gave pure 8: mp 131°; ir (KBr) 1500, 1440, 1265, 1025, 950, 700 cm^{-1}; pmr ($CDCl_3$) δ 7.46–7.24 (m, 5, aromatic), 5.84 (s, 2, $BzCH_2$), 2.72 (s, 6, CH_3).

Anal. Calcd for $C_{13}H_{13}N_5$: C, 65.26; H, 5.47; N, 29.27. Found: C, 65.05; H, 5.73; N, 29.23.

1-Benzyl-5- (or 6-) methyl-1,2,3-triazolo[4,5-*b*]pyrazine (9).—To a solution of 1.0 g of 40% aqueous pyruvic aldehyde and 1.0 g (0.005 mol) of 5 in ethanol was added 3 drops of concentrated HCl. The addition of HCl caused an immediate red color. The solution was warmed at 60° for 1 hr. Concentration *in vacuo* produced a red syrup, which was chromatographed on 100 g of silica gel and eluted with ethyl acetate. The first fraction afforded 0.3 g (30%) of crude 9. Three recrystallizations from ether–hexane gave 9: mp 69°; pmr ($CDCl_3$) δ 8.56 (s, 1, pyrazine ring proton), 7.50–7.20 (m, 5, aromatic), 5.86 (s, 2, $BzCH_2$), 2.76 (s, 3, CH_3).

Anal. Calcd for $C_{12}H_{11}N_5$: C, 63.99; H, 4.92; N, 31.09. Found: C, 63.70; H, 4.74; N, 31.08.

Ethyl 3-[(5-Amino-1-benzyl-1,2,3-triazol-4-yl)amino]crotonate (10).—A solution of 1.0 g (0.005 mol) of 5 in 5.0 g (0.04 mol) of ethyl acetoacetate was heated at 60° for 15 min. The orange solution which resulted was diluted with chloroform and then treated with a large excess of hexane. The precipitate was collected and recrystallized by repeating the above procedure. This treatment produced 1.35 g (90%) of 10: mp 125°; ir (KBr) 3400, 3300, 3190, 1650, 1600, 1240, 800, 700 cm^{-1}; pmr ($CDCl_3$) δ 9.61

(27) R. H. Wiley, K. F. Hussung, and J. Moffat, *J. Org. Chem.*, **21**, 190 (1956).

(s, 1, NH), 7.44–7.10 (m, 5, aromatic), 5.39 (s, 2, $BzCH_2$), 4.75 (s, 1, C=CH), 4.11 (q, J = 7 Hz, ethyl CH_2), 3.43 (s, 2, NH_2), 1.84 (s, 3, CH_3), 1.25 (t, J = 7 Hz, ethyl CH_3).

Anal. Calcd for $C_{15}H_{19}N_5O_2$: C, 59.79; H, 6.35; N, 23.24. Found: C, 59.77; H, 6.38; N, 22.90.

4*H*,6*H*-1-Benzyl-7-methyl-1,2,3-triazolo[5,4-*b*][1,4]diazepin-5-one (11).—To a solution of 0.1 g (0.004 mol) of sodium in absolute alcohol was added 1.0 g (0.003 mol) of **10**. The yellow solution was refluxed for 5 hr. Concentration *in vacuo* afforded yellow, irregular prisms. The prisms were dissolved in water, the solution was made acid with hydrochloric acid, and the precipitate was collected. Treatment with hot benzene produced an insoluble bright yellow crop of crude **11b** or **11c**. The benzene solution afforded a crop of off-white, irregular prisms consisting of a mixture of **11a** and **11b**: ir (KBr) 3000, 1700, 1660, 1620, 1400, 1300, 710 cm^{-1}. Treatment of the mixture with chloroform, pyridine, or dimethyl sulfoxide converted it to pure **11b** or **11c**.

The yellow, irregular prisms (**11b** or **11c**) were collected: mp 244° dec; ir (KBr) 3200, 3100, 2990, 1610, 1580, 700 cm^{-1}; pmr (pyridine-d_5) δ 7.38–7.02 (m, 5, aromatic), 5.70 (s, 2, $BzCH_2$), 3.30 (s, 2, CH_2), 2.21 (s, 3, CH_3).

Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.19; H, 5.10; N, 27.44. Found: C, 60.90; H, 5.39; N, 27.47.

4-Acetamido-5-amino-1-benzyl-1,2,3-triazole (12).—A mixture of 1.0 g (0.005 mol) of **5** and 10 g of acetic anhydride was stirred at room temperature for 10 min. The precipitate that formed was collected and air dried. Two recrystallizations from water afforded 0.8 g (53%) of **12**: mp 177°; ir (KBr) 3350, 3200, 1660, 1650, 1600, 1280 cm^{-1}; pmr ($CDCl_3$) δ 7.41–7.18 (m, 5, aromatic), 5.36 (s, 2, $BzCH_2$), 2.20 (s, 3, $COCH_3$).

Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.66; N, 30.28. Found: C, 57.19; H, 5.63; N, 30.66.

4-Acetamido-1-benzyl-1,2,3-triazole (13).—Compound **12** (0.5 g, 0.003 mol) was converted to 0.7 g (100%) of the corresponding diazonium fluoroborate in the usual fashion.[28] After air drying for 3 hr, the diazonium salt was dissolved in 50 ml of methanol at 0° and treated with 0.05 g of sodium borohydride. The solution was stirred for 15 min, diluted with an equal volume of water, and extracted with 4 × 50 ml of methylene chloride. After drying over magnesium sulfate, the methylene chloride extract was concentrated *in vacuo* to a viscous syrup. The syrup was chromatographed on silica gel (100 g, ethyl acetate). Concentration of the first fraction afforded **13** in the form of buff, irregular prisms. Solution in methylene chloride, decolorization with charcoal, and precipitation with hexane gave 0.12 g of pure **13**: mp 197.5–198.5°; ir (KBr) 3180, 3000, 1660, 1560, 1420, 1280, 1045, 841, 715 cm^{-1}; pmr ($CDCl_3$) δ 8.02 (s, 1, C-5 proton), 7.40–7.22 (m, 5, aromatic), 6.02 (broad s, 1, NH), 5.28 (s, 2, $BzCH_2$), 2.27 (s, 3, $COCH_3$).

Anal. Calcd for $C_{11}H_{12}N_4O$: C, 60.87; H, 5.94; N, 25.82. Found: C, 60.81; H, 5.65; N, 25.76.

5-Acetamido-1-benzyl-1,2,3-triazole (14).—A solution of 1.0 g (0.006 mol) of 5-amino-1-benzyl-1,2,3-triazole in 7.5 ml of acetic anhydride was treated with 0.5 ml of sulfuric acid. The yellow solution was stirred at room temperature for 24 hr. The crude precipitate and solution were poured onto crushed ice, and the aqueous solution was concentrated *in vacuo* to a viscous oil. Treatment of the oil with hexane produced off-white, irregular prisms of **14**. Final purification by column chromatography using 100 g of silica gel and ethyl acetate as solvent afforded pure **14**: mp 132°; ir (KBr) 3300, 3200, 3000, 1690, 1550, 1230, 980, 705 cm^{-1}; pmr ($CDCl_3$) δ 9.39 (broad s, 1, NH), 7.78 (s, 1, C-4 proton), 7.36–7.02 (m, 5, aromatic), 5.50 (s, 2, $BzCH_2$), 2.04 (s, 3, $COCH_3$).

Anal. Calcd for $C_{11}H_{12}N_4O$: C, 60.87; H, 5.94; N, 25.82. Found: C, 60.90; H, 5.82; N, 25.79.

4,5-Diacetamido-1-benzyl-1,2,3-triazole (15).—A solution of 0.1 g (0.001 mol) of **5** in 1.0 g of acetic anhydride was kept at room temperature overnight. The precipitate that formed was collected and washed with water. Three recrystallizations from water afforded 0.12 g (45%) of analytically pure **15**: mp 194°; ir (KBr), 3445, 3250, 1660, 1610, 1570, 1520, 705 cm^{-1}; pmr ($CDCl_3$) δ 8.08 (broad s, 1, NH), 7.38–7.10 (m, 5, aromatic), 5.61 (s, 2, $BzCH_2$), 2.75 (s, 3, $COCH_3$), 2.08 (s, 3, $COCH_3$).

Anal. Calcd for $C_{13}H_{15}N_5O_2 \cdot {}^1/_4H_2O$: C, 56.21; H, 5.44; N, 25.21. Found: C, 56.15; H, 5.60; N, 25.11.

(28) R. Adams, "Organic Reactions," Wiley, New York, N. Y., 1949, p 193.

Registry No.—**1**, 20271-33-4; **3**, 36540-25-7; **4**, 36540-26-8; **5**, 36540-27-9; **5** monopicrate, 36540-28-0; **5a**, 36540-29-1; **6**, 36540-30-4; **6a**, 36540-31-5; **7**, 36540-32-6; **8**, 36540-33-7; **9a**, 36540-34-8; **9b**, 36540-35-9; **10**, 36540-36-0; **11a**, 36540-37-1; **11b**, 36540-38-2; **11c**, 36540-39-3; **12**, 36540-40-6; **13**, 36540-41-7; **14**, 36540-42-8; **15**, 36540-43-9.

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Cyclic Peroxides. XVII.[1] Solvolysis of Di-*n*-butylmalonoyl Peroxide[2]

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It is postulated that in the solvolysis of di-*n*-butylmalonoyl peroxide (**1**) in methanol or ethanol initially the monoperoxy malonic acid half ester **12** is formed. Analogous to simple peroxy acids, it is proposed that in methanol this peroxy acid intermediate suffers concerted deoxygenation to produce hydrogen methyl di-*n*-butylmalonate (**6**) as the major product, but in ethanol **12** undergoes homolysis of the peroxide bond, leading to di-*n*-butylmalonic acid (**10**) as the major product. In both cases, inhibition experiments indicate that a chain process involving the hydroxyalkyl radical, derived from the solvent, contributes in a minor way. Even at relatively low temperatures, in both solvents some decarboxylation of the malonoyl peroxide **1** occurs to give α-lactone **2**.

Recently we reported[4] on the synthesis of malonoyl peroxide **1**, a novel class of cyclic diacyl peroxides, which on photolysis decarboxylates to generate α-lactones **2** (eq 1). At −196° the α-lactone **2** is perfectly stable and can be preserved indefinitely, but on further photolysis **2** decarbonylates to afford ketone **4**.[5] Warming up to −100°, α-lactone **2** rapidly polymerizes into polyester **5**,[5] which can also be obtained in high yield by photolysis of a benzene solution of malonoyl peroxide **1**.[4] On the other hand, on photolysis of **1** in alcoholic solvents such as methanol or ethanol, the α-alkoxy acid **3** is produced in high yield, as expected from the addition of R′OH to the dipolar structure of

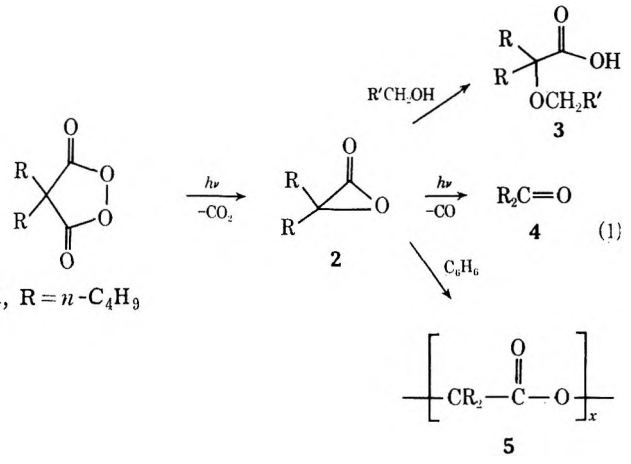
(1) This paper is dedicated to Professor Dr. Rudolf Criegee on his 70th birthday.

(2) Part XVI: W. Adam and J. C. Liu, *J. Amer. Chem. Soc.*, **94**, 2894 (1972).

(3) Presented in part at the Cyclic Peroxide Symposium, Metrochem 71, Regional Meeting of the American Chemical Society, San Juan, Puerto Rico, April 30, 1971.

(4) W. Adam and R. Rucktäschel, *J. Amer. Chem. Soc.*, **93**, 557 (1971).

(5) W. Adam, O. L. Chapman, O. Rodriguez, R. Rucktäschel, and P. W. Wojtkowsky, *ibid.*, **94**, 1365 (1972).



(1)

the α-lactone.[4] However, in the latter case we observed that concurrent with the photodecarboxylation of **1** in the alcoholic solvents, a direct reaction between the solvent and the malonoyl peroxide takes place in the dark.[3] In this article we describe our results on the systematic investigation of this direct solvolysis reaction of **1** in the dark.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Infracord 237-B using 0.1-mm sodium chloride cavity cells.

The nmr spectra were recorded on a Varian T-60 spectrometer using normal and semi-micro nmr tubes. The chemical shifts are given in δ units using TMS as internal standard.

The glpc analyses were carried out on a Varian Aerograph 202-B instrument, provided with TC detection, employing the following columns under the specified conditions: (a) 15 ft × 0.25 in. copper column, packed with 20% Carbowax 20M on 60/80 mesh Chromosorb W, operated at column, injector, and detector temperature of 175, 225, and 250°, respectively, and a helium flow of 60 ml/min (condition CX-1); and (b) 12 ft × 0.25 in. copper column, packed with 27% Apiezon M on 60/80 Chromosorb P, operated at column, injector, and detector temperatures of 214, 225, and 250°, respectively, and a helium flow of 60 ml/min (condition AZ-1). All melting points and boiling points are uncorrected.

Di-*n*-butylmalonoyl Peroxide.—Into four 25-ml round-bottom flasks, each provided with a spin bar and a drying tube, were placed each 2.50 g (0.0116 mol) of di-*n*-butylmalonic acid[6,7] and 12.5 ml of methanesulfonic acid. By means of remote control and stirring magnetically were charged into each flask a total of 4.5 ml of 98% hydrogen peroxide, 2.0 ml initially, 1.5 ml after 6 hr, and finally 1.0 ml after 10 hr of reaction time. The contents were stirred at room temperature for another 24 hr, after which time the suspended malonic acid had dissolved. The four reaction mixtures were combined and poured onto crushed ice, saturated ammonium sulfate was added, and the mixture was extracted well with *n*-pentane. The combined pentane extracts were washed with saturated aqueous ammonium sulfate, sodium bicarbonate, and water. After drying over magnesium sulfate and evaporation of the solvent, there was obtained 9.00 g (91%) of crude product. Fractional distillation at reduced pressure afforded 7.75 g (78%) of malonoyl peroxide, bp 49–50° (0.05 mm), $n^{22.5}$D 1.4350, 99.5% pure by iodometric titration. The spectral data are: ir (CCl_4) 1783, 1468, 1225, 1135, and 1075 cm^{-1}; nmr (60 MHz, CCl_4) δ 0.9 (m, 3, CH_3–), 1.3 (m, 4, $-CH_2-CH_2-$), and 1.85 (m, 2, $-CH_2CC{=}O$); uv (CCl_4) λ 220 nm (ε 350), 250 (100), 300 (11.2), and 350 (8.4).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47; mol wt, 214.3. Found: C, 61.59; H, 8.55; mol wt, 213.2 ± 1.0 (osmometry).

Dimethyl di-*n*-butylmalonate was prepared in 76% yield from di-*n*-butylmalonic acid by treatment with ethereal diazomethane solution,[8,9] bp 113.5–114.5° (4 mm), n^{20}D 1.4350, which on standing crystallized, mp 39°. The spectral data are: ir (CCl_4) 2990–2845, 1740 (shoulder), 1725 (ester carbonyl), 1255, 1210, 1155, and 1130 cm^{-1}; nmr (60 MHz, CCl_4) δ 0.95, 1.20, and 1.80 (m, 3:4:2, *n*-butyl) and 3.65 (s, 3, ester methyl).

Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.90; H, 9.90. Found: C, 64.09; H, 9.83.

Methyl Hydrogen Di-*n*-butylmalonate.—To a solution of 4.32 g (20 mmol) of di-*n*-butylmalonic acid in 90 ml of ether, cooled to 0°, was added slowly while stirring magnetically 76 ml of a 0.131 *M* solution of diazomethane in ether (freshly standardized by titration with acid). The colorless reaction mixture was then extracted three times with dilute sodium hydroxide, and the combined alkaline extracts were acidified while cooling with concentrated hydrochloric acid, and extracted three times with ether. The combined ether extracts were washed with water and dried ($MgSO_4$). Evaporation of the ether at 80° (20 mm) gave 3.5 g (76%) of a residue, n^{20}D 1.4449. On distillation 2.9 g (63%) of a colorless liquid was obtained, bp 102–105° (0.04 mm), which slowly crystallized on standing, mp 39–42°. Several recrystallizations from *n*-hexane at −20° gave the pure material, mp 45.5–46.5°. The spectral data are: ir (CCl_4) 3400–2500 (OH of acid), 1748 (ester carbonyl), 1705 (acid carbonyl), 1274, and 1201 cm^{-1}; nmr (60 MHz, CCl_4) δ 0.7–2.1 (m, 18, *n*-butyl), 3.71 (s, 3, ester $-OCH_3$), and 11.1 (s, 1, acid OH).

Anal. Calcd for $C_{12}H_{22}O_4$: acid equiv, 230.3. Found: acid equiv, 230 ± 1.

Ethyl Hydrogen Di-*n*-butylmalonate.—The procedure described by Büchi, *et al.*,[10] was employed, but modified as below. A solution of 10.9 g (40 mmol) of diethyl di-*n*-butylmalonate in 10 ml of 95% ethanol was placed into a 50-ml round-bottom flask provided with a spin bar, dropping funnel, and reflux condenser. While heating at 80°, a solution of 2.96 g (45 mmol) of KOH in 10 ml of 95% ethanol and 5 ml of water was added within 30 min, and the reaction mixture was allowed to stir for an additional 75 min at 90°. The ethanol was removed at reduced pressure [60° (20 mm)], 50 ml of water was added to the residue, and the mixture was extracted two times with *n*-hexane. The alkaline, aqueous solution was acidified with concentrated hydrochloric acid while cooling and extracted three times with 70-ml portions of ether. The combined ether extracts were washed with water and dried ($MgSO_4$), and the ether was evaporated [80° (20 mm)], affording 7.75 g (80%) of a viscous liquid, n^{20}D 1.4424. After distillation at reduced pressure there was obtained 5.1 g (53%) of a colorless liquid, bp 117–117.5° (0.08 mm), n^{20}D 1.4415. On standing at 20° for a day, this distillate crystallized partially, and collection of the crystals on a sintered-glass funnel gave 1.7 g (33%) of colorless crystals, mp 41–43°. The spectral data are: ir (CCl_4) 3400–2500 (acid OH), 1745 (ester carbonyl), 1705 (acid carbonyl), 1272, and 1200 cm^{-1}; nmr (60 MHz, CCl_4) δ 0.7–2.2 (m, and overlapping t at 1.25, 21, *n*-butyl and CH_3 of ethoxy group), 4.15 (q, 2, J = 7 Hz, CH_2 of ethoxy group).

Anal. Calcd for $C_{13}H_{24}O_4$: acid equiv, 244.3. Found: acid equiv, 244 ± 2.

Ethyl methyl di-*n*-butylmalonate was prepared in 96% yield from ethyl hydrogen di-*n*-butylmalonate by treatment with ethereal diazomethane,[8,9] n^{20}D 1.4346, and used without further purification. The spectral data are: ir (CCl_4) 1732 with shoulder at 1745 (ester carbonyl), 1255, 1205, and 1199 cm^{-1}; nmr (60 MHz, CCl_4) δ 0.7–2.2 (m and overlapping t at 1.25, 21, *n*-butyl and CH_3 of ethoxy group), 3.68 (s, 3, ester $-OCH_3$), and 4.14 (q, 2, J = 7 Hz, $-CH_2-$ of ethoxy group).

Ethyl 2-*n*-butylhexanoate was prepared in 73% yield from 2-*n*-butylhexanoic acid[11] according to the procedure of Dolique,[12] bp 110–111° (18 mm), $n^{21.5}$D 1.4220 [lit.[12] bp 110° (18 mm), $n^{22.5}$D 1.4218].

Methyl 2-*n*-butylhexanoate was prepared in 65% yield by treatment of 2-*n*-butylhexanoic acid[11] with a slight excess of ethereal diazomethane, bp 89.5–90° (9 mm), n^{23}D 1.4232 [lit.[13] bp 90° (9 mm), n^{23}D 1.4232].

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2-*n*-Butyl-2-methoxyhexanoic Acid.—A solution of 2.22 g (10.3 mmol) of methyl 2-*n*-butyl-2-methoxyhexanoate and 1.2 g (20 mmol) of KOH in 6 ml of methanol was refluxed for 7 hr. The solvent was removed at reduced pressure, and the residue was dissolved in water and extracted with ether. The aqueous layer was acidified with concentrated hydrochloric acid and extracted several times with ether. The combined ethereal extracts were dried ($MgSO_4$) and the solvent was evaporated, affording 2.1 g of slightly yellow liquid. Distillation gave 1.43 g (70%) of the acid, bp 94–95.5° (0.15 mm), $n^{20}D$ 1.4423. The spectral data are: ir (CCl_4) 3500–2500 (acid OH), 2830, 1780, and 1708 (ester carbonyl), and 1090 cm^{-1}; nmr (60 MHz, CCl_4) δ 0.95–1.70 (m, 18, *n*-butyl), 3.25 (s, 3, $-OCH_3$), and 10.5 (s, 1, $-CO_2H$).

Anal. Calcd for $C_{11}H_{22}O_3$: acid equiv, 202.3. Found: acid equiv, 202 ± 1.

Methyl 2-*n*-butyl-2-methoxyhexanoate was prepared in 51% yield following the methoxylation procedure of Diner, *et al.*,[14] bp 52° (0.05 mm), $n^{20}D$ 1.4315. The spectral data are: ir (CCl_4) 1740, 1727, and 1205 cm^{-1}; nmr (60 MHz, CCl_4) δ 0.9–1.6 (m, 18, *n*-butyl), 3.15 (s, 3, OCH_3), and 3.65 (s, 3, $-CO_2CH_3$).

Methyl 2-*n*-butyl-2-hydroxyhexanoate was prepared in 85% yield from 2-*n*-butyl-2-hydroxyhexanoic acid by treatment with excess diazomethane, bp 60–61° (0.1 mm), $n^{20}D$ 1.4310. The spectral data are: ir (CCl_4), 3540 (hydroxyl), 1725 (ester carbonyl), 1250, 1220, and 1165 cm^{-1}; nmr (60 MHz, CCl_4) δ 0.9–1.55 (m, 18, *n*-butyl), 3.55 (s, 1, –OH), and 3.70 (s, 3, $-CO_2CH_3$).

Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.30; H, 10.96. Found: C, 65.21; H, 11.05.

2-*n*-Butyl-2-hydroxyhexanoic acid was prepared in 90% yield by saponification of ethyl 2-*n*-butyl-2-hydroxyhexanoate with KOH in methanol, mp 85–86° (lit.[15] mp 87.5°).

Ethyl 2-*n*-butyl-2-hydroxyhexanoate was prepared in 60% yield, bp 114–116° (10 mm), $n^{20}D$ 1.4293, according to the procedure of Stoughton[16] and of Hepworth.[17]

Ethyl 2-*n*-butyl-2-methoxyhexanoate was prepared in 88% yield by treatment of 2-*n*-butyl-2-methoxyhexanoic acid with ethereal diazoethane,[18] and after bulb-to-bulb distillation at 125° (0.05 mm), $n^{21}D$ 1.4327, used without further purification. The spectral data are: ir (CCl_4) 1735 and 1725 (ester carbonyl) and 1200 cm^{-1}; nmr (60 MHz, CCl_4) δ 0.7–2.0 (m, 21, *n*-butyl and CH_3 of ethoxy), 3.1 (s, 3, $-OCH_3$), and 4.1 (q, 2, J = 7 Hz, $-CH_2-$ of ethoxy).

5-Nonanone was prepared in 40% yield, bp 83–84° (22 mm), $n^{21}D$ 1.4188 [lit.[19] bp 88° (22 mm), $n^{20}D$ 1.4195], from 2-*n*-butyl-2-hydroxyhexanoic acid by treatment with lead tetraacetate in dry benzene.

2-*n*-Butyl-2-ethoxyhexanoic acid was prepared by photolysis of 40 ml of a 0.116 *M* solution of di-*n*-butylmalonoyl peroxide in absolute ethanol in a 1.5-mm wall thickness Pyrex tube at 350 mm for 24 hr. Removal of the ethanol [50° (12 mm)] gave 855 mg (85%) of colorless liquid, $n^{20}D$ 1.4421, which was used without further purification. The spectral data are: ir (CCl_4) 3395 and 3500–2450 (acid OH), 1777 and 1704 (ester carbonyl), 1153, 1113, 1086, and 1043 cm^{-1}; nmr (60 MHz, CCl_4) δ 0.7–2.0 (m, 21, *n*-butyl and CH_3- of ethoxy), 3.42 (q, 2, J = 7 Hz, $-CH_2-$ of ethoxy), and 10.0 (s, 1, –OH).

Methyl 2-*n*-butyl-2-ethoxyhexanoate was prepared in 94% yield, $n^{20}D$ 1.4346, from 2-*n*-butyl-2-ethoxyhexanoic acid with ethereal diazomethane and used without further purification. The spectral data are: ir (CCl_4) 1727 and shoulder at 1740, and 1722 (ester carbonyl), 1198, and 1130 cm^{-1}; nmr (60 MHz, CCl_4) δ 0.7–2.5 (m, 21, *n*-butyl and CH_3 of ethoxy), 3.36 (q, 2, J = 7 Hz, $-CH_2-$ of ethoxy), and 3.61 (s, 3, $-OCH_3$).

***cis,trans*-2-Butyl-2-hexenoic Acid.**—Into a 10-ml round-bottom flask, provided with a 15-cm fractionation column with distilling head, was placed 3.76 g (20 mmol) of 2-*n*-butyl-2-hydroxyhexanoic acid, mp 84–86°, and the contents were heated for 5.5 hr at 200° to remove the water as it formed during the heating. The dark residue was fractionated at reduced pressure using a 20-cm Vigreux column, collecting a 1.60-g sample, bp 90.0–90.5° (0.3 mm), $n^{20}D$ 1.4586, which by nmr was shown to consist of a 70:30 mixture of cis(Z) and trans(E) isomers, as judged by the relative areas of the olefinic triplets at δ 6.0 and 6.9, respectively.[20] No further purification was attempted. The spectral data are: ir (CCl_4) 3400–2500 (acid OH), 1688 (acid carbonyl), and 1640 cm^{-1} (olefinic double bond); nmr (60 MHz, CCl_4) δ 0.7–2.7 (m, 16, *n*-butyl and *n*-propyl), 6.0 for cis(Z) and 6.9 for trans(E) [t, 1, J = 6.0 Hz for cis(Z) and 7.4 Hz for trans(E), olefinic =CH), and 12.1 (s, 1, acid OH).

Ethyl *cis,trans*-2-*n*-butyl-2-hexenoate was prepared in 83% yield by treatment of *cis,trans*-2-*n*-butyl-2-hexenoic acid with ethereal diazoethene, and after bulb-to-bulb distillation at 115° (7 mm), $n^{20}D$ 1.4405, used without further purification. The material was shown to be a 70:30 mixture of cis(Z) and trans(E) isomers by glpc analysis (conditions CX-1). The spectral data are: ir (CCl_4) 1710 with shoulder at 1730 (ester carbonyl), 1640 (olefinic double bond), 1205, and 1150 cm^{-1}; nmr (60 MHz, CCl_4) δ 0.7–2.6 (m, 19, *n*-butyl, *n*-propyl, and CH_3 of ethoxy), 4.15 (q, 2, J = 7 Hz, $-CH_2$ of ethoxy), and 5.78 for cis(Z) and 6.63 for trans(E) (t, 1, J = 7 Hz, olefinic =CH).

Methyl *cis,trans*-2-*n*-butyl-2-hexenoate was prepared in 95% yield by treatment of *cis,trans*-2-*n*-butyl-2-hexenoic acid with ethereal diazomethane and after bulb-to-bulb distillation at 115° (10 mm), $n^{20}D$ 1.4435, used without further purification. It was shown to be at 70:30 mixture of cis(Z) and trans(E) isomers by glpc (conditions CX-1). The spectral data are: ir (CCl_4) 1717 with shoulder at 1735 (ester carbonyl), 1643 (olefinic double bond), 1212, and 1150 cm^{-1}; nmr (60 MHz, CCl_4) δ 0.7–2.6 (m, 16, *n*-butyl and *n*-propyl), 3.67 (s, 3, $-CO_2CH_3$), and 5.79 for cis(Z) and 6.64 for trans(E) (t, 1, J = 7 Hz, olefinic =CH).

General Solvolysis Procedure of Di-*n*-butylmalonoyl Peroxide.—A stock solution of di-*n*-butylmalonoyl peroxide was prepared in the desired anhydrous alcohol (methanol or ethanol) at the appropriate concentration (0.25–0.30 *M*), distributed into constricted Pyrex test tubes, and sealed. These ampoules were placed into an oil bath, regulated within ±1° of the specified temperature, and aliquots of the reaction mixture were analyzed for peroxide titer. After the titer dropped below 0.5%, the remaining ampoules were opened and the contents were combined and treated with ethereal diazoalkane (in the case of methanol as solvent diazoethane was utilized, while in the case of ethanol as solvent diazomethane was used) until persistence of the yellow color. The solvent was removed at reduced pressure, the distillate was collected in a Dry Ice cooled vacuum trap, and the resulting oily product was submitted to bulb-to-bulb distillation, flushing several times with solvent distillate. The involatile residue, identified by ir as polyester,[4] was weighed to account for product balance. The molecular distillate and the solvent distillate were combined, adjusted to the appropriate volume, and submitted to glpc analysis, using conditions CX-1 and AZ-1. Each product formed in amounts greater than 0.1 mol % was collected and its structure was confirmed by comparison of glpc retention times and ir spectra with those of the authentic materials. The quantitative glpc results are collected in Table I, and reported as relative composition (mol %) of the volatile products. In all cases nearly 100% product balance, *i.e.*, volatile products and involatile residue, was achieved.

Solvolytic Stability of Di-*n*-butylmalonic Acid.—A solution of the malonic acid in the anhydrous alcohol was heated in an ampoule under identical conditions with the solvolysis of the malonoyl peroxide. The resulting reaction mixture was treated with the appropriate ethereal diazoalkane and submitted to glpc analysis (conditions AZ-1 and CX-1). At 80° after 60-hr reaction time 31% decarboxylation took place, while after 100 hr 48% took place, as evidenced by the formation of 2-*n*-butylhexanoic acid.

Solvolytic Stability of Hydrogen Alkyl Di-*n*-butylmalonate.—A solution of the appropriate malonate (alkyl as methyl or ethyl) in the anhydrous alcohol was heated in an ampoule under identical conditions with the solvolysis of the malonoyl peroxide. The resulting reaction mixture was treated with an ethereal solution of the appropriate diazoalkane and submitted to glpc analysis (conditions AZ-1 and CX-1). Small amounts of decarboxylation was observed at 80° within 100 hr, but at 140° for 2 hr 34 mol % of decarboxylation was established.

Rates.—Stock solutions (0.20–0.30 *M*) of the di-*n*-butylmalonoyl peroxide (1) in the anhydrous solvent were placed into

(14) U. E. Diner, F. Sweet, and R. K. Brown, *Can. J. Chem.*, **44**, 1591 (1966).

(15) C. W. Stacy and R. M. McCurdy, *J. Amer. Chem. Soc.*, **76**, 1915 (1954).

(16) R. W. Stoughton, *ibid.*, **63**, 2376 (1941).

(17) H. Hepworth, *J. Chem. Soc.*, **116**, 1206 (1919).

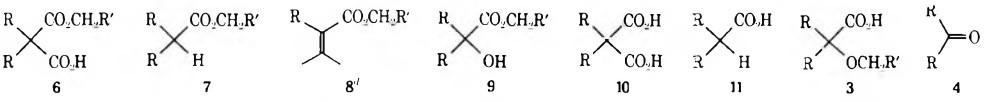
(18) A. L. Wilds and A. L. Maeder, Jr., *J. Org. Chem.*, **13**, 770 (1948).

(19) J. A. King and F. H. McMillan, *J. Amer. Chem. Soc.*, **68**, 1371 (1946).

(20) M. D. Nair and R. Adams, *ibid.*, **82**, 3786 (1960); **83**, 922 (1961); R. R. Frazer and D. E. McGreer, *Can. J. Chem.*, **39**, 505 (1961).

TABLE I

PRODUCT COMPOSITION OF THE SOLVOLYSIS OF MALONOYL PEROXIDE 1



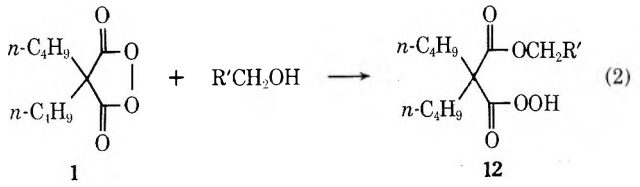
Solvent	Concn, M	Temp, °C	Time,[c] hr	Volatile products, mol %[a,b] 6	7	8[d]	9	10	11	3	4	Residue[e] 5
MeOH	0.302	22	2500	94	0.2	0.2	1.8	2.5	0.2	0.1	1.4	4
MeOH	0.300	50	566	93	1.1	0.1	1.0	3.4	0.7	0.1	0.7	15
MeOH	0.300	80	100	82	0.6	0.2	0.5	6.4	5.2	2.3	0.5	29
MeOH	0.276	80[f]	108	81	0.6	0.6	0.6	5.6	5.2	1.0	0.1	
EtOH	0.293	50	233	21.1	0.2	0.1	0.5	73.4	3.3	0.3	1.2	
EtOH	0.293	80	60	7.7	2.2	0.3	0.1	58.9	28.8	0.8	1.2	15
EtOH	0.270	80[g]	100	6.2	2.8	3.0	1.1	37.7	41.4	6.3	6.5	
EtOH	0.270	80	100	7.6	3.8	1.2	0.1	39.1	44.0	2.6	2.2	

[a] Relative composition of distilled, volatile products after treatment with diazoalkane. The $R'CH_2$– group stands for the alkyl group of the solvent. [b] Quantitative glpc analysis was carried out under conditions CX-1 and AZ-1. [c] Time required for peroxide titer (iodometry) to reach less than 0.5%. [d] Cis and trans mixture. [e] Per cent by weight, determined gravimetrically. [f] Run in open vessel by allowing solvent to reflux. [g] In the presence of 0.03 *M* inhibitor.

volumetric flasks, sealed with a serum cap, and placed into a constant-temperature bath. By means of a calibrated syringe, periodic samples were removed and analyzed for total peroxide content by iodometric titration and for the 1783-cm^{-1} carbonyl band of the malonoyl peroxide 1 by infrared. In the latter analysis the samples were appropriately diluted with carbon tetrachloride. The rates were reproducible within 10%. No efforts were made to improve on these preliminary solvolysis results, since the detailed kinetic study of the thermolysis of 1 in a variety of solvents shall be reported separately.

Results and Discussion

Preliminary kinetics in the alcoholic solvents methanol and ethanol reveals that the disappearance of the malonoyl peroxide 1783-cm^{-1} carbonyl band and the reduction of the peroxide titer proceed at the same rate within the experimental error (*ca.* 10%). However, under the same conditions the rate of thermal decomposition is negligible (*ca.* 2–3%) in hydrocarbon solvents such as benzene or hexane.[21] Thus, we postulate that the initial reaction involves solvolysis of **1** by $R'CH_2OH$ (R′ = H, Me) leading to the peracid half ester **12** (eq 2).



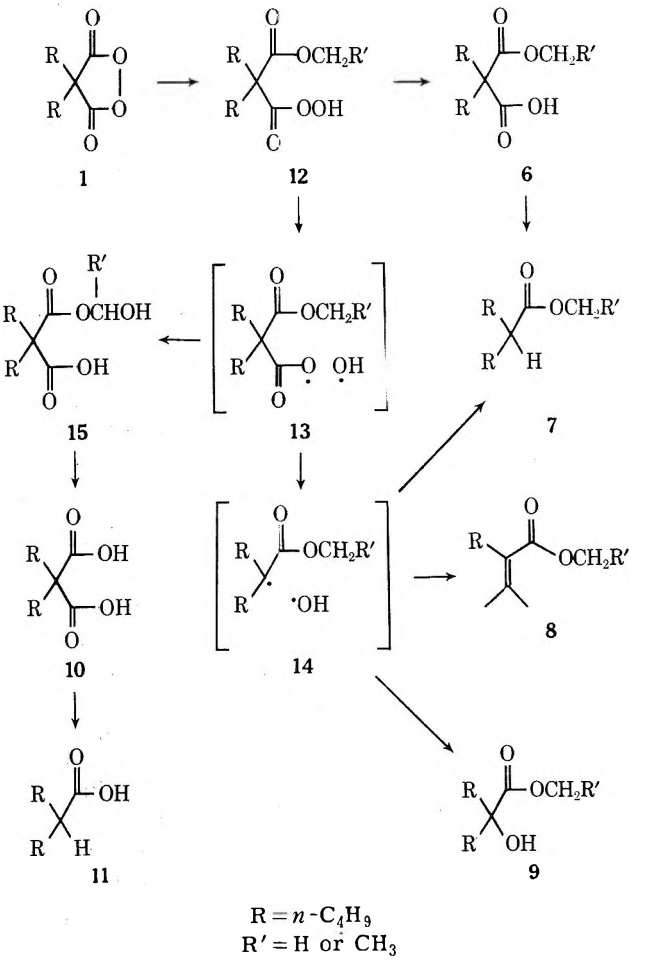
(2)

In the alcoholic solvent the peroxy half ester **12** is decomposing at least as fast as it is forming, since otherwise it should have built up and the peroxide titer should have diminished at a slower rate than the malonoyl peroxide carbonyl bond.

The complex product mixture (see Table I) obtained in the solvolysis of the malonoyl peroxide **1** in methanol or ethanol hints to the fact that the postulated initial solvolysis product, peroxy half ester **12**, undergoes a number of competitive decomposition modes (see Scheme I). However, before entering into detailed mechanistic interpretations, it is convenient to review

(21) A full account of the thermal decomposition of malonoyl peroxides is in preparation.

SCHEME I



R = *n*-C_4H_9
R′ = H or CH_3

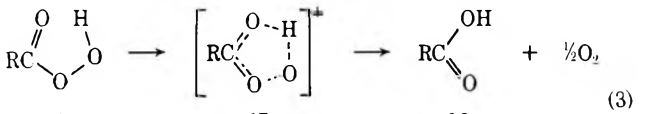
the behavior of simpler peracids, since they should reflect to a considerable degree on the fate of our intermediary peracid **12** in alcoholic solvents.

Detailed studies on the thermal decomposition of peroxylauric acid (**16**)[22,23] indicate two major competi-

(22) D. Lefort, C. Paquot, and Y. Sorba, *Bull. Soc. Chim. Fr.*, 1385 (1959); D. Lefort, Y. Sorba, and D. Rouillard, *ibid.*, 2219 (1961); V. Vorobiev, D. Lefort, S. Sorba, and D. Rouillard, *ibid.*, 1577 (1962).

(23) W. E. Parker L. P. Witnauer, and D. Swern, *J. Amer. Chem. Soc.*, **80**, 323 (1958).

tive modes. On one hand, we have the molecular pathway (eq 3) *via* the concerted transition state **17**,



16 **17** **18** (3)

affording lauric acid (**18**) and molecular oxygen. On the other hand, we have a free-radical chain pathway (eq 4)

$$\begin{aligned} RCO_2OH &\longrightarrow RCO_2\cdot + HO\cdot \\ RCO_2\cdot &\longrightarrow R\cdot + CO_2 \\ R\cdot + RCO_2OH &\longrightarrow ROH + RCO_2\cdot \end{aligned} \quad (4)$$

in which an alkyl radical R·, formed after decarboxylation of the acyloxy radical $RCO_2\cdot$, serves as chain carrier. Depending on the reaction conditions, the molecular path (eq 3) or the radical chain path (eq 4) prevails, but usually both take place concurrently. Since the activation enthalpy is lower for the molecular process in which molecular oxygen is extruded, it is observed that at moderate temperature (below 80°) the concerted decomposition predominates. Similarly, in the presence of inhibitors such as molecular oxygen or hydroquinone the radical chain process is suppressed in favor of the concerted path. Finally, in alcoholic solvents peracids decompose faster because a new radical chain process is initiated (eq 5)[23,24] in which the

$$\begin{aligned} RCO_2OH &\longrightarrow RCO_2\cdot + \cdot OH \\ RCO_2\cdot + R'CH_2OH &\longrightarrow RCO_2H + R'\dot{C}HOH \\ RCO_2OH + R'\dot{C}HOH &\longrightarrow RCO_2\cdot + R'CHOH \\ &\qquad\qquad\qquad\qquad\quad | \\ &\qquad\qquad\qquad\qquad\quad OH \end{aligned} \quad (5)$$

hydroxyalkyl radical R'CHOH becomes the chain carrier.

With these facts in mind on the thermal behavior of peracids, a class of peroxides for which it is difficult to obtain reproducible and reliable data in view of their propensity to catalytic decomposition by trace impurities,[22,24] we now return to our results on the solvolysis of di-*n*-butylmalonoyl peroxide (**1**). In the case of the methanolysis of **1** at 22° (first entry in Table I), the major product is hydrogen methyl di-*n*-butylmalonate (**6**, RCH_2 = Me), formed in 94% yield. As in the case of peroxylauric acid,[22,23] at relatively low reaction temperatues the intermediary peroxy half ester **12** prefers concerted deoxygenation affording half ester **6** (see Scheme I). At 50° (second entry in Table I) relatively little change in the product composition is provoked, since half ester **6** is the major product (93% yield) by far. However, at 80° (third entry in Table I) we note that, although **6** is still the major product (82% yield), the yields of di-*n*-butylmalonic acid (**10**), 2-*n*-butylhexanoic acid (**11**), and 2-methoxy-2-*n*-butylhexanoic acid (**3**) are significantly increased.

The latter product **3** is most likely formed by trapping of the α-lactone intermediate **2** (eq 1) by methanol,[4] and it is expected that this thermal decarboxylation of the malonoyl peroxide **1** should be enhanced at the higher temperature. Also, as expected, the homolytic decomposition of peroxy acid **12** is enhanced at the higher temperature, as evidenced in the products **10** and **11**. Here it is important to mention that a control experiment revealed that malonic acid **10** undergoes about 50% decarboxylation at 80° for 100 hr in methanol to give **11**. Consequently, practically all of the 2-*n*-butylhexanoic acid (**11**) is a secondary product, derived from the malonic acid **10**, and not directly from peroxy acid **12**.

The formation of the malonic acid **10** (see Scheme I) is conveniently explained, analogous to peroxylauric acid (**16**),[22,23] by homolytic fission of the peroxide bond in **12** to give the radical pair **13**. Internal hydrogen abstraction from the methoxy group by the carboxylate radical and coupling leads to acid **15**, which on loss of formaldehyde (on work-up the stench of formaldehyde was clearly noticeable) produces malonic acid **10**.

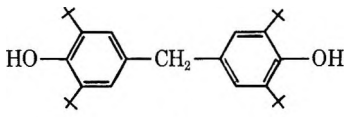
The minor products **8** and **9** probably are formed by decarboxylation of radical pair **13** to give **14**, which on coupling gives hydroxy ester **9** and by hydrogen abstraction a mixture of methyl *cis*(*Z*)- and *trans*(*E*)-2-*n*-butyl-2-hexenoate (**8**). No doubt, alternative radical chain processes (eq 4 and 5) can be written to account for the formation of **8** and **9**. However, we observed no significant differences in the product composition when the solvolysis in methanol was carried out in a sealed ampoule (third entry in Table I) *vs.* refluxing of the solvent in an open vessel (fourth entry), which would allow effusion of the molecular oxygen formed during the decomposition of **12**. In regard to peroxylauric acid (**16**), for which the radical chain process (eq 4) is inhibited by molecular oxygen that is generated in the concerted decomposition (eq 5)[22,23] the above result speaks in favor of our interpretation that in the radical pair **13** internal hydrogen abstraction prevails over external abstraction from the solvent.

To substantiate our hypothesis, we examined the reaction of the malonoyl peroxide **1** in ethanol. We argued that, if the initial step entails solvolysis of **1** by ethanol to give peroxy half ester **12** and if this step be rate determining, the rate of consumption of **1** should be about that in methanol, but more of the intermediary peracid **12** should be diverted into malonic acid **10** rather than half ester **6** because internal hydrogen abstraction should be more efficient in the ethyl (R′ = Me) than in the methyl (R′ = H) peroxy half ester **12**. Indeed, while the rate of solvolysis at 50° was only doubled in ethanol, the major product (73.4% yield) was now malonic acid **10**, while only 21.1% of the half ester **6** (R′ = Me) was obtained (fifth entry in Table I). At 80° the results are still more dramatic (sixth entry in Table I), since *ca.* 88% malonic acid **10** and only *ca.* 10% half ester **6** (R′ = Me) are formed. Into these figures the yield of acid **11** (decarboxylated **10**) and ester **7** (decarboxylated **6**), respectively, are incorporated because control experiments showed that under these solvolysis conditions extensive decarboxylation of **11** → **10** and **6** → **7** takes place.

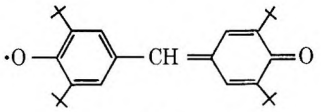
Consequently, as anticipated, in ethanol homolytic fission of **12** to give the radical pair **13** outweighs concerted deoxygenation into half ester **6**, while the reverse is the case in methanol. Further confirmation of our mechanistic interpretation was achieved through attempts at suppressing possible radical chain processes between **1** and ethanol by running the ethanolysis in the presence of trihydrogalvinoxyl (**19**), an excellent inhibitor.[25] The reaction rate was only reduced by *ca.*

(24) K. Tokumaru, O. Simamura, and M. Fukuyama, *Bull. Chem. Soc. Jap.*, **35**, 1673 (1962); K. Tokumaru and O. Simamura, *ibid.*, **36**, 72 (1963); K. Tokumaru and O. Simamura, *ibid.*, **36**, 333 (1963).

(25) W. Adam and W. T. Chiu, *J. Amer. Chem. Soc.*, **93**, 3687 (1971).



19



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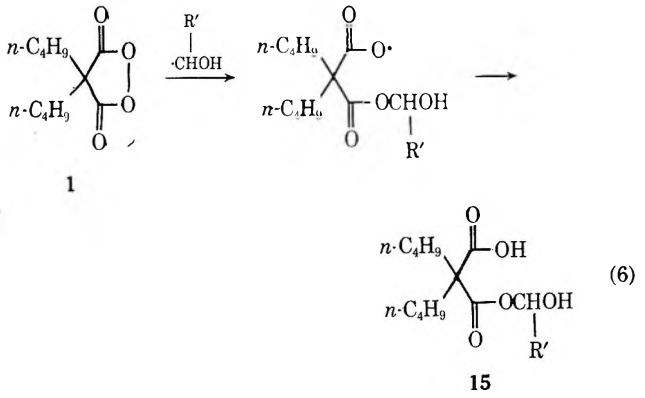
50% with **19** present. More important, no significant alteration in the yields of products **6** and **10** was observed (compare seventh and eighth entry in Table I). Therefore, chain propagation as shown in eq 6 to



1

15

(6)

produce malonic acid **10** *via* loss of RCHO from **15** cannot be a major process, unless very short chain lengths are involved. To be more definite on this point, we would have liked to use galvinoxyl (**20**) as a radical counter, but unfortunately **20** is unstable in ethanol.[25]

Registry No.—**1**, 30842-78-5; dimethyl di-*n*-butylmalonate, 36602-11-6; methyl hydrogen di-*n*-butylmalonate, 36602-12-7; ethyl hydrogen di-*n*-butylmalonate, 36602-13-8; ethyl methyl di-*n*-butylmalonate, 36602-14-9; 2-*n*-butyl-2-methoxyhexanoic acid, 36602-15-0; methyl 2-*n*-butyl-2-methoxyhexanoate, 36602-16-1; methyl 2-*n*-butyl-2-hydroxyhexanoate, 36602-17-2; ethyl 2-*n*-butyl-2-methoxyhexanoate, 36622-57-8; 2-*n*-butyl-2-ethoxyhexanoic acid, 36602-18-3; methyl 2-*n*-butyl-2-ethoxyhexanoate, 36602-19-4; *cis*-2-butyl-2-hexanoic acid, 36602-20-7; *trans*-2-butyl-2-hexenoic acid, 36602-21-8; ethyl *cis*-2-*n*-butyl-2-hexenoate, 36602-22-9; ethyl *trans*-2-*n*-butyl-2-hexenoate, 36602-23-0; methyl *cis*-2-*n*-butyl-2-hexenoate, 36602-24-1; methyl *trans*-2-*n*-butyl-2-hexenoate, 36602-25-2.

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Hydrogen Cyanide Chemistry. III. Synthesis of Diiminosuccinonitrile and Its Conversion to Diaminomaleonitrile[1]

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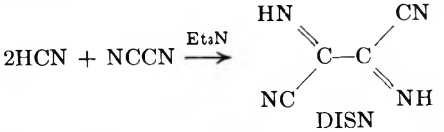
Diiminosuccinonitrile (DISN) is produced by base-catalyzed addition of hydrogen cyanide to cyanogen. Reduction of DISN yields diaminomaleonitrile (DAMN). Chlorination of DISN produces *N*-chlorodiiminosuccinonitrile or *N*,*N*′-dichlorodiiminosuccinonitrile.

Hydrogen cyanide has considerable synthetic potential that has not been fully utilized because it is toxic and explosive, and thus many research workers are reluctant to use it. We believe that hydrogen cyanide will eventually become a major building block for heterocyclic synthesis and are thus engaged in research to exploit its chemistry. Indeed, hydrogen cyanide has been suggested as the basic material from which purines, present in all living matter as components of nucleic acids, arose in prebiotic times.[2] Adenine (HCN pentamer) is commercially produced by heating HCN to 120° in liquid ammonia[3] and caffeine is readily accessible from diaminomaleonitrile (HCN tetramer).[4]

Some notable examples of other heterocyclic systems available by combination of HCN with other reagents are hydantoins,[5] imidazoles,[2] and *s*-triazines.[6]

Results and Discussion

Diiminosuccinonitrile (DISN) is formed quantitatively by base-catalyzed addition of hydrogen cyanide to cyanogen at −40°. DISN can also be prepared by passing chlorine into a toluene solution of HCN and trimethylamine at −15°.



DISN

$$4HCN + 2Me_3N + Cl_2 \longrightarrow DISN + 2Me_3NHCl$$

The first step in the formation of DISN is no doubt attack by cyanide ion on cyanogen. The resulting

(1) Paper I: R. W. Begland, A. Cairncross, D. S. Donald, D. R. Hartter, W. A. Sheppard, and O. W. Webster, *J. Amer. Chem. Soc.*, **93**, 4953 (1971), reported this work in part in a preliminary communication. Presented at 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 16, 1971, Abstract ORGN 126.

(2) R. A. Sanchez, J. P. Ferris, and L. E. Orgel *J. Mol. Biol.*, **30**, 223 (1967); *Science*, **153**, 72 (1966), and references cited therein.

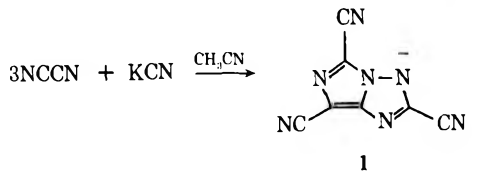
(3) H. Wakamatsu, Y. Yamada, T. Saito, I. Kumashiro, and T. Takenishi, *J. Org. Chem.*, **31**, 2035 (1966).

(4) D. W. Woodward, U. S. Patent 2,534,331 (1950); *Chem. Abstr.*, **45**, 5191 (1951).

(5) V. Migrdichian, "The Chemistry of Organic Cyanogen Compounds," Reinhold, New York, N. Y., 1947

(6) C. Grundmann, *Angew. Chem., Int. Ed., Engl.*, **2**, 309 (1963).

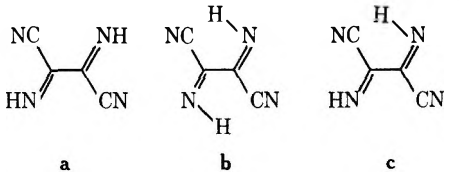
imino anion is quickly quenched by protonation. When protons are not available (aprotic solvent) cyanogen combines with cyanide to give the heterocyclic anion **1**.[7]



1

[A minor peak of m/e 182 ($C_7N_7^+$) is observed in the mass spectrum of DISN which could arise from traces of HC_7N_7, the conjugate acid of **1**.] A second mole of hydrogen cyanide adds to the initial adduct at a much faster rate than to cyanogen since only the 2:1 adduct, DISN, is formed even when 1:1 ratios of HCN and cyanogen are used.

On the basis of the proton nmr, δ 14.2 (major), 14.15, and 12.90 (minor), and dipole moment of 1.59 D (*vs.* 7.8 D for DAMN), DISN is proposed to be primarily transoid in structure and to be a mixture of two isomers with ΔF° = 1.6 kcal/mol. The major isomer, which must be symmetrical, is concluded to be either cis,cis or trans,trans imine isomer a or b; the minor constit-



a **b** **c**

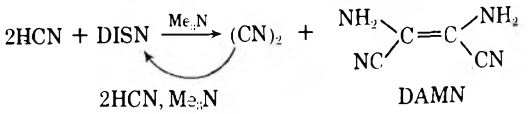
uent must be the unsymmetrical cis,trans isomer c. The succinonitrile structure is supported by the ^{13}C nmr, which shows only two types of carbon in a 1:1 ratio, 92.8 and 83.2 ppm upfield from $^{13}CS_2$.[8]

DISN has an oral toxicity ALD 90 mg/kg in rats. It causes severe irritation on contact with rabbit eyes and permanent damage is prevented only by immediate flushing with water. It causes mild skin and nose irritation. Also, since DISN produces hydrogen cyanide when wet or in contact with hydroxylic solvent, we strongly *caution that it be handled only in well-ventilated areas with adequate protection.*

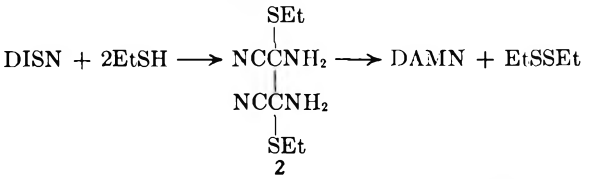
Dry samples of DISN are quite stable when stored in the dark but discolor slowly when exposed to light. In water, DISN slowly decomposes ($t_{1/2}$ about 2 weeks at ambient conditions). DISN decomposes more rapidly in dilute acid or base and in concentrated acid or base nearly instantly. Acid hydrolysis produces oxalic acid, ammonium salts, and hydrogen cyanide. Basic hydrolysis gives mainly tars.

Pure DISN is a stable white solid, mp 165–166°. However, if crude DISN in contact with solvent and basic catalyst is allowed to warm to room temperature before filtering, it decomposes extensively. This temperature effect may explain why DISN has not been previously reported. If excess hydrogen cyanide is present and the reaction mixture is warmed to room temperature, a modest amount of diaminomaleonitrile (DAMN, previously called HCN tetramer)[9] is produced as well as insoluble polymeric products. Since under comparable conditions the polymerization of HCN to DAMN is very slow, the DAMN must be produced by reduction of DISN with HCN. Cyanogen, the expected product from oxidation of HCN, would add HCN under the reaction conditions to give more DISN.

Up to 3 equiv of DAMN per 1 equiv of cyanogen have been obtained in the base-cyanogen-catalyzed tetramerization of HCN to DAMN at 0°.[10] About 30% of the product is an insoluble dark polymer.



DISN is reduced to DAMN quantitatively by hydrogen over palladium on carbon and in good yields by a number of chemical reducing agents, such as hydrogen sulfide, sodium borohydride, lithium aluminum hydride, phenylhydrazine, hydroquinone, and ethanethiol. In the last case an intermediate **2** can be isolated. On



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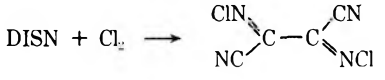
standing it slowly generates DAMN and diethyl disulfide. Dichlorodicyanobenzoquinone oxidizes DAMN to DISN.

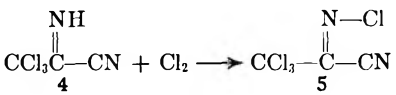
The reduction of DISN confirms its structure and provides the first high-yield synthesis of DAMN. Previously DAMN was obtained by the polymerization of HCN[11] or indirectly from 1-cyanoformamide *p*-toluenesulfonylhydrazone[12] and from aminomalononitrile *p*-toluenesulfonate.[13]

DISN is chlorinated quantitatively at −30° to give *N*,*N*′-dichlorodiiminosuccinonitrile (**3**), a white solid,



3

mp 164.5–165.5°. Under similar conditions DAMN gives **3** in about 50% yield. Its structure was assigned on the basis of a comparison of its infrared and ultraviolet spectra with those of α-(*N*-chloroimino)trichloropropionitrile (**5**), prepared by chlorination of α-



4 **5**

iminotrichloropropionitrile,[14] and the fact that it contains positive chlorine. Equimolar quantities of DISN

(7) O. W. Webster, U. S. Patent 3,093,653 (1963); D. W. Wiley, E. P. Blanchard, and O. W. Webster 3rd Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1968, Abstract H70.

(8) We thank Professor J. D. Roberts of California Institute of Technology for this measurement.

(9) Other HCN tetramers are diaminofumaronitrile[2] and 4-amino-5-cyanoimidazole.[2]

(10) Sanchez, *et al.*, ref 2, mention that cyanogen and other substances increase the rate of polymerization of aqueous hydrogen cyanide.

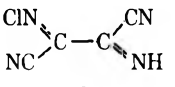
(11) R. P. Linstead, E. G. Noble, and J. M. Wright *J. Chem. Soc.*, 911 (1937); H. Bredereck, G. Schmötzer, and E. Oehler, *Justus Liebigs Ann. Chem.*, **600**, 81 (1956); D. W. Woodward, U. S. Patents 2,499,441 and 2,534,322 (2950); *Chem. Abstr.*, **44**, 5898i (1950); **45**, 5191 (1951); T. Okada and N. Asai, German Patent Application 2,022,243 (1970).

(12) R. E. Moser, J. M. Fritsch, T. L. Westman, R. M. Kliss, and C. N. Matthews, *J. Amer. Chem. Soc.*, **89**, 5673 (1967).

(13) J. P. Ferris and R. A. Sanchez *Org. Syn.*, **48**, 60 (1969).

(14) H. Zima, German Patent 1,053,500 (1959).

and **3** in refluxing MeCN disproportionate to *N*-chlorodiiminosuccinonitrile (**6**). This reaction is probably reversible since **3** and DISN can still be isolated after long reaction times.



6

DISN has proved to be a versatile intermediate, particularly for synthesis of heterocyclic compounds.[1] The extensive chemistry of DISN and its derivatives will be described in subsequent papers.[15]

Experimental Section

The infrared spectra were obtained on a Perkin-Elmer Model 21 spectrometer, the uv on a Cary Model 14, the nmr on a Varian A-60, and the mass spectra on a Du Pont CEC 21-110B high-resolution double-focusing instrument. Hydrogen cyanide was commercial grade inhibited with sulfuric acid and SO_2. The cyanogen was obtained from Matheson Gas Products, Inc., and contained up to 3% cyanogen chloride. All reactions were conducted under nitrogen in solvents dried over a molecular sieve.

Synthesis of Diiminosuccinonitrile (DISN). A. From Cyanogen and HCN.—A solution of 1800 ml of CH_2Cl_2, 320 g (11.85 mol) of HCN, and 294 g (5.65 mol) of cyanogen was cooled to −40°, and with moderate stirring, a solution of 25 ml (0.167 mol) of dry Et_3N in 75 ml of CH_2Cl_2 was added dropwise. After 25 ml of the catalyst solution was added, the reaction became exothermic and the initial precipitation of DISN was observed. During catalyst addition, the reaction solution was maintained at −45 to −40°. (*Caution*—If the temperature is maintained at below −45°, hydrogen cyanide crystallizes and the reaction proceeds at a much slower rate with the danger that solid HCN will be collected on the filter rather than DISN. Also, for large-scale reactions, a circulating cooling bath was used which could be quickly cooled to −80° in case the reaction temperature rose above −20°.)

After the addition was complete (2 hr), the precipitated product was collected while cold and washed with 1 l. each of cold CH_2Cl_2 and ether. On drying under N_2, there remained 577 g of a fine tan DISN (96% yield). The product obtained in this manner is sufficiently pure for most synthetic purposes.

For further purification DISN was dissolved in hot ethyl acetate, and the solution was treated with Darco and then evaporated to a slush. The slush was filtered and the solid DISN was washed with ether and dried in an inert atmosphere. An analytical sample was recrystallized from acetonitrile: mp 165–166°; sublimation point 100° (0.1 mm); crystal structure, orthorhombic, a = 7.83 Å, b = 9.80 Å, c = 6.71 Å, space group *Pcab;* uv max (MeCN) 292 nm (ε 280); ir (KBr) 3280, 2670, 2354, 2256, 1905, 1617, 1402, 1267, 1111, 932 cm^{-1}; nmr (DMSO) δ 14.2 (s) (major isomer), 14.15 (s) and 12.90 (s) (minor isomer); ^{13}C nmr δ 92.8, 83.2 ppm upfield from $^{13}CS_2$; dipole moment (dioxane) 1.59 D; mass spectrum *m/e* 26, 27, 52, 53, 79, 105; polarography no oxidation up to 2.3 V (*vs.* hydrogen, rotating Pt electrode), irreversible reduction at −1.45 V (*vs.* hydrogen, dropping Hg electrode); thermogravimetric analysis 5% weight loss at 194°, 50% at 202°; heat of combustion, 5090 cal/g; solubility (25°), acetone 21, DMAC 5.9, THF 21, MeCN 18, ether 1.5 g/100 ml; differential thermal analysis, endotherm 164°, exotherm 183°.

Anal. Calcd for $C_4H_2N_4$: C, 45.3; H, 1.9; N, 52.8. Found: C, 45.6; H, 2.1; N, 52.5.

B. From HCN and Cl_2.—To a solution of 306 ml (8.00 mol) of hydrogen cyanide, 387 ml (4.00 mol) of trimethylamine, and 2.5 l. of toluene at −20° was added 145 g (2.04 mol) of chlorine over 40 min. The mixture was stirred for 0.5 hr at −15° and filtered. The precipitate was washed with toluene, then twice with 500 ml of ice water, and air dried. There remained 135 g of diiminosuccinonitrile (65%) characterized by its infrared spectrum.

C. From Oxidation of Diaminomaleonitrile.—A solution of 3.24 g (0.03 mol) of DAMN in 75 ml of CH_3CN was treated with 6.78 g (0.03 mol) of dichlorodicyanobenzoquinone at room temperature. After 0.5 hr the reaction mixture was filtered to give 6.53 g of dichlorodicyanohydroquinone. On evaporation of the filtrate there remained 3.32 g of DISN containing a trace of dichlorodicyanohydroquinone (ir).

Synthesis of Diaminomaleonitrile (DAMN). A. Reduction of Diiminosuccinonitrile (DISN). Hydrogen.—In a 3-gallon autoclave equipped with a stirrer and cooling coils were placed 13 g of 10% Pd/C catalyst (Engelhardt), 760 g of DISN, and 2 gallons of THF.

The autoclave was closed, stirred, briefly evacuated, cooled, and pressured with 150 psi of hydrogen and then by small stages to 1500 psi so that the temperature was not allowed to exceed 35°. The reaction is exothermic; so it was necessary to stop temporarily at 1000 or 1500 psi. After the pressure drop ended (1–3 hr), the reaction was stirred for 1 hr at 1500 psi, 25–35°. The autoclave was immediately vented and flushed with nitrogen. The product was siphoned and the autoclave was rinsed with 1.5 l. of THF. The reaction solution from five runs was concentrated to give 3.68 kg (95%) of DAMN. This product was golden brown and was suitable for most reactions. For purification 200 g of DAMN was added to a boiling mixture of 2 l. of water and 160 g of carbon black. After 8–10 min the mixture was filtered quickly through a preheated thin Celite bed into a flask containing 1.6 kg of ice stirred and cooled in an ice bath. The filter cake was washed with 400 ml of boiling water. After the ice had melted, the DAMN (140 g) was collected on a filter and dried over P_2O_5 (0.1 mm). Two recrystallizations gave white DAMN.

DAMN produced by reduction of DISN was identical with that produced by other methods:[9] mp 184° dec; sublimation point 120° (0.1 mm); crystal structure, no molecular symmetry, a = 6.44 Å, b = 18.24 Å, c = 5.22 Å, space group $P2_1/c$; uv max (H_2O) 295 nm (ε 12,000), uv (EtOH) 300 (14,000); ir 3300–3500 (three bands), 2213, 2165, 1647, 1625 cm^{-1}; nmr (DMSO) δ 5.26; ^{13}C nmr δ 75.2 and 85.4 ppm upfield from $^{13}CS_2$; dipole moment, 7.8 D; mass spectrum *m/e* 52, 53, 54, 55, 81, 108; pK_b 2.18; toxicity, ALD 450 mg/kg in rats; TGA, 5% weight loss at 209°, 50% weight loss at 637°; DTA, endotherm 182°, exotherm 204°; heat of combustion, 5230 cal/g; density 1.29 g/cc; dielectric constant 4.5; conductivity $\rho > 3 \times 10^{10}$ ohm-cm; solubility (25°), acetone 15, DMAC 39, water 0.5, THF 14, MeCN 7, EtOAc 3.6, ether 0.4, MeOH 6.1, EtOH 3.6, isopropyl alcohol 2.6, dioxane 9.6, water (100°) 15 g/100 ml.

H_2S.—A stream of hydrogen sulfide gas was bubbled through a slurry of 10.0 g of DISN in 100 ml of methylene chloride for 0.5 hr. The reaction mixture was concentrated to dryness and the residue was extracted with CS_2 to remove sulfur. DAMN (8.6 g, 84%) remained and was identified by its infrared spectrum.

2,3-Diamino-2,3-bis(ethylthio)succinonitrile (2).—A solution of 2.0 g of DISN, 4 ml of ethanethiol, and 20 ml of methylene chloride was stirred at 26° for 15 min and was then refluxed for 30 min. Petroleum ether (bp 30–60°) (75 ml) was added and the mixture was filtered to give 0.9 g (43%) of DAMN. On standing 1.0 g of 2 (23%) crystallized from the filtrate. An analytical sample was recrystallized from ether: mp 104–106°; ir (KBr) 3376, 3320, 1630 ($-NH_2$), 2985, 2935, and 2875 (CH), 2248 (CN), 1379 cm^{-1} (CCH_3); nmr (acetone-d_6) δ 1.34 (t, 6), 3.02 (q + broad absorption, 8); mass spectrum *m/e* 230.

Anal. Calcd for $C_8H_{14}N_4S_2$: C, 41.7; H, 6.1; N, 24.3. Found: C, 41.8; H, 6.0; N, 24.3.

$NaBH_4$.—To a stirred solution of 3.0 g (0.028 mol) of DISN in 50 ml of methanol at −20° was added 1.0 g (0.026 mol) of $NaBH_4$ in small portions. The resulting solution was warmed to room temperature and poured into a flask containing 200 ml of water. Approximately 75 ml of solvent was removed on a rotary evaporator and the remaining aqueous solution was extracted with two 300-ml portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$ and the solvent was removed to give 2.4 g (79%) of light tan DAMN, identified by its infrared spectrum.

Lithium Aluminum Hydride.—To a slurry of 1.52 go of $LiAlH_4$ in 100 ml of dry ether was added 2.0 g (0.019 mol) of diiminosuccinonitrile in 200 ml of ether. After the addition was completed, the excess $LiAlH_4$ was destroyed with water and 20% NaOH. The resulting dark colored solution was filtered and the ether was removed to give 0.31 g (15%) of diaminomaleonitrile.

Phenylhydrazine.—To a solution of 5.3 g (0.05 mol) of diiminosuccinonitrile in 100 ml of ethanol and 50 ml of acetonitrile

(15) Paper IV: R. W. Begland and D. R. Hartter, *J. Org. Chem.*, **37**, 4136 (1972).

at 0° was added dropwise 10.8 g (0.10 mol) of phenylhydrazine in 50 ml of ethanol. The solution was allowed to warm to 25°, stirred for 1 hr, and stripped to dryness. The resulting solid was washed with ether and dried to give 3.3 g (61%) of diaminomaleonitrile.

Hydroquinone.—To a solution of 1.06 g (10 mmol) of DISN in 20 ml of CH_3CN was added 1.10 g (10 mmol) of hydroquinone. After 24 hr 230 mg of quinone was isolated by filtration. On evaporation of the filtrate there remained 1.86 g of a mixture of DAMN, DISN, hydroquinone, and quinone (ir).

B. From Cyanogen-Catalyzed Tetramerization of HCN.—A solution of 100 ml (70 g) of HCN and 300 ml of toluene was maintained at −15 to −10°. Trimethylamine (11 ml) was condensed into the solution and then 14 g of cyanogen was introduced over 5 hr. The solution turned black and 77 g of DAMN and higher polymers of HCN precipitated. DAMN (59 g, 84%) was isolated by extraction with tetrahydrofuran and precipitation with petroleum ether. Although dark colored, its infrared spectrum was identical with that of DAMN prepared by reduction of DISN. This represents a catalyst turnover number of approximately 2. A catalyst turnover number of 3 was obtained when DISN was used in place of cyanogen.

***N,N'*-Dichlorodiiminosuccinonitrile (3).**—A solution of 16.75 g of DISN in 250 ml of MeCN was cooled to −40° and about 100 ml of liquid Cl_2 (excess) was added. The mixture was stirred at −20° for 2 hr, and was then concentrated to dryness (the excess chlorine was trapped in aqueous NaOH). There remained 27.4 g of **3** (97%). Recrystallization from $CHCl_3$ gave 21.0 g of **3**: mp 164.5–165.5°; uv max 258 nm (ε 18,200), sh 300 (278); ir 2238 (C≡N), 1545 (C=N), 1013, 225 cm^{-1}; molecular weight (bp benzene) 175°.

Anal. Calcd for $C_4N_4Cl_2$: C, 27.5; N, 32.0; Cl, 40.5. Found C, 27.2; N, 32.0; Cl, 40.5.

***α-N*-Chloroiminotrichloropropionitrile (5).**—A 15.0-g (88 mmol) portion of **4** in 100 ml of CH_2Cl_2 [uv max 264 nm (ε 178); ir 3250 (NH), 1631 (C=N), 2270 cm^{-1} (C≡N)] was mixed with 20 ml of liquid Cl_2 at −30°. After 2 hr at −20° the solution was concentrated and the residue was distilled to give 15.2 g of **5**: bp 42° (3.5 mm); uv max 231 nm (ε 5860), sh 283 (97); ir 2233 (CN), 1572 (C=N), 841, 782, 710 cm^{-1}; mol wt (fp benzene) 206.

Anal. Calcd for $C_3N_2Cl_4$: C, 17.5; N, 13.6; Cl, 68.9. Found C, 17.7; N, 13.6; Cl, 68.6.

***N*-Chlorodiiminosuccinonitrile (6).**—A solution of 5.30 g (50 mmol) of DISN and 8.70 g (50 mmol) of **3** in 200 ml of CH_3CN was heated at reflux under N_2 for 24 hr. The product was preabsorbed on "SilicAR CC7" and chromatographed. Elution with CCl_4 removed 0.30 g of **3** while benzene–$CHCl_3$ (1:1) removed 3.50 g of **6** which was subsequently sublimed: white crystals; 2.50 g (35.7%); mp 120–122°; ir 3280 (NH), 2260 (CN), 1610 (C—NH), 1560 cm^{-1} (C=NCl); mol wt (fp benzene) 142.

Anal. Calcd for C_4HN_4Cl: C, 34.2; H, 0.7; N, 39.9; Cl, 25.2. Found: C, 34.4; H, 1.0; N, 40.0; Cl, 25.4.

Registry No.—**2**, 36601-97-5; **3**, 33420-44-9; **5**, 36601-99-7; **6**, 36602-00-3; HCN, 74-90-8; DISN, 28321-79-1; DAMN, 1187-42-4.

Hydrogen Cyanide Chemistry. IV. Diiminosuccinonitrile Reactions with Nucleophiles, Acyl Halides, and Carbonyl Compounds[1]

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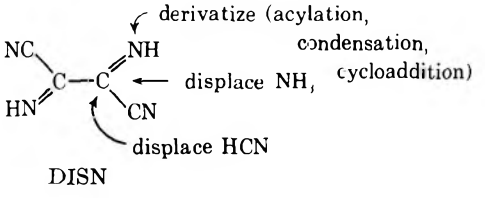
Contribution No. 1918 from the Central Research Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

Received August 9, 1972

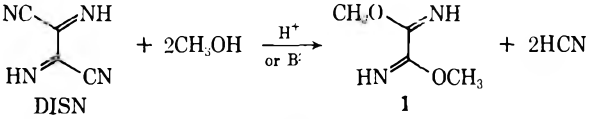
The reactions of diiminosuccinonitrile (DISN) with nucleophiles, acyl halides, and carbonyl compounds are described. Nucleophiles such as water, alcohols, and amines add to DISN giving products which result from displacement of either hydrogen cyanide or ammonia. Phosgene reacts with DISN to give a reactive imidazolidone from which several new polyfunctional derivatives have been prepared. Isoimidazoles, pyrazines, and oxazoles have been obtained by condensation of DISN with various ketones. Upon heating, some of these 2,2-dialkylisoimidazoles undergo a 1,5 shift of an alkyl group from carbon to nitrogen resulting in 1,2-dialkylimidazole formation.

Diiminosuccinonitrile (DISN), recently prepared in our laboratory by reaction of hydrogen cyanide with cyanogen,[2] has proven to be a valuable intermediate for the preparation of many polyfunctional heterocyclic and acyclic compounds. In this paper we describe the basic reactions of DISN which occur at either the carbon or nitrogen of the imine bonds.



Nucleophiles react with DISN giving products which result from displacement of either hydrogen cyanide or ammonia. For example, under neutral or basic reaction conditions the cyano groups are usually displaced while under acidic conditions loss of ammonia is the predominant process. Derivatization of the imine nitrogen occurs with a variety of reagents. Reactive halogen compounds such as sulfur dichloride, phosgene, and chlorine readily add to the imines of DISN; carbonyl compounds condense with DISN yielding isoimidazoles and pyrazines; and olefins react with DISN giving aziridines and tetrahydropyrazines.[3]

Reaction with Nucleophiles.—DISN behaves much like benzoyl cyanide in reactions with alcohols and aromatic amines. Thus, treatment of DISN with methanol under acid or base catalysis results in attack of the imine carbon by alcohol and loss of hydrogen cyanide. The dialkyl oxaldiimidate (**1**) thus formed can also be prepared by reaction of cyanogen with methanol.[4] In a similar manner aniline adds to DISN giving diphenyloxamidine (**2**).[5]



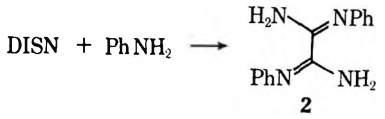
(1) Paper III: O. W. Webster, D. R. Hartter, R. W. Begland, W. A. Sheppard, and A. Cairncross, *J. Org. Chem.*, **37**, 4133 (1972).

(2) R. W. Begland, A. Cairncross, D. S. Donald, D. R. Hartter, W. A. Sheppard, and O. W. Webster, *J. Amer. Chem. Soc.* **93**, 4953 (1971).

(3) T. Fukunaga, *ibid.*, **94**, 3242 (1972).

(4) K. Brotherton and J. W. Lynn, *Chem. Rev.*, **59**, 841 (1959).

(5) Prepared by addition of aniline to cyanogen: A. W. Hofmann, *Justus Liebigs Ann. Chem.*, **66**, 130 (1848).



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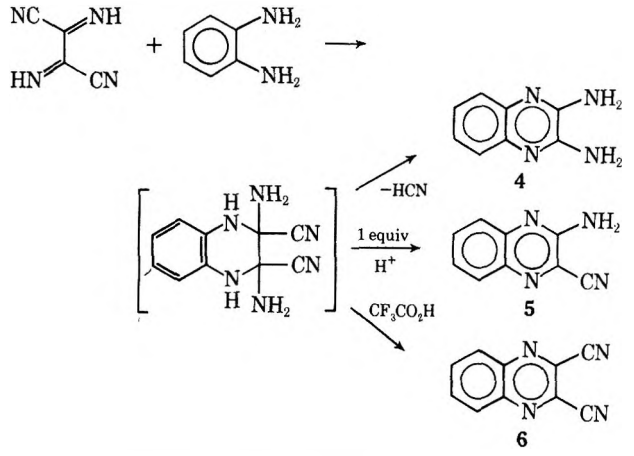
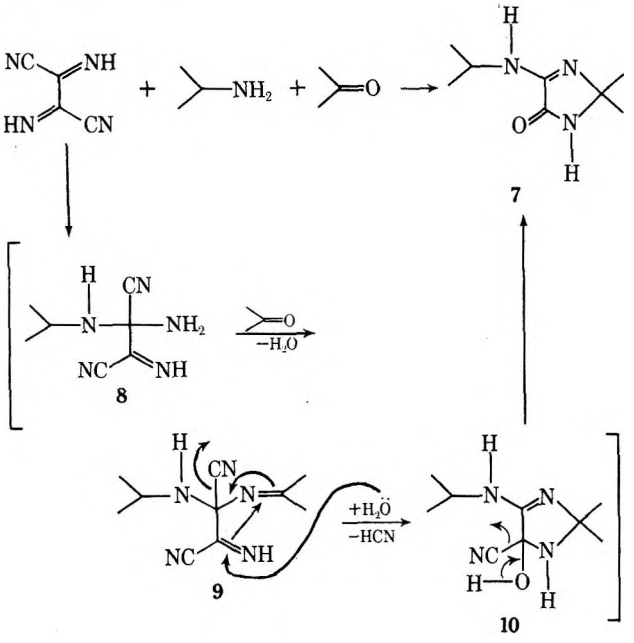
By varying the conditions, three different products can be obtained from the reaction of DISN with *o*-phenylenediamine. Under neutral reaction conditions two molecules of hydrogen cyanide are lost from proposed intermediate **3** forming 2,3-diaminoquinoxaline



4 5 6

(**4**).[6] Under acidic conditions, however, the primary amine in intermediate **3** is protonated making it a better leaving group than cyano. Thus, addition of 1 equiv of *p*-toluenesulfonic acid to the reaction mixture gives 2-amino-3-cyanoquinoxaline (**5**) in 31% yield. When trifluoroacetic acid is used as the solvent, two molecules of ammonia are eliminated from intermediate **3** and the product is dicyanoquinoxaline (**6**).

Aliphatic amines give only tars when added to DISN. However, addition of a ketone such as acetone to a mixture of isopropylamine and DISN gives a stable crystalline 1:1:1 adduct of DISN, amine, and ketone minus two molecules of hydrogen cyanide. This adduct has been assigned structure **7**. The first step in

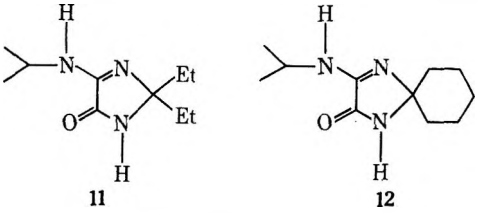


7 8 9 10

this reaction must be attack of the bisimine by isopropylamine to give **8**. A possible mechanism from

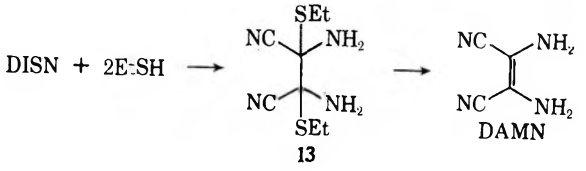
(6) H. Weidinger and J. Krany, *Chem. Ber.*, **97**, 1599 (1964).

here could involve condensation of intermediate **8** with acetone forming **9** as well as 1 equiv of water. Addition of water to the cyanoimine of **9**, followed by cyclization and loss of hydrogen cyanide, would give **10**. Loss of hydrogen cyanide from **10** then gives the isolated product **7**. Further examples of this reaction with 3-pentanone and cyclohexanone gave compounds **11** and **12**, respectively. Reaction of ethanethiol with



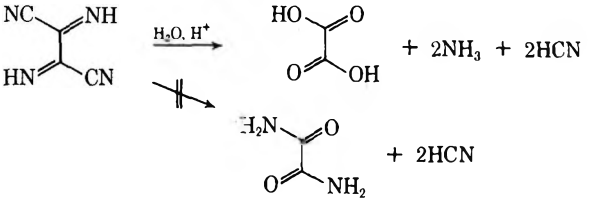
11 12

DISN does not result in the replacement of the cyano groups. Instead reduction of DISN occurs with the formation of diaminomaleonitrile (DAMN). The initial bisthiol adduct **13** can be isolated in this reaction.[1]

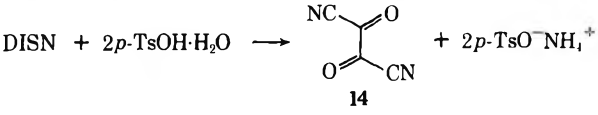


13

Hydrolytic Behavior (Oxalyl Cyanide).—DISN hydrolyzes slowly in water; however, if a catalytic amount of sodium hydroxide is added, tar forms immediately and no crystalline products are isolated. Hydrolysis of DISN in the presence of acid gives ammonia, oxalic acid, and hydrogen cyanide. The formation of oxalic acid indicates that ammonia is lost from DISN prior to the loss of hydrogen cyanide. If HCN was initially displaced by attack of water on DISN, then one would isolate oxamide, which is not hydrolyzed further under these conditions. The previously unknown oxalyl cyanide (**14**) is the intermediate in formation of oxalic



acid and can be isolated with controlled hydrolysis. Addition of 2 equiv of acid and water in the form of *p*-toluenesulfonic acid monohydrate to a solution of DISN, followed by removal of solvent and sublimation, gives oxalyl cyanide (**14**) as white crystals, mp 61–62°.

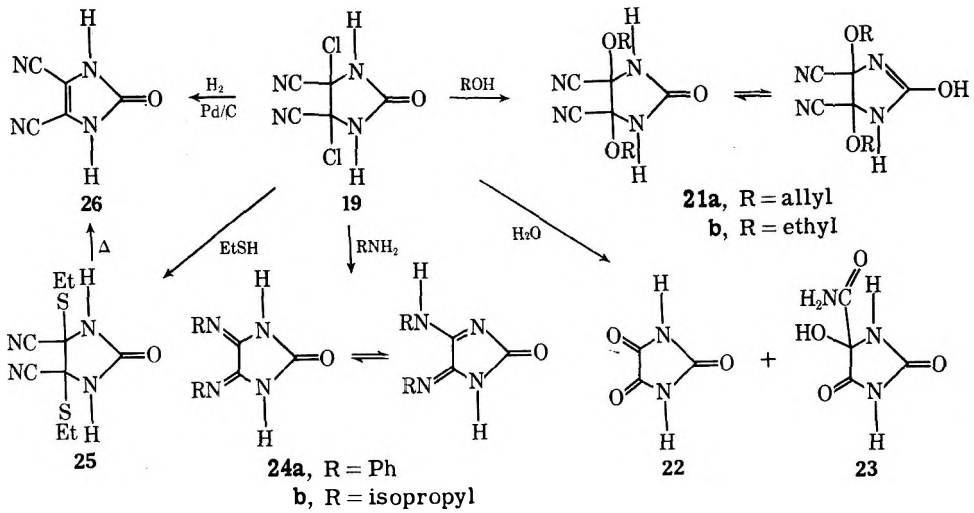


14

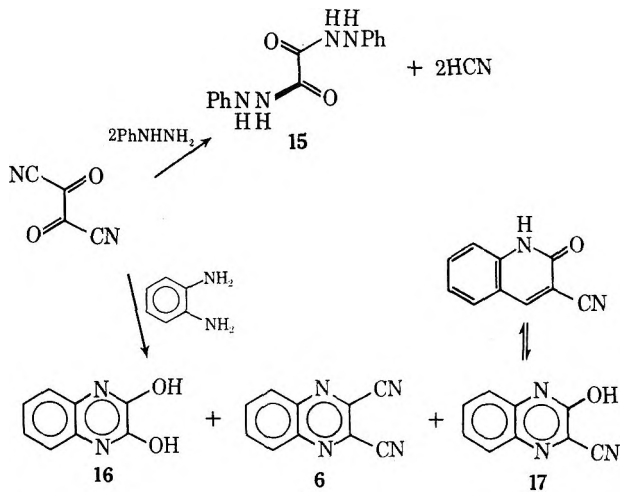
This compound is very moisture sensitive and rapidly hydrolyzes to oxalic acid and hydrogen cyanide if not kept under an anhydrous atmosphere. Owing to the high reactivity of oxalyl cyanide, it can be isolated only in poor yield and is therefore used in subsequent reactions without isolation.

The nitrile groups of oxalyl cyanide (**14**) are readily replaced by alcohols and amines. For example,

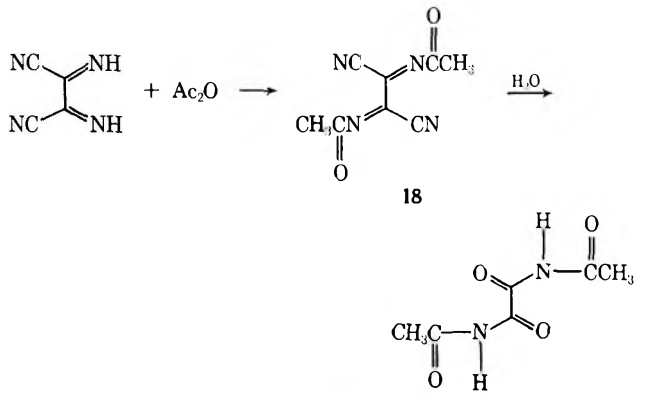
SCHEME I



phenylhydrazine adds to **14** giving oxamide derivative **15**. *o*-Phenylenediamine reacts with oxalyl cyanide to give the expected dihydroxyquinoxaline (**16**) along with low yields of dicyanoquinoxaline (**6**) and 2-hydroxy-3-cyanoquinoxaline (**17**).



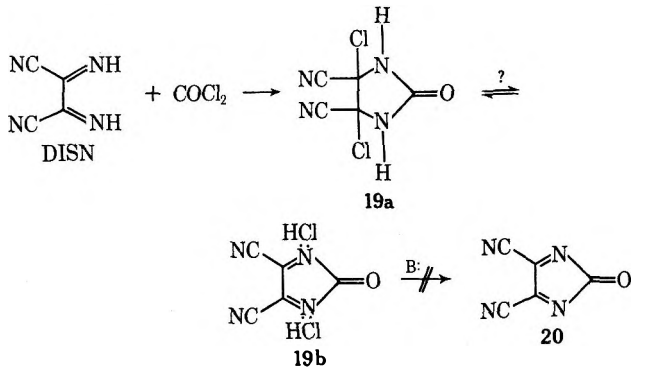
Reaction with Acyl Halides.—Reaction of DISN with acetyl chloride gave a very low yield of *N,N'*-diacetyldiiminosuccinonitrile (**18**). By using acetic



anhydride **18** was obtained in 11% yield. Hydrolysis of **18** in 20% aqueous acetonitrile gave the known *N,N'*-diacetyloxamide.[7]

(7) H. M. Woodburn and W. E. Hoffman, *J. Org. Chem.*, **23**, 262 (1958).

Phosgene adds to DISN readily at 0° giving a reactive 1:1 adduct which has been assigned imidazolidone structure **19**.



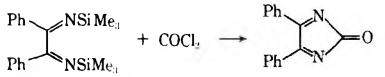
By removing the reaction solvent from a solution of **19** at room temperature and under anhydrous conditions one can isolate the imidazolidone as a light yellow powder. This material is readily hydrolyzed by moist air, forming hydrogen cyanide. It is therefore suggested that **19** be used in solution without isolation.

The possibility that imidazolidone **19a** is in equilibrium with **19b** has been considered; however, we have not been able to isolate imidazolone **20** by treatment of **19** with various bases.[8] In all examples tried only dark oils were obtained. Evidence for the structure of **19** has been obtained by its reduction and reactions with nucleophiles as outlined in Scheme I.

Alcohols add to **19** readily at room temperature, giving 4,5-dicyano-4,5-dialkoxy-2-imidazolidones (**21**) in good yield. Addition of water to **19** gives hydantoin **23** in low yield along with higher molecular weight products. If dilute sodium hydroxide is added so that the HCl initially formed is neutralized, then some parabanic acid (**22**) (identical with an authentic sample purchased from Aldrich) can be isolated.

Amines and thiols react with **19** much as they do with DISN. For example, aniline replaces both the chloro

(8) The diphenyl analog of **20** has been prepared and is a stable compound.

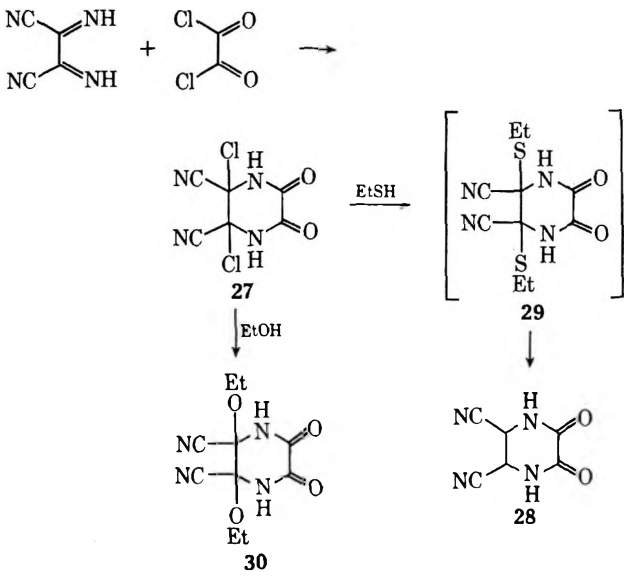


G. Tuchtenhagen and K. Ruhlmann, *Justus Liebigs Ann. Chem.*, **711**, 174 (1968).

and cyano groups of **19** to give 4,5-bis(phenylimino)-2-imidazolidinone (**24**) in 90% yield. Propylamine gives a similar product but in only low yield along with considerable tar formation. Parabanic acid (**22**) results from the hydrolysis of **24** (R = propyl). Ethanethiol replaces the chlorine substituents of **19**, giving 4,5-dicyano-4,5-bis(ethylthio)-2-imidazolidinone. This compound can be recrystallized from ether; however, when heated in higher boiling solvents such as acetone it is completely converted to 4,5-dicyanoimidazolone (**26**).[9] Hydrogenation of **19** in a Parr apparatus at room temperature over Pd/C also gives **26**.

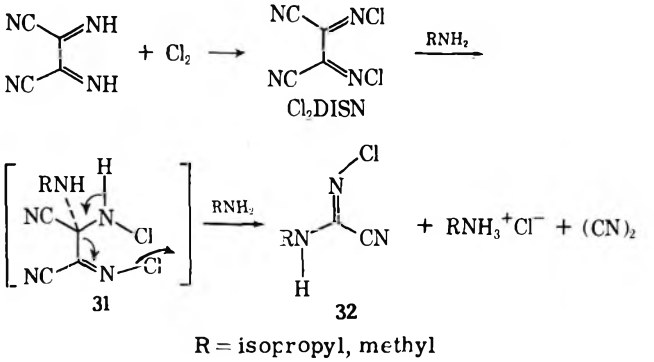
2,3-Diketo-5,6-dichloro-5,6-dicyanopiperazine (**27**) is formed from the reaction of DISN with oxalyl chloride. Like **19**, it can only be isolated and stored under anhydrous conditions. As shown in Scheme II, the chemistry of **27** is similar to that of the DISN–phosgene adduct **19**. Thus, addition of ethanethiol to **27** results in the formation of 2,3-dioxo-5,6-dicyano-1,2,3,4-tetrahydropyrazine (**28**);[10] the intermediate dithio adduct **29** was not isolated in this reaction. Alcohols readily add to **27** with replacement of the chlorine substituents, giving piperazines such as **30**.

SCHEME II

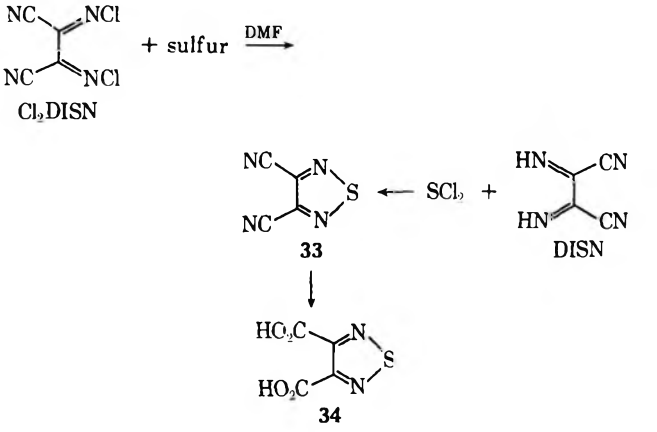


Dichloro DISN Reactions.—The addition of chlorine to DISN has been shown to give *N,N'*-dichlorodiiminosuccinonitrile (Cl_2DISN).[1] In contrast to the formation of isoimidazolone **7** from isopropylamine, DISN, and acetone, treatment of Cl_2DISN with an alkylamine results in cleavage of the central C–C bond, giving cyanoformamidine **32**. The driving force for this reaction may be the loss of HCl and cyanogen from intermediate **31**. Complete degradation of Cl_2DISN occurs upon refluxing in ethanol. The only products isolated were ammonium chloride and ethyl carbamate.

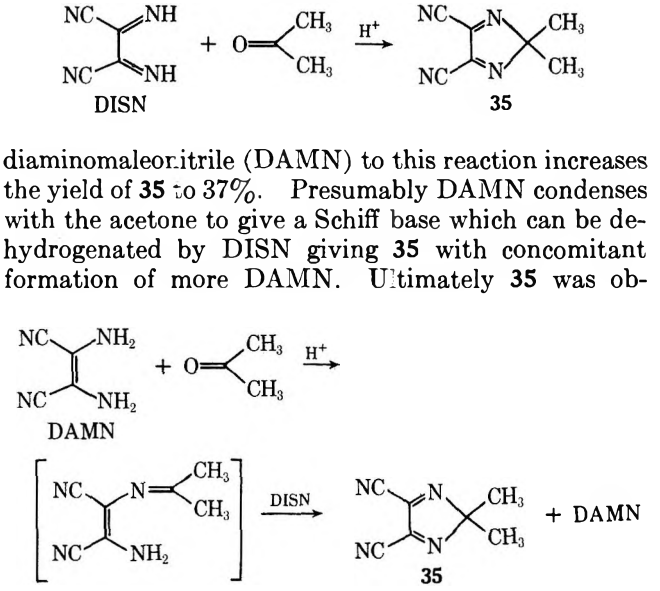
Reaction of sulfur with Cl_2DISN in dimethylformamide gives 3,4-dicyano-1,2,5-thiadiazole (**33**).[11] Thiadiazole **33** is also obtained by reaction of DISN with sulfur dichloride. The cyano groups of **33** are readily hydrolyzed to give diacid **34**.



R = isopropyl, methyl



Reaction with Carbonyl Compounds.—Refluxing an acetone solution of DISN with a catalytic amount of oxalic acid gives 2,2-dimethyl-4,5-dicyanoisoimidazole (**35**) in 15% yield. The addition of a small amount of diaminomaleonitrile (DAMN) to this reaction increases the yield of **35** to 37%. Presumably DAMN condenses with the acetone to give a Schiff base which can be dehydrogenated by DISN giving **35** with concomitant formation of more DAMN. Ultimately **35** was obtained in 80% yield by the addition of DISN to 2,2-dimethoxypropane in the presence of a catalytic amount of concentrated sulfuric acid.



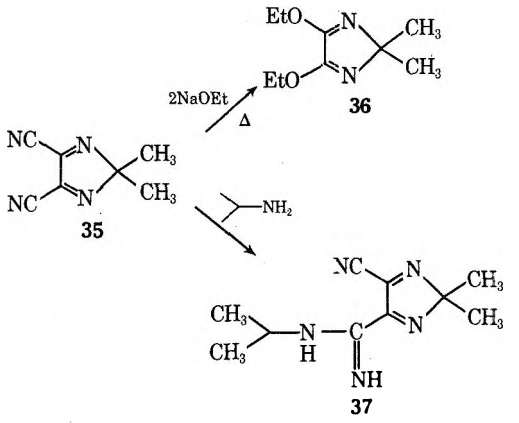
A study of the chemical reactivity of isoimidazole **35** shows that it is considerably less reactive than DISN. For example, while only a catalytic amount of sodium ethoxide in ethanol is necessary to replace the cyano groups of DISN, we have found that **35** must be treated

(9) Prepared from DAMN and $COCl_2$: D. W. Woodward, U. S. Patent 2,334,332 (1950).

(10) H. Bredereck and G. Schmotzer, *Justus Liebigs Ann. Chem.*, **600**, 95 (1956).

(11) M. Carmack, D. Shew, and L. M. Weinstock, U. S. Patents 2,990,408 and 2,990,409 (1961); *Chem. Abstr.*, **56**, 4775 (1952).

with 2 equiv of sodium ethoxide to obtain isoimidazole **36**. Reaction of **35** with isopropylamine proceeds by

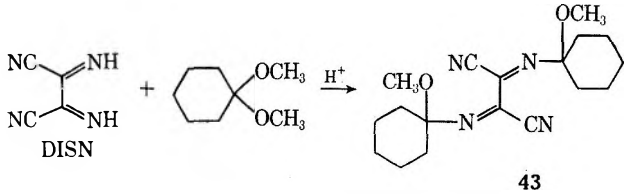


attack on the cyano group to give amidine **37**. In contrast, reaction of DISN with isopropylamine results in tar formation.

The condensation of DISN with ketones and ketals to give dicyanoisoimidazoles is by no means a general reaction. With the exception of acetone, all other ketones tried gave mixtures of products along with considerable amounts of unidentified dark oils.

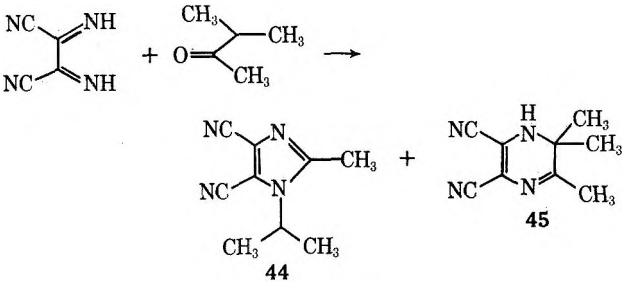
Condensation of DISN with 2-pentanone gave isoimidazole **38** along with a small amount of 2,3-dicyano-5-ethyl-6-methylpyrazine (**39**). Pyrazine **39** is presumably formed by the cycloaddition of the enol tautomer of 2-pentanone with DISN, giving intermediate **40**. Loss of water from **40** along with dehydrogenation would give pyrazine **39**. Reaction with 2-butanone gave 2-methyl-2-ethyl-4,5-dicyanoisoimidazole (**41**) in 20% yield and 2,3-dicyano-5,6-dimethylpyrazine (**42**)[12] in 4% yield.

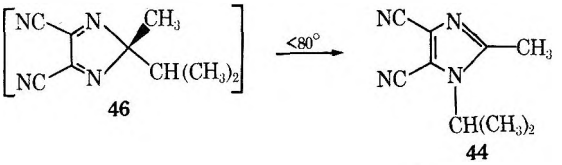
No isoimidazoles were obtained from ketones containing a group larger than $-CH_3$ on both sides of the carbonyl. For example, reaction of DISN with 3-pentanone gave 2,3-dicyano-5-ethyl-6-methyl pyrazine (**39**) in low yield as the only isolated product. No identifiable products could be isolated from reaction with cyclohexanone, and the acid-catalyzed addition of DISN to the dimethyl ketal of cyclohexanone gave bisimine **43** as the only isolatable product.



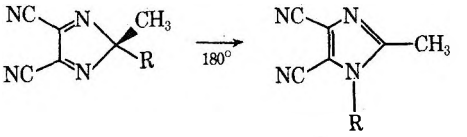
(12) L. E. Hinkel, G. O. Richards, and O. Thomas, *J. Chem. Soc.*, 1432 (1937).

Condensation of DISN with 3-methyl-2-butanone gave a very dark reaction mixture from which two compounds were isolated in low yield by column chromatography. The first compound was 1-isopropyl-2-methyl-4,5-dicyanoimidazole (**44**) rather than the expected isoimidazole. The second compound was 2,3-dicyano-5,6,6-trimethyl-1,6-dihydropyrazine (**45**). Imidazole **44** was not expected but can best be explained by assuming that isoimidazole **46** was initially formed and then thermally rearranged by a 1,5 shift of the isopropyl group. Several examples of this type of rearrangement (isoimidazole to imidazole) have recently appeared in the chemical literature,[13] thus supporting the intermediacy of **46**.



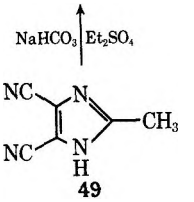


Further evidence for the intermediacy of **46** was obtained when it was found that isoimidazoles **38** and **41** rearranged cleanly at 180° to imidazoles **47** and **48**. No products resulting from migration of the methyl



38, R = *n*-propyl
41, R = ethyl

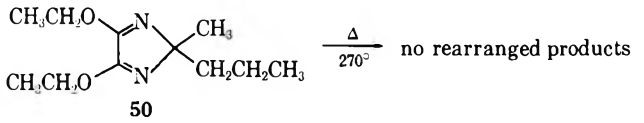
47, R = *n*-propyl
48, R = ethyl



(13) (a) G. V. Garver and H. Suschitzky, *Tetrahedron Lett.*, 169 (1971); (b) D. M. White, *J. Org. Chem.*, **35**, 2452 (1970); (c) D. R. Arnold, V. Y. Abraitys, and D. McLeod, Jr., *Can. J. Chem.*, **49**, 923 (1971), and references cited therein.

groups were observed. Structure proof of imidazole **48** was accomplished by treating the known 2-methyl-4,5-dicyanoimidazole (**49**)[14] with diethyl sulfate.

Dimethyl isoimidazole **35** did not rearrange at temperatures up to 250°, at which point it began to decompose. This was also the case for 2-methyl-2-propyl-4,5-diethoxyisoimidazole (**50**), which was prepared by treatment of **38** with sodium ethoxide.



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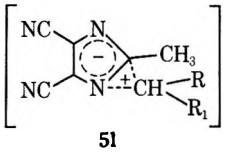
The size of the migrating alkyl group is certainly of importance in examining this rearrangement behavior, *i.e.*, methyl (**35**) does not rearrange up to 250°, ethyl (**41**) and *n*-propyl (**38**) rearrange at 180°, and isopropyl (**46**) rearranges in refluxing benzene. In considering electronic factors one notices that when the strongly electron-withdrawing cyano groups of **38** are replaced by ethoxy groups (**50**) the 1,5 shift no longer occurs. Thus, a polar transition state which is stabilized by electron-withdrawing groups is plausible. The rearrangement of **38** to **47** at 110° in acetic acid, compared to 180° in the melt, also indicates a polar transition state.

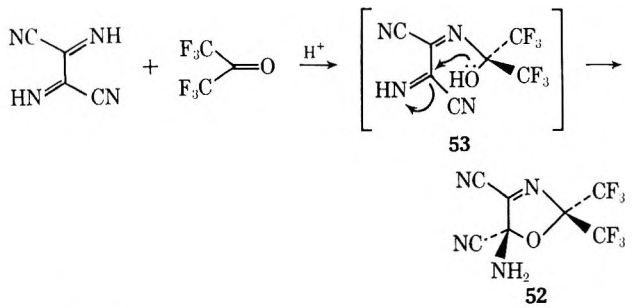
A transition state such as **51** can account for the ob-



51

served results. The cyano groups would stabilize the negatively charged ring, polar solvents such as acetic acid would increase the rate of reaction, and the ethyl or propyl group would be expected to migrate since it can stabilize a positive charge better than the methyl group. In addition we have observed no isomerization of the *n*-propyl group to an isopropyl group during this 1,5-alkyl shift. Thus, if an intermediate such as **51** is involved, it must be a tight ion pair with a sufficiently short lifetime to prohibit isomerization.

The acid-catalyzed addition of DISN to hexafluoroacetone did not give an isoimidazole. Instead a 1:1 adduct which still contained oxygen was isolated in 73% yield. The infrared spectrum of this adduct showed amino and cyano groups and the F nmr exhibited two quartets which could be explained by the presence of geminal trifluoromethyl groups in an unsymmetric ring. Based on this evidence and on mechanistic considerations, this adduct was assigned oxazoline structure **52**. The formation of **72** is not surprising when one realizes that protonation of the acidic alcohol group in intermediate **53** followed by loss of H_2O to give an isoimidazole would be a highly unfavorable process.



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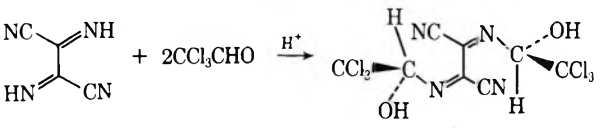
52

The addition of chloral to DISN under acid catalysis is exothermic and **54** can be isolated in 40%



54

yield. Even when only 1 equiv of chloral was added no oxazoline similar to **52** could be isolated. An examination of molecular models shows that in intermediate **53** the two trifluoromethyl groups prefer to flank the rest of the molecule, thus holding the alcohol oxygen in a favorable position for attack at the imine carbon. In adduct **54** models indicate that the trichloromethyl and alcohol groups prefer to be most distant from the cyanoimine function, thereby hindering oxazoline formation.

Experimental Section

The infrared spectra were obtained on a Perkin-Elmer Model 21 spectrometer, the uv on a Cary Model 14, the nmr on a Varian A-60, and the mass spectra on a Du Pont CEC 21-110B high-resolution double-focusing instrument. All reactions were conducted under nitrogen.

Dimethyl Oxaldiimidate (1).—To a solution of 10.6 g (0.10 mol) of diiminosuccinonitrile (DISN) in 150 ml of methanol at 0° was added 0.54 g (0.010 mol) of sodium methoxide in 75 ml of methanol. The solution was stirred for 1 hr and stripped to near dryness and 300 ml of ether was added. Filtering to remove the sodium cyanide and removing the ether gave 9.2 g (79.5%) of clear liquid: mp 28–30°; bp 79–80° (30 mm) [lit. mp 28–30°, bp 54–55° (22 mm)]; nmr ($CDCl_3$) δ 3.82 (s, 3), 8.50 (=NH).

Anal. Calcd for $C_4H_8O_2N_2$: C, 41.37; H, 6.94; N, 24.13. Found: C, 41.53; H, 6.79; N, 23.88.

***N,N'*-Diphenyloxamidine** (2).—To a solution of 6.0 g (0.057 mol) of DISN in 150 ml of THF was added dropwise 11.2 g (0.12 mol) of aniline. The resulting yellow solution was stirred for 18 hr, during which time a white precipitate appeared. Filtration gave 7.9 g of solid and removal of the solvent gave another 4.7 g of the same compound. Recrystallization from acetonitrile gave 12.3 g (91%) of white plates: mp 215–216°; ir 3440 and 3305 ($-NH_2$), 1638 (C=N), 1578, 1562, and 1490 cm^{-1} (NH_2 and C=C); uv (CH_3CN) 230 nm (ϵ 20,850), 278 (9290); nmr (DMSO-d_6) δ 6.33 (s, 4), 6.8–7.6 (m, 10).

Anal. Calcd for $C_{14}H_{14}N_4$: C, 70.56; H, 5.92; N, 23.51. Found: C, 70.22; H, 6.07; N, 23.64.

2,3-Diaminoquinoxaline (4).—A solution of 20 g (0.19 mol) of *o*-phenylenediamine in 275 ml of THF was added dropwise to a solution of 20 g (0.19 mol) of DISN in 250 ml of THF and the resulting dark brown solution was stirred at room temperature for 18 hr. Removal of the solvent and chromatography of the resulting brown solid–oil on SilicAR CC7 gave, with chloroform elution, 6.3 g (20%) of **4** as yellow crystals, mp >280° (lit.[6] mp >360°).

2-Amino-3-cyanoquinoxaline (5).—A solution of 10.6 g (0.10 mol) of DISN in 150 ml of THF was added dropwise over 1 hr to a slurry of 28.0 g (0.10 mol) of the *p*-toluenesulfonic acid salt of *o*-phenylenediamine in 350 ml of THF, then stirred at 24° for 20 hr. The heterogeneous solution was filtered and the filtrate was evaporated at reduced pressure, leaving a semisolid which was slurried with 500 ml of water. The insoluble material was collected, rinsed with water, dried (8.97 g), and recrystallized from EtOAc, 5.25 g (31%) of **5**, pale yellow needles: mp 196–200° dec; uv (CH_3CN) 394 nm (ϵ 5700), 307 (6150), 245 (24,600); ir (Nujol) 3490, 3300, 3110 (NH_2), 2220 (C≡N), 1650 (NH_2), 1605, 1550, 1525 cm^{-1} (C=C/C=N); nmr (DMSO-d_6) δ 7.33 (s, 2), 7.65 (m, 4).

Anal. Calcd for $C_9H_6N_4$: C, 63.52; H, 3.55; N, 32.93. Found: C, 63.37, 63.37; H, 3.51, 3.38; N, 33.07, 33.07.

(14) D. W. Woodward, U. S. Patent 2,534,331 (1950).

2,3-Dicyanoquinoxaline (6).—A powdered mixture of 20 g (0.189 mol) of DISN and 20 g (0.185 mol) of *o*-phenylenediamine was added over 0.5 hr to 300 ml of CF_3COOH while the temperature was maintained at *ca.* 20° with occasional ice-bath cooling. The resulting heterogeneous solution was stirred overnight at room temperature. The CF_3COOH was removed at reduced pressure, leaving a semisolid which was slurried with water to precipitate 6. The latter was collected, 21.2 g, and recrystallized from benzene, 15.4 g (46.3%): mp 218–220°; uv (CH_3CN) 258 nm (ε 54,700), 338 (4640), 352 (3890); ir (KBr) 2235 (C≡N), 1610, 1560, 1525, 1485 cm^{-1} (C=C/C=N); mass spectrum *m/e* 180.0434 (calcd *m/e* 180.0436).

Anal. Calcd for $C_{10}H_4N_4$: C, 66.66; H, 2.24; N, 31.10. Found: C, 66.41; H, 2.47; N, 31.06.

2,2-Dimethyl-4-isopropylamino-5-isoimidazolone (7).—To a solution of 10.1 g (0.095 mol) of DISN in 200 ml of THF at 25° was added dropwise 10.6 g (0.18 mol) of isopropylamine and 7.4 g (0.10 mol) of acetone in 60 ml of THF. The resulting dark solution was stirred for 18 hr and chromatographed on SilicAR. Chloroform to ether elution gave 8.1 g (50%) of 7 as off-white crystals. Recrystallization from $HCCl_3$–ether gave white crystals: mp 177–178°; ir (KBr) 3300, 3155, 3060 (-NH), 1730 (>C=O), 1645, 1540 cm^{-1}; uv (CH_3CN) 220 nm (ε 6360), 240 (5720); nmr ($CDCl_3$) δ 1.25 (d, 6), 1.49 (s, 6), 4.05 (septet, 1), 5.05 (d, 1), 9.05 (b, 1); mass spectrum *m/e* 169.1215 (calcd *m/e* 169.1215).

Anal. Calcd for $C_8H_{15}ON_3$: C, 56.78; H, 8.94; N, 24.83. Found: C, 56.62; H, 8.91; N, 25.15.

2,2-Diethyl-4-isopropylamino-5-isoimidazolone (11).—To a solution of 10.0 g (0.094 mol) of DISN in 300 ml of THF at −30° was added dropwise 11.2 g (0.19 mol) of isopropylamine. The resulting dark solution was warmed to 10°, 10.0 g (0.12 mol) of 3-pentanone was added, and the solution was stirred for 20 hr at room temperature. The solvent was removed and the crude oil was chromatographed on SilicAR. Elution with chloroform and recrystallization from ether–petroleum ether (bp 30–60°) gave 3.10 g (16.8%) of 11 as white needles: mp 97–99°; ir (KBr) 3300, 3215, 1725, 1720, 1645, and 1530 cm^{-1}; uv (CH_3CN) 230 nm (ε 7180), very broad; nmr ($CDCl_3$) δ 0.78 (t, 6), 1.26 (d, 6), 1.84 (q, 4), 4.0 (m, 1), 5.17 (d, 1), and 9.0 (s, 1).

Anal. Calcd for $C_{10}H_{19}ON_3$: C, 60.88; H, 9.71; N, 21.30. Found: C, 60.68; H, 10.01; N, 21.50.

2,2-Pentamethylene-4-isopropylamino-5-isoimidazolone (12).—In a reaction similar to that used for the preparation of 11 there was obtained (from 10.0 g of DISN, 11.2 g of isopropylamine, and 19.5 g of cyclohexanone) by chloroform–ether elution and recrystallization from ether 4.4 g (22%) of 12 as white needles: mp 138–140°; ir (KBr) 3405, 3180, 3080, 1710, 1650, 1525 cm^{-1}; uv (CH_3CN) 225 nm (ε 7890), 241 (8270); nmr ($CDCl_3$) δ 1.24 (d, 6), 1.64 (b, 10), 3.96 (m, 1), 5.10 (d, 1), and 9.8 (s, 1).

Anal. Calcd for $C_{11}H_{19}ON_3$: C, 63.12; H, 9.15; N, 20.08. Found: C, 66.06, 62.72; H, 9.06, 9.12; N, 20.52, 20.20.

Oxalyl Cyanide (14).—To a solution of 5.3 g (50 mmol) of DISN in 100 ml of anhydrous CH_3CN was added dropwise a solution of 19.05 g (0.10 mol) of *p*-TsOH·H_2O in 200 ml of anhydrous ether (10 min addition). The solvent was then slowly removed under nitrogen at aspirator pressure (required about 50 min) leaving an orange solid from which was sublimed [50° (0.5 mm)] 525 mg of 14: mp 61–62°; ir (Nujol) 2230 (C≡N), 1735 cm^{-1} (C=O); mass spectrum *m/e* 107.9953 (calcd *m/e* 107.9960), 82 (M^+ − CN), 54 ($M^+/2$), 26 (CN).

Anal. Calcd for $C_4N_2O_2$: C, 44.49; H, 0.00; N, 25.93. Found: C, 44.46; H, 0.26; N, 25.93.

2,3-Dihydroxyquinoxaline (16).—To a solution of 2.65 g (25 mmol) of DISN in 50 ml of anhydrous THF was added dropwise 9.50 g (50 mmol) of *p*-TsOH·H_2O in 50 ml of THF. The resulting mixture was stirred for 15 min and filtered under a nitrogen atmosphere to remove the precipitated ammonium tosylate. A solution of 2.70 g (25 mmol) of o-phenylenediamine in 70 ml of THF was added dropwise over 15 min to the oxalyl cyanide solution and the reaction mixture was stirred for 20 hr. Filtration gave 3.1 g of light tan solid which was washed with water to remove a little ammonium tosylate and dried, giving 2.85 g (70.5%) of 16: mp 285°; ir identical with that of an authentic sample of 2,3-dihydroxyquinoxaline.

The THF was removed from the above filtrate and the resulting sticky solid was chromatographed on SilicAR. Benzene elution followed by recrystallization from benzene gave 250 mg (5.6%) of dicyanoquinoxaline (6), mp 218–220°.

Elution with methylene chloride and recrystallization from the same solvent gave 345 mg (8.1%) of 2-hydroxy-3-cyanoquinoxaline (17) as yellow needles: mp 300° dec; ir (KBr) 3350–2500, 2235, 1670, 1605, 1535, 1495 cm^{-1}; uv (CH_3CN) 233 nm (ε 22,200), 307 (9400), and 387 (5810).

Anal. Calcd for $C_9H_5ON_3$: C, 63.16; H, 2.94; N, 24.55. Found: C, 63.30; H, 2.91; N, 24.85.

***N,N'*-Diacetyldiiminosuccinonitrile (18).**—A solution containing 5.0 g of DISN, 50 ml of acetonitrile, and 100 ml of acetic anhydride was stirred at 100° for 12 hr. The solvent and excess anhydride were removed under reduced pressure. The crude solid–oil thus obtained was recrystallized from chloroform to give 1.0 g (11%) of 18 as white crystals: mp 155–157°; ir (KBr) 3010, 2920, 2260, 1670, 1640 cm^{-1}; nmr (CD_3CN) δ 2.16 (s).

A 20-mg sample of 18 was refluxed in 50 ml of 20% aqueous acetonitrile for 3 hr and the solvent was removed, giving 178 mg of *N,N'*-diacetyloxamide, mp 238–240° (lit.[7] mp 236–238°).

Anal. Calcd for $C_8H_6O_2N_4$: C, 50.53; H, 3.18; N, 29.47. Found: C, 50.66; H, 3.29; N, 29.39.

4,5-Dichloro-4,5-dicyano-2-imidazolidone (19).—A solution of 5.0 g (47 mmol) of DISN in 50 ml of anhydrous THF was added dropwise to a solution of 10 ml of phosgene in 15 ml of ether at −20°. The resulting solution was allowed to warm to room temperature and stirred for 1 hr. The solvent was removed under reduced pressure (vacuum pump), leaving 9.5 g of light yellow powder: mp 152° (becomes sticky and slowly darkens); ir 3300, 3190, 3090, 2265, 1765, 1190, 1025, 760, 725 cm^{-1}.

Anal. Calcd for $C_5ON_4 \cdot 2HCl$: C, 29.29; H, 0.99; N, 27.33. Found: C, 30.70; H, 1.16; N, 27.34.

Imidazolidone 19 is reasonably stable if stored under anhydrous conditions; however, in the presence of moisture HCN is released. We thus suggest preparing and using 19 in solution without isolation. *All work with* 19 *should be carried out in a well-ventilated hood since there is always the possibility of HCN formation.*

4,5-Dicyano-4,5-bis(allyloxy)-2-imidazolidone (21a).—To a solution of 20 ml of phosgene in 50 ml of ether at −20° under N_2 was added dropwise a solution of 10.0 g (95 mmol) of DISN in 150 ml of THF. The resulting solution was stirred for 1 hr after warming to room temperature and the excess phosgene and ether were removed under vacuum. A solution of 25 g of allyl alcohol in 200 ml of THF was added to the above solution of 19 and the resulting mixture was stirred for 18 hr. Removal of the solvent gave 23.4 g of crude product. Recrystallization from $HCCl_3$–ether gave 19.2 g (82%) of 21a as a white powder: mp 150–151°; ir (KBr) 3195, 3100, 2247, 1735, 1655, 1095 cm^{-1}; nmr (acetone-d_6) δ 3.24 (b, 1), 4.43 (m, 4), 5.1–6.4 (m, 6), and 8.75 (b, 1).

Anal. Calcd for $C_{11}H_{12}O_3N_4$: C, 53.22; H, 4.87; N, 22.57. Found: C, 52.53; H, 4.92; N, 22.31.

4,5-Dicyano-4,5-diethoxy-2-imidazolidone (21b).—In a manner similar to that used for the preparation of 21a there was obtained 9.15 g (43%) of 21b as white needles from $HCCl_3$: mp 174–176°; ir (KBr) 3250, 3150, 2270, 1730, 1100 cm^{-1}; nmr (acetone-d_6) δ 1.32 (t, 6), 3.32 (s, 1), 3.93 (q, 4), and 8.47 (s, 1).

Anal. Calcd for $C_9H_{12}O_3N_4$: C, 48.21; H, 5.39; N, 24.99. Found: C, 48.13; H, 5.56; N, 24.88.

5-Carboxamide-5-hydroxyhydantoin (23).—To a solution of 0.14 mol of 19 in 200 ml of THF was added dropwise 25 ml of water. The temperature rose from 21° to 38° during the addition. The resulting solution was stirred for 18 hr and filtered, and the solvent was removed to give a light yellow oil. Addition of acetone to this oil caused precipitation of a little insoluble white solid, mp 190–191°, which was not characterized. Addition of ether to the acetone solution gave 6.4 g (29%) of 19 as a white powder. Recrystallization from methanol gave white crystals: mp 191–193°; ir (KBr) 3420, 3330, 3270, 1790, 1770, 1730, 1685, and 1595 cm^{-1}.

Anal. Calcd for $C_4H_5O_4N_3$: C, 30.19; H, 3.17; N, 26.41. Found: C, 30.53; H, 3.36; N, 26.22.

4,5-Diphenylimino-2-imidazolidone (24a).—To a solution of 0.095 mol of 19 (prepared as previously described from 10 g of DISN, 20 ml of $COCl_2$, 100 ml of ether, and 200 ml of THF) in 200 ml of THF at −50° was added 27.9 g (0.30 mol) of aniline in 100 ml of THF. The resulting mixture was warmed to room temperature, stirred for 20 hr, and filtered, giving 30.5 g of yellow solid. This material was washed with water to remove aniline hydrochloride, dried, and recrystallized from THF, giving 19.5 g (78%) of 24a as light yellow crystals: mp 280°; ir (Nujol) 3180, 3050, 1740, 1695, 1625, 1580, 1550, and 1485 cm^{-1}; uv (CH_3CN) 222 nm (ε 18,600) and 337 (14,800).

Anal. Calcd for $C_{15}H_{12}ON_4$: C, 68.14; H, 4.58; N, 21.20. Found: C, 67.63; H, 4.53; N, 21.36.

4,5-Bis(isopropylimino)-2-imidazolidone (24b).—To a solution of 0.095 mol of 19 in 200 ml of THF at −20° was added dropwise 34.5 g (0.60 mol) of isopropylamine in 75 ml of THF. Isopropylamine hydrochloride precipitated from the solution immediately. The resulting solution was allowed to warm to room temperature, and filtered to remove salts, and the solvent was removed, giving 22 g of dark oil. Chromatography of this oil on SilicAR gave, with chloroform elution, 1.60 g (8.6%) of **24b** as white crystals from $HCCl_3$–ether: mp 232–233°; ir (KBr) 3155, 3050, 1740, 1700, 1625, and 1530 cm^{-1}; uv (CH_3CN) 241 nm (ε 16,900), 287 (6080); nmr (acetone-d_6) δ 1.08 (d, 6), 1.25 (d, 6), and 2.5–4.0 (m, 4).

Anal. Calcd for $C_9H_{16}ON_4$: C, 55.08; H, 8.22; N, 28.55. Found: C, 54.87; H, 8.36; N, 28.62.

4,5-Dicyano-4,5-bis(ethylthio)-2-imidazolidone (25).—To a solution of 0.14 mol of **19** in 200 ml of THF was added 41.5 ml (~0.56 mol) of ethanethiol in 100 ml of THF. The resulting solution was stirred for 18 hr and the solvent was removed, leaving 30 g of tan solid. This solid was dissolved in acetone and filtered to remove a little insoluble material. Addition of ether precipitated 5.0 g (27%) of 4,5-dicyanoimidazolone (**26**) as white needles from dioxane–petroleum ether, mp 265–270° dec (lit.[9] mp 270° dec).

The acetone and ether were removed under reduced pressure and the resulting cream-colored crystalline solid was washed with ether and dried to give 12.5 g (35%) of **25**. Recrystallization of a small amount of **25** from hot acetone resulted in conversion to **26**. Recrystallization from ether gave white crystals of **25**: mp 207–208° dec; ir (KBr) 3180, 3080, 2810, 2240, 1700 cm^{-1}; nmr (acetone-d_6) δ 1.36 (t, 6), *ca.* 3.1 (q + broad peak, 6).

Anal. Calcd for $C_9H_{12}OS_2N_4$: C, 42.19; H, 4.72; N, 21.87. Found: C, 41.80; H, 4.68; N, 22.11.

4,5-Dicyano-2-imidazolone (26).—A solution of 18.9 mmol of **19** in acetonitrile–ether was hydrogenated over 200 mg of 10% Pd/C at 50 psi of H_2 for 5 hr. The solution was filtered and the solvent was removed to give 1.9 g of crude **26**. Recrystallization from dioxane–petroleum ether gave white needles: 1.02 g (37%); mp 260–264° dec (lit.[9] mp 270° dec); ir (Nujol) 3300, 2700–2600, 2235, 1720, 1600, 1005, and 835 cm^{-1}.

2,3-Dichloro-2,3-dicyano-5,6-dioxopiperazine (27).—To 30 ml of oxalyl chloride in 100 ml of ether was added dropwise with ice bath cooling 15.0 g (0.14 mol) of DISN in 150 ml of THF. The resulting solution was stirred for 2 hr at room temperature and the solvent was removed under vacuum to give a yellow paste. This paste was redissolved in 200 ml of acetonitrile and upon cooling to −35° a precipitate formed. Filtration of this cold solution under N_2 gave 16.0 g of light yellow powder: melting point (phase change) at 140° and then slowly darkened upon further heating; ir (Nujol) 3210, 3100, 2260 (w), 1735, 1210, 1040, 810, and 750 cm^{-1}. Satisfactory analysis could not be obtained on this compound (C, H, and N were close to calculated; however, Cl was ~6% low) possibly owing to its sensitivity to moisture.

2,3-Dioxo-5,6-dicyano-1,2,3,4-tetrahydropyrazine (28).—To a solution of 20 ml of oxalyl chloride in 50 ml of ether was added dropwise 10.0 g of DISN in 125 ml of THF keeping the temperature below 20°. The resulting solution was stirred for 2 hr at 25°, the solvent and excess oxalyl chloride were removed under vacuum, and the sticky solid (**27**) thus obtained was redissolved in 200 ml of THF.

To this solution was added dropwise 25 g (0.40 mol) of ethanethiol in 100 ml of THF. After the solution was stirred for 20 hr, the solvent and excess ethanethiol were removed to give a brown solid. This solid was dissolved in acetone and treated with DARCO, and the acetone was partially removed. Filtration and washing with ether gave 10.0 g (65%) of white, crystalline **28**, mp 268° dec (lit.[10] mp 270° dec). The ir of **28** was identical with that of an authentic sample prepared from DAMN and oxalyl chloride.

2,3-Diethoxy-2,3-dicyano-5,6-dioxopiperazine (30).—To a solution of 13 mmol of **27**, prepared as previously described, in 25 ml of acetonitrile was added 10 ml of absolute ethanol. The resulting solution was refluxed for 5 hr and filtered to remove a little precipitate, and the solvent was removed yielding a sticky white solid. Recrystallization from CH_3CN:CCl_4 (1:1) gave 1.40 g (43%) of **30** as white needles: mp 205–208°; ir (KBr) 3340–2860, 2245, 1725, and 1105 cm^{-1}; mass spectrum *m/e* 252.0849 (calcd *m/e* 252.0859).

Anal. Calcd for $C_{10}H_{12}O_4N_4$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.82; H, 4.82; N, 22.31.

***N*-Propyl-*N'*-chloro-1-cyanoformamidine (32).**—To a solution of 9.5 g (0.054 mol) of Cl_2DISN in 150 ml of THF at −50° was added dropwise 9.5 g (0.16 mol) of propylamine in 50 ml of THF. The resulting solution was stirred for 1 hr at −50° and 3 hr at 26°, and was then filtered to remove the amine hydrochloride salts. SilicAR (approximately 50 g) was added to the filtrate and the solvent was removed to give dry preabsorbed material which was subsequently chromatographed on another 100 g of SilicAR CC7. (The preabsorbed material should be covered with petroleum ether as soon as it is dry; on two occasions the dry material became very hot and decomposed upon standing.) Elution with CCl_4 gave an oil which crystallized upon cooling. Recrystallization from ether–petroleum ether gave 3.60 g (45%) of **32** as white needles: mp 39–41°; ir (KBr) 3300, 2255, 1610 cm^{-1}; uv (CH_3CN) 247 nm (ε 7450); nmr ($CDCl_3$) δ 1.00 (t, 3), 1.7 (m, 2), 3.47 (m, 2, to t when D_2O added), 6.25 (b, 1).

Anal. Calcd for $C_5H_8N_3Cl$: C, 41.18; H, 5.52; N, 28.90. Found: C, 41.15; H, 5.54; N, 28.77.

3,4-Dicyano-1,2,5-thiadiazole (33) from Diiminosuccinonitrile (DISN).—To a solution of 530 g (5.0 mol) of DISN in 2 l. of dichloromethane at room temperature was added dropwise over 1 hr 670 g (6.5 mol) of sulfur dichloride. *The reaction involves 245 l. of gaseous hydrochloric acid* which should be exited *via* a water scrubber. The reaction mixture was stirred for 0.5 hr, 250 g of DARCO and 1 l. of dichloromethane were added, the solution was stirred for 15 min and filtered, and the filter cake was washed with dichloromethane. Concentration of the filtrate gave 635 g (93%) of **33** as light yellow crystals, mp 51° (lit.[11] mp 49–50°). Colorless material can be obtained by distillation, bp 75–76° (1.0 mm).

3,4-Dicyano-1,2,5-thiadiazole (33) from Cl_2DISN.—A solution containing 8.74 g (0.05 mol) of Cl_2DISN and 3.21 g (0.10 mol) of sulfur in 100 ml of dimethylformamide was heated at 60° for 4 hr. The sulfur slowly dissolved, giving a red solution which was cooled and poured into 300 ml of cold water. The resulting aqueous solution was extracted with 2 × 200 ml of ether, the combined ether layers were washed with 100 ml of water and dried over anhydrous $MgSO_4$, and the ether was removed to give a yellow solid. Recrystallization and treatment with activated charcoal from methylene chloride–pentane gave 5.1 g (75%) of **33** as colorless crystals, mp 50–51°.

2,2-Dimethyl-4,5-dicyanoisoimidazole (35).—To a solution of 30.0 g (0.285 mol) of DISN and 63 g (0.60 mol) of dimethoxypropane in 750 ml of tetrahydrofuran was added 1.5 ml of concentrated sulfuric acid. An exotherm of 10° occurred over 5 min and the resulting solution was then stirred for 3 days. The solvent was removed and the dark brown solid thus obtained was recrystallized from benzene to give 33.2 g (80%) of **35** as white crystals: mp 139–140°; ir (KBr) 3010, 2960, 2880, 2250 (w), 1600, 1540, 1375, and 1350 cm^{-1}; uv (CH_3CN) 215 nm (ε 5300), 282 (26); nmr (acetone-d_6) δ 1.58 (s).

Anal. Calcd for $C_7H_6N_4$: C, 57.52; H, 4.14; N, 38.34. Found: C, 57.46; H, 4.45; N, 38.42.

2,2-Dimethyl-4,5-diethoxyisoimidazole (36).—To a solution of 4.8 g (0.21 mol) of sodium in 300 ml of absolute ethanol was added 15.3 g (0.105 mol) of **35** in 450 ml of ethanol. After the solution was stirred for 4 days the ethanol was removed and the resulting solid–oil was extracted with 200 ml of ether. The ether was removed and the solid–oil obtained was dissolved in 100 ml of water, neutralized with concentrated HCl, and extracted with 200 ml of ether. The ether extracts were dried over $MgSO_4$, the ether was removed, and the product was distilled to give 12.5 g (65%) of **36** as a colorless liquid: bp 78–80° (10 mm); ir (neat) 2980, 2945, 2865, 1647, and 1620 cm^{-1}; uv (CH_3CN) end absorption; nmr ($CDCl_3$) δ 1.40 (s, 6), 1.40 (t, J = 7.1 Hz, 6), 4.37 (q, J = 7.1 Hz, 4).

Anal. Calcd for $C_9H_{16}O_2N_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 57.97; H, 8.75; N, 15.19.

2,2-Dimethyl-4-cyano-5-*N*-(isopropylamidino)isoimidazole (37).—A solution of 5.0 g (0.034 mol) of **35** and 10.0 g of isopropylamine in 50 ml of THF was refluxed for 18 hr. The resulting solution was treated with DARCO, filtered, and stripped to give an oil which slowly crystallized. Recrystallization from ether–petroleum ether gave 3.98 g (57.5%) of white crystals: mp 82.5–84.0°; ir (KBr) 3500, 3400, 2260, 1655, 1620, and 1555 cm^{-1}; uv (CH_3CN) 208 nm (ε 9280), 293 (2130); nmr ($CDCl_3$) δ 1.25 (d, J = 6.1 Hz, 6), 1.55 (s, 6), 3.5 (b, 1), 5.1 (b, 1).

Anal. Calcd for $C_{10}H_{16}N_5$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.61; H, 7.43; N, 33.96.

2-Methyl-2-propyl-4,5-dicyanoisoimidazole (38) and 2-Methyl-3-ethyl-4,5-dicyanopyrazine (39).—A solution of 26.0 g (0.25 mol) of DISN, 2.0 g of oxalic acid, 2.0 g of DAMN, 200 ml of 2-pentanone, and 300 ml of benzene was refluxed overnight under a Dean–Stark trap. The resulting brown solution was preabsorbed and chromatographed on SilicAR. Petroleum ether elution gave 7.6 g (18%) of **38** as fluffy white needles: mp 90–91; ir (KBr) 2980, 2900, 2245, and 1545 cm^{-1}; uv (CH_3CN) 223 nm (ϵ 5500), sh 285 (30); nmr ($CDCl_3$) δ 0.8–1.4 (m, 5), 1.60 (s, 3), 2.0 (m, 2).

Elution with carbon tetrachloride gave 1.6 g of **39** as white crystals: mp 97.5–98.5°; ir (KBr) 2980, 2940, 2875, 1531 cm^{-1}; uv (CH_3CN) 245 nm (ϵ 11,750), 282 (7800); nmr ($CDCl_3$) δ 1.37 (t, J = 7.2 Hz, 3), 2.72 (s, 3), 3.00 (q, J = 7.2 Hz, 2).

Anal. Calcd for $C_9H_{10}N_4$ (**38**): C, 62.05; H, 5.79; N, 32.17. Found: C, 61.70; H, 5.80; N, 32.38.

Anal. Calcd for $C_9H_8N_4$ (**39**): C, 62.77; H, 4.68; N, 32.54. Found: C, 62.78; H, 4.61; N, 32.57.

2-Methyl-2-ethyl-4,5-dicyanoisoimidazole (41) and 2,3-Dimethyl-5,6-dicyanopyrazine (42).—A mixture of 25 g (0.236 mol) of DISN, 2 g of anhydrous oxalic acid, 2.0 g of DAMN in 250 ml of 2-butanone, and 300 ml of benzene was stirred at reflux for 18 hr, after which time the theoretical quantity of water (4.2 ml) had collected in a Dean–Stark trap. The reaction solution was filtered and evaporated to give a viscous oil which was chromatographed on SilicAR. Elution with CCl_4 removed **41**, which was recrystallized from CCl_4, 7.53 g (20.0%) of white needles, mp 94–95°. Elution with benzene removed **42**, which was recrystallized from benzene, 2.39 g (6.3%) of white prisms, mp 169–170° (lit.[12] mp 167–170°). Compound **41** had ir (KBr) 2990, 2960, 2890, 2250 (w), 1595, and 1540 cm^{-1}; uv (CH_3CN) 221 nm (ϵ 5600), 280 (29); nmr (acetone-d_6) δ 0.90 (t, 3), 1.57 (s, 3), 2.07 (q, 2).

Anal. Calcd for $C_8H_8N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 59.77; H, 4.88; N, 35.12.

***N,N'*-Bis(1-methoxycyclohexane)diiminosuccinonitrile (43).**—To a solution of 5.3 g (0.05 mol) of DISN and 8.7 g (0.06 mol) of cyclohexanone dimethyl ketal in 75 ml of THF was added 5 drops of concentrated sulfuric acid. The temperature rose from 24° to 36° and the solution darkened. After stirring overnight the solvent was removed and the resulting oil was chromatographed on SilicAR. Carbon tetrachloride to benzene elution gave an oil which solidified upon addition of a little petroleum ether. Recrystallization from petroleum ether gave 1.45 g (8.8%) of **43** as white plates: mp 125–127°; ir (KBr) 2990, 2950, 2930, 2855, 2835, 2230, 1639 cm^{-1}; uv (CH_3CN) 225 nm (ϵ 9340), sh 265 (4300), sh 330 (330); nmr ($CDCl_3$) δ 1.5–2.1 (m, 20), 3.28 (s, 6).

Anal. Calcd for $C_{18}H_{26}O_2N_4$: C, 65.43; H, 7.93; N, 16.96. Found: C, 65.68; H, 8.23; N, 17.09.

1-Isopropyl-2-methyl-4,5-dicyanoimidazole (44) and 2,3-Dicyano-5,6,6-trimethyl-1,6-dihydropyrazine (45).—This reaction was run in the same manner as that used for the preparation of **38**. From 0.20 mol of DISN there was obtained, by elution with benzene, 2.65 g (7.6%) of **44** as white needles from ether: mp 108–109°; ir (KBr) 2230, 1535, and 1510 cm^{-1}; uv (CH_3CN) 255 nm (ϵ 10,600); nmr ($CDCl_3$) δ 1.68 (d, J = 6.8 Hz, 6), 2.53 (s, 3), 4.67 (septet, J = 6.8 Hz, 1).

Chloroform elution gave 3.80 g (11%) of **45** as light tan crystals from chloroform–ether: mp 167.0–168.5°; ir (KBr) 3300, 2230, 2210, 1610, 1565, and 1505 cm^{-1}; uv (CH_3CN) 245 nm (ϵ 3300), 350 (5700); nmr (acetone-d_6) δ 0.92 (s, 6), 2.70 (s, 3).

Anal. Calcd for $C_9H_{10}N_4$: C, 62.05; H, 5.79. Found (**44**): C, 62.09; H, 5.69. Found (**45**): C, 62.22; H, 5.69.

1-Propyl-2-methyl-4,5-dicyanoimidazole (47).—A 0.90-g sample of **38** in a test tube was heated over 20 min from 150 to 190°. Small samples were removed every 10° and checked by infrared. At 170° only starting material was observed and at 180° there was complete rearrangement to **47**. This material was recrystallized from ether–petroleum ether to give 0.81 g of white crystals: mp 40.5–41.5°; ir (KBr) 2240, 1535, 1515, 1365 cm^{-1}; uv (CH_3CN) 255 nm (ϵ 11,000); nmr ($CDCl_3$) 1.02 (t, J = 7.0 Hz, 3), 1.9 (m, 2), 2.51 (s, 3), 4.11 (t, J = 7.4 Hz, 2).

Rearrangement of **38** to **47** was also found to occur at 110° in acetic acid; however, at 130° in *p*-xylene no rearrangement occurred.

Anal. Calcd for $C_9H_{10}N_4$: C, 62.05; H, 5.79; N, 32.17. Found: C, 62.12; H, 5.87; N, 32.35.

1-Ethyl-2-methyl-4,5-dicyanoimidazole (48).—In a similar manner to that used in the rearrangement of **38**, 0.50 g of **30a** was heated to 190° and gave 0.45 g of **48** as white crystals from ether–petroleum ether: mp 137–139°; ir (KBr) 2240, 1535, 1510, 1386 cm^{-1}; uv (CH_3CN) 255 nm (ϵ 11,100); nmr ($CDCl_3$) δ 1.50 (t, J = 7.3 Hz, 3), 2.52 (s, 3), 4.17 (q, J = 7.3 Hz, 2).

Anal. Calcd for $C_8H_8N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 59.88; H, 5.43; N, 34.70.

Ethylation of 2-Methyl-4,5-dicyanoimidazole (49).—To a slurry of 6.6 g (0.05 mol) of **49** in 100 ml of water was added 5.9 g (0.07 mol) of sodium bicarbonate. This solution was heated to 50° and 10 ml of diethyl sulfate was added dropwise. After stirring for 0.5 hr at 50° the solution was cooled and extracted with two 200-ml portions of ether. Removal of the ether gave a white solid, which was slurried with petroleum ether and filtered to give 3.6 g of starting material (**49**). Removal of the petroleum ether gave 2.7 g of white crystals identical with the previously prepared **48** by ir and melting point.

2-Methyl-2-propyl-4,5-diethoxyisoimidazole (50).—A solution of 5.22 g (0.03 mol) of **38** and 0.06 mol of sodium ethoxide in 100 ml of absolute ethanol was refluxed for 1 hr, stirred for 16 hr, and stripped to give a solid–oil. This material was washed with 200 ml of ether and filtered to remove the salts. The ether layer was washed with dilute HCl until neutral, dried, and distilled to give 3.1 g (47%) of clear liquid: bp 64–65° (0.3 mm); ir (neat) 2965, 2895, 1648, 1620, 1565, 1535 cm^{-1}; uv (CH_3CN) end absorption; nmr ($CDCl_3$) δ 0.9 (m, 3), 1.1–2.0 (m, 4), 1.34 (s, 3), 1.40 (t, J = 7.2 Hz, 6), 4.33 (q, J = 7.2 Hz, 4).

Anal. Calcd for $C_{11}H_{20}O_2N_2$: C, 62.23; H, 9.50. Found: 62.11; H, 9.42.

2,2-Bis(trifluoromethyl)-4,5-dicyano-5-amino-3-oxazoline (52).—A solution containing 10.0 g (94 mmol) of DISN in 150 ml of THF was cooled to −20° and 5 drops of concentrated sulfuric acid was added. Hexafluoroacetone (~0.2 mol) was then bubbled into the solution over 15 min. The resulting solution was allowed to warm to room temperature, stirred for 20 hr, treated with Darco, and filtered, and the solvent was removed, leaving a thick oil. Addition of 300 ml of petroleum ether caused crystallization of 17.9 g (72.7%) of **52** as off-white needles. Recrystallization from petroleum ether containing a little ether gave white needles: mp 87–89°; ir (Nujol) 3450, 3350, 3240, 2260, 1645, 1625 cm^{-1}; F nmr ($CDCl_3$, F-11 ext) δ −73.6, −74.4 (A_3B_3, J_{AB} = 8 Hz).

Anal. Calcd for $C_7H_2N_4F_6O$: C, 30.89; H, 0.74; N, 20.85; F, 41.89. Found: C, 30.78; H, 1.05; N, 20.97; F, 41.83.

***N,N'*-Bis(1-hydroxy-2,2,2-trichloroethyl)diiminosuccinonitrile (54).**—To a solution of 5.3 g (50 mmol) of DISN and 14.6 g (99 mmole) of chloral in 50 ml of THF was added 5 drops of concentrated H_2SO_4. The reaction was mildly exothermic (20° to 43° over 1.5 hr). After stirring overnight at room temperature, the solution was preabsorbed on SilicAR CC7 and chromatographed. Elution with benzene removed 10.1 g of crude **54** which was recrystallized from benzene, 7.95 g (40.2%): mp 181° dec; ir (Nujol) 3350, 2250 (w), 1140, 970, 840, 815, 775 cm^{-1}; nmr (DMSO-d_6) δ 5.90 (d, J = 2 Hz, 2), 7.69 (d, J = 2 Hz, 2), with D_2O, 7.69 exchanges and 5.90 collapses to singlet.

Anal. Calcd for $C_8H_4O_2N_4Cl_6$: C, 23.97; H, 1.01; N, 13.98; Cl, 53.07. Found: C, 23.88; H, 1.01; N, 13.82; Cl, 52.39.

Registry No.—**1**, 30986-09-5; **2**, 33420-38-1; **5**, 36597-16-7; **6**, 17132-92-2; **7**, 36597-18-9; **11**, 36597-19-0; **12**, 36622-56-7; **14**, 36086-83-6; **17**, 4188-11-8; **19a**, 33420-40-5; **21a**, 33420-41-6; **21b**, 36597-24-7; **23**, 36597-25-8; **24a**, 36597-26-9; **24b**, 36587-27-0; **25**, 36597-28-1; **26**, 33420-43-8; **27**, 36597-30-5; **30**, 36597-31-6; **32**, 36597-32-7; **33**, 23347-22-0; **35**, 33420-46-1; **36**, 36597-35-0; **37**, 36597-36-1; **38**, 36597-37-2; **39**, 36597-38-3; **41**, 36597-39-4; **43**, 36597-40-7; **44**, 36597-41-8; **45**, 36597-42-9; **47**, 36597-43-0; **48**, 36597-44-1; **50**, 36597-45-2; **52**, 36597-46-3; **54**, 36597-47-4; DISN, 28321-79-1; methyl alcohol, 67-56-1; aniline, 62-53-3; *o*-phenylenediamine,

95-54-5; isopropylamine, 75-31-0; cyclohexanone, 108-94-1; 3-pentanone. 96-22-0; acetonitrile, 75-05-8; phosgene, 75-44-5; allyl alcohol, 107-18-6; ethyl alcohol, 64-17-5; acetone, 67-64-1; oxalyl chloride, 79-37-8; ethanethiol, 75-08-1; Cl_2DISN, 33420-44-9; 2,2-dimethoxypropane, 77-76-9; 2-pentanone, 107-87-9; 2-butanone, 78-93-3; cyclohexanone dimethyl ketal, 933-40-4; sodium ethoxide, 141-52-6; 3-methyl-2-butanone, 563-80-4; hexafluoroacetone, 684-16-2; chloral, 75-87-6.

Anodic Oxidations. VI.[1] Para-Cyanation of Diphenylamines

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Electrochemical oxidation of diphenylamine and its monosubstituted derivatives in methanol containing sodium cyanide yields nuclear cyanation products in good yield. In the cases of the ortho- and meta-substituted diphenylamines as well as the unsubstituted, cyanation took place preferentially at the para position. Para-substituted diphenylamines showed quite different behaviors; *p*-methoxydiphenylamine remained almost intact while *p*-cyanodiphenylamine gave a product cyanated exclusively at the para position of the other phenyl ring. Coulometric data showed that on an average two electrons were lost per organic molecule. The overall reaction involves the initial oxidation of organic substrates.

Anodic cyanation is expected to provide a promising method for synthesis of nitriles by reason of its simple operation. However, the reaction is conducted in most cases in methanol owing to the limited solubility of cyanide salt, leading thus to the competitive formation of methoxylated products.[2-4] To avoid a concurrent methoxylation, tetraethylammonium cyanide–acetonitrile system has been examined.[5] The latter system is suitable for replacement of aromatic methoxyl by nitrile and introduction of a nitrile group in an α position of tertiary amines. For replacement of aromatic hydrogen, however, cyanide salt in methanol is a preferred medium.

Originally,[2] this reaction was depicted as a homolytic substitution reaction by anodically generated cyano radicals, but it was later shown[6] that the cyanation of anisole involved anodic oxidation of the aromatic species followed by reaction with cyanide ion as shown for anodic acetoxlation.[7] This is supported by the results of controlled potential anodic cyanation of other organic compounds[5,8] and by the comparative experiments with the photochemical cyanation.[9] It seems that methoxylation also proceeds *via* an analogous mechanism.[10]

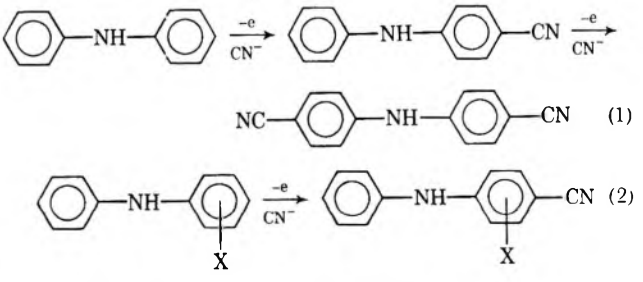
According to this mechanism, a factor controlling the relative prevalence of the two pathways leading to cyanation and side reaction, methoxylation, is ascribable to the relative reactivity of initially generated cation radicals toward different nucleophiles.[10] Stable (or less reactive) cationic species would react selectively with the stronger nucleophile, cyanide ion. Although the stability of cation radicals may not precisely be correlated with oxidation potential of the parent substrates, it does appear that substrates with lower oxidation potential are able to produce the more selective cation radical. A very stable cation radical such as tri-*p*-anisylamine cannot undergo cyanation but oxidizes cyanide ion to radical.[11]

With this practical view in mind, anodic oxidation of aromatic amines, which seem to have moderate oxidation potentials, was carried out in methanol containing sodium cyanide. It was found that nuclear cyanation took place effectively.

Results

Electrolyses were all conducted at anode potentials between 0.3 and 0.6 V. At these potentials only organic substrates are oxidized.[8] It was observed that nuclear cyanation occurred exclusively at a para position (Table I[12-14]).

With diphenylamine cyanation occurred at a para position to give *p*-cyanodiphenylamine (61% yield). In diphenylamines with methoxyl or methyl group in ortho or meta position, substitution occurred at the para position of the substituted phenyl group. *p*-Methoxydiphenylamine remained almost intact under the reaction conditions adopted. In diphenylamine



X = *o*- or *m*-CH_3 and OCH_3

with cyano group (strongly electron-withdrawing substituent) at a para position, cyanation occurred

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TABLE I

ANODIC CYANATION OF DIPHENYLAMINES[a]

Reactant	Decomposition[b] potential, V vs. sce	Oxidation potential, V vs. sce	Preparative anode potential, V vs. sce	Electricity, F	Product	Registry no.	Current efficiency, %	Yield,[g] %	n, F/mol
Diphenylamine	0.40	0.835[c]	0.42	0.017	4-Cyanodiphenylamine	36602-01-4	69	61 58[h]	1.7
2-Methoxydiphenylamine	0.33		0.35	0.008	2-Methoxy-4-cyano-diphenylamine	36602-02-5	34	44	2.6
4-Methoxydiphenylamine	0.28	0.59[d]	0.3–1.1	0.017	[f]				7.3
2-Methyldiphenylamine	0.40		0.40–0.42	0.011	2-Methyl-4-eyano-diphenylamine	36602-03-6	57	53	2.0
3-Methyldiphenylamine	0.35		0.33–0.40	0.012	3-Methyl-4-cyano-diphenylamine	36602-04-7	43	49	2.3
4-Cyanodiphenylamine	0.40		0 60	0.011	4,4′-Dicyanodiphenyl-amine	36602-05-8	29	31	2.2
N-Methyldiphenylamine	0 49	0.84[e]	0.60	0.013	*N*,*N*-Diphenylamino-acetonitrile	36602-06-9	57	65	2.3
					Diphenylamine		5	6	

[a] [NaCN], 0.8 *M*; [amine], 0.4 *M* (4-methoxydiphenylamine is less owing to its limited solubility); temp, 25°. [b] Data read from current–potential curve. [c] $E_{1/2}$, value from ref 12. [d] $E_{p/2}$, value from ref 13. [e] $E_{p/2}$, value from ref 14. [f] A small amount of unidentified nitrile. [g] Based on amine consumed. [h] Nonpotentiostatic oxidation (conversion, 50%; see Experimental Section).

at the para position of the other phenyl group; *viz.*, dicyanation is possible in the case of diphenylamine. Coulometric data showed an average of 2.2 electrons lost per organic molecule.

With *N*-methyldiphenylamine, cyanation occurred at a methyl group to give *N*,*N*-diphenylaminoacetonitrile in high yield. In addition, a small amount of diphenylamine was produced. These types of reaction in tertiary amines have already been observed by Andreades and Zahnow.[5] *N*,*N*-Dimethylaniline showed the same behavior as did *N*-methyldiphenylamine. Triphenylamine was almost inert under these conditions (cpe 0.78 V, n = 16.3) and aniline polymerized.

Discussion

One major advantage of the present reaction lies in its high selectivity with regard to the position of attack. The reaction products were para-cyanated phenylamines exclusively. Thus the reaction is the most convenient method for the syntheses of *p*-cyanodiphenylamine. It is not necessary to control an anode potential for the purpose of organic syntheses (see Table I). Other methods of synthesizing these compounds are troublesome and of poor yield in some cases (see the preparation of authentic sample in Experimental Section).[15]

Earlier electrochemical studies of diphenylamines have been concerned with the effects of structure on $E_{1/2}$, *i.e.*, the ease of oxidation.[16,17] It has recently been reported that diphenylamine gives diphenylbenzidine in acetonitrile.[12,18] In aqueous acetone the electrochemical oxidation of diphenylamines leads to benzoquinone and the corresponding amine.[19] In no case has an aromatic substitution by a nucleophile been reported.

In the electrochemical oxidation of diphenylamines, the first step is the oxidation of amines to cation radicals.[19] Oxidation with lead tetraacetate also gives cation radicals.[20] In view of these studies and the present results of controlled potential electrolyses, the primary electrode process is considered to be the oxidation of diphenylamine to a cation radical which subsequently reacts with cyanide ion. However, an unequivocal explanation for the attacking position is still lacking. Probably, it would be necessary to consider both the reactivity of initially generated cation radicals and the nature of nucleophiles.

As has already been described, both *p*-methoxydiphenylamine and triphenylamine are apparently inert under the present conditions even though they discharge practically. This phenomenon would be ascribable to the regeneration of aromatic amines by redox reaction between anodically generated cation radicals and cyanide ion, as has already been indicated by Papouchado, Adams, and Feldberg.[11]

There are two essentially important stages for anodic cyanation of organic compounds. The first stage is the electrochemical oxidation of organic compounds to cation radicals. We can readily obtain the information concerning this stage by voltammetry. The second step is the reaction of the anodically generated cation radical with cyanide ion. The information concerning this step is at present lacking. We cannot forecast precisely what structure of cation radicals will trap cyanide ion effectively prior to reactions with other nucleophiles such as the solvent methanol. In view of earlier successful anodic cyanation,[1-6,8,9] it seems that relatively stable (but, not too stable) cation radicals efficiently react with cyanide ion.

Experimental Section

The electrochemical and spectroscopic instrumentation and techniques were as previously described.[8]

Materials.—Methanol was purified by fractional distillation from magnesium activated with iodine. Reagent grade sodium cyanide was used with no purification other than drying.

Aniline, *N*,*N*-dimethylaniline, and *N*-methyldiphenylamine were obtained commercially and were purified by distillation before use. Diphenylamine and triphenylamine were purified by recrystallization. *o*-Methoxydiphenylamine was prepared

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by decarboxylation of *N*-*o*-anisylanthranilic acid:[21] bp 146–148° (2 mm); ir 3420 (NH), 2840 (OCH_3), 1595 (NH), 1240, 1120, 1025 (COC), 745, and 695 cm^{-1} (mono- and 1,2 substitution); nmr (CCl_4) τ 2.7–3.4 (9 H, m), 4.02 (1 H, broad), and 6.23 (3 H, s). *p*-Methoxydiphenylamine was prepared by treating acetyl-*p*-anisidine with excess bromobenzene[22] and was purified by column chromatography and recrystallization: mp 106–107° (from ethanol, lit.[22] mp 106°); ir 3410, 1600 (NH), 1245, 1185, 1035 (COC), 850, 755, and 695 cm^{-1} (mono- and 1,4 substitution); nmr ($CDCl_3$) τ 2.7–3.3 (9 H, m), 5.15 (1 H, broad), and 6.22 (3 H, s). *o*-Methyldiphenylamine was prepared by decarboxylation of *N*-*o*-tolylanthranilic acid:[21] bp 117° (3 mm); ir 3420, 1600 (NH), 750, and 695 cm^{-1} (mono- and 1,2 substitution); nmr (CCl_4) τ 2.8–3.9 (9 H, m), 4.85 (1 H, broad), and 7.83 (3 H, s). *m*-Methyldiphenylamine was prepared from potassium *m*-toluidide and bromobenzene:[23] bp 117–119° (3 mm); ir 3420, 1600 (NH), 870, 770, 750, and 690 cm^{-1} (mono- and 1,3-substitution); nmr (CCl_4) τ 2.8–3.5 (9 H, m), 4.70 (1 H, broad), and 7.80 (3 H, s).

An authentic sample of *p*-cyanodiphenylamine was prepared from *p*-aminobenzonitrile and iodobenzene by a modification of the method of Gilman and Shirley.[22] Attempts to prepare this compound from *p*-cyanohalobenzenes and aniline or by Sandmeyer reaction from *p*-aminodiphenylamine were unsuccessful, and numerous amounts of tarry substance were produced.

Potentiostatic Oxidations.—The organic compound (0.02 mol) in 50 ml of methanol–sodium cyanide (0.80 *M*) was electrolyzed at an controlled anode potential. The electrolyzed mixture was treated with water, and the organic material was extracted with ether as described earlier.[8,10] The ether was removed by distillation, and the residue was chromatographed on alumina using benzene as an eluent. Unreacted starting material was first eluted, followed by cyanated products. *N*-Phenylaminoacetonitriles were partially hydrolyzed to amides on column chromatography, which were eluted with ethyl acetate. *p,p'*-Dicyanodiphenylamine was also eluted by ethy acetate.

Nonpotentiostatic Oxidations.—Preparative-scale electrolysis was carried out in a two compartment H-type cell with glass frit separating the compartments fitted with platinum foil electrodes (20 × 30 mm^2). The anolyte was made up of 20.3 g (0.12 mol) of diphenylamine, 7.8 g (0.16 mol) of sodium cyanide, and 180 ml of methanol. The catholyte was a methanolic solution of sodium cyanide. The electrolysis was carried out at the terminal voltage of 24–32 V to maintain the current of 0.1 A for 32 hr under a nitrogen atmosphere. During the electrolysis, the solution was stirred magnetically and cooled externally with ice. The electrolyzed mixture was treated as usual.

Identification of Product.—Cyanated products were identified by elemental analyses, by ir, nmr, and mass spectra, and by comparison with authentic samples.

4-Cyanodiphenylamine: mp 101–102° (from ethanol); ir 3340 (NH), 2240 (CN), 825 (1,4 substitution), 760, and 690 cm^{-1} (monosubstitution); nmr ($CDCl_3$) τ 2.4–3.1 (9 H, m) and 3.85 (1 H, broad). *Anal.* Calcd for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42; mol wt, 194.24. Found: C, 80.25; H, 5.22; N, 14.36; mol wt, 194 (mass spectroscopy).

2-Methoxy-4-cyanodiphenylamine: mp 80–81° (from ethanol); ir 3345 (NH), 2235 (CN), 1266, 1134, 1032 (COC), 848, 810 (1,2,4 substitution), 750, and 688 cm^{-1} (monosubstitution); nmr (CCl_4) τ 2.60–3.15 (8 H, m), 3.58 (1 H, broad), and 6.08 (3 H, s); *Anal.* Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.48; mol wt, 224.26. Found: C, 74.69; H, 5.31; N, 12.46; mol wt, 224 (mass spectroscopy).

2-Methyl-4-cyanodiphenylamine: mp 116–116.5° (from carbon tetrachloride); ir 3380 (NH), 2240 (CN), 890, 825 (1,2,4 substitution), 750, and 695 cm^{-1} (monosubstitution); nmr (CCl_4) τ 2.6–3.1 (8 H, m), 4.35 (1 H, broad), and 7.75 (3 H, s). *Anal.* Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45; mol wt, 208.26. Found: C, 80.72; H, 5.82; N, 13.37; mol wt, 208 (mass spectroscopy).

3-Methyl-4-cyanodiphenylamine: mp 116.5–117° (from carbon tetrachloride); ir 3380 (NH), 2240 (CN), 870, 820 (1,2,4 substitution), 750, and 700 cm^{-1} (monosubstitution); nmr (CCl_4) τ 2.6–3.35 (8 H, m), 3.95 (1 H, broad), and 7.60 (3 H, s). *Anal.* Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45; mol wt, 208.26. Found: C, 80.87; H, 5.82; N, 13.44; mol wt, 208 (mass spectroscopy).

4,4'-Dicyanodiphenylamine: mp 265–266° (from ethyl acetate, lit.[24] mp 240–246°); ir 3360 (NH), 2230 (CN), and 825 cm^{-1} (1,4 substitution); nmr ($(CD_3)_2CO$) τ 1.37 (1 H, broad), 2.34 (4 H, d, J = 8.9 cps), and 2.66 (4 H, d, J = 8.9 cps). *Anal.* Calcd for $C_{14}H_9N_3$: C, 76.70; H, 4.14; N, 19.17; mol wt, 219.25. Found: C, 76.98; H, 4.06; N, 18.95; mol wt, 219 (mass spectroscopy).

***N*,*N*-Diphenylaminoacetonitrile**: bp 130° (1 mm); ir 2230 cm^{-1} (CN); nmr (CCl_4) τ 2.7–3.4 (10 H, m) and 5.80 (2 H, s); mol wt, 208 (mass spectroscopy).

***N*,*N*-Diphenylaminoacetamide**: mp 149–150° (from ethanol); ir 3470, 3360 (NH_2), and 1690 cm^{-1} (CO); nmr ($CDCl_3$) τ 2.6–3.1 (10 H, m), 3.55 (2 H, broad), and 5.57 (2 H, s). *Anal.* Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38; mol wt, 226.28. Found: C, 74.11; H, 6.26; N, 12.36; mol wt, 226 (mass spectroscopy).

***N*-Phenyl-*N*-methylaminoacetonitrile**: bp 100° (1 mm) (lit.[5] bp 161–168° (0.6 mm)); ir 2245 (CN), 758, and 690 cm^{-1} (monosubstitution); nmr (CCl_4) τ 2.65–2.95 (2 H, m), 3.10–3.30 (3 H, m), 6.07 (2 H, s), and 7.13 (3 H, s). *Anal.* Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.16; mol wt, 146.19. Found: C, 73.65; H, 6.96; N, 19.07; mol wt, 146 (mass spectroscopy).

***N*-Phenyl-*N*-methylaminoacetamide**: mp 167.5–168.5° (from ethanol); ir 3360, 3200 (NH_2), 1650 (CO), 752, and 690 cm^{-1} (monosubstitution); nmr ($CDCl_3$) τ 2.55–2.80 (2 H, m), 3.05–3.30 (3 H, m), 3.50 (2 H, broad), 6.15 (2 H, s), and 6.97 (3 H, s). *Anal.* Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06; mol wt, 164.21. Found: C, 66.03; H, 7.50; N, 17.12; mol wt, 164 (mass spectroscopy).

Registry No.—*N*,*N*-Diphenylaminoacetamide, 36602-07-0; *N*-phenyl-*N*-methylaminoacetonitrile, 36602-08-1; *N*-phenyl-*N*-methylaminoacetamide, 21911-76-2.

(21) S. P. Massie and P. K. Kadaba, *J. Org. Chem.*, **21**, 347 (1956).
(22) H. Gilman and D. A. Shirley, *J. Amer. Chem. Soc.*, **66**, 888 (1944).
(23) F. Scardiglia and J. D. Roberts, *J. Org. Chem.*, **23**, 629 (1958).
(24) J. N. Ashley, H. J. Barber, A. J. Ewins, G. Newbery, and A. D. H. Self, *J. Chem. Soc.*, 103 (1942).

Oxidations of Amines. XI. Kinetics of Fragmentation of Triethylenediamine Chlorammonium Cation in Aqueous Solution[1]

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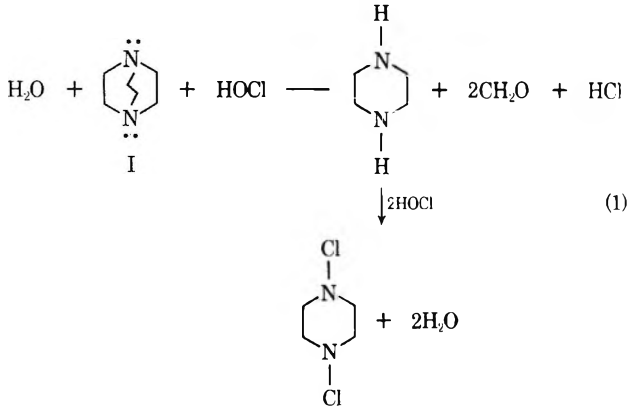
The reaction of hypochlorous acid with triethylenediamine has been studied by stopped-flow kinetics. A species identified as the chlorammonium cation was rapidly formed and detected by its ultraviolet absorption. Pre-steady-state and steady-state kinetics were obtained for the occurrence of the triethylenediamine cation radical. The data were analyzed in terms of two mutually exclusive mechanisms, either of which may be plausible, using the molar absorptivity of the cation radical obtained in previous work.[1] Related decompositions of aliphatic chlorammonium cations are discussed, as well as observations concerning the Hofmann–Loeffler reaction, in the light of these results and previous results of this series.

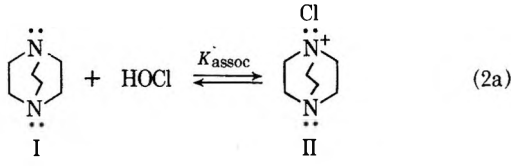
The action of hypochlorous acid on TED (triethylenediamine) differs markedly from its action on either simple aliphatic tertiary amines (such as triethylamine) or quinuclidine (which it resembles in important respects). With triethylamine, an aldehyde results without any carbon–carbon bond breaking.[2-4] With quinuclidine, the highly stable *N*-chloroquinuclidinium ion is formed[5] and reaction proceeds no further. By contrast, TED undergoes both carbon–carbon and carbon–nitrogen bond scission in an oxidative fragmentation reaction.[6]

Oxidative fragmentation of TED can occur both by two-electron processes, as most likely happens with perchloryl fluoride,[7] and by one-electron processes, as with chlorine dioxide.[1] By whatever process, the stoichiometry of the hypochlorous acid reaction is expressed by eq 1. The simplest *mechanism* for the

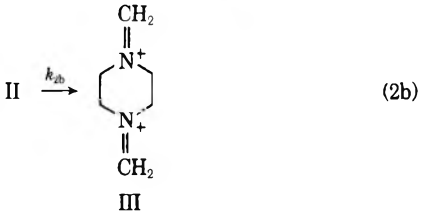


(1)

first step of reaction 1 would be the two-electron process (eq 2). Such a formulation is insufficient to explain one observed aspect of the reaction, namely, the appearance of the cation radical corresponding to

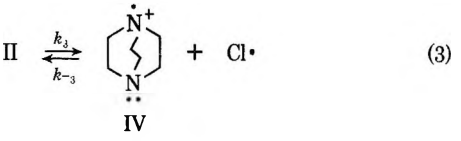


(2a)



(2b)

the loss of a single electron by TED.[8] This was tentatively identified[8] as a minor side reaction (eq 3).



(3)

In the present study, our previous investigations have been extended through the use of a stopped-flow spectrophotometric technique for kinetics, which has permitted experiments at higher pH levels and temperature. The objective was to explore more closely the role of the cation radical in reaction 1.

Results

A species, observable at 357 nm,[9] arose too rapidly (within 5 msec) for its rate of appearance to be followed. From its behavior, this ultraviolet absorber, a partial spectrum of which is shown in Figure 1, was postulated as the chloroammonium cation of triethylenediamine. Its absorptivity was proportional to the initial analytical concentration of hypochlorous acid and independent of amine concentration provided that the amine was in stoichiometric excess; therefore, the maximum ("instantaneous") concentration of this new species was assumed to be equal to the introduced concentration of hypochlorous acid. On this basis, the molar absorptivity of the chloroammonium species at 357 nm was estimated as 139 M^{-1} cm^{-1}. Attempts

(1) Previous paper of this series: G. T. Davis, M. M. Demek, and D. H. Rosenblatt, *J. Amer. Chem. Soc.*, **94**, 3321 (1972).

(2) H. Böhme and W. Krause, *Angew. Chem.*, **63**, 531 (1951).

(3) A. J. Ellis and F. G. Soper, *J. Chem. Soc.*, 1750 (1954).

(4) L. Horner and G. Podschus, *Angew. Chem.*, **63**, 531 (1951).

(5) T. Higuchi, A. Hussain, and I. Pitman, *J. Chem. Soc. B*, 626 (1969); T. Higuchi, A. Hussain, K. Ikeda, and A. Hurwitz, Final Report on Contract DA18-108-AMC-209(A), University of Wisconsin, Sept 27, 1966.

(6) W. H. Dennis, Jr., L. A. Hull, and D. H. Rosenblatt, *J. Org. Chem.*, **32**, 3783 (1967).

(7) D. M. Gardner, R. Helitzer, and D. H. Rosenblatt, *ibid.*, **32**, 1115 (1967).

(8) L. A. Hull, W. P. Giordano, D. H. Rosenblatt, G. T. Davis, C. K. Mann, and S. B. Milliken, *J. Phys. Chem.*, **73**, 2147 (1969).

(9) The ascending portion of the absorption curve at 357 nm was arbitrarily used with no attempt to locate a peak, because the absorptions of Cl(I) species were known to be negligible at this wavelength and the signal-to-noise ratio was less than at lower wavelengths.

were made to determine the dissociation constant[10] for this ion.

$$K_{assoc} = \frac{[II][OH^-]}{[I][HOCl]} = \frac{[II][OH^-]}{([I]_0 - [II])([HOCl]_0 - [II])} \times \frac{[H^+] + 5.89 \times 10^{-8}}{[H^+]} \frac{[H^+] + 1.18 \times 10^{-9}}{[H^+]}$$

The values obtained at pH 9.22–10.47 were poor, *i.e.*, $K_{assoc} = 3.22 \pm 1.28$, but support the view that hypochlorous acid is completely converted to II in the presence of excess amine in the pH range of the kinetic experiments, 8.92–9.09.

A second species, the cation radical IV, could be monitored at 465 nm[1] without interference from other species; it has a molar absorptivity,[1] ϵ_{IV}, of 2104 ± 231 M^{-1} cm^{-1}. Under stopped-flow conditions, it was observed not only at steady state (*i.e.*, about 500–20,000 msec after mixing), but also under applicable pre-steady-state conditions[11] (*i.e.*, about 5–50 msec after mixing).

The formation of II was complete in <5 msec. Its disappearance, over periods of 150–20,000 msec from the time of mixing, followed first-order kinetics, with the first-order rate constants, k_t, shown in Table I.

TABLE I

CONSTANTS FOR FIRST-ORDER DISAPPEARANCE OF II AT 357 mμ (μ = 0.200; T = 25.0°)

[Total amine], M	[Initial HOCl], M	pH	k_t, sec^{-1}
0.0500	3.48×10^{-3}	8.925	0.313
0.1000	7.49×10^{-4}	9.06	0.316
0.1000	7.49×10^{-4}	9.06	0.356
0.1000	3.75×10^{-3}	8.97	0.354
0.1000	3.75×10^{-3}	8.97	0.296
0.0100	7.54×10^{-4}	9.09	0.416
0.0100	7.54×10^{-4}	9.09	0.398
0.0100	6.95×10^{-4}	8.99	0.457[a]
0.544	3.48×10^{-3}	9.05	0.266[b]
0.544	3.48×10^{-3}	9.05	0.285[b]
0.0100	7.54×10^{-4}	9.09	0.525[a]
0.0100	7.54×10^{-4}	9.09	0.443[a]
		Mean	0.350 ± 0.036

[a] Scale expansion was made to cover 70–100 or 80–100% transmittancy. Not used in calculation of mean value. [b] μ = 0.544. Amine and conjugate acid functioned as the buffer. Nitrate salt was used instead of perchlorate. Not used in calculation of mean value.

The pre-steady-state formation of IV over 5–50 msec was essentially linear and could be calculated as pseudo zero order for each experiment, *i.e.*, $\Delta[IV]/\Delta t = k_0 M$ sec^{-1}, where $[IV] = A_{IV}/\epsilon_{IV}$ and A_{IV} was the absorptivity of IV at any particular time. Data are shown in Table II.

When data for the concentrations of II and IV were plotted in various ways, for the time frame 500–20,000 msec, a linear relationship was found only when [IV] was plotted against $[II]^{1/2}$. The slopes for these plots are shown in Table III.

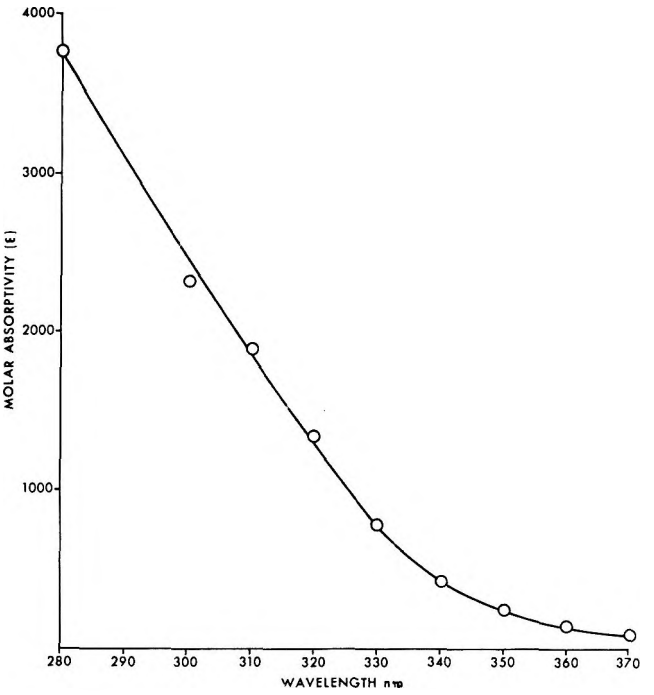


Figure 1.—Partial absorption spectrum of chlorammonium cation of triethylenediamine obtained in stopped-flow apparatus.

TABLE II

PRE-STEADY-STATE DATA FOR FORMATION OF IV (μ = 0.200; T = 25.0°)

[Total amine], M	[Initial HOCl], M	pH	k_0, M sec^{-1}
0.050	3.48×10^{-3}	8.925	0.989
0.100	7.49×10^{-4}	9.06	0.235
0.100	3.80×10^{-3}	8.97	1.269
0.0100	6.95×10^{-4}	8.99	0.235
0.544[a]	3.48×10^{-3}	9.05	0.981
0.100	7.54×10^{-4}	9.09	0.188

[a] μ = 0.544. Amine and conjugate acid functioned as the buffer. Nitrate salt was used instead of perchlorate.

Discussion

The disappearance of II can be attributed to either or both pathways shown in eq 2b and 3. Under pre-steady-state conditions, k_{-1}, even if real, may be ignored. For each of the pre-steady-state experiments reported in Table II, a first-order rate constant can be calculated by dividing k_0 by $[HOCl]_0$; this would be k_3, provided that there is no other process for production of IV. For steady-state kinetics, the experimental $k_t = k_{2b}$ (Table I). If we now add the steady-state assumption for processes 2 and 3, then $d[IV]/dt \sim k_3[II] - k_{-3}[IV][Cl\cdot]$, and, since $[Cl\cdot] \equiv [IV]$, $k_3[II] = k_{-3}[IV]^2$, whence $(k_3/k_{-3})^{1/2} = [IV]/[II]^{1/2}$. We identify these values with the values shown in Table III. From k_3 and $(k_3/k_{-3})^{1/2}$, k_{-3} can be calculated (see Table IV). Although the mechanism requires remarkable selectivity of the chlorine atom for exclusive reaction with the cation radical, we do not feel that it can be ruled out in the absence of detailed knowledge of the stability of solvated chlorine radicals in aqueous media, and in the absence of such knowledge concerning the patterns of chlorine atom reactivity

(10) The acid association constants for hypochlorous acid and monoprotonated TED at 0.200 M ionic strength were estimated as 5.89×10^{-8} and 1.18×10^{-9}, respectively, from thermodynamic data by R. Caramazza, *Gazz. Chim. Ital.*, **87**, 1507 (1957), and from ref 1.

(11) Ordinarily, a reaction observable at steady state reaches this condition too rapidly for the initial process to be studied. Only when chemical behavior can be followed over many orders of magnitude on the time scale, as with the stopped-flow apparatus, can both pre-steady- and steady-state kinetics readily be determined.

TABLE III

CONSTANTS FROM SQUARE ROOT PLOT FOR DECOMPOSITION OF CHLORAMMONIUM CATION OF TRIETHYLENEDIAMINE (μ = 0.200; T = 25.0°)

[Total amine], M	[Initial HOCl], M	pH	$[IV]/[II]^{1/2}$	$10^6 k_3/k_{-3} = 10^6 k_{4a}/k_{4c}$	$10^{-4} k_{-3}/2 = 10^{-4} k_{4c}$
0.0500	3.475×10^{-3}	8.925	2.83×10^{-3}	8.01	0.89
0.1000	7.49×10^{-4}	9.06	2.51×10^{-3}	6.30	1.13
0.1000	7.49×10^{-4}	9.06	2.67×10^{-3}	7.12	1.00
0.1000	3.746×10^{-3}	8.97	2.49×10^{-3}	6.20	1.15
0.1000	3.746×10^{-3}	8.97	2.84×10^{-3}	8.07	0.88
0.0100	7.536×10^{-4}	9.09	2.648×10^{-3}	7.01	1.01
0.0100	7.536×10^{-4}	9.09	2.751×10^{-3}	7.57	0.94
0.0100	7.536×10^{-4}	9.09	2.48×10^{-3}	6.16	1.16
				Mean	1.02 ± 0.09

TABLE IV

CONSTANTS DERIVED FROM MECHANISTIC MODELS CONSIDERED

$k_t = 0.350 \pm 0.036$ sec^{-1}
$k_3 = 0.141 \pm 0.13$ sec^{-1}
$k_{2b} = 0.371$ sec^{-1} (if pathway 3 is followed)
$k_{-3} = 2.04 \pm 0.18 \times 10^4\ M^{-1}$ sec^{-1}
$k_{4a} = 0.0713 \pm 0.0068$ sec^{-1}
$k_{2b} = 0.279$ sec^{-1} (if pathway 4 is followed)
$k_{4c} = 1.02 \pm 0.09 \times 10^4\ M^{-1}$ sec^{-1}

in water. Solvent effects on chlorine atom reactivity are known,[12] an increase in specificity being observed with charge transfer type solvation, but the cited studies have not included examination of aqueous media.

An alternative mechanism includes pathway 2b and, in place of pathway 3, takes cognizance of the more appealing concept that the electrophilic chlorine free radical is a very reactive species, and should not react with IV, which is present in quite low concentration, but should react rapidly with I, which is much more abundant. In this case there is no reverse reaction as in eq 3 and we represent the overall process as

$$\text{II} \xrightarrow{k_{4a}} \text{IV} + \text{Cl}\cdot \qquad (4a)$$

$$\text{I} + \text{Cl}\cdot \xrightarrow{\text{fast}} \text{IV} + \text{Cl}^- \qquad (4b)$$

Accordingly, $k_t = k_{2b} + k_{4a}$. We calculate k_{4a} as $k_0/2[\text{HOCl}]_0$. The final organic product, III, must be formed by the reaction

$$2\,\text{IV} \xrightarrow{k_{4c}} \text{I} + \text{III} \qquad (4c)$$

Under the steady-state assumption, $d(\text{IV})/dt = 2k_{4a}[\text{II}] - 2k_{4c}[\text{IV}]^2$. Hence $k_{4a}/k_{4c} = [\text{IV}]/[\text{II}]^{1/2}$. The disappearance of II by pathway 4, then, leads to results indistinguishable from those of pathway 3, and the data do not inherently indicate which is correct.

The constants obtained for the pathways discussed above are summarized in Table IV.

Mechanisms 3 and 4 cannot operate simultaneously, since according to eq 3 the dissociation of II must be reversible and according to eq 4 it must be irreversible (since [I] has no rate effect).

Identification of the ultraviolet-absorbing intermediate species as the chlorammonium ion follows by chemical analogy with the work of Böhme and Krause[2] and Ellis and Soper.[3] In their work, the chloroammonium ion of trimethylamine showed no ultraviolet absorption. However, some ultraviolet absorption has been observed for the stable chloroquinuclidinium ion.[5]

(12) G. A. Russell, *J. Amer. Chem. Soc.*, **80**, 4987, 4997 (1958).

While our work does not serve to establish a definite mechanism for the reaction of hypochlorous acid with triethylenediamine, it does show that *substantial* homolytic cleavage of the nitrogen–chlorine bond occurs, either in a competing equilibrium or in a process which leads to products. Also, a far *greater* amount of heterolytic cleavage occurs than homolytic cleavage in either of the postulated models; *i.e.*, mechanism A shows $k_{2b} > k_{4a}$ (Table IV), and mechanism 2 requires complete heterolytic cleavage for *product* generation. These results tend to increase confidence in the heterolytic mechanisms of Böhme and Krause[2] and Ellis and Soper[3] as being more important than the homolytic one proposed by Horner and Podschus[4] for reaction of HOCl with aliphatic amines. It is interesting to note that all of the findings of Horner and Podschus[4] which were interpreted as support for a free-radical mechanism, *except* for *polymerization initiation* by the chlorine radical, are equally accommodated by the heterolytic process described by Ellis and Soper.[3] Thus, the chlorine radicals detected by Horner and Podschus in reaction of hypochlorous acid with triethylamine are very likely a minor contributor to the overall reaction. Nevertheless, they are evidence for the corresponding production of small amounts of aminium cation radicals. It is further noteworthy that, in the hypochlorous acid–triethylenediamine system, the homolytic route would be unusually favored over the heterolytic route. There is additional thermodynamic stabilization of the cation radical due to delocalization[1] as well as kinetic stability conferred by the bridgehead structure which prevents proton loss (normal decomposition), since the latter would violate Bredt's rule. Further, the disproportionation (eq 4c) would be unusually favored, since the charge delocalization would allow easier approach of two cation radicals.

The fate of radicals generated from chloroammonium ions is an important consideration in the Hofmann–Loeffler reaction to form cyclic amines.[13] The need for *strongly acidic media* with light, heat, or free-radical initiators has been demonstrated for the reaction[14] and more recently reemphasized by Neale and coworkers.[15] The latter workers also found *addition* of aminium radicals to unsaturated hydrocarbons to be more facile and characteristic of aminium radicals than hydrogen-atom abstractions (such as postulated for the Hofmann–Loeffler rearrangement).[13] Aminium rad-

(13) M. E. Wolff, *Chem. Rev.*, **63**, 55 (1963).
(14) S. Wawzonek and J. D. Nordstrom, *J. Org. Chem.*, **27**, 3726 (1962).
(15) R. S. Neale, M. R. Walsh, and N. L. Marcus, *J. Org. Chem.*, **30**, 3683 (1965), and preceding papers.

icals have, in fact, been photolytically generated from secondary amines in strongly acidic media.[16] Paralleling our present results, spontaneous production of aminium radicals from protonated chloramines *under mild conditions* was observed,[15] and subsequent fast addition to unsaturated hydrocarbons. If ordinary aliphatic aminium radicals are generated in weakly basic, neutral, or weakly acidic aqueous media, we have found,[17] rapid loss of α protons occurs with subsequent oxidative dealkylation. Hence, the characteristic reactions of aminium ions near neutrality are different from those in strongly acidic media.

Experimental Section

Water and triethylenediamine perchlorate were purified as previously described.[1] Aqueous hypochlorous acid solutions were prepared by the procedure of Higuchi and Hasegawa.[18] The mononitrate salt was prepared analogously to the perchlorate salt, and recrystallized thrice from ethanol. It was transferred to stoppered containers in a drybox prior to weighing due to its hygroscopicity. Other salts and buffers used were of the purities previously described.[1]

For determination of hypochlorous acid, stock solutions were diluted and analyzed spectrophotometrically in the presence of excess iodide ion, as previously described,[2] using the molar absorptivity reported by Awtrey and Connick.[19]

Stopped-flow kinetics were obtained in the apparatus of ref 1, employing procedures used there. Hypochlorous acid solutions of known concentration were mixed in the apparatus 1:1 with known concentrations of triethylenediamine in buffered salt solutions to give final ionic strengths after mixing of 0.2. The chlorammonium species was observed at 357 nm and the cation radical[1] was followed at 465 nm.

Registry No.—II, 35666-89-8; IV, 35666-90-1.

(16) W. C. Danen and R. C. Rickard, *J. Amer. Chem. Soc.*, **94**, 3254 (1972).
(17) L. A. Hull, G. T. Davis, D. H. Rosenblatt, H. K. R. Williams, and R. C. Weglein, *ibid.*, **89**, 1163 (1967).
(18) T. Higuchi and J. Hasegawa, *J. Phys. Chem.*, **69**, 796 (1965).
(19) A. D. Awtrey and R. E. Connick, *J. Amer. Chem. Soc.*, **73**, 1842 (1951).

Steric Crowding in Organic Chemistry. VI. Reactivity of Tri-*tert*-butylethylene and Related Compounds[1]

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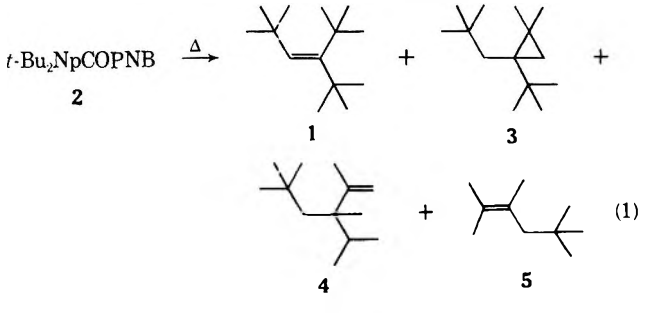
Received July 13, 1972

Pyrolysis of di-*tert*-butylneopentylcarbinyl *p*-nitrobenzoate (**2**) or benzoate (**7**) gives tri-*tert*-butylethylene (**1**), 1-*tert*-butyl-1-neopentyl-2,2-dimethylcyclopropane (**3**), and 2,3,5,5-tetramethyl-3-*tert*-butyl-1-hexene (**4**). A pathway to these products involving initial formation of an ion pair is proposed. Hydrogenation and bromination of **1** are relatively slow, presumably due to steric shielding of the double bond. Ozonation of **1** leads to cleavage of the double bond without formation of an epoxide. Hydroboration of **1** is slow and after oxidation with alkaline hydrogen peroxide gives 4-*tert*-butyl-2,2,5,5-tetramethyl-3-hexanone (**9**), *trans*-2,3-di-*tert*-butyl-4,4-dimethyltetrahydrofuran (**10**), and the expected 4-*tert*-butyl-2,2,5,5-tetramethyl-3-hexanol (**11**). Oxidation of the hydroboration product with *m*-chloroperbenzoic acid yields **10** and **11** but none of **9**. It is proposed that **9** arises from a free-radical oxidation route which competes with the retarded normal ionic oxidation by alkaline hydrogen peroxide but not with the faster ionic oxidation by *m*-chloroperbenzoic acid, while **10** is derived from cyclization of the initially formed borane to give a boron heterocycle **13** which leads to **10** on oxidation. Reaction of di-*tert*-butylacetyl chloride with *tert*-butyllithium leads to the formation of 9,11,tri-*tert*-butylcarbinol, 4-*tert*-butyl-4-hydroxy-2,2,5,5-tetramethyl-3-hexanone (**19**), 3,6-di-*tert*-butyl-5-hydroxy-2,2,7,7-tetramethyl-4-octanone (**20**), and 3,6-di-*tert*-butyl-2,2,7,7-tetramethyl-4,5-octadione (**21**). A mechanism involving radical and radical anion intermediates is proposed for this transformation.

There is a continuing intense interest in the influence of steric strain on the properties of olefins.[2b,3] These studies have involved olefins that are strained by their incorporation in rings[3a-c,e] and those strained by the presence of bulky substituents.[2b,4]

As part of a study of the effects of extreme steric crowding on the physical and chemical properties of organic compounds, tri-*tert*-butylethylene (**1**) has been prepared in this laboratory. Its synthesis has been described,[2b,4] as well as some aspects of its chemical reactivity[4] and studies of the effect of crowding on the Raman,[4] ultraviolet,[2b] and ^{13}C nmr[2c] spectra of olefins. This report contains a description of a number of chemical reactions of **1** and some related compounds which are potential precursors to a compound which is an as yet unrealized synthetic goal in this laboratory: tetra-*tert*-butylethylene. The unusual course taken in some of these reactions illustrates the remarkable influence of extreme steric crowding in affecting chemical reactivity.

Preparation of Tri-*tert*-butylethylene (1).—This synthesis was accomplished by the pyrolysis of di-*tert*-



(1)

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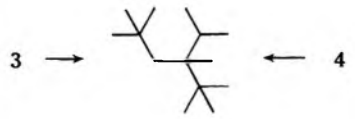
(1) Acknowledgment is made to the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. Part V, ref 2a; part IV, ref 2b; part VII, ref 2c.

(2) (a) G. J. Abruscato and T. T. Tidwell, *J. Amer. Chem. Soc.*, **94**, 672 (1972); (b) G. J. Abruscato, R. G. Binder, and T. T. Tidwell, *J. Org. Chem.*, **37**, 1787 (1972); (c) G. J. Abruscato, P. D. Ellis, and T. T. Tidwell, *Chem. Commun.*, 988 (1972).

(3) (a) C. C. Levin and R. Hoffmann, *J. Amer. Chem. Soc.*, **94**, 3446 (1972); (b) G. L. Buchanan and G. Jamieson, *Tetrahedron*, **28**, 1123, 1129 (1972); (c) W. L. Mock, *Tetrahedron Lett.*, 475 (1972); (d) L. Radom, J. A. Pople, and W. L. Mock, *ibid.*, 479 (1972); (e) R. Keese and E.-P. Krebs, *Angew. Chem., Int. Ed. Engl.*, **11**, 518 (1972).

(4) G. J. Abruscato and T. T. Tidwell, *J. Amer. Chem. Soc.*, **92**, 4125 (1970).

butylneopentylcarbinyl *p*-nitrobenzoate (**2**), which gave **1**, the cyclopropane **3**, the rearranged olefin **4**, and the fragmentation product **5** in isolated yields after gas chromatographic separation of 26, 10, 13, and about 1%, respectively. Compounds **3** and **4** were characterized by their spectral properties, analyses, and hydrogenation to the same product: methylisopropyl-*tert*-butylneopentylmethane (**6**). Compound **5** was identified by its spectral properties and its reported[5] formation as a by-product in the dehydration of di-*tert*-butylneopentylcarbinol.



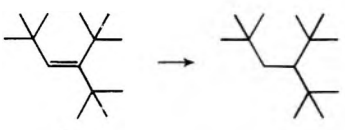
6

The hydrogenolysis of the cyclopropane **3** to **6** proceeded with some difficulty. Thus, no reaction was observed on treatment of **3** with PtO_2 in glacial acetic acid at 95° and 55 psi of hydrogen, or with Raney nickel in methanol at 110° and 1700 psi of hydrogen. Reaction at 25° and 60 psi of hydrogen with PtO_2 in acetic acid containing perchloric acid gave 90% starting material and 10% **6**. Compound **3** was shown to be stable to the reaction conditions including the perchloric acid but excluding the hydrogen.

The preparation of *p*-nitrobenzoate **2**, the precursor of **1**, by the published procedure[5] has been reported[5c] to involve "great difficulty" and in our hands gives variable yields in the range of 20–50%. The corresponding benzoate, di-*tert*-butylneopentylcarbinyl benzoate (**7**), was prepared by the use of the more soluble benzoyl chloride in 47% yield, and this reaction appeared to be more reproducible than the synthesis of the *p*-nitro derivative. Ester **7** was less reactive than **2**, but on pyrolysis at 225° and atmospheric pressure gave a 41% yield of purified **1**, as well as **3**–**5** and an additional product tentatively identified as 4-*tert*-butyl-2,6,6-trimethyl-2-heptene, presumably derived from acid-catalyzed ring opening of **3**. It has also been reported[5] that dehydration of di-*tert*-butylneopentylcarbinol by various techniques gives zero to good yields of **1**.

The formation of products of rearrangement and fragmentation in the pyrolyses of **2** and **7** suggests that these reactions proceed by ion pairs of carbonium ions and benzoate anions, as opposed to concerted elimination pathways. The formation of **1**, **3**, and **4** in the solvolysis of **2** supports this hypothesis. Formation of cyclopropane **3** as a product from a reaction involving a tertiary carbonium ion is most unusual. To our knowledge the only other reported examples of such processes involve deaminations of polycyclic amines,[7] although protonated cyclopropane intermediates have been invoked in rearrangements of tertiary cations in strong acids.[8,9] Since our initial publication[4] dehydrations of alcohols have also been observed[5b] to give rise to **3** and related cyclopropanes.

Hydrogenation of 1.—Treatment of **1** with 60 psi of hydrogen over PtO_2 in glacial acetic acid gave a product containing 20% unreacted **1** and 80% of the saturated hydrocarbon 3-*tert*-butyl-2,2,5,5-tetramethylhexane (**8**).



1 8

Under similar conditions **4** was completely hydrogenated to **6**, suggesting some steric inhibition to hydrogenation in the crowded **1**. This phenomenon has been observed previously for 1,1-dineopentylethylene[10] and hexaisopropenylbenzene.[11]

Bromination.—Addition of bromine to **1** in CCl_4 in the dark at 25° resulted in rapid but not instantaneous decoloration of the bromine and evolution of acidic vapor. The nmr spectrum of the reaction product showed a large number of signals in regions ascribable to the protons of aliphatic bromides and rearranged olefins. The product was not characterized further. Apparently addition–elimination and rearrangement pathways for the reaction were predominating, as would be expected for the crowded structure. Such reactions apparently occur in the bromination of 1,1-dineopentylethylene,[10] hexaisopropenylbenzene,[11] and α,o,o,p-tetramethylstyrene.[12a] Qualitatively **1** did not decolorize bromine as fast as did cyclohexene, showing that there was a steric barrier to the initial electrophilic attack. Quantitative rate studies for bromination of **1** confirm the low reactivity of this olefin.[12b]

Ozonolysis.—The reaction of **1** with ozone proceeded normally and gave as the only observed products di-*tert*-butyl ketone and pivalaldehyde (eq 2). Thus, **1**

$$t\text{-BuCH}{=}\underset{\mathbf{1}}{\text{C}}\text{-}t\text{-Bu}_2 \xrightarrow[2.\ (\text{MeO})_3\text{P}]{1.\ O_3} t\text{-BuCH}{=}\text{O} + t\text{-Bu}_2\text{C}{=}\text{O} \quad (2)$$

differs from hexaisopropylbenzene, which does not react with ozone,[11] and various other crowded olefins which give epoxides on ozonation.[13] The possibility remains that an intermediate epoxide may have been destroyed by excess ozone or trimethyl phosphite.

Hydroboration.—The reaction of **1** with diborane proceeded slowly so that relatively long reaction times were needed to avoid the recovery of substantial amounts of starting material. Hydroboration of **1** with *in situ* generation of diborane, followed by oxidation with alkaline hydrogen peroxide, gave 35% 4-*tert*-butyl-2,2,5,5-tetramethyl-3-hexanone (**9**), 32% *trans*-2,3-di-*tert*-butyl-4,4-dimethyltetrahydrofuran (**10**), and

(5) (a) J. E. Dubois, J. S. Lomas, and D. S. Sagatys, *Tetrahedron Lett.*, 1349 (1971); (b) J. S. Lomas, D. S. Sagatys, and J.-E. Dubois, *ibid.*, 165 (1972); (c) *ibid.*, 599 (1971).

(6) P. D. Bartlett and T. T. Tidwell, *J. Amer. Chem. Soc.*, **90**, 4421 (1968).

(7) W. G. Dauben and P. Laug, *Tetrahedron*, **20**, 1259 (1964).

(8) G. M. Kramer, *J. Amer. Chem. Soc.*, **92**, 4344 (1970); (b) M. Saunders and P. Vogel, *ibid.*, **93**, 2559, 2561 (1971).

(9) An additional example of cyclopropane formation from a tertiary carbonium ion has been observed in the solvolysis of phenyl di-*tert*-butylcarbinyl *p*-nitrobenzoate: H. Tanida and H. Matsumura, *ibid.*, in press.

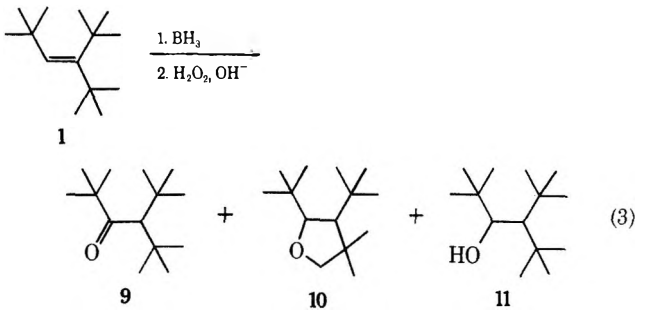
(10) P. D. Bartlett, G. L. Fraser, and R. B. Woodward, *J. Amer. Chem. Soc.*, **63**, 495 (1941).

(11) E. M. Arnett, J. M. Bollinger, and J. C. Sanda, *ibid.*, **87**, 2050 (1965).

(12) (a) E. S. Huyser and L. Kim, *J. Org. Chem.*, **33**, 1243 (1968); (b) J.-É. Dubois and M. Loizos, *C. R. Acad. Sci., Ser. C.*, **274**, 1130 (1972).

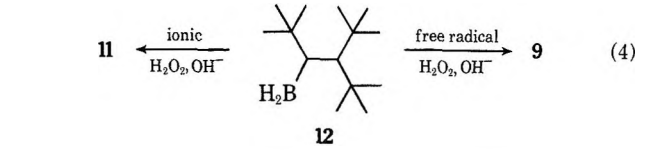
(13) (a) P. D. Bartlett and M. Stiles, *J. Amer. Chem. Soc.*, **77**, 2806 (1955); (b) P. S. Bailey, J. W. Ward, and R. E. Hornish, *ibid.*, **93**, 3552 (1971).

21% 4-*tert*-butyl-2,2,5,5-tetramethyl-3-hexanol (**11**) (eq 3). Ketone **9** and alcohol **11** were identified by their



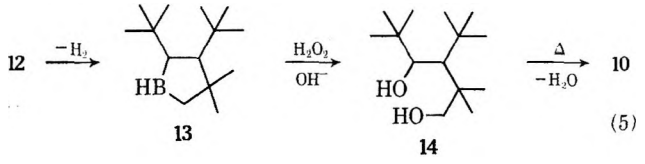
spectral properties, the oxidation of **11** to **9** with chromic acid, and the independent synthesis of **9** and **11** by the reaction of di-*tert*-butylacetyl chloride with *tert*-butyllithium (*vide infra*).[14] The nmr spectrum of **11** is unique in that the geminal *tert*-butyl groups are diastereotopic and nonequivalent in the nmr. To our knowledge **11** and compound **20** (*vide infra*) are the only examples of compounds with *tert*-butyl groups rendered nonequivalent by a neighboring asymmetric atom. The tetrahydrofuran **10** was identified on the basis of its spectral properties and elemental analysis, and tentatively assigned the trans arrangement of the *tert*-butyls on the basis of steric considerations. The spin–spin coupling between the 2,3 hydrogens in **10** is 5 Hz, which is consistent with but not definitive for the trans geometry.[15]

Ketone **9** is probably formed by a free-radical reaction of borane **12**. It has been proposed[16] that radical reactions of boranes in basic solutions of hydrogen peroxide may become important when the normal ionic oxidations are made less favorable, as may be the case with the highly crowded **12**. Confirmatory evidence for this hypothesis was obtained by the reaction of **12** with the more effective oxidizing agent *m*-



chloroperbenzoic acid,[17] which gave a mixture of products including the normal alcohol **11** but no ketone.

The presumed route for the formation of the tetrahydrofuran **10** involves cyclization of **12** to borane **13**, which on oxidation either forms **10** directly or forms the diol **14** which cyclizes during the work-up (eq 5). The

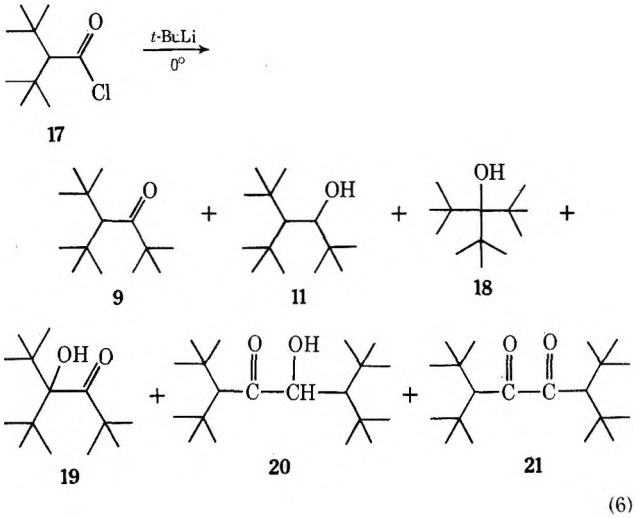


cyclization of alkylboranes is a well-known phenomenon, particularly in sterically crowded molecules.[18] Cyclic boranes yield diols on oxidation in some cases[18a,b] and cyclic ethers in others,[18c] but it may be that the latter examples involving vigorous oxidation proceed through diols, inasmuch as the crowded 3,3,4,4-tetramethylheptane-2,5-diol is known[19] to cyclize to a tetrahydrofuran at 100°.

An attempt was made to isolate the boranes formed in the reaction by omitting the oxidation step, but the only materials isolated were alcohols and carbonyl compounds of unknown structure, apparently formed by air oxidation of the boranes.

Reaction of Ethyl and Methyl Di-*tert*-butylacetates with *tert*-Butyllithium.—In an attempt to develop an alternative synthesis of the tri-*t*-butylethane skeleton the reactions of ethyl di-*tert*-butylacetate (**15**) and methyl di-*tert*-butylacetate (**16**) with *tert*-butyllithium were examined. Either of these esters with 1 equiv of *tert*-butyllithium gave di-*tert*-butylacetic acid and unreacted starting material as the only observed products. The reaction of the esters at the alkyl group presumably reflects the low reactivity of the carbonyl group due to steric hindrance, so that cleavage reactions similar to those observed between ethers and alkyllithiums[20] predominate. The cleavage of hindered esters by *tert*-butyllithium has been observed previously.[21]

Reaction of Di-*tert*-butylacetyl Chloride (17) with *tert*-Butyllithium.—Addition of *tert*-butyllithium to **17** in pentane at 0° led after work-up to the isolation of 79% of starting material (obtained as the acid after base hydrolysis) and the surprising array of products shown in eq 6. The yields of **9**, **11**, **18**, **19**, **20**, and **21** were 2, 2.5, 1, 3.6, 5%, and trace (impure), respectively.



Compounds **9** and **11** were identified by comparison with samples prepared in this work, and tri-*tert*-butylcarbinol (**18**) was identical with material prepared by

(14) Ketone **9** has been independently prepared but the only reported characterization was the carbonyl stretching frequency: J.-É. Dubois and M. Boussu, *C. R. Acad. Sci., Ser. C*, **268**, 1603 (1969).

(15) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, p 287.

(16) D. J. Pasto, S. K. Arora, and J. Chow, *Tetrahedron*, **25**, 1571 (1969).

(17) The oxidation of organoboranes with peracids has been examined previously: (a) J. R. Johnson and M. G. Van Campen, Jr., *J. Amer. Chem. Soc.*, **60**, 121 (1938); (b) G. Wilke and P. Heimbach, *Justus Liebegs Ann. Chem.*, **652**, 7 (1962).

(18) (a) T. J. Logan and T. J. Flautt, *J. Amer. Chem. Soc.*, **82**, 3446 (1960); (b) H. C. Brown, K. J. Murray, H. Müller, and G. Zweifel, *ibid.*, **88**, 1443 (1966); (c) P. F. Winternitz and A. A. Carotti, *ibid.*, **82**, 2430 (1960).

(19) M. F. Ansell, W. J. Hickerbottom, and P. G. Holton, *J. Chem. Soc.*, 349 (1955).

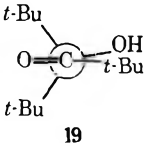
(20) G. E. Coates and K. Wade, "Organometallic Compounds," Vol. 1, 3rd ed, Methuen and Co., London, 1967, Chapter 1.

(21) (a) E. P. Kaplan, S. V. Zakharova, and A. D. Petrov, *Zh. Obshch. Khim.*, **33**, 2103 (1963); *J. Gen. Chem. USSR*, **33**, 2048 (1963); (b) A. D. Petrov, E. P. Kaplan, and M. Kurash, *Zh. Obshch. Khim.*, **32**, 19 (1962); *J. Gen. Chem. USSR*, **32**, 20 (1962).

the known route.[13a] The ketol 4-*tert*-butyl-4-hydroxy-2,2,5,5-tetramethyl-3-hexanone (**19**) was identified by its elemental analysis, infrared spectrum (OH at 3632 and C=O at 1687 cm^{-1}), nmr spectrum (two *tert*-butyls at δ 1.10 and one at 1.23, and the OH at 1.79), and independent preparation from pivalil (**22**) and *tert*-butyl-

$$t\text{-BuCOCO-}t\text{-Bu} \xrightarrow{t\text{-BuLi}} \mathbf{19}$$
22

lithium. The intramolecular hydrogen bond generally observed[22] in α-hydroxy ketones was absent in the case of **19**, presumably due to the prevalence of the conformation shown.



19

3,6-Di-*tert*-butyl-5-hydroxy-2,2,7,7-tetramethyl-4-octanone (**20**) and 3,6-di-*tert*-butyl-2,2,7,7-tetramethyl-4,5-octadione (**21**)[23] (the latter compound was obtained pure in another reaction, *vide infra*) were characterized by their elemental analyses and spectral properties. The nmr spectrum of **20** showed three *tert*-butyl absorptions, indicating magnetic nonequivalence of the two diastereotopic *tert*-butyls at C-6.

Another experiment at −70° with addition of **17** to excess *tert*-butyllithium eliminated the presence of starting material in the product and gave **9**, **11**, **18**, **20**, and **21** in isolated yields of 3.5, 9, 4, 20, and 10%, respectively. Ketol **19** was not observed.

The mechanism shown in Scheme I is proposed to account for these results, although many of these steps are speculative and reasonable alternatives can be written. *tert*-Butyllithium in alkane solutions is known to exist as tetramers,[24] and the electron-transfer process shown in eq 7–9 has been proposed as a significant reaction pathway for alkyllithiums.[25] The acyloin condensation[26] is known to occur with acid chlorides, and eq 10 suggests a plausible route to diketone **21**, which could undergo reduction by *tert*-butyllithium to form the acyloin **20**. There has been a previous report[21b] of acyloin condensation of ethyl benzoate induced by isopropyl- or *tert*-butyllithium, although the mechanism proposed[21b] involved the intervention of free lithium metal, which was presumably not present in the commercial *tert*-butyllithium in pentane utilized in this work. The diketone **21** has been obtained from the reaction of **17** with ethylmagnesium bromide and copper catalysts.[23] A radical mechanism was proposed[23] for the latter reaction, but the absence of products analogous to **18** and **19** shows that it is only superficially related to that shown in eq 6.

The formation of di-*tert*-butylmethyl radical or anion (eq 13, 14) would lead to the presence of di-*tert*-butylmethane in the product. Based on this prediction, a search was made of the volatile portion of the reaction mixture, and the presence of this compound was con-

Scheme I
Reaction of Di-*tert*-butylacetyl Chloride (**17**) with *tert*-Butyllithium

$$t\text{-Bu}_4\text{Li}_4 + t\text{-Bu}_2\text{CHCOCl} \longrightarrow \underset{\mathbf{17}}{}$$

$$t\text{-Bu}_4\overset{+\cdot}{\text{Li}}_4\text{-}t\text{-Bu}_2\text{CHCOCl}\cdot^- \quad (7)$$
23

$$\mathbf{23} \longrightarrow t\text{-Bu}_3\text{Li}_4^+ + t\text{-Bu}_2\text{CH}\underset{\text{Cl}}{\overset{\text{O}^-}{\text{C}}}\text{—}t\text{-Bu} \quad (8)$$
24

$$\mathbf{23} \longrightarrow t\text{-Bu}_4\overset{+\cdot}{\text{Li}}_4 + t\text{-Bu}_2\text{CHCOCl}\cdot^- \quad (9)$$
25

$$2\,\mathbf{25} \longrightarrow t\text{-Bu}_2\text{CH}\underset{\text{Cl}}{\overset{\text{O}^-}{\text{C}}}\text{—}\underset{\text{Cl}}{\overset{\text{O}^-}{\text{C}}}\text{H-}t\text{-Bu}_2 \xrightarrow{2\text{Cl}^-}$$

$$t\text{-Bu}_2\text{CH}\overset{\text{O}}{\overset{\|}{\text{C}}}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{H—}t\text{-Bu}_2 \quad (10)$$
21

$$\mathbf{24} \xrightarrow{-\text{Cl}^-} t\text{-Bu}_2\text{CH}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—}t\text{-Bu} \quad (11)$$
9

$$\mathbf{9} \xrightarrow{t\text{-BuLi}} \text{CH}_2\text{=C(CH}_3)_2 + t\text{-Bu}_2\text{CH}\overset{\text{OLi}}{\text{CH}}\text{—}t\text{-Bu} \quad (12)$$

$$\mathbf{24} \longrightarrow t\text{-Bu}_2\dot{\text{C}}\text{H} + t\text{-BuCOCl}\cdot^- \quad (13)$$

$$\mathbf{9} \xrightarrow{t\text{-BuLi}} t\text{-Bu}_2\text{CHC(O}^-\text{)-}t\text{-Bu}_2 \longrightarrow$$
26

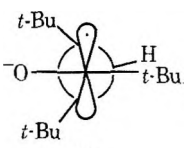
$$t\text{-Bu}_2\text{CH}^- + t\text{-Bu}_2\text{C=O} \quad (14)$$

$$t\text{-Bu}_2\text{C=O} \xrightarrow{t\text{-BuLi}} t\text{-Bu}_3\text{COLi} \quad (15)$$

$$t\text{-Bu}_2\text{C=O} + t\text{-BuCOCl}\cdot^- \xrightarrow{-\text{Cl}^-} t\text{-Bu}_2\text{C(O}\cdot\text{)CO-}t\text{-Bu}$$
27 (16)

firmed by isolation and comparison with an authentic specimen. The absence of **19** from the reaction product when **17** was added to *tert*-butyllithium is in accord with this mechanism, as the di-*tert*-butyl ketone formed would be rapidly consumed by the excess *tert*-butyllithium.

Radical Anion of 4-*tert*-Butyl-2,2,5,5-tetramethyl-3-hexanone (9).—A sample of **9** was provided to Professor G. A. Russell and coworkers, who measured the esr spectrum of ketyl **28** formed from reduction of **9** with



28

potassium in dimethoxyethane. The hyperfine splittings of the α hydrogen and the carbonyl carbon were $A_\alpha^H < 1.8$ and $A_{CO}^C = 34$ G, respectively.[27] The small magnitude of the former value supports the importance of the conformation shown, which is similar to the conformation proposed for the ketol **19**.

(22) L. Joris and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **90**, 4599 (1968).
(23) Dione **21** has been prepared independently but the full characterization has not been reported: J.-E. Dubois and M. Boussu, *Tetrahedron Lett.*, 2523 (1970).
(24) H. L. Lewis and T. L. Brown, *J. Amer. Chem. Soc.*, **92**, 4664 (1970).
(25) C. G. Screttas and J. F. Eastham, *ibid.*, **88**, 5668 (1966).
(26) S. M. McElvain, *Org. React.*, **4**, 256 (1948).
(27) G. A. Russell, D. F. Lawson, H. L. Malkus, and P. R. Whittle, *J. Chem. Phys.*, **54**, 2164 (1971).

Experimental Section

Elemental analyses were performed by Galbraith Laboratories or the Bernhardt Microanalytisches Laboratorium. Melting points and boiling points are uncorrected. Infrared spectra were run on Perkin-Elmer 257 or 337 grating spectrophotomers. Nmr spectra were run on a Varian A-60 or XL-100 spectrometer in carbon tetrachloride solution with tetramethylsilane as an internal standard. Mass spectra were obtained using a Perkin-Elmer Hitachi RMU instrument. Vapor phase chromatography was carried out using Varian Aerograph 90-P3 and 1820-1 instruments and the following columns: SE-52 (10 ft × 0.375 in., 30% SE-52 on Chromosorb W), FFAP-1 (20 ft × 0.375 in., 30% FFAP on Chromosorb W), FFAP-2 (10 ft × 0.375 in., 30% FFAP on Chromosorb W), QF-1 (10 ft × 0.375 in., 30% QF 1 on Chromosorb W), Carbowax (10 ft × 0.375 in., 30% Carbowax 20M on Chromosorb W) (all used on 90-P3), SE-30 (10 ft × 0.375 in., 30% SE-30 on Chromosorb W), and DEGS (10 ft × 0.375 in., 30% DEGS on Chromosorb W) (last two used on 1820-1).

Tri-*tert*-butylethylene (1).—The preparation and physical properties of this compound have been described.[2b,4] The first fraction from the vpc separation (SE-52, 165°, 100 ml/min He) of the product from pyrolysis of 15.5 g (0.0428 mol) of di-*tert*-butylneopentylcarbinyl *p*-nitrobenzoate (**2**) appeared to be a trace of **1,2,2-trimethyl-1-neopentylethylene (5)**:[5] nmr (CCl_4) δ 0.99 (s, 9, *t*-Bu), 1.64 (s, 9, 3 Me), and 1.98 (s, 2, CH_2Bu); mass spectrum (70 eV) molecular ion *m/e* 140. The second vpc fraction consisted of 2.22 g (26%) of **1**, and the third fraction was separated by vpc (FFAP-1, 80°, 75 ml/min He) into two components. The first component, retention time 4 hr, was 0.84 g (10%) of **1-*tert*-butyl-1-neopentyl-2,2-dimethylcyclopropane (3)**: ir (CCl_4) 3060 cm^{-1} (cyclopropyl CH); near-ir[28] (CCl_4) 6115 cm^{-1} (cyclopropyl overtone); nmr (CCl_4) δ 0.65 (s, 2, CH_2 of cyclopropyl), 1.00 (s, 9, *t*-Bu), 1.02 (s, 9, *t*-Bu), 1.12 (s, 3, Me), 1.38 (s, 3, Me), and 1.60 and 1.74 (center peaks of an AB quartet of diastereotopic CH_2 of the neopentyl, J = 16 Hz); mass spectrum (70 eV) molecular ion *m/e* 196.

Anal. Calcd for $C_{14}H_{28}$ (196.38): C, 85.63; H, 14.37. Found: C, 85.00; H, 14.95.

The second component, retention time 4.5 hr, was 1.09 g (13%) of **3-*tert*-butyl-2,3,5,5-tetramethyl-1-hexene[6] (4)**: ir (CCl_4) 1625 cm^{-1} (C=C); nmr (CCl_4) δ 0.90 (s, 9, *t*-Bu), 0.99 (s, 9, *t*-Bu), 1.15 (s, 3, saturated Me), 1.20 and 1.45 (center peaks of an AB quartet of the diastereotopic CH_2 of the neopentyl, J = 15 Hz), 1.82 (d, 3, vinyl Me, J = 2 Hz), 4.79 (d, 1, vinyl H, J = 2 Hz), and 4.95 (m, 1, vinyl H, J = 2 Hz); mass spectrum (70 eV) molecular ion *m/e* 196.

Anal. Calcd for $C_{14}H_{28}$ (196.38): 85.63; H, 14.37. Found: C, 85.16; H, 14.71.

Hydrogenolysis of 3.—Cyclopropane **3** (85 mg, 0.4 mmol) was treated with 60 psi of hydrogen and 86 mg of PtO_2 in 10 ml of glacial acetic acid containing one drop of 70% perchloric acid for 23 hr at 25°. The mixture was filtered and the filtrate was made basic with KOH solution and extracted with pentane. The pentane was washed with saturated NaCl, dried (Drierite), concentrated, and separated by vpc (FFAP-1, 125°, 80 ml/min He) into two components. The major component was unreacted **3** (90%). The second component was 10% of **4-*tert*-butyl-2,2,4,5-tetramethylhexane (6)**: nmr (CCl_4) δ 0.92 (s, 9, *t*-Bu), 1.02 (s, 9, *t*-Bu), 1.01 (d, 6, $CHMe_2$, J = 8 Hz), 1.11 (s, 3, Me), 1.43 (q, 2, diastereotopic CH_2, J = 18 Hz), and 2.08 (septet, 1, $HCMe_2$, J = 8 Hz).

Anal. Calcd for $C_{14}H_{30}$ (198.40): C, 84.76; H, 15.24. Found: C, 84.90; H, 15.08.

Repetition of the experiment in the absence of hydrogen gave only unreacted **3**. Hydrogenation of **4** under similar conditions but without perchloric acid gave only **6**.

Di-*tert*-butylneopentylcarbinyl benzoate (7) was prepared according to the procedure for the *p*-nitrobenzoate **2**, with benzoyl chloride in pentane being added to the lithium salt of di-*tert*-butylneopentylcarbinol in pentane. Fractional crystallization from pentane gave 47% of **7**: mp 64–68°; nmr (CCl_4) δ 1.10 (s, 9, *t*-Bu), 1.30 (s, 18, 2 *t*-Bu), 2.42 (s, 2, CH_2), and 7.3–7.9 (m, 5, aromatic).

Pyrolysis of 7.—Benzoate **7** (16 g, 0.49 mol) was heated slowly to 225° in a glass tube with an outlet to a Dry Ice trap at atmospheric pressure. The tube was cooled and rinsed with pentane, and the solid benzoic acid was filtered off. The filtrate was separated by vpc (SE-52, 135°, 75 ml/min He) into five fractions: 0.16 g (0.25%) of the material tentatively identified as **5** (*vide supra*), 0.5 g (5%) of material tentatively identified as 4-*tert*-butyl-2,6,6-trimethyl-2-heptene (presumably derived from **3**), nmr (CCl_4) δ 0.80 (s, 9, *t*-Bu), 0.82 (s, 9, *t*-Bu), 1.23 (m, 2, CH_2), 1.59 (d, 3, Me, J = 2 Hz), 1.67 (d, 3, Me, J = 2 Hz), 1.96 (m, 1, HC-*t*-Bu), and 4.89 (d, 1, vinyl H, J = 10 Hz), 0.4 g of an unidentified olefin, 3.94 g (41%) of **1**, and a mixed fraction. This last fraction was separated by vpc (DEGS, 80°, 50 ml/min He) into 0.63 g (7%) of **3** and 2.37 g (25%) of **4**.

Solvolysis of 2.—A solution of 208 mg (0.5 mmol) of **2** in 100 ml of 60% aqueous dioxane was put into a constant temperature bath at 55° for 25 hr. The dioxane solution was diluted with water and extracted with pentane. The pentane extract was washed with saturated NaCl, dried (Drierite), and concentrated. Separation by vpc (FFAP-1, 110°, 75 ml/min He) afforded 10% of **1**, 5% of **3**, 5% of an unidentified olefin, and 80% of **4**.

Hydrogenation of 1.—A mixture of 138 mg (0.73 mmol) of **1** and 39 mg of PtO_2 in 20 ml of glacial HOAc was shaken for 11 hr in a Parr hydrogenation apparatus at a pressure of 60 psi of hydrogen. The mixture was filtered and the filtrate was diluted with water and extracted with pentane. The pentane extract was washed with saturated Na_2CO_3 and NaCl, dried (Drierite), and concentrated. Separation of the residue by vpc (Carbowax, 130°, 75 ml/min He) afforded 88% of unreacted **1** and 12% of material assigned the structure **3-*tert*-butyl-2,2,5,5-tetramethylhexane (8)**: nmr (CCl_4) δ 0.93 (s, 9, *t*-Bu), 1.01 (s, 18, 2 *t*-Bu), and 1.2–1.5 (undefined, overlapping multiplets due to $-CH_2$ and $-CH$).

Anal. Calcd for $C_{14}H_{30}$ (198.40): C, 84.76; H, 15.24. Found: C, 85.01; H, 14.97.

Hydrogenation of 183 mg (0.935 mmol) of **1** with 145 mg of PtO_2 in 10 ml of acetic acid for 24 hr at 60 psi of hydrogen gave after vpc separation a 50% recovery of material consisting of 20% unreacted **1** and 80% **8**. These were the conditions under which **4** underwent complete hydrogenation.

Ozonolysis of 3.—A solution of the olefin (186 mg, 0.95 mmol) in 50 ml of dry CH_2Cl_2 was put into a glass tube fitted with a fritted bubbler extending to its bottom. Ozone (generated by a Welsbach ozonator) was bubbled into the solution at −70°. A trap containing 2% aqueous KI was placed to receive the effluent gases from the reaction tube, and after 15 min began showing evidence of an excess of ozone by turning slightly yellow. After another 15 min, the KI solution was colored a dark orange. The bubbling was continued for an additional 15 min to ensure complete reaction. The reaction mixture was transferred to a flask and stirred overnight with 50 ml of trimethyl phosphite. After removal of the CH_2Cl_2 by distillation, the solution was analyzed by vpc (QF-1, 125°, 75 ml/min He) and found to contain pivalaldehyde and di-*tert*-butyl ketone by comparison of their retention times with those of authentic material; no starting material was observed. The solution was made basic with aqueous NaOH to hydrolyze the trimethyl phosphite and was extracted with pentane. The pentane extract was washed with water and saturated NaCl, dried (Drierite), and concentrated. Separation by vpc (QF-1, 100°, 75 ml/min He) of the residue yielded a small amount of pivalaldehyde and 50 mg (37%) of di-*tert*-butyl ketone. There was not a sufficient amount of the aldehyde to obtain definitive spectral data, but it was enough to yield a DNPH derivative melting at 204–209° (lit.[29] mp 209°). The identity of the ketone was confirmed by ir and nmr spectral comparison with that of authentic material.

Bromination of 1.—The olefin (72.4 mg, 0.37 mmol) in 1 ml of CCl_4 was put into a flask and wrapped with aluminum foil to keep out light, and 2 ml of a 0.172 *M* solution of bromine in CCl_4 was added slowly in the dark. During the addition acidic vapors, assumed to be HBr, were evolved. An nmr spectrum of the reaction mixture, after the disappearance of the bromine color, showed a multitude of peaks at δ 1.5–2 ppm presumably due to $BrCCH_3$ and/or vinyl methyl groups; at δ 3–4 ppm due to BrCH and/or $BrCH_2$; and at δ 5–6 ppm due to vinyl protons other than the vinyl hydrogen of the starting material.

Hydroboration–Oxidation of 1.[30]—A 100-ml flask, equipped with a magnetic stirrer and an addition funnel and protected

(28) Determined with a Cary 14 ultraviolet–visible spectrophotometer.

(29) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "Systematic Identification of Organic Compounds," 5th ed, Wiley New York, N. Y., 1965, p 320.

(30) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).

from outside moisture with a drying tube, was charged with 1.08 g (5.5 mmol) of 1 and 0.68 g (18 mmol) or $NaBH_4$ in 3 ml of anhydrous THF. The flask was immersed in an ice bath and 3.46 g (24.3 mmol) of $BF_3 \cdot OEt_2$ in 5 ml of anhydrous THF was added over 35 min with stirring. The mixture was stirred at 0° for 2.5 hr and then at 25° for 18 hr. The excess hydride was decomposed with water and the solution was made basic with 5 ml of 3 *N* NaOH. The mixture was heated to 40–50° and 5 ml of 30% H_2O_2 was added dropwise with stirring. The reaction mixture was then stirred at 25° for 9 hr, saturated with NaCl, and extracted with ether. The ethereal extract was dried (Drierite), concentrated, and separated into four fractions by vpc (SE-30, 200°, 75 ml/min He). The first fraction consisted of a trace amount of unreacted starting material. The second amounted to 0.375 g (35%) of **4-*tert*-butyl-2,2,5,5-tetramethyl-3-hexanone (9)**:[14] ir (CCl_4) 1688 cm^{-1} (lit.[14] ir 1688.4 cm^{-1}); nmr (CCl_4) δ 1.07 (s, 18 2 *t*-Bu), 1.18 (s, 9, *t*-Bu), and 2.89 (s, 1, HCC=O).

Anal. Calcd for $C_{14}H_{28}O$ (212.38): C, 79.18; H, 13.29. Found: C, 79.06; H, 13.25.

The third fraction was 0.369 g (32%) of **trans-2,3-di-*tert*-butyl-4,4-dimethyltetrahydrofuran (10)**: nmr (CCl_4) δ 0.97 (s, 9, *t*-Bu), 1.04 (s, 9, *t*-Bu), 1.12 (s, 3, Me), 1.23 (s, 3, Me), 1.55 (d, 1, HCCO, J = 5 Hz), 3.31 (s, 2, CH_2), and 3.59 (d, 1, HCO, J = 5 Hz).

Anal. Calcd for $C_{14}H_{28}O$ (212.38): C, 79.18; H, 13.29. Found: C, 78.98; H, 13.07.

The last fraction, 0.249 g (21%), was identified as **4-*tert*-butyl-2,2,5-5-tetramethyl-3-hexanol (11)**: ir (CCl_4) 3630 cm^{-1} (OH); nmr (CCl_4) δ 0.97, 1.08, and 1.15 (each s, 9, *t*-Bu), 1.41 (s, 1, OH), 1.43 (broad s, 1, HCCOH), and 3.75 (broad s, 1, HCOH).

Anal. Calcd for $C_{14}H_{30}O$ (214.39): C, 78.43; H, 14.10. Found: C, 78.21; H, 13.93.

Oxidation of 11 with chromic acid in acetone gave 9, but treatment of 11 under the oxidative work-up conditions of the hydroboration above gave only recovered alcohol.

Hydroboration of 1 in diglyme with external generation of diborane by the published procedure[30] but a reaction period of 8 hr gave after oxidation 9 and 10 in the ratio of 3:2 as the only products.

Hydroboration of 1 in THF for 4 hr followed by the addition of excess *m*-chloroperbenzoic acid in chloroform and stirring for 2 hr gave after treatment with base and extraction a product which contained unreacted 1, several unidentified compounds, and 10 and 11 in the ratio of 1:4. No ketonic products were observed in the infrared spectrum of the crude reaction mixture or in any of the components isolated by vpc.

Reaction of Pivalil (22) with *tert*-Butyllithium.—*tert*-Butyllithium (31.1 mmol, obtained as a 1.6 *M* solution in pentane from the Foote Mineral Co.) was placed in a 100-ml flask and immersed in a Dry Ice–isopropyl alcohol bath. Pure **22** (0.9 g, 5.3 mmol) in 1 ml of anhydrous pentane was added dropwise over 3 min at −70° with stirring under an atmosphere of helium. The reaction was stirred at −70° for 1 hr, allowed to warm slowly to 25°, and then stirred for an additional 30 min. The reaction mixture was cooled to −60° and water was added to stop reaction. After extraction with pentane, the pentane was washed with saturated NaCl, dried (Drierite), concentrated, and separated by vpc (SE 30, 175°, 75 ml/min He) into four components. The first was 40% of unreacted **22**, then next was 40% of pivaloin, the third was about 5% of an unidentified alcohol, and the last was about 15% of **4-*tert*-butyl-4-hydroxy-2,2,5,5-tetramethyl-3-hexanone (19)**: mp 112–116°; ir (CCl_4) 3632 (OH) and 1687 cm^{-1} (C=O); nmr (CCl_4) δ 1.10 (s, 18, 2 *t*-Bu), 1.23 (s, 9, *t*-Bu), and 1.79 (s, 1, OH).

Anal. Calcd for $C_{14}H_{28}O_2$ (228.38): C, 73.63; H, 12.36. Found: C, 73.70; H, 12.19.

Addition of tert-Butyllithium to Ethyl Di-tert-butylacetate (15).—*tert*-Butyllithium (100 ml, 0.125 mol) was added dropwise over 1 hr to 24.5 g (0.122 mol) of **15** [prepared from di-*tert*-butylacetyl chloride (**17**)[31] and ethanol] in 25 ml of anhydrous pentane with stirring under helium. The reaction was refluxed for 30 min and then decomposed with ice and concentrated H_2SO_4. The pentane layer was separated, washed with saturated solutions of Na_2CO_3 and NaCl, dried (Drierite), concentrated, and distilled at reduced pressure to give 14 g (57%) of unreacted **15**.

Acidification of the basic Na_2CO_3 wash yielded 7.5 g (36%) of di-*tert*-butylacetic acid.[31] No other products were detected upon analysis of the recovered ester and the residue from the distillation by vpc.

Addition of *tert*-Butyllithium to Methyl Di-*tert*-butylacetate (16).—*tert*-Butyllithium (55 ml, 0.068 mol) was added over 1 hr to a solution of 12.5 g (0.067 mol) of **16** [prepared from di-*tert*-butylacetyl chloride (**17**)[31] and methanol] in 25 ml of anhydrous pentane while stirring under helium. The solution was refluxed for 15 min and worked up as in the preceding example to give 1.2 g (9.5%) of unreacted starting material and 10.3 g (90%) of di-*tert*-butylacetic acid.

Addition of *tert*-Butyllithium to Di-*tert*-butylacetyl Chloride (17).—*tert*-Butyllithium (30 ml, 0.038 mol) was added dropwise at 0° over 30 min to a solution of 7 g (0.037 mol) of **17**[31] in 15 ml of anhydrous pentane with stirring and with helium flowing through the system. The reaction was refluxed for 30 min and then decomposed onto ice. The pentane layer was separated, washed with aqueous NaOH and saturated NaCl, dried (Drierite), concentrated, and refrigerated to yield 0.6 g of an impure solid after filtration. This solid was separated by fractional sublimation into 0.3 g (3.6%) of **4-*tert*-butyl-4 hydroxy-2,2,5,5-tetramethyl-3-hexanone (19)** and 0.3 g (5%) of **3,6-di-*tert*-butyl-5-hydroxy-2,2,7,7-tetramethyl-4-octanone (20)**: mp 163–167°; ir (CCl_4) 3480 (OH) and 1699 cm^{-1} (C=O); nmr (CCl_4) δ 1.07 (s, 18, 2 *t*-Bu), 1.15 (s, 9, *t*-Bu), 1.16 (s, 9, *t*-Bu), 1.95 (d, 1, HCCOH, J = 2 Hz), 2.58 (s, 1, HCC=O), 3.01 (d, 1, OH, J = 5 Hz), and 4.28 (d, 1, CHOH, J = 5 Hz, fine splitting, J = 2 Hz).

Anal. Calcd for $C_{20}H_{40}O_2$ (312.54); C, 76.86; H, 12.90. Found: C, 77.02; H, 13.00.

The filtrate from the crystallization above was separated by vpc (SE-52, 150°, 75 ml/min He) into five components. The first component, tri-*tert*-butylcarbinol (**18**),[13a] was estimated to be a 1% yield based on the relative peak height of the chromatogram. The second component was less than a 1% yield of an unidentified solid. The third component consisted of 0.16 g (*ca.* 2%) of **9**, and the fourth amounted so 0.75 g (9.5%) of **11**. The last component was a small amount of a yellow liquid, apparently impure **21** (*vide infra*).

Acidification of the basic NaOH wash yielded *ca.* 5 g (78%) of di-*tert*-butylacetic acid.

Addition of Di-*tert*-butylacetyl Chloride (17) to *tert*-Butyllithium.—A solution of 5 g (26.2 mmol) of **17** in 10 ml of anhydrous pentane was added dropwise over 15 min at −70° to 88 mmol of *tert*-butyllithium with stirring and with helium flowing through the system. The reaction was stirred for 30 min while the temperature of the Dry Ice–isopropyl alcohol bath, in which the reaction flask was immersed, rose to −20°. At this temperature, water was added to stop the reaction. The pentane layer was separated, washed with aqueous NaOH and saturated NaCl, dried (Drierite), concentrated, and refrigerated to yield 0.8 g (20%) of **20**. The filtrate gave up an additional orange, crystalline solid upon standing for several days. This solid was filtered off and after column chromatography on silica gel with pentane gave 0.4 g (10%) of a bright yellow solid identified as **3,6-di-*tert*-2,2,7,7-tetramethyl-4,5-octadione (21)**: mp 123–128°; ir (CCl_4) 1700 cm^{-1} (C=O); nmr (CCl_4) δ 1.02 (s, 36, 4 *t*-Bu), and 3.65 (s, 2, HC-*t*-Bu_2).

Anal. Calcd for $C_{20}H_{38}O_2$ (310.52): C, 77.36; H, 12.33. Found: C, 77.28; H, 12.26.

The mother liquor remaining after filtration of the above two solids was separated into three fractions by column chromatography on Woelm neutral alumina, eluting with pentane. Each fraction obtained was further purified by vpc (SE-52, 150°, 75 ml/min He) to give 0.2 g (4%) of **18**, 0.2 g (3.5%) of **9**, and 0.5 g (9%) of **11**. Acidification of the basic NaOH wash yielded about 0.1 g (2%) of di-*tert*-butylacetic acid.

Registry No.—**1**, 28923-90-2; **3**, 36146-53-9; **4**, 36146-54-0; **6**, 28923-92-4; **7**, 36146-56-2; **8**, 36191-47-6; **9**, 24534-83-6; **10**, 36138-82-6; **11**, 36146-58-4; **19**, 36146-59-5; **20**, 36146-60-8; **21**, 29679-00-3.

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Alkylation of Benzene with 8-Methyl-1-nonene. V. Effect of the Catalyst on the Isomerization of Secondary Carbonium Ions

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8-Methyl-1-nonene alkylates benzene in the presence of Friedel–Crafts catalysts to afford various amounts of secondary and tertiary alkylbenzenes. With $AlCl_2 \cdot HSO_4$ the positive charge barely reaches the tertiary position which is eight carbon atoms away from the double bond. However, with HF and *n*-hexane the tertiary isomer accounts for more than 70% of the product alkylbenzene. Other alkylation catalysts afford results that lie between these two extremes. Very strong catalysts such as $AlCl_3 \cdot HCl$ interfere in the results by isomerizing the secondary alkylbenzenes and dealkylating the tertiary isomer. The presence of a methyl group on the alkyl chain changes the general pattern of the chromatogram of the product alkylbenzenes.

Alkylation of benzene with a long-chain olefin such as 1-dodecene in the presence of Friedel–Crafts catalysts affords all the possible phenylalkanes except the 1-phenyl isomer.[1,2] The mechanism of the reaction and the relative rates of isomerization and alkylation of the intermediate carbonium ions have been discussed in a number of publications and need not be repeated here.[1-5] The extent of the isomerization reaction depends on the experimental conditions such as choice of the catalyst, solvent, and temperature of the reaction.[4,5] This raises the interesting question as to how far down the chain does the positive charge reach before the attack on benzene takes place. Such a question cannot be answered from the alkylation of benzene with an α olefin such as 1-dodecene since an isomer such as 2-phenyldodecane can be produced from either the second or eleventh carbon atom. On the other hand, an olefin such as 8-methyl-1-nonene (1) permits the determination of the precursor of each phenylalkane.

Results and Discussion

The synthesis of 1 was carried out by standard reactions and the details are given in Experimental Section. Benzene was alkylated with 1 in the presence of various catalysts under conditions which do not permit product isomerization and the products were analyzed by gas–liquid chromatography (Figures 1a and 1b). Selected peaks of the chromatogram were identified by the use of authentic samples of methyl-substituted phenylnonanes. The 2-methyl-2-phenylnonane was obtained by alkylation of benzene with 2-methyl-1-nonene,[6] and the 2-methyl-3-phenyl, 2-methyl-4-phenyl, and 2-methyl-5-phenyl isomers were obtained by the Grignard reactions of the corresponding alkyl bromides and ketones. The resulting alcohols were dehydrated with $KHSO_4$ and the alkenes were hydrogenated in the presence of 10% palladium on charcoal. All the samples were distilled in a ten-plate column, and all showed a purity of 95% or better by glc. The other peaks were readily identified from their position in the chromatogram in a manner similar to that of straight-chain alkylbenzenes.[1,2,4]

Table I lists the amounts of the various isomers obtained. As in the reaction of benzene with 1-dodecene, HF–*n*-hexane permitted extensive isomerization of the secondary cations to the tertiary prior to alkylation. On the other hand, $AlCl_2 \cdot HSO_4$ led to relatively slower isomerization, much less 2-phenyl derivative (9.7%) and a significant rise in the amount of the 8 isomer (61.3%). This result parallels our experience with 1-dodecene and *trans*-6-dodecene, where in the presence of HF–*n*-hexane the alkylation step is sufficiently slow to permit the intermediate carbonium ions to attain the equilibrium conditions thus rendering the position of the double bond in the olefin immaterial.[4]

In the absence of *n*-hexane, *i.e.*, in the presence of HF alone, the rate of the alkylation reaction is increased relative to the isomerization reaction and the amount of the tertiary isomer decreases from 71.0 to 56.5%. The smallest amount of 2-methyl-2-phenylnonane produced in the absence of product isomerization is obtained with $AlCl_2 \cdot HSO_4$ where, in contrast to the HF–*n*-hexane system, only 9.7% is obtained (Figure 1b). This small amount of the tertiary alkylbenzene is accompanied by a significant rise in the amount of the 8 isomer (61.3%). Apparently the presence of a large anion in the ion pair slows down the isomerization reaction and permits the alkylation reaction to compete more effectively.[5,7]

Alkylation in the presence of $AlCl_3 \cdot HCl$ at 35° results in the smallest amount of the tertiary isomer. However, this is not because the charge fails to reach the end of the chain, but rather because of the vulnerability of the tertiary alkylbenzene to attack by the strong catalyst $AlCl_3 \cdot HCl$ which results in dealkylation of the product. Under these conditions the yield of alkylbenzene drops to 30%, and the reaction is accompanied by the formation of substantial amounts of isoparaffins. Under the same conditions an authentic sample of 2-methyl-2-phenylnonane suffered extensive dealkylation and even isomerization to the secondary alkylbenzenes. When the alkylation reaction is carried out at 0° and in the presence of recycled aluminum chloride, which is known to be weakened by the presence of strong organic bases,[8,9] dealkylation is suppressed, the amount of the tertiary isomer increases to 22.9%, and the yield of alkylbenzene rises to 80%. Attenuation of $AlCl_3$ with nitromethane

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(3) S. N. Patinkin and B. S. Friedman in "Friedel–Crafts and Related Reactions," Vol. II, G. Olah, Ed., Interscience, New York, N. Y., 1964, Chapter 14, p 3.
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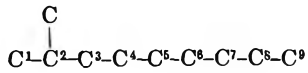
(8) G. A. Olah and M. W. Meyer, ref 3, Vol. I, p 736.
(9) N. C. Deno, *Progr. Phys. Org. Chem.*, **2**, 141 (1964).

TABLE I

GLC ANALYSIS OF 2-METHYL-*n*-PHENYLNONANE



Reaction	Catalyst	Temp, °C	Yield, %	2-Phenyl[c]	3-Phenyl[c]	4-Phenyl[c]	5-Phenyl[c]	6-Phenyl[c]	7-Phenyl[c]	8-Phenyl[c]
1	HF	0–5	88	56.5	0.8	2.9	8.9	6.5	8.9	15.5
2	HF + *n*-hexane	0–5	86	71.0	0.5	2.1	6.9	4.6	5.8	9.1
3	HF[a]	55	86	30.7	0.6	1.9	8.1	8.0	15.7	35.0
4	$AlCl_2 \cdot HSO_4$	35–40	75	9.7	0.1	0.8	4.3	5.1	18.7	61.3
5	$AlCl_3 \cdot CH_3NO_2$	35–40	75	24.8	0.5	1.8	8.6	8.3	16.7	39.3
6	$AlCl_3 \cdot HCl$	35–40	30	3.2	1.2	8.6	11.7	12.7	21.2	41.4
7	$AlCl_3 \cdot HCl$[b]	0–5	80	22.9	0.5	1.6	8.0	8.1	17.1	41.8

[a] Reaction was carried out in the absence of a liquid catalyst phase to minimize isomerization under these conditions.[5] [b] Recycled aluminum chloride was used in this experiment to prevent product isomerization or dealkylation.[4] [c] Registry no.: 2-phenyl, 36614-69-4; 3-phenyl, 36614-70-7; 4-phenyl, 36614-71-8; 5-phenyl, 36614-72-9; 6-phenyl, 36614-73-0; 7-phenyl, 36614-74-1; 8-phenyl, 36614-75-2.

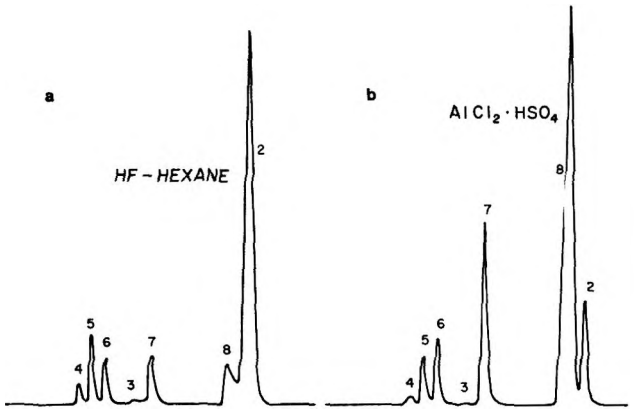


Figure 1.—Gas–liquid chromatograms for methylphenyldodecanes obtained from alkylation of benzene with 8-methyl-1-nonene in the presence of (a) HF–hexane and (b) $AlCl_2 \cdot HSO_4$.

also suppresses the dealkylation reaction and leaves the tertiary alkylbenzene intact. It is interesting to note that the amount of the 8-phenyl isomer is greater than that of the 7 isomer in spite of the fact that the positive charge is allowed to reach the other end of the chain. This indicates that the 8-carbonium ion, located near the end of the chain, reacts more rapidly with benzene than the other secondary carbonium ions and is in accord with the behavior of the dodecenes where the amount of 2-phenyldodecane is greater than that of the 3 isomer even from *trans*-6-dodecene where the positive charge is introduced near the center of the chain.[5] This is also in agreement with Nenitzescu's observation that some of the carbonium ions may react with benzene without undergoing rearrangement.[10]

An interesting feature of the isomer distributions reported in Table I is the sharp drop in the amount of the 4 and 3 isomers compared to the 5 isomer and other secondary alkylbenzenes and the subsequent rise in the amount of the tertiary alkylbenzene. Except for the case with $AlCl_3 \cdot HCl$, which involves product isomerization, the amount of the 3 isomer is below 1% of the total alkylbenzene obtained. This can also be seen from Figures 1a and 1b. Apparently the rate of the alkylation reaction from the corresponding carbonium ion is slow due to the presence of an isopropyl group next to the carbon atom carrying the positive charge. This steric factor is probably responsible for the absence of secondary alkylbenzene from the alkylation of benzene with 3-methyl-1-butene.[11] The failure of the secondary isomer to form is not only due to the great speed with which the secondary carbonium ion isomerizes to the tertiary but also to the fact that the alkylation reaction is greatly slowed down by the adjacent isopropyl group. It is quite probable that addition of only one or two more carbon atoms to the chain would result in some secondary alkylbenzene from the carbon atoms other than the one next to the isopropyl group. This conclusion is in agreement with the results of Geiseler, *et al.*, on the alkylation of benzene with 1-heptene in which they find the isomerization of the double bond to be only about six times faster than the alkylation reaction.[12]

As noted above alkylation with $AlCl_2 \cdot HSO_4$ produces the smallest amount of 2-methyl-2-phenylnonane. In fact, by the time the positive charge migrates from the C-8 to the C-5 atoms nearly 90% of the carbonium ions react with benzene. Had the methyl group on the chain not interfered with the alkylation rates of the carbonium ions from the C-3 and C-4 atoms, it is probable that these two positions would be the extent to which the positive charge reaches in alkylations with $AlCl_2 \cdot HSO_4$. In other words the charge migrates about five carbon atoms with this catalyst. On the other hand, alkylation with the HF–hexane system, which affords 71.0% of the tertiary alkylbenzene, obviously permits the charge to migrate much farther down the chain in the absence of a methyl group.

Experimental Section

Synthesis of 8-Methyl-1-nonene.—The reaction between a Grignard solution prepared from 2 mol of isoamyl bromide and 2.1 mol of ethylene oxide was carried out as described by Dreger.[13] The product, isoheptyl alcohol, distilled at 99–103° (45 mm) (lit.[14] 98–101° (45 mm), yield 58% of theoretical.

The product was converted into the bromide by reaction with hydrobromic and sulfuric acids as described by Kamm and Mar-

(10) C. D. Nenitzescu, *Rev. Roum. Chim.*, **9**, 5 (1964).

(11) V. N. Ipatieff, H. Pines, and L. Schmerling, *J. Amer. Chem. Soc.*, **60**, 353 (1938).

(12) G. Geiseler, P. Hermann, and G. Kürzel, *Chem. Ber.*, **98**, 1695 (1965).

(13) E. E. Dreger, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 306.

(14) J. Cason, *J. Amer. Chem. Soc.*, **64**, 1109 (1942).

vel.[15] The isoheptyl bromide[16] was obtained in 90% yield and distilled at 84–85° (45 mm) [lit.[14] 83° (45 mm)].

The Grignard reagent from 1 mol of isoheptyl bromide was prepared and treated with allyl bromide according to the directions of Vogel.[17] The product, 8-methyl-1-nonene, was distilled in a ten-plate column at 170–171°. No impurities could be detected in the product by glpc analysis. *Anal.* Calcd for $C_{10}H_{20}$: C, 85.63; H, 14.37. Found: C, 85.36; H, 14.41.

Alkylation of Benzene with 8-Methyl-1-nonene.—All the alkylation reactions have been described previously.[4,5] The crude akylbenzenes were analyzed by glpc before distillation to avoid any discrepancy due to the fact that the internal alkylbenzenes tend to have slightly lower boiling points than the ones near the end of the chain. The chromatograph used was an F & M Model 810 equipped with a recorder and an Infotronics digital readout system. The stainless steel column was 200 ft × 0.01 in. and was coated with OV7.[18] The crude products were then distilled in a ten-plate column, and the fraction boiling at 100–108° (2 mm) (n^{25}D 1.4810) was collected. The yields and isomer distributions appear in the table.

Registry No.—**1**, 26741-24-2; benzene, 71-43-2.

(15) O. Kamm and C. S. Marvel, ref 13, p 30.

(16) A recent investigation of the reaction of alcohols with hydrobromic acid showed that primary alcohols do not undergo isomerization during the reaction: W. Gerrard and H. R. Hudson, *J. Chem. Soc.*, 2310 (1964).

(17) I. Vogel, "Practical Organic Chemistry," Wiley, New York, N. Y., 1961, p 240.

(18) This is 20% phenyl-substituted methyl silicone available from Supelco, Inc., Bellefonte, Pa. 16823.

The Base-Catalyzed Condensation of Acetophenone and Isobutyraldehyde. A Reexamination of the Monomeric and Dimeric Adducts

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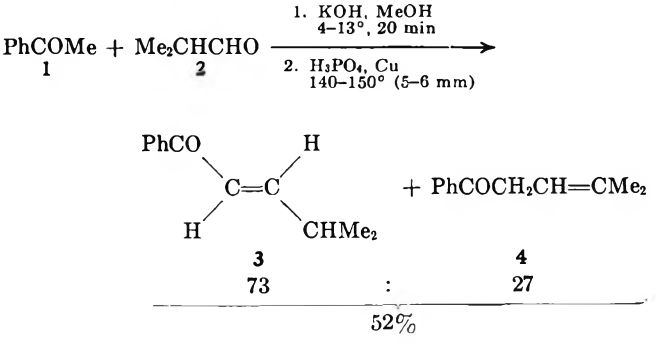
The base-catalyzed condensation of acetophenone (1) and isobutyraldehyde (2) at 4–13° followed by dehydration at 140–150° with phosphoric acid and copper gave a 73:27 mixture of 1-phenyl-4-methyl-*trans*-2-penten-1-one (3) and 1-phenyl-4-methyl-3-penten-1-one (4). Condensation of 1 and 2 at 55° gave both diastereomers of 3-isopropyl-2-(2-methylpropenyl)-1,5-diphenyl-1,5-pentanedione (5 and 6) and a ~70:30 mixture of 4 and 3. Heating the high-melting diastereomeric dimer 5 with sodium acetate at 170–200° gave a 72:28 mixture of 4 and 3. Attempted equilibration of 3 and 4 with potassium hydroxide in methanol gave rapid conversion of the conjugated isomer 3 to 1-phenyl-3-methoxy-4-methyl-1-pentanone (10) followed by a slower reaction of 3, 4, and probably 10 to give the dimers 5 and 6. This paper clarifies some earlier reports on the products of the base-catalyzed condensation of 1 and 2.

The base-catalyzed condensation of acetophenone (1) and isobutyraldehyde (2) (and dehydration) under a variety of conditions has been reported to give either the α,β-unsaturated ketone **3** (stereochemistry unspecified)[1-5] and/or the dimer **5** (stereochemistry unspecified).[3,6] The dimer **5** on heating with sodium acetate reportedly gave the ketone **3**.[3] During the course of some other work we had need of the ketone **3**, which we set out to prepare by the methods described above. It became apparent very soon after our work was initiated that most of the literature reports of the synthesis of **3** were partially in error. This paper describes our work on the unraveling of the major processes which occur during the reaction of acetophenone (1) and isobutyraldehyde (2) in the presence of base, and on some of the subsequent transformations of the products of these reactions.

Results

The low-temperature base-catalyzed condensation of acetophenone (1) and isobutyraldehyde (2) and subsequent dehydration were carried out according to the procedure of Stanishevskii and Tishchenko.[5] The exact details of part of the process were not reported by these authors. In addition to the reported product **3** (determined to be mainly trans), an appreciable amount of the unconjugated isomer **4** also was obtained (73:27 ratio, 52% yield). A small amount



(≤5% of **3**) of the cis isomer **7** of **3** may have been formed (see Experimental Section). The structure proof of both isomers **3** and **4** will be presented below.

The high-temperature condensation of the ketone **1** with the aldehyde **2** was carried out as described by Kulka and coworkers.[3] In addition to the high-melting dimer **5**, another lower melting dimer **6** also was isolated. On the basis of nmr data which are described below, these dimers tentatively have been assigned the diastereomeric structures reported by Anet.[6] After the addition of sodium acetate a small amount of the monomers **3** and **4** could be distilled from the reaction mixture, but the major isomer was the unconjugated one, **4**. Kulka and coworkers[3] reported the isolation of the high-melting dimer in 60% yield and the conjugated monomer **3** in 22% yield.

(1) H. Thoms and H. Kahre, *Arch. Pharm. (Weinheim)*, **263**, 241 (1925).

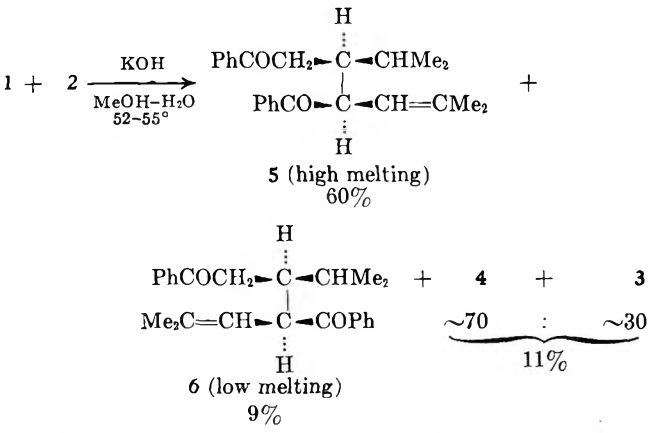
(2) W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 5739 (1957).

(3) K. Kulka, R. J. Eiserle, J. A. Rogers, Jr., and F. W. Richter, *J. Org. Chem.*, **25**, 270 (1960).

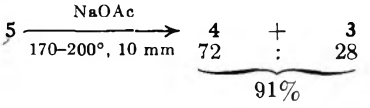
(4) R. A. Rao and R. R. Rao, *Indian J. Chem.*, **4**, 280 (1966); *Chem. Abstr.*, **65**, 13623 (1966).

(5) L. S. Stanishevskii and I. G. Tishchenko, *Vestsi Akad. Navuk Belarus. SSR, Ser. Khim. Navuk*, 123 (1967); *Chem. Abstr.*, **67**, 32422 (1967).

(6) R. Anet, *J. Org. Chem.*, **26**, 246 (1961).



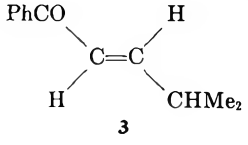
The high-melting dimer was converted to essentially the same mixture of monomers as obtained in the preceding experiment by heating under vacuum with sodium acetate as described by Kulka and coworkers.[3]



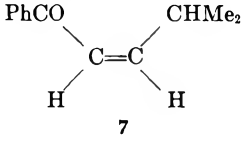
A trace amount (~5% of **3**) of the cis isomer **7** may have been formed.

Although the monomers **3** and **4** were not isolated in pure form, samples of greater than 70% purity of each isomer were available from the above reactions, making it possible to determine some nmr and infrared spectral data for each. The impurity in each case was the other isomer. The isomeric monomers were not separable on a silicone rubber gas chromatographic column. Mixtures of the two could be analyzed conveniently by nmr spectroscopy. Mass and ultraviolet spectra were also determined on the mixtures. The spectral details are given in the Experimental Section. We note here the most significant features which serve to define the structures.

The nmr spectrum of the conjugated isomer **3** exhibited a one-proton doublet of doublets (J = 15.6 and 5.1 Hz) at −7.08 ppm and a one-proton doublet (J = 15.6 Hz) at −6.74 ppm for the olefinic protons. The common coupling constant, 15.6 Hz, is reasonable

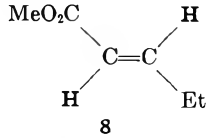


3

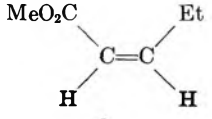


7

for the trans stereochemistry. The cis isomer **7** would be expected to have a vicinal olefinic coupling constant of 11–12 Hz based on the model compounds **8** and **9**.[7,8]



8
J_{trans} = 15.6 Hz



9
J_{cis} = 11.5 Hz

The nmr spectrum of **3** also exhibited a one-proton multiplet at −2.5 ppm for the methine proton and a six-proton doublet split 6.7 Hz by the methine proton at −1.11 ppm for the two equivalent methyl groups. In each sample of the monomers a weak doublet also was observed at −1.04 ppm with a 6.7-Hz coupling constant. The relative areas of the doublets at −1.11 and −1.04 ppm were ~95:5, respectively. These two doublets may be due to the trans (**3**) and cis (**7**) isomers, respectively. The olefinic proton resonances of **7** could not be detected. The nmr spectrum of the unconjugated isomer exhibited a one-proton triplet with further fine structure at −5.44 ppm coupled by 7.0 Hz to the methylene group, which appeared as a two-proton doublet at −3.65 ppm. The two nonequivalent vinylic methyl groups appeared mainly as singlets with small splittings at −1.74 and −1.68 ppm. The aromatic region of the spectrum of each monomer **3** and **4** had the typical benzoyl pattern.

The infrared spectrum of the conjugated isomer **3** had a carbonyl stretching band at a frequency, 1675 cm^{-1}, slightly lower than that of the unconjugated isomer **4**, 1695 cm^{-1}. The carbon–carbon double bond absorption was much more intense,[9] 1630 cm^{-1}, for the conjugated isomer **3**, than for the unconjugated isomer **4**. This band in **4** is probably at 1635 cm^{-1}, but there were several medium-intensity bands in this region which made this assignment tenuous.

The mass spectrum of each mixture (Table I) confirmed the monomeric character of each isomer **3** and **4**. In addition several features of these spectra were consistent with the assigned structures. The more highly conjugated isomer **3** gave the more intense molecular ion peak.[10] Isomer **3**, which contains an isopropyl group, gave more intense ion peaks for the loss of this fragment, m/e 131, and for that fragment, m/e 43. The loss of a phenyl group from the molecular ion, m/e 97, of isomer **3** leaves a more stable ion, $Me_2CHCH{=}CHCO^+$, than the corresponding ion from the other isomer **4**, $Me_2C{=}CHCH_2CO^+$.

TABLE I

MASS SPECTRA OF MIXTURES OF KETONES **3** AND **4**[a]

	Rel intensity		
	73% **3** + 27% **4**	72% **4** + 28% **3**	
m/e			Assignment
174	21.8	9.6	M^+
159		3.1	$M^+ - CH_3$
145	2.6		$M^+ - C_2H_5$
131	2.6		$M^+ - C_3H_7$
116	3.2		$M^+ - C_3H_6O$ or C_4H_{10}
115	3.9		$M^+ - C_3H_7O$ or C_4H_{11}
105	100.0	100.0	$PhCO^+$
97	5.1	1.5	$M^+ - Ph$
91	3.9		$C_7H_7^+$
81	1.9		$CH_2{=}CHCH{=}CHCO^+$
77	34.6	46.5	Ph^+
69	2.6	2.7	$Me_2CHCH{=}CH^+$
55	1.9		$C_4H_7^+$
53	2.6	2.3	$C_4H_5^+$
51	10.9	9.2	$C_4H_3^+$
50	3.2		$C_4H_2^+$
43	4.5	1.5	$C_3H_7^+$ or CH_3CO^+
41	12.2	9.6	$C_3H_5^+$
39	5.1	3.9	$C_3H_3^+$

[a] Direct probe sample introduction, 40°.

(7) P. Laszlo and P. v. R. Schleyer, *Bull. Soc. Chim. Fr.*, 87 (1964).

(8) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, pp 301–302.

(9) C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press, New York, N. Y., 1963, p 147.

(10) F. W. McLafferty, "Interpretation of Mass Spectra, An Introduction," W. A. Benjamin, New York, N. Y., 1966, p 212.

TABLE II
DESCRIPTION OF 100-MHz PROTON NMR SPECTRA OF DIMERS 5 AND 6[a]

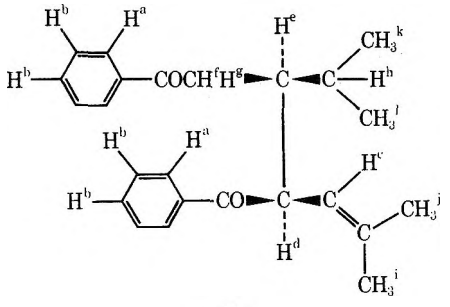
Absorption	Center, ppm: δ[b]	Center, ppm: 6	Number of protons	Description[c]
H^a	−7.95		4	m
		−7.95	4	m
H^b	−7.45		6	m
		−7.45	6	m
H^c	−5.016 (−5.03)		1	d (10.5 Hz) of m (1.3 Hz)
		−5.209	1	d (10.2 Hz) of m (~1.4 Hz)
H^d	−4.392 (−4.4)		1	d (10.5 Hz) of d (8.9 Hz)
		−4.520	1	d (10.2 Hz) of d (7.4 Hz)
H^e	−3.15			
		−2.77	3 (5)	5, complex
H^f	−3.05		3 (6)	6, X_2Y appearance with Y further split, "J" ≅6 Hz
		−3.00[d]		
H^g	−2.75			
		−3.00[d]		
H^h	−1.777 (~−1.9)		1	m (7 Hz) of d (3.4 Hz)
		−1.951	1	m (7 Hz) of d (3.4 Hz)
H^i	−1.663 (−1.66)		3	d (1.3 Hz)
		−1.663[e]	3	d (1.35 Hz)
H^j	−1.354 (−1.40)		3	d (1.3 Hz)
		−1.663[e]	3	d (1.35 Hz)
H^k	−0.949 (−1.1)		3	d (6.9 Hz)
		−0.920	3	d (6.9 Hz)
H^l	−0.869 (−1.0)		3	d (6.9 Hz)
		−0.870	3	d (6.9 Hz)

[a] Solutions were 10% (w/v) in $CDCl_3$ with internal Me_4Si as shift reference. [b] Data (for $CDCl_3$ solution) reported by Anet[6] given in parentheses. [c] d = doublet, m = multiplet (≥5 lines). [d] These features are superimposed in $CDCl_3$ solution and separate upon addition of Eu(fod)$_3$. [e] These features are superimposed in $CDCl_3$ solution and separate upon addition of Eu(fod)$_3$.

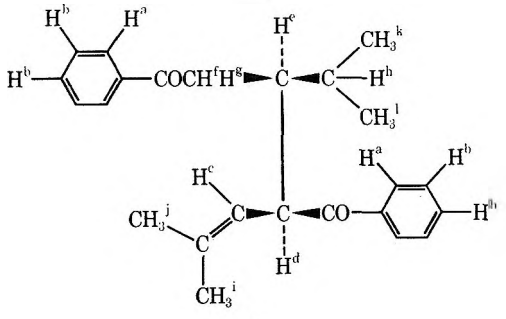
The ultraviolet spectra of the two isomer mixtures also served to confirm the structures. The sample rich in the conjugated isomer **3** exhibited both $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ band maxima at longer wavelengths than did the sample rich in the nonconjugated isomer **4**.

The mass spectra of the dimers **5** and **6** confirmed their molecular weights and were generally consistent with the assigned structures.

The diastereomeric structures of **5** and **6** (erythro



5



6

and threo, respectively) were assigned on the basis of their nmr spectra. Spectral features observed in deuteriochloroform solution at 100 MHz are described in Table II. The data (60 MHz) reported by Anet[6] for the high-melting isomer **5** are also shown for comparison.

Spin–spin coupling among the protons was determined by selective decoupling experiments. Complete decoupling was performed in all cases. The relative signs of the coupling constants were not sought, because the net behavior is typical of the anticipated vicinal and geminal placements. The apparent values of the coupling constants are listed in Table III. It

TABLE III
APPARENT COUPLING CONSTANTS AT 100 MHz[a]

Protons coupled	Coupling constant, Hz: δ[b]	Coupling constant, Hz: 6	Assignment
cd	10.5 (10)	10.2	Vicinal, trans or cis
ci	1.3 (1.5)	1.35	Long range, $CH_3C{=}CH$
cj	1.3 (1.3)	1.35	Long range, $CH_3C{=}CH$
de	8.9 (8.75)	7.4	Vicinal
ef	7.6[c]	5.0[c]	Vicinal
eg	5.0[c]	5.8[c]	Vicinal
eh	3.4	3.4	Vicinal, gauche
fg	17.6[c]	17[c]	Geminal
hk	6.9 (7.2)	6.9	Vicinal
hl	6.9 (7.2)	6.9	Vicinal

[a] Solutions were 10% (w/v) in $CDCl_3$. [b] Data (for $CDCl_3$ solution) reported by Anet[6] given in parentheses. [c] Obtained from 60-MHz spectrum with Eu(fod)$_3$ added.

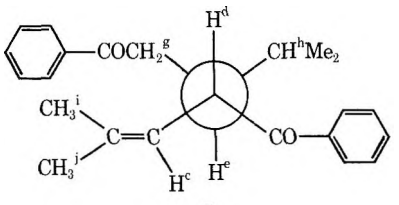
is apparent that the structures of **5** and **6** must be very similar. The chemical shifts of the protons and the couplings among them are fully consistent with the gross structures of **5** and **6**. Based on the concept of least nonbonded steric repulsions the conformations **5a** and

TABLE IV

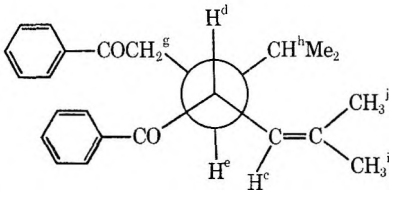
PARAMAGNETIC SHIFTS AT 60 MHz INDUCED BY ADDITION OF Eu(fod)$_3$ IN $CDCl_3$

	5				6			
Proton	Chemical shift, Hz[a] Initial	+Eu(fod)$_3$	Δ (change), Hz	Rel effect, $100\Delta/\Sigma_c^1\Delta$	Chemical shift, Hz[a] Initial	+Eu(fod)$_3$	Δ (change), Hz	Rel effect, $100\Delta/\Sigma_c^1\lvert\Delta\rvert$
c	301	531	230	15.7	313	314	1	0.1
d	262	429	167	11.4	270	342	72	10.0
e	191	641	450	30.7	165	363	98	13.5
f, g	175	344	169	11.5	180	300[b]	220	30.4
h	105	200	95	6.5	117	143	26	3.6
i	99.5	164	64.5	4.4	99.5	121	21.5	3.0
j	72	111	39	2.7	99.5	95	−4.5	−0.6
k	57	96	39	2.7	54	85.5	31.5	4.4
l	52.5	97	44.5	3.0	52.5	81.5	29	4.0
a	477	556, 567	80, 90	5.5, 6.1[c]	477	538	61	8.8[c]
b	448	468	20	1.4[c]	448	456	8	1.2[c]

[a] Downfield from internal Me_4Si. [b] Center of both lines which had separated. [c] On same relative scale as c–l.



5a



6a

6a are probably the predominant rotational isomers wherein protons H^d and H^e are trans; H^e and H^h are gauche; and H^c and H^d are cis or trans.

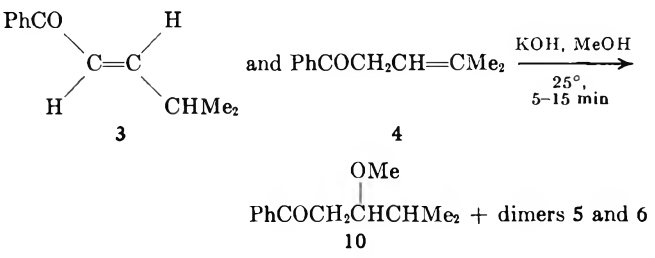
The only large difference between the spectra of the two isomers 5 and 6 lies in the relatively high shielding of one of the vinylic methyl groups of isomer 5, H^j, tentatively assigned as the methyl group which is cis to the olefinic proton H^c. This shielding can occur if the methyl group is situated above the plane of a phenyl ring while the other methyl group, H^i, geminal to it is not. This is accomplished readily in the molecular conformation of 5a, which satisfies the predominant conformational criteria of the preceding paragraph, with protons H^c and H^d being trans to each other. In this conformation, the methyl group, $CH_3{}^j$, can lie close to and directly over the far phenyl ring, $PhCOCH_2$–, while the methyl group, $CH_3{}^i$, trans to proton H^c, and H^e itself do not lie above this ring. In this conformation, also, it is possible to have the two carbonyl groups pointed unhindered in opposite directions and coplanar with their respective phenyl rings. This chemical shift difference between H^i and H^j in isomer 5 and their near equivalence in isomer 6 is the basis for making these tentative diastereomeric assignments.

The addition of the paramagnetic shift reagent Eu(fod)$_3$ to the deuteriochloroform solutions aided in confirming assignments of the CH_2CH systems because it shifted the three protons apart from one another, as well as shifting them downfield. Significant shifting of most other protons occurred also, and could serve as a basis for structure and conformation assignments when the origins of such shifts are understood well. Table IV gives nominal shifts of the various protons from internal tetramethylsilane at 60 MHz for original and shifted species. The greatest shifts occur for those protons which lie close to one or both carbonyl groups. The most dramatic difference between the isomers lies in the greater fractional deshielding change for the methyl groups H^i and H^j (H^i and H^j are not necessarily in the same relative positions in the two isomers) and protons H^c, H^e, H^f, and H^g. It appears that the differences reflect proximity of these protons to both carbonyl groups, with greater deshielding occurring when the protons are closer.

The infrared spectra of both dimers 5 and 6 were consistent with the assigned structures (see Experimental Section); each exhibited a carbonyl stretching band at 1680 cm^{-1}.

The ultraviolet spectra of the dimers 5 and 6 were nearly the same as that of acetophenone, in agreement with the proposed structures. As expected, the extinction coefficients (see Experimental Section) for the $\pi \rightarrow \pi^*$ bands of 5 and 6 were approximately twice that of acetophenone. Unexpectedly the $n \rightarrow \pi^*$ bands of the dimers 5 and 6 in hexane solution were approximately seven times as intense as that of acetophenone.

In an attempt to determine the equilibrium constant for the presumed prototropy of the conjugated 3 and unconjugated 4 ketones, each isomer mixture (0.1–0.9 M) was subjected to brief treatment with potassium hydroxide (0.1–1.0 M) in methanol. Extended treatment led to dimer 5 (and 6) formation.[3] Instead of isomerization, the initial rapid reaction was addition of methanol, presumably to the conjugated isomer 3, to give the methyl ether 10. Dimer 5 and a small amount of dimer 6 were also formed at the longer reaction time. The results of these experiments



3 4 10

are shown in Table V. Trace amounts of unidentified product(s) were also detected by nmr spectroscopy.

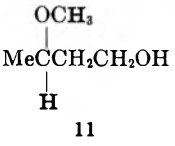
TABLE V

REACTIONS OF KETONES 3 AND 4 WITH POTASSIUM HYDROXIDE IN METHANOL AT 25°

Reaction no.	Time, min	Initial concn [3 + 4], M	Initial concn KOH, M[a]	Product composition, %[b] Ketone 3[c]	Ketone 4	Ether 10	Dimer 5[d]	Ratio of 3:4	Material balance, %
e	0			75	25			75:25	100
1	5	0.097	0.10	41	20	39	~0	68:32	93
2	15	0.84	1.0	~20	~15	~35	~30	~60:40	~80
f	0			26	74			26:74	100
3	5	0.098	0.10	19	69	12	~0	21:79	95
4	15	0.85	1.0	~5	~50	~10	~30	~10:90	~90

[a] In methanol before addition of ketones 3 and 4. [b] Compositions accurate to *ca.* ±2% for starting materials and reactions 1 and 3; *ca.* ±5–10% for reactions 2 and 4 (rounded to nearest 5%). [c] Possibly a trace of the cis isomer was present. [d] A small amount of the diastereomeric dimer 6 was also present. [e] Starting material for reactions 1 and 2. [f] Starting material for reactions 3 and 4.

The ether **10** was not isolated in pure form, but spectroscopic examination of reaction mixture 1 (Table V) left little doubt as to its identity. The mass spectrum showed ion peaks at *m/e* 206 (M^+), 191 ($M^+ - CH_3$), and 175 ($M^+ - CH_3O$). The nmr spectrum in deuteriochloroform solution exhibited a singlet at −3.30 ppm for the methoxy protons, a doublet (J = 6.7 Hz) at −0.95 ppm for the isopropyl methyl groups, a multiplet at −3.6 ppm for the methine proton, and a multiplet at −3.0 ppm due to the two methylene protons which are nonequivalent owing to the adjacent asymmetric center. The other expected peaks were obscured by the resonances from the ketones **3** and **4**. The chemical shifts for the methoxy and methine protons are in good agreement with those observed for the model compound **11** ($CDCl_3$ solution, $-OCH_3$ at



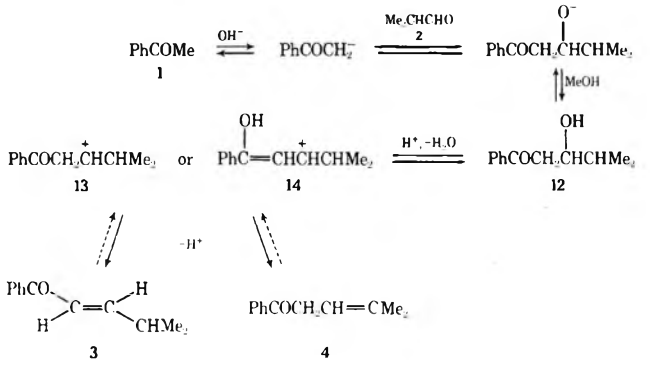
11

−3.33 and −OCH at −3.55 ppm).[11] The infrared spectrum of the ether **10** showed a CH stretching vibration for the methoxy group at 2835 cm^{-1} and a carbonyl stretching vibration at 1695 cm^{-1}.

Discussion

In the low-temperature condensation of acetophenone (**1**) and isobutyraldehyde (**2**), both the conjugated ketone **3** and the unconjugated isomer **4** presumably arise by acid-catalyzed (phosphoric acid and copper) dehydration of the intermediate ketol **12** (Scheme I).

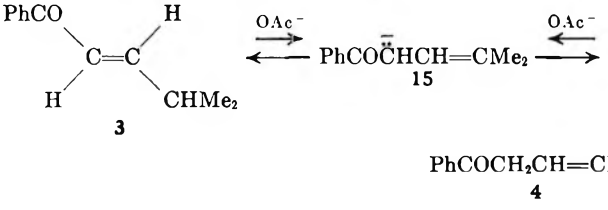
SCHEME I



(11) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., National Press, 1962, No. 120.

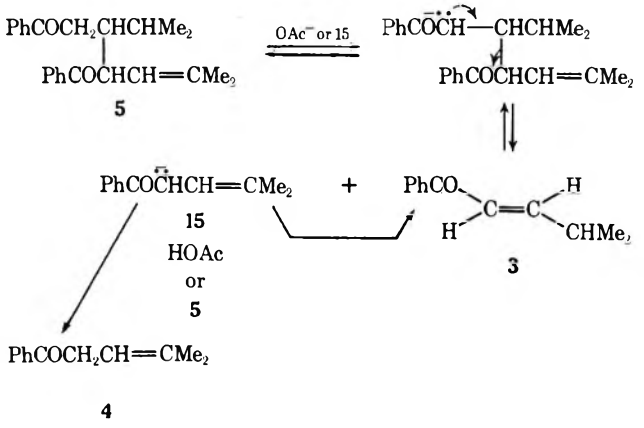
The ketones **3** and **4** may isomerize slightly under the reaction conditions, but the 73:27 ratio obtained in this reaction probably is not the equilibrium distribution, since other data (see below) indicate that the unconjugated isomer **4** probably is the more stable isomer. Thus the distribution of isomers **3** and **4** obtained in this reaction represents at least partial kinetic control. It seems reasonable that kinetic control in the proton loss from either cation **13** or **14** would favor formation of the conjugated ketone **3**. The kinetically more acidic protons in cations **13** and **14** undoubtedly are those α to the carbonyl and the hydroxylic proton, respectively.

In contrast to the above results, the base-catalyzed dedimerization of the dimer **5** gave predominantly the unconjugated isomer (72:28). We feel that this ratio probably is nearer the equilibrium distribution than is the ratio obtained in the dehydration reaction which followed the low-temperature condensation. The conjugated isomer **3** should predominate in the dedimerization if the products were stable under the reaction conditions. According to the probable mechanism for the dedimerization (Scheme II) the conjugated isomer should constitute greater than 50% of the product (50% plus the fraction of the enolate ion **15** which is protonated at the 4 position). Since the unconjugated ketone **4** is the predominant product, some of the conjugated isomer **3** must isomerize under the reaction conditions.

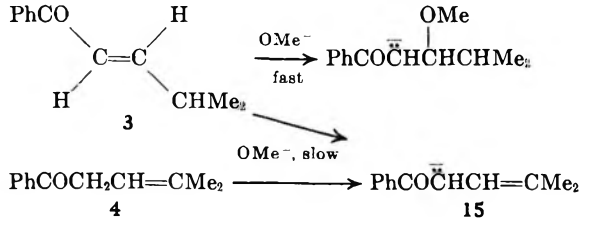


Several reasons can be advanced to explain the apparent greater stability of the unconjugated ketone **4**. First, the loss of conjugation energy in going from **3** to **4** is probably not so great as one might suspect, since the carbonyl group is already conjugated with the phenyl ring. The conjugation in **3** is only cross conjugation. Thus the loss is conjugation energy is less than a related aliphatic system would suffer. The unconjugated ketone **4** is a trisubstituted olefin while the conjugated isomer **3** is only a disubstituted olefin, a factor which favors isomer **4**. The cis isomer **7** would be expected to be less stable than **3** or **4** owing to excessive steric repulsion between the benzoyl and isopropyl groups.

SCHEME II



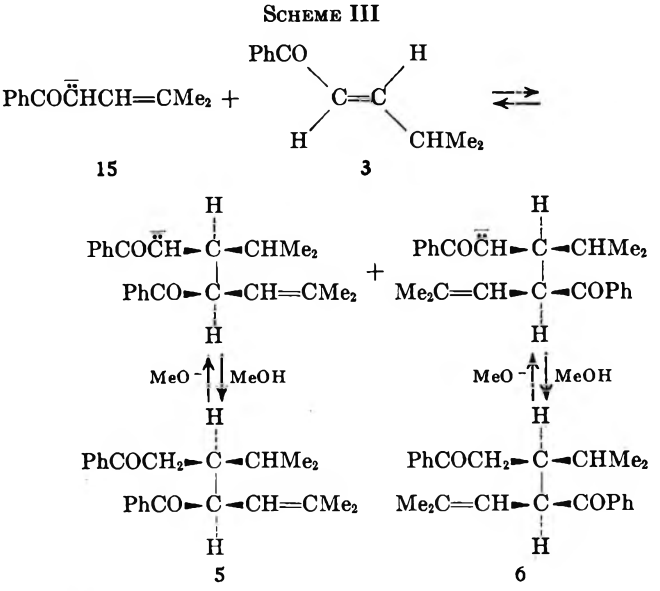
The attempt to determine the equilibrium constant between the ketones **3** and **4** in the presence of potassium hydroxide in methanol was thwarted by the rapid formation of the methyl ether **10**. From an examination of Table V it is apparent that the conjugated isomer **3** disappears much more rapidly than the unconjugated isomer **4**. Also, more ether **10** is formed from the unsaturated ketone sample which contains the higher concentration of **3**; the amount of ether **10** formed is roughly proportional to the initial concentration of isomer **3**. Thus the addition of methoxide ion to **3** is a faster reaction than is proton removal from either **3** or **4**. The methyl ether **10** appears to form rapidly



and reach a steady concentration (Table V), while the dimers **5** and **6** form at a slower rate. The ether **10** probably is formed reversibly, thus accounting for the leveling off of the amount formed at higher conversions of the ketones **3** and **4**. The ether **10** is also likely formed in the condensation reaction of the ketone **1** and aldehyde **2** in methanol, but probably breaks down to the monomer **3**.

The enolate **15**, once formed, appears to undergo addition to the conjugated ketone **3** (Scheme III) more often than it reprotonates. The distribution of dimers **5** and **6** from the reactions in which dimer **5** precipitates from solution may not represent the thermodynamically controlled distribution, but may be a consequence of the less soluble dimer's (**5**) being removed from the reaction medium, thus shifting the equilibrium toward that isomer. Alternatively, although unlikely, the observed ratio could be the kinetically controlled distribution. In one experiment, Table V, no. 2, the dimer **5** did not precipitate, and the less soluble dimer **5** was again the major dimer formed. Thus the erythro dimer **5** is likely the more stable, assuming thermodynamic control. Based on estimated nonbonded repulsions one might predict conformer **5a** to be more stable than **6a**. Also the two highly dipolar carbonyl groups can be separated further in **5a** than in **6a**. Dimer **5a**, by the same argument as above, might be expected to be the major kinetically controlled product also.

SCHEME III



None of the reactions of the supposed conjugated ketone **3**, which were reported by previous workers as partial structure proofs, is incompatible with the actual material which these workers probably had in hand, namely a mixture of the ketones **3** and **4** and in some cases predominantly **4**. Catalytic hydrogenation of **4** would give the same products as from the supposed **3**.[3,4] Borohydride or Meerwein–Ponndorf–Verlay reduction of **4** would give an unsaturated alcohol which on catalytic hydrogenation and hydrogenolysis would give (4-methylpentyl)benzene, since the hydroxyl group would still be benzylic.[3] Ketone **4** is capable of undergoing base-catalyzed dimerization to **5**,[3a] as shown by our own experiments on the attempted equilibration of **3** and **4**. The infrared carbonyl absorptions for **3** and **4** are rather similar and could be mistaken for one another without both isomers in hand.[3]

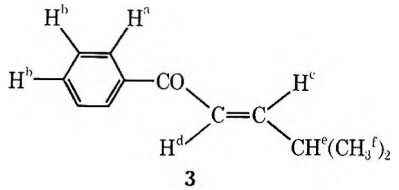
The supposed synthesis of authentic ketone **3** reported by Kulka and coworkers[3] involving the Friedel–Crafts reaction of β-isopropylacrylyl chloride and the condensation of benzoylacetic acid and aldehyde **2** followed by decarboxylation are reactions which could easily lead to the unconjugated ketone **4** as well as **3**.

Experimental Section

General.—Melting points were taken in capillary tubes and were not corrected. Boiling points were not corrected. Elemental microanalyses were determined by Mr. L. E. Swim and coworkers. Infrared spectra were obtained by Mr. F. L. Beman and coworkers with a Perkin-Elmer 337 grating infrared spectrophotometer. Ultraviolet spectra were obtained by Mr. Beman and coworkers with a Perkin-Elmer 202 ultraviolet–visible spectrophotometer. Wavelengths were calibrated with the mercury arc lines at 253.7, 296.7, 313.2, and 365.0 mμ. The 60-MHz nmr spectra were obtained by Mr. Beman and coworkers with a Varian A-60 analytical spectrometer. All data reported are for 60-MHz spectra unless otherwise specified. The 100-MHz nmr spectra of the dimers **5** and **6** were obtained on 10% (w/v) chloroform-*d* solutions with a Varian HA-100 high-resolution spectrometer. Decoupling experiments were performed on this instrument. The spectra of **5** and **6** with Eu(fod)$_3$ [(*t*-BuCOCHCO-*n*-C_3F_7)$_3$Eu] added were obtained with a 60-MHz spectrometer. Mass spectra were obtained by Mr. J. H. Mark with an Atlas CH4B spectrometer which employed a direct probe

sample introduction system. The molecular formulas assigned for various ion peaks are only tentative and have not been confirmed by high-resolution measurements. Gc analyses were carried out with a F & M 500 temperature-programmed gas chromatograph equipped with a thermal conductivity detector.

Low-Temperature Base-Catalyzed Condensation of Acetophenone (1) and Isobutraldehyde (2). Preparation of a 73:27 Mixture of 1-Phenyl-4-methyl-*trans*-2-penten-1-one (3) and 1-Phenyl-4-methyl-3-penten-1-one (4).—The general procedure of Stanishevskii and Tishchenko[5] was followed. Commercial isobutyraldehyde (40.4 ml, 32.1 g, 0.445 mol) was added to a stirred solution of commercial acetophenone (50.0 ml, 51.4 g, 0.428 mol) and potassium hydroxide (85.9% assay) (14.0 g, 0.21 mol) in 80 ml of methanol at 4–13° over a period of 15 min. The bright yellow solution was stirred for an additional 5 min, diluted with 175 ml of water, and neutralized with glacial acetic acid. The resulting mixture was extracted twice with methylene chloride (100, 50 ml), and the combined extracts were washed with water (3 × 50 ml). The methylene chloride was evaporated under vacuum, and 22.2 g of colorless liquid (probably acetophenone) was removed by distillation, bp 36–37.5° (0.6 mm). To the cooled distillation residue were added 85.7% phosphoric acid (4.89 g, 0.0428 mol) and copper powder (2.72 g, 0.0428 g-atom). The mixture was heated at 140–150° in a distillation pot connected to a 24-in. Vigreux column under vacuum. After a forerun of 2.85 g, a pale yellow liquid fraction (21.84 g, 29.3%, 52% based on unrecovered ketone 1), bp 120–129° (5–6 mm) [lit. bp 101–102° (0.5 mm),[12] 130° (8 mm),[3] 136–137° (10 mm),[5] 146° (12 mm)[4]], $n^{25}D$ 1.5375 (lit[5] $n^{20}D$ 1.5390), was collected: $\nu_{max}^{CCl_4}$ 3095 (w), 3070 (w), and 3040 (w) (ArH, =CH), 2970 (m), 2940 (m), and 2880 (m) (CH), 1695 (sh, m), 1675 (s, C=O of **3**), 1630 (s, C=C of **3**), 1455 cm^{-1} (m, CH_3); $\nu_{max}^{CS_2}$ 1174 (m, *i*-Pr), 979 (m, *trans*-CH=CH), 693 cm^{-1} (s, Ph); λ_{max}^{hexane} (ϵ) *247.5*[13] (13,420, $\pi \rightarrow \pi^*$), 280 (sh, 1460), 315 (sh, 100), *340* (57, n → π^*), 351 (sh, 54), 364 (sh, 45), 379 mμ (sh, 29); λ_{max}^{MeOH} (ϵ) 252 (13,160, $\pi \rightarrow \pi^*$), 333 (sh, 108, n → π^*); nmr ($CDCl_3$) a multiplet at −8.1 to −7.8 (2.9 H relative area, H^a, $H^{a'}$), a multiplet at −7.6 to −7.1 with maxima at −7.50 and −7.46 (5.2 H, H^b, $H^{b'}$), an



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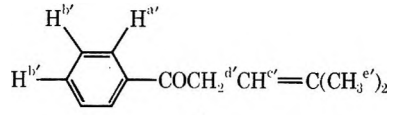

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unsymmetrical doublet of doublets centered at −7.08 (low-field peaks partially obscured by H^b signal [H^c, J_{cd} = 15.6 Hz (assumed), J_{ce} = 5.1 Hz] incompletely resolved from an unsymmetrical doublet centered at −6.74 (H^d, J_{cd} = 15.6 Hz) (2.0 H total, H^d and high-field peaks of H^e), a multiplet (see below) at −5.44 (0.21 H, $H^{e'}$), a doublet (see below) at −3.65 (0.6 H, $H^{d'}$), a multiplet at −2.7 to −2.3 which consisted of at least five lines centered at ∼−2.5 (∼1.2 H, H^e), multiplets (see below) centered at −1.74 and −1.68 (2.5 H, $H^{e'}$), a doublet centered at −1.11 (6.0 H, H^f, J_{ef} = 6.7 Hz), a weak doublet centered at −1.04 ppm [J = 6.7 Hz, probably $-CH(CH_3)_2$ of **7**, area ratio of doublets at −1.11 and −1.04 ∼>95:<5]. The ratio of isomers **3** and **4** was 73:27 based on the areas of the H^c, H^d, H^f, $H^{c'}$, $H^{d'}$, and $H^{e'}$ nmr signals. The distillation residue amounted to 19 g.

High-Temperature Base-Catalyzed Condensation of Acetophenone (1) and Isobutyraldehyde (2). Preparation of Diastereomers of 3-Isopropyl-2-(2-methylpropenyl)-1,5-diphenyl-1,5-pentanedione (5 and 6).—This reaction was carried out in essentially the same manner as that reported by Kulka and coworkers.[3] Isobutyraldehyde (90.9 ml, 72.1 g, 1.00 mol) was added to a stirred mixture of acetophenone (117.3 ml, 120.7 g, 1.00 mol) and potassium hydroxide (85.9% assay) (17.0 g, 0.26 mol) in 125 ml of methanol and 125 ml of water at 52–55° over a period of 105 min. The bright yellow solution was stirred at this temperature for an additional 220 min, during which time a large amount of solid separated. After the reaction mixture stood at ∼25° for ∼16 hr, glacial acetic acid was added until the mixture was acidic. The solid was filtered and washed several times with methanol until colorless. The washings were combined with the filtrate, A, for processing later. The solid was air dried to give 103.7 g (60%) of white powder, mp 137–140°. The nmr, infrared, and ultraviolet spectra of this crude material were essentially identical with those of the purified sample of **5** described in the Results section and below. A 50.0-g portion was recrystallized twice from a 70:30 (v/v) mixture of methanol and benzene to give 34.0 g (40%) of the dione **5** as white needles: mp 142.5–143.5° (lit. mp 137.5°,[1] 139–140°,[2] 142–143°,[14] 144.5–145°[3]), $\nu_{max}^{Fluorolube}$ 3065 (w, ArH), 2965 (m), 2930 (m), and 2875 (m) (CH), 1680 (s, C=O), 1455 cm^{-1} (m, CH_3); ν_{max}^{Nujol} 753 (s) and 693 cm^{-1} (s, Ph); λ_{max}^{hexane} (ϵ) 240 (24,400, $\pi \rightarrow \pi^*$), 278 (sh, 1670), 286 (sh, 1160), 317 (sh, 206), 328 (253, n → π^*), 338.5 (249), 354 (sh, 159), 372 mμ (sh, 44); λ_{max}^{MeOH} (ϵ) *244.5* (24,600, $\pi \rightarrow \pi^*$), 278 (sh, 3090), 287 (sh, 2020), 315 (sh, 344), *326.5* (373, n → π^*), 336 mμ (sh, 342); mass spectrum (direct probe sample introduction, 115°) *m/e* (rel intensity) 41 (10.5, $C_3H_5^+$), 51 (6.8, $C_4H_3^+$), 69 (5.3, $Me_2C{=}CHCH_2^+$), 76 (36.3, $C_6H_4^+$), 105 (*100.0*, $PhCO^+$), 106 (10.5, $PhCO^+$ with one ^{13}C), 109 [5.0, $Me_2C{=}CHCH(CO)CH^+$, $M^+ - PhCOCH_2$, Ph, C_3H_7), 124 (40.8, $Me_2CHCH{=}CHCH{=}CMe_2^+$, $M^+ - PhCO$, $PhCOCH_2$], 174 (5.0, $PhCOCH{=}CHCHMe_2^+$), 175 (5.3, $PhCOCH_2C^+HCHMe_2$), 185 (5.1, $M^+ - PhCOCH_2$, C_3H_7, H), 229 (2.4, $M^+ - PhCOCH_2$), 243 (4.5, $M^+ - PhCO$), 305 (2.6, $M^+ - C_3H_7$), 348 (1.6, M^+).

Partial evaporation of the solvent from filtrate and washings, A, gave a solid which was filtered and washed with methanol several times. The washings were combined with the filtrate, B, for processing later. The solid was air dried to give 15.7 g (9%) of white solid whose infrared and nmr spectra were essentially identical with those of the purified sample of dimer **6** described below. Recrystallization of an 8.0-g sample twice from methanol gave 4.6 g (5%) of fine white crystals of the dimer **6**: mp 84–85°; $\nu_{max}^{Fluorolube}$ 3065 (w, ArH), 2970 (m), 2935 (m), 2915 (m), and 2880 (m) (CH), 1680 (s, C=O), 1455 cm^{-1} (m, CH_3); ν_{max}^{Nujol} 749 (s) and 689 cm^{-1} (s, Ph); λ_{max}^{hexane} (ϵ) *241* (25,100, $\pi \rightarrow \pi^*$) 279 (sh, 1870), 288 (sh, 1270), *330* (253, n → π^*), 337 (sh, 248), 353 (sh, 162), 371 mμ (sh, 43); λ_{max}^{MeOH} (ϵ) *244* (23,900, $\pi \rightarrow \pi^*$), 280 (sh, 2330), *326* (375, n → π^*), 338 mμ (sh, 329); mass spectrum (direct probe sample introduction, 125°) *m/e* (rel intensity) 41 (5.8, $C_3H_5^+$), 51 (4.6, $C_4H_3^+$), 69 (4.0, $Me_2C{=}CHCH_2^+$), 76 (27.0, $C_6H_4^+$), 105 (*100.0*, $PhCO^+$), 106 (5.7, $PhCO^+$ with one ^{13}C), 109 [6.5, $Me_2C{=}CHCH(CO)CH^+$, $M^+ - PhCOCH_2$, Ph, C_3H_7], 124 (34.7, $Me_2CHCH{=}CHCH{=}CMe_2^+$, $M^+ - PhCO$, $PhCOCH_2$), 174 (4.4, $PhCOCH{=}CHCHMe_2^+$), 175 (3.9, $PhCOCH_2C^+HCHMe_2$), 185 (3.6, $M^+ - PhCOCH_2$, C_3H_7, H), 229 (2.3, $M^+ - PhCOCH_2$), 243 (2.2, $M^+ - PhCO$), 305 (3.2, $M^+ - C_3H_7$), 348 (1.1, M^+).

Anal. Calcd for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10; mol wt, 348. Found: C, 82.42, 82.56; H, 8.00, 8.09; mol wt, 348 (mass spectrometry).

The filtrate and washings, B, were evaporated at ∼35° (∼10 mm) to give 135.1 g of yellow oil. Most of the remaining solvent and unreacted starting materials **1** and **2** were removed by distillation (up to 75° head temperature at 25 mm). No monomer **3** or **4** could be obtained by further heating. To the yellow solid distillation residue was added 3 g of anhydrous sodium acetate. Distillation through a 24-in. Vigreux column gave 12.0 g of yellow liquid, bp 67° (10 mm)–139° (8 mm), whose nmr spectrum indicated the presence of acetophenone and acetic acid. A second pale yellow fraction, 15.5 g, bp 135–145° (9 mm), consisted of an approximately 70:30 mixture of the unconjugated ketone **4** and the conjugated ketone **3**, respectively, as determined by nmr and infrared analysis. Addition of more sodium acetate to the distillation residue, and continued distillation, gave another 4.1 g (total 19.6 g, 11%) of the 70:30 mixture of **4** and **3**, bp 126–129° (10 mm). No more distillate could be obtained with the pot temperature at 270°.

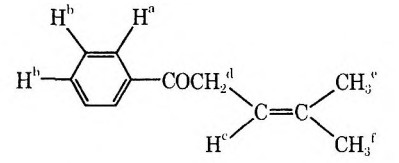
Dedimerization of High-Melting Diastereomer of 3-Isopropyl-2-(2-methylpropenyl)-1,5-diphenyl-1,5-pentanedione (5) with Sodium Acetate. Preparation of a 72:28 Mixture of 1-Phenyl-4-methyl-3-penten-1-one (4) and *trans*-1-Phenyl-4-methyl-2-penten-

(12) N. M. Malenok and S. D. Kul'kina, *Zh. Org. Khim.*, **3**, 814 (1967); *J. Org. Chem. USSR*, **3**, 782 (1967).

(13) Italic value designates principal band in series.

(14) K. C. Brannock, R. D. Burpitt, and J. G. Thweatt, *J. Org. Chem.*, **28**, 1462 (1963).

1-one (**3**).—Essentially the same procedure as described by Kulka and coworkers[3] was used. A mixture of the high-melting dimer **5** (50.0 g, 0.143 mol) and anhydrous sodium acetate (1.5 g, 0.018 mol) was heated at 170–200° under vacuum in a distillation flask connected to a 24-in. Vigreux column. One fraction of slightly yellow liquid, 45.5 g (91%), was collected: bp 130° (8 mm)–144° (10 mm) [lit.[3] bp 130° (8 mm)]; $n^{25}D$ 1.5374 (lit.[3] $n^{20}D$ 1.5385); $\nu_{max}^{CCl_4}$ 3100 (w), 3075 (w), and 3045 (w) (ArH, =CH), 2980 (m), 2945 (m), 2925 (m), and 2885 (m) (CH), 1695 (s, C=O of **4**), 1680 (sh, m), 1665 (m), 1635 (m), 1605 (m), 1455 cm^{-1} (m, CH_3); $\nu_{max}^{CS_2}$ 747 (m) and 692 cm^{-1} (s, Ph); λ_{max}^{hexane} (ϵ) *241* (12,430, $\pi \rightarrow \pi^*$), 280 (sh, 1150), 288 (sh, 750), 316 (sh, 65), 327.5 (81), *339* (82, n $\rightarrow$ π^*), 353 (sh, 62), 369 mμ (sh, 33); λ_{max}^{MeOH} (ϵ) 245.5 (12,160, $\pi \rightarrow \pi^*$) 321 mμ (sh, 134, n $\rightarrow$ π^*); nmr ($CDCl_3$) a multiplet at −8.1 to −7.8 (3.0 H, H^a, $H^{a'}$), a multiplet at −7.6 to −7.2 with maxima at −7.50 and −7.47 (4.7 H,



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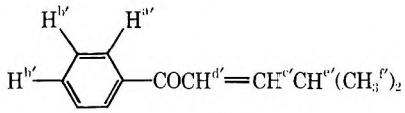

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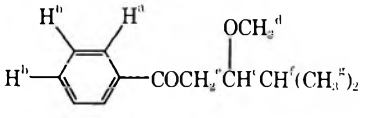
H^b, $H^{b'}$), a multiplet (see above) at −7.0 to −6.6 (0.7 H, $H^{e'}$, $H^{d'}$), a triplet of triplets centered at −5.44 with further ill-defined splitting (1.0 H, H^e, J_{cd} = 6.9 Hz, $J_{ce,cf} \cong$ 1.4 Hz), a doublet centered at −3.65 (1.9 H, H^d, J_{cd} = 6.9 Hz), a multiplet (see above) at −2.7 to −2.2 (0.35 H, $H^{e'}$), a doublet centered at −1.74 with further ill-defined splitting (H^e, J_{ce} = 1.1 Hz) incompletely resolved from a singlet at −1.68 with ill-defined splitting (H^f) (6.1 H total), a doublet (see above) at −1.11 (2.4 H, $H^{f'}$) and a weak doublet centered at −1.04 ppm (J = 6.7 Hz, area ratio of doublets at −1.11 and −1.04 ~95:5). The ratio of isomers **4** and **3** was 72:28 based on the areas of the H^c, H^d, H^e, H^f, $H^{e'}$, $H^{d'}$, $H^{e'}$, and $H^{f'}$ nmr signals. Gc analysis (2 ft × 0.25 in. column packed with 20% 410 silicone gum rubber on 60–80 mesh Chromosorb Z, column and injection port temperature 150°, He flow rate 48 ml/min) showed only one (>99.8% by area) major peak, retention time 5.8 min. The material did not elute from a 10-ft UCON column at 200°.

Attempted Equilibration of *trans*-1-Phenyl-4-methyl-2-penten-1-one (3) and 1-Phenyl-4-methyl-3-penten-1-one (4). A. Isomer 3 in 0.1 *M* Potassium Hydroxide for 5 Min. Characterization of 1-Phenyl-3-methoxy-4-methyl-1-pentanone (10).—A 0.1 *M* solution of methanolic potassium hydroxide was prepared by dissolving 6.53 g (85.9% assay, 0.100 mol) of potassium hydroxide in enough methanol to make 1 l. of solution. A portion (28.7 ml, 2.87 mmol of KOH) was purged with nitrogen for 10 min in a serum capped flask. A mixture of the isomeric ketones **3** and **4** (75 ± 2% **3**, 25 ± 2% **4**) (0.50 ml, 0.49 g, 2.8 mmol) was added in one portion at 25° to give a clear yellow solution (0.097 *M* ketones). The solution was allowed to stand at 25.0° in a water bath for 5 min. Water (25 ml) was added, and the resulting mixture was neutralized with glacial acetic acid. The neutral solution was extracted with methylene chloride (2 × 20 ml, 10 ml), and the combined extracts were washed with water (2 × 20 ml, 10 ml). After drying over anhydrous calcium sulfate the solvent was removed under vacuum to give 0.492 g of colorless oil. The nmr spectrum ($CDCl_3$) showed the peaks due to the ketones **3** and **4** and the methyl ether **10**, a low-intensity multiplet at −3.8 to −3.4 (H^e, partially obscured by the −3.65 ppm doublet of the ketone **4**), a high-intensity singlet at −3.30 (H^d), at least a four-



10

line multiplet of medium intensity at −3.2 to −2.9 (H^e, no simple splitting pattern), and a high-intensity doublet centered at −0.95 ppm (H^g, $J_{fg} \cong$ 6.7 Hz). The relative intensities were in reasonable accord with the structure **10**. The resonances due to the other protons, H^a, H^b, and H^f, were obscured by the corresponding resonances for the ketones **3** and **4**. The molar ratio of products **3**, **4**, and **10** was 41:20:39, respectively, based on the peak areas at −6.8 (**3**), −5.4 (**4**), and −3.3 ppm (**10**). Essentially no dimers **5** and **6** were detected. The infrared spectrum (CCl_4) showed bands in addition to those due to ketones **3** and **4** at 2835 (OCH_3[15] of **10**), 1695 (more intense than in spectrum of starting mixture of ketones **3** and **4**, C=O of **10**), (CS_2) 1110 and 1091 cm^{-1} (CO[16]). The mass spectrum (direct probe sample introduction, 40°) showed ion peaks for the ketones **3** and **4**, and in addition showed significant peaks at m/e (rel intensity) 206 (0.4, M^+ of **10**), 192 (0.4, $M^+ - CH_2$), 191 (3.2, $M^+ - CH_3$), 176 (0.4, $M^+ - CH_2O$), 175 (1.1, $M^+ - CH_3O$), 172 (2.1, $M^+ - CH_3OH, H_2$), 163 (7.0, $M^+ - CO, CH_3$) [reference peaks, m/e 174 (7.0, $M^+ - CH_3OH$ and M^+ of **3** and **4**) and 105 (*100.0*, $PhCO^+$)].

B. Isomer 4 in 0.1 *M* Potassium Hydroxide for 5 Min.—As in the preceding experiment, a mixture of the ketones **4** and **3** (74 ± 2% **4**, 26 ± 2% **3**) (0.50 ml, 0.50 g, 2.9 mmol) in 28.7 ml of the 0.1 *M* methanolic potassium hydroxide solution (0.098 *M* ketones) was allowed to react for 5 min at 25.0°. The resulting yellow solution was worked up as described in part A to give 0.485 g of colorless oil. Nmr analysis ($CDCl_3$) indicated a molar ratio of 19:69:12 of **3**, **4**, and **10**, respectively, based on peak areas at −6.8 (**3**), −5.4 and −1.7 (**4**), and −3.3 ppm (**10**). Essentially no dimers **5** and **6** were detected.

C. Isomer 3 in 1 *M* Potassium Hydroxide for 15 Min.—A 1 *M* solution of methanolic potassium hydroxide was prepared by dissolving 6.53 g (85.9% assay, 0.100 mol) of potassium hydroxide in enough methanol to make 100 ml of solution. A portion (2.87 ml, 2.87 mmol of KOH) was purged with nitrogen for 5 min in a serum capped vial. A mixture of the isomeric ketones **3** and **4** (75 ± 2% **3**, 25 ± 2% **4**) (0.50 ml, 0.49 g, 2.8 mmol) was added in one portion at 25° to give a brigh yellow solution (0.84 *M* ketones). The solution was allowed to stand at 25.0 ± 0.2° for 15 min. Water (3 ml) was added and the cloudy white mixture, which contained a white solid, was neutralized with glacial acetic acid. The neutral mixture was extracted with methylene chloride (2 × 2 ml, 1 ml). The solid dissolved in the methylene chloride. The combined extracts were washed with water (2 × 2 ml, 1 ml) and dried over anhydrous calcium sulfate. Evaporation of the solvent under vacuum gave 0.406 g of waxy white solid. Nmr analysis ($CDCl_3$) indicated a molar ratio of ~20:~15:~35:~30 (all ±5–10%) of **3**, **4**, **10**, and **5**, respectively, based on peak areas at −6.8 (**3**), −5.4 and −1.74 (**4**), −3.3 (**10**), and −5.0, −4.4, and −1.4 ppm (**5**). A trace (few per cent) of the dimer **6** was present as determined by shoulders in the −0.9 ppm region.

D. Isomer 4 in 1 *M* Potassium Hydroxide for 15 Min.—As described in part C above, a mixture of the ketones **4** and **3** (74 ± 2% **4**, 26 ± 2% **3**) (0.50 ml, 0.50 g, 2.9 mmol) in 2.87 ml of the 1 *M* methanolic potassium hydroxide solution (0.85 *M* ketones) was allowed to react for 15 min at 25.0 ± 0.2°. The solution had set up to a crystalline mass during this time. This mixture was worked up as described in part C to give 0.442 g of waxy white solid. Nmr analysis ($CDCl_3$) indicated a molar ratio of ~5:~50:~10:~30 (all ±5–10%) of **3**, **4**, **10**, and **5**, respectively, based on peak areas at −6.8 and −1.1 (low-field branch) (**3**), −3.7 (**4**), −3.3 (**10**), and −1.4 ppm (**5**). A trace (few per cent) of the dimer **6** was present as shown in part C.

Registry No.—**1**, 98-86-2; **2**, 78-84-2; **3**, 36597-08-7; **4**, 36597-09-8; **5**, 36597-10-1; **6**, 36597-11-2; **10**, 36597-12-3.

Acknowledgment.—The authors wish to thank Professors J. C. Martin and M. Stiles for helpful discussions.

(15) Reference 9, p 133.
(16) Reference 9, p 189.

Vinyl Radicals. VIII. A Study of the Possibility of Aryl Migration in 2-Arylvinyl Radicals

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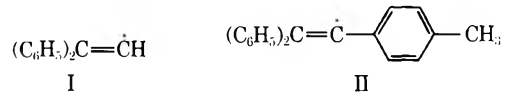
The 2,2-diphenylvinyl (I) and 1-(*p*-tolyl)-2,2-diphenylvinyl (II) radicals are formed by the thermal decomposition of the appropriate *tert*-butyl peresters in solvents such as cumene and *tert*-butylbenzene. The radicals are quenched by hydrogen donors to give the corresponding olefins in varying yields, according to the nature of the hydrogen donor, temperature, and perester concentration. Rearranged products, *cis*- and *trans*-stilbene and diphenylacetylene from I and 1,2-diphenyl-1-(*p*-tolyl)ethylene from II, are not found; depending on the particular reaction conditions, approximately 0.2–1.5% yields of rearranged products would have been detected.

1,2-Aryl migrations are firmly established in the chemistry of 2-arylalkyl cations, radicals, and carbanions (organometallics).[2] The corresponding aryl shift is also known for 2-arylvinyl cations.[3-6] This paper reports a study of the potential for aryl migration in appropriately structured vinyl radicals.

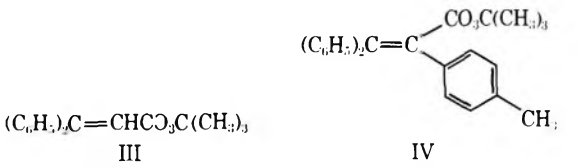
Rearrangements of 2-aryl vinyl radicals have been considered previously. Koehl[7] observed phenyl migration in the anodic oxidation of 3,3-diphenylacrylic acid in acetic acid. Products characteristic of radical reactions were unrearranged, while those of carbonium ion origin were both rearranged and unrearranged; the migration therefore, was attributed to the 2,2-diphenylvinyl cation rather than the radical. Köbrich[8] observed diphenylacetylene (rearranged product) in the thermal decomposition of silver 2-halo-3,3-diphenylacrylates and 1-chloro-2,2-diphenylvinyl silver. While there is evidence for a homolytic component to these decompositions, Köbrich concludes that the rearrangement is attributable to a carbenoid species, rather than to vinyl radical intermediates. In both of these studies, the behavior and lifetimes of the 2-arylvinyl radicals are not well defined. The aim of the present work was to generate vinyl radicals I and II from the corresponding peresters, under conditions where the subsequent chemistry would be straightforward.



I II

Results

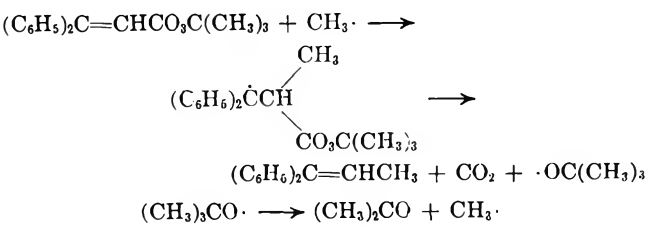
tert-Butyl 3,3-diphenylperacrylate (III) and *tert*-butyl 2-(*p*-tolyl)-3,3-diphenylperacrylate (IV), the precursors of the desired radicals, are readily prepared by the reactions of the corresponding acyl chlorides with sodium *tert*-butyl peroxide in methylene chloride at 0°.



III IV

Both peresters are obtained as crystalline solids and give satisfactory spectroscopic and analytical data. The peresters were thermally decomposed under a variety of conditions (solvent, temperature, concentration) to give the vinyl radicals I and II. Large-scale decompositions allowed isolation and qualitative identification of reaction products; carbon dioxide and nonvolatile products were determined quantitatively in some of these experiments. Most yields were determined by gas chromatographic (gc) analyses of reaction mixtures from small-scale decompositions in sealed, deoxygenated ampoules. The results of these product studies are presented in Table I for the diphenyl perester and in Table II for the triaryl perester.

Most of the products of the decomposition of the diphenyl perester III are anticipated by previous studies of the homolytic decomposition of α,β-unsaturated peresters.[9,10] Thus, acetone, *tert*-butyl alcohol, and dicumyl reveal the radical nature of the perester fragmentation. 4-Phenylcoumarin and 3,3-diphenylacrylic acid reflect the intermediacy of acyloxy radicals. Decarboxylation of the acyloxy radical gives CO_2 and the desired vinyl radical I, which abstracts hydrogen to give 1,1-diphenylethylene. 1,1-Diphenylpropene-1 is presumably the result of an induced decomposition initiated by addition of methyl radical to the perester.



Similar induced pathways have been observed for other α,β-unsaturated peresters.[11]

The dependence of the yields of diphenylpropene (induced product) and diphenylethylene (normal product) on the radical-scavenging ability of the solvent and the concentration of the initial perester are in ac-

(1) From the Ph.D. Thesis of J. K. Haynes, Jr., University of Rochester, 1971.

(2) Reviews: Y. Pocker, C. Walling, and H. E. Zimmerman in "Molecular Rearrangements," Part I, P. de Mayo, Ed., Wiley, New York, N. Y., 1963, Chapters 1, 6, and 7.

(3) M. A. Imhoff, R. H. Summerville, P. v. R. Schleyer, A. G. Martinez, M. Hanack, T. E. Dueber, and P. J. Stang, *J. Amer. Chem. Soc.*, **92**, 3802 (1970); P. J. Stang, *Progr. Phys. Org. Chem.*, in press.

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(6) M. S. Newman and C. D. Beard, *ibid.*, **92**, 7564 (1970), and previous papers.

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(8) G. Köbrich, H. Fröhlich, and W. Drischel, *J. Organometal. Chem.*, **6**, 194 (1966); G. Köbrich and H. H. Fröhlich, *Chem. Ber.*, **98**, 3637 (1965).

(9) J. A. Kampmeier and R. M. Fantazier, *J. Amer. Chem. Soc.*, **88**, 1959 (1966).

(10) L. A. Singer and N. P. Kong, *ibid.*, **88**, 5213 (1966).

(11) N. Muramoto, T. Ochiai, O. Simamura, and M. Yoshida, *Chem. Commun.*, 717 (1968).

TABLE I

YIELDS[a] OF PRODUCTS FROM THE THERMAL DECOMPOSITION OF *tert*-BUTYL-3,3-DIPHENYLPERACRYLATE (III)

	Cumene				*tert*-Butylbenzene,	Benzene	
	110° 0.07 *M*	110° 0.007 *M*	200° 0.07 *M*	200° 0.007 *M*	200° 0.007 *M*	200° 0.07 *M*	200° 0.007 *M*
Product	III	III	III	III	III	III	III
Carbon dioxide	34[b]						
3,3-Diphenylacrylic acid	17[b]		17		4		
1,1-Diphenylethylene	13	29	33	52	17	3	5
1,1-Diphenylpropene-1	*c*	*c*	*c*	*c*	6	19	6
4-Phenylcoumarin	27	15	21	11	13		21
Acetone	9	9	27	30	63		
tert-Butyl alcohol	75	73	64	63	22		
Dicumyl	26	45	42	63			
1,1-Diphenyl-2-(x-*tert*-butylphenyl)ethylene[d]					25	6[e]	21[e]

[a] Each entry is the average of several independent determinations. Reaction times: 5 hr at 110°; 1 hr at 200°. [b] 10-hr reaction time. [c] Present in small amounts, but not measured. [d] Mixture of isomers; ortho:meta:para, ~1:3:1. [e] Triphenylethylene.

TABLE II

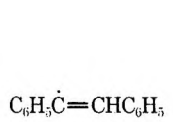
THERMAL DECOMPOSITION OF *tert*-BUTYL 2-(*p*-TOLYL)-3,3-DIPHENYLPERACRYLATE (IV)[a]

		Yield,[b] %		
Solvent	Temp, °C[c]	1,1-Diphenyl-2-(*p*-tolyl)-ethylene	Acetone	*tert*-Butyl alcohol
Cumene[d]	110	82	10	78
tert-Butylbenzene	110	41	45	43
tert-Butylbenzene	200	43		
Benzene	200	40		

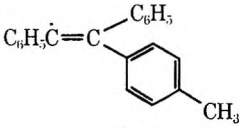
[a] [IV] = 1.5×10^{-2} *M*. [b] Each entry is the average of several independent determinations. [c] Reaction times: 5 hr at 110°; 1 hr at 200°. [d] Dicumyl was formed in 70% yield.

cord with this induced scheme. Methyl radical attack on the O–O bond is apparently not a competing induced pathway, since methyl 3,3-diphenylacrylate is not formed (<0.3%) in decompositions of the perester in solvents where diphenylpropene is an important product (*e.g.*, benzene and *tert*-butylbenzene). Finally, the formation of triarylethylenes in benzene and *tert*-butylbenzene indicates that vinyl radicals are scavenged by addition to aromatic rings when the solvent is a poor hydrogen donor.[12] The decomposition of the triaryl perester IV is apparently more straightforward than that of perester III. The olefin derived from the triarylvinyl radical II is a major product. Acyloxy radical products are not observed and 1,1-diphenyl-2-(*p*-tolyl)propene-1 is, at best, a minor product (1–2% in benzene).

While there is clear evidence in Tables I and II for competing pathways and side reactions, the main point is that both peresters give useful yields of the olefins derived from the intermediate vinyl radicals I and II. The salient point in these product studies is that products derived from rearranged vinyl radicals V and VI are not observed.



V



VI

(12) P. Spagnolo and M. Tiecco, *Tetrahedron Lett.*, 2313 (1968).

Control Experiments.—The stilbenyl radical V was generated by Singer and Kong[10] by the decomposition of the isomeric *tert*-butyl 2,3-diphenylperacrylates in cumene and observed to give *cis*- and *trans*-stilbene (90:10) and diphenylacetylene. These products, therefore, are expected from the rearrangement of the diphenylvinyl radical I. The stability of these products to the reaction conditions was tested by decomposing the diphenyl perester III in *tert*-butylbenzene at 200° in the presence of the anticipated rearrangement products at concentrations of about 20% each, based on starting perester. Analysis of the reaction mixture showed that >95% of the added materials survived the perester decomposition reaction. Conservative limits of detectability of the anticipated rearrangement products were determined for representative decomposition conditions by careful gc comparison of reaction mixtures before and after addition of known amounts of authentic *cis*- and *trans*-stilbene and diphenylacetylene. In almost all experiments, there were no observable gc peaks corresponding to the rearrangement products in the undoped reaction mixtures. Detectability limits are summarized in Table III.

TABLE III

LIMITS OF DETECTABILITY OF REARRANGEMENT PRODUCTS FROM THE 2,2-DIPHENYLVINYL RADICAL, I

			Limit of detectability[a]		
			Stilbene		
[III], *M* × 10³	Solvent	Temp, °C	*cis*-	*trans*-	Diphenylacetylene
7	Cumene	110[b]	0.75	1.2	1.3
68	Cumene	200[b]	0.30	0.25	0.14[c]
7	Cumene	200	0.76	1.2	1.4
8	*tert*-Butylbenzene	200	0.69	1.1	1.2
72	*tert*-Butylbenzene	200		0.25[c]	0.14

[a] Expressed as per cent yield based on initial [III]. [b] Reaction times: 5 hr at 110°; 1 hr at 200°. [c] Trace peaks observed at the appropriate retention times; the areas of these peaks correspond to yields less than the conservative limits cited.

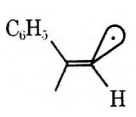
Rearrangement of the triaryl vinyl radical II would give radical VI, which should be converted to a mixture of *cis*- and *trans*-1,2-diphenyl-1-(*p*-tolyl)ethylene by reaction with hydrogen donors. The stability of the olefins to decomposing perester mixtures was tested by doping separate perester solutions with known amounts of rearranged and unrearranged olefins.

The observed olefin yields were compared to those from undoped perester decompositions. In each case, ~75% of the added olefin remained; olefins are consumed to a small extent, but the rearranged products are not preferentially destroyed. 1,1-Diphenyl-2-(*p*-tolyl)ethylene and the rearranged cis and trans isomers were not separated under any of our gc conditions. Control experiments with doped samples showed that rearranged olefins could be readily detected (0.2% yield based on initial perester) by isolation of the olefin mixture by chromatography on alumina, ozonolysis of the olefin mixture, and subsequent gc analysis for 4-methylbenzophenone. Actual mixtures from the decomposition of triaryl perester IV in *tert*-butylbenzene at 110° gave trace gc peaks at the retention time of 4-methylbenzophenone; the area of these peaks corresponded to <0.03% yield of rearranged olefin, based on initial perester concentration. *tert*-Butylbenzene is the medium of choice for control tests of the stability and limits of detectability of rearranged products, since the relatively poor hydrogen donor characteristics of the solvent should accentuate any destruction of the olefins by radical reactions. Vinyl radicals should also have a longer lifetime in *tert*-butylbenzene than in cumene, allowing greater opportunity for a rearrangement.

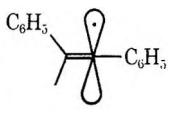
Discussion

The data cited in the preceding section clearly indicate that 1,2-phenyl migration in vinyl radicals I and II does not compete to any significant extent with the reactions which consume the radicals. Control experiments certify that the rearranged products would be observed if they had been formed in yields greater than about 0.2–1.5% depending on the specific reaction conditions. It is important to note that the potential rearrangement is in competition with radical-scavenging reactions; it is conceivable that rearrangement might be observed if the radical scavenging processes were slowed dramatically.

Radicals I and II were chosen because of their different geometries. A number of studies indicate that vinyl radicals with a hydrogen in the 1 position (such as I′) are bent.[13] In contrast, several lines of evidence point to a linear structure for 1-phenyl vinyl radicals (II′).[14,15] In particular, it seemed that the linear



I′



II′

geometry of II′ might be more suitable for rearrangement because of a more favorable spatial interaction of the radical orbital with the neighboring aromatic ring. Vinyl cations are isostructural with the linear vinyl radicals and are known to rearrange.[3-4] In spite of the geometric similarities, electronic factors are apparently more conductive to the cation rearrangement.[16]

(13) L. A. Singer in "Selective Organic Transformations," Vol. II, B. S. Thyagarajan, Ed., Wiley, New York, N. Y., 1972, p 239.

(14) R. M. Kopchik and J. A. Kampmeier, *J. Amer. Chem. Soc.*, **90**, 6733 (1968); L. A. Singer and J. Chen, *Tetrahedron Lett.*, 4849 (1969).

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(16) H. E. Zimmerman and A. Zweig, *J. Amer. Chem. Soc.*, **83**, 1196 (1961).

Experimental Section

Melting points are corrected and boiling points are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian Associates A-60 spectrometer and on a Japan Electron Optics Laboratory Company 4H-100 spectrometer by Mrs. Judy Lewis. Infrared spectra were recorded on Perkin-Elmer Model 137 and Perkin-Elmer Model 421 spectrophotometers. Ultraviolet spectra were recorded on a Cary Model 11MS spectrophotometer. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6E mass spectrometer by Mrs. Judy Lewis and Mr. Jacob M. Hoffman, using direct sample introduction or a tandem arrangement with a Perkin-Elmer Model 900 gas chromatograph equipped with a hydrogen flame ionization detector with helium as the carrier gas. Vapor phase chromatographic studies were conducted on F & M Model 700 chromatographs equipped with a thermal conductivity detector with WX filaments or with a hydrogen flame ionization detector. Thin layer chromatography (tlc) analyses were conducted on 25 × 75 mm microscope slides with E. Merck AG silica gel G as the stationary phase. Elemental analyses were conducted by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

Cumene (Eastman White Label) was shaken with portions of concentrated sulfuric acid until the extracts were no longer yellow, washed three times with distilled water, dried over anhydrous magnesium sulfate, and distilled from freshly cut sodium through a 2.5 × 38 cm Vigreux column; a center cut was collected, bp 150–151°, and stored under a nitrogen atmosphere over 4 Å molecular sieves. The cumene was periodically examined for peroxide formation.[17] *tert*-Butylbenzene (Aldrich Chemical Co.) was distilled through a 2.5 × 38 cm Vigreux column; a center cut was taken, bp 169–170°, and stored over 4 Å molecular sieves. Benzene (Mallinckrodt SpectrAR grade) was used as received.

***tert*-Butyl 3,3-Diphenylperacrylate (III).**—To 14.54 g (0.0648 mol) of 3,3-diphenylacrylic acid[18,19] and 0.6 ml of dimethylformamide at −78° was added dropwise with stirring 14.0 g (0.110 mol) of oxalyl chloride in 20 ml of anhydrous ether.[20] The solution was brought to 0° stirred for a total of 15 hr. Solvent and excess oxalyl chloride were removed at room temperature with a water aspirator and finally by evacuation at 0.06 mm for 5 hr. 3,3-Diphenylacryloyl chloride is obtained as a yellow-green, crystalline solid, 15.77 g (100%), mp 64–69° (uncorrected), ir (CCl_4) 1770 cm^{-1}.

A solution of 15.77 g (0.065 mol) of the acid chloride in 250 ml of dry methylene chloride was added to a stirred suspension of 11.65 g (0.104 mol) of sodium *tert*-butyl peroxide[21] in 500 ml of dry methylene chloride at 0°. Stirring was continued for 3 hr at 0°. The mixture was filtered and the methylene chloride was removed under reduced pressure to give a light tan oil which was chromatographed on alumina at 10° with petroleum ether (bp 30–60°) as eluent. Crystallization of the resulting colorless oil from petroleum ether gave 10.86 g (56.3%) of *tert*-butyl 3,3-diphenylperacrylate as white plates, mp 66.5–67°, homogeneous by tlc on silica gel with chloroform, R_f 0.76. Recrystallization from ethyl ether–petroleum ether gave perester with a peroxide content of 96.2% by iodometric titration[22] and no improvement in melting point: uv $\lambda_{max}^{95\%\ EtOH}$ 220 nm (shoulder) (ϵ 16,700) and 282 (15,000); ir ($CHCl_3$) 3045, 1750, 1605, 1365, and 1095 cm^{-1}; nmr ($CDCl_3$) τ 2.68 (10 H), 3.70 (s, 1 H), 8.85 (s, 9 H); mass spectrum (75 eV, inlet 60°) *m/e* (rel intensity) 296 (1.3, M^+), 270 (7), 224 (17.2), 208 (24), 207 (100), 179 (30.5), 178 (37), 152 (9), and 57 (15.7).

Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.07; H, 6.75.

***tert*-Butyl 2-(*p*-Tolyl)-3,3-diphenylperacrylate (IV).**—2-(*p*-Tolyl)-3,3-diphenylacryloyl chloride was prepared by the cautious addition of 22.3 g (0.176 mol) of oxalyl chloride in 40 ml of anhydrous ethyl ether over a period of 45 min to a rapidly stirred suspension of 15.025 g (0.0478 mol) of 2-(*p*-tolyl)-3,3-diphenyl-

(17) C. D. Wagner, R. H. Smith, and E. D. Peters, *Anal. Chem.*, **19**, 976 (1947).

(18) F. Bergmann, M. Weizmann, E. Dimant, J. Patai, and J. Szmuskowicz, *J. Amer. Chem. Soc.*, **70**, 1612 (1948).

(19) M. S. Kharasch, S. S. Kane, and H. C. Brown, *ibid.*, **64**, 333 (1942).

(20) H. H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, **42**, 1653 (1959).

(21) J. P. Lorand and P. D. Bartlett, *J. Amer. Chem. Soc.*, **88**, 3294 (1966).

(22) L. S. Silbert and D. Swern, *Anal. Chem.*, **30**, 385 (1958).

acrylic acid[23] and 0.85 ml of dimethylformamide[20] in 40 ml of anhydrous ether at 0°; stirring was continued for 8 hr at 0°. Removal of the ether and excess oxalyl chloride at room temperature with a water pump followed by evacuation at 0.05 mm for 30 min yielded 17.50 g (110%) of 2-(*p*-tolyl)-3,3-diphenylacryloyl chloride as a pale yellow solid.

To a suspension of 10.0 g (0.0892 mol) of sodium *tert*-butyl peroxide[21] in 350 ml of dry methylene chloride at 0° was added dropwise 17.50 g of chloride in 200 ml of dry methylene chloride over a period of 4 hr. The reaction was stirred for 5 hr at 0° and filtered, and the organic layer was washed with three 50-ml portions of 5% sodium bicarbonate and three 100-ml portions of water and dried over magnesium sulfate. Evaporation of the methylene chloride yielded a solid which was recrystallized from methylene chloride–petroleum ether at −78° to yield 13.73 g (74.4%) of *tert*-butyl 2-(*p*-tolyl)-3,3-diphenylperacrylate as a white solid, mp 123–124°, 89.2% peroxide by titration.[22] Recrystallization from methylene chloride–petroleum ether and chromatography on alumina (Alcoa chromatographic alumina F-20) with benzene, followed by recrystallization from benzene–petroleum ether, yielded 10.57 g (57.3%) of perester: mp 123–124°; 92.3% peroxide content by titration; uv $\lambda_{max}^{95\%\ EtOH}$ 237 nm (ϵ 21,600) and 300 (9970); ir ($CHCl_3$) 1745 (s), 1460 (m), 1365 (m), 1180 (s), and 1130 cm^{-1} (s); nmr ($CDCl_3$) τ 2.68–2.91 (14 H), 7.75 (s, 3 H), 8.94 (s, 9 H); mass spectrum (75 eV, inlet 140°) *m/e* (rel intensity) 386 (2.8, M^+), 314 (4.7), 286 (5.3), 270 (14.3), 269 (20.4), 253 (6.2), 178 (4.4), 165 (4.3), 91 (35), 78 (88), 77 (20), and 59 (100).

Anal. Calcd for $C_{26}H_{26}O_3$: C, 80.80; H, 6.78. Found: C, 80.93; H, 6.93.

1,1-Diphenyl-2-(*p*-tolyl)propene-1.—To 0.30 g (0.0432 g-atom) of lithium metal, flattened into thin disks, in 30 ml of anhydrous ethyl ether under a nitrogen atmosphere was added with stirring at 25° 2.44 g (0.0172 mol) of methyl iodide in an additional 30 ml of ether over a period of 30 min. The mixture was refluxed for 15 min, during which time all of the lithium dissolved. To this was added 2.01 g (7.02 mmol) of α,α-diphenyl-4-methylacetophenone[24] in 50 ml of ether, and the mixture was refluxed for 11 hr. Water (5 ml) was added dropwise and the mixture was stirred for 1 hr. The reaction mixture was washed with two 30-ml portions of water and dried over anhydrous sodium sulfate, and the ether was removed to yield a viscous oil whose infrared spectrum (film) showed absorptions at 3640 and 3540 cm^{-1}. The oil was dissolved in 50 ml of acetyl chloride and refluxed for 5.5 hr. Removal of the excess acetyl chloride gave a red oil, which was dissolved in 50 ml of ether and extracted with three 10-ml portions of 5% sodium bicarbonate and then chromatographed on silica gel with petroleum ether as eluent. The total olefin fraction was refluxed in 200 ml of benzene with 0.5 ml of methanesulfonic acid for 3 hr. Work-up and crystallization from petroleum ether gave 1.073 g (53.8%) of 1,1-diphenyl-2-(*p*-tolyl)-propene-1 as white needles: mp 83–84°; ir (CCl_4) 3150, 3090, 2980, 2910, 1595, 1510, 1490, 1440, 1375, 1020, and 910 cm^{-1}; nmr ($CDCl_3$) τ 2.70 (5 H), 2.98 (9 H), 7.75 (s, 3 H), and 7.90 (s, 3 H).

Anal. Calcd for $C_{22}H_{20}$: C, 92.91; H, 7.09. Found: C, 93.03; H, 7.08.

α,α-Diphenyl-4-*tert*-butylacetophenone.—Diphenylacetic acid (8.50 g, 0.040 mol) was refluxed with thionyl chloride for 30 min. Excess thionyl chloride was removed under reduced pressure and the resulting acid chloride was dissolved in 20 ml of *tert*-butylbenzene and added dropwise to a stirred suspension of 12.0 g (0.090 mol) of aluminum chloride powder in 10 ml of *tert*-butylbenzene. After 3.5 hr at 95°, the reaction mixture was poured into 100 ml of ice-cold, dilute hydrochloric acid and stirred for 14 hr at 25°. The mixture was extracted with ether, and the ether solution was washed with two 50-ml portions of 5% sodium bicarbonate and two 50-ml portions of water. The ether solution was boiled with 15 g of activated charcoal for 15 min, filtered, and evaporated to yield an oil which was treated with cold petroleum ether to yield 1.93 g of α,α-diphenyl-4-*tert*-butylacetophenone as a white solid, mp 119–121°. Chromatography on silica gel gave an additional 4.89 g of material in the fraction eluted with 4:1 petroleum ether–benzene for a total yield of 6.82 g (51.9%) of the ketone. Tlc of these two fractions on silica gel with 1:1 petroleum ether–benzene showed single spots of identical R_f values; ir (CCl_4) 3120, 3080, 3015, 1685, 1600, 1495, 1450, and 1110 cm^{-1}; nmr ($CDCl_3$) showed an A_2B_2 quartet centered at τ 2.00 and 2.56 (4 H), 2.69 (s, 10 H), 3.93 (s, 1 H), and 8.71 (s, 9 H).

Anal. Calcd for $C_{24}H_{24}O$: C, 87.76; H, 7.37. Found: C, 87.88; H, 7.31.

1,1-Diphenyl-2-(*p*-*tert*-butylphenyl)ethylene.—To 0.144 g (3.79 mmol) of lithium aluminum hydride in 25 ml of dry tetrahydrofuran under nitrogen was added dropwise a solution of 1.004 g (3.06 mmol) of α,α-diphenyl-4-*tert*-butylacetophenone in a total of 15 ml of tetrahydrofuran over a period of 15 min. The reaction mixture was refluxed for 19.5 hr, cooled, and hydrolyzed by the careful addition of 5 ml of water. Extraction with three 50-ml portions of methylene chloride followed by evaporation to dryness yielded a pale yellow oil presumed to be 1-hydroxy-1-(*p*-*tert*-butylphenyl)-2,2-diphenylethane. Without further characterization, this oil was dehydrated by refluxing in benzene with a trace of sulfuric acid for 15 hr. Work-up gave an oil which solidified. Gc analysis of the oil on Apiezon L (6 ft × 0.25 in., 10% on Chromosorb W, temperature programmed from 150 to 275° at 5°/min, He = 100 ml/min) and also on silicon rubber SE-30 (methyl) (6 ft × 0.25 in., 10% on Chromosorb W, 250°, He = 100 ml/min) showed two peaks with retention times of 41.0 and 44.6 and 7.6 and 8.4 min, respectively. The first peak was tentatively assigned to the *m*-*tert*-butyl isomer (4.5%) while the major component is the desired *p*-*tert*-butyl isomer (95.5%). Column chromatography on silica gel with petroleum ether as eluent yielded 0.744 g (77.9% crude) of 1,1-diphenyl-2-(*p*-*tert*-butylphenyl)ethylene as an amorphous white solid, mp 63.5–71.5°. Recrystallization of the isomer mixture from petroleum ether yielded pure (by gc analysis) 1,1-diphenyl-2-(*p*-*tert*-butylphenyl)ethylene: mp 74–76°; ir ($CHCl_3$) 3020, 1595, 1500, 1490, 1440, 1360, 1270, 1105, 1070, 1025, 890, and 830 cm^{-1}; nmr ($CDCl_3$) τ 2.75–3.08 (15 H) and 8.76 (s, 9 H).

Anal. Calcd for $C_{24}H_{24}$: C, 92.26; H, 7.74. Found: C, 92.32; H, 7.67.

Small-Scale Perester Decompositions.—The following procedures are typical. Solutions of perester III were introduced into glass tubes, and the samples were degassed at 0.02 mm with three freeze–pump–thaw cycles and sealed. Each tube was placed in a stainless steel bomb with 1.0 ml of cumene to minimize tube breakage and to aid in heat transfer, and heated. The tubes were cooled and opened, and known amounts of the internal standard were added. The tubes were analyzed for 1,1-diphenylethylene, dicumyl, and 4-phenylcoumarin on an Apiezon L column [6 ft × 0.25 in., 10% on Chromosorb W (acid washed), temperature programmed from 150 to 275° at 5°/min, detector 278°, injector 258°, He 100 ml/min], using biphenyl and triphenylmethane as internal standards. Triplicate injections were made for each tube analyzed.

Acetone and *tert*-butyl alcohol yields were determined in a similar fashion on a Carbowax 20M column [10 ft × 0.25 in., 25% on Chromosorb P (acid washed), 60/80 mesh, column 80°, detector 275°, injector 245°, He 100 ml/min] using ethanol as internal standard.

1,1-Diphenyl-2-(*p*-tolyl)ethylene from decomposition of perester IV and dicumyl were determined on Apiezon L as described above using triphenylethylene and triphenylmethane, respectively, as internal standards. Replicate determinations gave about ±5% agreement.

Large-Scale Perester Decompositions.—A 100-ml flask fitted with a nitrogen bubbler was connected to two Dry Ice–acetone traps in series which led to a three-way stopcock connected to two pairs of Ascarite/$Mg(ClO_4)_2$ absorption tubes arranged in parallel so that tubes could be periodically removed and weighed while the gases were vented through the other side of the system. In a typical run, a solution of 1.003 g (3.384 mmol) of *tert*-butyl 3,3-diphenylperacrylate in 60 ml of purified cumene ([perester] = 0.0564 *M*) was cooled to −78°, evacuated to 0.35 mm for 10 min, warmed to 25°, and purged with purified nitrogen. This cycle was repeated three times. The flask was connected to the decomposition train, purged with a 75 ml/min flow of purified nitrogen, and placed in an oil bath at 110 ± 0.2° for 10 hr. The Ascarite/$Mg(ClO_4)_2$ tubes absorbed a total of 0.0528 g (35.5%) of carbon dioxide.

The materials in the first trap were analyzed by gc on a 10 ft × 0.25 in. Carbowax 20M column (column 80°, He 100 ml/min). Acetone, *tert*-butyl alcohol, and cumene were characterized by coinjection with authentic samples.

The reaction mixture was extracted with five 50-ml portions of 10% sodium carbonate; the carbonate solution was back-

(23) N. P. Buu-Hoi and J. Lecocq, *J. Chem. Soc.*, 641 (1947).

(24) P. I. Pollak and D. Y. Curtin, *J. Amer. Chem. Soc.*, **72**, 961 (1950).

extracted with ether, acidified, and extracted with ether, and the ether was worked up to give 0.1113 g (14.7%) of 3,3-diphenylacrylic acid, mp 157–159°, ir ($CHCl_3$) superimposable with that of known acid.[18,19]

The remaining cumene solution was evaporated at approximately 0.25 mm at room temperature to a mixture of a viscous oil and needlelike crystals. The nonacidic materials from three such large-scale runs were combined and chromatographed on neutral Woelm alumina, grade I. Dicumyl, mp 116–118°, 1,1-diphenylethylene,[25] and 4-phenylcoumarin,[18] mp 105–107°, were isolated and characterized by comparison of ir and nmr spectra with those of authentic materials.

Large-scale decompositions of IV gave 1,1-diphenyl-2-(*p*-tolyl)ethylene,[26] isolated by molecular distillation and column chromatography, mp 69.5–71.5°, mmp 69–72°, ir and nmr superimposable with those of authentic samples. 1,1-Diphenyl-2-(*p*-tolyl)propene-1 was characterized by coinjection with an authentic sample as a trace product of the decomposition of IV. Procedures similar to those described for perester III did not give identifiable samples of 2-(*p*-tolyl)-3,3-diphenylacrylic acid or 3-(*p*-tolyl)-4-phenylcoumarin from the decomposition of perester IV.

In another series of experiments, large-scale decompositions of III in benzene and *tert*-butylbenzene were carried out on deoxygenated solutions in sealed Carius tubes. The nonpolar olefin fraction of each decomposition was isolated by chromatography on alumina; the olefin fractions from the runs in *tert*-butylbenzene were further fractionated by molecular distillation at 0.11 mm by varying the bath temperature from 34 to 190°. The fraction distilling at 115–190° (0.11 mm) from the experiments in *tert*-butylbenzene and the total olefin fraction from the benzene run were examined by vpc on a 6 ft × 0.125 in. 10% UC-W98 silicone rubber column. The gas chromatographic eluents were vented *via* a gas separator into an RMU-6E mass spectrometer, and their mass spectra (ionization voltage 75 eV) were scanned and compared with the spectra obtained in a similar manner for authentic 1,1-diphenyl-2-(*p*-*tert*-butylphenyl)ethylene and triphenylethylene.

Triphenylethylene (column 255°, retention time 2.5 min) showed a M^+ ion at *m/e* (rel intensity) 256 (12.6) and other prominent peaks at 178 (20.4), 168 (64.5), 167 (58.7), 165 (30.3), 92 (54), 91 (100), 78 (83.6), and 77 (38.8). Identical fragmentation pattern and gc behavior were obtained for authentic material.

The 1,1-diphenyl-2-(*o*-, *m*-, and *p*-*tert*-butylphenyl)ethylenes [column 270°, *o*- (3.0), *m*- (3.25), and *p*- (3.45 min)] partially overlapped under the conditions of vpc analysis. In all cases, however, consecutive scans of the eluting isomer mixture as a function of time gave a M^+ ion at *m/e* 312 and other prominent peaks at *m/e* 209, 207, 179, 178, 168, 167, 165, 152, 134, 133, 119, 105, 92, 91, and 78. These peaks were common to all three isomers but varied in intensity. The peak eluting at 3.45 min and known para isomer (3.5 min) showed nearly identical fragmentation patterns. Besides the above fragments, major peaks were observed at *m/e* 297, 282.7 (metastable), 256, 224, and 219 of similar relative intensities for both known and suspected para isomer. Further, both of these compounds had identical retention times (44.5 min) on a 10% Apiezon L column (temperature programmed 150–275° at 5°/min). The major isomer (3.25 min) was assigned as the meta isomer by analogy.[12]

Control Experiments. *cis*- and *trans*-Stilbene and Diphenylacetylene.—A stock solution of the two stilbenes and diphenylacetylene in *tert*-butylbenzene was prepared. Run 1 represents the decomposition of two solutions of *tert*-butyl 3,3-diphenylperacrylate (III) in the stock solution. Run 2 is the stock solution and provides a reference point for the analyses. Detector response factors were determined for *cis*- and *trans*-stilbene and diphenylacetylene using the data from the control tubes of run 2. Because *cis*-stilbene has the same retention time as 1,1-diphenylethylene under the analysis conditions, the yields of *cis*-stilbene in run 1 were obtained by subtracting an average yield for 1,1-diphenyl-2-ethylene of 17.2%, determined in separate experiments (Table I), from the total yield of *cis*-stilbene and 1,1-diphenylethylene. The data are presented in Table IV and show that *cis*- and *trans*-stilbene and diphenylacetylene are consumed to only a small extent in the presence of decomposing perester.

(25) C. F. H. Allen and S. Converse, "Organic Syntheses," Collect. Vol. I, H. Gilman, Ed., Wiley, New York, N. Y., 1941, p 226.

(26) A. C. Cope, P. A. Trumbull, and E. R. Trumbull, *J. Amer. Chem. Soc.*, **80**, 2844 (1958).

TABLE IV

DECOMPOSITION OF III IN THE PRESENCE OF *cis*- AND *trans*-STILBENE AND DIPHENYLACETYLENE AT 200° IN *tert*-BUTYLBENZENE

	Yield, %					
	cis-Stilbene		*trans*-Stilbene		Diphenylacetylene	
Run	Found	Added	Found	Added	Found	Added
1[a]	21.8[b]	23.5	20.4	21.8	19.4	19.8
	22.1[b]	23.5	20.5	21.8	18.9	19.8
2[c]	23.4	23.5	21.9	21.8	19.6	19.8
	23.9	23.5	21.8	21.8	20.1	19.8

[a] [III] = 7.83 × 10^{-3} *M*, *cis*-stilbene (2.76 × 10^{-6} mol), *trans*-stilbene (2.56 × 10^{-6} mol), and diphenylacetylene (2.32 × 10^{-6} mol) added per tube. [b] Corrected yield (see text). [c] *cis*-Stilbene (2.76 × 10^{-6} mol, 1.84 × 10^{-3} *M*), *trans*-stilbene (2.56 × 10^{-6} mol, 1.71 × 10^{-3} *M*), diphenylacetylene (2.32 × 10^{-6} mol, 1.55 × 10^{-3} *M*).

Limits of Detection of Products from the Decomposition of *tert*-Butyl 3,3-Diphenylperacrylate.—Several *tert*-butyl 3,3-diphenylperacrylate decomposition mixtures were selected as representative of all of the reaction conditions investigated. Detection limits were established for *cis*- and *trans*-stilbene, diphenylacetylene, and methyl 3,3-diphenylacrylate by comparing the hydrogen flame detector gc chromatograms of known amounts of these decomposition mixtures with identical samples doped separately with known amounts of these compounds. The analysis for *cis*-stilbene was conducted on a Carbowax 20M column [20 ft × 0.125 in., 25% on Chromosorb P (acid washed), 60/80 mesh, column 220°, injector 240°] to give retention times of 46.6, 49.9, and 52.5 min for 1,1-diphenylethylene, *cis*-stilbene, and 1,1-diphenylpropene-1, respectively. The analysis for diphenylacetylene and *trans*-stilbene in the 7 × 10^{-3} *M* perester range was conducted on an Apiezon L column (6 ft × 0.125 in., 3% on Chromosorb G, column 160°, injector 285°) to give retention times of 11.1 and 17 min, respectively. In the 7 × 10^{-2} *M* perester range, limits were established for diphenylacetylene on a 3% Apiezon L column (column 167°, injector 276°), while *trans*-stilbene was determined under similar conditions on a SE-30 (methyl) column (6 ft × 0.125 in., 10% on Chromosorb W, column 170°). The data are reported in Table III. Limits (<0.3%) for the formation of methyl 3,3-diphenylacrylate[27] in *tert*-butylbenzene and in benzene were determined on the 3% Apiezon L column (column 195°, injector 286°). In all cases, the limit of detectability is taken as the concentration necessary to give a well-defined unambiguous gc peak; the limits are conservative.

Decomposition of *tert*-Butyl 2-(*p*-Tolyl)-3,3-diphenylperacrylate in the Presence of Added 1,1-Diphenyl-2-(*p*-tolyl)ethylene and *cis*- and *trans*-1,2-Diphenyl-1-(*p*-tolyl)ethylene.—*tert*-Butyl 1-(*p*-tolyl)-3,3-diphenylperacrylate was decomposed in *tert*-butylbenzene at 110° for 5 hr in the presence of added 1,1-diphenyl-2-(*p*-tolyl)ethylene (run 1) and, in a separate experiment, *cis*- and *trans*-1,2-diphenyl-1-(*p*-tolyl)ethylene (run 2). In run 3, perester IV was decomposed in the absence of added olefin to establish the expected yield of 1,1-diphenyl-2-(*p*-tolyl)ethylene. 1,1-Diphenyl-2-(*p*-tolyl)ethylene and the cis–trans isomer mixture of 1,2-diphenyl-1-(*p*-tolyl)ethylene were not separated under the analysis conditions. The yields of added olefin remaining after reaction were obtained by subtracting the yield of 1,1-diphenyl-2-(*p*-tolyl)ethylene in run 3 from the measured total olefin yields in runs 1 and 2. The results are presented in Table V; it is apparent that both olefins are consumed to comparable extents under these reaction conditions.

Limit of Detection for 1,2-Diphenyl-1-(*p*-tolyl)ethylene.—The validity of the ozonization procedure employed in the analysis for 1,1-diphenyl-2-(*p*-tolyl)ethylene and rearranged 1,2-diphenyl-1-(*p*-tolyl)ethylene was tested. Synthetic mixtures of unrearranged and rearranged triaryl olefin were prepared corresponding to 5.01, 2.64, and 1.08% rearrangement on a mole basis. These samples were ozonized in the presence of a slight mole excess of TCNE in ethyl acetate. Analysis on the dual column F & M 700 flame gas chromatograph on matched FFAP columns [10 ft × 0.125 in., 15% on Chromosorb P (acid washed) 60/80 mesh, column 222°, injector 240°] gave four peaks which were assigned

(27) D. D. E. Newman and L. N. Owen, *J. Chem. Soc.*, 4722 (1952).

TABLE V

DECOMPOSITION OF IV IN THE PRESENCE OF ADDED 1,1-DIPHENYL-2-(*p*-TOLYL)ETHYLENE AND *cis*- AND *trans*-1,2-DIPHENYL-1-(*p*-TOLYL)ETHYLENE IN AND *tert*-BUTYLBENZENE AT 110°

Run	Found olefin, %[a]	Added olefin, % 1,1-Diphenyl-2-(*p*-tolyl)-ethylene	Added olefin, % 1,2-Diphenyl-1-(*p*-tolyl)-ethylene
1[b]	15.2	19.3	
	15.4	19.3	
2[c]	15.2		19.1
	14.4		19.1
3[d]	40.1		
	38.7		

[a] Corrected yield (see text). [b] [IV] = 1.51×10^{-2} *M*, 1,1-diphenyl-2-(*p*-tolyl)ethylene added (2.92×10^{-6} mol/tube). [c] [IV] = 1.51×10^{-2} *M*, 1,2-diphenyl-1-(*p*-tolyl)ethylene added (2.88×10^{-6} mol/tube). [d] [IV] = 1.50×10^{-2} *M*, no added olefin.

to benzaldehyde (2.5), 4-methylbenzaldehyde (3.5), benzophenone (23), and 4-methylbenzophenone (33 min) on the basis of retention times and relative peak heights. Assuming a detector response ratio of unity for the two ketones, relative yields of 4.91, 2.67, and 1.12% were calculated for 4-methylbenzophenone derived from rearranged olefin in the three samples. Analysis of these same samples on an Apiezon L column (6 ft × 0.25 in., 10% on Chromosorb W, column 150–275° at 5°/min, He 100 ml/min) showed that no olefin remained.

Two 100-ml samples, 0.0139 *M* IV in *tert*-butylbenzene, were placed in Carius combustion tubes, degassed at 0.02 mm by three freeze–pump–thaw cycles, sealed, and heated in an oil bath at 110° for 5 hr. A control sample was prepared which was 5.79×10^{-3} *M* in 1,1-diphenyl-2-(*p*-tolyl)ethylene and 2.93×10^{-5} *M* in 1,2-diphenyl-1-(*p*-tolyl)ethylene in *tert*-butylbenzene. This synthetic mixture contained 0.50% rearranged olefin and was carried through the work-up and analytical procedures in parallel with the perester decomposition mixtures. The three samples were each concentrated at 0.25 mm and 60° for 2 hr to yield a viscous oily residue which was chromatographed on a 1.3 × 16.0 mm column of silical gel with benzene as eluent. Thin layer, nmr, and gc indicated that the samples from the perester decompositions were still badly contaminated with several extraneous unidentified materials. The decomposition mixtures and the control sample were rechromatographed on silica gel; the olefin fraction was shown by tlc to be in the fractions eluted with 9:1 hexane–benzene.

Each of the three olefin samples was examined on an F & M 700 flame gas chromatograph on a silicone rubber UC-W98 column (column 235°, injector 250°, detector 360°, N_2 1.0 on flow meter). The olefinic fractions from the perester decompositions contained at least four contaminants of shorter retention time than that of the 1,1-diphenyl-2-(*p*-tolyl)ethylene; the major contaminant had the same retention time as authentic 1,1-diphenyl-2-(*p*-tolyl)propene-1. On the basis of relative peak area measurements, the decomposition samples contained 94% of the potential triaryl olefin mixture; the control sample was shown to contain only the synthetic mixture of unrearranged and rearranged triaryl olefins.

Each of the three olefin mixtures was dissolved in ethyl acetate containing a slight molar excess of tetracyanoethylene[28] and treated with an ozone–oxygen mixture. After 30 min, excess ozone was purged from the mixtures with oxygen. The reaction mixtures were analyzed on a matched pair of 15% FFAP column (column 226°, injector 230°) on an F & M 700 flame instrument. All four control ozonolysis samples were analyzed as standards along with the ozonolysis mixtures from the two perester decompositions. From the sums of the area measurements for the benzophenone and 4-methylbenzophenone peaks in each of the 5.01, 2.64, 1.08, and 0.50% control samples, a working curve was constructed converting measured 4-methylbenzophenone area percentages to 1,2-diphenyl-1-(*p*-tolyl)ethylene mole percentages. A very small peak in both perester decomposition mixtures had the same retention time under the analysis conditions as the peak assigned to 4-methylbenzophenone in the control sample; this peak was determined to be equivalent to 0.075 mol % of rearranged 1,2-diphenyl-1-(*p*-tolyl)ethylene in the perester decomposition mixtures. On the basis of the purity established for the olefin mixtures of 94%, this peak corresponds to 0.08 mol % of rearranged olefin or 0.03% yield of rearranged olefin, based on initial perester. Since neither 4-methylbenzophenone nor rearranged olefin were rigorously shown to be present, 0.03% represents a maximum yield for rearranged olefin.

Registry No.—I, 36595-08-1; II, 36595-09-2; III, 35286-77-2; IV, 35286-78-3; 3,3-diphenylacrylaryl chloride, 4456-79-5; 1,1-diphenyl-2-(*p*-tolyl)-propene-1, 36601-67-9; α,α-diphenyl-4-*tert*-butylacetophenone, 36601-68-0; 1,1-diphenyl-2-(*p*-*tert*-butylphenyl)ethylene, 36601-69-1.

Acknowledgment.—This work was supported by the National Science Foundation (GP-29494).

(28) R. Criegee and P. Günther, *Chem. Ber.*, **96**, 1564 (1963).

Restricted Rotation in Benzamidinium Systems

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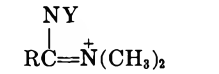
Variable-temperature nmr examination of *N'*-phenyl-, *N'*-benzyl-, *N'*-ethyl-, and *N'*-*tert*-butyl-*N,N*-dimethylbenzamidine shows the existence of rotational conformers with barriers to rotation about the C–N$(CH_3)_2$ bond of 12–13 kcal/mol. The corresponding salts have barriers of *ca.* 20 kcal/mol. Comparison with results of others on *N'*-acyl-*N,N*-dimethylbenzamidines shows that the electronic effect is not large. The report (Raison, 1949) of the existence of *N,N,N'*-trimethyl-*N'*-phenylbenzamidinium iodide in two forms must be a case of crystalline modifications, for the nmr spectra are identical; the barrier to rotation about the C–N$(CH_3)_2$ bond is about 14 kcal/mol. The coalescence temperature of the nmr signals of the geminal methyl groups in this compound is markedly raised by the addition of anions of oxy acids, as well as by the use of aromatic solvents. Three tetrasubstituted amidinium salts bearing geminal dimethyl groups—*N,N*-dimethyl-*N',N'*-dibenzylbenzamidinium iodide, *N,N,N'*-trimethyl-*N'*-benzylbenzamidinium iodide, and *N,N,N'*-trimethyl-*N'*-benzylformamidinium iodide—show magnetic nonequivalence of the geminal methyl groups owing to restricted rotation at lower temperatures, but show no evidence for the existence of different rotational conformations of the more heavily substituted amino group.

Although restricted rotation in amides has been extensively studied,[1] such rotation in amidinium systems has attracted less attention. Rotational barriers about the C–N bond in amidines have been determined by variable-temperature nmr for *N,N*-dimethylformamidines containing the following substituents on N′ (*i.e.*, the imine N): *p*-nitrophenyl (ΔG = 15.9 kcal/mol),[2] *p*-tolyl (ΔG = 14.1 kcal/mol),[2] chloromethanesulfonyl ($\Delta G_{418.2°K}$ = 23.3 kcal/mol),[3] and *tert*-butyl (ΔG = 11.9 kcal/mol).[4] Schwenker and Rosswag[5] reported barriers for a series of *N,N*-dimethylbenzamidines in which the N′ substituents were H, COPh, SO_2Ph, and $PO(OPh)_2$. They observed a weak correlation between the electronegativity of the N′ substituent and the magnitude of the rotational barrier about the central C–N bond, according to the importance of the contribution of dipolar structures that increase the double-bond character of the C–N$(CH_3)_2$ bond. The effect of differences in electronegativity was considerably smaller than expected, however, a fact that Jakobsen and Senning have attributed to steric effects[3] (see below).



Aromatic solvents have been found to raise the coalescence temperature (but not the rotational barrier[2]) for several *N'*-aryl-*N,N*-dimethylformamidines[6] by increasing the magnetic nonequivalence, $\Delta\nu$, of the two methyl groups.

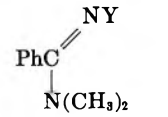
Restricted rotation in a few amidinium salts has also been noted.[6] Barriers have been obtained for acetamidinium chloride (estimated as 9–25 kcal/mol),[7] *N,N*-dimethylacetamidinium chloride (21.8 ± 1.0 kcal/mol), and nitrate (21.5 kcal/mol),[8] and *N,N,N',N'*-tetramethylformamidinium perchlorate (17.8 kcal/mol).[9]

Conformational isomerism of the N substituents in some *N,N'*-diaryl- and *N*-aryl-*N'*-*tert*-butylformamidinium trifluoroacetates has been examined,[10] and the existence of only one conformational isomer for *N,N'*-dimethylacetamidinium chloride has been observed.[4] A possible example of the existence of stable rotational isomers was reported long ago by Raison,[11] who found that *N,N,N'*-trimethyl-*N'*-phenylbenzamidinium iodide could be obtained in two states, with distinct melting points. The cause of this phenomenon could not be adequately investigated at that time, when nmr spectroscopy was not available.

In connection with other studies concerning the alkylative behavior of amidines, we have had occasion to prepare a variety of benzamidinium compounds, which provided an opportunity to extend the limited previous studies, and to reexamine the phenomenon reported by Raison and that disputed by Rosswag and Jakobsen and Senning.

Results and Discussion

The nmr spectra of *N,N*-dimethylbenzamidines bearing an *N'*-phenyl (Ia), *N'*-benzyl (Ib), *N'*-ethyl (Ic), or *N'*-*tert*-butyl substituent (Id) showed singlets for the geminal *N*-methyl protons at ambient temperature (*ca.* 35°) in methylene chloride. At lower temperatures, however, Ia, Ib, and Ic showed two equally intense singlets for these protons. The rotational barriers (ΔG_{Tc}) about the C–N$(CH_3)_2$ bonds in amidines Ia and Ib at the coalescence temperatures were determined using an approximative method[12]



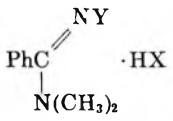
Ia, Y = Ph
b, Y = CH_2Ph
c, Y = C_2H_5
d, Y = $C(CH_3)_3$

(1) *E.g.*, W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **70**, 517 (1970).
(2) D. T. Bertelli and J. T. Gehrig, *Tetrahedron Lett.*, 2481 (1967).
(3) H. J. Jakobsen and A. Senning, *Chem. Commun.*, 1245 (1968).
(4) D. L. Harris and K. M. Wellman, *Tetrahedron Lett.*, 5225 (1968).
(5) G. Schwenker and H. Rosswag, *ibid.*, 2691 (1968).
(6) J. P. Marsh, Jr., and L. Goodman, *ibid.*, 683 (1967).
(7) G. S. Hammond and R. C. Neuman, *J. Phys. Chem.*, **67**, 1655 (1963).
(8) R. C. Neuman, Jr., and Y. Jonas, *ibid.*, **75**, 3532 (1971).
(9) J. Rauft and S. Dahne, *Helv. Chim. Acta*, **47**, 1160 (1964).
(10) K. M. Wellman and D. L. Harris, *Chem. Commun.*, 256 (1967).
(11) C. G. Raison, *J. Chem. Soc.*, 3319 (1949).
(12) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956). Although the use of approximative methods can in some cases lead to considerable error [A. Allerhand, *et al.*, *J. Amer. Chem. Soc.*, **88**, 3185 (1966)], the barriers obtained here correlate well with both those in the literature and those calculated using a more exact rate equation (Allerhand, *et al.*). Recently, the validity of using approximate equations for determining K_c has been discussed [D. Kost, E. H. Carlson, and M. Raban, *Chem. Commun.*, 656 (1971)].

to be *ca.* 13 and 12 kcal/mol, respectively.[13] These values are compatible with those obtained by Schwenker and Rosswag for *N,N*-dimethylbenzamidines in which the N′ substituents were the more electronegative groups, PhCO (15.2 kcal/mol), $PhSO_2$ (16.4 kcal/mol), and $PO(OPh)_2$ (17.6 kcal/mol).[5]

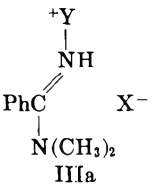
The substantial barriers to rotation in Ia and Ib are of special interest with respect to the controversy over the fact that the barrier in *N,N*-dimethylbenzamidine (I, Y = H; ΔG = 18.2 kcal/mol) is not markedly smaller than that in its benzenesulfonyl derivative (I, Y = $PhSO_2$), even after a correction of 13 kcal/mol for the estimated role of hydrogen bonding. Jakobsen and Senning[3] have proposed that this may not be due to insensitivity to electronic effects, as originally suggested, but to counteracting steric effects resulting from the vastly different spatial requirements of H and $PhSO_2$. However, the spatial requirements of benzyl groups are much closer to those of benzenesulfonyl or benzoyl than to hydrogen, but the electronic effects are very different; thus the small difference in the energy barriers that we have found (about 4 kcal/mol) between Ib, Y = $C_6H_5CH_2$, and I, Y = $C_6H_5SO_2$, confirms that the influence of electronic factors is not large (although it is not so small as had appeared from data involving the ambiguity presented by hydrogen bonding). (The lack of nmr evidence for restricted rotation in Id may be due to too small a value for the magnetic nonequivalence of the methyl groups.[14])

At ambient temperature (*ca.* 35°), the nmr spectra of the corresponding amidinium salts (IIa = Ia HCl; IIb = Ib HCl; IIc = Ic HCl; IId = Id HI; IIe = I HI, Y = CPh_3) showed two equally intense signals for the $N(CH_3)_2$ protons. These signals cannot

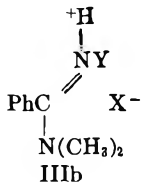


IIa, Y = Ph; X = Cl
b, Y = CH_2Ph; X = Cl
c, Y = C_2H_5; X = Cl
d, Y = $C(CH_3)_3$; X = I
e, Y = CPh_3; X = I

arise from coupling with NH (if protonation had occurred at the tricoordinate nitrogen), since the two signals persist when the solvent is deuterium oxide.[15] Although the two $-N(CH_3)_2$ absorptions could arise from the presence of a 1:1 mixture of the two rotational isomers, IIIa and IIIb, assuming free rotation about the C–$N(CH_3)_2$ bond, the persistence of the equal intensity of the NCH_3 absorptions upon varying the size of Y, which should affect the relative population of IIIa and IIIb, argues against this interpretation. Furthermore, the spectra of salts IIc and IId showed absorptions attributable to only one type of alkyl group.[16] The preceding observations can be satisfactorily accounted for by restricted rotation about the C–N-$(CH_3)_2$ bond.[17]

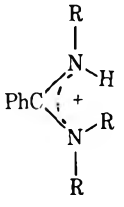


IIIa

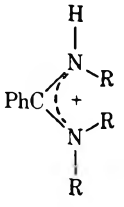


IIIb

In protonated amidines, both nitrogens are capable of sharing the positive charge and would be expected to do so[18] if a planar configuration is possible. If the protonated nitrogen does bear substantial charge, the barrier to rotation about the C–NHY bond should be enhanced proportionally to the magnitude of the share. In this regard, it is of interest that none of the ambient-temperature spectra of the protonated benzamidines indicated the existence of the two possible rotational isomers IVa and IVb. Even when the N



IVa



IVb

substituents were larger than the N′ substituent, as in *N,N*-dibenzyl-*N*′-methylbenzamidinium chloride, two absorptions were observed for the N substituents and only one for the N′ substituent. This circumstance may be a reflection of either a substantially lower rotational barrier about the C–N′ bond than about the C–N bond (*i.e.*, C–NHR *vs.* C–NR_2), corresponding to localization of charge largely on $-NR_2$, or a higher barrier that fixes the existence of exclusively IVa (or IVb).[19] Space-filling molecular models demonstrate that the *Z* isomer, IVb, is sterically much more congested than the *E* isomer, IVa.[20] Consequently, if charge delocalization is substantial, the isomer IVa would be expected to predominate.

The barriers to rotation about the C–N bond in the salts IIa, IIb, and IId were determined from variable-temperature spectra in nitrobenzene to be 20.4,

(13) The low-temperature spectra could alternatively be interpreted in terms of *Z* and *E* isomerism about the dicoordinate nitrogen. However, in order to account for the equal intensity of the NCH_3 absorptions, such an interpretation necessitates a 1:1 mixture of *Z* and *E* isomers for both amidines Ia and Ib, in which the steric bulk of the N′ substituent differs considerably; consequently, this alternative interpretation is less attractive. A referee has correctly pointed out that the energy barrier to rotation might be lowered as a consequence of severe crowding, which would raise the energy of the ground state relative to the transition state.

(14) Restricted rotation has been observed in *N,N*-dimethyl-*N*′-butylformamidine dissolved in aromatic solvents, which presumably increase the magnetic nonequivalence of the geminal *N*-methyl groups.[4]

(15) Similar behavior was observed for the hydrochloride salts of *N,N*-dimethyl-*N*′-arylformamidines.[6]

(16) The spectrum of the amidinium salt IIb in deuteriochloroform exhibited coupling between the NH proton and the benzyl protons ($J \cong 6$ Hz).

(17) The hydrochloride of *N*-benzyl-*N*-methyl-*N*′-phenylbenzamidine also exhibits hindered rotation at ambient temperature, as evinced by two NCH_3 and two NCH_2Ph absorptions in which the high- and low-field NCH_3 signals are correlated by relative intensities with the low- and high-field NCH_2Ph signals, respectively. If there were free rotation about the C–$N(CH_3)CH_2Ph$ bond, the methyl and benzyl protons in either of the rotamers would be expected to be shifted in the same direction. Accordingly, the high-field methyl and benzyl protons would correspond to one isomer and the low-field protons to the other.

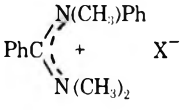
(18) J. Sandstrom [*J. Phys. Chem.*, **71**, 2318 (1967)] using MO methods has calculated the delocalization energy in a positively charged amidinium system to be 0.632β.

(19) R. Kwok and P. Pranc [*J. Org. Chem.*, **32**, 738 (1967)] have concluded from ambient-temperature spectra that the positive charge in the hydrochloride of *N*-ethyl-*N*′-methyl-*N*-phenylbenzamidine is localized on the nitrogen bearing the ethyl and phenyl groups. However, a fixed conformation about the C–$NHCH_3$ bond would be consistent with their data.

(20) For a discussion of the *Z* and *E* nomenclature see J. E. Blackwood, *et al.*, *J. Amer. Chem. Soc.*, **90**, 509 (1968); J. E. Blackwood, *et al.*, *J. Chem. Soc.*, **8**, 30 (1968).

20.1, and 19.7 kcal/mol,[21] respectively. That the N′ substituent has very little effect on the barrier is presumably due to dominance of steric effects. As expected, these barriers are higher than those in the free bases and are comparable to the reported barrier in *N*,*N*-dimethylacetamidinium chloride (E_{act} = 21.8 kcal/mol)[8] (and also to those in simple *N*,*N*-dimethylbenzamides).[22]

Quaternary amidinium salts (N,N,N′,N′ tetrasubstituted) are of interest because they lack a proton substituent, with its small size, great mobility, and capacity for hydrogen bonding. At ambient temperature in deuteriochloroform and methylene chloride, the nmr spectra of *N*,*N*,*N*′-trimethyl-*N*′-phenylbenzamidinium iodide (Va) in either of the two forms reported by Raison[11] and tetrafluoroborate (Vb) were identical and consisted of two NCH_3 absorptions (relative intensity 1:2), corresponding to the methyl protons on the phenyl-substituted nitrogen and those on the other nitrogen, respectively.[23] At lower temperatures the spectra showed two broad peaks (*ca.* 1:1) corresponding to the geminal *N*-methyl groups; the other methyl peak was also broadened, but remained a singlet at temperatures as low as −50°. The estimated rotational barriers were approximately 14 and 15 kcal/mol, respectively. These results show that the two forms of Va obtained by Raison must have been different crystalline modifications, rather than different rotational conformations.

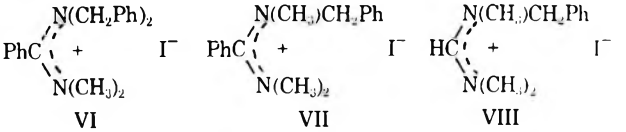


Va, X = I
b, X = BF_4

The ambient-temperature spectra of Va and Vb were dramatically influenced by changes in the medium. The addition of trifluoroacetic, trichloroacetic, fluorosulfonic, nitric, or formic acid to deuteriochloroform solutions of these salts, or dissolution of the salts in any of the liquid acids, caused the absorption corresponding to the geminal *N*-methyl protons to separate into two absorptions of equal intensity ($\Delta\nu \cong$ 6 Hz). On the other hand, no effect on the spectra was observed when glacial acetic, HCl-saturated glacial acetic, DMSO–acetic, concentrated hydrochloric, 48% hydriodic, *p*-toluenesulfonic, or dilute sulfuric acid was added. Phosphoric acid caused only broadening of the $N(CH_3)_2$ peak. The nmr spectra ($CDCl_3$) of the trifluoroacetate or the nitrate, prepared *in situ* from silver trifluoroacetate and nitrate and the amidinium iodide, were virtually identical with that observed for the iodide plus trifluoroacetic or nitric acid. The perchlorate, prepared similarly, showed a very closely spaced doublet. It is evident that the nature of the anion, rather than the acidity of the medium, causes the splitting, and the cause cannot be the presence of free base, which Neuman and Jones[8] found to be the cause of anomalous behavior of *N*,*N*-dimethylacetamidinium salts.

The spectrum of the amidinium iodide (Va) in trifluoroacetic acid and in formic acid was examined at higher temperatures. The two methyl groups coalesced at 63° (CF_3CO_2H) and 54° (HCO_2H) and the free energies of the exchange processes based upon $\Delta\nu_\infty$ = 9 and 6 Hz, respectively, were estimated to be 17 kcal/mol,[24] consistent with restricted rotation as the cause. Other amidinium salts, *e.g.*, VI, VII, and VIII, showed equivalent geminal *N*-methyl groups in the presence of various oxy acids, but the foregoing anion effect would not have been observed if the coalescence temperature, even though raised, remained below ambient (*ca.* 35°). Neuman and Jones have reported[8] a higher $\Delta\nu_\infty$ for *N*,*N*-dimethylacetamidinium nitrate (5.17 Hz, 38°) than for the chloride (1.8 Hz, 37.8°); the values of E_a (21.3 ± 0.3 and 22.8 ± 0.7) and ΔG (21.5 and 21.8 kcal/mol at 25°) for rotation about the central C–N bond were very similar. The foregoing effect seems to be associated with the presence of bidentate anions, and is presumably a result of differences in association or solvation.[25]

Aromatic media also affect the spectrum; at ambient temperature (*ca.* 35°) the amidinium iodide in $CDCl_3$–C_6H_6 (*ca.* 1:5) showed a doublet ($\Delta\nu$ = 5 Hz) corresponding to the geminal *N*-methyl groups. The effect of aromatic solvent and the anion may arise in part from an enhancement of the rotational barrier or, alternatively, solely from increased magnetic nonequivalence ($\Delta\nu$) of the geminal *N*-methyl groups. The aromatic solvent effect observed for rotation in *N*′-aryl-*N*,*N*-dimethylformamidines stems solely from an increase in $\Delta\nu$, since the free energies of activation are affected negligibly. Interestingly, however, the enthalpy and entropy of activation for rotation in the *N*′-*p*-nitrophenyl derivative are considerably enhanced. With regard to the benzamidinium salts, stronger association of the aromatic solvent with the positively charged substrate may affect the free energy as well as the enthalpy and entropy of activation.



VI VII VIII

The low-temperature spectra of salts VI–VIII demonstrate the importance of steric effects upon the conformation of the amidinium system. Restricted rotation about the C–$N(CH_3)_2$ bond was observed in each compound by the nonequivalence of the signals of the two *N*-methyl groups. Hindrance to rotation about the other carbon–nitrogen bond was not observed even at −50°. These observations can be interpreted to imply that the positive charge is borne predominantly by the nitrogen bearing the two *N*-

(21) These barriers, determined from the coalescence temperatures, agreed well with those calculated using eq 12, A. Allerhand, *et al.*, ref 12.

(22) L. M. Jackman, T. E. Kavanagh, and R. C. Haddon, *Org. Magn. Resonance*, **1**, 109 (1969).

(23) This assignment is supported by the spectra of the deuteriomethylated iodides, *N*,*N*-dimethyl-*N*′-(methyl-d_3)-*N*′-phenylbenzamidinium and *N*,*N*′-dimethyl-*N*′-(methyl-d_3)-*N*-phenylbenzamidinium iodide, prepared by deuteriomethylation of *N*,*N*-dimethyl-*N*′-phenylbenzamidine and *N*,*N*′-dimethyl-*N*-phenylbenzamidine, respectively.

(24) Although examination of spectra at temperatures below ambient may reveal larger frequency differences ($\Delta\nu$) and thus smaller rotational barriers, in order to obtain a calculated barrier less than 17 kcal/mol for the trifluoroacetate, the limiting frequency difference ($\Delta\nu_\infty$) would have to be >31 Hz. The highly polar acids used as solvents may, of course, influence the magnitude of the barrier.

(25) R. C. Neuman, Jr., and V. Jonas, *J. Phys. Chem.*, **75**, 3550 (1971), have observed a difference in the degree of ion pairing between amidinium chloride and nitrate.

methyl groups, an explanation that requires that the geminal methyl groups lie in the N–C–N plane but that the C–N–C plane formed by the larger substituents on the other nitrogen be twisted substantially out of the N–C–N plane. An alternative explanation, applicable only to VII and VIII, is that the N–C–N and both C–N–C planes may be coplanar, but that the configuration of the $-N(CH_3)CH_2Ph$ moiety is fixed with the benzyl group exo, owing to its bulk. A configuration with both C–N–C planes parallel, but partially twisted out of the N–C–N plane, capable of conformational inversion by concerted conrotatory motion, is inconsistent with our observations.

A tentative assignment of the position (endo or exo) of the methyl groups in the protonated amidines can be made on the basis of the spectrum of the hydrochloride of *N*-benzyl-*N*-methyl-*N'*-phenylbenzamidine. The ambient-temperature spectrum of the salt in deuteriochloroform reveals the existence of two rotational isomers in a ratio of *ca.* 3.8:1.[26] The rotamer in lower concentration possesses the higher field methyl signal and the lower field benzyl signal. If this rotamer is that in which the bulkier group (benzyl) is endo, then the high- and low-field geminal *N*-methyl signals for the protonated amidines can be assigned to the *exo*- and *endo*-methyl groups, respectively.[27] In all of the protonated amidines studied, the lower field methyl signal has a larger width at half-height than does the higher field methyl signal (the larger signal width of the *endo*-methyl can perhaps be attributed to selective long-range coupling with the NH proton).

Curiously, in the quaternary amidinium salts studied here, the width of the low-field methyl signal appears to be smaller than that for the high-field methyl signal. At low temperatures, the spectra of the *N,N,N'*-trimethylbenzamidinium salts contain three methyl signals (*ca.* 1:1:1), in which the signal corresponding to the *N'*-methyl groups and the high-field *N*-methyl signal are wider than the low-field *N*-methyl signal. Extrapolation from the assumed correlation between signal width and position in the protonated amidines would suggest that in the methylated amidinium salts, the high-field *N*-methyl signal corresponds to the endo methyl group. Since these assignments are based purely on signal width and steric arguments, however, they must at present be viewed with caution.[28]

As the temperature is lowered from 0 to −60°, both the *N'*-methyl signal and the high-field *N*-methyl signal broaden considerably and to the same extent. This line broadening is similar to that observed by Dewar[29] for the methyl signals of bis(dimethylamino)-phenylborane and is consistent with the above assignment, assuming the *N'*-methyl group to be endo.

In summary, restricted rotation about the formal C–N single bond in amidines appears generally to have a lower barrier than in amidinium salts, and lower than in amides. It is more sensitive to steric than to electronic effects. There is no evidence for the separate existence at ambient temperatures of rotational isomers of amidines or amidinium salts, and the RR'N moiety has an overwhelming preference for the conformation with the bulkier group in the exo orientation.

(26) This ratio represents an equilibrium mixture, since approximately the same ratio was obtained when the nmr sample was heated to induce coalescence and then allowed to cool.

(27) Presumably, the anisotropic effect of the benzene nucleus is at least in part responsible for the upfield position of the protons of the exo group. Hammond and Neuman[7] observed that in the spectrum of *N,N'*-dimethylacetamidinium chloride, the protons of the exo groups were *downfield* relative to the protons of the endo groups.

(28) The need for such caution is dramatically illustrated and advocated by Frucht, Lewin, and Bovey [*Tetrahedron Lett.*, 3707 (1970)].

(29) M. J. S. Dewar and R. Rona, *J. Amer. Chem. Soc.*, **91**, 2259 (1969).

Experimental Section

General Procedures.—Nuclear magnetic resonance spectra were recorded using a Varian A-60 spectrometer; chemical shifts are referred to tetramethylsilane as internal standard unless otherwise stated. The temperatures recorded for the variable-temperature spectra were determined by calibration with the spectra of ethylene glycol and methanol as recommended by Varian[30] and, accordingly, are accurate to 2°. All of the nmr solutions used in the variable-temperature studies were 1 *M*.

The rotational barriers were calculated using the approximative equation $k_{Tc} = (\pi/\sqrt{2})\Delta\nu$ and the Eyring equation.[12] The pertinent data are given in Tables I and II.

TABLE I

C–N(CH$_3$)$_2$ ROTATIONAL BARRIERS IN BENZAMIDINES AND THEIR HYDROHALIDES

PhC(=NX)N(CH$_3$)$_2$

Compd	X	Δν, Hz (temp, °C)	Coalescence temp (T_c), °C	ΔG_{Tc}, kcal/mol	Solvent[a]
Ia	Ph	24 (−55)	−16	13.0	CH_2Cl_2
IIa(Ia·HCl)		47 (≃35)	135	20.4[b]	$PhNO_2$
Ib	$PhCH_2$	33 (−55)	−40	12.0	CH_2Cl_2
IIb (Ib·HCl)		47 (∼35)	130	20.4	$PhNO_2$
Ic	CH_3CH_2		∼−55		CH_2Cl_2
IIc (Ic·HCl)		36 (∼35)			$PhNO_2$
Id	$(CH_3)_3C$		<−70		CH_2Cl_2
IId (Id·HCl)		44 (∼35)	120	19.7	$C_2H_2Cl_4$

[a] All concentrations were 1 *M*. [b] E_a = 20.8 kcal/mol; log *A* = 13; $\Delta H^{\pm}$ = 20.0 kcal/mol [calculated using eq 12, A. Allerhand, *et al.*, *J. Amer. Chem. Soc.*, **88**, 3185 (1966)].

The preparative data for the benzamidines and their salts are given in Tables III and IV. The benzamidines were prepared by the treatment of N-substituted benzimidoyl chlorides[31] with amines. In some cases, disubstituted amidines prepared in this manner were subsequently methylated with methyl iodide to afford the desired trisubstituted amidines. The preparations of *N'*-benzyl-*N,N*-dimethylbenzamidine (Ib), *N*-methyl-*N'*-*tert*-butylbenzamidine (IX), and *N,N*-dimethyl-*N'*-*tert*-butylbenzamidine (Id) are illustrative.

The hydrochloride salts were prepared from the amidine and hydrogen chloride; the preparation of *N*-benzyl-*N*-methyl-*N'*-phenylbenzamidinium chloride is illustrative. Hydrochlorides which were quite hygroscopic (see Table III) were prepared *in situ* by bubbling anhydrous hydrogen chloride through nitrobenzene solutions (1 *M*) of the amidines. The solutions were degassed with nitrogen prior to nmr examination.

***N'*-Benzyl-*N,N*-dimethylbenzamidine (Ib).**—To an ice-cooled, stirred solution of 11.9 g (0.052 mol) of *N*-benzylbenzimidoyl chloride[31] in 200 ml of benzene was gradually added 40 ml of a benzene solution of dimethylamine (*ca.* 20% by volume). The resulting solution was allowed to assume room temperature and was stirred for 20 hr. During this period a white precipitate formed. The reaction mixture was treated with an additional 10 ml of the dimethylamine solution, refluxed on a steam bath for 20 min, and then left to stand at room temperature overnight. Dimethylamine hydrochloride (4.2 g) was removed by filtration and washed with ether. The filtrate and ether washings were combined and concentrated *in vacuo* to afford 11.7 g of a pale yellow liquid. *N'*-Benzyl-*N,N*-dimethylbenzamidine was obtained in a total yield of 8.7 g (70%) as two fractions by distillation under reduced pressure: fraction A, wt 0.6 g, bp 152–154° (1–1.25 mm), $n^{27}D$ 1.5785; fraction B, wt 8.1 g, bp 154° (1.5

(30) "Varian Variable Temperature Accessory Manual," 87-202-006.

(31) (a) J. v. Braun and W. Pimpernelle, *Ber.*, **67**, 1218 (1934); (b) I. Ugi, F. Beck, and U. Fetzer, *Chem. Ber.*, **95**, 126 (1962).

TABLE II

C–N(CH$_3$)$_2$ ROTATIONAL BARRIERS IN QUATERNARY BENZAMIDINIUM SALTS

[PhC(NXCH$_3$)NYZ]$^+$An$^-$

Compd	X	Y	Z	$\nu\Delta$, Hz (temp, °C)	Coalescence temp (T_c), °C	ΔG_{Tc}, kcal/mol	Solvent[a]
Va (Ia CH$_3$I)	Ph	CH$_3$	CH$_3$	15 (−60)	1	14.2	CH_2Cl_2
Va (Ia CH$_3$I)				9 (~35)	63	17.8	CF_3CO_2H
Va (Ia CH$_3$I)				6 (~35)	54	17.5	HCO_2H
Vb (Ia CH$_3$BF$_4$)				17 (−45)	31	15.6	CH_2Cl_2
VI (XI CH$_3$I)	CH$_3$	PhCH$_2$	PhCH$_2$	23 (−50)	31	15.5	CH_2Cl_2
VII (Ib CH$_3$I)	PhCH$_2$	CH$_3$	CH$_3$		<−40		CH_2Cl_2

[a] All concentrations 1 *M*.

TABLE III

BENZAMIDINES AND THEIR HYDROHALIDES[a]

	Chemical shifts, τ[b] X		Y		Z		Bp, °C (mm)	Mp, °C	Yield, %
Ia[c]	Ph		CH$_3$	7.05	CH$_3$	7.05		71–72[d]	87
IIa (Ia HCl)				6.4 (6.06)[e]		7.0 (6.83)[e]		*f*	
Ib[c]	PhCH$_2$	5.89	CH$_3$	7.23	CH$_3$	7.23	152–154 (1.25)		70
IIb (Ib HCl)		5.85		6.47 (6.13)[d]		7.20 (6.90)[e]		*f*	
Ic[c]	CH$_3$CH$_2$	7.09	CH$_3$	7.30	CH$_3$	7.30	78 (2)[g]		100
IIc (Ic HCl)				6.5		7.1		*f*	
Id[h]	(CH$_3$)$_3$C	9.03	CH$_3$	7.35	CH$_3$	7.35	50 (0.1–0.05)		75
IId (Id HI)[i]		8.68		6.27		7.05		202–203	93
IIe (X CH$_3$I)[j]	Ph$_3$C		CH$_3$	6.15	CH$_3$	7.0		146–148	56
IX[k]	(CH$_3$)$_3$C	8.62	H	6.2	CH$_3$	7.20	63–66 (0.5)		66
X[k]	Ph$_3$C		H	7.8	CH$_3$	7.8		135–136	56
XI[k]	CH$_3$	7.21	PhCH$_2$	5.70	PhCH$_2$	5.70		71–72	79

[a] All new compounds gave satisfactory elemental analysis; boiling and melting points are uncorrected. [b] All values refer to chemical shifts in $CHCl_3$. [c] Prepared from dimethylamine and the appropriate N-substituted benzimidoyl chloride. [d] Reported mp 73–74°: H. von Peckmann, *Ber.*, **28**, 2362 (1895). [e] Chemical shift in $PhNO_2$. [f] These compounds were hygroscopic and consequently were prepared *in situ*. [g] Reported bp 130° (12 mm): P. Oxley and W. F. Short, *J. Chem. Soc.*, 382 (1947). [h] Prepared from *N*-methyl-*N'*-*tert*-butylbenzamidine and methyl iodide. [i] Prepared by treatment of IX with methyl iodide. [j] Prepared by treatment of X with methyl iodide. [k] Prepared from the appropriate amine and *N*-methylbenzimidoyl chloride.

TABLE IV

QUATERNARY AMIDINIUM SALTS[a]

[RC(NXY)N(CH$_3$)$_2$]$^+$An$^-$

	Chemical shifts, τ[b] R	X		Y		$(CH_3)_2$	Mp, °C	Yield, %
Va (Ia CH$_3$I)	Ph	Ph		CH$_3$	6.45	6.85	142–143, 180–181[c]	97
Vb (Ia CH$_3$BF$_4$)	Ph	Ph		CH$_3$	6.56	7.0	103–104	85
VI (XI CH$_3$I)	Ph	PhCH$_2$	5.65	PhCH$_2$	5.65	6.55	153–153.5	79
VII (Ib CH$_3$I)	Ph	PhCH$_2$	5.42	CH$_3$	6.79	6.69	119–120	85
VIII[d]	H	PhCH$_2$	5.06	CH$_3$	7.7	6.54	148–149	96

[a] All new compounds gave satisfactory elemental analyses, and melting points are uncorrected. [b] Chemical shifts in $CDCl_3$. [c] Reported[11,32] mp 144–145, 180–182°. [d] An$^-$ = I$^-$; prepared by treatment of *N'*-benzyl-*N*,*N*-dimethylformamidine[34] with methyl iodide.

mm), n^{27}D 1.5813. Spectral and elemental analyses were performed on fraction B: ir (neat) 1600 (C=C or C=N) and 1620 cm^{-1} (C=N); nmr ($CDCl_3$) τ 2.92 (m, 10, aromatic), 5.89 (s, 2, NCH_2Ph), and 7.23 [s, 6, N(CH$_3$)$_2$].

Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.77; H, 7.66; N, 11.84.

***N'*-Methyl-*N*-*tert*-butylbenzamidine (IX).**—To an ice-cooled, stirred solution of 20.0 g (0.13 mol) of *N*-methylbenzimidoyl chloride[31b] in 90 ml of benzene was gradually added 19.0 g (0.26 mol) of recently distilled *tert*-butylamine. After the addition was completed, the reaction mixture was allowed to assume room temperature and was then refluxed on a steam bath for 5 hr. The resulting mixture was cooled to room temperature, filtered to remove the white, crystalline precipitate (wt 14.8 g, mp 298–299°), and concentrated. Vacuum distillation of the residual yellow oil afforded 16.4 g (66%) of a colorless liquid: bp 63–66° (0.5 mm); ir (neat) 1365 and 1395 (*tert*-butyl), 1605, 1620 (C=N), and 3425 cm^{-1} (NH); nmr ($CDCl_3$) τ 2.62–2.95 (m, 5, aromatic), 6.2 (b s, 1, NH), 7.20 (s, 3, NCH_3), and 8.62 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53; N, 14.72. Found: C, 75.70; H, 9.56; N, 14.80.

***N*,*N*-Dimethyl-*N'*-*tert*-butylbenzamidine (Id) and *N*,*N*-Dimethyl-*N'*-*tert*-butylbenzamidinium Iodide (IId).**—To a solution of 15.0 g (0.08 mol) of *N*-methyl-*N'*-*tert*-butylbenzamidine (IX) in 45 ml of benzene was added 22.4 g (0.16 mol) of methyl iodide. The mixture was allowed to stand at room temperature for 12 min, then heated at 50° for 4 hr, and was finally left at room temperature overnight. The cream-colored hydriodide (IId) was collected by filtration, washed with benzene, and air dried: yield 24.8 g; mp 191–192.5° (crude), 202–203° after two recrystallizations from 95% ethanol; nmr ($CDCl_3$) τ 2.48 (s, 5, aromatic), 6.27 (s, 3, NCH_3), 7.05 (s, 3, NCH_3), and 8.68 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{13}H_{21}N_2$: C, 47.00; H, 6.38; N, 8.43. Found: C, 47.08; H, 6.39; N, 8.52.

A stirred, ice-cooled, aqueous suspension of 22 g of the salt IId was made alkaline with aqueous sodium hydroxide and then extracted with ether until all of the solid material had disappeared and the ether extracts left no oil upon evaporation. The combined extracts were dried (Na_2CO_3) and evaporated to give 12.2 g (75% overall, based on 24.8 g of crude hydroiodide) of a colorless liquid. An analytical sample of compound Id was obtained from two distillations under reduced pressure: bp 50°

(0.1–0.5 mm); ir (neat) 1360 and 1390 (*tert*-butyl), 1605 and 1625 cm^{-1} (C=N); nmr ($CDCl_3$) τ 2.67–30.7 (m, 5, aromatic), 7.35 [s, 6, $N(CH_3)_2$], and 9.03 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.21; H, 9.87; N, 13.67.

The picrate salt was prepared in methanol from the purified amidine, mp 174–175.5° (after two recrystallizations from methanol).

Anal. Calcd for $C_{13}H_{20}N_2 \cdot C_6H_3N_3O_7$: C, 52.65; H, 5.35; N, 16.16. Found: C, 52.70; H, 5.29; N, 16.04.

***N*-Benzyl-*N*-methyl-*N'*-phenylbenzamidinium Chloride.**—*N*-Benzyl-*N*-methyl-*N'*-phenylbenzamidine (10 g) in 300 ml of ether (dried over sodium) was treated with anhydrous hydrogen chloride. The resultant gummy, pale-yellow precipitate was collected by filtration, washed with ether, and recrystallized once from chloroform–ethyl acetate to afford 5.6 g of *N*-benzyl-*N*-methyl-*N'*-phenylbenzamidinium chloride as a white, crystalline solid, mp 204–205° [lit.[11] mp 206–207° (corrected)]. The nmr spectrum possessed two sets of *N*-methyl and *N*-benzyl absorptions at τ 6.3 and 7.0 and at 4.4 and 5.4, respectively, with the relative intensities 5.7:1.5:1:3.8, corresponding to two rotational isomers in a ratio of *ca.* 3.8:1.

***N,N,N'*-Trimethyl-*N'*-phenylbenzamidinium iodide (Va)** was prepared according to the method of Pyman.[32] As reported by Raison,[11] two different melting points (142–143°, 180–181°) were obtained, depending upon the reaction conditions. The infrared and nmr spectra of the two differently melting forms were identical. In the nmr spectrum ($CDCl_3$) there were *N*-methyl absorptions at τ 6.45 [s, 3, $N(CH_3)Ph$] and 6.85 [s, 6, $N(CH_3)_2$].

***N,N,N'*-Trimethyl-*N'*-phenylbenzamidinium tetrafluoroborate (Vb)** was prepared in 85% yield by alkylation of either *N,N*-dimethyl-*N'*-phenyl- or *N,N'*-dimethyl-*N*-phenylbenzamidine in methylene chloride with trimethyloxonium tetrafluoroborate.[33] The salt was purified by recrystallization from chloroform–ethyl acetate (*ca.* 1:5): mp 103–104°; nmr ($CDCl_3$) τ 2.45 (m, 10, aromatic), 6.56 [s, 3, $N(CH_3)Ph$], and 7.0 [s, 6, $N(CH_3)_2$].

Anal. Calcd for $C_{16}H_{19}N_2BF_4$: C, 58.92; H, 5.87; N, 8.59. Found: C, 58.91; H, 5.95; N, 8.61.

***N',N'*-Dibenzyl-*N,N*-dimethylbenzamidinium Iodide (VI).**—A mixture of 2.0 g (6.4 mmol) of *N,N*-dibenzyl-*N'*-methylbenzamidine (XI), 1.8 g (*ca.* 12.8 mmol) of methyl iodide, and 3 ml of benzene was heated at 55° for 2.5 hr and then allowed to stand for 4 hr at room temperature. Concentration of the mixture *in vacuo* afforded a pale yellow, viscous solid, which was thoroughly digested with ether. The insoluble *N,N*-dibenzyl-*N',N'*-dimethylbenzamidinium iodide was collected by filtration, washed with more ether, and dried in air, yield 2.3 g (79%), mp 149–152°. The nmr spectrum of the crude material contained two broad absorptions at τ 5.65 and 6.55 (relative intensities *ca.* 2:3, respectively) in addition to aromatic absorption and weak absorptions corresponding apparently to traces of the substrate amidine and the hydroiodide salt. Attempted recrystallizations from common solvents and solvent mixtures, such as ethanol–water, chloroform–ligroin, chloroform–ether, chloroform–ethyl acetate, and acetonitrile–ethyl acetate, afforded only oils. An analytical sample was finally obtained as off-white crystals, mp 153–153.5°, by repeated trituration with hot ethyl acetate.

Anal. Calcd for $C_{23}H_{25}N_2I$: C, 59.47; H, 5.67; N, 6.30. Found: C, 59.63; H, 5.57; N, 6.17.

***N'*-Benzyl-*N,N,N'*-trimethylbenzamidinium Iodide (VII).**—A mixture of 1.0 g (4.2 mmol) of *N'*-benzyl-*N,N*-dimethylbenzamidine (Ib), 0.3 g of methyl iodide (dried over sodium carbonate), and 5 ml of acetonitrile (dried by distillation from phosphorus pentoxide) was refluxed for 7 hr (gradual darkening). The addition of 25 ml of anhydrous ether to the cooled reaction mixture precipitated a dark orange oil which settled to the bottom of the reaction vessel. Decantation followed by trituration of the oil with one 25-ml and three 15-ml portions of boiling ether afforded a light orange, viscous mass. The mass was taken up in 5 ml of chloroform (dried by passage through alumina), and 25 ml of ethyl acetate (similarly dried) was added. After 5 min, a white solid began to precipitate. The mixture was allowed to stand for 0.5 hr and then cooled in an ice bath. The white precipitate, *N'*-benzyl-*N',N,N*-trimethylbenzamidinium iodide, was collected by filtration, washed with ethyl acetate, and dried in air: yield 1.35 g (85%); mp 117–118°; nmr ($CDCl_3$) τ *ca.* 2.5 (m, 10, aromatic), 5.42 [s, 2, $N(CH_3)CH_2Ph$], 6.69 [s, 6, $N(CH_3)_2$], and 6.79 [s, 3, $N(CH_3)CH_2Ph$].

An analytical sample, mp 119–120°, was prepared by recrystallization from chloroform–ethyl acetate mixtures.

Anal. Calcd for $C_{17}H_{21}N_2I$: C, 53.69; H, 5.57; N, 7.36. Found: C, 53.58; H, 5.57; N, 7.43.

***N*-Benzyl-*N,N,N'*-trimethylformamidinium Iodide (VIII).**—A mixture of 0.5 g (3.1 mmol) of *N'*-benzyl-*N,N*-dimethylformamidine,[34] 1.3 g (*ca.* 9.2 mmol) of methyl iodide, and 4 ml of acetonitrile was maintained at 60° for 6 hr and then was refluxed for 1 hr. Upon cooling to room temperature, a white solid precipitated. It was collected by filtration and washed with anhydrous ether, yield 0.7 g, mp 147–148°. The filtrate and ether washings were combined and concentrated to a yellow oil. Addition of a small amount of ether precipitated white crystals, which were collected and washed with ether, yield 0.2 g, mp 146–148°. The total yield of *N'*-benzyl-*N,N,N'*-trimethylformamidinium iodide was 0.9 g (96%). Recrystallization from 95% ethanol gave white crystals: mp 148–149°; nmr ($CDCl_3$) τ 2.55 (m, 5, aromatic), 5.06 [s, 2, $N(CH_3)CH_2Ph$], 6.54 [b s, 6, $N(CH_3)_2$], and 7.7 (s, 3, $N(CH_3)CH_2Ph$].

Anal. Calcd for $C_{11}H_{17}N_2I$: C, 43.43; H, 5.64; N, 9.21. Found: C, 43.34; H, 5.67; N, 9.40.

Registry No.—Ia, 2397-36-6; Ib, 36529-77-8; Ic, 36529-78-9; Id, 36529-79-0; Id picrate, 36529-80-3; IIa, 36488-79-6; IIb, 36529-81-4; IIc, 36476-55-8; IId, 36476-56-9; IIe, 36476-57-0; Va, 36476-58-1; Vb, 36476-59-2; VI, 36476-60-5; VII, 36476-61-6; VIII, 36476-62-7; IX, 36476-63-8; X, 36476-64-9; XI, 36476-65-0.

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Notes

On the Application of Dewar's Definition of Resonance Energy to the Hückel Method

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In the 1940's Hückel delocalization energy appeared to be a theoretical parameter that promised to correlate with the experimental chemist's concept of aromaticity. However, as more computations were made, it was found that almost all conjugated systems, even those such as fulvene which subsequently were determined not to be aromatic, have substantial Hückel delocalization energies. The Hückel method seemed therefore to fail in the prediction of aromatic character, and more elaborate schemes were investigated. Many of these failed too, but in 1969 Dewar and de Llano[1] published calculations based on the Pariser–Parr–Pople (PPP) method[2,3] which gave strikingly good predictions of aromaticity. However, in computing resonance energy, they made use of a polyene reference structure instead of the usual reference of isolated double bonds. It turns out that it is this change in reference rather than the switch to a more sophisticated computational method which is crucial. We have found[4-7] that, with a reference structure analogous to Dewar's, the simple Hückel method can make as accurate predictions of aromaticity as can Dewar's more elaborate procedure.

Use of a polyene reference structure goes back to the work of Dewar and Gleicher,[8] who found that the π energy of acyclic polyenes computed by the PPP method can be represented accurately as the sum of bond energy terms. Two such terms, one for double and one for single bonds, were found to be sufficient. Resonance energy was then defined as the difference between the calculated π energy and the sum of bond energy terms. This difference vanishes for acyclic polyenes, is positive for aromatics, and is negative for antiaromatics. For example, in the case of benzene, E (resonance) = E (PPP of benzene) − 3 [E (double bond) + E (single bond)].

In applying Dewar's idea of a polyene reference structure to Hückel calculations, we found that we were unable to reproduce the Hückel energies of the acyclics to a sufficient accuracy using only two bond-energy terms. Instead we required the eight listed in Table I.

Table I

π Bond Types and Energy Terms for Carbon–Carbon Double and Single Bonds

Bond	Type	E_{ij} (β)
CH_2=CH	23	2.0000
CH=CH	22	2.0699
CH_2=C	22′	2.0000
CH=C	21	2.1083
C=C	20	2.1716
CH—CH	12	0.4660
CH—C	11	0.4362
C—C	10	0.4358

Two papers similar to ours have also appeared recently. In the one by Milun, Sobotka, and Trinajstić[9] the simple Hückel method was used; the other by Figeys[10] employed an iterative modification (LCAO–BETA). Both used only two bond types. We wish to compare here the results of these two methods with ours and comment upon the problem of eight *vs.* two bond types.

In the bond energy terms of Table I, the subscript ij refers to a bond of nominal order i with j attached H atoms. Although for convenience we have classified bonds according to the number of attached hydrogens, a more significant index would probably be $(4 - j)$ = the number of links to the conjugated system. It is of course not surprising that we are able to fit the acyclic energies with eight parameters; the point is that the use of these bond energy terms, fit to the *total* π energy of *acyclics*, gives *resonance* energies for *cyclic* compounds that are in excellent agreement with the experimental properties of a wide range of both alternant and nonalternant hydrocarbons.[4-7] Further, there is evidence for more than two bond types from Dewar's own work. Computed bond lengths[1,11] for acyclic compounds are shown in Figure 1 grouped according to our bond types.[4] The double bonds do fall into five types of different lengths, although the single bond types overlap.

It is impossible to construct a compound with arbitrary numbers of each of the bond types in Table I. There are in fact two linear relations connecting the numbers of the various bond types.[4,7] It follows that two of the bond energy terms can be fixed arbitrarily. Therefore no attempt should be made to correlate bond length with bond energy term. Other, but equally valid, choices of the two arbitrary energies can reverse the order of bond energies, can give single bond energies greater than double, or can give negative bond energies. All choices lead to identical resonance energies for all molecules.

Aromatic Stabilities (A_s) of Trinajstić.—Trinajstić has reported the calculation of "aromatic stabilities" (A_s) using the Hückel method,[9] and two bond-energy terms obtained from the linear acyclic polyenes. While

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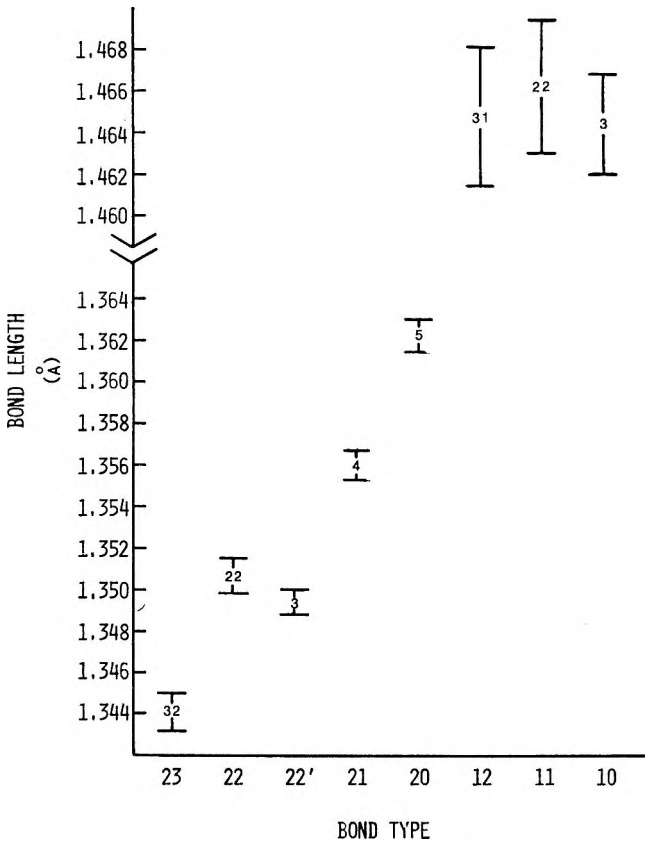
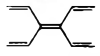


Figure 1 .—Calculated bond lengths[1,11] in acyclic hydrocarbons. The bond types are those in Table I. The numbers between bars give the number of bonds of a type in the indicated range (*e.g.*, there are 32 bonds of type 23 computed to have length between 1.343 and 1.345 Å). Note the break in scale between 1.36 and 1.46 Å.

indeed these terms can be used to obtain the π energies of linear acyclic polyenes, they do not give additivity for many branched acyclic polyenes (see Table II).

TABLE II

COMPARISON OF ADDITIVITY OF BRANCHED ACYCLIC POLYENES USING TWO AND EIGHT BOND TYPES WITH THE HÜCKEL AND LCAO–BETA METHODS

Compd	Hückel REPE (β)		LCAO–BETA REPE (eV)	
	Two bond types[a]	Eight bond types[b]	Two bond types[c]	Eight bond types[d]
	−0.024	0.004	−0.012	0.004
	−0.029	0.003	−0.021	0.003
	−0.016	0.001	−0.011	0.001

[a] Bond energies in ref 9 used. [b] Reference 4. [c] Bond energies in ref 10 used. [d] Eight bond energies obtained using LCAO–BETA energies of 40 acyclics in ref 4.

Hence a basic premise of Dewar's definition—the additivity of all acyclic polyenes—does not hold. Furthermore, a comparison of our HMO resonance energies per π electron (REPE) with Trinajstić's aromatic stability per π electron (A_s/e) (see Table III) indicates that while for many compounds the two methods give very similar results there are notable exceptions. The REPE of fulvene suggests that it is nonaromatic, while

TABLE III

HÜCKEL RESONANCE ENERGY PER π ELECTRON (REPE), INDICIES OF AROMATIC STABILITIES PER π ELECTRON (A_s/e), AND LCAO–BETA RESONANCE ENERGIES PER π ELECTRON (LCAO–BETA REPE)

Registry no.	Compd	REPE (β)	A_s/e (β)	LCAO–BETA REPE (eV)[a]
71-43-2	Benzene	0.065	0.073	0.075
91-20-3	Naphthalene	0.055	0.056	0.064
129-00-0	Pyrene	0.051	0.049	0.060
83-32-9	Acenaphthalene	0.039	0.038	0.047
275-51-4	Azulene	0.023	0.024	0.027
3227-90-5	Trimethylenecyclopropane	−0.002	−0.043	−0.001
497-20-1	Fulvene	−0.002	−0.016	−0.002
250-25-9	Pentalene	−0.018	−0.018	−0.020
5291-90-7	Dimethylenecyclobutene	−0.028	−0.058	−0.028
6249-23-6	Calicene	0.043	0.043	0.050
4026-23-7	Benzocyclobutadiene	−0.027	−0.027	−0.020
4095-06-1	Methylenecyclopropene	0.005	−0.020	0.005

[a] Obtained using eight bond-energy terms calculated from the energies of the 40 acyclics in ref 4.

the A_s/e indicates that it is antiaromatic. The same is true for methylenecyclopropene and trimethylenecyclopropane.

The LCAO–BETA Method of Figeys.—Using an iterative method to adjust the Hückel parameters Figeys has also determined that the energies of the linear acyclic polyenes are additive when only two bond energy terms are considered and has used these terms to obtain resonance energies of the annulenes.[10] However, as in the simple Hückel method, we have found that these terms do not give accurate additivity of branched acyclic polyenes (see Table II). We have carried out a treatment of the LCAO–BETA results in a fashion exactly analogous to our treatment of the simple Hückel results.[4] One is able to obtain eight bond-energy terms which do give additivity of all acyclic polyene energies. Furthermore, resonance energies obtained with these terms are almost exactly analogous to the Hückel resonance energies obtained by our method (Table III). Hence it appears that nothing is gained over the simple Hückel method in going to the more complex LCAO–BETA method.

Heterocycles Containing a d-Orbital Acceptor Atom. Consideration of the Dependence of Structural and Reactivity Effects on Whether the Number of Ring Atoms Is Odd or Even

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Received July 11, 1972

I wish to call attention to a ring-size effect upon the symmetry of planar cycloalkane filled molecular orbitals. The effect is such that heterocycles containing

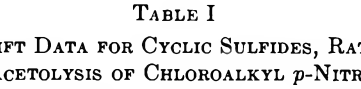
a d-orbital acceptor atom in the ring are predicted to show properties which depend on whether the ring size is odd or even.

The extension of the Walsh formulation of cyclopropane molecular orbitals to cyclobutane has recently been discussed.[1] Orbitals for planar rings of larger size may be similarly constructed from sp^2 carbon atoms. The overlapping sp^2 orbitals within the ring are analogous to the orbitals for cyclic π sytems. The energies for such orbitals may be obtained by inscribing a polygon with vertex *down* in a circle with radius equal to the energy of the most bonding orbital.[2] Coefficients of the orbitals are sine or cosine functions of appropriate angles.[2]

A second set of orbitals results from the overlap of the p orbitals outside the ring. Whereas the inside orbitals always exhibit one all-bonding combination, outside orbitals have a possible fully antibonding combination. Furthermore, the alternation of positive and negative lobes leads to other outside molecular orbitals having antibonds corresponding to the *bonds* of inside molecular orbitals.[2c] Accordingly, the energies of the outside molecular orbitals are represented by inscribing a polygon with vertex *up* in a circle whose radius is the energy of the fully antibonding orbital.[2c] Coefficients for the unoccupied inside orbitals become those for occupied outside orbitals.[2c]

In Figure 1 occupied orbitals and their symmetries with respect to *yz* and *xz* planes (the plane of the paper is *xz*) are shown for ring sizes 3, 4, 5, and 6. Replacement of the carbon atom at the bottom vertex of each ring by a d orbital containing electronegative heteroatom will cause the filled ring orbitals to mix with the vacant d orbitls of the same symmetry, leading to a decrease of the energy of the electron pair. Since there are two d orbitals of Ss symmetry and only one of As symmetry, the ring Ss orbitals are subject to a double decrease and may be stabilized to a greater extent than ring As orbitals which are subject to a single decrease. Odd-sized rings, in which the number of Ss orbitals exceed by one the number of As orbitals may, accordingly, be stabilized in comparison with even-sized rings and may have more electron density displaced from the ring to the heteroatom. (The d_{xy} and d_{yz} orbitals, having Aa and As symmetry, respectively, do not interact with ring orbitals.) The more difficult to evaluate overlaps and energy differences between the mixing orbitals also must be considered, suggesting that resort to experimental data be made for possible verification of odd–even effects.

Although ^{13}C nmr data for cyclic sulfides (Table I, column 2) provide some evidence for the odd–even effect, the phenomenon is expected to be most pronounced for molecules in which the heteroatom is positively charged. In Table I we cite data for cyclic halonium and sulfonium ions which suggest that the effect is observable for ring sizes beyond those where planarity is expected. Cyclic three-membered and five-membered chloronium, bromonium, and iodonium ions are well known, both as stable species in SbF_5–SO_2 and as reaction intermediates obtained by neighboring-group participation.[3] However, attempts to obtain six-membered species have led exclusively to five-membered rings (eq 1).[4] Under solvolytic con-



(1)

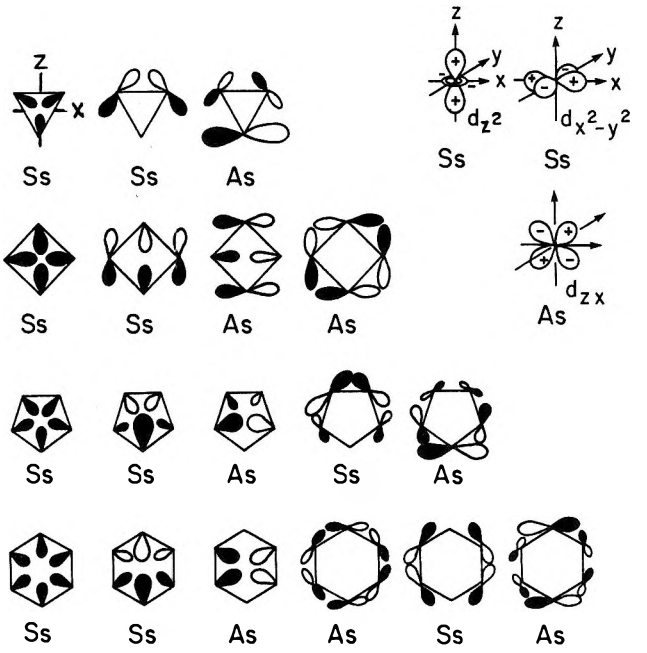
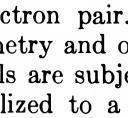
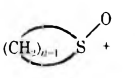


Figure 1.—Cycloalkane Walsh type filled molecular orbitals and the d-acceptor orbitals of the same symmetries.

TABLE I

CHEMICAL SHIFT DATA FOR CYCLIC SULFIDES, RATE DATA FOR TRIFLUOROACETOLYSIS OF CHLOROALKYL *p*-NITROBENZENESULFONATES, RATES OF H–D EXCHANGE IN CYCLIC METHYLSULFONIUM ICNS, AND PER CENT REDUCTION OF CYCLIC SULFOXIDES BY SODIUM HYDROGEN SULFITE

Ring size, *n*	$\Delta\delta,\alpha$-^{13}C cyclic sulfide[a]	Estd $k\Delta^b$ to give 	Rel *k*, α-ring H[c]	Rel *k*, H in CH_3-S^+[c] 	% redn, 60 min,[d]
3	21.5	0.09			
4	4.4	<0.0003[e]	<2.5[f]	770[f]	18
5	6.2	52	20	4.6	100
6	1.8	1.4	1.2	7.3	16
7		0.065	12	3.1	52
Cyclic			0.7–1.9[g]	3.7–6[g]	

[a] Difference between the α-carbon chemical shift and that of the cycloalkane of the same ring size: G. E. Maciel and G. B. Savitsky, *J. Phys. Chem.*, 69, 3925 (1965). [b] Reference 5, 10^5k, sec^{-1}. [c] Reference 9. [d] Reference 10. [e] <5% of k_{total} based on data for the trifluoromethanesulfonate.[6] [f] For the β,β-dimethyl compound. [g] Range for diethyl, dipropyl, diisopropyl, and diisobutylmethyl sulfonium salts.[9]

(1) R. Hoffmann and R. B. Davidson, *J. Amer. Chem. Soc.*, **93**, 5699 (1971), and references cited therein.

(2) (a) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, pp 47, 257. (b) L. Salem, "The Molecular Orbital Theory of Conjugated Systems," W. A. Benjamin, New York, N. Y., 1966, pp 113–118. (c) A mathematical demonstration that the orbitals and their coefficients are those described here will appear following these pages in the microfilm edition of this journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-72-4180. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(3) P. E. Peterson, *Accounts Chem. Res.*, **4**, 407 (1971).

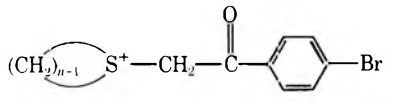
(4) (a) G. A. Olah and P. E. Peterson, *J. Amer. Chem. Soc.*, **90**, 4675 (1968); (b) P. E. Peterson, P. R. Clifford, and F. J. Slama, *ibid.*, **92**, 2480 (1970).

ditions partial formation of a five-membered ring apparently occurred during an attempt to obtain an intermediate six-membered ring in solvolysis of 5-chloro-1-hexyl *p*-nitrobenzenesulfonate.[5] A similar attempt to obtain a four-membered-ring iodonium ion intermediate apparently gave partial formation of the three-membered ring.[6] Furthermore, numerous attempts to obtain stable four-membered halonium ions in SbF_5–SO_2 led exclusively to three- and five-membered rings or both.[7]

Rate data (Table I, third column) emphasize the preference for three- and five-membered-ring halonium ion formation in solvolysis reactions, although participating groups not having d orbitals show a substantially similar pattern.[8] In the case of cyclic sulfonium ions, recently published rates of base-catalyzed hydrogen-deuterium exchange (Table I) provide striking odd–even effects.[9] Electron transfer from the five- and seven-membered ring carbons to sulfur can account for the increased exchange rate of the endocyclic α hydrogens. For the four- and six-membered rings electron transfer from the methyl group is facilitated, since the endocyclic orbitals are relatively ineffective in filling the d orbitals.

The last column in Table I gives data for per cent reduction of cyclic sulfoxides to cyclic sulfides by sodium hydrogen sulfite.[10] The data suggest that the rate of reduction shows alternation as ring size is incremented, althouth detailed interpretation of the multistep mechanism would be premature.

Finally, we note that pK_a data for the protonated form of sulfur containing ylides,[11] shown below, is consistent with the H–D exchange results in Table I, in that protons exocyclic to six-membered S-containing rings are more acidic than those of the comparable five-membered-ring compound.



$pK_a = 7.54$, $n = 5$ $pK_a = 7.00$, $n = 6$

The consideration mentioned above suggests a plethora of interesting experiments and theoretical investigations, covering a range of heterocycles incorporating d-orbital atoms. Several referees have pointed out that the magnitude of the interactions mentioned in this paper may be too small to dominate the chemistry of such heterocycles. However, we feel that consideration of the proposed orbital effect should be made in conjunction with studies of such heterocycles, and we accordingly present the concept in its present form. Even greater generality would obtain if the well-known general difficulty of obtaining four-membered rings[8] could be incorporated into our correlation. Possible selective stabilization of electron pairs in odd-ring orbitals having orbital dipole moments and/or large coefficients at the heteroatom deserve investigation.

Acknowledgment.—Support by the National Science Foundation (Grant GP 30684) is gratefully acknowledged. We are grateful for a discussion with Dr. B. M. Gimarc.

(5) P. E. Peterson and J. F. Coffey, *J. Amer. Chem. Soc.*, **93**, 5208 (1971).
(6) P. E. Peterson and W. F. Boron, *ibid.*, **93**, 4076 (1971).
(7) G. Olah, J. M. Bollinger, Y. K. Mo, and J. M. Brinich, *ibid.*, **94**, 1164 (1972).
(8) *Cf.* E. M. Kosower, "An Introduction to Physical Organic Chemistry," Wiley, New York, N. Y., 1968, p 104.
(9) G. Barbarella, A. Garbesi, and A. Fava, *Helv. Chim. Acta*, **54**, 2297 (1971).
(10) C. R. Johnson, C. C. Bacon, and J. J. Rigau, *J. Org. Chem.*, **37**, 919 (1972).
(11) K. W. Ratts, *ibid.*, **37**, 848 (1972).

Spectroscopic Differences between Crystalline and Amorphous Phases of Indigo

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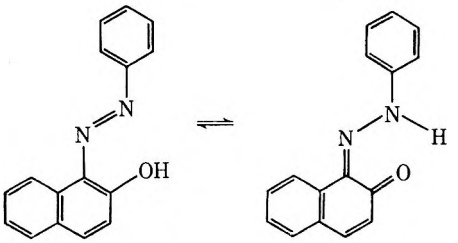
The vacuum evaporation of organic molecules has been used by a number of workers as a method of producing a desired polymorphic phase of the material.[1] It has been found for some organic systems that the amorphous state is initially formed upon vacuum evaporation and that the amorphous organic state is surprisingly stable under ambient conditions for periods ranging from days to years.[2] Of major interest are the wide variations in both spectral and electrical properties between the crystalline and amorphous phases of a given organic compound.[2] For example, the trans hydroxyazo aromatics show profound differences between the preferred species in the amorphous solid state and the crystalline phases. The lowest energy electronic transition of crystalline hydroxyazo compounds is red shifted ~1000 Å relative to that for the amorphous solid state or fluid media. This anomalous absorption characteristic of the crystalline phase has been attributed to intermolecularly hydrogen bonded hydrazone aggregates, whereas the amorphous state and solution state have been identified as being composed of a hydrazone–azo tautomeric equilibrium.[3]



azo hydrazone

Indigo has also been reported[4] to show visible absorption at considerably longer wavelengths (600–700 Å) in the solid phase than in organic solvents. From the electronic spectral observations and supporting

(1) P. A. Barrett, C. E. Deuland, and R. P. Linstead, *J. Chem. Soc.*, 1719 (1936); F. W. Karasek and J. C. Decius, *J. Amer. Chem. Soc.*, **74**, 4716 (1952); J. H. Sharp and M. Lardon, *J. Phys. Chem.*, **72**, 3230 (1968).
(2) A. R. Monahan, J. B. Flannery, Jr., J. E. Kuder, and G. E. Johnson, presented at the Organic Solid State Chemistry Symposium, 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 1972.
(3) A. R. Monahan and J. B. Flannery, Jr., *Chem. Phys. Lett.*, in press.
(4) J. Weinstein and G. M. Wyman, *J. Amer. Chem. Soc.*, **78**, 2387 (1956).

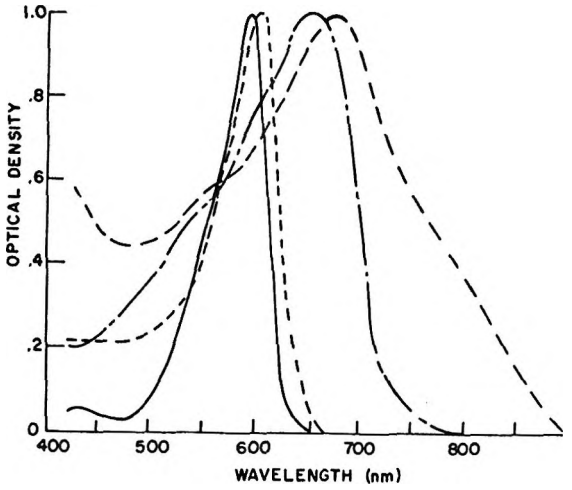


Figure 1.—Absorption spectra of indigo in ———, chloroform; - - - - - - - -, ethanol; —— - ——, amorphous solid state; — — —, crystalline solid state.

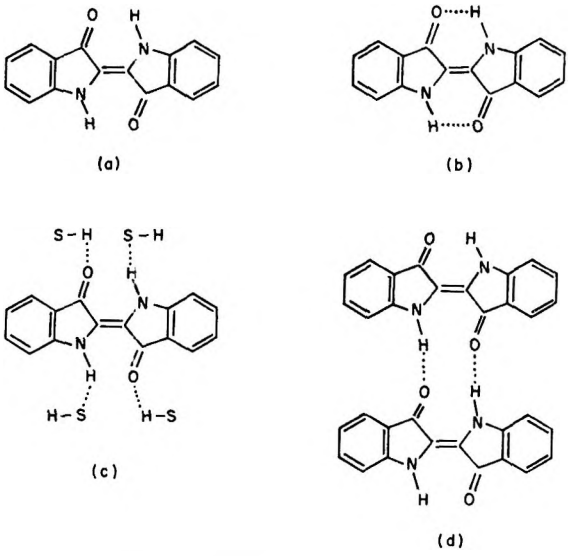


Figure 2.—Indigo with various hydrogen-bonding interactions considered.

infrared spectroscopic studies on model compounds, it was concluded that, in the solid state, indigo dyes are associated by means of intermolecular hydrogen bonding. While spectral shifts of dyes in solvents of different dielectric constant are well known, the spectral differences between the amorphous and crystalline phases of a given compound have received less attention. In this note are presented some comparative spectroscopic studies on indigo which clearly differentiate between the spectral properties in solution and in the amorphous and crystalline solid phases. These differences in spectral properties between the three phases can be conclusively attributed to variations in hydrogen bonding interactions. Quantum chemical calculations support the formation of associated species in the solid.

Experimental Section

Sample Preparation.—Indigo is commercially available (J. T. Baker) and was purified by recrystallization from chloroform prior to vacuum sublimation. (*Anal.* Calcd for indigo: C, 73.3; H, 3.8; N, 10.7; O, 12.2. Found: C, 73.3; H, 3.6; N, 10.9; O, 12.3.) Thin films of indigo were prepared by vacuum evaporation (10^{-6} Torr) of the purified material onto 0.5-in. diameter KBr flats and 0.5-in.-diameter quartz Suprasil windows held at ambient temperatures. The evaporations were carried out in a Bendix Balzers Model BA-3 evaporator. The thin films of indigo were determined to be amorphous by means of a polarizing microscope and X-ray diffraction techniques. Thin films of crystalline indigo were obtained by heat treating the amorphous films for 2 hr at 350°. Several crystalline samples for spectroscopic analyses were also prepared from the recrystallized material using the Nujol mull technique. Visible absorption spectra of indigo were also obtained in Matheson Coleman and Bell spectroquality chloroform and ethanol (J. T. Baker).

Spectroscopy.—The visible absorption spectra of indigo were recorded on a Cary Model 14R automatic spectrophotometer at 25°. The infrared spectra of amorphous and crystalline films of indigo were recorded on a Beckman Model IR-12 spectrometer. The visible and infrared absorption spectra of crystalline indigo were found to be identical whether the spectra were obtained in Nujol mull using the recrystallized material or from the amorphous phase crystallized directly on the optical windows.

Results and Discussion

The spectra of indigo in various media are shown for comparison in Figure 1. The wavelength maxima of the lowest $\pi-\pi^*$ transition occur at 590 nm, carbon tetrachloride; 604 nm, chloroform; 610 nm, ethanol; 640 nm, amorphous solid; 668 nm, crystalline solid.[5] Weinstein and Wyman[4] have explained the strong bathochromic shift in the crystalline phase as being due to the formation of hydrogen-bonded dimers or higher polymers. In addition, X-ray crystallographic studies by von Eller[6] have also stressed the importance of hydrogen bonding in the crystalline state of indigo. In view of these findings and the wide spectral variations apparent in Figure 1, a Hückel molecular orbital (HMO) treatment of some of the factors affecting the spectrum of indigo was undertaken. The interactions involved in the calculation are illustrated in Figure 2. First, calculations were done on the free molecule (Figure 2a) using standard HMO parameters for the heteroatoms.[7] In view of the possibility of intramolecular hydrogen bonding (Figure 2b), this is then included in the calculation in the manner proposed by Pullman and Pullman.[8] The same atoms of the molecule may also be involved in intermolecular hydrogen bonding (Figure 2c) to solvent (S–H) and this is treated as was done previously for azo compounds.[9] A final possibility considered in this note is that of a hydrogen-bonded dimer (Figure 2d).

The results of the calculation are shown in Table I, where the energies (β units) of the highest occupied (HO) and lowest unoccupied (LU) orbitals are given together with their separation.

Somewhat surprisingly, the Pullman model indicates that the formation of an intramolecular hydrogen bond, case b, should increase the energy of the lowest electronic transition relative to the molecule without hydrogen bonding, case a. Thus, the strength of H

(5) In carbon tetrachloride the maximum appears at 590 nm and otherwise resembles the shape of the chloroform spectrum.

(6) H. von Eller, *Bull. Soc. Chim. Fr.*, 1433 (1955); 316 (1957).

(7) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961.

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(9) J. E. Kuder, *Tetrahedron*, **28**, 1973 (1972).

TABLE I

	HO	LU	ΔE	Phase	λ_{max}, nm
(a) No H bond	0.579	−0.021	0.600	Vapor[a]	540
(b) Intramolecular H bond	0.640	0.000	0.640		
(c) Intramolecular H bond	0.564	0.026	0.538	$CHCl_3$	604
				Ethanol	610
(d) H-bonded dimer	0.612 (a_u)	0.011 (b_g^*)	0.601 ($a_u \rightarrow b_g^*$)	Crystal	560
	0.516 (b_g)	−0.013 (a_u^*)	0.529 ($b_g \rightarrow a_u^*$)		668

[a] Reference 10.

bonding decreases in the order ethanol, $CHCl_3$, and CCl_4 as reflected by the absorption maxima in these solvents. At the same time, intermolecular hydrogen bonding, case c, is indicated to decrease the energy of the lowest transition. In practice, it may not be possible to distinguish between a and b, and case a quite likely represents a hypothetical situation. It is thought that case d resembles the situation in the crystalline solid state. In the dimer, which belongs to point group C_{2h},[11] the HOMO and LUMO of the monomer are each split into dimer orbitals of a_u or b_g symmetry. The allowed[11] electronic transitions are then $a_u \rightarrow b_g^*$ and $b_g \rightarrow a_u^*$ which, as indicated in Table I, are predicted to appear at lower energies than those of the free molecule, in agreement with experimental findings. Similarly, the lower transition energy in the situation involving intermolecular hydrogen bonding is also in agreement with experiment.

The general features of the hydrogen-bonding models for the amorphous state of indigo were confirmed by infrared spectroscopy. Thus, the crystalline state is completely H bonded, as seen by the dominance of an NH bonded frequency at 3285 cm^{-1}. The infrared spectrum of the amorphous state is characterized by both free NH (3378 cm^{-1}) and bonded NH (3285 cm^{-1}) transitions. Also the carbonyl region[4] indicates that free C=O sites are in greater abundance in the amorphous state than in the crystalline phase. Therefore it is not surprising that the λ_{max} of the lowest $\pi-\pi^*$ transition in amorphous indigo (640 nm) lies at higher energy than the crystal (668 nm). The amorphous form, most likely, represents a disordered array of the H-bonded situations shown in Figure 2.

It is pertinent to note that similar changes in spectral features do not occur where the NH moiety in indigo is replaced by O, S, or Se. In addition, indigoid molecules with bulky substituents on the 4, 5, and/or 7 positions do not show hydrogen-bonding shifts between solution and solid phases,[4] since the sterically hindering groups prevent the interaction of CO and NH groups on neighboring molecules. For example, 5,5′,7,7′-tetrabromoindigo in either $CHCl_3$ or the solid state shows no discernible difference between the peak maxima in the visible region.[4] The electronic absorption properties supported by the simple MO model do, however, clearly demonstrate that dramatic spectral differences are to be expected between the spectra of crystalline and amorphous dyes when strong H-bonding forces are the dominant intermolecular interaction.

Registry No.—Indigo, 482-89-3.

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Reactions of N-Substituted Maleamic Acids with Thionyl Chloride and Chloroacetyl Chloride

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N-Substituted maleamic acids are dehydrated to either the corresponding maleimide or the maleisoimide, depending on the dehydration conditions and the nature of the substituent.[1] When powerful dehydrating agents such as trifluoroacetic anhydride, *N,N′*-dicyclohexylcarbodiimide, or ethyl chloroformate are allowed to react with maleamic acids in the presence of triethylamine, maleisoimides are formed as the main products. Other dehydrating agents yield the corresponding imides or mixtures of imides and maleisoimides.[2] Recently N-substituted maleisoimides have been prepared using mild dehydrating agents, such as acetyl chloride, or even weak dehydrating agents, such as acetic anhydride, under controlled conditions.[1a,b] In this report the effects of thionyl chloride and chloroacetyl chloride on N-substituted maleamic acids will be presented.

The behavior of thionyl chloride toward N-substituted maleamic acids depends on the nature of the substituent and also on the temperature. A few reports have been published regarding the effects of thionyl chloride on N-substituted maleamic acids. Feuer and Rubenstein[3] reported the preparation of *N*-benzenesulfonylaminomaleimide and bismaleimide by refluxing the corresponding maleamic acids with thionyl chloride. The bismaleimide was found recently to have the bismaleisoimide structure.[4] Others[5] have utilized boiling thionyl chloride for the prepara-

*Department of Chemistry, University of Sulaimania. Sulaimania, Iraq.
(1) (a) T. M. Pyriadi and H. J. Harwood, *J. Org. Chem.*, **36**, 821 (1971); (b) T. M. Pyriadi, Ph.D. Thesis, The University of Akron, Akron, Ohio, 1970.
(2) R. J. Cotter, C. K. Sauers, and J. M. Whelan, *J. Org. Chem.*, **26**, 10 (1961).
(3) H. Feuer and H. Rubinstein, *J. Amer. Chem. Soc.*, **80**, 5873 (1958).
(4) H. Feuer, *J. Org. Chem.*, **36**, 3372 (1971).
(5) W. R. Roderick and P. L. Bhatia, *ibid.*, **28**, 2018 (1963), and references cited therein.

TABLE I

PRODUCTS FROM THE REACTION OF THIONYL CHLORIDE WITH N-SUBSTITUTED MALEAMIC ACIDS AT DIFFERENT CONDITIONS

NR	Temp, °C	Mol of $SOCl_2$	Mol of Et_3N	Time, min	Product	Yield, %
Phenyl	−20	1	1	30	*N*-Phenylmaleimide	9
Phenyl	0–5	1	2	17	α-Chloro-*N*-(phenyl)succinimide	26
Phenyl	25	1	2	40	α-Chloro-*N*-(phenyl)succinimide	40
Phenyl	40	Excess[a]	0	10	α-Chloro-*N*-(phenyl)succinimide	50
Phenyl	78	Excess[a]	0	30	α-Chloro-*N*-(phenyl)succinimide	57
Propyl	−20	1	1	40	*N*-Propylmaleimide	3
Propyl	78	Excess[a]	0	10	*N*-Propylmaleimide	6
Ethyl	25	1	1	45	*N*-Ethylmaleimide	16
p-Methoxyphenyl	−20	1	1	30	*N*-(*p*-Methoxyphenyl)maleimide	4
p-Methoxyphenyl	78	Excess[a]	0	40	*N*-(*p*-Methoxyphenyl)maleimide and α-chloro-*N*-(*p*-methoxyphenyl)succinimide in the ratio 1:6	62
p-Nitrophenyl	25	1	2	40	α-Chloro-*N*-(*p*-nitrophenyl)succinimide	8
p-Nitrophenyl	78	Excess[a]	0	45	α-Chloro-*N*-(*p*-nitrophenyl)succinimide	85

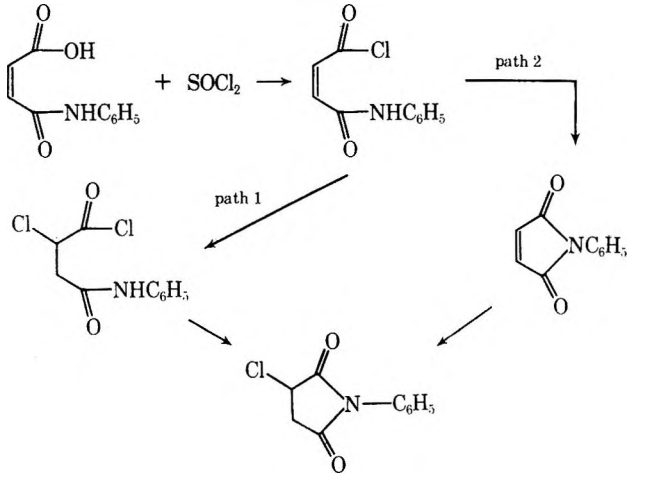
[a] The maleamic acid was refluxed in excess thionyl chloride; otherwise methylene chloride was used as a solvent.

tion of maleimides. On the other hand, Kretov and Kul'chitskaya[6] reported the preparation of several *N*-arylimides of chorosuccinic acid by allowing thionyl chloride to react with *N*-arylmaleamic acids at temperatures ranging from 12 to 78°. These reactions and related ones have been studied here at temperatures from −25 to 78° with and without triethylamine as a catalyst.

The reaction of *N*-phenylmaleamic acid with thionyl chloride in methylene chloride in the presence of 1 or 2 equiv of triethylamine at 0–5° yielded only α-chloro-*N*-phenylsuccinimide. When the reaction was conducted at −20°, *N*-phenylmaleimide was the sole product. Excess thionyl chloride alone reacted with *N*-phenylmaleamic acid at room temperature, 40°, and at reflux, yielding always α-chloro-*N*-phenylsuccinimide.

It seems possible that the chlorosuccinimide arose from the addition of hydrogen chloride, formed in the reaction, to either *N*-phenylmaleimide or an intermediate product, perhaps *N*-phenylmaleamoyl chloride, as shown in Scheme I.

SCHEME I



In another experiment, *N*-phenylmaleimide in methylene chloride solution was mixed with thionyl chloride, and 1 equiv of water was added to the mixture; no α-chloro-*N*-phenylsuccinimide could be detected in the mixture. This result was confirmed by another experiment in which moist hydrogen chloride was passed through a solution of *N*-phenylmaleimide in acetic acid, using the precedure of Roderick;[7] but no addition of hydrogen chloride to the maleimide was observed. The procedure was repeated using *N*-(*p*-methoxyphenyl)maleamic acid, and a 12% yield of α-chloro-*N*-(*p*-methoxyphenyl)succinimide was obtained. The conclusion here is that addition of hydrogen chloride must be mostly to the *N*-phenylmaleamoyl chloride or to the maleamic acid in Scheme I.

When *N*-(*p*-methoxyphenyl)maleamic acid was refluxed with thionyl chloride, a mixture of *N*-(*p*-methoxyphenyl)maleimide and α-chloro-*N*-(*p*-methoxyphenyl)succinimide was formed. This result is in contrast to the report of Kretov and Kul'chitskaya,[6] where they have reported the preparation of α-chloro-*N*-(*p*-anisyl)succinimide by treating thionyl chloride with *N*-(*p*-anisyl)maleamic acid. The general results of Kretov's report, however, agree with the findings here, in that their reported yields of α-chloro-*N*-arylsuccinimides are relatively higher for compounds having electron-accepting groups on the nitrogen [the highest yield reported is for α-chloro-*N*-(*p*-nitrophenyl)succinimide, 84%, while the yield of the corresponding *N*-(*m*-nitrophenyl) derivative is 79%].

When *N*-ethyl- and *N*-propylmaleamic acids were allowed to react with thionyl chloride in the presence of triethylamine at −20 or 25°, the products were *N*-ethylmaleimide and *N*-propylmaleimide, respectively. The last product was also obtained when *N*-propylmaleamic acid was refluxed with thionyl chloride.

On the other hand, when *N*-(*p*-nitrophenyl)maleamic acid was dehydrated with thionyl chloride at room temperature in the presence of excess triethylamine, the product was only α-chloro-*N*-(*p*-nitrophenyl)succinimide. The results of these experiments are listed in Table I.

Therefore, it seems that the products of the dehydration of N-substituted maleamic acids with thionyl chloride are highly dependent on the nature of the substituent. Generally, electron-releasing substituents favor the formation of the maleimide, while electron-accepting substituents tend to favor the formation of α-chloro N-substituted succinimides. This conclusion is in accord with the results obtained in

(6) A. E. Kretov and N. E. Kul'chitskaya, *J. Gen. Chem. USSR*, **26**, 221 (1956).

(7) W. R. Roderick, *J. Org. Chem.*, **79**, 1710 (1957).

the reactions of 1,2-bis(3-carboxyacryloyl)hydrazine and 1-benzenesulfenyl-2-(3-carboxyacryloyl)hydrazine with boiling thionyl chloride.[3] The result is also in accord with the preparation of *N*-phenyl, *N*-(*p*-nitrophenyl), and *N*-(*m*-nitrophenyl) derivatives of α-chlorosuccinimide.[6]

Generally, the addition of hydrogen chloride to N-substituted maleimides is expected to be slower than addition to the corresponding maleamoyl chlorides suggested in Scheme I. However, substituents on the nitrogen of the maleimide would have a great effect on the rate of addition of hydrogen chloride. Such an effect would be opposite to the conclusions mentioned above regarding the addition to N-substituted maleamoyl chloride (Scheme I).

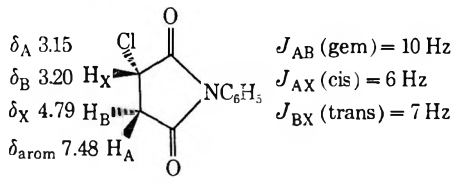
It appears that thionyl chloride may form N-substituted maleisoimides provided that the products are highly stabilized. The bismaleisoimide, prepared by Feuer,[4] seems to be the first maleisoimide reported from the dehydration of maleamic acids with thionyl chloride.

Chloroacetyl chloride reacted with *N*-phenylmaleamic acid in the presence of 1 molar equiv of triethylamine at 0–5°, forming *N*-phenylmaleisoimide in 54% yield.[8] When 2 molar equiv of triethylamine was employed, the product was only *N*-phenylmaleimide, no isoimide being detected in the infrared spectrum of the compound. These results are in agreement with previously suggested mechanism.[1a]

Experimental Section

Preparation of Maleamic Acids.—The procedures used here were similar to those in a previous work.[1a]

Reaction of *N*-Phenylmaleamic Acid with Thionyl Chloride in Presence or Absence of Triethylamine.—To a solution of 0.025 mol of *N*-phenylmaleamic acid in 100 ml of methylene chloride, 0.025 mol of triethylamine was added. The mixture was cooled in an ice bath to 0.5°. Thionyl chloride (0.025 mol) was added dropwise during 5 min, after which stirring was continued for 10 min. A violent reaction and fuming was observed at the beginning and an orange solution formed. The mixture was filtered from a small amount of triethylamine hydrochloride and the filtrate was stirred with excess dilute sodium bicarbonate solution for 30 min. The methylene chloride layer was then washed with water and dried with anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The orange-yellow solid that remained was recrystallized from boiling water to obtain 0.2 g (26%) of α-chloro-*N*-phenylsuccinimide, mp 118–119°. Ir (CCl_4) showed C=O absorption at 1728 cm^{-1} and no absorption was observed around 1650 cm^{-1}, indicating the absence of a carbon–carbon double bond. The nmr spectrum showed an ABX-type pattern as follows.[9]



Using excess triethylamine in this reaction resulted in a 40% yield of α-chloro-*N*-phenylsuccinimide when the reaction was conducted at 25°. When *N*-phenylmaleamic acid was allowed to react with excess thionyl chloride at 40°, the yield was 50%. The optimum yield (57%) was obtained when the last mixture was refluxed for 0.5 hr. When the amic acid and 1 equiv of thionyl chloride were allowed to react at −20° (Dry Ice–acetone bath), the product was *N*-phenylmaleimide (9.5% yield), mp 88° (lit.[10] mp 89–89.8°).

Reaction of Thionyl Chloride with *N*-Phenylmaleimide in Presence of Water.—In a three-necked flask *N*-phenylmaleimide[10] (0.01 mol) and thionyl chloride (0.01 mol) in 40 ml of methylene chloride were stirred and warmed to about 30°. Water (0.01 mol) was then added drop by drop. A violent reaction occurred in the beginning and hydrogen chloride was evolved, but without any change in the color of the solution. The solution was washed with water and dried with anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was unchanged *N*-phenylmaleimide, mp 88–89°.

Separation of *N*-(*p*-Methoxyphenyl)maleimide from α-Chloro-*N*-(*p*-methoxyphenyl)succinimide.—The solid yellow product left from refluxing thionyl chloride with *N*-(*p*-methoxyphenyl)-maleamic acid was dissolved in alcohol by heating, filtered, and cooled. A white precipitate was obtained by filtration. When the filtrate was evaporated, yellow crystals of *N*-(*p*-methoxyphenyl)maleimide were obtained, mp 148° (lit. mp 148–149°).[7] This last compound showed the presence of chlorine on sodium fusion, while the corresponding imide did not.

Anal. Calcd for $C_{11}H_{10}O_3NCl$: C, 55.12; H, 4.21; N, 5.84. Found: C, 55.27; H, 4.03; N, 5.64. *Anal.* Calcd for $C_{11}H_9O_3N$: C, 65.02; H, 4.43; N, 6.89. Found: C, 65.11; H, 4.42; N, 6.77.

Registry No.—Thionyl chloride, 7719-09-7; chloroacetyl chloride, 79-04-9; *N*-phenylmaleamic acid, 555-59-9; *N*-propylmaleamic acid, 36342-07-1; *N*-ethylmaleamic acid, 4166-67-0; *N*-(*p*-methoxyphenyl)maleamic acid, 24870-10-8; *N*-(*p*-nitrophenyl)maleamic acid, 36342-10-6; 2-chloro-*N*-phenylsuccinimide, 36342-11-7; *N*-phenylmaleimide, 941-69-5; *N*-(*p*-methoxyphenyl)maleimide, 1081-17-0; 2-chloro-*N*-(*p*-methoxyphenyl)succinimide, 36342-13-9.

Acknowledgment.—The author is grateful to the College of Pharmacy, University of Baghdad, for providing space, reagents, and equipment.

(8) For experimental procedure see ref 1a.

(9) The coupling constants were calculated according to A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969.

(10) *Org. Syn.*, **41**, 94 (1961).

The Bromination of Perdeuterionaphthalene[1]

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Aromatic bromination is known to proceed by the two-step sequence shown.

$$ArH + Br_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ArHBr^+ + Br^-$$

$$ArHBr^+ \xrightarrow{k_2} ArBr + H^+$$

If the first step is rate controlling ($k_2 \gg k_{-1}$), the observed rate constant varies with bromide ion concentration according to the equation $k_{obsd} = k_1K/(K + Br^-)$ (eq 1), where K is the dissociation constant of the tribromide ion and k_1 the true rate constant of bromination by free, uncomplexed bromine.[3] If the second step is partially or completely rate determining, a different dependence on bromide ion is obtained.[4,5] In

(1) Kinetics of Aromatic Halogenation. XIII.

(2) Taken from the M. A. Thesis of Albert Ehrlich, Bryn Mawr College, 1969.

(3) E. Berliner and M. C. Beckett, *J. Amer. Chem. Soc.*, **79**, 1425 (1957).

(4) E. Berliner, J. B. Kim, and M. Link, *J. Org. Chem.*, **33**, 1160 (1968).

(5) B. T. Baliga and A. N. Bourns, *Can. J. Chem.*, **44**, 363, 379 (1966).

almost all cases conducted in aqueous acetic acid eq 1 is satisfied.[6] Consequently, no significant deuterium isotope effects, and no base catalysis, have been observed in bromination,[7] except when the position of substitution is sterically crowded.[8]

An isotope effect, if obtained, should increase with the bromide ion concentration, because the latter will affect the reversal of the first step, and lead to the condition k_{-1} (Br^-) $\gg k_2$, on which the isotope effect depends. In an earlier investigation of the bromination of 4,4′-dideuteriobiphenyl, the bromide ion concentration was varied only slightly, and the small, invariant isotope effect observed was interpreted as a secondary isotope effect.[9]

We now report the bromination of perdeuterionaphthalene (octadeuterionaphthalene) in 50% aqueous acetic acid in which the bromide ion concentration was varied over the wider range 0.1–0.8 *M* at a constant ionic strength of 0.8 *M* ($NaClO_4$). The bromination of naphthalene had previously been studied at an ionic strength of 0.5 *M*,[3] and this study was repeated at the higher ionic strength. Results are shown in Table I.

TABLE I

THE BROMINATION OF NAPHTHALENE AND PERDEUTERIONAPHTHALENE IN 50% AQUEOUS ACETIC ACID[a,b]

[NaBr], mol/l.	[$NaClO_4$], mol/l.	$(10^2k_{obsd})_H$	$(10^2k_{obsd})_D$	$(k_{obsd})_H/(k_{obsd})_D$
0.10	0.70	6.44	7.88	0.817
0.20	0.60	3.68[c]	4.25	0.866
0.30	0.50	2.50	2.84	0.880
0.40	0.40	1.99	2.13	0.934
0.50	0.30	1.59	1.66	0.958
0.60	0.20	1.31	1.36	0.963
0.70	0.10	1.13	1.12	1.01
0.80	0.00	0.974	0.973	1.00

[a] Naphthalene $\cong$0.007 *M*, perdeuterionaphthalene $\cong$0.005 *M*, $Br_2 \simeq$ 0.002 *M*, temperature 24.9°. [b] All rate constants are in l. mol^{-1} sec^{-1}. [c] A value of 3.64 × 10^{-2}, obtained under the same conditions, is reported in ref 3.

As shown earlier, the bromination of naphthalene follows eq 1, and so does the bromination of perdeuterionaphthalene (Figure 1). The bromination of fully deuterated naphthalene therefore obeys the same rate law as naphthalene, and the first step must be rate controlling ($k_2 \gg k_{-1}$). The true rate constants (the least-squares slopes in Figure 1) are 0.474 ± 0.005 for naphthalene[10] and 0.572 ± 0.002 l. mol^{-1} sec^{-1} for deuterionaphthalene. The ratio $(k_1)_H/(k_1)_D$ is 0.829 and the reaction has a secondary inverse isotope effect.

The data in Table I reveal that the isotope effects at different bromide ion concentration actually increase with bromide ion concentration (last column in Table I). This could be interpreted to mean that there is indeed a slight return of the intermediate to reactants, and that at sufficiently high bromide ion concentration a positive isotope effect might be obtained. By methods used earlier,[4,5] one can then calculate that the reversibility ratio $(k_2/k_{-1})_H$ is 13.0,[11] and the ratio $(k_2/k_{-1})_D$ = 3.48. The extent of return thus calculated is only very small. For every molecule of intermediate that returns to reactants, 26 go on to form products in the case of naphthalene, and seven in the case of perdeuterionaphthalene at a 0.5 *M* bromide ion concentration. It is sufficiently small that eq 1 is hardly perturbed.[12] As expected, a peri hydrogen in naphthalene provides much less steric crowding in the intermediate than a peri-methyl group, because in the bromination of 1,5-dimethylnaphthalene, only one molecule of intermediate goes on to products for every eight that return.[4] The ratio of C–H to C–D bond breaking, k_{2H}/k_{2D}, the isolated primary isotope effect, which would be observed if the second step were fully rate controlling, is calculated to be 3.74.[13]

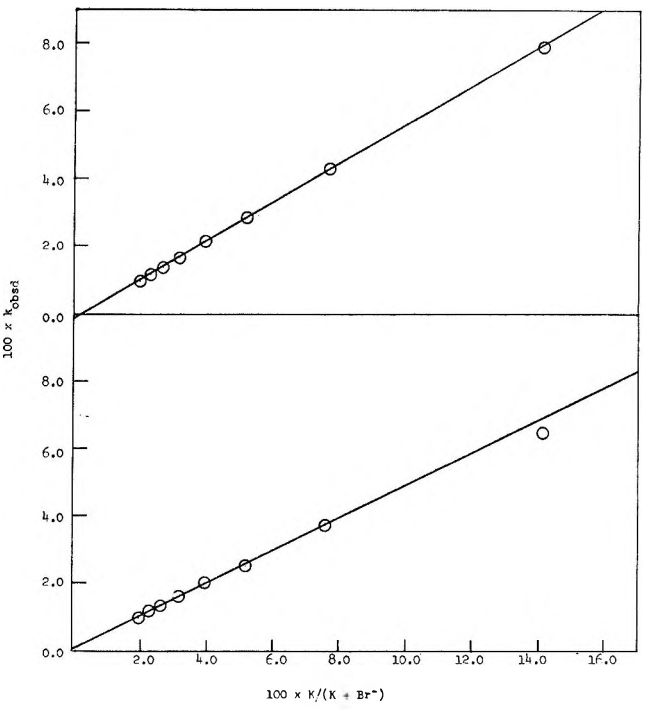

Figure 1.—The dependence of the rate of bromination on the bromide ion concentration: lower line, naphthalene; upper line, naphthalene-d_8.

The possibility, however, also exists that this trend in individual rate constants, or part of the trend, is a kinetic artifact caused by the high ionic strength of the medium. If eq 1 were to hold strictly, the lines in Figure 1 should pass through the origin. The line for naphthalene has a small positive intercept, (6.93 ± 2.15) × 10^{-4}, which has been interpreted as being due to a small amount of bromination by the tribromide ion.[3] The line for deuterionaphthalene has a small negative intercept of (−1.49 ± 0.16) × 10^{-3} which has no physical significance. It is likely that NaBr and $NaClO_4$ do *not* have the same effect on the ionic strength of the medium and on the activities of naphthalene and deuterionaphthalene, and it is possible that the difference in the intercepts, and hence the trend, or part of the trend, in the individual k_H/k_D values is due to this effect. The deviation (negative intercept) is in the direction expected if the condition in footnote 12 does

(6) L. Altschuler and E. Berliner, *J. Amer. Chem. Soc.*, **88**, 5837 (1966); U. P. Zimmerman and E. Berliner, *ibid.*, **84**, 3953 (1962); E. Berliner and J. C. Powers, *ibid.*, **83**, 905 (1961); E. Berliner and B. J. Landry, *J. Org. Chem.*, **27**, 1083 (1962).

(7) E. Berliner, *Progr. Phys. Org. Chem.*, **2**, 253 (1964); H. Zollinger, *Advan. Phys. Org. Chem.*, **2**, 163 (1964).

(8) P. C. Myhre, *Acta Chem. Scand.*, **14**, 219 (1960); E. Helgstrand, *ibid.*, **19**, 1583 (1965); E. Helgstrand and A. Nilsson, *ibid.*, **20**, 1463 (1966).

(9) E. Berliner and K. E. Schueller, *Chem. Ind. (London)*, 1444 (1960).

(10) Compared to 0.341 l. mol^{-1} sec^{-1} at an ionic strength of 0.5 *M*.

(11) Only the five points at higher bromide ion concentration were used.

(12) This means that the bromide ion concentration is almost negligible relative to the term k_2/k_{-1} in the steady-state equation. See eq 3 in ref 4.

(13) The usual assumption is made that $(k_{-1})_H = (k_{-1})_D$.

not hold, which will be more the case for naphthalene-d_8 than for naphthalene, because $(k_2/k_{-1})_H > (k_2/k_{-1})_D$. This would seem to argue in favor of the former interpretation.

There is no ambiguity about the inverse isotope effect in the first step. According to Streitwieser and coworkers,[14] secondary inverse isotope effects can be caused by the rehybridization of the carbon–hydrogen bonding orbitals from sp^2 to sp^3, which are, however, often compensated by hyperconjugation in the transition state which leads to the intermediate. An additional factor ought to be of importance in the present instance. Because of anharmonicity effects, C–D bonds behave as if they were more electron releasing than C–H bonds.[15] The inductive effect of seven C–D bonds not involved in the reaction must combine with the rehybridization effect to more than compensate for the rate-decreasing effect of hyperconjugation and thus lead to the inverse isotope effect observed here.

Experimental Section

Materials and kinetic procedures were as described before.[3] A sample of naphthalene was recrystallized five times from ethanol and had mp 80.1–80.5° (corrected). The sample of naphthalene-d_8, obtained from Merck Sharpe and Donm of Canada Limited, was recrystallized three times and had mp 79.6–80.2°. Its nmr spectrum showed no indication of incomplete deuteration. The rate constants listed in Table I are averages of at least two runs. More runs were conducted if average runs differed by more than 2%.

Registry No.—Perdeuterionaphthalene, 1146-65-2; naphthalene, 91-20-3.

Acknowledgment.—This work was supported by National Science Foundation Grant GP-4986, which is gratefully acknowledged.

(14) A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Amer. Chem. Soc.*, **80**, 2326 (1958).
(15) E. A. Halevi, *Progr. Phys. Org. Chem.*, 1, 109 (1963).

Hydrogen–Deuterium Exchanges in Pyrimidine *N*-Oxides

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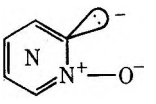
Acid- and base-catalyzed H → D exchange processes in pyridine *N*-oxides,[1] pyrazine *N*-oxides,[2] and pyridazine *N*-oxides[3] have been the subject of several recent papers.

The general conclusions that can be drawn from these studies are as follows.

(1) The hydrogens on the carbon atom α to the *N*-oxide group are much more readily exchanged under base catalysis than are any of the other ring protons.

(2) The exchange process occurs *via* "anionic ylides" such as depicted by structure **1**.



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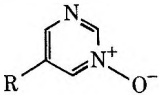
(3) The replacement of a ring =CH function in a pyridine *N*-oxide by a =N atom has a dramatic rate-enhancing effect on these exchange reactions.

This pattern is significantly different from that observed in the nonoxidized parents of these compounds where the hydrogens α to the ring nitrogen atom exchange *less* readily than do the other ring protons.[4–6] (The relative $H_2:H_4:H_5$ exchange rates in pyrimidine, for example, are 1:3.25:46.7). A comparison of the α-proton exchange rate in pyridine with those in pyrimidine and in pyrazine show that the latter two compounds undergo this exchange 100 times as readily. An even more dramatic increase is noted when the α-proton exchange rate in pyridine is compared with that observed in pyridazine, where the latter exchanges 1000 times as readily as the former.

Zoltewicz and coworkers[6] have suggested that the rate difference between the exchange of α protons and those further removed from the ring nitrogen atom is due to a decreased s character of the carbon–hydrogen bond adjacent to the sp^2 nitrogen atom and the repulsive interaction between the electron pairs on nitrogen and the (developing) carbanion.

In an effort to delineate the effect that sp^2 nitrogen atoms have upon the H → D exchange rates of "azapyridine *N*-oxides" we have now examined the behavior of several 5-substituted pyrimidine 1-oxides when they are subjected to base-catalyzed H → D exchange (Table I). In these *N*-oxides (**2a–e**) we expect H-2 as well as H-6 to exchange.



2a, R = H
b, R = CH_3
c, R = Br
d, R = OCH_3
e, R = $N(CH_3)_2$

The second-order rate constants, determined as described in the previous paper of this series,[2] for H-2 and H-6 of pyrimidine *N*-oxide (2a) are 1.8×10^{-3} and 4.7×10^{-2} l. mol^{-1} min^{-1}, respectively. Thus, H-6 exchanges 26 times as rapidly as does H-2, while both of these protons exchange much less readily than do H-2 and H-6 in pyrazine 1-oxide (0.16 l. mol^{-1} min^{-1}). Thus, the nonoxidized nitrogen atom, when situated ortho or para to the exchanging proton, is much less effective in faciliting H → D exchange than when it is located meta to the exchanging position.

Zoltewicz and coworkers[6] have shown that in the diazines themselves the activating effects of the sp^2 nitrogen atoms are in the order para ≈ meta ≫ ortho. This positional reactivity differs from that found in

(1) J. A. Zoltewicz and G. M. Kauffman, *Tetrahedron Lett.*, 337 (1967).
(2) W. W. Paudler and S. A. Humphrey, *J. Org. Chem.*, **35**, 3467 (1970).
(3) Y. Kawazoe, Y. Yoshioka, M. Yamada, and N. Igeta, *Chem. Pharm. Bull.*, **15**, 2000 (1967).
(4) J. A. Zoltewicz and C. L. Smith, *J. Amer. Chem. Soc.*, **89**, 3358 (1967).
(5) J. A. Zoltewicz and C. L. Smith, *Tetrahedron*, **25**, 4331 (1969).
(6) J. A. Zoltewicz, G. Grahe, and C. L. Smith, *J. Amer. Chem. Soc.*, **91**, 5501 (1969).

TABLE I

SECOND-ORDER RATE CONSTANTS FOR H–D EXCHANGE IN NaOD/D_2O[a,b] OF SOME 5-X-PYRIMIDINE 1-OXIDES

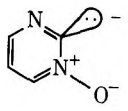
X	Compd no. (*cf.* Figure 1)	k_{H-6},[c] l. mol^{-1} min^{-1}	k_{H-2},[c] l. mol^{-1} min^{-1}
Br	1	$5.4 \pm 0.5 \times 10^{2}$	*d*
CH_3O	2	4.7 ± 0.5	$3.1 \pm 0.3 \times 10^{-3}$
$(CH_3)_2N$	3	$1.7 \pm 0.2 \times 10^{-1}$	*e*
CH_3	4	$9.8 \pm 0.9 \times 10^{-2}$	$1.7 \pm 0.2 \times 10^{-2}$
H	5	$4.7 \pm 0.5 \times 10^{-2}$	$1.8 \pm 0.2 \times 10^{-3}$

[a] The various concentrations of NaOD used were 0.3–0.002 *N*. The pyrimidine *N*-oxide concentrations employed varied from 0.5 to 0.2 *M*. [b] The rate constants were obtained at 31 ± 0.5°, the HA-100 probe temperature, as determined with methanol and ethylene glycol in the usual manner. In order to ascertain the temperature stability, several runs were made using a capillary insert in the nmr tube which contained methanol, and the signal separation between the methyl and hydroxyl protons were checked at 5-min intervals. In several cases adjustments were made to assure identical ionic strengths of the solutions. No significant changes in the rate constants were noted. [c] The indicated errors represent standard deviations. [d] No exchange was observed within 23 days at 0.1 *N* NaOD. [e] No exchange was observed within 14 days in 0.1 *N* NaOD.

pyridine 1-oxide, *N*-methylpyridinium ion, and monosubstituted benzenes which contain an activating group, since the sequence in these compounds is ortho ≫ meta > para, the order expected if the inductive effect is the controlling factor.

When one considers the exchange rates of H-2 (1.2×10^{-4}), H-4 (3.9×10^{-4}), and H-5 (6.5×10^{-3}) in pyrimidine, we note that H-4 exchanges 3.25 times as rapidly as does H-2. Thus, the presence of a 1-oxide function either decreases the H-2 or increases the H-4 exchange rates relative to each other.

In view of the fact that the presence of the negative charge on the oxide function would be expected to decrease the ease of formation of the "anionic ylide" **3** much more so than the lone pair repulsion hinders the formation of the corresponding pyrimidine anion **4** it is not surprising that the H-4/H-2 exchange ratio



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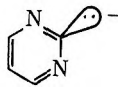


4

is greater in pyrimidine 1-oxide than it is in pyrimidine. Some, but not all, of this difference may also be due to the fact that the pyrimidine exchange reactions were done at a temperature 135° higher than the exchange reactions in the pyrimidine *N*-oxides.

A comparison of these various rate constants nevertheless suggests that the activating influence of an sp^2 nitrogen in "azapyridine 1-oxides" is meta > para > ortho. Thus, the presence of the *N*-oxide function significantly alters the relative activating effect of an additional sp^2 nitrogen atoms in comparison to its nonoxidized isomer.

An examination of the exchange rates of H_2 and H_6 of various 5-substituted pyrimidine 1-oxides reveals that, akin to the behavior of 3-substituted pyrazine 1-oxides,[2] there exists a linear free energy relationship between log k_{H-6} and σ_I substituent constants. Thus, the inductive effect of a 5 substituent situated ortho

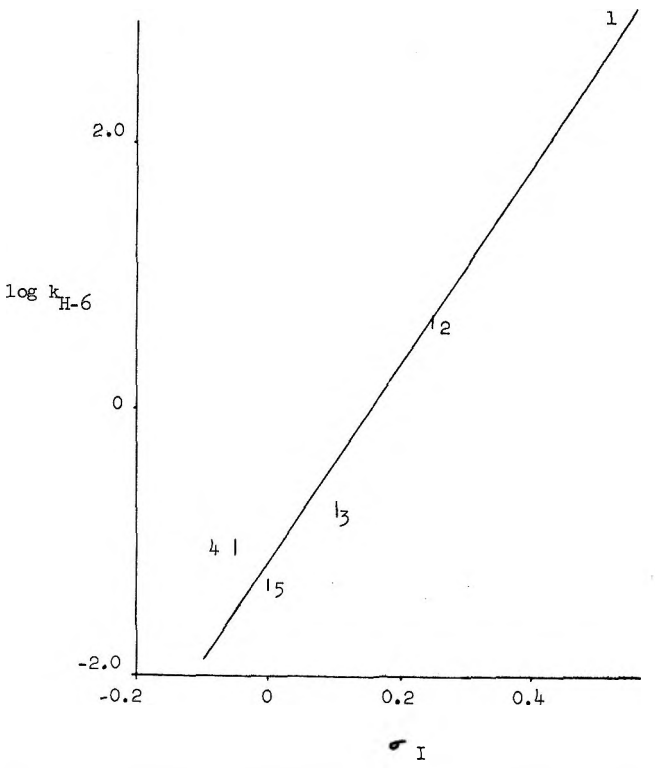
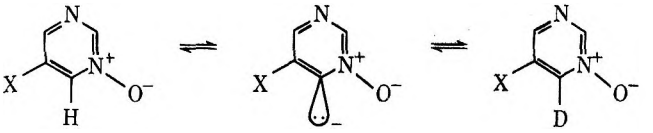


Figure 1.—Hammett correlation for base-catalyzed H-6 → D-6 exchange of some 5-X-pyrimidine 1-oxides.

to the exchanging proton is the controlling factor in this exchange process.



A comparison of the slope of the Hammett correlation (Figure 1) for the pyrazine 1-oxides (5.71) as compared with that of the pyrimidine 1-oxides (6.67) reveals that the pyrimidine 1-oxide exchange reactions are more strongly influenced by an electron-withdrawing substituent than are the pyrazine 1-oxides.

The effect of the substituent on the rate of exchange for the para hydrogen (H-2 in 5-X-pyrimidine 1-oxides) is, as in the pyrazine 1-oxides, considerably muted. The exchange rates for H-2 cannot be correlated with any substituent constant. It is hoped that the factors influencing these exchange rates may become more clear with the results of further studies on other heterocyclic ring systems.

When the exchange reactions of some of the pyrimidine *N*-oxides were studied in strongly basic media (0.3 *N* NaOD) the pmr spectra (Table II) revealed the existence of a "new" compound in addition to the pyrimidine *N*-oxide. The amount of this material increases with increasing base concentration. In pyrimidine *N*-oxide one finds, in addition to the "*N*-oxide" peaks, a one-hydrogen singlet at δ 8.08, one-hydrogen doublets at δ 8.07 and δ 8.76, and a one-hydrogen triplet at δ 5.70. A correlation of the rate of disappearance of these signals, for what must be a covalently hydrated species, with the rate of disappearance of the protons in the known positions of the "free" *N*-oxide makes it possible to assign the peaks at δ 8.08, 8.07, 6.76, and 5.70 to H-2, H-6, H-4, and H-5, respectively.

TABLE II
PMR CHEMICAL SHIFTS (δ) OF SOME PYRIMIDINE 1-OXIDES[a]

Compd	H_2	H_4	H_5	H_6	Substituent
Pyrimidine 1-oxide	9.14	8.62	7.75	8.66	
5-Methylpyrimidine 1-oxide	8.97	8.51		8.59	2.44
5-Bromopyrimidine 1-oxide	9.08	8.70		8.96	
5-Methoxypyrimidine 1-oxide	8.78	8.38		8.44	4.73
5-Dimethylaminopyrimidine 1-oxide	8.38	8.00		8.11	3.03
4-Methylpyrimidine 1-oxide	9.03		7.64	8.55	2.63
6-Methylpyrimidine 1-oxide	9.12	8.47	7.74		2.61

[a] Dilute 0.2 *M* solutions in D_2O.

Neutralization of these strongly basic solutions regenerates the pyrimidine *N*-oxides quantitatively. That these covalent hydration processes are indeed independent of the exchange reactions was shown by converting the pyrimidine *N*-oxide to its totally covalently hydrated species (as shown by pmr) by dissolving it in 2.5 *N* NaOD. After 3 hr, the pyrimidine *N*-oxide was recovered unchanged (no H → D exchange) upon acidification.

Studies that are directed towards establishing the structures of these products and the equilibria involved in these processes are in progress.

Experimental Section

Nmr spectra were obtained with a Varian HA-100 spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6E instrument equipped with a solid sample injector. The ionizing voltage employed was 80 eV. Elemental analyses were determined by Mrs. K. Decker and Mrs. V. Gindelsperger of this department.

Preparation of the *N*-Oxides.—The pyrimidine *N*-oxides[7] and the methylpyrimidine *N*-oxides[8] were prepared by known procedures.

5-Bromopyrimidine 1-Oxide.—This compound was prepared according to the oxidation procedure described by Kobayashi, Kumadaki, and Sato.[9] The compound was obtained in 19% yield, mp 166–167°. *Anal.* Calcd for $C_4H_3N_2BrO$: C, 27.44; H, 1.73; N, 16.01. Found: C, 27.43; H, 2.03; N, 15.79.

5-Methoxypyrimidine 1-Oxide.—This compound was prepared from 5-methoxypyrimidine in 61% yield by the procedure described in ref 9, mp 161.5–162.5°. *Anal.* Calcd for $C_5H_6N_2O_2$: C, 47.61; H, 4.80; N, 22.22. Found: C, 47.70; H, 4.83; N, 22.21.

5-Dimethylaminopyrimidine 1-Oxide.—This compound was prepared by heating a solution of 5-bromopyrimidine 1-oxide (0.1 g, 0.57 mmol) in 40% aqueous dimethylamine (3 ml) in a sealed tube on a steam bath for 4 hr. The cooled solution was made basic and continuously extracted with chloroform. The chloroform extract was dried, and the solvent was removed *in vacuo*. The crude product was purified by sublimation followed by recrystallization from carbon tetrachloride to afford 0.46 g (20%) of 5-dimethylaminopyrimidine 1-oxide, mp 153–154°. *Anal.* Calcd for $C_6H_9N_3O$: C, 51.79; H, 6.52; N, 30.20. Found: C, 51.70; H, 6.55; N, 30.23.

Determination of Rate Constants.—The appropriate *N*-oxide was weighed into an nmr tube and 0.4 ml of D_2O was added. The solution was then allowed to come to 31°, and the HA-100 instrument was adjusted. An initial spectrum was then obtained, and 0.1 ml of the appropriate concentration of aqueous NaOD at 31° was then added with shaking.

Registry No.—**1**, 36529-69-8; **2**, 36529-70-1; **3**, 36529-71-2; **4**, 17758-50-8; **5**, 17043-94-6; 4-methylpyrimidine 1-oxide, 17758-54-2; 6-methylpyrimidine 1-oxide, 33342-83-5.

(7) T. Kato, H. Yamanaka, and T. Shibata, *Yakugaku Zasshi*, **87**, 1096 (1967).

(8) M. Ogata, H. Watanabe, K. Togi, and H. Kamo, *Tetrahedron Lett.*, 19 (1964).

(9) Y. Kobayashi, I. Kumadaki, and H. Sato, *Chem. Pharm. Bull.*, **17**, 1045 (1969).

Selective Dehydration of Secondary Alcohols with Methyltriphenoxyphosphonium Iodide in Hexamethylphosphoramide

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The perennial problem of effecting mild dehydrations of alcohols without rearrangement and the recent interest in elimination reactions induced by nucleophiles in polar aprotic solvents[2] prompt this report of the use of methyltriphenoxyphosphonium iodide (MTPI) in hexamethylphosphoramide (HMPA) as a mild reagent system for the selective dehydration of secondary alcohols.

An attempt to convert *trans*-4-*tert*-butylcyclohexanol into the corresponding cis iodide with MTPI[3] in HMPA resulted instead in an excellent yield (88%) of 4-*tert*-butylcyclohexene in only 15 min at room temperature. In view of the ease and effectiveness of the procedure and its potential utility as a mild dehydration method, the generality of the reaction was investigated.

A variety of alcohol types was subjected to MTPI and the results presented in Table I. In each case the alcohol was treated with a twofold excess of MTPI in HMPA (5 ml per mmol of alcohol) at the temperature listed. The reactions were conveniently monitored by glpc using internal standards and, upon completion, worked up by dilution with water or aqueous potassium hydroxide and extraction with cyclohexane. The results indicate that secondary alcohols are effectively dehydrated with no indication of rearrangements detected. Furthermore, in most cases a high predominance of the more stable Saytzeff alkene is formed (entries 5, 7, 8, 12, 13), often with substantial stereoselectivity for the *E* geometric isomer (entries 12, 14, 15). Primary alcohols are converted into the corresponding iodide in excellent yield (entry 16), but subsequent dehydrohalogenation is evidently slow under

(1) Undergraduate National Science Foundation Fellow, 1971.

(2) (a) G. Biale, D. Cook, D. J. Lloyd, A. J. Parker, I. Stevens, J. Takahashi, and S. Winstein, *J. Amer. Chem. Soc.*, **93**, 4735 (1971); (b) G. Biale, A. J. Parker, S. G. Smith, I. Stevens, and S. Winstein, *ibid.*, **92**, 115 (1970); (c) D. J. Lloyd, D. M. Muir, and A. J. Parker, *Tetrahedron Lett.*, 3015 (1971); (d) D. J. Lloyd and A. J. Parker, *ibid.*, 637 (1971); (e) J. Avraamides and A. J. Parker, *ibid.*, 4043 (1971).

(3) Methyltriphenoxyphosphonium iodide is an efficient reagent for conversion of alcohols into the corresponding iodides; see S. R. Landaner and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953); J. Verheyden and J. Moffat, *J. Org. Chem.*, **36**, 2319 (1970). A review of the use of various phosphorus derivatives for the preparation of iodides is provided by H. R. Hudson, *J. Chem. Soc. B*, 664 (1968).

TABLE I

DEHYDRATION OF SECONDARY ALCOHOLS WITH METHYLTRIPHENOXYPHOSPHONIUM IODIDE IN HEXAMETHYLPHOSPHORAMIDE

Entry	Alcohol[a]	Temp, °C	Time, hr	Alkene yield, %[b] (isolated) Saytzeff		Hofmann
1	*trans*-4-*tert*-Butylcyclohexanol	25	0.25		88	
2	*cis*-4-*tert*-Butylcyclohexanol	25	2.5		84	
3	3-β-Cholestanol	75	6.0		(84)[c]	
4	Cholesterol	75	5.0		84 (76)	
5	*cis*-2-Methylcyclohexanol	75	1.0	82		5
		25	3.0	83		3
		25[d]	107.0	82		6
6	*trans*-2-Methylcyclohexanol	75	2.0	47		47
		25	1.0	46		7
			4.0	54		26
7	*cis*-2-Phenylcyclohexanol	75	4.0	87		5[e]
8	*trans*-2-Phenylcyclohexanol	25	24.0	71		16[e]
		75	24.0	84		14[e]
9	1-Menthol	75	1.0	54		27
10	Cyclododecanol	25	2.0		94[f]	
11	5-Nonanol	75	2.0		88	
12	2-Decanol	75	7.0	72		5
			25.0	80[g]		4
13	2-Methyl-3-octanol	75	1.0	82		10
			2.0	90		10
14	1-Phenylbutanol	75	1.0		96[h]	
15	1,2-Diphenylethanol	75	1.0		100[i] (86)	
16	1-Dodecanol	75	0.25		0[j]	
			6.5		tr[j]	
			29.0		tr[j]	
17	4-Propyl-4-heptanol	75	6.0		tr[k]	
			27.0		12[k]	
18	1-*n*-Butylcyclohexanol	25	24.0		tr[k]	

[a] Solutions 0.2 *M* alcohol–0.4 *M* methyltriphenoxyphosphonium iodide. [b] Yields determined by glpc analysis using internal standards and detector response factors, unless otherwise noted. [c] Mixture of 2- and 3-cholestene. [d] Demonstrates lack of equilibration under reaction conditions. [e] Glpc response factor assumed to be equal to that of 1-phenylcyclohexene. [f] *Ca.* 2:1 ratio of *E* and *Z* isomers, respectively. [g] 63% *E*, 17% *Z*. [h] *Ca.* 99% E, tr. *Z*. [i] 99% (*E*)-stilbene, *ca.* 1% (*Z*)-stilbene. [j] Product was 1-dodecyl iodide. [k] The remainder was starting alcohol.

the reaction conditions.[4] Tertiary alcohols are practically inert toward the reagent system (entries 17, 18) thus permitting secondary cases to be selectively dehydrated in their presence.[5]

The mechanism of the dehydration apparently involves initial conversion into the corresponding inverted iodide followed by dehydrohalogenation induced by iodide[2] and HMPA.[4,6] Evidence for this is provided by the faster rate of *trans*-4-*tert*-butylcyclohexanol over the cis isomer (Figure 1); in the former the initial axial iodo group is more favorably disposed for anticoplanar elimination. Treatment of 2-iodooctane with HMPA gave elimination, but the reaction was much faster in the presence of MTPI (Figure 2) indicating iodide anion is primarily responsible for dehydrohalogenation. The mechanism is also consistent with the unreactivity of tertiary alcohols.

The selectivity exhibited for the more stable (Saytzeff) alkenes with *E* stereochemistry has been noted for eliminations employing strong carbon bases in polar aprotic solvents (E2C eliminations)[2] and attributed to very productlike transition states.

The dehydrations of *cis*- and *trans*-2-methylcyclohexanol (entries 5 and 6) and of the corresponding 2-phenyl derivatives (entries 7 and 8) are unusual in that the Saytzeff alkene is the major product irrespective of the alcohol stereochemistry (except for entry 6). This is expected for the trans isomers in that conversion of the equatorial alcohol into the axial iodide enables anti-elimination to occur to the more stable alkene. However, the cis isomers should give the corresponding equatorial iodides which can eliminate in an anti-mechanism by ring inversion, but only with the 3-axial hydrogen to give the less substituted Hofmann product. The reluctance of forming the less stable products apparently results from competing Sn2 displacement by iodide to generate the axial iodo derivative which readily eliminates to the observed Saytzeff alkenes.

Experimental Section

Gas chromatographic analysis were performed on a Hewlett-Packard Model 5250B chromatograph using either a 6 ft × 1/8 in. or 10 ft × 1/8 in. column packed with 10% OV-1 on 80–100 mesh Chromosorb W (DMCS). Analyses were performed using internal standards and predetermined detector response factors using authentic samples of the products. Hexamethylphosphoramide was distilled from calcium hydride and stored over 13A molecular sieves. Methyltriphenoxyphosphonium iodide was

(4) Dehydrohalogenation of primary alkyl halides occurs in HMPA, but more severe conditions are required (180–210°); see R. S. Monson, *Chem. Commun.*, 113 (1971).

(5) This was demonstrated by a competitive dehydration experiment between 1-*n*-butylcyclohexanol and cis-2-methylcyclohexanol; after 3 hr, 65% of 1-methylcyclohexene and 4% of 3-methylcyclohexene were produced while 80% of the 1-*n*-butylcyclohexanol was recovered.

(6) R. Hanna, *Tetrahedron Lett.*, 2105 (1968).

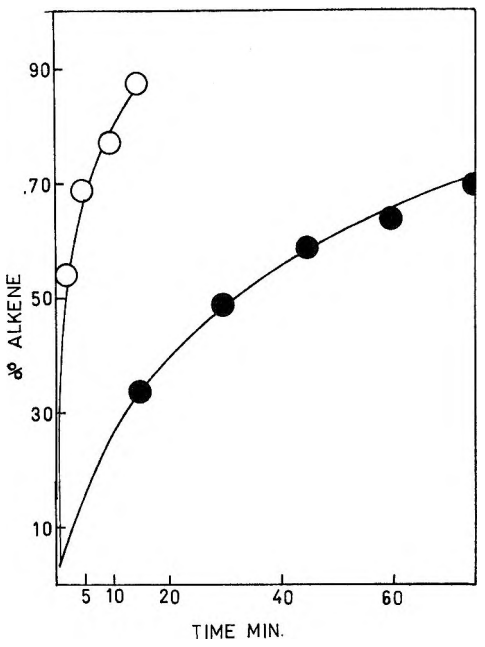

Figure 1.—Reaction of *cis*- and *trans*-4-*tert*-butylcyclohexanols with methyltriphenoxyphosphonium iodide in hexamethylphosphoramide at 75°. Reactions were 0.2 *M* in the alcohol, 0.4 *M* in the iodide. The percentages of alkenes were determined by glpc analysis using internal standards: ●, *cis*-4-*tert*-butylcyclohexanol; ○, *trans*-4-*tert*-butylcyclohexanol.

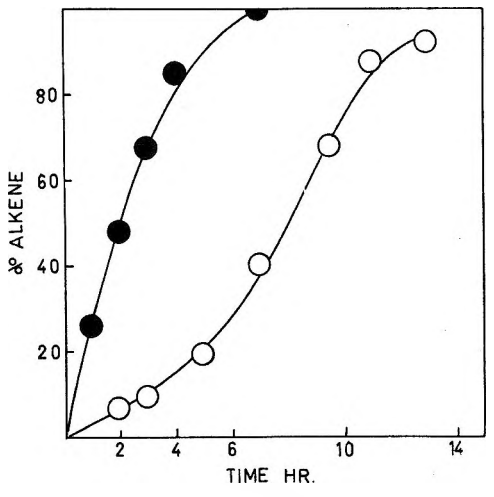

Figure 2.—Dehydrohalogenation of 2-iodooctane in hexamethylphosphoramide at 75°. Reactions were 0.2 *M* in 2-iodooctane. The percentages of alkenes were determined by glpc using internal standards: ●, no methyltriphenoxyphosphonium iodide; ○, solution 0.4 *M* in methyltriphenoxyphosphonium iodide.

prepared as described[3] and stored under dry ether. The alcohols used were commercial products except for *cis*- and *trans*-4-*tert*-butyl and *cis*- and *trans*-2-phenylcyclohexanols which were prepared by stereoselective reductions of the ketones ($IrCl_4$ complex for the cis,[7] $LiAlH_4$–$AlCl_3$ for the trans[8]).

Dehydration of Alcohols. General Procedure.—The method is presented in the text. The relative amount of solvent may be reduced for preparative applications. The isolation procedure is illustrated for the preparation of (*E*)-stilbene.

(*E*)-**Stilbene.**—A solution of 1,2-diphenylethanol (1.19 g, 6.0 mmol) and MTPI (5.4 g, 12 mmol) in 20 ml of HMPA was stirred at 75° for 1.0 hr, poured into 100 ml of aqueous KOH, and extracted three times with 25 ml of cyclohexane. The cyclohexane solution was washed three times with water and dried ($MgSO_4$). Removal of the solvent at reduced pressure and recrystallization of the resulting solid from ethanol afforded 928 mg (86%) of product as colorless plates, identical in all respects with authentic (*E*)-stilbene.

(7) E. L. Eliel, T. W. Doyle, R. O. Hutchins, and E. C. Gilbert, *Org. Syn.*, **50**, 13 (1970).

(8) E. L. Eliel, R. J. L. Martin, and D. Nasipuri, *ibid.*, **47**, 16 (1967).

Registry No.—**1**, 937-06-4; **2**, 937-05-3; **3**, 80-97-7; **4**, 57-88-5; **5**, 7443-70-1; **6**, 7443-52-9; **7**, 16201-63-1; **8**, 2362-61-0; **9**, 1490-04-6; **10**, 1724-39-6; **11**, 623-93-8; **12**, 1120-06-5; **13**, 2653-34-6; **14**, 614-14-2; **15**, 614-29-9; **16**, 112-53-8; **17**, 2198-72-3; **18**, 5445-30-7; MTPI, 17579-99-6; HMPA, 680-31-9.

Acknowledgment.—We wish to thank the National Science Foundation for an undergraduate fellowship for C. A. M. and the Petroleum Research Fund administered by the American Chemical Society for partial support of this work.

Oxidation Products of Ethyl α-Safranate

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Carotenoids with six-membered alicyclic end groups are widespread in nature.[1] Many organisms are capable of introducing carbonyl and/or alcohol functions at C-3 and C-4 into the α- or β-ionone rings of such carotenoids, while a few bacteria and the Japanese sea sponge have the ability to dehydrogenate the terminal cyclohexene rings to their aromatic counterparts. Relatively few methods have been developed for the total synthesis of such end groups[2] and it became of interest to inquire whether ethyl α-safranate (**1**), for which we recently described a simple and efficient synthesis,[3] could be transformed to versatile monocyclic intermediates and then to carotenoids.

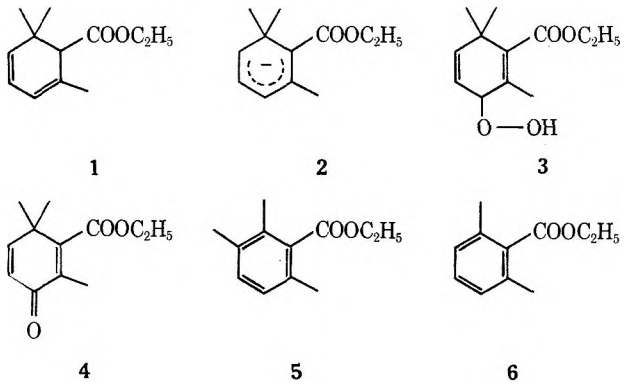
Addition of ethyl α-safranate (**1**) to a solution of potassium *tert*-butoxide in glyme produced an orange solution undoubtedly containing the anion **2**. This color was discharged quickly when oxygen was bubbled through the solution and after work-up the hydroperoxide **3** (34%), the keto ester **4** (43%), and ethyl 2,6-dimethylbenzoate (**6**) (3%) could be isolated by chromatography. The structures of **3** and **4** rest on their spectral properties exclusively (see Experimental Section) while the aromatic ester **6** was compared with an authentic sample. The relative proportions of hydroperoxide **3** and ketone **4** depend on the method of isolation, and not unexpectedly the hydroperoxide **3** turned out to be a very labile compound and readily lost the elements of water, giving the ketone **4**. Injection into a gas chromatograph caused its decomposition to a mixture of **4**, **5**, and **6** in a ratio of 8:1:1. Mechanistic studies on the formation and decomposition of the hydroperoxide **3** were not undertaken but it seems to be the initial product derived from addition of oxygen

(1) B. C. L. Weedon in "Carotenoids," O. Isler, Ed., Birkhäuser Verlag, Basel, 1971, p 29.

(2) H. Mayer and O. Isler in "Carotenoids," O. Isler, Ed., Birkhäuser Verlag, Basel, 1971, p 325.

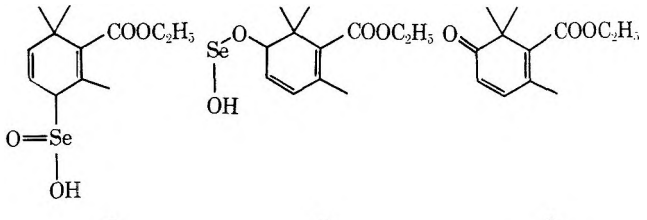
(3) G. Büchi and H. Wüest, *Helv. Chim. Acta*, **54**, 1767 (1971).

to the U-shaped pentadienyl carbanion 2. Such anions are known to be protonated preferentially at the central carbon atom[4] and there is no reason to suspect that oxygen addition should occur elsewhere, particularly when the steric crowding around the termini of the anion is taken into account. The keto ester **4** and the two aromatic esters **5** and **6** produced from the hydroperoxide **3** on chromatography seem to be the result of acid-catalyzed heterolysis.[5] Protonation of the hydroxylic oxygen followed by O–O heterolysis gives the ketone **4**, while protonation of the other oxygen atom followed by loss of hydrogen peroxide leads to a carbonium ion which can undergo a Wagner–Meerwein rearrangement to ethyl 2,3,6-trimethylbenzoate (**5**) or fragment to ethyl 2,6-dimethylbenzoate (**6**).



1 2 3 4 5 6

In the course of efforts to introduce oxygen at C-2 ethyl α-safranate (**1**) was oxidized with selenium dioxide. In hot acetic acid ethyl 2,3,6-trimethylbenzoate (**5**) was formed in 63% yield. Oxidation in refluxing dioxane gave a new keto ester **9** with intense ultraviolet absorption at 309 nm, while the isomeric ester **4** absorbs at 241 nm. The formation of the two oxidation products can be rationalized if the allyl selenic acid[6] **7** undergoes a [2,3] sigmatropic rearrangement[7] to the selenium(II) ester **8**. In acetic acid solution this ester undergoes solvolysis with concurrent Wagner–Meerwein rearrangement, while in dioxane solution it decomposes to the ketone **9** and selenium.



7 8 9

(4) R. B. Bates, D. W. Gosselink and J. A. Kaczynski, *Tetrahedron Lett.*, 199 (1967).

(5) R. Hiatt in "Organic Peroxides," Vol. 2, D. Swern, Ed., Wiley-Interscience, New York, N. Y., 1971, p 1.

(6) K. B. Wiberg and S. D. Nielsen, *J. Org. Chem.*, **29**, 3353 (1964).

(7) This mechanism of olefin oxidation by selenium dioxide was suggested to us by Professor K. B. Sharpless, M. I. T., who will publish his observations elsewhere. It has advantages over those proposed previously: ref 6; J. P. Schaefer, B. Horvath, and H. P. Klein, *J. Org. Chem.*, **33**, 2647 (1968); E. N. Trachtenberg, C. H. Nelson, and J. R. Carver, *ibid.*, **35**, 1653 (1970); D. H. Olson, *Tetrahedron Lett.*, 2053 (1966).

Experimental Section

Microanalyses were performed in the laboratory of Dr. F. Gautschi, Firmenich et Cie., Geneva. Boiling points are uncorrected. Gas–liquid chromatography was performed on a F & M 720 instrument, using silicon rubber gum SE-30 and Carbowax 20M columns. Silicic acid "Mallinckrodt" 100 mesh was used for column chromatography. The following spectrometers were used: nmr, Varian T-60; ir, Perkin-Elmer Model 247; uv, Cary Model 14; mass spectrum, Hitachi RM-U6D.

Autoxidation of Ethyl α-Safranate (1).—To a solution of 3.4 g (30 mmol) of potassium *tert*-butoxide in 150 ml of glyme (distilled from $LiAlH_4$) was added, at −70°, 5.8 g (30 mmol) of ethyl α-safranate (1) in 60 ml of dry ether. Oxygen was then bubbled through the mixture at −70°. When the initially orange color turned to light yellow (~20 min), 5 ml of acetic acid was added, followed by evaporation of most of the solvent *in vacuo*. The mixture was extracted with hexane, washed with water, dried (Na_2SO_4), and evaporated. The remaining oil (6.0 g) was chromatographed on 175 g of silicic acid. Elution with hexane and 2% AcOEt gave 0.3 g of a mixture of starting material and ester **6**. With hexane and 10% AcOEt 1.8 g of keto ester **4** was eluted: bp 72° (0.1 mm); ir ($CHCl_3$) 1715, 1655, 1630 cm^{-1}; uv (EtOH) 241 nm (ε 13,200); nmr (CCl_4) δ 1.3 (6 H, s), 1.3 (3 H, t, J = 7 Hz), 1.8 (3 H, s), 4.3 (2 H, q, J = 7 Hz), 6.1 (1 H, d, J = 11 Hz), 6.7 (1 H, d, J = 11 Hz); mass spectrum (70 eV) m/e (rel intensity) 208 (18), 135 (100).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.01; H, 7.51.

Later fractions eluted with hexane and 20% AcOEt yielded 1.8 g of a mixture of keto ester **4** and hydroperoxide **3**, followed by 1.4 g of pure hydroperoxide **3**: ir ($CHCl_3$) 3550, 3400, 1715 cm^{-1}; nmr (CCl_4) δ 1.1 (3 H, s), 1.2 (3 H, s), 1.3 (3 H, t, J = 7 Hz), 1.8 (3 H, s), 4.2 (2 H, q, J = 7 Hz), 4.5 (1 H, s), 5.7 (2 H, m), 8.5 (1 H, broad).

Injection of hydroperoxide **3** on glc (4-ft Carbowax 20M at 180°, injection port temperature 250°) produced compounds **5**, **6**, and **4** in the ratio of ~1:1:8. Retention times and spectra of collected samples were identical with those of authentic samples.

Selenium Dioxide Oxidation of Ethyl α-Safranate (1). A.—A mixture of 1.94 g (10 mmol) of ethyl α-safranate (1), 1.33 g (10 mmol) of selenium dioxide, and 12 ml of acetic acid was heated at 100–110° for 15 min. Water was added and the mixture was extracted with pentane. The organic layer was washed with 5% sodium bicarbonate solution and water and then dried (Na_2SO_4) and evaporated. Distillation of the residue afforded 1.22 g (63%) of ester **5**: bp 61° (0.1 mm); ir ($CHCl_3$) 1720 cm^{-1}; uv (EtOH) 235 nm (ε 1610), 277 (900); nmr (CCl_4) δ 1.3 (3 H, t, J = 7.5 Hz), 2.1 (3 H, s), 2.2 (6 H, s), 4.3 (2 H, q, J = 7.5 Hz), AB system centered at 6.9 (2 H); mass spectrum (70 eV) m/e (rel intensity) 192 (54), 147 (100).

B.—A solution of 5.82 g (30 mmol) of ethyl α-safranate and 3.55 g (32 mmol) of selenium dioxide in 50 ml of dioxane was heated at reflux for 30 min. The mixture was poured into water and extracted several times with ether. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated. Chromatography on silicic acid with hexane and 15% AcOEt as eluent yielded 2.47 g (40%) of keto ester **9**: bp 59° (0.1 mm); ir ($CHCl_3$) 1710, 1665, 1635 cm^{-1}; uv (EtOH) 309 nm (ε 6150); nmr (CCl_4) δ 1.3 (6 H, s), 1.35 (3 H, t, J = 7 Hz), 2.0 (3 H, s), 4.3 (2 H, q, J = 7 Hz), 6.0 (1 H, d, J = 10 Hz), 6.8 (1 H, d, J = 10 Hz); mass spectrum (70 eV) m/e (rel intensity) 208 (60), 134 (100).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.26; H, 7.59.

Registry No.—**1**, 35044-57-6; **3**, 36596-64-2; **4**, 36596-65-3; **5**, 36596-66-4; **6**, 36596-67-5; **9**, 36596-68-6.

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The Reaction of Sulfur Dichloride with *o*-Divinylbenzene

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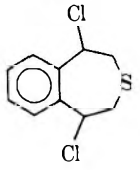
Several investigations on the addition of sulfenyl chlorides to alkyl-substituted terminal olefins have concluded that steric factors control the direction of ring opening of the cyclic thiiranium cation by chloride, thus resulting in anti-Markovnikov products.[2-5] However, the product ratio can be drastically changed by the presence of a phenyl group. For example, styrene, which is capable of forming a benzyl cation, affords Markovnikov addition products with greater than 98% selectivity.[6,7] We have investigated the reaction of *o*-divinylbenzene with sulfur dichloride[8] in anticipation of forming the cyclic dichlorosulfide (**1**). The dehydro-



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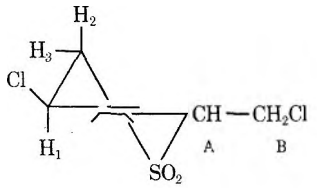
halogenation of **1** was viewed as a likely route to the unknown benzo[*d*]thiepin, a molecule for which extensive MO calculations have recently been reported.[9]

Under high dilution conditions, simultaneous addition of sulfur dichloride and *o*-divinylbenzene (**2**) affords a 98% yield of an unstable product whose complex, unsymmetrical nmr spectrum (see Experimental Section) strongly suggests a mixture of cis and trans isomers of 3,4-dihydro-1-chloromethyl-4-chloro-1*H*-2-benzothiopyran (**3**) (Scheme I). Oxidation of **3** with *m*-chloroperbenzoic acid yielded the sulfone (**4**) in 90% yield as a



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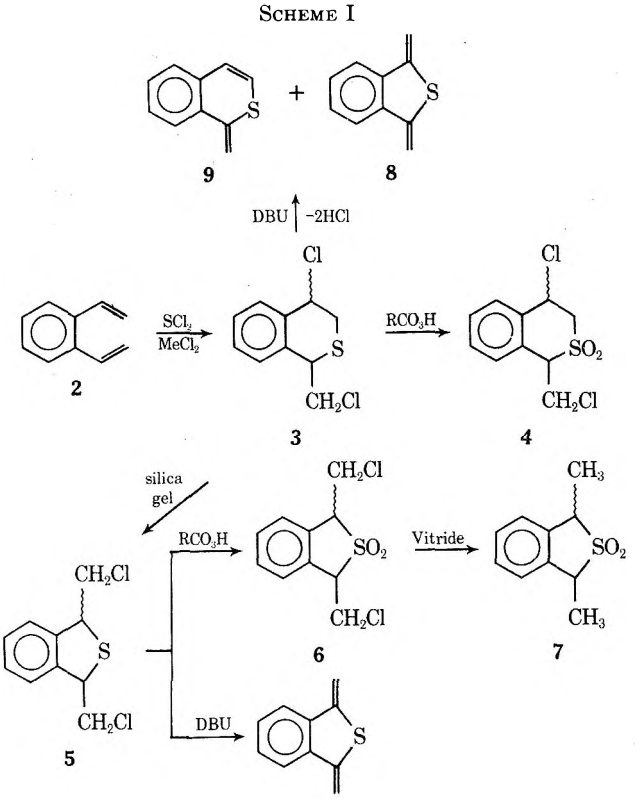
SCHEME I



mixture of cis and trans isomers from which a single isomer (**4a**, mp 98–100°) could be isolated by fractional recrystallization. The structure of **4a** was deduced from nmr analysis (*vide infra*).

The nmr spectrum of **4a** shows a clean doublet for H_B at δ 3.82 and a triplet for H_A centered at 5.61 (J_{AB} = 6.0 Hz). Irradiation at δ 5.61 collapses the doublet to a singlet at δ 3.82. H_1 appears as a doublet of doublets centered at δ 4.85 which collapses to a doublet with irradiation at H_2 or H_3. H_2 and H_3 appear as two overlapping doublets of doublets which simplify to two doublets centered at δ 4.40 and 4.15 with irradiation at H_1 ($J_{1,2}$ = 6.6, $J_{1,3}$ = 4.0, and $J_{2,3}$ = 11.5 Hz).

Upon standing at room temperature **3** rearranges to a mixture of **3** and an isomer (**5**). Complete destruction of **3** can be affected by percolation of a solution of **3** through a silica gel column, a procedure which yields **5** (cis–trans isomer mixture) as the sole isolable product. The nmr spectrum [two doublets at δ 3.82 and 3.84 (4 H), two triplets at 4.60 and 4.80 (2 H) (J = 6 Hz)] does not by itself allow conclusive differentiation between **5** and **1**.

Structure **1** was ruled out through peracid oxidation of **5** to sulfone **6** (85% yield), followed by reductive dechlorination (Vitride) to **7**. The nmr spectrum of **7** showed two methyl doublets [δ 1.61 and 1.59 (J = 7 Hz)] thereby eliminating structure **1** from consideration and establishing the dihydrobenzo[*c*]thiophene system (**5**) as the rearrangement product from **3**.

Additional evidence for the proposed structures is found in the DBU dehydrochlorination of a mixture of cis and trans isomers of **5** to cleanly provide only one unsaturated product, **8**. While the extreme instability of neat **8** precluded isolation, the nmr spectrum [δ 5.24 (d, 2 H); (5.78, (d, 2 H, J_{gem} = ~1 Hz); (7.50 (m, 4 H)] was

(1) Gulf Oil Predoctoral Fellow, 1971–1972.
(2) F. Lautenschlager, *J. Org. Chem.*, **33**, 2620 (1968).
(3) W. H. Mueller and P. E. Butler, *J. Amer. Chem. Soc.*, **88**, 2866 (1966).
(4) G. M. Beverly and D. R. Hogg, *Chem. Commun.*, 138 (1966).
(5) We adopt the usual convention of "Markovnikov" indicating addition of the chlorine on a secondary or tertiary carbon atom and "anti-Markovnikov" addition of the chlorine on the terminal carbon.
(6) W. H. Mueller and P. E. Butler, *J. Amer. Chem. Soc.*, **90**, 2075 (1968).
(7) For a review of thiiranium ions, see W. H. Mueller, *Angew. Chem., Int. Ed. Engl.*, **8**, 482 (1969).
(8) For reviews of diolefin–sulfur dichloride additions, see L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1967, p 1121, and Vol. 2, 1969, p 391.
(9) M. J. S. Dewar and N. Trinajstić, *J. Amer. Chem. Soc.*, **92**, 1453 (1970).

unambiguous. Similar treatment of **3** with DBU afforded **9** along with **8**, the latter presumably arising from partial isomerization of **3** to **5** under the reaction conditions.

The isomerization of **3** to **5** has precedence in the literature from alkyl-substituted, linear diolefins which rearrange through thiiranium ions with the ring-size preference 5 > 6 > 7.[10] The finding that the six-membered-ring sulfide (**3**) is the initially observed product, therefore, does not rule out the possibility that **1** is the initial product. Indeed our results do not deny the possibility of initial formation of **1**, rearrangement to **3**, and a slower rearrangement to **5**. However, attempts to observe **1** under quite mild conditions have been uniformly unsuccessful.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer. Proton nmr spectra were determined on a Varian Model A-60 or a Hitachi R20-B spectrometer for decoupling studies using TMS as an internal standard. Mass spectra were obtained on an Atlas CH-4 spectrometer. All melting points are uncorrected. Elemental analyses were performed by Ilse Beetz, Kronach, West Germany. Commercial sulfur dichloride (Matheson Coleman and Bell) was purified as previously described.[11] *o*-Divinylbenzene was prepared by the method of Hauser[12] and purified by distillation at 56–58° (8 Torr).

Addition of Sulfur Dichloride to o-Divinylbenzene. 3,4-Dihydro-1-chloromethyl-4-chloro-1*H*-2-benzothiopyran (3).—Solutions of *o*-divinylbenzene (6.90 g, 53 mmol) and freshly distilled sulfur dichloride (5.46 g, 53 mmol) in 125 ml of dry methylene chloride were simultaneously added to 125 ml of stirred methylene chloride. The addition was completed after 1 hr and the solvent was removed *in vacuo* to afford 12.0 g (98.2%) of yellow oil (**3**), which was allowed to stand at room temperature. The nmr spectrum then revealed that rearrangement to a mixture of **3** and **5** had occurred, thus necessitating the immediate use of **3** in subsequent experiments: ir (film) 1490, 1445, 1300, 1255, 1025, 770, 740 cm^{-1}; nmr ($DCCl_3$) δ 7.20 (m, 4 H), 5.24–5.68 (m, 1 H), 2.80–4.22 (m, 5 H); mass spectrum *m/e* 232 (M^+), 234 (70% of M^+).

Oxidation of 3 with *m*-Chloroperbenzoic Acid. 3,4-Dihydro-1-chloromethyl-4-chloro-1*H*-2-benzothiopyran 2,2-Dioxide (4).—To a solution of **3** (2.17 g, 9.3 mmol) in 5 ml of chloroform was added dropwise 3.77 g (18.6 mmol) of 85% *m*-chloroperbenzoic acid in 50 ml of chloroform over a period of 5 min. After 1 hr, *m*-chlorobenzoic acid was removed by filtration and the filtrates were washed with 10% sodium sulfite until neutral to KI solution. Excess acid was removed by extraction with 5% sodium bicarbonate and the chloroform layer was dried over $MgSO_4$. Removal of solvent *in vacuo* afforded 2.0 g (81.9%) of *cis*- and *trans*-**4** as a colorless oil which solidified upon standing. Repeated recrystallization from chloroform–ether yielded a white solid, mp 98–100°, as one pure isomer (**4a**): ir (KBr) 1140, 1330 cm^{-1}; nmr ($DCCl_3$) δ 3.82 (d, 2 H), 5.61 (t, 1 H), 4.85 (q, 1 H), 4.19–4.34 (2 d, 2 H), 7.50 (s, 4 H); mass spectrum *m/e* (rel intensity) 264 (45, M^+), 266 [31, $(M + 2^+)$], 228 (80, M − HCl), 200 (63, M − $HClSO_2$), 165 (100, M − $C_2H_5Cl_2SO_2$).

Anal. Calcd for $C_{10}H_{10}Cl_2O_2S$: C, 45.30; H, 3.80; Cl, 26.74; S, 12.09. Found: C, 45.45; H, 3.99; Cl, 26.75; S, 11.93.

Rearrangement of 3 to 1,3-Dihydro-1,3-bis(chloromethyl)benzo[c]thiophene (5).—Compound **3** (2.3 g) was chromatographed on a 3 × 40 cm column of silica gel with elution by 3 l. of hexane. Concentration *in vacuo* left 1.47 g (63%) of a red liquid. A small fraction was distilled at 80° (0.1 Torr) to afford a colorless liquid for an analytical sample. Both the crude and purified samples had the same isomer ratio and were in all respects identical by nmr. (The ratio of isomers was approximately 70:30 by nmr, but severe overlap reduces the confidence level of this number.) The purified product darkens rather rapidly and must be stored under nitrogen at 0° in solution. The same conversion was found to occur on neutral alumina. An nmr spectrum of chromatographed material shows no evidence of **3**; ir (thin film), 450, 700, 750, 1435, 1455, 1480 cm^{-1}; nmr ($DCCl_3$) δ 3.82 and 3.84 (2 d, 4 H), 4.60 and 4.80 (2 t, 2 H, J = 6 Hz), 7.20 (symmetrical m, 4 H); mass spectrum *m/e* (rel intensity) 232 (6, M^+), 234 [4, $(M + 2^+)$], 183 (100, M − CH_2Cl), 134 (39, M − $C_3H_4Cl_2$).

Anal. Calcd for $C_{10}H_{10}Cl_2S$: C, 51.55; H, 4.32; Cl, 30.41; S, 13.75. Found: C, 51.74; H, 4.45; Cl, 30.32; S, 13.56.

Oxidation of 5 with *m*-Chloroperbenzoic Acid. 1,3-Dihydro-1,3-bis(chloromethyl)benzo[c]thiophene 2,2-Dioxide (6).—The procedure employed was identical with the oxidation of **3** (*vide supra*). From 0.410 g of **5** was obtained 0.390 g (85%) of yellow oil which was readily crystallized from methylene chloride–ether as a pale yellow solid: mp 117–119°; ir (KBr) 1490, 1330, 1150, 1120, 730, 540 cm^{-1}; nmr ($DCCl_3$), two doublets centered at δ 4.07 and 4.10 (4 H), a triplet at δ 4.60 (2 H), a singlet at 7.49 (4 H); mass spectrum *m/e* (rel intensity) 264 (35, M^+), 266 [24, $(M + 2^+)$], 200 (100, M − SO_2^+).

Anal. Calcd for $C_{10}H_{10}Cl_2O_2S$: C, 45.30; H, 3.80; Cl, 26.74; S, 12.09. Found: C, 45.46 H, 3.93; Cl, 26.71; S, 12.04.

Reduction of 6 with Vitride. 1,3-Dihydro-1,3-dimethylbenzo[c]thiophene 2,2-Dioxide (7).—To a solution of **6** (0.584 g, 2.2 mmol) in 50 ml of sodium-dried benzene was added 0.80 cc (2.8 mmol) of a 70% benzene solution of Vitride [$NaAlH_2(OCH_2CH_2OCH_3)_2$, Eastman Kodak] *via* syringe and the solution was refluxed for 12 hr. The reaction was cooled to 0° and neutralized with 20% H_2SO_4.

The benzene layer was separated, washed with 10 ml of H_2O, dried over K_2CC_3, and concentrated to 0.480 g of yellow oil: ir (film) 770, 1140, 1320 cm^{-1}; nmr ($DCCl_3$) δ 4.22 (q, 2 H), 1.61 and 1.59 (2 d, 6 H, J = 7 Hz), 7.3 (s, 4 H); mass spectrum *m/e* (rel intensity) 196 (14, M^+), 132 (100, M − SO_2); high resolution mass spectrum 196.057587 (observed), 196.055796 (calculated), 0.001791 (Δ).

Dehydrochlorination of 5 with DBU. 1,3-Bis(methylene)benzo[c]thiophene (8).—To a solution of 0.870 g (3.73 mmol) of **5** in 30 ml of acetonitrile was added 1.07 g (7.04 mmol) of 1,5-diazobicyclo[5.4.0]undec-5-ene (DBU) in 3 ml of acetonitrile and this solution was stirred for 5 min. The reaction mixture was concentrated to ~2 ml, 20 ml of chloroform was added, and residual acetonitrile and DBU salts were removed by washing with water. The chloroform layer was dried over anhydrous potassium carbonate and concentrated under a nitrogen atmosphere. The structure assignment was based on the nmr spectrum since the instability of **8** precluded its purification despite numerous attempts. Oxidation of **8** with *m*-chloroperbenzoic acid in an attempt to obtain a stable sulfone derivative failed to afford an isolable product. The olefinic protons appeared as sharp peaks at δ 5.24 and 5.78 (each slightly split by geminal coupling, J = 1 Hz) and the aromatic protons as a symmetrical multiplet at 7.50.

Dehydrochlorination of 3 with DBU. 1-Methylene-2-benzothiopyran (9).—The procedure was the same as described above for the reaction of **5** with DBU. The isomeric diolefin **9** was also unstable to isolation, and its structure was based on the appearance of four olefinic peaks at δ 5.15, 5.50, 6.42, and 6.48. The two olefinic peaks of **8** were also observable.

Registry No.—**2**, 91-14-5; *cis*-**3**, 36736-00-2; *trans*-**3**, 36736-01-3; *cis*-**4**, 36736-02-4; *trans*-**4**, 36736-03-5; *cis*-**5**, 36736-04-6; *trans*-**5**, 36736-05-7; *cis*-**6**, 36736-06-8; *trans*-**6**, 36736-07-9; *cis*-**7**, 36736-08-0; *trans*-**7**, 36736-09-1; **8**, 36740-03-1; **9**, 36740-04-2; sulfur dichloride, 10545-99-0.

Acknowledgment.—The authors are grateful to the Public Health Service (Grant No. GM-16689, National Institutes of Health) and to the Petroleum Research Fund, administered by the American Chemical Society (PRF No. 1152-G1), for its generous support of this work.

(10) F. Lautenschlager, *Quart. Rep. Sulfur Chem.*, **2**, 331 (1967).
(11) T. J. Barton and R. G. Zika, *J. Org. Chem.*, **35**, 1729 (1970).
(12) C. F. Hauser, *ibid.*, **28**, 372 (1963).

Organic Disulfides and Related Substances. 36. Some Oxodisulfide Cleavage Reactions to Form Disulfides and Trisulfides[1]

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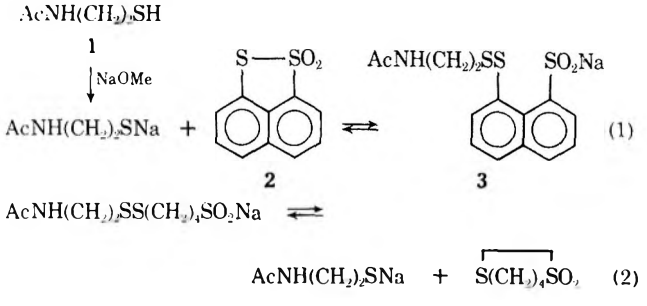
Several applications of 1,2-dithiane 1,1-dioxide and 1,1,2,2-tetroxide to synthesis of otherwise difficultly obtainable classes of disulfides were described earlier.[2] Preparation of similar products containing a varied number of substituted or unsubstituted methylene groups separating an –SS– moiety from a functional group based on a sulfinate moiety should be possible, since cyclic disulfides containing from 3 to 13 methylene groups are known.[3]

This paper reports further tests of the generality and nature of reactions of disulfide dioxides, which for convenience are called "oxodisulfide cleavages." 2-Acetamidoethanethiol (1) and sodium sulfide were used to afford disulfides and trisulfides, respectively. The thiol 1 was used as a model in the hope that the products also might be of interest as antiradiation drugs.[4] Disulfide 1,1-dioxides were used that would begin to afford insight into the effect on the cleavage of fused-on aromatic systems and of chain substitution.

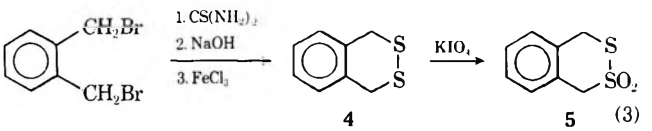
The most striking neighboring-group effect of $-SO_2Na$ on –SS– yet encountered was seen at the outset. Thioalkylation of 1 with the known disulfide dioxide 2[5] evidently led by oxodisulfide cleavage to a hydrate of the sulfinate salt 3 (eq 1). This presumed hydrate



could not be obtained analytically pure. The cyclization shown in eq 2 occurs in *ca.* 1 hr in a water–benzene mixture at 60° and, when the salt of the thiol 1 was trapped with *N*-ethylmaleimide, 1,2-dithiane 1,1-dioxide was isolated in 39% yield.[1a] The sulfinate salt 3 shows a similar neighboring-group attack of SO_2Na on –SS– even more dramatically; for example, warming for 5 min led to 33% of 2 (MeOH, 50°). In another experiment, an aqueous solution of 3 was extracted from time to time with chloroform. Isolation and characterization by ir and mixture melting point confirmed the rapid cyclization of 3 to give 2, the cumulative per cent yield of 2 being as follows (hours in parentheses, ~25°): 43 (0.17), 59 (4), 69 (8), 77 (16). The rapid cyclization of 3 to 2, complicated by disproportionation of the unsymmetrical disulfide 3 to the two possible symmetrical ones, presumably is a cause of the inability to obtain analytically pure 3. Indeed, a major problem with 3 lies in preventing the ring closure of the salt 3 to the starting material 2. Efforts to trap 3 were unpromising. These included attempts to make the ferric sulfinate (hopefully, too sparingly soluble to revert to 1), the sulfinic acid (2 separated in 49% yield) or its formaldehyde adduct, or sulfones. Presumably, the coplanarity of 3 greatly enhances the neighboring-group attack of $-SO_2Na$ on the –SS– bond, thus causing the extremely facile reversion of 3 to 2 observed in all these efforts.

Confirmation that the reaction of eq 1 occurs as formulated is afforded by several kinds of evidence. (1) Thiolate disappears, since the solution of the thiolate salt of 1 is very basic but after reaction with 2 is neutral; furthermore, a strong nitroprusside test at the beginning becomes negative after *ca.* 2 min. The strong absorption by $-SO_2-$ of 2 at 1110 and 1290 cm^{-1} is not seen in the product; hence 2 is consumed as well. (2) The product shows one major tlc spot, although one to two minor ones also always were seen (presumably caused by equilibrium *via* eq 1 and/or disproportionation of 3 to two symmetrical disulfides). The product shows very strong *new* ir bands at *ca.* 1000 cm^{-1}, as expected for the $-SO_2Na$ moiety of 3, as well as the ir absorption expected for the amide linkage of 3. (3) Ferric chloride at pH *ca.* 6 gave an abundant precipitate with the product, consistent with expectation for an arenesulfinic acid from 3;[6] that the yield was 99% of expectation for the usual 1:3 stoichiometry is strong confirmation for the sulfinate moiety. (4) The product was initially insoluble in acetone but dissolved (and could not be reprecipitated) after *ca.* 0.3 hr, consistent with cyclization of 3. (5) As mentioned, the product 3 reverted readily to 2 under a variety of conditions (neutral, acidic, and weakly basic), as formulated for 3 in eq 1.

The dioxide 5 should lead to a product with a thiol quite different from 3 in ease of reconversion to the dioxide, since this product would not be constrained into the coplanar arrangement that seems to be the root of trouble with 3. First, we attempted to prepare dioxide 5 according to a sequence developed by Lüttringhaus and Hägele (eq 3).[7] We were able to prepare 4 in



83% yield (lit.[7] 84%), but oxidation with *m*-chloroperbenzoic acid under a variety of conditions gave very low yields (*ca.* 4%) of 5. Fortunately, in light of a report that a sulfide can be oxidized to a sulfone by so-

(1) (a) Paper 35: Y. H. Khim and L. Field, *J. Org. Chem.*, **37**, 2714 (1972). (b) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DADA 17-69-C-9128.

(2) L. Field and R. B. Barbee, *J. Org. Chem.*, **34**, 1792 (1969).

(3) *Cf.*, for example, A. Schöberl and H. Gräfje, *Justus Liebigs Ann. Chem.*, **614**, 66 (1958).

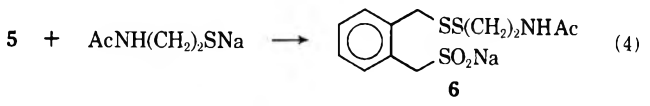
(4) *Cf.* earlier papers in this series for other such uses of this compound as a model.

(5) A. Zweig and A. K. Hoffmann, *J. Org. Chem.*, **30**, 3997 (1965).

(6) (a) L. Ackerman, *Ind. Eng. Chem., Anal. Ed.*, **18**, 243 (1946); (b) J. Thomas, *J. Chem. Soc.*, **95**, 342 (1909).

(7) A. Lüttringhaus and K. Hägele, *Angew. Chem.*, **67**, 304 (1955).

dium metaperiodate in refluxing methanol,[8] we have been able recently to oxidize *trans*-1,2-dithiane-4,5-diol diacetate to the corresponding dioxide by use of potassium metaperiodate in aqueous isopropyl alcohol with iodine as a catalyst.[9] Dioxide **5** could be obtained in 60% yield by oxidizing a solution of **4** by essentially the latter procedure. This dioxide (**5**) then was cleaved with the sodium salt of the thiol **1** to give disulfide sulfinate **6** in 73% yield (eq 4). The ir spectrum was consistent with structure **6**.



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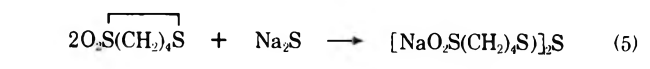
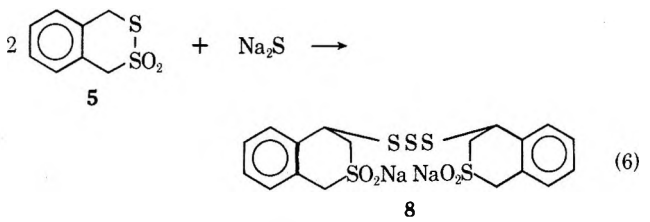
Recently the trisulfide **7** was prepared as a highly hygroscopic salt that forms a dihydrate (eq 5).[10] Prom-



(5)

7

ising activity of **7** as an antiradiation drug is noteworthy, since **7** does not contain a nitrogen function.[10] Hence we were tempted to prepare the corresponding trisulfides **8** and **10** from dioxides **5** and **9** using Na_2S as a nucleophile. For synthesis of **8** (eq 6), a solution of



(6)

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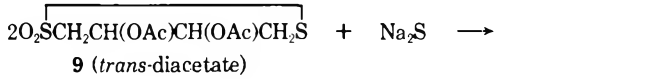
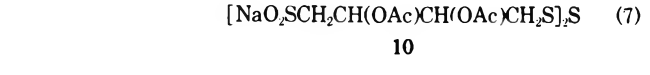


9 (*trans*-diacetate)



(7)

10

Na_2S was added slowly to one of the dioxide **5**; the pH of the mixture went below 7 at first but finally became *ca.* 7. Addition of a large amount of ether then precipitated **8** (84%), which was purified by reprecipitation. A similar procedure gave **10** in 90% yield (eq 7), possibly as a mixture of two diastereoisomers.

It is worth adding that most of the sulfinate salts discussed (**3**, **8**, and **10**) are quite hygroscopic and acquire enough moisture during ordinary handling to give hydrates (without contact with water *per se*, except possibly from $Na_2S \cdot 9H_2O$). Only **6** gave no such problem. Hydration, combined with the difficulty of purifying sensitive salts that presumably both cyclize and disproportionate readily, precluded fully satisfactory elemental analyses in several instances. Unfortunate also was the fact that nmr was of little help in confirming structures of disulfides because changes of the spectrum occurred during observation. Infrared spectra, however, as well as the very fact of conversion of starting materials to highly water-soluble salts in each instance, reassured us as to the identity of **3**, **6**, **8**, and **10**.

(8) L. L. Replogle and J. R. Maynard, *J. Org. Chem.*, **32**, 1909 (1967).
(9) L. Field and Y. H. Khim, *J. Org. Chem.*, **37**, 2710 (1972).
(10) L. Field and Y. H. Khim, *J. Med. Chem.*, **15**, 312 (1972).

Experimental Section[11]

Sodium 8-(2-Acetamidoethyldithio)naphthalene-1-sulfinate (3).—Naphtho[1,8-*cd*]-1,2-dithiole 1,1-dioxide (**2**) was prepared essentially by the procedure of Zweig and Hoffmann.[5] 1-Aminonaphthalene-8-sulfonic acid (60 g) was diazotized using 30 g of $NaNO_2$. The solid diazonium sulfonate obtained, treated with aqueous Na_2S_2, gave 47 g (67%) of crude disodium 8,8′-dithiodi(1-naphthalenesulfonate). This material was dried and powdered, and, in our modification, was treated with 30 g (0.14 mol) of PCl_5, added slowly so that the reaction mixture did not rise above −5°; any higher temperature led to much lower yields. This mixture was allowed to warm to *ca.* 25° and then to stand for 5 hr. It was then extracted with benzene, as usual.[5] The extracts were concentrated, and the residue was taken up in hot MeOH and treated with charcoal. Cooling gave 7 g (17%) of **2** as pale yellow needles, mp 148–149° (lit.[5] mp 148–149°); **2** had ir maxima at 1110 and 1290 cm^{-1} (−SO_2−).

For its conversion to **3**, the dioxide **2** (1.11 g, 5.0 mmol) was dissolved in MeOH (100 ml). A solution prepared by dissolving sodium (0.115 g, 5.0 mg-atoms) in MeOH (10 ml) and mixing in 2-acetamidoethanethiol (**1**, 0.59 g, 4.95 mmol)[12] then was added dropwise with stirring during 0.5 hr. Dry acetone then was added until no more precipitate appeared. This solid was separated, and purification was attempted by adding dry ether to a solution in MeOH at 0–5° until no more precipitate formed: yield of **3**, 1.20 g (67%); mp 200–202° dec; ir 3400 (CONH), 3020, 1690, 1630 (CONH), 1580 (CONH), 1540, 1470, 1400, 1000 (SO_2Na), 960, 940, 800, 740, 690 cm^{-1}. *Anal.* Calcd for $C_{14}H_{14}NNaO_3S_3 \cdot H_2O$: C, 44.09; H, 4.19; S, 25.2. Found: C, 44.14; H, 4.13; S, 21.58. The following experiments illustrate the ease with which **3** cyclizes to **2**. (a) When **3** (1.0 g, 2.7 mmol) was dissolved in MeOH (5 ml) and was warmed for *ca.* 5 min at 50°, on cooling and dilution 0.2 g (33%) of **2** was isolated, mp and mmp 147–148°. (b) The salt **3** (1 g, 2.7 mmol) was dissolved in H_2O (100 ml) and HCl was added (pH *ca.* 3). Within *ca.* 3 min, **2** separated. Filtration gave 0.3 g (49%) of **2**, mp and mmp 147–148°.

2,3-Benzodithian (4).[7]—Thiourea (250 mmol), α,α′-dibromo-*o*-xylene (100 mmol), and EtOH (250 ml) were refluxed (6 hr). The EtOH was removed, the residue was dissolved in H_2O (500 ml), and NaOH (16 g) in H_2O (150 ml) was added. After 6 hr of reflux, cooling, acidification, and extraction gave α,α′-dimercapto-*o*-xylene (82%). To this thiol (82.3 mmol) in 200 ml each of MeOH and AcOH, $FeCl_3 \cdot 6H_2O$ (119 mmol) in AcOH (50 ml) was added at 60–70° (1 hr, to a faint color of $FeCl_3$). Removal of MeOH and addition of H_2O gave **4** (83%), mp 78–79° (lit.[7] mp 80°).

2,3-Benzodithian 2,2-Dioxide (5). A. *Via* *m*-Chloroperbenzoic Acid (*cf.* Ref 7).—The peracid (29.5 mmol) in $CHCl_3$ was added slowly to **4** (10 mmol) in $CHCl_3$ at 0°. After 4 hr, solvent was removed and excess oxidant was destroyed (aqueous Na_2SO_3). Extraction ($CHCl_3$) left polymer. Concentration, then washing with aqueous $NaHCO_3$, left **5** (4%): mp (from MeOH) 108–109° (lit.[7] mp 108°); ir bands at 1090 and 1280 cm^- (−SSO_2−).

B. *Via* Potassium Metaperiodate (KIO_4).—A solution of **4** (0.84 g, 5.0 mmol) in *i*-PrOH (200 ml) was added to KIO_4 (3.4 g, 14.8 mmol) in H_2O (100 ml) containing a crystal of iodine. The reaction mixture was stirred continuously at *ca.* 80° for 4 hr. The *i*-PrOH then was removed, and the residue was extracted with $CHCl_3$. Removal of $CHCl_3$ gave 0.6 g (60%) of dioxide **5**, which was recrystallized from MeOH, mp 108–109°. This **5** showed ir bands at 1090 and 1280 cm^{-1} (−SSO_2−) and was identical with **5** obtained by the oxidation of **4** in A.

(11) Melting points are corrected. Ir spectra were obtained using KBr pellets and a Beckman Model IR-10 spectrophotometer; bands reported were at least of medium intensity. Tlc spots were obtained using Brinkmann F-254 sheets of silica gel (0.25 mm) on aluminum and were developed by exposure to I_2 vapor in a sealed container. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Moist extracts ordinarily were dried over anhydrous $MgSO_4$ and solvent then was removed using a rotating-flask evaporator. Yields of materials which became hydrated were calculated on an anhydrous basis, since the point at which water was acquired was uncertain.
(12) R. Kuhn and G. Quadbeck, *Chem. Ber.*, **84**, 844 (1951).

Sodium [2-(2-Acetamidoethyldithiomethyl)phenyl]methanesulfinate (6).—Sodium (460 mg, 20 mg-atoms) dissolved in MeOH (20 ml) was added dropwise to a mixture of **5** (4.00 g, 20.0 mmol) and **1** (2.38 g, 20.0 mmol) in MeOH (50 ml) with stirring at *ca.* 25°. After addition was complete (*ca.* 10 min), dry Et_2O (*ca.* 500 ml) was added to the reaction mixture until no more precipitate appeared. Solvent was decanted, and the white precipitate was redissolved in MeOH (10 ml) and reprecipitated with dry Et_2O. Decantation and drying at 0.1 mm for 24 hr at 25° gave 5.00 g (73%) of white **6**, mp 110–112° dec. Tlc showed one spot (1:1 MeOH:Me_2CO); ir 3400, 1650, 1530, 1010, 960, and 750 cm^{-1}. Additional tlc spots appeared a few minutes after dissolution of **6** in H_2O or (more slowly) MeOH.

Anal. Calcd for $C_{12}H_{16}NNaO_3S_3$: C, 42.22; H, 4.69; N, 4.10; S, 28.15. Found: C, 42.33; H, 4.65; N, 3.72; S, 27.95.

Disodium 2,2′-(Trithiodimethyl)bis(phenylmethanesulfinate) (8).—A solution of commercial $Na_2S \cdot 9H_2O$ (1.5 mmol) in MeOH (5 ml) was added slowly to the dioxide **5** (0.60 g, 3.00 mmol) in MeOH (25 ml) at 0–5° with good stirring during 30 min. After the addition was complete (the pH then was 7), the reaction mixture showed only one spot for **8** by tlc (1:1 MeOH:Me_2CO) and none for **5**. Addition of Et_2O (600 ml) at 0° gave a white precipitate. Most of the solvent was decanted, after which drying at 0.1 mm gave 0.60 g (84%) of white **8**, mp 192–194° dec. This **8** was dissolved in a little MeOH, and a small amount of dry Et_2O was added until a cloudy precipitate began to appear. A colorless, clear solution then resulted upon removal of the small amount of precipitate by centrifugation as quickly as possible. Dry Et_2O again was added to this solution until appearance of a white precipitate was complete. Decantation and drying at 0.1 mm for 24 hr at *ca.* 25° gave 0.50 g (70%) of **8**, mp 192–194 dec. Tlc showed one spot (1:1 MeOH:Me_2CO); ir 3400 (H_2O), 1640 (H_2O), 1010 and 970 (very strong, SO_2^-), and 760 cm^{-1}. Additional tlc spots appeared a few minutes after dissolution of **8** in H_2O or (more slowly) MeOH.

Anal. Calcd for $C_{16}H_{16}Na_2O_4S_5 \cdot 3H_2O$ (dried at 25°): C, 36.09; H, 4.13; S, 30.07. Found: C, 36.28, 36.36; H, 4.24, 4.40; S, 29.60, 29.45.

Drying to constant weight (100° overnight) gave hygroscopic, anhydrous **8**.

Anal. Calcd for $C_{16}H_{16}O_4S_5Na_2$: C, 40.17; H, 3.34; S, 33.47. Found: C, 39.42; H, 3.81; S, 31.66.

When the analyst kindly exposed anhydrous **8** for *ca.* 2 days to ambient air and then redried, the weight loss was 10.64% (calcd for $8 \cdot 3H_2O$, 10.13%).

Disodium 4,4′-Trithiobis(*threo*-2,3-diacetoxybutanesulfinate) (10).—A solution of $Na_2S \cdot 9H_2O$ (3.6 mmol) in MeOH (20 ml) was added dropwise to the *trans*-diacetate dioxide **9** (2.00 g, 7.46 mmol)[13] in MeOH (50 ml) at 0–5° with good stirring. After addition was complete (the pH then was *ca.* 7), the reaction mixture showed one spot for **10** by tlc (1:1 MeOH:Me_2CO). Addition of Et_2O (500 ml) at 0° gave a white precipitate. As with **8**, the **10** was redissolved in a little MeOH and a little dry Et_2O was added until a precipitate began to appear. Centrifugation as quickly as possible again removed a little solid and left a clear solution. Dry Et_2O was added to this solution until appearance of a white precipitate was complete. Decantation and drying at 0.1 mm for 24 hr at 25° gave 2.0 g (90%) of **10**, mp 178–180° dec. Tlc showed one spot (1:1 MeOH:Me_2CO); ir 3440 (H_2O), 1730, 1620 (H_2O), 1380, 1220, 1030 (broad), 950 cm^{-1}.

Anal. Calcd for $C_{16}H_{24}Na_2O_{12}S_5 \cdot H_2O$: C, 30.37; H, 4.11; S, 25.31; H_2O, 2.84. Found: C, 29.80; H, 4.19; S, 26.19; H_2O, 3.15.

Drying to constant weight (100° overnight, then 120°) of a sample moderately dried for the foregoing analysis removed only 1.02% H_2O.

Anal. Calcd for $C_{16}H_{24}O_{12}S_5Na_2$: C, 31.27; H, 3.90; S, 26.05. Found: C, 29.85, 29.75; H, 4.04, 4.24; S, 26.40, 26.36.

Registry No.—**3**, 36540-20-2; **6**, 36540-21-3; **8**, 36540-22-4; **10**, 36540-23-5.

(13) We are indebted to Dr. Y. H. Khim for the preparation of **9**, as reported by L. Field and Y. H. Khim in ref 9.

Preparation of Orthocarbonates from Thallous Alkoxides and Carbon Disulfide

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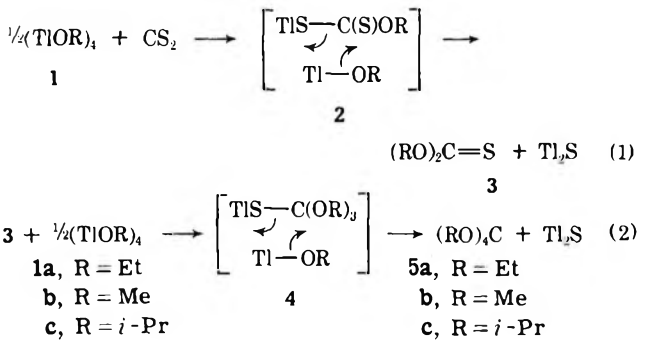
During our studies on new types of orthocarbonate syntheses from organometallic alkoxides and carbon disulfide,[2,3] Lee reported that dimethylthallium alkoxide reacted with carbon dioxide, carbon disulfide, and sulfur dioxide to form insertion products across the thallium(III)–oxygen bond.[4] Although insertion reactions of heterocumulenes are well known for R_3SnOR[5] and other organometallic alkoxides, the syntheses of orthocarbonates could be realized only in the case of the reactions of bis(trialkyltin) glycolates[2] and dialkyltin dialkoxides[3] with carbon disulfide.

In this note, we report the reaction of thallium(I)–oxygen compounds with carbon disulfide and dioxide, and show a new type of utilization of thallous alkoxides for orthocarbonate syntheses.

Thallous ethoxide reacted with an equimolar amount of carbon disulfide in dry methylene dichloride to afford tetraethyl orthocarbonate in 97% yield. The orthocarbonate formed was identified by comparison with the melting point and ir and nmr spectra of an authentic sample.[3] Tetramethyl orthocarbonate was also obtained in good yield by the reaction of thallous methoxide with carbon disulfide.

Furthermore, when thallous ethoxide was treated with an excess of carbon disulfide, the ir spectrum of the reaction mixture indicated the presence of a small amount of diethyl thioncarbonate. Consequently, the reaction scheme may be formulated by eq 1 and 2, as in the reactions of dialkyltin dialkoxides with carbon disulfide.[2]



The adducts of carbon disulfide with trialkyltin alkoxides[5] [$R_3SnSC(S)OR'$], dimethylthallic alkoxide, and thallous phenoxide[4,6] were found to be stable at room temperature, while the adducts of thallous alkoxides are unstable and decomposed to give thioncarbonates, **3**, or orthocarbonates, **5**. These results are in-

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(2) S. Sakai, Y. Kiyohara, K. Itoh, and Y. Ishii, *J. Org. Chem.*, **35**, 2347 (1970).

(3) S. Sakai, Y. Kobayashi, and Y. Ishii, *ibid.*, **36**, 1176 (1971).

(4) A. G. Lee, *J. Chem. Soc. A*, 467 (1970).

(5) A. G. Davies, *Synthesis*, 56 (1969); *J. Chem. Soc. C*, 1309, 1313 (1967).

(6) A. G. Lee, *Organometal. Chem. Rev., Sect. B*, 310 (1970).

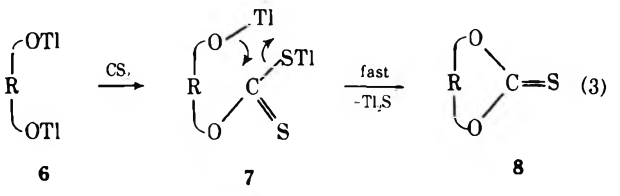
teresting but difficult to explain at present. However, both the stability of the adduct and the reactivity of alkoxide might be affected by the acidity of the metal atom toward a sulfur atom and by the nucleophilicity of the alkoxyl group. Bonati and coworkers showed that the mean degrees of association of organotin(IV), dimethylthallic, and thallous dithiophosphinates were about 1.0, 1.5, and 2.0, respectively,[7] suggesting that intermolecular coordination to the sulfur atom is in the order thallium(I) > dimethylthallium(III) > trialkyltin(IV). Furthermore, thallous–oxygen compounds, such as thallous hydroxide and ethoxide, are strong bases, while organotin–oxygen compounds are weak bases.[8,9] Therefore, the nucleophilic attack of the alkoxyl group at the electron-deficient carbon atom in the coordination transition state such as **2** or **4** will be facilitated by the larger basicity of thallous alkoxide. Moreover, an association of thallous alkoxide to form cubic tetramer[10,11] would probably assist sterically reactions 1 and 2.

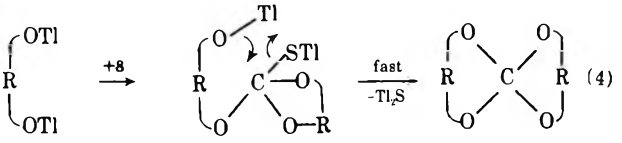
Thallous isopropoxide was prepared by the alcoholysis reaction of thallous methoxide with isopropyl alcohol, and reacted with carbon disulfide in benzene at room temperature to afford tetraisopropyl orthocarbonate in a moderate yield. This new compound is more liable to hydrolysis to give diisopropyl carbonate than primary orthocarbonates.[12] The high reactivity of thallous isopropoxide gave a new route to prepare an acyclic secondary orthocarbonate, which is not obtainable by other methods, although bis(2,3-butylene) spiroorthocarbonate, a cyclic secondary orthocarbonate, was afforded by the reaction of bis(trialkyltin) 2,3-butylene glycolate with carbon disulfide.[2]

Preparation of spiroorthocarbonates from dithallous glycolates were also examined. Pure dithallous alkylene glycolates are difficult to prepare by the alcoholysis reactions of thallous ethoxide with glycols, because mono- and dithallous glycolates are insoluble in organic solvents and sensitive to moisture and carbon dioxide in the atmosphere. However, the crude glycolates reacted with equimolar amounts of carbon disulfide in benzene at room temperature for 2 hr, affording moderate yields of bis(alkylene) spiroorthocarbonates, **10**.

When an excess amount of carbon disulfide was used in the reaction, ethylene thioncarbonate (**8**, R = CH_2-CH_2) and bis(ethylene) orthocarbonate (**10a**) were formed (eq 3 and 4), as in the reactions of bis(tributyltin) alkylene glycolates.[2]

Dithallous ethylene glycolate also reacted with carbon dioxide to give a solid which showed strong ir absorption bands at 1681, 1610, 1309, and 1073 cm^{-1}, assigned to the adduct resulting from addition of carbon dioxide across the thallium–oxygen bond. The adduct is stable in the solid state for 3 hr at 90° or in refluxing dichloroethane for several hours. These results show that the reactions of carbon disulfide with





6a, R = CH_2CH_2
b, R = CH_2CHMe
c, R = $(CH_2)_3$
d, R = $(CH_2)_4$

9

10a, R = CH_2CH_2
b, R = CH_2CHMe
c, R = $(CH_2)_3$
d, R = $(CH_2)_4$

thallous alkoxide are only successful for preparations of orthocarbonates.

Experimental Section

General.—Melting points and boiling points were uncorrected. Analyses were performed by the Analysis Center of Kyoto University or by Toa-gosei Chemical Co., Ltd. Ir and nmr spectra were recorded on a JASCO Model IR-S spectrometer and on a Japan Electron Optics Model HL-60 spectrometer (TMS as a internal standard), respectively.

All operations were carried out under a dry nitrogen atmosphere.

Materials.—Carbon disulfide, alcohols, and solvents used were strictly dried by common methods. Thallous ethoxide, methoxide, and isopropoxide were prepared by the methods of Kahlbaum,[13] Sidgwick,[10] and Dahl,[11] respectively.

Dithallous glycolates were prepared and isolated by the deForcrand procedure.[14] Elemental analyses indicated that the formed dithallous glycolates were impure. Their analyses were very difficult because they are sensitive to moisture and carbon dioxide in air. Typical cases of isolations and analytical data of the glycolates follow.

To the solution of thallous ethoxide (20 mmol) in benzene (30 ml), was slowly added the glycol (10 mmol), with stirring for 2 hr at 50–60°. The reaction mixture was filtered, and the white residue was washed with dry benzene. The crude glycolate **6** was dried on silica gel, obtained in nearly quantitative yield, and was insoluble in ordinary organic solvents, thereby preventing further purifications. The melting points of the glycolates were in the range of 200–209° dec. Analytical data follow. **6a**: Calcd for $C_2H_4O_2Tl_2$: C, 5.16; H, 0.86. Found: C, 6.03; H, 1.07. **6c**: Calcd for $C_3H_6O_2Tl_2$: C, 7.46; H, 1.25. Found: C, 7.79; H, 1.22. **6d**: Calcd for $C_4H_8O_2Tl_2$: C, 9.67; H, 1.62. Found: C, 8.71; H, 1.67.

Reaction of Thallous Ethoxide with CS_2.—Thallous ethoxide (**1a**) (4.95 g, 19.8 g mmol) was allowed to react with CS_2 (0.42 g, 5.5 mmol) in dry dichloromethane (30 ml) with stirring for 4 hr at room temperature. A black precipitate, Tl_2S, formed soon after the addition of CS_2, was filtered off and washed with CS_2. Thallium sulfide was obtained in 97% yield. The filtrate was evaporated *in vacuo*, giving crude tetraethyl orthocarbonate in 94% yield (0.90 g). Distillation of the crude orthocarbonate gave the pure orthocarbonate in 69% yield. Its ir and nmr spectra coincided well with those of an authentic sample, bp 48–51° (18 mm) [lit.[3] bp 47–52° (24 mm)].

When an excess amount of CS_2 (1.42 g, 18.7 mmol) was treated with thallous ethoxide (4.77 g, 9.1 mmol) in the same manner, the ir spectrum of the filtrate from the reaction mixture showed strong ν_{C-O} bands of tetraethyl orthocarbonate (**5a**) at 1195 and 1120 cm^{-1}, and weak bands of diethyl thioncarbonate (**3**, R = Et) at 1312, 1291, and 1232 cm^{-1}.

Reaction of Thallous Methoxide with CS_2.—Thallous methoxide (**1b**) (9.42 g, 40 mmol) was allowed to react with CS_2 (0.84 g, 11 mmol) as in the case of thallous ethoxide. The crude product showed a strong ν_{C-O} band at 1125 cm^{-1} in the ir spectrum ($CHCl_3$), and distillation gave a 72% yield of tetramethyl orthocarbonate (**5b**), bp 61–64° (lit.[3] bp 62–63°).

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(8) E. W. Abel, D. A. Armitage, and D. B. Brady, *Trans. Faraday Soc.*, **62**, 3459 (1966).
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(12) R. H. DeWolfe, "Carboxylic Ortho Acid Derivatives," Academic Press, New York, N. Y., 1970, p 137.
(13) G. W. A. Kahlbaum, *Z. Anorg. Chem.*, **29**, 177 (1902).
(14) M. R. deForcrand, *C. R. Acad. Sci.*, **176**, 20 (1923).

Reaction of Thallous Isopropoxide with CS_2.—Thallous isopropoxide (1c) (10.5 g, 40 mmol) was allowed to react with CS_2 (0.80 g, 10.5 mmol) as in the case of thallous ethoxide. Distillation of the filtrate from the reaction mixture afforded tetraisopropyl orthocarbonate (5c) in 55% yield (1.35 g, 5.5 mmol): bp 47–51° (3.5 mm); ir ($CHCl_3$) 1471, 1384, 1188, 1155, 1080 (strong), and 961 cm^{-1}; nmr ($CHCl_3$) τ 8.85 (d, 24, J = 6.0 Hz, CH_3C) and 5.94 (heptet, 4, J = 6.0 Hz, CHO).

Anal. Calcd for $C_{13}H_{28}O_4$: C, 62.87; H, 11.37. Found: C, 62.51; H, 10.98.

The orthocarbonate 5c was rapidly hydrolyzed by moisture in air to give diisopropyl carbonate, and the $\nu_{C=O}$ band of the carbonate at 1738 cm^{-1} emerged during the ir measurement.

When the crude thallous isopropoxide, prepared by the alcoholysis of thallous ethoxide with isopropyl alcohol, and containing about 20 mol % of thallous ethoxide, was submitted to reaction with CS_2, a small amount of diisopropyl dithiocarbonate was formed along with the ethyl and isopropyl orthocarbonates. The dithiocarbonate in the reaction mixture was detected by its characteristic peaks at τ 4.23 (heptet, J = 6.0 Hz) in the nmr spectrum.

Reaction of Dithallous Ethylene Glycolate with CS_2. A.—Dithallous ethylene glycolate (6a) (1.32 g, 2.81 mmol) was dispersed in dry benzene (30 ml), and CS_2 (0.083 g, 1.1 mmol) was introduced slowly into the dispersion, which was stirred for 2 hr at room temperature. The thallous sulfide formed was filtered off, and benzene in the filtrate was evaporated to separate the crude crystals of the spiroorthocarbonate 10a in 60% yield (0.070 g, 0.50 mmol). This compound showed a strong ν_{C-O} band at 1058 cm^{-1} in the ir spectrum (benzene) and a peak at τ 6.40 (s, 8, CH_2) in the nmr spectrum (benzene), which were the same values as for an authentic sample,[2] mp (CCl_4) 140.5–141.0° (lit.[2] mp 143–144°).

B.—Dithallous ethylene glycolate (6a) (0.49 g, 1.04 mmol) was allowed to react with an excess of CS_2 (3.05 g, 40 mmol) for 2.5 hr at room temperature with stirring. The ir spectrum in carbon disulfide of the crude product displayed absorption bands at 1360, 1250, 1210, 1140, 1058, 1018, and 958 cm^{-1} (but a ν_{OH} band at ~3600 cm^{-1} was not observed), and the nmr peaks at τ 5.45 (s) and 6.13 (s) coincided with those of a mixture of 40 mol % of ethylene thioncarbonate and 60 mol % of bis(ethylene) orthocarbonate (10a).

Reactions of CS_2 with Dithallous 1,2- or 1,3-Propylene and 1,4-Butylene Glycolates.—The dithallous glycolates 6b, 6c, and 6d were allowed to react with CS_2 as in procedure A described above, giving the crude orthocarbonates 10b (about 50% yield), 10c (73% yield), and 10d (35% yield), respectively. The products, purified by distillations or by recrystallizations, were identified by comparisons of boiling point, melting point, ir, and nmr spectra with those of authentic samples.

Registry No.—5a, 78-09-1; 5c, 36597-49-6; 6a, 36597-50-9; 6c, 36601-78-2; 6d, 36601-79-3; 10a, 24471-99-6; carbon disulfide, 75-15-0.

Observations Related to the Alkylation of Thallium Enolates of β-Keto Sulfoxides, β-Diketones, and β-Keto Esters. An Alternative Viewpoint

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The alkylation[1,2] of β-keto sulfoxides[3] (as their sodium enolates), followed by reductive fission of the sulfoxide function,[1,4] represents a useful alternative to the acetoacetic ester route for the synthesis of ketones. Mono- and dialkylated derivatives are formed in good yields,

$$RCOCH_2SOCH_3 \longrightarrow \underset{Na^+}{RCOCHSOCH_3} \longrightarrow \underset{R'}{RCOCHSOCH_3} \longrightarrow RCOCH_2R'$$

but attempts to extend this method to secondary halides have as yet been unpromising, resulting in "extremely poor yields of alkylation product."[2]

In the light of prior results, we investigated the use of thallium enolates for this purpose, since Tl derivatives of 1,3-dicarbonyl compounds (β-diketones or β-keto esters) are reported to possess a variety of attractive synthetic features.[5-7] Thallium enolates (i) are easily formed in virtually quantitative yield, (ii) are crystalline, stable, nonhygroscopic solids, and (iii) react with alkyl iodides to give *exclusively*, in essentially quantitative yield, *the product of C-alkylation*—even for secondary substrates (isopropyl iodide). In addition, the heterogeneous thallium cation–ambident anion combination reportedly avoids *all* the traditionally encountered obstacles associated with β-dicarbonyl anion alkylations (O-alkylation, dialkylation, Claisen-type condensations, β-keto cleavage, oxidative coupling, etc.).[5]

For exploratory synthetic purposes we considered that Tl β-dicarbonyl enolates might serve as reasonable models for Tl β-keto sulfoxides since in each parent substrate the active methylene is flanked by two atoms each of which is "doubly" bonded to oxygen. Moreover, Tl enolates are highly insoluble, and, among the several factors responsible for promoting predominant C- rather than O-alkylation of ambident anions, heterogeneity[8] plays a significant role.[9]

Reaction of keto sulfoxide 1 with thallous ethoxide[10] led to quantitative precipitation of salt 2 (eq 1). The

$$\underset{1}{C_6H_5COCH_2SOCH_3} \xrightarrow{TlOC_2H_5} \underset{2}{C_6H_5COCHSOCH_3} \quad (1)$$
$$Tl^+$$

results of heterogeneous alkylation experiments employing 2 with methyl, ethyl, or isopropyl iodide are summarized in eq 2 (see Experimental Section for

$$\underset{Tl^+}{C_6H_5COCHSOCH_3} \xrightarrow{RI} \underset{3}{C_6H_5COCHSOCH_3} + \underset{4}{C_6H_5C(OR)=CHSOCH_3} + \underset{5}{C_6H_5COCH_2SCH_3} \quad (2)$$

Alkylating agent	Isolated product yield, % 3	4	5
CH_3I	81		
C_2H_5I	38	17	28
i-C_3H_7I		42	36

(1) G. A. Russell and G. J. Mikol, *J. Amer. Chem. Soc.*, **88**, 5498 (1966); G. A. Russell and G. Hamprecht, *J. Org. Chem.*, **35**, 3007 (1970).

(2) P. G. Gassman and G. D. Richmond, *ibid.*, **31**, 2355 (1966).

(3) H-D. Becker, G. J. Mikol, and G. A. Russell, *J. Amer. Chem. Soc.*, **85**, 3410 (1963); H-D. Becker and G. A. Russell, *J. Org. Chem.*, **28**, 1896 (1963).

(4) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **86**, 1639 (1964).

(5) E. C. Taylor, G. H. Hawks, III, and A. McKillop, *ibid.*, **90**, 2421 (1968).

(6) E. C. Taylor and A. McKillop, *Accounts Chem. Res.*, **3**, 338 (1970).

(7) E. C. Taylor and A. McKillop, *Aldrichimica Acta*, **3**, 1 (1970).

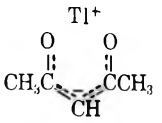
(8) N. Kornblum and A. Lurie, *J. Amer. Chem. Soc.*, **81**, 2705 (1959).

(9) An excellent and extensive discussion appears in H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., 1972, Chapter 9.

(10) Available from Aldrich Chemical Co., Inc., Milwaukee, Wis.

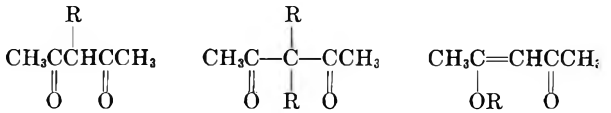
details). Only methylation resulted in the exclusive formation of C-alkylate. Since reaction of CH_3I with the corresponding sodium enolate of **1** gave yields of 86%[1] (or 70%[2]) of **3** (R = CH_3), no advantage accrues using the Tl enolate. Ethylation of **2** was complex and clearly inferior to ethylation of the Na analog in promoting efficient C-alkylation.[1,2] Keto sulfide **5**[11-13] is not reported to be a product of Na enolate alkylations of **1**. No C-alkylate was obtained from reaction of **2** with isopropyl iodide.

To gain additional experience and confirm our technique, we sought to duplicate prior findings.[5] In our hands, heterogeneous alkylation of **6** (from $TlOC_2H_5$



6

and acetylacetone) with methyl, ethyl, or isopropyl iodide, gave exclusively C-alkylation products only with methyl iodide, but alkylate **7** (R = CH_3, 85%) was also accompanied by formation of *ca.* 6% of dialkylate **8** (R = CH_3). Reaction of **6** with C_2H_5I produced a mixture of **7** (R = C_2H_5, 65%), **8** (R = C_2H_5,



7 **8** **9**

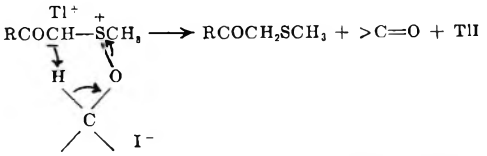
4%), and enol ether **9** (R = C_2H_5, 13%). Isopropyl iodide reacted with **6** to produce O-alkylate **9** (R = *i*-C_3H_7 as the major product (62%), accompanied by a 20% yield of **7** (R = *i*-C_3H_7).

To check independently our synthetic **6**, commercially available **6**[10] was alkylated with isopropyl iodide. Under conditions identical with those employed for synthetic **6** (and as previously described[5]), there was obtained enol ether **9** (R = *i*-C_3H_7, 62%) and C-alkylate **7** (R = *i*-C_3H_7, 20%).

Reaction of the Tl enolate of ethyl acetoacetate (**10**) with C_2H_5I produced a mixture of alkylates **11** (R = C_2H_5, 80%), **12** (R = C_2H_5, 2%), and **13** (R = C_2H_5, 5%). Isopropyl iodide reacted with **10** to furnish a mixture of **11** (R = *i*-C_3H_7, 67%) and **12** (R = *i*-C_3H_7, 20%).

In contrast to the heterogeneous acetylacetone–Tl enolate reactions, it is difficult for us to state with confidence that the latter alkylations were totally heterogeneous.[5-7] Admixture of **10** with either C_2H_5I or

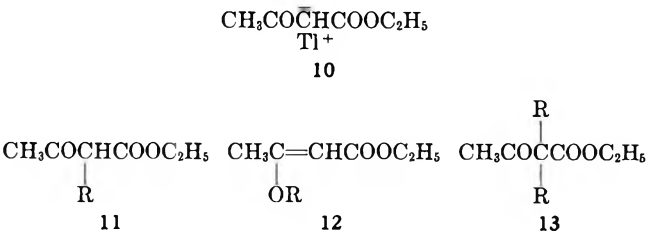
(11) Although the mechanism for keto sulfide formation has not been established, one plausible pathway involves initial O-alkylation (on sulfoxide oxygen), followed by inter- or intramolecularly promoted elimination, *viz.*



The reduction of dimethyl sulfoxide by alkyl halides is well documented.[12,13]

(12) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, and W. M. Weaver, *J. Amer. Chem. Soc.*, **79**, 6562 (1957).

(13) A. P. Johnson and A. Pelter, *J. Chem. Soc.*, 520 (1964).



10

11 **12** **13**

i-C_3H_7I led to the formation of cloudy mixtures (no solid particles were evident) with the gradual development of a yellow coloration and ultimate deposition of (yellow) TlI.

In view of the complex array of products observed, we conclude that Tl enolates of β-keto sulfoxides or β-diketones, despite their heterogeneity, and Tl enolates of β-keto esters (despite their apparent "heterogeneity"), offer no special synthetic advantages for promoting *exclusive* mono-C-alkylation.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Nmr spectra were run on a Varian A-60 or Hr-100 spectrometer in deuteriochloroform with tetramethylsilane as internal standard and are reported in τ units. Gas chromatographic (gc) analyses were performed using the following columns: column A, 10 ft × 1/4 in. 15% XF-1150 on 60/80 Chromosorb W; column B, 5 ft × 1/8 in. 10% QF-1 on 60/80 Chromosorb W; column C, 10 ft × 1/4 in. 15% Apiezon L on 60/80 Chromosorb W; column D, 15 ft × 1/8 in. 15% SE-30 on 60/80 Chromosorb W; column E, 10 ft × 1/4 in. 10% SE-30 on 60/80 Chromosorb W. All alkylation products, in both the quantitative (corrected for peak response) analytical and preparative gc work, are listed in order of elution. Infrared spectra were recorded on a Unicam SP 1000 spectrometer. Mass spectra were determined by Dr. A. Hogg and his associates at 70 eV using an A.E.I. MS-2 or MS-9 mass spectrometer. Analytical thin layer chromatography (tlc) was performed on silica gel plates. Precoated silica gel F_{254} plates, 20 × 20 × 0.2 cm (E. Merck, Darmstadt), were used for preparative tlc. Microanalyses were performed by the Microanalytical Laboratory, University of Alberta.

Caution! Thallium compounds are insidious poisons and should be handled with great care.

Reaction of Thallous Ethoxide with ω-(Methylsulfinyl)acetophenone (1) to Form Salt 2.—To a solution of 1.5 g (6.0 mmol) of thallous ethoxide[10] in 25 ml of anhydrous tetrahydrofuran, magnetically stirred under a nitrogen atmosphere, was added a solution of 0.91 g (5.0 mmol) of ω-(methylsulfinyl)acetophenone in 25 ml of tetrahydrofuran. After stirring for *ca.* 5 min, the initially formed yellow coloration disappeared, and a white precipitate formed. The mixture was stirred (30 min), 40 ml of anhydrous ligroin was added, and stirring was continued for an additional 15 min. The solid was filtered, washed (ligroin), and dried to provide 1.9 g (100%) of product: mp 139–141°; mass spectrum *m/e* (rel intensity) M^+ 386, 384 (2), 371 (31), 369 (13), 205 (100), 203 (37), 120 (6), 105 (95), 77 (58).

Anal. Calcd for $C_9H_9O_2STl$: C, 28.04; H, 2.33; S, 8.32. Found: C, 28.00; H, 2.11; S, 8.31.

Alkylation of 2 with Alkyl Iodides. General Procedure.—To 5.0 mmol of **2** was added 40 ml of the freshly distilled alkyl iodide under a nitrogen atmosphere. After the magnetically stirred mixture had reacted for the times and at the temperatures indicated below, it was filtered through a Florisil column. The column was washed with tetrahydrofuran (two 40-ml portions), and the solutions were combined and concentrated on a rotary evaporator. Products were isolated by column chromatography using Florisil as adsorbent.

With Methyl Iodide.—After a reaction time of 30 min at 25°, there was obtained 0.87 g of colorless oil. Chromatography on 50 g of Florisil (elution with ether–acetone, 7:3 by volume) afforded 0.79 g (81%) of diastereomeric sulfoxides **3**: ir ($CHCl_3$) 1675 (C=O), 1050 cm^{-1} (SO); nmr (60 MHz, $CDCl_3$) τ 8.44 (d, 3, CH_3), 8.40 (d, 3, CH_3), 7.55 (s, 3, $SOCH_3$), 7.50 (s, 3, $SOCH_3$), 5.35 (q, 1, CH), 5.10 (q, 1, CH), 2.80–1.95 (m, 10, arom).

Crystallization from ether–ethyl acetate yielded white crystals, mp 74–76° (lit.[2] mp 77–78°).

With Ethyl Iodide.—After 1.5 hr at 55° there was obtained 0.97 g of pale yellow oil. Chromatography on 50 g of Florisil (elution with ether) afforded 0.24 g (28%) of **5**, the ir and nmr spectra of which were identical with those of a sample independently prepared from reduction of **1** with sodium metabisulfite.[14]

Further elution with ether–acetone (4:1) provided 0.64 g of colorless oil, shown to be a two-component mixture by analytical tlc. By preparative tlc (ethyl acetate development) there was obtained as the more mobile component, 0.39 g (38%) of diastereomeric keto sulfoxides, **3** (R = C_2H_5): ir (liquid film) 1670 (C=O), 1060 cm^{-1} (SO); nmr (60 MHz, $CDCl_3$) τ 8.95 (t, 3, CH_3), 7.60–8.10 (m, 2, CH_2), 7.45 (s, 3, $SOCH_3$), 5.10–5.45 (m, 1, CH), 2.65–1.75 (m, 5, arom); mass spectrum M^+ 210. The less mobile component, **4** (0.175 g, 17%), was a colorless oil: ir (liquid film) 1605 (C=C), 1070 (C–O), 1040 cm^{-1} (SO); nmr (60 MHz, $CDCl_3$) τ 8.68 (t, 3, CH_3), 7.27 (s, 3, $SOCH_3$), 6.00 (q, 2, CH_2), 3.98 (s, 1, C=CH), 2.30–2.65 (m, 5, arom); mass spectrum M^+ 210.

With Isopropyl Iodide.—After 6 hr at 65° there was obtained 0.91 g of pale yellow oil. Column chromatography on Florisil (ether elution) provided 0.325 g of pale yellow oil. Molecular distillation at 90–100° (bath temperature) (1 mm) yielded 0.300 g (36%) of **5**. The ir and nmr spectra were identical with those of an authentic sample.[14]

Further elution with ether–acetone (4:1) provided 0.467 g (42%) of **4** (R = *i*-C_3H_7): ir (liquid film) 1605 (C=C), 1060 (CO), 1040 cm^{-1} (SO); nmr (60 MHz, $CDCl_3$) τ 8.70 (q, 6, CH_3), 7.27 (s, 3, $SOCH_3$), 5.72 (m, 1, CH), 4.00 (s, 1, C=CH), 2.40–2.75 (m, 5, arom); mass spectrum M^+ 224. The structure was further confirmed by conversion (2 *N* HCl, 50°, 15 min) into the Pummerer rearrangement product $C_6H_5COCH(OH)SCH_3$:[1] ir ($CHCl_3$) 1670 (C=O), 3460 cm^{-1} (OH); nmr (60 MHz, $CDCl_3$) τ 8.00 (s, 3, SCH_3), 5.66 (s, 1, OH), 3.83 (s, 1, CH), 1.80–2.70 (m, 5, arom); mass spectrum M^+ 182.

Preparation of 6.—To a solution of 11.0 g (110 mmol) of 2,4-pentanedione in 20 ml of anhydrous ligroin was added, all at once, a solution of 25 g (100 mmol) of thallous ethoxide in 30 ml of anhydrous ligroin. A heavy white precipitate formed immediately, and the mixture was magnetically stirred for *ca.* 30 min. The solid was collected (vacuum filtration) and dried to afford 30.3 g (100%) of **6**, mass spectrum M^+ 304.

Reaction of 6 with Alkyl Iodides. General Procedure.—A heterogeneous mixture of 50 mmol of **6** in 45 ml of the freshly distilled alkyl iodide was magnetically stirred and refluxed (N_2 atmosphere) for the times indicated.[5] The mixture was then cooled to room temperature and the supernatant passed through a Florisil column. The solid residue was washed with tetrahydrofuran (2 × 25 ml), and the THF washings were also passed through the Florisil column. Yields were established by quantitative gc analysis. Each component was isolated by preparative gc, and where amounts permitted, further purified by molecular distillation.

With Methyl Iodide.—After a reflux period of 4 hr and processing as described above, quantitative gc analysis (column B, 125°) gave the following results: 2,4-pentanedione, 5%; **7** (R = CH_3), 85%; and **8** (R = CH_3), 6%. The isolated (column A, 155°) materials had the following properties: 2,4-pentanedione: ir and nmr spectra identical with those of an authentic sample;[10] **7** (R = CH_3), after molecular distillation at 75–77° (bath) (20 mm): ir (liquid film) 3410 (enol OH), 1720, 1700 (C=O), 1610 cm^{-1} (C=C enol); nmr (60 MHz, $CDCl_3$) τ 8.68 (d, 3, CH_3), 7.80 (s, 6, CH_3CO), 6.33 (q, 1, CH), and in addition signals due to *ca.* 25% enol content, τ 8.17 (s, 3, C=CCH_3), 7.89 (s, 3, $CH_3C(O)$=C), 7.80 (s, 3, CH_3CO), ~6.42 (OH, exch by D_2O); mass spectrum M^+ 114; **8** (R = CH_3): ir (liquid film) 1710 cm^{-1} (C=O); nmr (60 MHz, $CDCl_3$) τ 8.65 (s, 6, CH_3), 7.87 (s, 6, $COCH_3$); mass spectrum M^+ 128.

With Ethyl Iodide.—After a reflux period (16 hr) and processing as above, quantitative gc (column D, 155°) indicated: 2,4-pentanedione, 3%; **7** (R = C_2H_5), 65%; **9** (R = C_2H_5), 13%; and dialkylate **8** (R = C_2H_5), 4%. Properties of isolated (column E, 170°) materials follow: 2,4-pentanedione: spectroscopically (ir, nmr) identical with authentic material;[10] **7** (R = C_2H_5), after molecular distillation at 73–75° (bath) (20 mm): ir (liquid film) 3410 (OH enol), 1725, 1700 (CO), 1600 cm^{-1} (C=C enol); nmr (60 MHz, $CDCl_3$) τ 9.08 (t, 3, CH_3), 8.11 (m, 2, CH_2), 7.82 (s, 6, CH_3CO), 6.44 (t, 1, CH); mass spectrum M^+ 128; **9** (R = C_2H_5): ir (liquid film) 1680 (CO), 1585 cm^{-1} (C=C); nmr (60 MHz, $CDCl_3$) τ 8.65 (t, 3, CH_3), 7.87 (s, 3, $CH_3C(O)$=C), 7.73 (s, 3, CH_3CO), 6.17 (q, 2, CH_2), 4.57 (s, 1, C=CH); mass spectrum M^+ 128; **8** (R = C_2H_5): ir (liquid film) 1700 cm^{-1} (CO); nmr (60 MHz, $CDCl_3$) τ 9.28 (t, 6, CH_3), 8.06 (q, 4, CH_2), 7.92 (s, 6, CH_3CO); mass spectrum M^+ 156.

With Isopropyl Iodide.—The reaction mixture was processed as above after being refluxed for 14 hr. The yields (quantitative gc analysis, column D, 170°) were 20% for **7** (R = *i*-C_3H_7), and 62% for **9** (R = *i*-C_3H_7). Isolation (column C, 200°) provided **7** (R = *i*-C_3H_7), which after molecular distillation at 72–76° (bath) (18 mm) displayed ir (liquid film) 1725, 1700 cm^{-1} (CO); nmr (100 MHz, $CDCl_3$) τ 9.10 (d, 6, CH_3), 7.83 (s, 6, CH_3CO), 7.20–7.80 (m, 1, CH), 6.60 (d, 1, COCH); mass spectrum M^+ 142; and **9** (R = *i*-C_3H_7): ir (liquid film) 1675 (CO), 1580 cm^{-1} (C=C); nmr (60 MHz, $CDCl_3$) τ 8.74 (d, 6, CH_3), 7.88 (s, 3, $CH_3C(O)C$=C), 7.76 (s, 3, CH_3CO), 5.60 (m, 1, CH), 4.58 (s, 1, C=CH); mass spectrum M^+ 142.

Preparation of 10.—To ethyl acetoacetate (110 mmol) in a mixture of 20 ml of ligroin and 20 ml of toluene was added, all at once, a solution of thallous ethoxide (100 mmol) in 30 ml of ligroin. A white precipitate formed, and the mixture was magnetically stirred under N_2 for *ca.* 30 min. After filtration and drying there was obtained 32 g (96%) of **10**, mp 90–91°, mass spectrum M^+ 334.

Alkylation of 10 with Alkyl Iodides. General Procedure.—A mixture of 50 mmol of **10** in 45 ml of the freshly distilled alkyl iodide was magnetically stirred and refluxed under a nitrogen atmosphere for the times indicated. The mixtures were then processed as described for the alkylations of **6**.

With Ethyl Iodide.—Admixture of the reagents resulted in cloudiness, but no solid particles were evident. Upon reflux (4 hr) the mixture turned yellow and TlI precipitated. After processing as described above, the yields (column D, 170°) were ethyl acetoacetate, 2%; **11** (R = C_2H_5), 80%; **12** (R = C_2H_5), 2%, and **13** (R = C_2H_5), 5%. Isolation (column A, 200°) provided materials with the following properties: ethyl acetoacetate: ir and nmr identical with authentic sample; **12** (R = C_2H_5): ir (liquid film) 1710, 1625 cm^{-1}; nmr (100 MHz, $CDCl_3$) τ 8.70 (m, 6, CH_3), 7.72 (s, 3, $CH_3C(O)$=C), 6.20 (q, 2, C=$C(O)CH_2$), 5.86 (q, 2, $COOCH_2$), 5.01 (s, 1, C=CH); mass spectrum M^+ 158; **11** (R = C_2H_5) (after molecular distillation at 87–88° (bath) (20 mm): ir (liquid film) 1740, 1720 cm^{-1}; nmr (60 MHz, $CDCl_3$) τ 9.07 (t, 3, $CCCH_3$), 8.73 (t, 3, $OCCH_3$), 8.11 (m, 2, CCH_2C), 7.78 (s, 3, CH_3CO), 6.65 (t, 1, CH), 5.79 (q, 2, OCH_2C); mass spectrum M^+ 158; **13** (R = C_2H_5): ir (liquid film) 1735, 1710 cm^{-1}; nmr (60 MHz, $CDCl_3$) τ 9.24 (t, 6, $CCCH_3$), 8.74 (t, 3, $OCCH_3$), 8.07 (q, 4, CCH_2C), 7.88 (s, 3, CH_3CO), 5.80 (q, 2, OCH_2C); mass spectrum M^+ 186.

With Isopropyl Iodide.—The initial cloudy mixture (no solid particles) turned yellow, and TlI precipitated upon refluxing the mixture (19 hr). After processing as above, the yields (column A, 165°) were 20% for **12** (R = *i*-C_3H_7) and 67% for **11** (R = *i*-C_3H_7). Separation (column A, 195°) afforded **12** (R = *i*-C_3H_7), which after molecular distillation at 86–88° (bath) (18 mm) displayed ir (liquid film) 1700 (C=O), 1615 cm^{-1} (C=C); nmr (100 MHz, $CDCl_3$) τ 8.74 (d, 6, $C(CH_3)_2$), 8.74 (t, 3, CH_3C), 7.75 (s, 3, $CH_3C(O)$=C), 5.89 (q, 2, CH_2), 5.62 (m, 1, OCH), 5.03 (s, 1, C=CH); and **11** (R = *i*-C_3H_7), after molecular distillation at 83–86° (bath) (20 mm) showed ir (liquid film) 1740, 1715 cm^{-1}; nmr (60 MHz, $CDCl_3$) τ 9.06 (q, 6, $C(CH_3)_2$), 8.75 (t, 3, $OCCH_3$), 7.81 (s, 3, CH_3CO), 7.3–7.8 (m, 1, CH), 6.83 (d, 1, COCH), 5.85 (q, 2, CH_2).

Registry No.—**2**, 36623-33-3; **3** (R = Me), 7715-08-4; **3** (R = Et), 36623-35-5; **4** (R = Et), 24378-06-1; **4** (R = *i*-Pr), 36623-37-7; **6**, 25955-51-5; **7** (R = Me), 815-57-6; **7** (R = Et), 1540-34-7; **7** (R = *i*-Pr), 1540-38-1; **8** (R = Me), 3142-58-3; **8** (R = Et), 15119-66-1; **9** (R = Et), 1540-24-5; **9** (R = *i*-Pr), 1540-25-6; **10**, 36623-46-8; **11** (R = Et), 607-97-6; **11** (R = *i*-Pr), 1522-46-9; **12** (R = Et), 998-91-4; **12** (R = *i*-Pr), 1540-21-2; **13** (R = Et), 1619-57-4.

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A Trimer of 1,3-Diphenylcyclobutadiene

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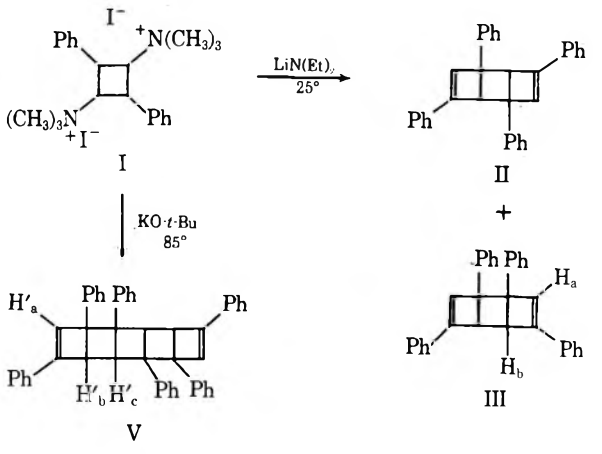
In an earlier paper[2] we reported the isolation of tricyclic compounds II and III from the reaction of 1,3-diphenyl-2,4-cyclobutanebis(trimethylammonium) iodide (I) with base; presumably a dimerization of 1,3-diphenylcyclobutadiene (IV) was involved (Chart I).[3]

CHART I

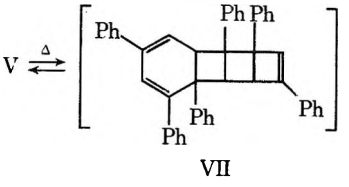


We now report on several minor products from the reaction: a trimer (V) of IV, a butadiene (VI), and an uncharacterized polymer of IV.

The trimer to which we assign structure V (1,2,5,7,8,-11-hexaphenylpentacyclo[8.2.0.0.^{2,9}0.^{3,8}0^{4,7}]dodeca-5,11-diene) was obtained by chromatography of the total reaction product on alumina. The fraction containing both compounds V and the cyclooctatetraene derived from III[2] was triturated with cold hexane, leaving V as a white residue. The elemental analysis and molecular weight determination led to the formula $C_{48}H_{36}$, a trimer of the elements of diphenylcyclobutadiene.

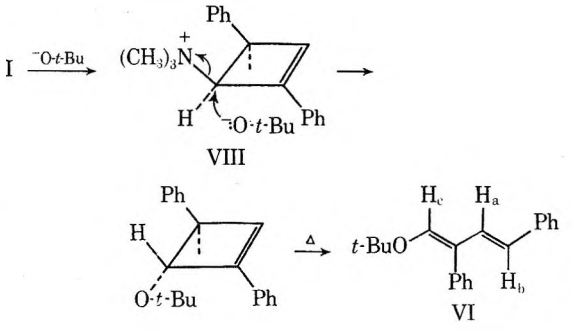
Compound V is thermally stable at room temperature, but at elevated temperatures in the solid state ($\geq$200°) it is quantitatively converted into 2 mol of 1,2,4-triphenylbenzene.[4] Pyrolysis experiments in sealed capillaries indicated intermediate species in the conversion but they were not characterized. Compound V is readily hydrogenated with the uptake of 2 molar equiv of hydrogen, indicating by inference four other units of unsaturation. The nmr spectrum shows vinyl signals at τ 3.82 (2 H, d, J = 2.5 cps), an allylic doublet at 6.54 (2 H, J = 2.5 cps), and a broad singlet for the methine hydrogens at 6.73 (2 H). The pair of doublets with weak 1,3 coupling (AX system) is similar to those found for dimer III[5] and they can be assigned to the a and b hydrogens of V. The lack of strong coupling is consistent with the dihedral angle between these protons of >70° as indicated by models. The ultraviolet maximum at 263 nm (log ϵ 4.59) is also consistent with structure V, which contains two phenylcyclobutene chromophores.[6]

Unlike dimer III, which readily isomerizes into the cyclooctatetraene form in solution ($t_{1/2}^{25°}$ = 12 hr),[2] compound V is stable under similar conditions. This difference may result from the fact that in III the thermal opening of one cyclobutane ring leads to a system with only a single σ bond to be cleaved to form the cyclooctatetraene and this σ bond is weakened by a double allylic interaction. Compound V, on the other hand, can undergo the initial ring opening (VII), but a further "unzipping" is not as facile as in III because of the strong bonds remaining to be cleaved. If each bond but the last is broken reversibly, a statistical factor would also favor the closed form of V.



(1)

The second compound isolated was assigned structure VI (1,3-diphenyl-4-*tert*-butoxy-1,3-butadiene). The formation of this butadiene can be accounted for by a displacement reaction on a ring atom of the cyclobutene intermediate VIII,[7] followed by a conrotatory ring opening of the product (eq 2).



(2)

The nmr spectrum of VI shows the expected aromatic multiplet at τ 2.3–3.0 (10 H), the *tert*-butyl protons as a singlet at 8.76 (9 H), a vinyl singlet corresponding to the isolated proton H_c at 3.28 (1 H), and an AB pair of doublets at 3.15 and 3.82 (1 H each) with a coupling constant of 16 cps (trans)[8] corresponding to protons H_a and H_b.[9] The infrared spectrum shows strong

(1) Author to whom all inquiries should be addressed.

(2) E. H. White and H. C. Dunathan, *J. Amer. Chem. Soc.*, **86**, 453 (1964).

(3) Dimers formed *via* cyclobutadienes have been extensively reported (see M. P. Cava and M. J. Mitchell, "Cyclobutadiene and Related Compounds," Academic Press, New York, N. Y., 1967, for references through 1966), but evidence indicates that in some cases other reaction paths are involved: E. K. G. Schmidt, L. Brener, and R. Pettit, *J. Amer. Chem. Soc.*, **92**, 3240 (1970), and M. Avram, I. G. Dinulescu, T. Marica, G. Matesson, E. Sliam, and C. D. Nenitzescu, *Chem. Ber.*, **97**, 382 (1964).

(4) In several runs using potassium *tert*-butoxide as base in the treatment of I, 1,2,4-triphenylbenzene was isolated directly as a reaction product.

(5) Compound III has its vinyl and allyl hydrogens at τ 3.30 and 6.20, respectively, with a coupling constant at 2.5 cps.[2]

(6) 1-Phenylcyclobutane has λ_{max} at 255 nm (log ϵ 4.02) [J. W. Wilt and J. D. Roberts, *J. Org. Chem.*, **27**, 3430 (1962)] and compound III, containing two phenylcyclobutene chromophores, has λ_{max} at 261 nm (log ϵ 4.57).[2]

(7) The chloride salt of VIII has been prepared and characterized.[2]

(8) *cis*-1,3-Diphenylbutadiene has been synthesized [M. H. Goodrow and T. L. Jacobs, *J. Org. Chem.*, **23**, 1653 (1958)], but the trans isomer has not been reported. The best model we have found for the absorption spectrum is 1,3-diphenyl-1,3-cyclohexadiene, which has its uv absorption maxima at 255 and 311 nm (log ϵ 4.39) (private communication from Professor G. F. Woods, University of Maryland).

(9) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959.

vinyl ether bands at 1630, 1260, and 1150 cm^{-1}.[10] A long-wavelength absorption at 304 nm (log ϵ 4.51) in the ultraviolet is consistent with the assigned structure and inconsistent with the presence of only styrene type chromophores.

In a few runs, a highly fluorescent polymer $(C_{16}H_{12})_n$ was also found. It melted sharply at ~273° and it was thermally stable to about 225°, but pyrolysis at 285° yielded 1,3,5-triphenylbenzene together with several other unidentified products.

Experimental Section

The nmr spectra were run on a Varian A-60 spectrometer with tetramethylsilane (TMS) as an internal standard. Ultraviolet spectra were determined on a Cary 14 spectrophotometer. Infrared spectra were taken in potassium bromide discs on either a Perkin-Elmer 337 or 521 spectrophotometer. Melting points were taken on a Kofler hot stage apparatus and are uncorrected.

1,2,5,7,8,11-Hexaphenylpentacyclo[8.2.0.0^{2,8}.0^{3,8}.0^{4,7}]dodeca-5,11-diene (V).—The crude product (8.0 g) from the potassium *tert*-butoxide driven elimination reaction of 25.0 g (43.4 mmol) of 1,3-diphenyl-2,4-cyclobutanebis(trimethylammonium) iodide (I)[2,11] was carefully chromatographed on an alumina column using increasing amounts of ether in benzene as the eluent. From the early fractions (0.5–10% ether), 0.369 g (1.3 mmol, 3%) of butadiene VI was isolated; from the middle fractions (15–19% ether), 3.46 g (8.4 mmol, 39.2%) of the cyclooctatetraene formed from II was obtained; and from the fractions with 20–25% ether, 2.55 g (6.3 mmol, 28%) of the cyclooctatetraene derived from III containing some V was obtained. Recrystallization of this material from methylene chloride–ethanol followed by trituration of the solid with cold hexane gave a residue of 0.54 g (0.89 mmol, 2.0%) of compound V as white microcrystals. In other runs, yields of 0–2% were obtained. Crystallization of V from methylene chloride–ethanol gave tiny white plates: mp 220.5° dec; uv λ_{max}^{ether} 263 nm (log ϵ 4.59), 255 sh (4.56), 271 (4.56), 285 sh (4.20), 293 (3.60); nmr, see text.

Anal. Calcd for $C_{48}H_{36}$: C, 94.08; H, 5.92; mol wt, 612.8. Found: C, 94.08; H, 5.81; mol wt, 608 (Signer–Barger).

Pyrolysis of Compound V.—Compound V (38.89 mg, 0 0636 mmol) was sublimed at 200° (15 μ). The total sublimate was then carefully washed from the cold finger of the sublimator and the solvent was removed to give 39.5 mg (0.129 mmol, 101%) of 1,2,4-triphenylbenzene. Ultraviolet and infrared comparisons as well as melting points and mixture melting points proved the identity of the product. Thin layer chromatography (silica gel) using 1:4 benzene–petroleum ether (bp 30–60°) gave a single spot, R_f 0.46.

Small amounts of the trimer V were heated in evacuated capillaries at various temperatures for different time intervals to detect possible intermediates. At 155° for 15 min, no change was found by tlc but at 180°, three compounds were observed: a possible intermediate at R_f 0.22, starting material V, and 1,2,4-triphenylbenzene. At 240° for 30 hr, only 1,2,4-triphenylbenzene was detected.

Hydrogenation of Compound V.—V (25 mg, 0.041 mmol) was hydrogenated in 5 ml of ethyl acetate containing 20 mg of prereduced 10% Pd/C. Uptake of hydrogen (corrected) was 1.6 equiv in 15 min and 1.95 equiv in 1 hr. At the end of 17 hr, no additional hydrogen had been absorbed.

1,3-Diphenyl-4-*tert*-butoxy-1,3-butadiene (VI).—From the earliest fractions of the chromatography above (5–10% ether in hexane), 369 mg (1.3 mmol, 3.0%) of compound VI was isolated after removal of the solvent. Crystallization from isopentane gave colorless needles: mp 101–103°; uv λ_{max}^{MeOH} 230 nm (log ϵ 4.12) and 303 (4.51); ir 3030 (w), 2980 (s), 2940 (w), 1630 (s), 1260 (s), 1150 (vs), and 1105 cm^{-1} (s). A qualitative test for nitrogen was negative.

Anal. Calcd for $C_{20}H_{22}O$: C, 86.28; H, 7.97. Found: C, 86.33; H, 8.03.

Miscellaneous Products.—In several runs, a highly fluorescent white solid was isolated in the chromatography fractions immediately following the elution of 1,3,5,7-tetraphenylcyclooctatetraene (derived from II) with yields up to 1.5% (based on a trimeric structure). After crystallization from dichloromethane–ethanol to a constant melting point, white plates were obtained, mp 273.0–273.5°. The ultraviolet spectrum had a single maximum at 267 nm (log ϵ 4.32 based on the molecular weight for a trimer, 612.8).

Anal. Calcd for $(C_{16}H_{12})_n$: C, 94.08; H, 5.92. Found: C, 94.10; H, 6.02; mol wt, 426, 508 (micro Rast).

The compound sublimed unchanged at 225° (15 μ) but at 285° it was converted into at least four different compounds; one was identified as 1,3,5-triphenylbenzene by tlc (color formation and R_f at 0.48; silica gel with 1:4 benzene–petroleum ether).

In later chromatographic fractions using solvent containing more than 25% ether, extremely viscous, highly colored oils remained on evaporation of the solvent. In the infrared, these oils showed strong carbonyl absorption at 1700–1750 cm^{-1}. A random fraction from one run was chosen for analysis (100% ether fraction).

Anal. Found: C, 90.70; H, 6.08; N, 0.00.

Registry No.—IV polymer, 36812-97-2; V, 36789-10-3; VI, 36789-11-4.

Acknowledgment.—We thank the Petroleum Research Fund administered by the American Chemical Society (PRF 328-A) for support of this work and Dr. J. D. Rose (Imperial Chemical Industries Ltd., Manchester, England) for a generous sample of 1,2,4-triphenylbenzene.

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 115.

(11) R. L. Stern, Ph.D. Thesis, The Johns Hopkins University, 1963; Earl W. Friend, Jr., Ph.D. Thesis, The Johns Hopkins University, 1967.

Thallium in Organic Synthesis. XXXI. Oxidative Cleavage of Glycols by Thallium Salts[1]

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Glycol cleavage reactions are of considerable utility in both synthesis and degradation, and from a practical point of view periodate and lead(IV) acetate are generally the oxidants of choice.[2,3] A wide range of oxidants has been investigated with respect to glycol cleavage and Rigby has defined the efficiency of such reagents as oxidants "which concern elements which (a) can reasonably be envisaged as capable of forming a preliminary cyclic compound with the glycol, and (b) exist in two stable oxidation states which are two valence units apart, the lower representing a substance which is not an oxidizing reagent under ordinary conditions [Pb(II) or Bi(III)] or which no longer fulfills condition a (the IO_3^- ion)."[4] According to this definition, thallium(III) salts, which are isoelectronic with lead(IV) salts, should function as efficient glycol

(1) Part XXX: E. C. Taylor, R. L. Robey, and A. McKillop, *Angew. Chem.*, **84**, 60 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 48 (1972).

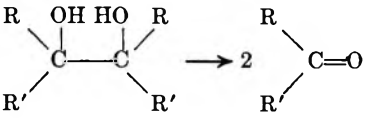
(2) A. S. Perlin in "Oxidation: Techniques and Applications in Organic Synthesis," R. L. Augustine, Ed., Marcel Dekker, New York, N. Y., 1969, pp 189–212.

(3) C. A. Bunton in "Oxidation in Organic Chemistry," K. B. Wiberg, Ed., Academic Press, New York, N. Y., 1965, pp 367–407.

(4) W. Rigby, *J. Chem. Soc.*, 1907 (1950).

TABLE I

OXIDATIVE CLEAVAGE OF GLYCOLS WITH THALLIUM SALTS



Registry no.	Compd	R	R′	Oxidant[a]	Aldehyde or ketone yield, %[b]
492-70-6	1	H	C_6H_5	A	61
5132-85-4	2	CH_3	C_6H_5	A	63
464-72-2	3	C_6H_5	C_6H_5	A	91
				B	85
2002-32-8	4	C_6H_5	2-$CH_3C_6H_4$	A	83
				B	70
808-12-8	5	C_6H_5	4-$CH_3C_6H_4$	A	86
				B	83
912-17-4	6	C_6H_5	4-ClC_6H_4	A	84
				B	90
3073-51-6	7	Fluorenone pinacol		A	89
				B	95
6272-59-9	8	Xanthone pinacol		A	91
				B	90

[a] A = $Tl(NO_3)_3 \cdot 3H_2O/CH_3COOH$; B = $TlOC_2H_5/C_2H_5OH$. [b] Based on pure redistilled or recrystallized material.

cleavage reagents, since both of the criteria a and b used by Rigby are satisfied. Furthermore, the mechanisms of oxidation postulated for lead(IV) acetate glycol cleavage are, theoretically, equally applicable to thallium(III) salts. There is only one reference in the literature to the reactions of glycols with a thallium(III) salt. Kabbe reported that treatment of glycols with thallium(III) acetate resulted in complete reduction of the inorganic reagent. He was, however, unable to isolate any products of oxidation of the glycols.[5]

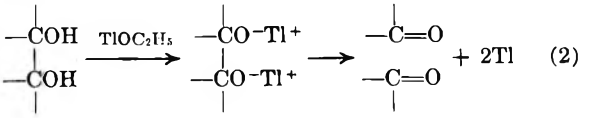
We have examined the reactions of a wide variety of glycols with thallium(III) acetate, trifluoroacetate (TTFA), and nitrate (TTN) under different reaction conditions and have found that certain types of glycols are cleaved smoothly with all three salts. The most efficient reagent system in terms of product yield and rate of reaction was a solution of TTN in acetic acid, but glycol cleavage occurred only with substrates which contained vicinal aromatic substituents. Thus, irrespective of the stereochemistry of the hydroxyl groups, no oxidation was observed with the following compounds: ethylene glycol, pinacol, pinacolone pinacol, diethyl tartrate, 2,3-dihydroxy-2-methyl-3-phenylbutane, bicyclopentyl-1,1′-diol, bicyclohexyl-1,1′-diol, *cis*- and *trans*-1,2-dihydroxycyclohexane, 1,2-dihydroxycyclododecane, and *cis,exo*-2,3-dihydroxycamphane. With substrates which contained at least two aromatic substituents, glycol cleavage took place smoothly. Yield data are summarized in Table I.

It has been known for over 30 years that treatment of certain tetraaryl-substituted glycols with alkali metal alkoxides in ether–benzene solution results in carbon–carbon bond cleavage and formation of equal quantities of the corresponding ketone and secondary alcohol (eq 1).[6] These reactions, which were originally

$$Ar_2C(OH)-C(OH)Ar_2 \longrightarrow Ar_2C{=}O + Ar_2CHOH \quad (1)$$

thought to be free radical in nature, have recently been reexamined by Schenck and his coworkers and shown to proceed by both ionic and free-radical pathways.[7] We have found that thallium(I) ethoxide in ethanol reacts smoothly with tetraaryl-substituted glycols, but the reactions are significantly different from those of the alkali metal alkoxides. Thus, bond cleavage occurs virtually instantaneously at 50° in ethanol, thallium(I) ethoxide is reduced quantitatively to thallium metal, and the corresponding diaryl ketones are formed in high yield. Conversion data are summarized in Table I.

Unlike the reactions with other metal alkoxides, very little (0–14%) of the corresponding benzhydrol was formed in the thallium(I) oxidations. Conversion of the glycol into the ketone represents a two-electron oxidation, while reduction of thallium(I) to thallium(0) is a one-electron process. We suggest that the most probable mechanism is formation of the dithallium salt followed by rapid, concerted radical decomposition to products (eq 2). Attempts to de-



$$-COH \\ -COH \xrightarrow{TlOC_2H_5} -CO\text{-}Tl^+ \\ -CO\text{-}Tl^+ \longrightarrow -C{=}O \\ -C{=}O + 2Tl \quad (2)$$

tect radical intermediates, however, were unsuccessful. In none of the reactions were the characteristic red-blue colorations due to ketyl radicals observed,[6] and no evidence for radical species was obtained by esr spectroscopy. Moreover, acrylamide is an efficient radical trap,[8] and addition of this compound to glycol fission reactions known to proceed by free-radical pathways has been shown to result in almost total suppression of oxidation.[8] When acrylamide was added to a mixture of thallium(I) ethoxide and benzopinacol, however, the reduction in yield of benzophenone was only 13%. Consequently, it appears that if radical

(5) H.-J. Kabbe, *Justus Liebigs Ann. Chem.*, **656**, 204 (1962).
(6) W. E. Bachmann, *J. Amer. Chem. Soc.*, **55**, 355 (1933).
(7) G. O. Schenck, G. Matthias, M. Pape, M. Cziesla, G. von Bunau, E. Roselius, and G. Koltzenburg, *Justus Liebigs Ann. Chem.*, **719**, 80 (1968).
(8) W. S. Trahanovsky, L. H. Young, and M. H. Bierman, *J. Org. Chem.*, **34**, 869 (1969).

intermediates are involved they must be extremely short lived, and in no sense "free" radicals.

Experimental Section[9]

Starting Materials.—Compounds 1 and 3 (Table I) were commercial samples and were purified prior to use. Compounds 2 and 4–8 were prepared by bimolecular coupling of the appropriate ketones with anhydrous magnesium iodide according to the procedure described by Gomberg and Bachmann.[10]

General Procedure for Glycol Cleavage with TTN.—A mixture of 2.74 mmol of the glycol and 2.74 mmol of TTN in 25 ml of acetic acid was stirred and heated at 75° for 30 min. The reaction mixture was then cooled, diluted with 50 ml of water, and extracted with chloroform, and the extracts were washed with saturated aqueous sodium bicarbonate solution. Evaporation of the dried chloroform extract gave the crude product, which was freed from traces of inorganic thallium salts by passage through a short column of alumina using chloroform as eluent. The pure ketone was then obtained by crystallization or distillation of the concentrated eluent.

General Procedure for Glycol Cleavage Using Thallium(I) Ethoxide.—Thallium(I) ethoxide (2.74 mmol) was added to a suspension of 2.74 mmol of the glycol in 25 ml of ethanol and the mixture was gently heated to about 50°. After a few seconds thallium metal was deposited. After 5 min excess powdered potassium iodide was added to remove traces of thallium(I) salts as thallium(I) iodide. The reaction mixture was filtered concentrated, and passed through a short column of alumina using chloroform as eluent. Concentration of the eluate gave the crude product, which was purified as described above.

Direct nmr examination of the crude reaction product obtained after chromatography showed in some cases a small peak at *ca.* τ 4.5 due to the methine proton of the corresponding benzhydrol. The amount of this by-product was easily determined from the relative integrations of the aromatic and methine proton areas. Standard control experiments established that benzhydrols are oxidized to benzophenones only very slowly by thallium(I) ethoxide; the alcohol did not therefore serve as precursor to the ketone.

Registry No.—$Tl(NO_3)_3$, 13746-98-0; $TlOC_2H_5$, 20398-06-5.

(9) Melting points were determined on a Kofler hot-stage melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model PE 237 grating infrared spectrophotometer using the normal liquid film and Nujol mull techniques. Nuclear magnetic resonance spectra were recorded in carbon tetrachloride solution, using tetramethylsilane as internal standard, on a Perkin-Elmer R12 60-MHz spectrometer.

(10) M. Gomberg and W. E. Bachmann, *J. Amer. Chem. Soc.*, **49**, 236 (1927).

Ethyl 3-Oxo-2,2-dimethylcyclobutanecarboxylate

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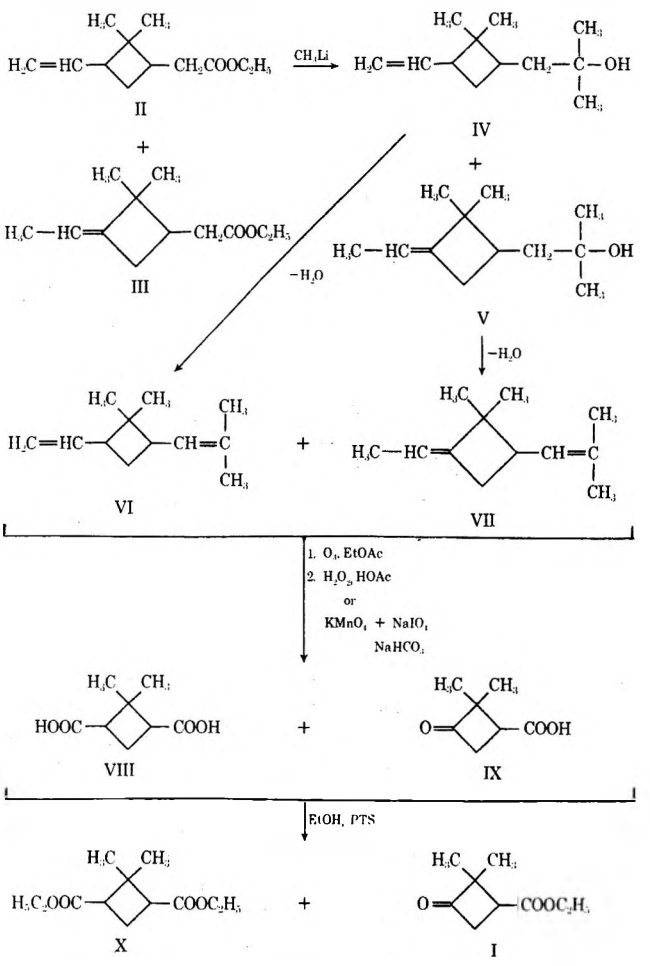
In connection with work toward the synthesis of bridgehead-substituted bicyclobutanes[1] as monomers for polymers containing cyclobutane rings, the synthesis of ethyl 3-oxo-2,2-dimethylcyclobutanecarboxylate (I) from readily accessible α-pinene and its degradation products was investigated.

A mixture of ethyl pinenates [ethyl 2,2-dimethyl-3-vinylcyclobutaneacetate (II) and ethyl 2,2-dimethyl-3-ethylidene cyclobutaneacetate (III)] described by Park, *et al.*,[2] formed the starting material for the synthesis of ethyl 3-oxo-2,2-dimethylcyclobutanecarboxylate. Reaction of a 60:40 mixture of ethyl pinenates with methyllithium afforded a mixture of 1-(2-methyl-2-hydroxypropyl)-3-vinyl-2,2-dimethylcyclobutene (IV) and 1-(2-methyl-2-hydroxypropyl)-3-ethylidene-2,2-dimethylcyclobutane (V). The mixture of alcohols was dehydrated using anhydrous oxalic acid to give a mixture of 1-(2,2-dimethylvinyl)-3-vinyl-2,2-dimethylcyclobutane (VI) and 1-(2,2-dimethylvinyl)-3-ethylidene-2,2-dimethylcyclobutane (VII). Oxidation of this mixture with sodium periodate–potassium permanganate[3] as well as by ozonolysis followed by cleavage of the ozonide with hydrogen peroxide and acetic acid afforded a mixture of norpinic acid (VIII) and 3-oxo-2,2-dimethyl-



cyclobutanecarboxylic acid (IX), which was esterified with ethanol and *p*-toluenesulfonic acid to give a mixture of diethyl norpinate (X) and ethyl 3-oxo-2,2-dimethylcyclobutanecarboxylate (I). Separation was effected by fractional distillation and the keto ester was characterized as its 2,4-dinitrophenylhydrazone derivative.

Experimental Section

Mixture of 1-(2-Methyl-2-hydroxypropyl)-3-vinyl-2,2-dimethylcyclobutane (IV) and 1-(2-Methyl-2-hydroxypropyl)-3-ethylidene-2,2-dimethylcyclobutane (V).—Methyllithium was prepared by the addition of methyl iodide (42.6 g, 0.3 mol) in anhydrous ether (75 ml) to lithium wire (4.2 g, 0.6 g-atom) in anhydrous ether (150 ml). The lithium was contained in a three-necked

(1) H. K. Hall, Jr., C. D. Smith, E. P. Blanchard, Jr., S. C. Cherkofsky, and J. B. Sieja, *J. Amer. Chem. Soc.*, **93**, 121 (1971).

(2) J. D. Park, R. L. Settine, and G. W. Hedrick, *J. Org. Chem.*, **27**, 902 (1962).

(3) R. V. Lemiux and E. Von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955).

500-ml flask equipped with mechanical stirrer, Dry Ice condenser, nitrogen inlet–outlet, and an addition funnel. The addition of methyl iodide to lithium was performed at ice–salt temperature in about 2 hr. After an additional 2 hr all lithium had reacted. The methyllithium solution was cooled in an acetone–Dry Ice bath and a solution of a 60:40 mixture of ethyl 2,2-dimethyl-3-vinyl- and ethyl 3-ethylidene-2,2-dimethylcyclobutaneacetate (19.6 g, 0.1 mol) in anhydrous ether (25 ml) was added dropwise with rapid stirring. After addition was complete, the mixture was allowed to warm to room temperature and stirred in a nitrogen atmosphere overnight. The reaction slurry was poured onto 300 g of crushed ice containing 100 ml of concentrated ammonia. The mixture was stirred rapidly for 1 hr. The ether layer was separated and the aqueous layer was extracted with 2 × 100 ml of ether. The combined ether solutions were washed with water and dried over anhydrous sodium sulfate. Removal of ether under reduced pressure yielded a colorless liquid (17.5 g, 96% yield). Distillation of this liquid afforded 16.3 g, bp 58° (0.4 mm). The infrared spectrum of this liquid exhibited hydroxyl absorption at 3400 cm^{-1} and absorptions due to *gem*-dimethyl groups at 1355 and 1375 cm^{-1}; the nmr ($CDCl_3$) was consistent for the mixture of alcohols.

Anal. Calcd for $C_{12}H_{22}O$: C, 79.05; H, 12.16. Found: C, 78.80; H, 12.01.

Mixture of 1-(2,2-Dimethylvinyl)-3-vinyl-2,2-dimethylcyclobutane (VI) and 1-(2,2-Dimethylvinyl)-3-ethylidene-2,2-dimethylcyclobutane (VII).—To a mixture of alcohols (12.0 g) contained in a 50-ml distilling flask was added anhydrous oxalic acid (4.5 g). The flask was fitted with a 4 by 0.5 ft Vigreux column equipped with distillation head, condenser, and receiving flask. The system was connected to the water aspirator and the pressure was held at 45–50 mm. The reaction flask was heated and the water began to distil. After water ceased to distil the reaction flask was cooled and the residue in the pot was taken up in ether. The ether extract was washed with sodium bicarbonate solution and then with water and finally dried over anhydrous sodium sulfate. Removal of ether and distillation of the residual liquid afforded colorless liquid, 10.3 g (94% yield), bp 94–96° (42 mm). The infrared spectrum exhibited no hydroxyl absorption and had bands at 3050 (m, vinyl CH), 1668 (m, C=C), and 1375 and 1355 cm^{-1} (s, *gem*-dimethyl doublet).

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.64; H, 12.48.

Ozonolysis of This Mixture of Diolefins (VI and VII).—A mixture of diolefins (9.0 g) was taken up in 150 ml of ethyl acetate and ozonized oxygen was passed through the solution at 0° for 2 hr until the exit gas turned acidified potassium iodide solution brown. To this solution was added acetic acid (15 ml) and hydrogen peroxide (30%, 10 ml) and this mixture was allowed to stand at room temperature overnight. The reaction mixture was taken up in ether and the acidic components were extracted with 2 *N* Na_2CO_3 solution. The ether layer yielded a neutral fraction of 3.2 g, whereas acidification of the sodium carbonate extract with sulfuric acid and extraction with ether gave a viscous oil, 4.5 g. The infrared spectrum of this oil exhibited carboxylic acid absorption at 2900–2550 cm^{-1} (broad) and two different bands due to keto absorption as well as the acid carbonyl. On standing with a small amount of ether this oil afforded 1.2 g of white powder, mp 160–163° (mp of *cis*-norpinic acid ~170°). The residual oil in its ir exhibited two different carbonyls at 1785 and 1740 cm^{-1}.

Ethyl 3-Oxo-2,2-dimethylcyclobutanecarboxylate (I) and Diethyl Norpinate (X).—The mixture of diolefins (11.1 g, 0.068 mol) in *tert*-butyl alcohol (50 ml) was added dropwise to a stirred mixture of sodium bicarbonate (33.6 g, 0.39 mol), sodium periodate (150 g, 0.069 mol), and potassium permanganate (3 g) in water (1000 ml). After this mixture was stirred for 48 hr, it was acidified with dilute sulfuric acid and filtered to remove insoluble salts and the oxidate was extracted with ether. The ether solution was extracted with 2 *N* Na_2CO_3 solution. The ether layer yielded a neutral 2.2 g, identified as unreacted starting material, whereas acidification of the sodium carbonate extract with sulfuric acid and extraction with ether gave viscous oil (5.8 g). The infrared spectrum of this oil exhibited absorptions due to carboxylic acid and two carbonyl absorptions at 1780 and 1730 cm^{-1}. This crude acid (4.5 g) was dissolved in benzene (75 ml) and esterified with ethanol using *p*-toluenesulfonic acid (0.50 g) as catalyst. Benzene was removed and the crude product was taken up in ether. The ether solution was washed with sodium carbonate solution and then with water and finally dried over anhydrous sodium sulfate. Removal of ether afforded brownish colored liquid (4.2 g). The infrared spectrum exhibited two different carbonyl absorptions at 1790 and 1735 cm^{-1}. This liquid (3.65 g) was distilled to give two main fractions: (1) 1.02 g of ethyl 3-oxo-2,2-dimethylcyclobutanecarboxylate (I), bp 57–60° (0.3 mm), and (2) 2.20 g of diethyl norpinate (X), bp 86–89° (0.3 mm).

Ethyl 3-oxo-2,2-dimethylcyclobutanecarboxylate (I) in its ir spectrum exhibited two carbonyl absorptions at 1805 (keto) and 1755 cm^{-1} (ester). Its nmr spectrum ($CDCl_3$) exhibited signals at δ 4.1 (octet, 2 H, $-CH_2-$), 3.4 (m, 2 H, $CH_2C{=}O$), 2.2–1.6 [m, 1 H, $-CHC(=O)O$], and 1.1–1.4 (m, 9 H, *gem*-methyls, $-CH_3$).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.53; H, 8.24. Found: C, 64.01; H, 9.10.

These analyses indicates that the keto ester may contain a small amount of the diester.

The 2,4-dinitrophenylhydrazone was obtained as a yellow precipitate, mp 118–120°, which was purified by chromatography on alumina, using benzene as an eluent. The yellow band was eluted with benzene. After removal of benzene, crystallization from ethanol gave a yellowish powder, mp 122–123°.

Anal. Calcd for $C_{15}H_{18}N_4O_6$: C, 51.43; H, 5.14; N, 16.00. Found: C, 51.68; H, 5.37; N, 15.81.

Registry No.—I, 36611-75-3; I DNP, 36611-76-4; IV, 36611-77-5; V, 36611-78-6; VI, 36611-79-7; VII, 36611-80-0.

Acknowledgments.—This is a partial report of the work done under the contract with the Western and Southern Utilization Research and Development Divisions, Agricultural Research Service, U. S. Department of Agriculture, and authorized by the Research and Marketing Act of 1946. The contract is supervised by Dr. Glen Hedrick of Naval Stores Research Laboratory, Olustee, Fla. The authors wish to thank Dr. Glen Hedrick for a generous sample of the mixture of ethyl pinenates which was used in these experiments.

Ditetrazolylbenzene Dianions. Potential Precursors of the Phenylenedimethylenes[1]

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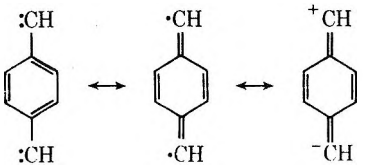
Arylmethylenes have received attention from the synthetic[2] and theoretical[3] viewpoints. Of particular interest are arylpolycarbene systems, few of which have as yet been generated.[3] Molecule **1** (*p*-phenylenedimethylene), for example, presents intriguing possibilities with regard to electronic distribution,



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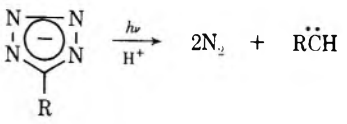
(1) This research was supported by grants from the Petroleum Research Fund, administered by the American Chemical Society, and the Research Foundation of the City University of New York.

(2) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, Chapter 5.

(3) A. M. Trozzolo, *Accounts Chem. Res.*, **1**, 329 (1968).

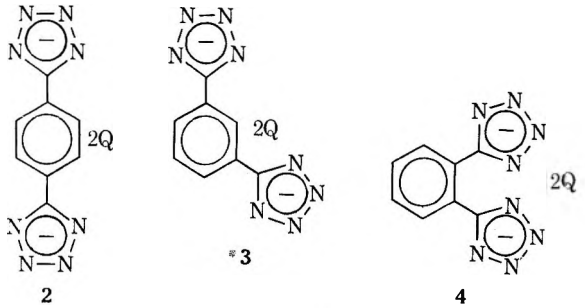
configuration, and consequent chemical reactivity. Attempts to prepare structures such as **1** or its isomers have been hindered by lack of suitable precursors. Convenient starting materials amenable to the requisite low-temperature esr, emission, and absorption spectroscopic investigations have not been generally available.

Recently Griffin and coworkers demonstrated the feasibility of 1,4-bis(2,3-diphenyloxiranyl)benzene as a new precursor for *p*-phenylene bis(phenylmethylene).[4] Photolysis of the bisoxirane in methanol produced the bismethyl ether (OH insertion product) and benzaldehyde, indicating a stepwise fragmentation through carbene intermediates. We report similar evidence for a photolytic route to the simplest aryldicarbenes, the isomeric *o*-, *m*-, and *p*-phenylenedimethylenes.



Previous work has shown that 5-phenyltetrazolide anion photolyzes with loss of 2 equiv of nitrogen to phenylcarbene.[5,6] This mode of photolysis is general and has served as a source of several monosubstituted carbenes.[7] It therefore appeared likely that under suitable conditions dicarbenes could be produced by irradiation of ditetrazolide anions.

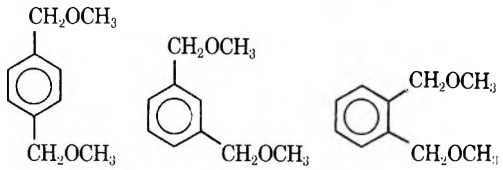
The required 1,2-, 1,3-,[8] and 1,4-di(5-tetrazolyl)-benzenes[9] were readily obtained by the addition of azide to the corresponding dicyanobenzenes. Treatment of the di(5-tetrazolyl)benzenes with 2 equiv of sodium methoxide gave the bissodium salts (**2a**, **3a**, **4a**); similarly, the bistetrabutylammonium salts (**2b**, **3b**, **4b**) were prepared with tetrabutylammonium hydroxide. The latter, owing to their appreciable solubility, were investigated in anticipation of synthetic and spectroscopic work in less polar organic solvents.



2 **3** **4**

a, Q = Na^+
b, Q = $N^+(C_4H_9)_4$

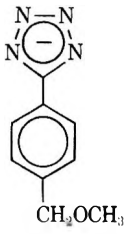
Deoxygenated methanol solutions (0.020–0.017 *M*) of the salts (**2**, **3**, **4**) irradiated with 254-mμ light produced 4 equiv of nitrogen per ditetrazolide anion. The simple work-up (removal of solvent, dilution with water, and ether extraction) afforded satisfactory yields of essentially pure product, the corresponding α,α′-bismethoxyxylenes (**5**, **6**, **7**). The products were



5 **6** **7**

identified by comparison (ir and vpc retention time) with authentic samples. Identical results were obtained with either the sodium or the tetrabutylammonium salts.

Formation of methyl ethers by insertion into methanol has frequently served as a diagnostic for carbene formation.[10] However, it is unlikely that dicarbenes were present in the room-temperature photolyses described above. These reactions most probably proceeded in a stepwise fashion, first giving α-methoxytolyl-5-tetrazolides (*e.g.*, **8**) *via* carbene intermediates.



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Subsequent photolysis through a second monocarbene intermediate would then result in the observed products. Nevertheless, as Griffin has pointed out,[4] the possibility of observing dicarbenes exists in rigid matrices at −196° or lower, where bimolecular reactions are excluded. The results obtained indicate that phenylenedimethylenes are probable intermediates under such conditions. Spectroscopic observation will depend on the inherent lifetimes of these species. Work in this area and synthetic applications of di(5-tetrazolyl)benzene dianion photolysis are in progress.

Experimental Section

Ir spectra were obtained on 5% chloroform solutions with a Perkin-Elmer 700 spectrophotometer. Vpc analyses were made with a Varian Aerograph Model 700 using a 5 ft, 3% SE-30 column at 140° and He carrier gas.

1,2-Di(5-tetrazolyl)benzene.—A suspension of 25.6 g (0.20 mol) of *o*-dicyanobenzene, 28.6 g (0.44 mol) of sodium azide, and 7.0 g of ammonium chloride in 200 ml of anhydrous DMF was stirred and maintained at 110–115° for 4 days. Solvent was removed under reduced pressure. The residue was dissolved in 220 ml of water and acidified with concentrated hydrochloric acid. Caution: HN_3 was evolved. Following aspiration (20 min) to remove HN_3, the white precipitate was collected and washed with water. Recrystallization from 60% aqueous methanol gave 26.2 g (61%) of 1,2-di(5-tetrazolyl)benzene hemihydrate, mp 233–234° dec. Five additional crystallizations gave the analytical sample, mp 236–237° dec.

Anal. Calcd for $C_8H_6N_8 \cdot {}^1/_2H_2O$: C, 43.05; H, 3.16; N, 50.20; mol wt, 223.2. Found: C, 43.19; H, 3.10; N, 50.28; mol wt, 226.6 (titration).

Salts of Di(5-tetrazolyl)benzenes.—Ten millimoles of the di(5-tetrazolyl)benzene suspended in 100 ml of methanol was

(4) N. R. Bertoniere, S. P. Rowland, and G. W. Griffin, *J. Org. Chem.*, **36**, 2956 (1971).

(5) (a) P. Scheiner, *J. Org. Chem.*, **34**, 199 (1969); (b) P. Scheiner, *Tetrahedron Lett.*, 4863 (1969).

(6) Substituted tetrazoles photolyze in an entirely different manner. See P. Scheiner and J. F. Dinda, *Tetrahedron*, **26**, 2619 (1970), and ref 5a.

(7) P. Scheiner, *Tetrahedron Lett.*, 4489 (1971).

(8) R. Huisgen, C. Axen, and H. Seidl, *Chem. Ber.*, **98**, 2966 (1965).

(9) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Amer. Chem. Soc.*, **80**, 3908 (1958).

(10) W. Kirmse, L. Horner, and H. Hoffman, *Justus Liebigs Ann. Chem.*, **614**, 19 (1958).

treated with 20 mmol of sodium methoxide or 20 mmol of tetrabutylammonium hydroxide (25% in methanol). The resulting colorless solution was evaporated under reduced pressure to give the salt. The sodium salts (**2a**, **3a**, **4a**) are white, microcrystalline solids melting above 300°. The tetrabutylammonium salts are hygroscopic but may be recrystallized with difficulty from ethyl acetate–hexane mixtures. Unpurified salts were used for the photolytic work.

Photolysis. General Procedure.—A solution of 2.0–2.5 mmol of the bis salt in 100–120 ml of methanol was placed in a cylindrical quartz tube fitted with a purging inlet and an outlet connected to a gas buret. Purified nitrogen was passed through the solution (*ca.* 20 min), and the reaction tube and gas buret were closed under a nitrogen atmosphere. The magnetically stirred solution was irradiated (254 mμ) in a Rayonet Chamber reactor until greater than 65% reaction, as measured by evolved nitrogen. Photolyses ran from 48 to 80 hr.

After removal of methanol under reduced pressure, the resulting paste or oil was suspended in 20 ml of water and extracted with three 15-ml portions of diethyl ether. The combined extracts were washed with saturated sodium chloride solution (dilute HCl washing was included with **2b**, **3b**, **4b**), dried ($MgSO_4$), and evaporated to give the product. Yields of α α′-bismethoxyxylenes ranged from 85% (**5**, **6**) to 45% (**7**). Only trace amounts of additional products were detected by vpc.

α,α′-Bismethoxyxylenes (**5**, **6**, **7**).—Compound **5** was purchased (Aldrich Chemical Co.). Compounds **6**[11] and **7**[12] were prepared by conventional Williamson synthesis from 1,3- and 1,2-bischloromethylbenzene and sodium methoxide in methanol.

Registry No.—**2a**, 36631-14-8; **2b**, 36608-46-5; **3a**, 36608-47-6; **3b**, 36608-48-7; **4a**, 36608-49-8; **4b**, 36631-38-6; 1,2-di(tetrazolyl)benzene, 36631-39-7.

(11) F. G. Mann and F. H. C. Stewart, *J. Chem. Soc.*, 2819 (1954).
(12) L. A. Errede, U. S. Patent 3,242,205 (Cl 260-475) (March 22, 1966); S. Murahashi, *Sci. Pap. Inst. Phys. Chem. Res., Tokyo*, **30**, 180 (1936).

A Novel Photochemical Reaction of *p*-Benzoquinone with a Nitroalkene[1]

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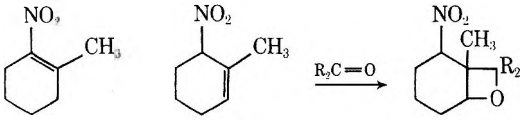
The chromophoric resemblance of nitro olefins to unsaturated ketones makes them potentially interesting substrates in photochemical reactions. Yet only few studies on the photochemical behavior of nitro compounds are available.[2] In a study of the properties of vinyl and allyl nitro olefins (*i.e.*, **1** and **2**), we examined their photochemical lability as well as their reactions with carbonyl compounds leading to possible oxetan formation (*i.e.*, **2** → **3**).

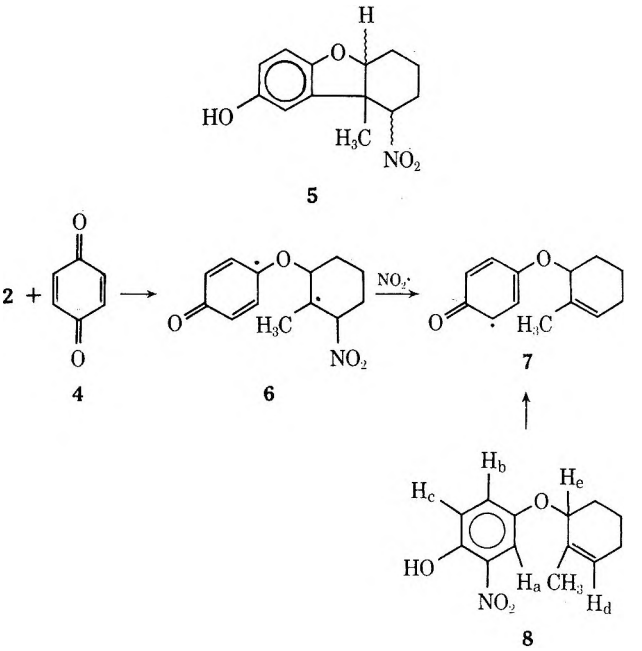


1 **2** **3**

Irradiation of a mixture of **1** and **2** at 3660 Å led to isomerization of the vinyl to the allyl nitro isomer (**1** → **2**) and formation of polymer. When nitro olefin **2** was irradiated in deoxygenated benzene solution in the presence of *p*-benzoquinone (**4**) (either a Hanovia 450-W medium-pressure lamp with a Pyrex immersion well or a Rayonet reactor using 3100- or 3600-Å lamps was used), a yellow-orange product was found by tlc. Separation from excess *p*-benzoquinone and **2** yielded, after column chromatography on silica gel, a yellow-orange solid, mp 57–58°, in *ca.* 4% yield (ignoring recovered nitro olefin). The analysis and mass spectrum were consistent with a 1:1 adduct but the other spectral properties showed that the product was not the expected oxetan.

Although it is well known that *p*-benzoquinone reacts with olefins such as cyclohexene to form isolable oxetans,[3] several factors limit the generality of this reaction.[4] One factor is the triplet energy of the olefinic component, which is expected to be low in the case of **1** or **2**; another is a steric factor during ring closure of intermediate **6**. No reaction was observed even when benzophenone was irradiated with **2**.

The nmr spectrum of the 1:1 photoadduct showed three aromatic protons which were in a 1,2,4 relationship [τ 2.45 (d, J = 3 Hz, H_a deshielded by $-NO_2$), 2.77 (q, J = 3 and 10 Hz, H_b), 3.00 (d, J = 10 Hz, H_c)]. A dienone–phenol type rearrangement to yield **4** was ruled out because the phenolic proton occurs at τ −0.18, indicating intramolecular hydrogen bonding. Further, one vinyl proton (H_d) is present (τ 4.32) and the methyl singlet at τ 8.25 is characteristic of a methyl group on a double bond. The allylic proton α to the ether oxygen (H_e) appears at τ 5.47. The infrared spectrum (KBr disk) defined one major structural feature. The nitro group is still present, but it absorbs at *ca.* 1500 cm^{-1}, typical of an aromatic or highly conjugated $-NO_2$. On the basis of this evidence we propose structure **8** for the adduct. The mass spectrum



(1) Chemistry of Nitro Compounds. VIII. For Paper VII see A. Hassner, J. E. Kropp, and G. J. Kent, *J. Org. Chem.*, **34**, 2628 (1969).
(2) See, for instance, O. L. Chapman, A. A. Griswold, E. Hoganson, G. Lenz, and J. Reasoner, *Pure Appl. Chem.*, **9**, 585 (1964); O. L. Chapman, P. G. Cleveland, and E. D. Hoganson, *Chem. Commun.*, 101 (1966); J. T. Pinhey and E. Rizzardo, *ibid.*, 362 (1965).
(3) D. Bryce-Smith, A. Gilbert, and M. G. Johnson, *J. Chem. Soc. C*, 383 (1967).
(4) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, New York, N. Y., 1967, p 210.

is consistent with this structure, showing a parent peak at m/e 249 and the base peak at m/e 95 (the allylic methylcyclohexenyl cation).

Initial excitation of the *p*-benzoquinone and intersystem crossing to the triplet is probably followed by O–C coupling to produce the more favorable "diradical species" **6** (or a similar intermediate).[5] Instead of undergoing ring closure to an oxetan, **6** loses a $NO_2\cdot$, which is immediately trapped by the phenoxy radical **7**. It is not known whether the NO_2 radical becomes attached directly to the benzene ring or to the oxygen to yield a phenyl nitrate, which rearranges to the *o*-nitrophenyl compound **8**. The low yield may be partially attributed to loss of NO_2 from the solvent cage before recombination can occur.

Although photolytic fragmentation of nitro compounds has been observed before, this photochemical addition reaction appears to be the first case involving transfer of a nitro group.

Experimental Section

3-Nitro-2-methylcyclohexene (2).—Nitration of 29 g of 1-methylcyclohexene with nitric acid–acetic anhydride as described by Bordwell and Garbisch[6] led to 22.4 g of a mixture of nitro acetate and nitro nitrate, as well as of nitro olefin **2**, which on refluxing with a benzene solution of 1,4-diazabicyclooctane fractional distillation, monitored by glc, afforded 8.9 g of 3-nitro-2-methylcyclohexene (**2**), bp 48–49° (0.3 mm), and a mixture of nitro acetate and nitro nitrate. The latter (8.5 g) was refluxed with a benzene solution of 1,4-diazabicyclooctane to yield, after work-up with water, 2.7 g of a 2:3 mixture of nitro olefins **1** and **2**, bp 42–44° (0.2 mm), as determined by glc.

Irradiation of Nitro Olefins 1 and 2.—A solution of 150 mg of a 2:3 mixture of **1** and **2** (see above) in 10 ml of cyclohexane was irradiated at 3660 Å and the course of the reaction was monitored by glc, using triglyme as an internal standard. Initial conversion of **1** and **2** was evident during the first 6 hr; then polymer formation was observed with concomitant slow disappearance of **1** and **2**.

4-(2′-Methylcyclohex-2′-enoxy)-2-nitrophenol (8).—3-Nitro-2-methylcyclohexene (**2**, 5.3 g) and *p*-benzoquinone (7.8 g) were dissolved in benzene (110 ml). The solution was deoxygenated by bubbling through N_2 and then irradiated at 3130 Å in the Rayonet reactor. The reaction was followed by tlc [silica gel/50% CH_2Cl_2:50% petroleum ether (bp 60–70°)]. After 47 hr the solution was evaporated to a dark oil containing some solid. Pentane was added and the mixture was filtered to yield a yellow-brown solution, containing the product, and an almost black solid. Distillation of the solution under reduced pressure removed the solvent and unchanged nitro olefin. The residue was chromatographed on silica gel in petroleum ether containing increasing concentrations of benzene. The yellow-orange solution was evaporated to an oil which was crystallized by dissolution in petroleum ether and cooling to Dry Ice temperature. The yield of yellow crystalline **8** was 365 mg (4%).

Anal. Calcd: C, 62.64; H, 6.07; N, 5.62. Found C, 62.37; H, 6.02; N, 5.46.

Registry No.—**1**, 36601-70-4; **2**, 36291-55-1; **4**, 106-51-4; **8**, 36601-72-6.

Acknowledgment.—We thank the U. S. Public Health Service, National Air Pollution Control Administration Grant AP-00596, for support of this work.

(5) The photosensitized conversion of **2** to **1** followed by photoaddition of benzoquinone has not been ruled out.

(6) F. G. Bordwell and E. W. Garbisch, Jr., *J. Amer. Chem. Soc.*, **82** 3588 (1960).

Photooxidative Synthesis of *p*-Methoxycarbonylperbenzoic Acid, a Stable and Convenient Reagent for Epoxidation and Baeyer–Villiger Oxidation[1]

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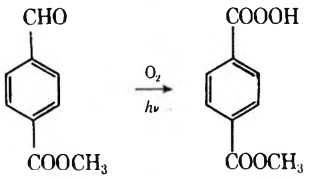
During the course of the photooxidation study of methyl *p*-formylbenzoate (**1**), a simple synthesis of *p*-methoxycarbonylperbenzoic acid (**2**) has been found.



1 **2**

The present note describes the synthesis and chemical behavior of **2** as one of the useful reagents for epoxidation of olefins and Baeyer–Villiger oxidation of carbonyl compounds.

Photooxidation of benzaldehyde is well known as a typical autooxidation, yielding benzoic acid readily.[2] Jorissen and van der Beek first succeeded in isolating perbenzoic acid in 63% yield, by exposing a solution of benzaldehyde in acetone to sunlight.[3] Swern, Findley, and Scanlan prepared perbenzoic acid in 40% yield by employing ultraviolet radiation and carbon tetrachloride.[4] *p*-Bromobenzaldehyde, *p*-chlorobenzaldehyde, and *m*-chlorobenzaldehyde, however, yield little or no peracid when similarly treated.[5]

The photooxidation of **1** afforded mainly *p*-methoxycarbonylbenzoic acid along with a trace of the peracid in the solvents such as acetic acid, formic acid, chloroform, acetone, and benzene, consuming about 0.5 molar equiv of oxygen. However, 1 molar equiv of oxygen was rapidly consumed in the case of carbon tetrachloride,[6] and the reaction product consisted of essentially *p*-methoxycarbonylperbenzoic acid (**2**) which was isolated in a pure crystalline form. The yield was 80–95%.

Differential thermal analysis showed that the peracid began to decompose at 125°, the exothermic decomposition reached its maximum at 134°, and the endothermic point was at 218°, corresponding to the melting point[7] of *p*-methoxycarbonylbenzoic acid. The peracid **2** is as stable as *m*-chloroperbenzoic acid, and showed less than 5% decomposition after 1-year storage at 10°.

(1) Presented at the 21st Annual Meeting of the Chemical Society of Japan, Osaka, April 1968.

(2) H. J. L. Bächström, *J. Amer. Chem. Soc.*, **49**, 1460 (1927).

(3) W. P. Jorissen and P. A. A. van der Beek, *Recl. Trav. Chim. Pays-Bas*, **46**, 42 (1927).

(4) D. Swern, T. W. Findley, and J. T. Scanlan, *J. Amer. Chem. Soc.*, **66**, 1925 (1944).

(5) P. A. A. van der Beek, *Recl. Trav. Chim. Pays-Bas*, **51**, 411 (1932).

(6) It is very important to remove any trace of heavy metal ion from the solvent and the starting aldehyde. Otherwise, the yield of **2** is markedly decreased by autooxidation of the aldehyde with heavy metal ions.

(7) M. J. S. Dewar and J. P. Schroeder, *J. Org. Chem.*, **30**, 2296 (1965).

The reactivity of 2 was investigated by the reactions to carbon–carbon double bonds and carbonyl compounds, and the results are shown in Table I. The

TABLE I
REACTIVITY OF *p*-METHOXYCARBONYLPERBENZOIC ACID

Olefin or ketone	Yield of oxidation product, %	Yield with perbenzoic acid, %
Cyclohexene	90	100[c]
1-Methylcyclohexene	77	50–75[c]
1,5,9-*cis,trans,trans*-Cyclododecatriene	76[a]	64–90[d]
4-Vinylcyclohexene	72[b]	82[e]
Styrene	60	69–75[c]
Cyclopentanone	74	70–80[f]
Cyclohexanone	64	71[f]
Acetophenone	85	50–80[g]

[a] Reacted with only one of trans double bonds. [b] 4-Vinylcyclohexene oxide. [c] D. Swern, "Organic Reactions," Vol. VII, R. Adams, Ed., Wiley, New York, N. Y., 1953, p 378. [d] Peracetic acid was used: G. Wilke, *Angew. Chem.*, 69, 397 (1957). [e] F. C. Frostick, Jr., B. Phillips, and P. S. Starcher, *J. Amer. Chem. Soc.*, 81, 3350 (1959). [f] S. L. Friess, *ibid.*, 71, 2571 (1949). [g] S. L. Friess and A. H. Soloway, *ibid.*, 73, 3968 (1951).

yields of the epoxidation and Baeyer–Villiger reaction ranged from 60 to 90% and 64 to 85%, respectively, generally corresponding to the reactivity of perbenzoic acid and monoperoxyphthalic acid. The peracid 2 is fairly soluble in dioxane, ethanol, acetone, acetonitrile, and *N*,*N*-dimethylformamide, and less soluble in chloroform, benzene, and ether.

The by-product of the reaction is *p*-methoxycarbonylbenzoic acid, which is far less soluble than 2, and may be separated easily since it precipitates out from the reaction system when a suitable solvent is employed.

Although a more extensive application of the peracid 2 to other organic compounds is necessary, the fact that 2 may be simply prepared and is relatively stable is sufficient to commend it as a new convenient reagent for epoxidation and Baeyer–Villiger oxidation.

Experimental Section

All melting points are uncorrected. The ir spectra were obtained on a Hitachi EPI-S2 spectrophotometer and the nmr spectra on a Varian A-60 spectrometer.

A 2-kW mercury quartz lamp made by Toray Engineering Laboratories was used without any filter.

Preparation of Methyl *p*-Formylbenzoate (1).—The method of Lieberman and Connor was applied to the oxidation of methyl *p*-methylbenzoate.[8]

The crude aldehyde, 52 g (43.8%), was recrystallized from ether or subjected to column chromatography with Woelm neutral alumina (activity I) using ether as an eluent, showing mp 62–63°.[9]

Preparation of *p*-Methoxycarbonylperbenzoic Acid (2).—Methyl *p*-formylbenzoate (1) (2 g) and 50 ml of carbon tetrachloride were placed in a cylindrical glass reactor (50 mm diameter × 250 mm length) equipped with a gas inlet tube connected to a gas buret. The reaction mixture, which was a suspension, was vigorously shaken under an atmosphere of oxygen and irradiated with the 2-kW high-pressure mercury lamp.

Oxygen (290 ml) was absorbed in 0.5 hr at room temperature (theoretical volume was 298 ml at 25°). The material which separated as white crystalline powder was collected and dried. The product was confirmed to be mainly *p*-methoxycarbonylperbenzoic acid (2) (2.0 g, 84% yield). An iodometric titration showed that the purity of the crude product was about 90%. No explosion occurred by heating in a capillary tube and no decomposition point was observed. The peracid thus obtained was pure enough for general oxidation reactions, but, if a purer product is desired, it may be recrystallized from methanol: ir (KBr) 3268 (OH), 1730 cm^{-1} (COOOH); nmr (dioxane) δ 3.91 (s, 3, OCH_3), 8.09 (s, 4, aromatic), and 12.36 (s, 1, OH).

Anal. Calcd for $C_9H_8O_5$: C, 55.10; H, 4.11; mol wt, 196. Found: C, 55.21; H, 4.11; mol wt, 179 (Rast).

One should be careful in using the peracid, since it irritates the nasal membranes and causes sneezing. The yield of the peracid is greatly influenced by the purity of methyl *p*-formylbenzoate and the presence of heavy metal ions.

Reaction with Cyclohexene.—In a 300-ml three-necked flask equipped with a mechanical stirrer, a thermometer, and a dropping funnel were placed 6.112 g of 2 and 200 ml of chloroform. Cyclohexene (2.544 g) dissolved in 20 ml of chloroform was added dropwise to the suspension, keeping the temperature below 20°. After addition, it was allowed to stand overnight with stirring at this temperature.

Precipitates of *p*-methoxycarbonylbenzoic acid (4.650 g) were removed by filtration and the filtrate was washed two times with 100 ml of 10% aqueous sodium carbonate solution, with 2 g of sodium hydrogen sulfite in 100 ml of water, and with a saturated aqueous solution of sodium chloride. After drying, the solvent was removed at atmospheric pressure, and an oily residue was distilled under reduced pressure to obtain 2.763 g of 7-oxabicyclo-[4.1.0]heptane as a colorless oil. The yield was 90%.

Reaction with Cyclopentanone.—In a 300-ml erlenmeyer flask equipped with a dropping funnel, 7.632 g of 2 and 150 ml of chloroform were placed and the flask was cooled in an ice bath. Then cyclopentanone (1.628 g) dissolved in 30 ml of chloroform was added to the solution. After addition, the mixture was magnetically stirred under cooling for 4 hr and allowed to stand for 4 days at room temperature. Precipitates of *p*-methoxycarbonylbenzoic acid (6.63 g) were removed by filtration and the filtrate was washed two times with 100 ml of 10% aqueous sodium carbonate solution and washed with a saturated aqueous solution of sodium chloride. After drying, the solvent was removed at atmospheric pressure, and an oily residue was distilled under reduced pressure to obtain 1.437 g of 5-pentanolide as a colorless oil. The yield was 75%. The same procedure was applied to other olefins and carbonyl compounds.

Registry No.—2, 28276-78-0.

(8) S. L. Lieberman and R. Connor, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1955, p 441.

(9) H. B. Hass and M. L. Bender, *J. Amer. Chem. Soc.*, 71, 1767 (1949).

The Conversion of Podocarpic Acid to an 18-Nor Steroid

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The use of podocarpic acid[1] (1a) and other resin acids as starting materials for the synthesis of steroids has been investigated by several groups.[2–5] We now report the synthesis of an 18-nor steroid (5b) from 1a.

(1) J. L. Simonsen and D. H. R. Barton, "The Terpenes," University Press, Cambridge, 1961, Vol. III, p 472.

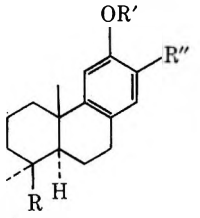
(2) Cambie and his coworkers[3] devised a route for removing the geminal methylcarboxyl group in podocarpic acid and producing a Δ^4-3-one system in ring A; their final product was 12-methoxy-18,19-bisnorpodocarpa-4,8,11,13-tetraen-3-one. Davis and Watkins[4] converted the methyl ether of methyl podocarpate to 4β-methoxycarbonyl-4α-methyl-12-methoxy-18-norandrosta-8,11,13-trien-15-one, a steroid with ring C aromatic, and also the corresponding D-homo steroid.

(3) C. R. Bennett and R. C. Cambie, *Tetrahedron*, 23, 927 (1967); R. C. Cambie and W. A. Denny, *Aust. J. Chem.*, 22, 1699 (1969); C. R. Bennett, R. C. Cambie, R. A. Franith, and T. J. Fullerton, *ibid.*, p 1711.

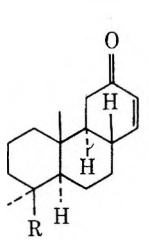
(4) B. R. Davis and W. B. Watkins, *Tetrahedron*, 24, 2165 (1968); *Aust. J. Chem.*, 21, 1611 (1968).

(5) J. W. Huffman, *J. Org. Chem.*, 35, 478 (1970).

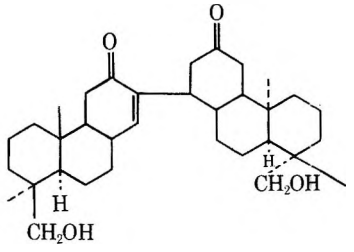
Podocarpic acid (**1a**) was converted into the unsaturated ketones **2a**[6-9] (which is best prepared by Bell



1a, R = COOH; R′ = R″ = H
b, R = $COOCH_3$; R′ = CH_3; R″ = Ac
c, R = COOH; R′ = CH_3; R″ = Ac
d, R = COOH; R′ = CH_3; R″ = $CHOHCH_3$
e, R = $COOCH_3$; R′ = CH_3; R″ = $CHOHCH_3$



2a, R = $COOCH_3$
b, R = CH_2OAc
c, R = CH_2OH



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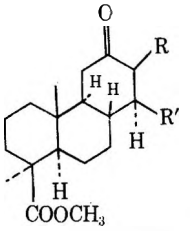


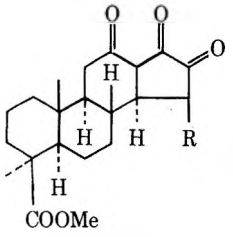
4a, R = H; R′ = $CH(COOC_2H_5)_2$
b, R = H; R′ = $CH(COOH)_2$
c, R = H; R′ = CH_2COOH
d, R = H; R′ = CH_2COOCH_3
e, R = $COCOOCH_3$; R′ = CH_2COOCH_3
f, R = H; R′ = $CH(COOCH_3)_2$

and Gravestock's route[6,7,9]) and **2b**.[7,9,10] In the course of unsuccessful attempts[9] to improve the route to **2a** and **2b** *via* the Birch reduction of derivatives of **1a**,[7,9] we prepared the compounds **1c**, **1d**, and **1e**.

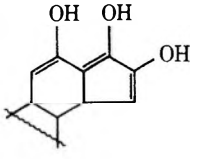
Attempts to use the keto acetate **2b** as an acceptor in Michael additions were complicated by **2b** undergoing a self-condensation to give **3**, the structure of which follows from its analytical and spectral data and its preparation by keeping **2b** in ethanol in the presence of sodium ethoxide. Clearly the mechanism involves a Michael addition of the anion from **2b** or **2c** with another molecule of **2b** or **2c**. Similar dimerizations have been reported for other compounds.[11]

In contrast to **2b**, **2a** showed no tendency to undergo the self-condensation; there is no obvious reason for this difference in behavior. Addition of diethyl malonate to **2a** took place smoothly to give **4a**, whose nmr spectrum showed signals for the two ethyl groups in slightly different positions. The triester was hydrolyzed to the diacid **4b**, which on decarboxylation gave the monoacid **4c**. Methylation with diazomethane gave the diester **4d**. The nmr spectrum of **4d** showed two sharp singlets corresponding to the methoxy groups, thus indicating that **4d** is a single isomer; the stereochemistry of the C_{14} side chain is suggested on the basis that Michael additions of malonate in protonated solvents give the equatorial epimer.[12]

After attempts to convert **4c** to its homolog *via* the Arndt–Eistert synthesis failed,[9] we tried to complete ring D by condensing **4d** with dimethyl oxalate.[13] As the products of these condensations hydrolyzed easily, the reactions were only successful when done under rigorously defined conditions. Condensation of **4d** with dimethyl oxalate in the presence of sodium methoxide gave **4e** as a mixture of tautomers. When the condensation was done in the presence of sodium hydride in dimethylformamide, a product soluble in sodium hydroxide was isolated. The spectral data indicated that the product was mainly **5a**. As we were not able to purify this product, we converted it to crystalline **5b** by hydrolysis and decarboxylation



5a, R = COOMe
b, R = H



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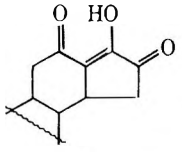

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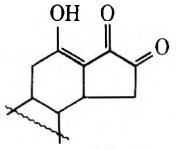

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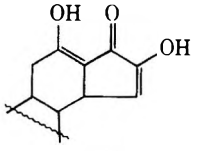

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under acid conditions. The structure **5b** is supported by the spectral data recorded in the Experimental Section. The properties of **5b** indicate that it exists to a large extent as one or more of seven possible tautomeric enols. Consideration of the observed ultraviolet maxima in conjunction with maxima calculated[14] for each of the possible enols suggests that the tautomer **6** (λ_{max}^{calcd} 307 nm) and one or more of the forms **7** (λ_{max}^{calcd} 266 nm), **8** (λ_{max}^{calcd} 272 nm), and **9** (λ_{max}^{calcd} 272 nm) are the main enolic forms.

(6) R. A. Bell and M. B. Gravestock, *Can. J. Chem.*, **47**, 3661 (1969).
(7) R. H. Bible and R. R. Burtner, *J. Org. Chem.*, **26**, 1174 (1961).
(8) T. A. Spencer, R. A. J. Smith, D. L. Storm, and R. M. Villarica, *J. Amer. Chem. Soc.*, **93**, 4856 (1971).
(9) For details see P. R. Witt, Ph.D. Thesis, University of Nebraska, 1970.
(10) R. C. Cambie, W. A. Denny, T. R. Klose, and L. N. Mander, *Aust. J. Chem.*, **24**, 99 (1971).
(11) N. J. Leonard and W. J. Musliner, *J. Org. Chem.*, **31**, 639 (1966); J. E. Engelhart and J. R. McDivitt, *ibid.*, **36**, 367 (1971).
(12) R. A. Abramovitch and D. L. Struble, *Tetrahedron*, **24**, 357 (1968).
(13) *Cf.* J. J. Korst, J. D. Johnston, K. Butler, E. J. Bianco, L. H. Conover, and R. B. Woodward, *J. Amer. Chem. Soc.*, **90**, 439 (1968).
(14) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Macmillan, New York, N. Y., 1964, pp 50, 60–71, 257, and 264–269.

Experimental Section[15]

The Base-Catalyzed Self-Condensation of 19-Acetoxypodocarp-13-en-12-one (2b).—A solution of sodium (120 mg, 5 mg-atoms) in absolute ethanol (5 ml) was added to 19-acetoxypodocarp-13-en-12-one (**2b**),[9,10] (150 mg, 0.5 mmol) in ethanol (4 ml) in a nitrogen atmosphere. After stirring for 1.25 hr the solution was diluted with water (75 ml) containing concentrated hydrochloric acid (1 ml). The precipitate (100 mg, 78%), 19-hydroxypodocarp-13-en-12-one-13-(14-(19-hydroxypodocarp-12-one)) (**3**), crystallized from ethyl acetate–acetonitrile to give product with mp 231–250°, which showed as a single spot on tlc: ν_{max} 3640, 1705, and 1670 cm^{-1}; nmr δ 0.60–2.63 (45 H, m with strong s at 0.87, 0.90, and 0.93), 3.52 (4 H, m, $-CH_2OH$), and 6.37 (1 H, d, J = 1 Hz, =CH); λ_{max} 241 nm (ϵ 5500).

Attempted Michael reactions of diethyl malonate with **2b** were complicated by the formation of the dimer, **3**.

Anal. Calcd for $C_{34}H_{52}O_4$: C, 77.82; H, 9.99. Found: C, 77.44; H, 9.76.

Methyl 14-(Diethylmalonyl)-12-ketopodocarp-19-oate (4a).—A solution of the unsaturated keto ester **2a**[6,8,9] (290 mg, 1 mmol) in ethanol (4 ml) was added dropwise to a stirred solution of sodium (12 mg, 0.5 mg-atom) and diethyl malonate (320 mg, 2 mmol) in ethanol (6 ml) at room temperature in a nitrogen atmosphere. The mixture was stirred for 4 hr and diluted with water (125 ml) containing concentrated hydrochloric acid (7 drops). The product was recovered by extraction with ether and the ethereal extract was washed with water and saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the ether *in vacuo* gave an oil which was refluxed (30 min) with glacial acetic acid (0.5 ml), ethanol (5 ml), and Girard's "T" reagent (0.52 g). The cooled mixture was diluted with water (25 ml) and saturated aqueous sodium chloride (5 ml), and the nonketonic material was removed by extraction with ether. The aqueous layer was acidified to pH 2, kept for 2 hr, and then extracted with ether. The ethereal extract was washed three times with water and once with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the ether *in vacuo* yielded the adduct **4a** (225 mg, 50%) as a yellow oil: ν_{max} 1740 (shoulder) and 1720 cm^{-1}; nmr δ 0.65–2.9 (30 H, m with strong s at 0.69 and 1.19 and triplets at 1.27 and 1.30), 3.48 [1 H, d, J = 7 Hz, $C(COOC_2H_5)_2\mathbf{H}$], 3.67 (3 H, s, $-OCH_3$), and 4.21 and 4.26 (2 H each, q, J = 7 Hz, $-OCH_2CH_3$).

In a similar way dimethyl malonate was added to keto ester **2a**. The product (**4f**), which was obtained in 56% yield, had ν_{max} at 1715 (shoulders at 1730 and 1750) cm^{-1} and nmr δ 0.6–3.00 (22 H, m with sharp s at 0.70 and 1.20), 3.48 (1 H, d, J = 7 Hz), 3.82 (3 H, s, OCH_3), and 3.93 (6 H, 2s, OCH_3).

Dimethyl 12-Keto-14-(acetic acid)podocarp-19-oate (4d).—A solution of the unsaturated keto ester **2a** (363 mg, 1.25 mmol), diethyl malonate (588 mg, 3.68 mmol), and sodium (9 mg, 0.375 mg-atom) in absolute ethanol (7.5 ml) was stirred under nitrogen for 3.5 hr. A solution of sodium hydroxide (0.68 g, 17 mmol) in water (6.6 ml) was added and the mixture was stirred (15 min) and then refluxed (45 min). The cooled solution was diluted with water (20 ml) and saturated aqueous sodium chloride (20 ml) and was extracted with ether, and the extracts were discarded. The aqueous layer was acidified with hydrochloric acid (6 *N*) at 0° and extracted with ether. The combined ethereal extracts were washed with water and saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the ether under reduced pressure gave the diacid **4b** (384 mg, 78%) as a white foam. The diacid was heated (150–170°) in a nitrogen atmosphere for 1 hr, producing a glass which crystallized from ether–light petroleum to give the acid **4c**, mp 157–163° (293 mg, 67%). Recrystallization gave mp 161–165°; ν_{max} 3490 and 1720 cm^{-1}; nmr δ 0.55–2.85 (26 H, m with strong s at 0.72 and 1.20) and 3.67 (3 H, s, OCH_3).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.57; H, 8.77.

The methyl ester **4d** was prepared by treating the acid **4c** (2.22 g, 6.35 mmol) in ether with excess ethereal diazomethane. Removal of the ether *in vacuo* afforded a yellow oil which on crystallization from ether–hexane gave the ester **4d**: mp 72.5–75.5° (1.97 g, 85%), ν_{max} 1720 cm^{-1}; nmr δ 0.6–2.75 (26 H, m with sharp s at 0.70 and 1.18) and 3.65 (6 H, 2 s, OCH_3).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 68.80; H, 8.99.

4α-Methyl-4β-carbomethoxy-18-norandrostane-12,16,17-trione (5b).—Sodium hydride (520 mg of 50% dispersion in mineral oil, 10.9 mmol) was added to a mixture of the methyl ester **4d** (944 mg, 2.75 mmol) and dimethyl oxalate (650 mg, 5.48 mmol) in dimethylformamide (7 ml). The addition of methanol (7 drops), *ca.* 2.75 mmol) to this mixture led to a vigorous evolution of hydrogen. The mixture was stirred at room temperature for 65 min and then was heated for 30 min at 50–80°. The cooled (ice) mixture was acidified with glacial acetic acid (1 ml) and poured into water (75 ml). The aqueous mixture was extracted with ether and the ethereal extract was washed four times with water and once with saturated aqueous sodium chloride and dried (Na_2SO_4). The ethereal solution was treated with charcoal and the ether was removed *in vacuo* to yield an orange-brown foam (1.08 g). A solution of the foam in ether was extracted with 0.5 *N* sodium hydroxide solution and the aqueous extract was acidified with 2 *N* hydrochloric acid and extracted with ether. The ethereal extract was washed with water and saturated aqueous sodium chloride and filtered through anhydrous sodium sulfate, and the ether was removed *in vacuo* to yield a yellow foam (520 mg, 50%). The product gave a strong color with ethanolic ferric chloride: ν_{max} 3550–3000, 1740 (sh), 1725, 1660, and 1625–1600 cm^{-1}; nmr (broad singlets) δ 0.66, 1.20, 3.66, and 8.16; λ_{max} 218 nm (ϵ 3600) and 295 (5900) shifted to 240 (inflection) (ϵ 5000), 330 (7200), and 370 (6700) in ethanol–0.01 *N* sodium hydroxide solution. Structure **5a** is assigned to this material.

A solution of crude **5a** (92 mg, 0.22 mmol) in glacial acetic acid (1.75 ml), concentrated hydrochloric acid (1.25 ml), and water (5 drops) was heated at 90–100° for 1 hr in a nitrogen atmosphere. The cooled mixture was diluted with water (8 ml) and extracted with ether. The ethereal extract was washed twice with water and then with 1% aqueous sodium hydrogen carbonate until the final washing was basic to litmus. (Vigorous agitation during these basic washings was avoided.) The ethereal solution was filtered through anhydrous sodium sulfate and evaporated *in vacuo* to yield a tan foam (54 mg, 69%), which crystallized from ether–hexane. Recrystallization from ether gave **5b** as fine tan crystals: mp 174–178° (16 mg, 20%) (red-brown color with methanolic ferric chloride); ν_{max} 3550–3025, 1752 (sh), 1725, 1660, and 1600 cm^{-1}; nmr δ 0.50–3.00 (24 H, m with strong s at 0.69 and 1.21), 3.64 (3 H, s, OCH_3), and 7.50 (1 H, broad s, disappears on addition of D_2O, C=COH); λ_{max} 223 nm (ϵ 4500), 267 (3500), and 295 (4200) shifted to 240 (4200), 271 (2200), and 367 (5300) in ethanol–0.01 *N* sodium hydroxide; *m/e* (rel intensity) 356 (56), M^+ 332 (100), M − 28, 304 (11), M − 28 − 28, 301 (11), M − 59, 273 (9), M − 59 − 28, 272 (7), M − 60 − 28, 244 (7), M − 28 − 28 − 60, 221 (35), possibly rings A and B with C_{11}, 189 (9), 221 − 32, 161 (52), 221 − 60, 136 (32), 135 (22), 134 (20), 123 (31), 121 (35), 109 (17), 107 (16), 82 (15), and 81 (16).

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.46; H, 7.90.[16]

Methyl 12-Methoxy-13-(1-hydroxyethyl)podocarpa-8,11,13-trien-19-oate (1e).—A solution of sodium borohydride (0.125 g, 3.4 mmol) in water (5 ml) was added dropwise to methyl 12-methoxy-13-acetylpodocarpa-8,11,13-trien-19-oate (**1b**)[10,17] (0.516 g, 1.5 mmol) in ethanol (15 ml) at 0°. The mixture was kept at 0° for 1 hr, stirred at room temperature for 23 hr, and then acidified to congo red with dilute hydrochloric acid. The ethanol was removed under reduced pressure, and water (30 ml) was added. The product, which was isolated through extraction of the acidified mixture with chloroform, crystallized from aqueous ethanol to yield **1e** (0.381 g, 76%) as fine crystals: mp 113–116°; ν_{max} 3575, 1720, and 1607 cm^{-1}; nmr δ 0.95–3.0 (20 H, m with s at 1.03 and 1.27 and a d at 1.65, J = 7 Hz), 3.68 (3 H, s, $-OCH_3$), 3.82 (3 H, s, OCH_3), 5.03 (1 H, q, J = 7 Hz, $CHOHCH_3$), 6.77 (1 H, s, C_{arom} H), and 7.03 (1 H, s, C_{arom} H).

(15) Spectra were measured with Perkin-Elmer 237, Cary 14, Hitachi RMU-6D, and Varian A-60 instruments; unless otherwise specified, ir spectra are for dichloromethane solutions, uv spectra for ethanol solutions, nmr spectra for solutions in deuteriochloroform (tetramethylsilane as internal standard), and mass spectra were determined at an ionization potential of 70 eV, with samples being introduced through the direct inlet. Light petroleum had bp 60–69°. The condensations of **4d** were carried out in a dry box under N_2 using carefully dried reagents and solvents (kept over molecular sieves). In the work-up of these reactions cold dilute solutions of acids and bases were used and extractions were done rapidly.

(16) Although the carbon figure is outside the normally acceptable limits, the mass spectral data confirm the structure. Shortage of material precluded reanalysis.

(17) W. P. Campbell and D. Todd, *J. Amer. Chem. Soc.*, **64**, 929 (1942).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73; O, 18.47. Found: C, 72.71; H, 8.82; O, 18.43.

12-Methoxy-13-acetylpodocarpa-8,11,13-trien-19-oic Acid (1c).[18]—A solution of methyl 12-methoxy-13-acetylpodocarpa-8,11,13-trien-19-oate (1b) (0.500 g, 1.51 mmol) in concentrated sulfuric acid (6 ml) was kept at room temperature for 5 min and then poured over ice. A solution of the precipitate in aqueous sodium hydroxide was filtered. Acidification of the filtrate with hydrochloric acid gave a solid which crystallized from aqueous ethanol to give 1c (0.280 g, 59%) as needles: mp 205–207°; a second crop (0.037 g) brought the yield to 65%; ν_{max} 3490, 1720, 1690, 1670, and 1600 cm^{-1}; nmr δ 1.05–3.05 (20 H, m with s at 1.14, 1.36, and 2.60), 3.87 (3 H, s, OCH_3), 6.82 (1 H, s, C_{arom} H), and 7.48 (1 H, s, C_{arom} H).

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.41; H, 8.07.

12-Methoxy-13-(1-hydroxyethyl)podocarpa-8,11,13-trien-19-oic Acid (1d).—A solution of sodium borohydride (90 mg, 2.4 mmol) in water (5 ml) was added to a solution of 1c (0.237 g, 0.72 mmol) in 0.2 *N* sodium hydroxide (4.5 ml). The mixture was kept in ice water for 30 min and then was stirred at room temperature for 5 min. The solution was acidified with dilute hydrochloric acid and the resulting tan precipitate was crystallized from aqueous ethanol to yield 1d (0.184 g, 78%) as fine needles: mp 160–168°; $\nu_{max}^{CHCl_3}$ 3600–2350 (broad absorption), 1695, and 1615 cm^{-1}; nmr δ 0.95–3.0 (20 H, m with s at 1.05 and 1.32 and a d at 1.49), 3.65 (3 H, s, OCH_3), 6.77 (1 H, s, C_{arom} H) and 7.00 (1 H, s, C_{arom} H).

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49; O, 19.25. Found: C, 72.27; H, 8.50; O, 19.06.

Registry No.—**1a**, 5947-49-9; **1c**, 30801-46-8; **1d**, 36504-20-8; **1e**, 36504-21-9; **3**, 36504-22-0; **4a**, 36504-23-1; **4c**, 36504-24-2; **4d**, 36504-25-3; **4f**, 36504-26-4; **5a**, 36504-27-5; **5b**, 36504-28-6.

Acknowledgments.—P. R. W. was an NDEA Title IV Fellow, 1966–1969. Financial support was also supplied by NSF Grant GU-2054 and the Research Council of the University of Nebraska. We are grateful for this support and also to the Searle Company for a gift of rimu resin, to Drs. R. H. Bible and D. Goldsmith for details of unpublished work, and Dr. M. M. Wheeler for assistance.

(18) The acid 1c was first prepared by Picha[19] who reported mp 198–202.5°. Our preparation is based on unpublished work by Bible.[20]

(19) G. M. Picha, U. S. Patent 2,774,784 (Dec 18, 1956); *Chem. Abstr.*, **51**, 9695*e* (1957).

(20) R. H. Bible, Abstracts, 138th National Meeting of the American Chemical Society, New York, N. Y., Sept 1960, p 49p.

Dehydrogenase Enzyme Models. Approximation of an Alcohol and a Pyridinium Ring

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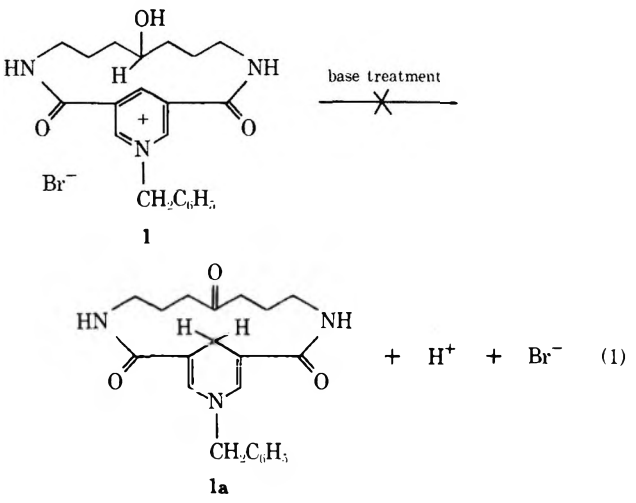
The pyridine nucleotides (NAD^+, $NADP^+$) with their reduced forms (NADH, NADPH) are coenzymes in many biological oxidation–reduction reactions,[2] *e.g.*, the interconversions of ethanol ⇌ acetaldehyde and lactate ⇌ pyruvate, which are catalyzed by the dehydrogenase enzymes liver alcohol dehydrogenase and muscle lactate dehydrogenase, respectively. Although it has been possible to achieve the nonenzymatic reduction of reactive carbonyl compounds *via* direct hydride transfer from several 1,4-dihydropyridine reductants, the reverse reaction, the oxidation of an alcohol by a pyridinium salt (NAD^+ model), has not been reported.[2] Attempts in this direction involving flexible intramolecular model systems[3] were unsuccessful and involved in part addition of the side chain to the 2 position of the pyridinium ring. We wish to report studies of a rigid model system, **1**, in which intramolecular hydride transfer to positions other than the 4 position is precluded, and to report that the mere existence of intramolecular approximation is *not* sufficient to guarantee intramolecular hydride transfer, as depicted in eq 1. Compound **1** appeared to be a likely



candidate for the observation of intramolecular hydride transfer since, even though transannular hydride migrations in 14-membered rings has to our knowledge not been reported, space-filling models (CPK) show that the hydroxyl methine hydrogen and the pyridinium 4 position are held tightly together and that conformations of the 14-membered ring do exist in which hydride addition could occur perpendicular to the plane of the pyridinium ring. Moreover attempts to make analogs of **1** with only five bridging methylenes were unsuccessful, presumably owing to the even tighter fit in this case.[4]

The synthesis of **1** by high-dilution cyclization followed the route used by Stetter[5] for the preparation of macrocyclic bisamides of isopthalic acid, and is outlined in Scheme I. For the cyclization step, the hydroxyl group was blocked as the *tert*-butyl ether. The crucial step in this synthesis, high-dilution cyclization of **4** with dinicotinoyl dichloride, was affected in 6.6% yield as described in the Experimental Section. The 4-deoxy analog, **7**, was prepared by similar cyclization in 6.9% yield.

(1) (a) NIH Postdoctoral Fellow, 1969–1971, Columbia University; (b) Address inquiries to author at this address.

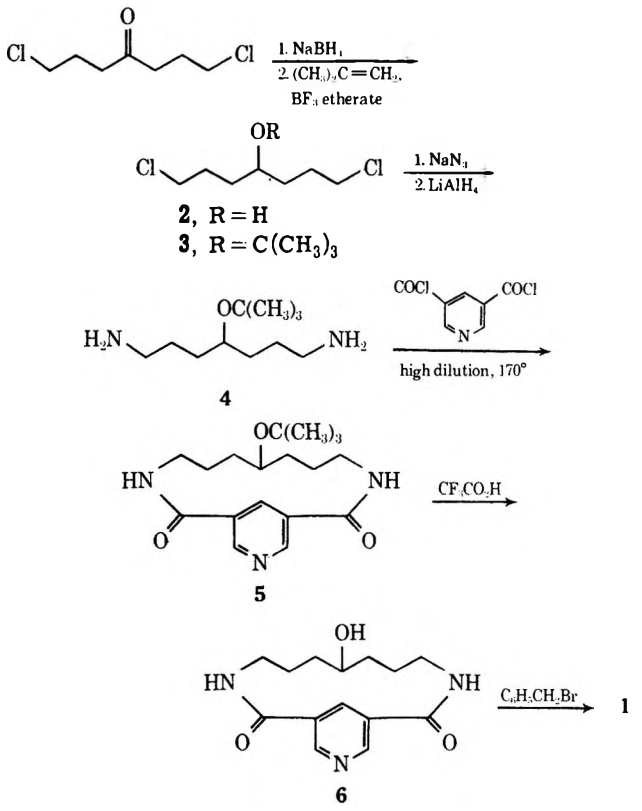
(2) (a) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966, Chapter 9; (b) S. Chaykin in "Annual Review of Biochemistry," Vol. 36, Part 1, P. D. Boyer, Ed., Annual Reviews, Inc., Palto Alto, Calif., 1967, pp 149–170.

(3) E. J. Gabbay, Ph.D. Thesis, Columbia University, New York, N. Y., 1965.

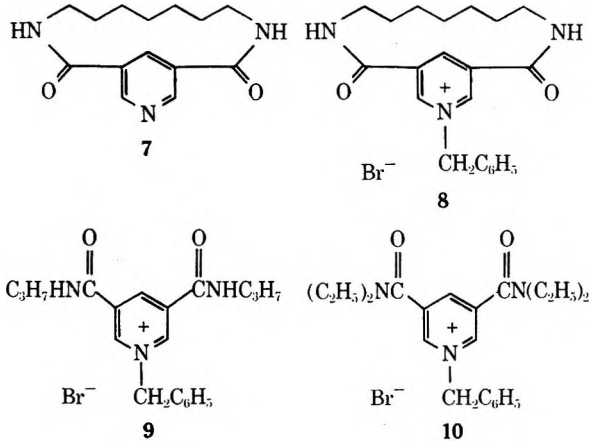
(4) High-dilution cyclization of dinicotinoyl dichloride and 1,5-diaminopentane afforded no macrocyclic bisamide, and only a dimeric tetraamide (*m/e* 466) could be isolated.

(5) H. Stetter, L. Marx-Moll, and H. Rutzen, *Chem. Ber.*, **91**, 1775 (1958).

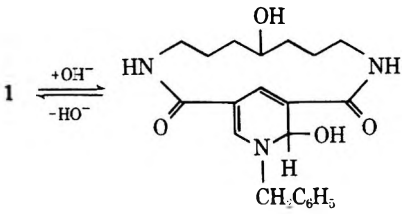
SCHEME I



Initial attempts to effect intramolecular hydride transfer involved treatment of **1** with aqueous base. When an aqueous solution of **1** was basified to pH 12, two new peaks in the uv spectrum at 272 nm (ϵ 10 × 10^3) and 345 (7.7 × 10^3) were obtained. That these new peaks were not related to the formation of the ketodihydropyridine **1a** was apparent from the observed similar behavior at pH 12 of the deoxy analogs **8** [λ_{max} 274 nm (ϵ 14 × 10^3) and 348 (8.6 × 10^3)] and



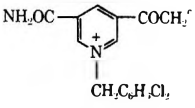
9 [λ_{max} 273 nm (ϵ 12 × 10^3) and 346 (8.0 × 10^3)]. In all cases the spectral changes observed at high pH were completely reversible, the spectra of the original salt being obtained upon acidification. That one is not observing simple titration of the NH hydrogens is evident from the similar behavior of **10** [λ_{max} 281 nm (ϵ 12 × 10^3) and 336 (10 × 10^3), 1.0 *M* NaOH)].[6] The simplest explanation for the uv changes at high pH is the reversible addition of hydroxide to the pyridinium ring, as illustrated for **1** in eq 2. Consistent with this inter-



pretation are nmr experiments which show that the addition of 1 drop of 1 *N* NaOH to **9** (0.4 ml of a 0.06 *M* solution in 1:1 H_2O–methanol) results in the immediate disappearance of the resonances of the pyridine aromatic hydrogens, which can be then regenerated by the addition of 1 drop of acetic acid. Hydroxide addition is certainly occurring at the 2 position, since in all cases two distinct absorption maxima which are characteristic of a cross-conjugated 3-carboxamido-1,2-dihydropyridine (or a 3,5-dicarboxamide-1,2-dihydropyridine)[7,8] are observed. Table I summarizes the uv

TABLE I

UV MAXIMA OF 3,5-DICARBOXAMIDODIHYDROPYRIDINES[a]

Bromide salt λ_{max}, nm (ϵ)	λ_{max}, nm (ϵ): 1,4-Dihydropyridine ($Na_2S_2O_4$ product)	λ_{max}, nm (ϵ): 1,2-Dihydropyridine ($NaBH_4$ product)
	378 (7.9 × 10^3)[b] Shoulder 255 (10 × 10^3)	391 (7.4 × 10^3)[b] 286 (15.4 × 10^3)
Shoulder 275 (4.1 × 10^3)[b]		
9	379 (8.0 × 10^3)[c,f]	386 (7.5 × 10^3)[c,g]
Shoulder 283 (9.9 × 10^3)	Shoulder 255 (10 × 10^3)	287 (14 × 10^3)
1	No reduction[d]	387 (8 × 10^3)[h]
Shoulder 243 (7.0 × 10^3)	product isolated	285 (12 × 10^3)

[a] Solvent methanol unless otherwise noted. [b] K. Wallenfels and H. Schuly, *Justus Liebigs Ann. Chem.*, 621, 106 (1957). [c] Crude, chloroform-soluble reduction product, in chloroform; extinction coefficient calculated assuming quantitative reduction. [d] No chloroform-soluble product from the dithionite reduction (excess aqueous $Na_2S_2O_4$, 25°, 18 hr) could be isolated. [e] Registry no., 36608-50-1. [f] Registry no., 36611-99-1. [g] Registry no., 36612-00-7. [h] Registry no., 36612-01-8.

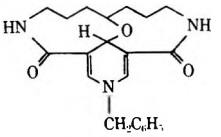
spectra of some authentic 1,2- and 1,4-dihydro-3,5-dicarboxamidopyridines prepared in this and other work by selective reduction of the corresponding pyridinium salts with either sodium borohydride or sodium dithionite.

In order to avoid hydroxide addition to the pyridinium ring, treatment of **1** with basic catalysts under rigorously anhydrous conditions in the nonnucleophilic solvent hexamethylphosphoramide (HMPA) was investigated. A variety of bulky, relatively nonnucleophilic bases have been tried in an unsuccessful attempt

(6) For a report of the spectral changes resulting from ionization of the NH hydrogens of benzyl nicotinamide, see R. B. Martin and J. G. Hull, *J. Biol. Chem.*, **239**, 1237 (1964).

(7) For a discussion of the preparation and uv absorption spectra of 1,4- and 1,2-dihydropyridines, see ref 2a, pp 310–343.

(8) The uv spectrum undoubtedly also rules out the tricyclic ether i as the product formed from base treatment of **1**, since this should also show a single absorption maximum.



to convert **1** into **1a**.[9] For example, when **1** was treated with a threefold excess of the weak base aluminum isopropoxide, the nmr spectrum indicated that alkoxyl interchange had occurred to form the aluminum alkoxide of **1** as judged from the appearance of 1 equiv of isopropyl alcohol [doublet (J = 4 Hz) 161 Hz downfield from HMPA]. The aluminum alkoxide of **1**, however, does not undergo intramolecular hydride transfer, as the nmr spectrum of the pyridinium hydrogens are unchanged after 12 hr at 30°. Typical of the results with strong bases is the treatment of **1** with 1 equiv of freshly sublimed lithium bis(trimethylsilyl)-amide, which results in the destruction of **1** without the production of **1a** as determined by both the absence in the product of a carbonyl absorption in the ir spectrum and maximum at 380 nm in the uv spectrum.[10]

Although intramolecular approximation is often an effective method of modeling enzymatic processes,[2a,11] simple approximation of a secondary alcohol and the 4 position of an electron-deficient[12] pyridinium salt does not in the case of **1** lead to intramolecular hydride transfer. Possibly the preferred conformation of the medium ring in **1** is such that the hydroxyl methine hydrogen and the 4 position of the pyridinium ring, although spatially close, are not held in the proper orientation for hydride transfer, a situation which undoubtedly is not the case in the corresponding enzyme bound coenzyme–substrate complex.

Experimental Section[13]

1,7-Dichloro-4-heptanol (**2**).—A solution of 1,7-dichloro-4-heptanone[14] (18.3 g, 0.10 mol) and 100 ml of absolute ethanol was added dropwise over 15 min to a stirred mixture of $NaHCO_3$ (16.8 g, 0.20 mol), sodium borohydride (3.78 g, 0.10 mol), and 300 ml of absolute ethanol at 0° under a nitrogen atmosphere. After stirring for an additional 6 hr at 0°, the mixture was neutralized with 50% HCl, 200 ml of ether and 200 ml of saturated aqueous NaCl solution were added, and then enough water was added to just dissolve the inorganic salts. The ether layer was separated and washed with 200 ml of saturated $NaHCO_3$ solution, and the product was isolated[13a] and distilled to afford 11.2 g (61%) of **2**: bp 110–115° (0.4 Torr); ν_{max}^{plates} 3100–3700 cm^{-1} (OH); $\tau_{CDCl_3}^{TMS}$ 6.2–6.6 (m, 5 H, CH_2Cl and CHOH), 7.60 (s, exchangeable with D_2O, 1 H, OH). This substance deteriorated rapidly (with evolution of HCl) even when stored at 0° and it was therefore used immediately after distillation.

4-*tert*-Butoxy-1,7-dichloroheptane (**3**).—A solution of **2** (10.0 g, 54.0 mmol) and 75 ml of methylene chloride in a 250-ml pressure bottle was cooled in a Dry Ice–acetone bath. Freshly distilled boron trifluoride etherate (2.50 ml, 19.0 mmol), 100% phosphoric acid (1.04 ml, 19.0 mmol), and condensed isobutylene (50 ml, 0.60 mol) were added, the pressure bottle was closed, and the solution was warmed to 25° in a water bath. After the solution was stirred for 1 hr at 25°, the pressure bottle was cooled in a Dry Ice–acetone bath and opened, and the contents were poured into 500 ml of saturated $NaHCO_3$ solution. This procedure was repeated on two more batches using an additional 18.1 g of **2**. Isolation[13a] of the product with methylene chloride afforded 34.6 g of a colorless oil, which was diluted with 20 ml of hexane–ether (3:2) and chromatographed on 1 lb of silica gel. Elution with hexane–ether (3:2) afforded 14.19 g (39%) of pure (tlc) **3**.

The analytical sample was prepared by evaporative distillation [110° (0.1 Torr)]: ν_{max}^{plates} 1195 cm^{-1} (CO-*t*-Bu); $\tau_{CDCl_3}^{TMS}$ 6.2–6.6 (m, 5 H, CH_2Cl and CHOR), 8.83 [s, 9 H, $C(CH_3)_3$].

Anal. Calcd for $C_{11}H_{22}OCl_2$: C, 54.77; H, 9.19; Cl, 29.40. Found: C, 54.67; H, 9.23; Cl, 29.12.

4-*tert*-Butoxy-1,7-diaminoheptane (**4**).—A solution of **3** (14.19 g, 58.9 mmol), sodium azide (38.2 g, 589 mmol), 600 ml of dimethylformamide (reagent grade), and 40 ml of water was stirred for 2 hr under a nitrogen atmosphere at 85–90°. After cooling to room temperature, the solution was diluted with 300 ml of water and after isolation[13a] with ether 13.98 g of crude diazide (ν 2090 cm^{-1}) was obtained as a yellow oil. This material was dissolved in 120 ml of anhydrous ether and added dropwise during 0.5 hr to a stirred mixture of lithium aluminum hydride (9.00 g, 237 mmol) and 600 ml of anhydrous ether. Nitrogen was vigorously evolved and the addition rate had to be carefully controlled. After the addition was complete the mixture was stirred at 25° for an additional 6 hr. Tetrahydrofuran (500 ml) was then added followed by the careful addition of 50 ml of 1:1 tetrahydrofuran–H_2O and 220 ml of 10% NaOH. Isolation[13a] of the ether-soluble product and distillation afforded 8.54 g (72%) of **4**: bp 92–98° (1 Torr); ν_{max}^{plates} 3240 and 3200 (NH_2), 1195 cm^{-1} (CO-*t*-Bu); $\tau_{CDCl_3}^{TMS}$ 6.52 (quintet, J = 2.7 Hz, 1 H, CHOR), 7.1–7.5 (m, 4 H, CH_2NH_2), 8.78 (s, exchangeable with D_2O, 4 H, NH_2), 8.81 [s, 9 H, $C(CH_3)_3$]; bisbenzamide mp 138–139.5°.

Anal. Calcd for $C_{25}H_{34}N_2O_3$ (bisbenzamide): C, 73.14; H, 8.35; N, 6.82. Found: C, 73.28; H, 8.31; N, 6.74.

7-*tert*-Butoxy-2,12-dioxo-3,11,15-triazabicyclo[11.3.1]hepta-deca-1(17),13,15-triene (**5**).—The general procedure of Stetter[5] was followed. A 5-l. flask was fitted with two "constant addition rate" funnels,[15] a nitrogen inlet, and a mechanical stirrer. The entire apparatus was flame dried under a stream of dry, carbon dioxide free nitrogen (passed through a trap of Dreirite and Ascarite). One of the addition funnels was removed and under an atmosphere of dry nitrogen 3 l. of *o*-dichlorobenzene was distilled from molecular sieves [Linde 4A, activated at 220° (1 Torr)] into the reaction flask. In a similar manner 500 ml *o*-dichlorobenzene was distilled into each addition funnel.

To one funnel dry **4** (6.06 g, 30 mmol, freshly vacuum distilled from CaH_2) was added and to the other funnel freshly sublimed 3,5-dicarbochloropyridine[16] (3.06 g, 15 mmol). The two solutions were added dropwise at the same rate over a period of 18 hr to the stirred reaction solution, which was maintained at 165–175° by means of a heating mantel and a Thermowatch (I^2R). After the addition was complete the funnels were removed, the flask was fitted with a distillation head, and the *o*-dichlorobenzene was removed by vacuum distillation (40 Torr). The residual brown glass was powdered, placed in a Soxhlet, and continuously extracted with chloroform for 22 hr. The crystalline chloroform-soluble material (2.353 g) was dissolved in 10 ml of chloroform–methanol (9:1) and chromatographed on 120 g of Florisil. Elution with 4% methanol in chloroform afforded 329 mg (6.6%) of pure (tlc) **5**, R_f 0.50 (silica, 50% chloroform, 40% acetone, 10% diethylamine).

The analytical sample was prepared by sublimation [175° (5×10^{-4} Torr)]: mp 310–312° dec; ν_{max}^{KBr} 3280 (NH), 1658 (C=O), and 1195 cm^{-1} (CO-*t*-Bu); $\tau_{DMSO\text{-}d_6}^{TMS}$ 0.8–1.4 (m, 3 H, pyridine H), 1.7–1.9 (m, exchangeable with D_2O/OD^-, 2 H, NH), 6.3–7.3 (m, 5 H, CH_2N and CHOR), 8.98 [s, 9 H, $C(CH_3)_3$];

(9) The bases which have been tried are sodium hydride, lithium bis(trimethylsilyl)amide, potassium *tert*-butoxide, *tert*-butyllithium, and aluminum isopropoxide.

(10) Although we were not able to prepare an authentic sample of a macrocyclic 1,4-dihydropyridine (see footnotes to Table I), it is not unreasonable to expect that **1a**, if formed, would show absorption maxima similar to that of the 1,4-dihydropyridine derived from **9**. The similarity in the uv maxima of the 1,2-dihydro products formed from **9** and **1** indicates that the distortion resulting from the fused macrocyclic ring probably does not seriously perturb the uv spectrum.

(11) T. C. Bruice in "The Enzymes," Vol. II, 3rd ed, P. D. Boyer, Ed., Academic Press, New York, N. Y., 1970, Chapter 4.

(12) The failure of **1** to undergo intramolecular hydride transfer is surely not a result of the low oxidizing power of the pyridinium compound chosen, since **1** is much more reactive toward the addition of hydroxide than benzyl nicotinium bromide itself.[2]

(13) (a) The isolation procedure consisted of thorough extractions with the specified solvent, washing the combined extracts with saturated aqueous sodium chloride solution, drying the extracts over anhydrous magnesium sulfate, and removal of solvent from the filtered extracts under reduced pressure on a rotary evaporator. Amines were dried over anhydrous potassium carbonate. (b) Microanalyses were performed by Schwarzkopf Laboratories, New York, N. Y., or Chemalytics, Inc., Tempe, Ariz. (c) All ultraviolet spectra were run in 1-cm quartz cells on a Cary Model 15 recording spectrophotometer at 25.0 ± 0.1°.

(14) O. E. Curtis, Jr., J. M. Sandri, R. E. Crocker, and H. Hart, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 278.

(15) The addition funnels described by Setter[5] were modified to use Teflon adjustable stopcocks and to hold a volume of 600 ml.

(16) Mp 69–70° [reported 66°: H. Meyer and H. Tropsch, *Monatsh. Chem.*, **35**, 782 (1914)].

mass spectrum m/e (rel intensity) 333 (42, M^+), 305 (19, M − CO), 276 (100, M − C_4H_9), 260 (56, M − OC_4H_9).

Anal. Calcd for $C_{18}H_{27}N_3O_3$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.56; H, 8.31; N, 12.46.

2,12-Dioxo-7-hydroxy-3,11,15-triazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (6).—A mixture of **5** (60.8 mg, 0.182 mmol) and 20 ml of anhydrous trifluoroacetic acid was swirled for 5 min, at which time a solution was obtained. The trifluoroacetic acid was quickly removed *in vacuo* at 25–35°, 2 ml of chloroform and 1 ml of methanol were added, and the solution was allowed to crystallize at 0°. The insoluble precipitate was isolated by filtration, washed three times with a total of 1 ml of methanol, and dried to afford 39.6 mg (78%) of **6**, mp 316–318° dec. Recrystallization from methanol afforded pure (tlc) **6**: R_f 0.15 (silica, 50% chloroform, 40% acetone, 10% diethylamine); mp 320–323° dec; ν_{max}^{KBr} 3100–3600 (NH, OH), 1663 (sh), and 1640 cm^{-1} (C=O); $\tau_{DMSO\text{-}d_6}^{TMS}$ 0.9–1.4 (m, 3 H, pyridine H), 1.7–2.2 (m, exchangeable with D_2O/OD^-, 2 H, NH), 6.2–7.4 (m, 5 H, CH_2N and CHOH); mass spectrum m/e (rel intensity) 277 (4, M^+), 260 (9, M − OH), 249 (25, M − CO), 105 (100, M − C_4H_5NCO).[17]

15-Benzyl-2,12-dioxo-7-hydroxy-3,11,15-triazoniumbicyclo[11.3.1]heptadeca-1(17),13,15-triene Bromide (1).—A solution of **6** (27.7 mg, 0.10 mmol), freshly vacuum distilled benzyl bromide (170 mg, 1.00 mmol), and 10 ml of dimethylformamide (distilled from CaH_2) was stirred under a nitrogen atmosphere at 75–85° for 2.5 hr. Dimethylformamide and excess benzyl bromide were removed *in vacuo* at 60°, 20 ml of methyl ethyl ketone was added, and the resulting solid was isolated by filtration to afford 47.7 mg of a light brown solid, mp 242–244° dec. This material was dissolved in water, decolorized with Norit, and recrystallized from methanol–methyl ethyl ketone (1:4) to afford 30.7 mg (68%) of **1**, mp 236–241° dec.

The analytical sample was prepared by two recrystallizations from ethanol–acetone: mp 239–241° dec; ν_{max}^{KBr} 3250–3550 (OH, NH), 3140 (NH), 1670 (C=O); $\tau_{D_2O}^{TMS}$ 0.6–0.8 (m, 2 H, pyridine H-2 and H-6), 1.36 (broad s, 1 H, $W_{1/2}$ = 6 Hz, pyridine H-4), 2.58 (s, 5 H, C_6H_5), 4.13 (s, 2 H, $CH_2C_6H_5$), 6.3–7.3 (m, 5 H, CH_2N and CHOR); $\lambda_{max}^{H_2O\ (pH\ 6)}$ 243 mμ (sh, ε 7.0 × 10^3).

Anal. Calcd for $C_{21}H_{26}N_3O_3Br$: C, 56.25; H, 5.86; N, 9.37; Br, 17.82. Found: C, 56.34; H, 6.14; N, 9.06; Br, 17.58.

2,12-Dioxo-3,11,15-triazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (7).—Following the procedure used for the preparation of **5**, dry 1,7-heptanediamine (1.300 g, 10 mmol, freshly vacuum distilled from CaH_2) was condensed under high dilution conditions with freshly sublimed 3,5-dicarbochloropyridine[16] (1.030 g, 5 mmol) to afford after continuous extraction ($CHCl_3$) and sublimation (250°, 1 Torr) 180 mg (6.9%) of **7**, mp 334–337° dec.

The analytical sample was prepared by recrystallization from methanol to afford platelets: mp 334–337° dec; ν_{max}^{KBr} 3265 (NH), 1654, and 1637 cm^{-1} (C=O); $\tau_{DMSO\text{-}d_6}^{TMS}$ 0.8–1.4 (m, 3 H, pyridine H), 1.6–1.8 (m, exchangeable with D_2O/OD^-, 2 H, NH), 6.3–7.2 (m, 4 H, CH_2N); mass spectrum m/e (rel intensity) 261 (83, M^+), 233 (11, M − CO), 204 (71, M − CO and/or CH_2=NH), 105 (100, M − C_5H_4NCO).

Anal. Calcd for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.15; H, 7.42; N, 16.02.

15-Benzyl-2,12-dioxo-3,11,15-triazoniumbicyclo[11.3.1]heptadeca-1(17),13,15-triene Bromide was prepared from **7** in 79% yield following a procedure identical with that for the preparation of **1**. The analytical sample was prepared by two recrystallizations from ethanol–acetone: mp 261–262° dec; ν_{max}^{KBr} 3270 (NH), 1665 cm^{-1} (C=O); $\tau_{D_2O}^{TMS}$ 0.6–0.8 (m, 2 H, pyridine H-2 and H-6), 1.30 (s, 1 H, $W_{1/2}$ = 6 Hz, pyridine H-4), 2.53 (broad s, 5 H, C_6H_5), 4.03 (s, 2 H, $CH_2C_6H_5$), 6.4–7.4 (m, 4 H, CH_2N).

Anal. Calcd for $C_{21}H_{26}N_3O_2Br$: C, 58.34; H, 6.06; N, 9.72. Found: C, 58.49; H, 6.24; N, 9.50.

1-Benzyl-*N'*,*N''*-dipropyl-3,5-dicarboxamidopyridinium Bromide (9).—A solution of reagent grade *n*-propylamine (0.84 ml, 10 mmol), 3,5-dicarbochloropyridine[16] (424 mg, 2.0 mmol), and 25 ml of distilled benzene was stirred at 25° under an atmosphere of nitrogen for 2 hr. The benzene was removed *in vacuo*, and the residue was washed with water and recrystallized from ethanol–water to afford 489 mg (95%) of *N,N'*-dipropyl-3,5-dicarboxamidopyridine, mp 180–181°.

Quaternization with benzyl bromide following the procedure used for the preparation of **1** afforded 745 mg (95%) of **9**, mp 236–238°. The analytical sample was prepared by two recrystallizations from ethanol–acetone: mp 233–234°; ν_{max}^{KBr} 3195 (OH, NH), 1670 cm^{-1} (C=O); $\tau_{DMSO\text{-}d_6}^{TMS}$ 0.20 (broad s, 2 H, pyridine H-2 and H-6), 0.45 (broad s, 1 H, pyridine H-4), 0.70 (s, J = 5 Hz, exchangeable with D_2O/OD^-, 2 H, NH), 2.15–2.65 (m, 5 H, C_6H_5), 3.93 (s, 2 H, $CH_2C_6H_5$), 6.41–6.83 (m, 4 H, CH_2N), 8.15–8.60 (m, 4 H, $CH_2CH_2CH_3$), 9.08 (unsymmetrical t, J = 7 Hz, 6 H, CH_3).

Anal. Calcd for $C_{20}H_{26}N_3O_2Br$: C, 57.14; H, 6.24; N, 10.00; Br, 19.01. Found: C, 57.04; H, 6.19; N, 10.08; Br, 18.68.

Treatment of 1 with Strong Bases under Anhydrous Conditions.[18] **A. Aluminum Isopropoxide.**—**1** (12.1 mg 0.027 mmol) was weighed into a predried nmr tube and under an argon stream 0.40 ml of dry HMPA[18a] was added *via* syringe. After the tube was filled with an argon atmosphere, the cap was sealed with Parafilm, and the tube was heated at 80° for 10 min until **1** dissolved. After the tube was allowed to cool to room temperature, freshly distilled aluminum isopropoxide[18c] (17.5 mg, 0.086 mmol) was added under an argon stream, and the tube was filled with an argon atmosphere and the cap sealed with Parafilm. The nmr[21] spectrum was nearly identical with that of **1** before the addition of aluminum isopropoxide and showed absorptions (downfield from HMPA) of 440–480 (broad m, 2 H, NH), 450 (s, ~1 H, $W_{1/2}$ = 8 Hz, pyridine H-4), 396 (broad s, $W_{1/2}$ = 17 Hz, 2 H, pyridine H-2 and H-6), 342–312 (m, 2 H, *o*-C_6H_5), 304–270 (m, 3 H, *m*- and *p*-C_6H_5), 240 Hz (s, 2 H, $CH_2C_6H_5$), and a peak assigned to the hydroxyl hydrogen of isopropyl alcohol at 161 Hz (d, J = 4 Hz, 1.3 H). Addition of 20 μl of isopropyl alcohol increased the peak at 161 Hz. After 12 hr the above sample was quenched by the addition of 1 drop of glacial acetic acid, and the nmr spectrum was unchanged except that the peak at 450 Hz was noticeably sharper having the same $W_{1/2}$ (5 Hz) as did the sample before the addition of aluminum isopropoxide.

B. Sodium Hydride.—Following the same procedure as described above in experiment A, **1** (12.1 mg, 0.024 mmol) was treated with sodium hydride[18b] (5 mg, 52.6% dispersion in oil) in 0.35 ml of dry HMPA.[18d] The nmr spectrum (downfield from HMPA) showed the complete absence of signals in the pyridine aromatic region (360–480 Hz), a poorly resolved increase in intensity in the C_6H_5 region (270–350 Hz), and the absence of the benzyl methylene hydrogens of **1** at 240 Hz. After 15 min the reaction was quenched by the addition of 1 drop of glacial acetic acid. The nmr spectrum was unchanged. HMPA was removed by vacuum sublimation at 60–70° (1 Torr) using a Dry Ice cooled cold finger, and the resulting yellow residue was triturated with 3 ml of hot chloroform. The absence of any dihydropyridine product in the concentrated chloroform extract (10 mg of a light red oil) was apparent from the absence of singlet absorption for the benzyl methylene of a dihydropyridine in the ~ 4.5–5.5 region[22] and the absence of ketone carbonyl absorption (1680–1720 cm^{-1}) in the ir spectrum.

C. Potassium *tert*-Butoxide or Lithium Bis(trimethylsilyl)amide.[23]—Treatment of **1** (2×10^{-3} *M* in HMPA)[18a] for 10 min

(17) Correct analyses could not be obtained for this compound. All preparations analyzed approximately 1% low for carbon.

(18) The bases and solvents used were purified as follows. (a) Hexamethylphosphoramide (HMPA) (Aldrich) was vacuum (5–10 Torr) distilled from CaH_2 directly into the reaction flask. The still was constructed such that the vacuum could be replaced by argon before the reaction flask was removed. (b) Sodium hydride (Metal Hydrides Inc.), a 52% dispersion in mineral oil, was washed twice with distilled pentane, covered with dry HMPA, and transferred into the reaction flask as a slurry in HMPA. (c) Aluminum isopropoxide (MCB) was distilled [bp 130–140° (7 Torr)] directly before use and stored under an argon atmosphere in a desiccator over P_2O_5. (d) Potassium *tert*-butoxide was prepared by the procedure of Johnson,[19] sublimed [220° (1 Torr)] directly before use, and stored under an argon atmosphere in a desiccator over P_2O_5. (e) Lithium bis(trimethylsilyl)amide was prepared by the procedure of Smith[20] [bp 115° (1 Torr)], sublimed [60° (1 Torr)] directly before use, and stored under an argon atmosphere in a desiccator over P_2O_5.

(19) W. S. Johnson and W. P. Schneider, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 132.

(20) E. H. Amonoo-Neizer, R. A. Shaw, D. O. Sklovlin, and B. C. Smith, *J. Chem. Soc.*, 2997 (1965).

(21) The nmr spectra of benzyl salts **1**, **8**, **9**, and **10** show considerable solvent variations. The most dramatic differences were observed for the C_6H_5 group which appeared as a sharp singlet ($W_{1/2}$ = 4 Hz) in D_2O and a complex multiplet in DMSO or HMPA.

(22) H. Dieckman, G. Englert, and K. Wallenfels, *Tetrahedron*, **20**, 281 (1964).

(23) These experiments were conducted in a drybox under an argon atmosphere.

at 25° with 1 equiv of potassium *tert*-butoxide[18d] afforded after quenching with acetic acid and chloroform isolation[13a] a yellow oil which contained no **1a** as judged by the absence of carbonyl absorption in the ir spectrum and the absence of a uv maximum at wavelength longer than 330 nm (observed λ_{max}^{EtOH} 328 and shoulder 260 nm).

Nearly identical results were obtained from similar experiments using lithium bis(trimethylsilyl)amide[18c] as the base.

Registry No.—**1**, 36612-02-9; **2**, 869-95-4; **3**, 36612-04-1; **4**, 36612-05-2; **5**, 36612-06-3; **6**, 36612-07-4; **7**, 36612-08-5; **8**, 36635-93-5; **9**, 36612-09-6.

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Reaction of Trialkyl Phosphites with Haloamides[1]

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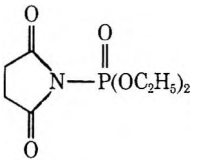
Synthetic routes to insecticidally active *O,S*-dialkyl *N*-acylphosphoramidothioates are multistep and often result in poor yields.[2] In seeking alternate routes to these compounds, the reactions between *N*-bromoacetamide (**1**) and triethyl phosphorothioite and between *N*-chlorobenzamide (**2**) and trimethyl phosphorothioite were investigated. In each case, no dialkyl *N*-acylphosphoramidothioate could be isolated although the starting materials were consumed and alkyl halides were evolved.

In an attempt to understand these reactions it was decided to investigate the reaction between *N*-haloamides and trialkyl phosphites, as the products from these reactions have not been fully elucidated.[3] *N*-Chlorosuccinimide[4] (**3**) and *N*-bromosuccinimide[5] (**4**) react with trialkyl phosphites to give the Arbuzov products. *N*-Chloro-*N*-alkylamides, on the other hand, react with trialkyl phosphites to give imidoyl chlorides and trialkyl phosphates.[6] Similarly, *N*-chloro-*N*-ethylbenzamide and triphenylphosphine react to give *N*-ethylbenzimidoyl chloride and triphenylphosphine oxide.[7] However, the action of triphenylphosphine on *N*-bromoamides results in the corresponding nitrile and triphenylphosphine oxide.[8]

This note describes the products obtained from the reaction between trialkyl phosphites and the following *N*-haloamides: *N*-bromoacetamide (**1**), *N*-chlorobenzamide (**2**), *N*-chlorosuccinimide (**3**), *N*-bromosuccinimide (**4**), *N*-bromo-2-pyrrolidinone (**5**), *N*-chloroacetamide (**6**), *N*-chloro-*N*-methylacetamide (**7**), and *N*-bromobenzamide (**8**).

The cyclic haloamides or imides (**3**–**5**) reacted with 1 equiv of triethyl phosphite to give ethyl halide and phosphoramidate **9** or **10**. The product **9**, which was



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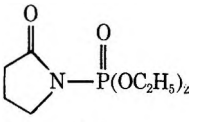

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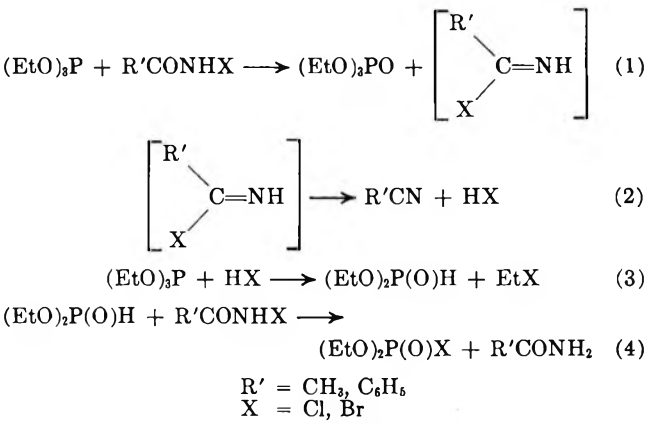
the same whether prepared from **3** or **4**, was identical with that reported previously.[5]

The acyclic primary haloamides (**1**, **2**, **6**, and **8**) did not give the expected Arbuzov products but instead reacted to give products (Table I) consistent with Scheme I.

SCHEME I[a]



$$(EtO)_3P + R'CONHX \longrightarrow (EtO)_3PO + \left[\begin{matrix} R' \\ \diagdown \\ C{=}NH \\ \diagup \\ X \end{matrix}\right] \quad (1)$$

$$\left[\begin{matrix} R' \\ \diagdown \\ C{=}NH \\ \diagup \\ X \end{matrix}\right] \longrightarrow R'CN + HX \quad (2)$$

$$(EtO)_3P + HX \longrightarrow (EtO)_2P(O)H + EtX \quad (3)$$

$$(EtO)_2P(O)H + R'CONHX \longrightarrow (EtO)_2P(O)X + R'CONH_2 \quad (4)$$

R′ = CH_3, C_6H_5
X = Cl, Br

[a] Square brackets are used to indicate intermediates that were never isolated.

When *N*-chloro-*N*-methylacetamide (**7**) and trialkyl phosphite were allowed to react, the only products were the trialkyl phosphate and *N*-methylacetimidoyl chloride,[6] analogous to step 1 in the scheme. For the primary haloamides, Scheme I is supported by the following evidence.

(1) Reaction of 1 equiv of primary haloamide with 1 equiv of triethyl phosphite led to the formation of approximately 0.5 equiv of ethyl halide, nitrile, amide, triethyl phosphate, and diethyl halophosphate (*cf.* Table I).

(2) The reaction was exothermic until almost 2 equiv of triethyl phosphite had been added. At this point, no triethyl phosphite could be isolated when it was introduced rapidly.

(3) Addition of 2 equiv of triethyl phosphite to 1 equiv of primary haloamide gave in good yields the products indicated in eq 5 (the summation of steps 1–3). Small amounts of amide and diethyl halophosphate (the products of step 4) also were isolated.

$$2(EtO)_3P + R'CONHX \longrightarrow (EtO)_2P(O)H + (EtO)_3PO + R'CN + EtX \quad (5)$$

(1) This investigation was supported in part by a Research-Training Grant from The Rockefeller Foundation and by Research Grant No. EP-00806 from the Environmental Protection Agency, Washington, D. C.

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TABLE I

PRODUCTS OBTAINED FROM THE REACTION BETWEEN *N*-HALOAMIDES AND TRIETHYL PHOSPHITE AT 25°

Haloamide	Liquid vehicle	Moles of reagents: Haloamide	Moles of reagents: Phosphite	Moles of products: RCN	RCONH$_2$	EtX	(EtO)$_2$P(O)X	(EtO)$_2$P(O)H	(EtO)$_3$P(O)
1	Toluene	0.5	1.0	0.46	<0.04	0.45	~0	0.36	0.41
2	CCl_4	0.5	1.0	0.44	0.02	0.25	0.07	0.32	0.45
2	Ether	1.0	1.0	0.34	0.42		0.32	0.02	0.47
2	Benzene	1.0	1.0	0.41	0.48	0.48	0.36	<0.01	0.41
6	Benzene	1.0	1.0	0.47	0.48	0.50	0.42	~0	0.36
8	CCl_4	0.5	1.0	0.48	<0.02	0.50	0.03	0.36	0.36
8	CCl_4	1.0	1.0	0.48	0.44	0.50	0.37	0.05	0.46
8	Ether	1.0	1.0	0.44	0.46	0.37	0.43	0.06	0.43

(4) When 1 equiv of triethyl phosphite was treated with 1 equiv of **1** in the presence of pyridine, the ratio of acetonitrile to ethyl bromide increased and pyridinium hydrobromide was isolated (*cf.* Table II).

TABLE II

EFFECT OF HBr ON THE REACTION BETWEEN *N*-BROMOACETAMIDE AND TRIETHYL PHOSPHITE IN BENZENE

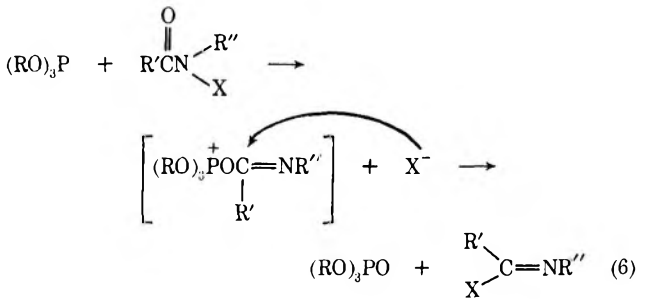
Moles of reagents: Haloamide	Phosphite	Other	Moles of volatile products: EtBr	CH_3CN
1.0	1.0		0.37	0.48
1.0	1.0	HBr 1.0	0.74	0.08
1.0	1.0	Pyridine 1.0	0.26	0.68

Pyridine, by acting as a scavenger for HBr formed in step 2, decreased the availability of HBr to react with triethyl phosphite (step 3).

(5) When 1 equiv of triethyl phosphite was treated with 1 equiv of **1** in the presence of 1 equiv of HBr, the ratio of ethyl bromide to acetonitrile increased, indicating that HBr can compete with **1** for triethyl phosphite under the conditions of the reaction (*cf.* Table II).

(6) The reactions given in steps 2,[7,9] 3,[10,11] and 4[12] are known to occur readily.

The first step in the reaction sequence (eq 1) for acyclic *N*-haloamides probably occurs through the imidoyl phosphonium halide as shown below.



$R = CH_3,\ C_2H_5,\ n\text{-}C_4H_9$
$R' = CH_3,\ C_6H_5$
$R'' = H,\ CH_3$
$X = Cl,\ Br$

The formation of the imidoyl phosphonium halide is required by the isolation of *N*-methylacetimidoyl chloride from **7**[6] and the isolation of the respective nitriles from **1**, **2**, **6**, and **8**. The structure of the reactive phosphonium intermediate has been discussed for **3** and **4**.[4,5] The presence of a phosphonium intermediate in the reaction between **4** and trialkyl phosphites has been argued from the products obtained by carrying out the reaction in the presence of excess nucleophile.[5] A similar procedure was used in this work for **1**–**3** and **5**–**8** and the products obtained were consistent with the formation of a reactive phosphonium intermediate (*cf.* Table III). Nucleophiles used were alcohols and water, resulting in the formation of phosphates and dialkyl phosphoric acids, respectively.

TABLE III

PRODUCTS FROM THE REACTIONS BETWEEN *N*-HALOAMIDES AND (RO)$_3$P IN THE PRESENCE OF WATER, METHANOL, OR ETHANOL

Reagents: Haloamide	R	Nucleophile	Liquid vehicle	Product, % yield: Amide	(RO)$_3$PO	(RO)$_2$P(O)OH
1	Et	EtOH	C_6H_6	100[a]	100[a]	
2	Et	H_2O	Ether	95		78
2	Et	EtOH	Ether	100[a]	100[a]	
3	Et	H_2O	Ether	96		57
5	Et	H_2O	Ether			58
5	Me	MeOH	Ether	93	96	
6	Et	EtOH	C_6H_6	84	66	
7	Et	EtOH	C_6H_6	93	71	
8	Me	MeOH	C_6H_6	82	84	
8	Et	H_2O	C_6H_6	88		48

[a] Based on tlc analysis.

The reaction between trimethyl phosphorothioite and **2** was reinvestigated in the light of this knowledge. One equivalent of trimethyl phosphorothioite reacted with 1 equiv of **2** to give approximately 0.3 equiv each of benzamide, benzonitrile, and methyl chloride together with other products that were not identified. These products in large part explain the failure to isolate any dimethyl *N*-benzoylphosphoramidothioate from this reaction.

The probable initial reaction (Scheme I, step 1) between acyclic *N*-haloamides and trialkyl phosphites and phosphorothioites thus resembles the reaction between *N*-haloamides and phosphines[7,8] leading to the formation of tertiary phosphorus oxides rather than to the formation of the Arbuzov products.

The choice of liquid vehicle did not affect the product ratios significantly (*cf.* Table I). The reactions described above occurred with carbon tetrachloride as liquid vehicle, even though this solvent itself is known to react with trialkyl phosphites to form Arbuzov products.[13]

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Experimental Section

Compounds **3** and **4** were purchased from Matheson Coleman and Bell. Compounds **1**,[14] **2**,[15] **5**,[16] **6**,[17] **7**,[6] and **8**[17] were prepared by known procedures. All starting materials were purified by distillation or recrystallization prior to use. Melting points were taken on a Fisher-Johns melting point apparatus and all melting and boiling points are uncorrected. Pmr spectra were taken on a Varian T-60 spectrometer using TMS as an internal standard. Ir spectra were determined in a Perkin-Elmer Model 21 spectrophotometer; mass spectra in a Finnegan 1015 mass spectrometer. In most cases, product verification and quantitation was accomplished by gas–liquid chromatography using an F & M Model 402 gas chromatograph equipped with columns made from 5% Carbowax 20 n on Gas-Chrom Q, 1800 mesh (system A), and 1.5% OV-3 on Gas-Chrom Q, 80/100 mesh (system B), at a flow rate of 60 ml of carrier gas (nitrogen) per minute. Retention times of the products from the reaction between the various *N*-haloamides and phosphates are given in Table IV.

TABLE IV

RETENTION TIMES (MIN) AT FLOW RATE OF 60 ML/MIN

Compd	Column	Temp, °C	Retention time
$(EtO)_2P(O)Cl$	A[a]	108	2.20
	A	116	1.62
	B[b]	115	0.50
$(EtO)_2P(O)H$	A	108	2.75
	A	116	1.75
	B	115	0.38
$(EtO)_2P(O)Br$	A	108	2.45
	B	116	0.30
C_6H_5CN	A	116	2.40
$(EtO)_3PO$	A	116	2.38
	B	115	1.12
$(EtO)_2P(O)NHPr$	B	115	5.49
	B	171	0.51

[a] Column A, 5% Carbowax 20 n on Gas-Chrom Q, 1800 mesh. [b] Column B, 1.5% OV-3, on Gas-Chrom Q, 80/100 mesh.

All organophosphorus compounds were detectable at the nanogram level. Diethyl halophosphates also were identified and quantitated by converting them to *O,O*-diethyl *N*-propylphosphoramidates by reaction with excess propylamine and subsequent analysis by glc. This reaction was shown to be quantitative in control experiments. Benzonitrile also was quantitated from the nitrile absorption peak at 2250 cm^{-1}. Tlc systems used were silica/ether–petroleum ether (bp 30–60°) (1:1), silica/chloroform, alumina/chloroform, alumina/ether, and cellulose/benzene.

Reaction of Triethyl Phosphite and *N*-Bromoacetamide.—To a vigorously stirred suspension of 6.9 g (0.05 mol) of *N*-bromoacetamide in 30 ml of toluene at room temperature was added rapidly 16.6 g (0.1 mol) of triethyl phosphite. The reaction was exothermic and, after cooling, the mixture was distilled through a Vigreux column at atmospheric pressure to give 4.88 g (90%) of ethyl bromide, bp 40–41°, and 1.90 g (93%) of acetonitrile, bp 82–84°. Toluene was removed under reduced pressure and distillation of the residue gave 5.05 g (73%) of diethyl hydrogen phosphite, bp 66–74° (8.0–8.5 mm), $n^{25}D$ 1.4068 [lit.[18] bp 75° (15 mm), $n^{25}D$ 1.4080], and 7.6 g (83%) of triethyl phosphate, bp 94–96° (8.0 mm), $n^{25}D$ 1.4040 [lit.[19] bp 90° (10 mm), $n^{25}D$ 1.4039]. Products also were verified by tlc and ir.

Reaction of Triethyl Phosphite and *N*-Chlorobenzamide.—*N*-Chlorobenzamide (1.55 g, 0.01 mol) was added in small portions over 15 min to a stirred suspension of 3.32 g (0.02 mol) of triethyl phosphite in 10 ml of carbon tetrachloride under a nitrogen atmosphere. Ethyl chloride was removed under reduced pressure and identified by pmr. The reaction mixture was cooled and benzamide, mp 128–130°, was collected. Diethyl phosphorochloridate, diethyl hydrogen phosphite, benzonitrile, and triethyl phosphate were identified and quantitated by glc.

***N*-(Diethylphosphinyl)-2-pyrrolidinone.**—To a stirred suspension of *N*-bromo-2-pyrrolidinone (6.6 g) in 10 ml of benzene was added over 30 min triethyl phosphite (6.65 g) in 6 ml of benzene. The ratio of ethyl bromide to total ethoxy protons was shown to be 1:2 by pmr spectroscopy. Rapid chromatography (alumina/$CHCl_3$) gave 8.4 g (94%) of *N*-(diethylphosphinyl)-2-pyrrolidinone, *m/e* 221, unstable to distillation: pmr (CCl_4) τ 8.87–8.49 (m, 6), 8.24–7.55 (m, 4), 7.14–6.52 (m, 2), 6.31–5.47 (m, 4).

Reaction of Triethyl Phosphite with *N*-Chlorosuccinimide in the Presence of Water.—To a stirred suspension of 6.65 g of *N*-chlorosuccinimide in a mixture of 10 ml of ether, 2 ml of acetone, and 2 ml of water was added 8.4 g of triethyl phosphite over 20 min at room temperature. The solvent was removed under reduced pressure and the residue was washed with cold ether and filtered to give 4.75 g (96%) of succinimide, mp 118.5–119.5°. The etheral filtrate was distilled to yield 4.33 g (57%) of diethylphosphoric acid, bp 130–135° (0.025 mm), $n^{25}D$ 1.4143 (lit.[20] $n^{25}D$ 1.4148).

Reaction of Trimethyl Phosphite with *N*-Bromobenzamide in the Presence of Methanol.—To a stirred suspension of 10 g of *N*-bromobenzamide in 10 ml of benzene and 5 ml of methanol was added 6.2 g of trimethyl phosphite over 30 min. The resulting solution was concentrated under reduced pressure and diluted with petroleum ether. Benzamide (4.95 g, 82%), mp 127–129°, was removed by filtration and the filtrate was distilled to give 5.9 g (84%) of trimethyl phosphate, bp 73–75° (10 mm), $n^{25}D$ 1.3954 [lit.[19] bp 73° (10 mm), $n^{25}D$ 1.3950].

Reaction of *N*-Chlorobenzamide and Trimethyl Phosphorothioite.—To a stirred suspension of *N*-chlorobenzamide (0.77 g) in benzene (10 ml) was added at room temperature trimethyl phosphorothioite (0.70 g) in benzene (5 ml). Methyl chloride (1.5×10^{-3} mol) was removed in a stream of nitrogen and identified by pmr. The reaction mixture was concentrated and filtered to give benzamide (0.21 g, 1.7×10^{-3} mol). Benzonitrile (1.6×10^{-3} mol) was identified by ir.

Registry No.—**1**, 79-15-2; **2**, 1821-34-7; **3**, 128-09-6; **4**, 128-08-5; **5**, 2401-40-3; **6**, 598-49-2; **7**, 5014-39-1; **8**, 19964-97-7; triethyl phosphite, 122-52-1; ethyl bromide, 74-96-4; acetonitrile, 75-05-8; *N*-(diethylphosphinyl)-2-pyrrolidinone, 36614-67-2; diethyl phosphoric acid, 598-02-7; trimethyl phosphite, 121-45-9; trimethyl phosphorothioite, 36614-68-3.

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Reaction of *N*-Iodosuccinimide with Tertiary Alcohols

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The reaction of secondary alcohols with *N*-iodosuccinimide (NIS) has been shown to produce ketones or cyclic ethers. Secondary alcohols in steroid systems with the hydroxy group in the axial position on carbon 6 produce the cyclic ethers,[1] while oxidation of 1-phenylethanol with NIS gives the ketone.[2] The formation of a cyclic ether from an alcohol and NIS indicates that

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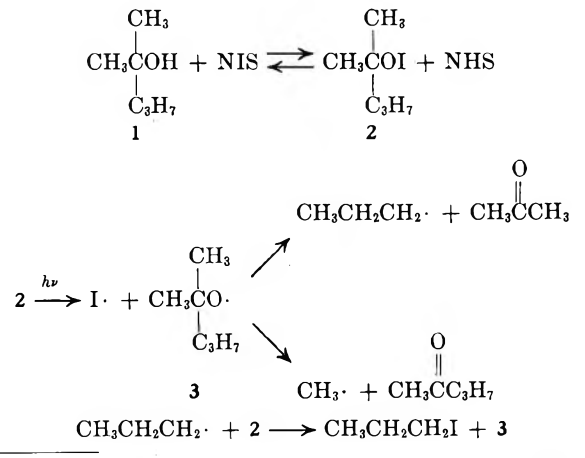
an intermediate hypoiodite is probably formed, while the production of a ketone allows for either hypohalite formation or for succinimidyl radical oxidation of the alcohol. To study the possibility that alkyl hypoiodites might be a general product when NIS and alcohols are heated together, we decided to investigate the reaction of *tert*-alkyl alcohols with *N*-iodosuccinimide.

This paper describes the successful conversion of several tertiary alcohols by NIS to alkyl iodides and ketones. Reported here are the reactions of four tertiary alcohols with NIS: *tert*-butyl alcohol, 3-ethyl-3-pentanol, 3-methyl-3-pentanol, and 2-methyl-2-pentanol (**1**). Two of the alcohols, *tert*-butyl alcohol and 3-ethyl-3-pentanol, are symmetrical alcohols and the proposed hypoiodite intermediates that are formed can give only one ketone and one alkyl iodide product. *tert*-Butyl alcohol in benzene with NIS gave 54–57% yields of acetone and 47–60% yields of methyl iodide when the mixtures were irradiated. The irradiation of a mixture of NIS and 3-ethyl-3-pentanol in benzene gave yields of 95–99% of 3-pentanone and 91–100% of ethyl iodide. Succinimide was recovered in 73–80% yields.

The products formed from the reaction of *N*-iodosuccinimide with 3-methyl-3-pentanol and 2-methyl-2-pentanol give more evidence that an alkyl hypoiodite is an intermediate when tertiary alcohols react with NIS. The alkyl iodides and ketones formed follow the β-scission order found by Walling and Padwa[3] in the decomposition of *tert*-alkyl hypochlorites. 3-Methyl-3-pentanol with NIS produced 85–91% yields of ethyl iodide. (The 2-butanone peak could not be separated from the benzene solvent peak on the glc and was not determined.) The reaction of 2-methyl-2-pentanol in benzene with NIS gave 40–52% of acetone and 52–58% of *n*-propyl iodide. The formation of acetone and *n*- propyl iodide is believed to occur by the following pathway. The formation of the intermediate *tert*-hypoiodite **2** is very likely an equilibrium step, as Barton and coworkers[4] have prepared *N*-iodoamides with *tert*-butyl hypoiodite. The decomposition of the *tert*-hypoiodite **2** follows the expected light-induced cleavage of the O–I bond producing an iodine atom and *tert*-alkoxy radical **3**, which decomposes to produce the *n*-propyl radical and acetone. The *n*-propyl radical then forms *n*-propyl iodide by abstracting an iodine atom from **2**. We had expected that the



(3) C. Walling and A. Padwa, *J. Amer. Chem. Soc.*, **85**, 1593 (1963).
(4) D. H. R. Barton, A. L. J. Beckwith, and A. Goosen, *J. Chem. Soc.*, 181 (1965).

major product of the decomposition of the hypoiodite **2** might be 2,2-dimethyltetrahydrofuran, which would require an intramolecular hydrogen-abstracting step[3] by the *tert*-alkoxy radical **3**. The gas chromatographic analysis of the products showed only one small unidentified peak which could not account for more than 10–20% of the starting NIS. The major products formed under our reaction conditions came from C–C bond cleavage of the intermediate alkoxy radical **3** and not from intramolecular hydrogen abstraction.

Experimental Section

Analyses were carried out using a Perkin-Elmer 810 glc and a Varian Aerograph Model 700 glc. Infrared analyses were done using a Perkin-Elmer 337 grating infrared spectrophotometer. Circulation of ice water through the condensers was accomplished by means of a Cole-Parmer water pump, Model 7020-C with Masterflex SCR controller. Irradiation of the reaction mixtures was effected with a G. E. Projector Spot 150-W, 130-V tungsten lamp. The NIS was purchased from K & K Laboratories and was not recrystallized. The alcohols, ketones, and internal standards were purchased from Matheson Scientific and were fractionally distilled. Analyses of the *tert*-butyl alcohol and 2-methyl-2-pentanol reactions were performed using a 6-ft column of 15% SE-30–5% Carbowax 20M adsorbed on 60–80 mesh base-washed Chromosorb P, while the 3-ethyl-3-pentanol and 3-methyl-3-pentanol reactions were analyzed using a 6-ft column of 20% Carbowax 20M adsorbed on 60–80 mesh base-washed Chromosorb P. All reactions were run at reflux. A description of the oxidation of 3-ethyl-3-pentanol with NIS (Table I) is given in detail. The oxidations of *tert*-butyl alcohol, 3-methyl-3-pentanol, and 2-methyl-2-pentanol with NIS were run under identical conditions and the results of these oxidations are given in Tables II, III, and IV.

TABLE I
OXIDATION OF 3-ETHYL-3-PENTANOL WITH NIS

Conditions (Solvent, irradiation, time)	Yield of products, % 3-Pentanone	Ethyl iodide
Benzene, $h\nu$, 1 hr	99	100
Benzene, $h\nu$, 0.5 hr	95	91
Benzene, dark, 2.5 hr	31	26
p-Dioxane, $h\nu$, 0.5 hr	95	86
Pentane, $h\nu$, 10 hr	64	70
Diethyl ether, $h\nu$, 3 hr	70	80

TABLE II
OXIDATION OF *tert*-BUTYL ALCOHOL WITH NIS

Conditions (Solvent, irradiation, time)	Yield of products, % Acetone	Methyl iodide
Benzene, $h\nu$, 5 hr	54	60
Benzene, $h\nu$, 6 hr	57	50
Benzene, $h\nu$, 5 hr	54	60
Benzene, $h\nu$, 5 hr	54	47
tert-Butyl alcohol, $h\nu$, 25 min	54	47
tert-Butyl alcohol, $h\nu$, 2 hr	61	73
Benzene, dark, 9 hr	Trace	Trace

TABLE III
OXIDATION OF 3-METHYL-3-PENTANOL WITH NIS[a]

Conditions (Solvent, irradiation, time)	Yield of product, % Ethyl iodide
Benzene, $h\nu$, 20 min	85
Benzene, $h\nu$, 30 min	91
Benzene, dark, 3 hr	20
Benzene, dark, 20 hr	44

[a] The 2-butanone peak was not separated on the glc from the benzene peak and its per cent yield was not determined. Only trace amounts of methyl iodide and 3-pentanone were found.

TABLE IV

OXIDATION OF 2-METHYL-2-PENTANOL WITH NIS[a]

Conditions (Solvent, irradiation, time)	Yield of products, % Acetone	Yield of products, % n-Propyl iodide
Benzene, $h\nu$, 2 hr	40	52
Benzene, $h\nu$, 1.5 hr	52	58

[a] Only trace amounts of methyl iodide and 2-pentanone could be found. An unknown glc peak, 10–20% of the starting NIS, appeared between the benzene and *n*-propyl iodide peaks and was believed to be 2,2-dimethyltetrahydrofuran. No identification of the peak was attempted.

Oxidation of 3-Ethyl-3-pentanol with NIS.—Five milliliters of a solution of 0.516 *M* 3-ethyl-3-pentanol (2.58 mmol) and 0.596 *M* chlorobenzene (2.88 mmol) in dry benzene were added to 302 mg (1.34 mmol) of NIS. The mixtue was irradiated and heated to reflux for 1 hr. Glc analysis indicated yields of 101% ethyl iodide and 99% 3-pentanone. Water extractions of the reaction mixture produced 97 mg (0.98 mmol) of succinimide. Identification was made by mixture melting point and ir comparison with known succinimide. The results of all reactions of NIS with 3-ethyl-3-pentanol are given in Table I.

Registry No.—NIS, 516-12-1; *tert*-butyl alcohol, 75-65-0; 3-ethyl-3-pentanol, 597-49-9; 3-methyl-3-pentanol, 77-74-7; 2-methyl-2-pentanol, 590-36-3.

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The Solvolysis and Rearrangement of 2-Phenylethyl Tosylate in Trifluoroethanol[1]

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2,2,2-Trifluoroethanol (TFE) was first introduced as a solvent for the study of solvolytic reactions by Scott.[3] Subsequently, Trahanovsky and Doyle[4] pointed out that the low nucleophilicity of TFE promotes the formation of cyclized products from 5-hexenyl arenesulfonates. In a comprehensive study, Shiner, *et al.*,[5] have evaluated many of the desirable properties and characteristics of TFE for solvolysis studies. Bentley and Lacadie[6] have shown that TFE accentuates differences in reactivity of diverse benzyl chlorides more than does ethanol, aqueous dioxane, or acetic acid.

We have investigated the utility of TFE for the study of the solvolytic rearrangement of β-arylethyl tosylates. Our results indicate that TFE has considerable potential in this regard.

Solvolysis of 2-phenylethyl tosylate (**1**) in TFE is substantially *more rapid* than that for a model compound, ethyl tosylate (**2**). Electron-donating substituents in the aromatic moiety cause a marked further increase in the observed rates (Table I). From 2-(*p*-methylphenyl)ethyl tosylate (**3**) and 2-(*p*-methoxyphenyl)ethyl tosylate (**4**) a ρ of -2.5 (using σ^+) is obtained. This value is comparable to that observed for similar solvolytic rearrangements in acetic acid.[7]

TABLE I

RATE CONSTANTS FOR THE SOLVOLYSIS OF ARYLETHYL TOSYLATES IN TRIFLUOROETHANOL

Compound solvolyzed[a]	T, °C	$k_t \times 10^6$, sec^{-1}	Added salt
1	75.0	4.83 ± 0.05	
	100.0	37.5 ± 0.6	
	75.0	5.35 ± 0.1	NaOAc[b]
	74.8	64.9[c]	
	75.0	67.7[c]	NaOAc[b]
2	75.0	3.87 ± 0.04[c]	
	90.0	12.5 ± 0.2[c]	
	109.6	5.38 ± 0.06	
	109.6	...[d]	NaOAc[b]
3	75.0	53.1 ± 1	
4	75.0	339 ± 5	
5	75.0	3.98 ± 0.05	
6	75.0	...[e]	
	75.0	13.1	NaOAc[b]

[a] Kinetic solutions were 0.02 *M* in sulfonate. [b] Sodium acetate, 0.03 *M*. [c] *p*-Nitrobenzenesulfonate rather than tolysate solvolyzed. [d] Non-first-order kinetics; apparent "first-order rate constant" from initial rate data, 26.6×10^{-6} sec^{-1}. [e] Decomposition occurs.

Isotopically substituted **1**, 2-phenyl-*1,1*-d_2-ethyl tosylate (**5**) shows essentially complete scrambling in the products of solvolysis. Furthermore, the secondary deuterium isotope effect upon the rate is large, k_H/k_D = 1.21, which is apparently near maximum, and is as large as the ratios observed in the formolysis of activated β-arylethyl systems.[8] This high k_H/k_D is evidence for the dominance of the participating pathway, k_Δ, over the k_s pathway in the trifluoroethanolysis of **1** and supports an unsymmetrical partially bridged transition state.

A final point of interest, which is germane to present mechanistic discussions regarding the role of the phenonium ion in these solvolyses is the sharp *qualitative* difference in behavior between **1** and **2** when solvolyses are carried out in TFE with the addition of sodium acetate. The rate constant for **1** increases, and the magnitude of the increase is typical of normal salt effects. **2**, on the other hand, gives non-first-order behavior under these conditions, suggestive of bimolecular reaction between **2** and acetate ion.

A further study had been carried out examining the solvolysis of 2-(2-furyl)ethyl tosylate (**6**) in TFE buffered with sodium acetate.[9] This reaction is clean kinetically, in contrast to preliminary results with **6** in formic acid and sodium formate. In formic acid **6** shows appreciable extraneous decomposition and severe darkening of the kinetic solution before the apparent first half-period is complete.

Thus TFE shows promise for the study of β-arylethyl sulfonates. It accentuates the participating

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(2) National Science Foundation Graduate Trainee, 1969–1971.

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(6) M. D. Bentley and J. A. Lacadie, *Tetrahedron Lett.*, 741 (1971).

(7) M. G. Jones and J. L. Coke, *J. Amer. Chem. Soc.*, **91**, 4284 (1969).

(8) W. H. Saunders, Jr., and R. Glaser, *ibid.*, **82**, 3586 (1960); C. C. Lee and L. Noszko, *Can. J. Chem.*, **44**, 2491 (1966).

(9) Details of a complete study of **6** will be presented in a forthcoming manuscript, including a study of the isotopic rearrangement.

pathway and gives large rate increases over nonassisted solvolysis. For acid-sensitive substrates it holds advantages over formic acid (or trifluoroacetic acid).

Experimental Section

Materials.—The sulfonates were prepared by standard procedures and had properties in accordance with literature values: **1**, mp 37–38° (lit.[10] mp 37.5–38.2°); **2**, mp 31–32° (lit.[11] mp 33.5–34.2°); **3**, mp 65.7–66.5° (lit.[12] mp 68.6–69.2°); **4**, mp 57.0–57.5° (lit.[13] mp 57–58°); 2-phenylethyl *p*-nitrobenzenesulfonate, mp 97–98° (lit.[14] mp 101.5–102°); ethyl *p*-nitrobenzenesulfonate, mp 90.2–91.0° (lit.[15] mp 91°).

2-(2-Furyl)ethanol was prepared by lithium aluminum hydride reduction of 2-furylacetic acid.[16] After work-up in the usual fashion, the furylethanol was characterized by nmr, and converted directly into the rather unstable tosylate (**6**), mp 29–30° (from hexane), characterized by nmr.

2,2,2-Trifluoroethanol was purchased from Halocarbon Products Corp., Hackensack, N. J., dried over molecular sieves (Union Carbide Corp. 4A),[17] and distilled prior to initial use. Shiner, *et al.*,[5] outline efficacious recovery procedures.

Kinetic Methods.—The usual sealed ampoule technique was used. Titrations were carried out with standardized 0.01 *N* potassium hydroxide in TFE, using a Metrohn Model E-336-A potentiograph with an EA 120 U electrode. The midpoint of the derivative titration curve was used as the end point. For the solutions buffered with sodium acetate, the titrant was a standardized solution of perchloric acid (0.03 *N*) in TFE. The same electrode was used with the potentiograph.

Rate constants were generally determined from 16 to 18 points, which were treated by the least-squares program LSKIN 1.[18]

Registry No.—**1**, 4455-09-8; **2**, 80-40-0; **3**, 14503-40-3; **4**, 5107-52-8; **5**, 36809-05-9; **6**, 36809-06-0; trifluoroethanol, 75-89-8.

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(11) S. Winstein and H. Marshall, *ibid.*, **74**, 1120 (1952).
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(17) L. L. Ferstandig, private communication, reports that this is a very effective way of drying TFE.
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The Reaction of Nitrous Acid with Oximes

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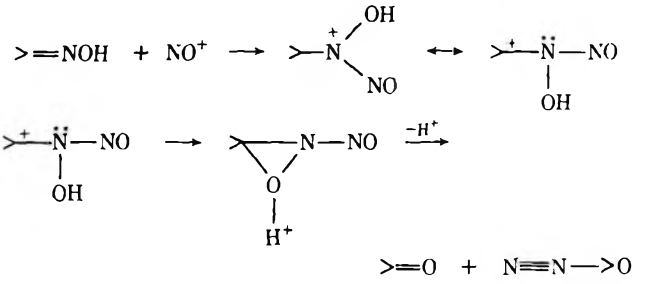
The oxidation of oximes with nitrous acid is a known procedure for the recovery of aldehydes and ketones from the parent oximes. Although this method has been widely utilized, little has appeared in the literature concerning the mechanism of the reaction. Kainz and Huber[1] have studied the reaction of nitrous acid with the oximes of cyclohexanone, benzoin, and acetone. They found that N_2O predominated as the off-gas with N_2 being formed in lesser amount. They hypothesized the intermediacy of both a nitrimine and nitramide from which N_2O could be derived. No mechanistic explanation was offered, however, for N_2 formation. Furthermore, Horner *et al.*, have reported that aldoximes react with "nitrous gases" to give azine bisoxides, and that these azine bisoxides give either N_2O and carbonyl compound or a nitrimine.[2]

More recently Wieland and Grim[3] reported that treatment of butanedione monooxime with ^{18}O-enriched nitrous acid under N_2 resulted in an 89% enrichment of nitrous oxide ($N_2{}^{18}O$), the oxygen of which came only from the nitrous acid and not from the oxime. They therefore proposed the following mechanism.



In this report, we shall deal with the ^{15}N nitrous acid catalyzed decomposition of oximes and the probable modes of formation of N_2O, N_2, and NO therefrom.

Experimental Section[4]

In a typical experiment equimolar amounts of oxime and ^{15}N sodium nitrite was dissolved in a solution containing 45 ml of H_2O and 125 ml of dioxane. Helium was passed through the reaction system and the attached gas sampling tubes. When a helium atmosphere had been obtained, an amount of 50% aqueous sulfuric acid was introduced equivalent to either the amount of sodium nitrite or to a twofold excess. Gas samples were taken at predetermined times, and the reaction mixture was analyzed for aldehyde and other organic products by standard quantitative methods.[5] The gas samples were analyzed by mass spectroscopy and compared to an assay on the ^{15}N sodium nitrite, which was decomposed by aqueous acid under helium. A quantitative estimate of the contribution by oxime and nitrous acid to the various products could then be made by comparing the amount of ^{15}N products in the assay to the ^{15}N products from the reactions.

Results

The results of our experiments are given in Table I. In the reaction of butyraldoxime, the presence of excess mineral acid has a pronounced effect on both the yield of butyraldehyde and on the distribution of gas between N_2O and NO. While the difference in yield between that reaction and the one with only nitrous acid can be attributed partially to a difference in rate of reaction, the difference in gas distribution is too great to allow for this simple explanation. It should also be noted that the nitrogen in N_2O and N_2 comes almost equally from the oxime and nitrous acid, while the nitrogen in NO comes exclusively from

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(3) T. Wieland and D. Grim, *ibid.*, **96**, 275 (1963).
(4) Mass spectra were obtained on a CEC21-130 mass spectrometer by Mr. B. E. Wilkes, UCC Analytical Department.
(5) S. Siggia, "Quantitative Organic Analysis," 3rd ed, Wiley, New York, N. Y., 1967; and The Union Carbide Chemicals Company Laboratory Manual, General Methods of Analysis.

TABLE I

Aldoxime	$H^+/Na^{15}NO_2$/ Oxime	% $H^{15}NO_2$ Reacted	Yield, % Aldehyde	Formic acid	Glyoxylic acid	Benzoic acid	Composition of off-gases,[a] % from $H^{15}NO_2$ N_2O	NO	N_2
Butyraldoxime	2.0/1.0/1.0	97.8	100.0				76.7 (50.6)	2.4 (100.0)	20.4 (53.1)
Butyraldoxime	1.0/1.0/1.0	90.8	69.8				22.1 (53.3)	67.2 (101.9)	10.7 (53.8)
Phenylglyoxaldoxime	2.0/1.0/1.0	79.4	58.8	14.2		13.6	30.7 (53.0)	56.5 (100.0)	12.9 (56.9)
Phenylglyoxaldoxime	1.0/1.0/1.0	52.1	20.3	21.8		18.4	36.1 (56.4)	44.3 (100.0)	21.4 (55.1)
Glyoxime	4.0/2.0/1.0	100.0	33.4	17.7[b]	16.5		50.1 (48.2)	40.4 (98.2)	8.7 (53.4)
Glyoxime	2.0/2.0/1.0	93.8	12.7	30.0[b]	25.8		12.2 (53.5)	82.0 (99.2)	5.8 (50.1)

[a] Gas samples were taken at appropriate intervals and were measured by wet-test meter. The yields of gases varied between 90–100% of theoretical. [b] Based upon 2 mol of formic acid per 1 mol of glyoxime.

HNO_2. Nitrogen is produced in almost the same order of magnitude in either reaction. However, in the reaction catalyzed by strong acid, almost 77% of the gas is N_2O and 2% is NO, whereas in the mineral acid free reaction (*i.e.*, weak acid catalyzed), the roles are reversed, *i.e.*, 67% of the gas is NO and 22% is N_2O.

In the reactions of phenylglyoxaldoxime the effect of excess mineral acid is less pronounced. The distribution of gases remains approximately the same, although in the case where no excess acid was present somewhat less reaction had taken place, as evidenced by both the amount of nitrous acid that reacted and the yield of products. This reaction also distinguishes itself from that of butyraldoxime with two features: the fragmentation to give formic acid, and the majority of off-gas being nitric oxide in either strong or weak acid.

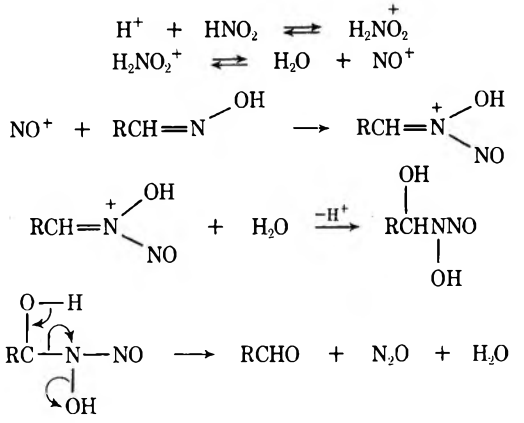
The reactions of glyoxime seem to be more like the butyraldoxime with the change in relative amounts of NO and N_2O going from strong to weak acid conditions. In the strong acid case, about equal amounts of N_2O and NO are produced. When no excess mineral acid is present, the N_2O is reduced drastically while NO production is increased twofold. The nitrogen evolution remains constant. Another striking aspect of this reaction is the low yields of glyoxal, concurrent with very high yields of the fragmentation product, formic acid. The yield of formic acid is even higher in the weak acid medium, to the detriment of glyoxal formation. In either case, the amount of glyoxime reacted (the remainder of glyoxime is either recovered unreacted or gives unobserved products) to give observed products is quite low.

Discussion

The reaction of butyraldoxime with nitrous acid in the presence of strong mineral acid follows the same general course described by Kainz and Huber[1] in that the gas mixture consists of ~76% N_2O and ~20% N_2 with a trace of NO. The high yield (100%) of butyraldehyde speaks for the completeness of the reaction.

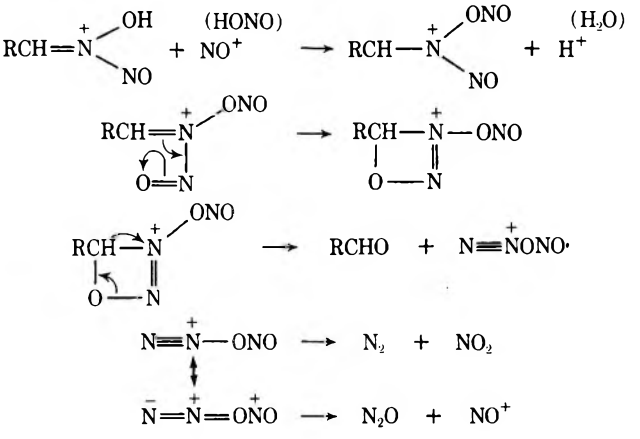
The mechanism proposed by Wieland[2] suffers from one defect. Wieland's reactions were carried out in a nitrogen atmosphere and therefore nitrogen evolution was never measured. Thus the mechanism contains no means for its formation. Furthermore, the utilization of a three-membered ring to describe what could more easily be envisioned as the addition and loss of water tends to complicate the situation.

Alternatively, we envision that the mechanism for N_2O formation is as follows.



This mechanism allows for Wieland's ^{18}O results and also necessitates that half of the nitrogen in N_2O come from oxime and nitrous acid.

For N_2 formation, we propose the following steps initially involving the nitrosated oxime.



The NO_2^+ thus formed can be eliminated by reaction with nitrous acid to give N_2O_4, a precursor of nitric and nitrous acids, both of which are acceptable oxidizing agents. The final step is an alternative step for nitrous oxide formation which allows for only the oxygen of the oxime to wind up in the nitrous oxide. This pathway, then, might explain Wieland's observation of only 89% enrichment in his studies.

The above mechanistic scheme is quite similar to those proposed by Doyle[6] for the reactions of nitrosonium ions with imines and azines.[6] Furthermore, the equal abundance of ^{15}N from nitrous acid and oxime is also explained.

(6) M. P. Doyle, Abstracts, 161st National Meeting of the American Chemical Society Los Angeles, Calif., March 28–April 2, 1971, ORGN-15.

The reaction of butyraldoxime with nitrous acid without excess mineral acid must follow, in part, a different pathway because the major off-gas is NO (67%). As in the excess mineral acid catalyzed reaction, both the N_2 and N_2O show a 50% enrichment in ^{15}N. Thus these gases come equally from nitrous acid and oxime. The fact that so much NO is produced and that it all comes from the nitrous acid forms the basis for our considerations in this case. It should be emphasized that this NO does indeed come from a reaction of nitrous acid with the oxime. Under the same conditions of solvents, concentration, and temperature, nitrous acid does not react in a self-decomposition to give NO as an off-gas. Only when the oxime is added is NO produced.

One possibility that might explain the difference is as follows. In the presence of mineral acid a rapid reaction takes place to give the nitrosonium ion, and it is this NO^+ which is doing the reacting at an extremely

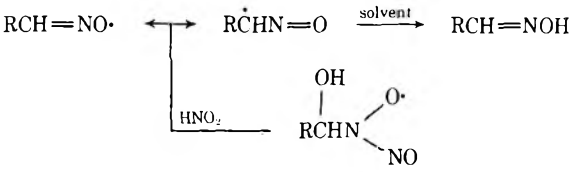
$$H^+ + HNO_2 \rightleftharpoons H_2NO_2^+$$
$$H_2NO_2^+ \rightleftharpoons H_2O + NO^+$$

rapid rate. On the other hand, when there is no excess mineral acid present, it is nitrous acid, HNO_2, which is reacting as an oxidizing agent.

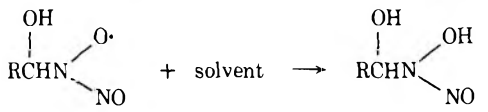
Other oxidizing agents that have been reported to react with oximes are ceric ion,[7] palladium(IV) acetate,[8] lead tetraacetate,[8] and NO_2.[8] The proposed intermediate product of these reactions is the iminoxyl radical, RCH=NO·. We similarly propose that, in the absence of mineral acid, nitrous acid reacts with butyraldoxime to give the iminoxyl radical, NO, and water.[9]

$$RCH{=}NOH + HNO_2 \longrightarrow RCH{=}NO\cdot + NO + H_2O$$

In compliance with our observations, the NO thus produced will come only from the nitrous acid. The iminoxyl radical thus produced can now react in one of two ways. It can abstract a hydrogen from the solvent to give back the starting oxime, or it can react with more nitrous acid in an addition across the double bond to give another radical.



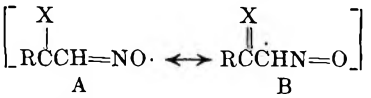
This new radical can abstract a hydrogen from the solvent to give the precursor already postulated to give the aldehyde and N_2O.



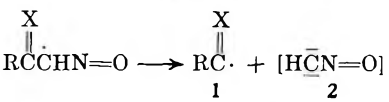
The remaining N_2O and N_2 would be derived from a scheme similar to those proposed above for the reactions carried out in strong acid.

(7) J. W. Bird and D. G. M. Diaper *Can. J. Chem.* **47**, 145 (1969).
(8) M. M. Frojomovic and G. Just, *Can. J. Chem.*, **46**, 3719 (1968).
(9) A similar bimolecular hydrogen abstraction has been proposed for the oxidation of formic acid by nitrous acid in dilute acidic media: J. V. L. Longstaff and K. Singer, *J. Chem. Soc.*, 2604 (1954).

The major difference between the foregoing butyraldoxime reaction with nitrous acid and the reaction of phenylglyoxaldoxime or glyoxime seems to lie in the degree to which either the free radical (iminoxyl) or ionic (nitrosonium ion) enters reaction. In the case of the iminoxyl route, the intermediate would be



The above resonance hybrid could react with nitrous acid either as A or B. If it reacts as A, the reaction would follow the same course as previously described. On the other hand, B would be highly prone to acyl cleavage and might therefore react as follows.



Further oxidation and hydrolysis of **1** or **2** would give the observed cleavage products, formic acid and benzoic acid. The glyoxylic acids observed are most probably derived *via* oxidation of the parent aldehydes.

Registry No.—Nitrous acid, 7782-77-6; butyraldoxime, 110-69-0; phenylglyoxaldoxime, 522-34-9; glyoxime, 557-30-2.

Acknowledgment.—We should like to thank Dr. M. P. Doyle for his help in formulating some of the mechanisms described herein.

A Simple High Yield Synthesis of Methanol-^{18}O and Ethanol-^{18}O[1]

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Received August 7, 1972

In the course of studies of kinetic oxygen isotope effects, we developed a simple high yield method for the synthesis of methanol-^{18}O and ethanol-^{18}O with negligible dilution of the label from starting $H_2{}^{18}O$. To our knowledge, no method affording these alcohols in good yield and not requiring $H_2{}^{18}O$ in large excess has yet appeared in the literature.[2] These isotopically labeled alcohols are available commercially, but a recent quotation[3] shows methanol-^{18}O (80 atom %) at $1170 per gram, and ethanol-^{18}O (80 atom %) at $950 per 0.5 g, or 5.6 and 12.8 times the molar cost of $H_2{}^{18}O$ (80 atom %), respectively.

Methanol-^{18}O was prepared by the hydrolysis of tri-*n*-butyl orthoformate (in excess) by $H_2{}^{18}O$ in the presence of HCl, followed by lithium aluminum hydride

(1) Supported by NIH Grant No. GM 12278 and NSF Grant No. GB 8529 to J. F. Kirsch, and by PHS Training Grant No. 5 T01 GM 31-12.
(2) For a review, see J. L. Borowitz, A. Raviv, P. Rona, D. Sadeh, D. Samuel, and F. S. Klein, *J. Label. Compounds*, **1**, 259 (1966). The yield reported for their preparation of labeled methanol amounts to 20% based on labeled water consumed. The total amount of water used was 16 times the molar yield of methanol, which had 95% of the ^{18}O excess of the water.
(3) Miles Laboratories, Inc., Research Products Division, Catalog C, Kankakee, Ill.

reduction of the resulting butyl formate-*carbonyl*-^{18}O. Similarly, ethanol-^{18}O was prepared by the acid-catalyzed hydrolysis of 1,1-dipropoxyethane with removal of the acetaldehyde-^{18}O as formed, followed by reduction to the alcohol.[4] Within the experimental error of $\pm 0.2\%$ of the ^{18}O excess, there was no isotopic dilution in the preparations. Overall yields were about 85%.

Experimental Section[5]

Tri-*n*-butyl Orthoformate.[6]—A mixture of 11 ml of redistilled trimethyl orthoformate and 30 ml of 1-butanol was refluxed with 100 mg of *p*-toluenesulfonic acid monohydrate while the theoretical amount of methanol (12 ml, bp 65–67°) was slowly removed by distillation through a Vigreux column. The remaining material was distilled and, after removal of the excess butanol, 20 g was collected, bp 120–124° (15 mm). Only the last 10 g collected was used in the following preparation.

***n*-Butyl Formate-*carbonyl*-^{18}O.**—A mixture of 7.5 ml (28.2 mmol) of tri-*n*-butyl orthoformate, 5 ml of diglyme (distilled at 15 mm from $LiAlH_4$), and 0.5 ml (27.6 mmol) of $H_2{}^{18}O$[7] (1.530 ± 0.001 atom %) was protected from atmospheric moisture as 2.5 ml of anhydrous HCl was introduced from a syringe onto the surface with magnetic stirring. The mixture immediately became homogeneous and was distilled through a small Vigreux column. *n*-Butyl formate-*carbonyl*-^{18}O and 1-butanol were collected over the range bp 107–118° for use in the following step.

Methanol-^{18}O.—A mixture of 40 ml of anhydrous diglyme and 1.6 g (42 mmol) of lithium aluminum hydride in small lumps was gently warmed with magnetic stirring under nitrogen in a 250-ml flask until the lumps disintegrated. The mixture of *n*-butyl formate-*carbonyl*-^{18}O and 1-butanol from above was added slowly with stirring while the reaction mixture was cooled in ice. After 20 min at room temperature, the resulting suspension was again cooled in ice and stirred as 0.8 ml of water was carefully dropped in. Then 5 ml of ethylene glycol was added.[8] Distillation through a small Vigreux column afforded methanol-^{18}O (bp 64.5–65.6°), yield 0.76 g (86% based on starting $H_2{}^{18}O$).

Methyl Formate-*methoxy*-^{18}O.—Methanol-^{18}O was refluxed with eight times the theoretical amount of redistilled 98% formic acid while methyl formate-*methoxy*-^{18}O (bp 31.5–32.5°) was collected. Typical yields were 90%. Mass spectrometry showed 1.531 ± 0.002% ^{18}O in the methoxyl position.

This preparation was repeated starting with 0.100 ml of $H_2{}^{18}O$ (65.1 atom %).[9] The resulting methyl formate (0.240 g, 72%) showed 66 ± 1 atom % label in the methoxyl position.

Acetaldehyde-^{18}O.—To a stirred mixture of 3.1 ml (17.5 mmol) of freshly distilled 1,1-dipropoxyethane[10] and 0.25 ml (12.8 mmol) of water-^{18}O (65.1 atom %) was added 0.8 ml of dry HCl as before. Slow distillation through a Vigreux column afforded acetaldehyde-^{18}O (bp 21–24°), yield 0.60 g (95%). The receiver was cooled to −78°, and the product was kept cold until used.

Ethanol-^{18}O.—A suspension of 0.15 g (3.9 mmol) of lithium aluminum hydride in 10 ml of anhydrous diglyme was prepared as before and stirred under nitrogen at 0° while a solution of 0.56 g (12 mmol) of acetaldehyde-^{18}O in 6 ml of anhydrous diglyme was slowly added. After the cautious addition of 0.6 ml of water, distillation through a Vigreux column afforded 0.53 g of ethanol–water azeotrope (bp 78–79°), yield 90%. Mass spectrometry showed the ethanol to be 65.1 ± 0.1 atom % ^{18}O.

Analysis.—Mass spectra were obtained on a CEC Model 21-614 residual gas analyzer modified for use as a mass spectrometer. Water was assayed by the method of Boyer.[11] Methyl formate and ethanol were assayed by examination of the parent peaks P and P + 2. The presence of a P − 2 fragment for ethanol was compensated for. The position of the label in methyl formate was confirmed by examination of the fragments at *m/e* 31 and 33.[12] The relative error in determination of isotopic excess was ±0.2% for the low ^{18}O content material.

Registry No.—*n*-Butyl formate-*carbonyl*-^{18}O, 36794-39-5; methanol-^{18}O, 5770-05-8; methyl formate-*methoxy*-^{18}O, 36794-41-9; acetaldehyde-^{18}O, 3752-37-2; ethanol-^{18}O, 36794-43-1.

Acknowledgment.—The author wishes to thank Dr. Jack F. Kirsch for many helpful discussions.

(4) This method can be generalized to the preparation of many primary and secondary alcohols by use of the appropriate ethylene acetal or ketal.

(5) All temperatures are uncorrected.

(6) Available from Fisher Scientific Co., Pittsburgh, Pa.

(7) Yeda Research and Development Co., Ltd., Rehovoth, Israel.

(8) The use of ethylene glycol to liberate methanol from the alkoxides avoids the problem of separating methanol from large amounts of butanol–water azeotrope (bp 93°).

(9) Bio-Rad Laboratories, Richmond, Calif.

(10) Preparation analogous to that of acetal as described by Adkins and Nissen in "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 1.

(11) P. D. Boyer, D. J. Graves, C. H. Suelter, and M. E. Dempsey, *Anal. Chem.*, **33**, 1906 (1961).

(12) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, pp 174, 175.

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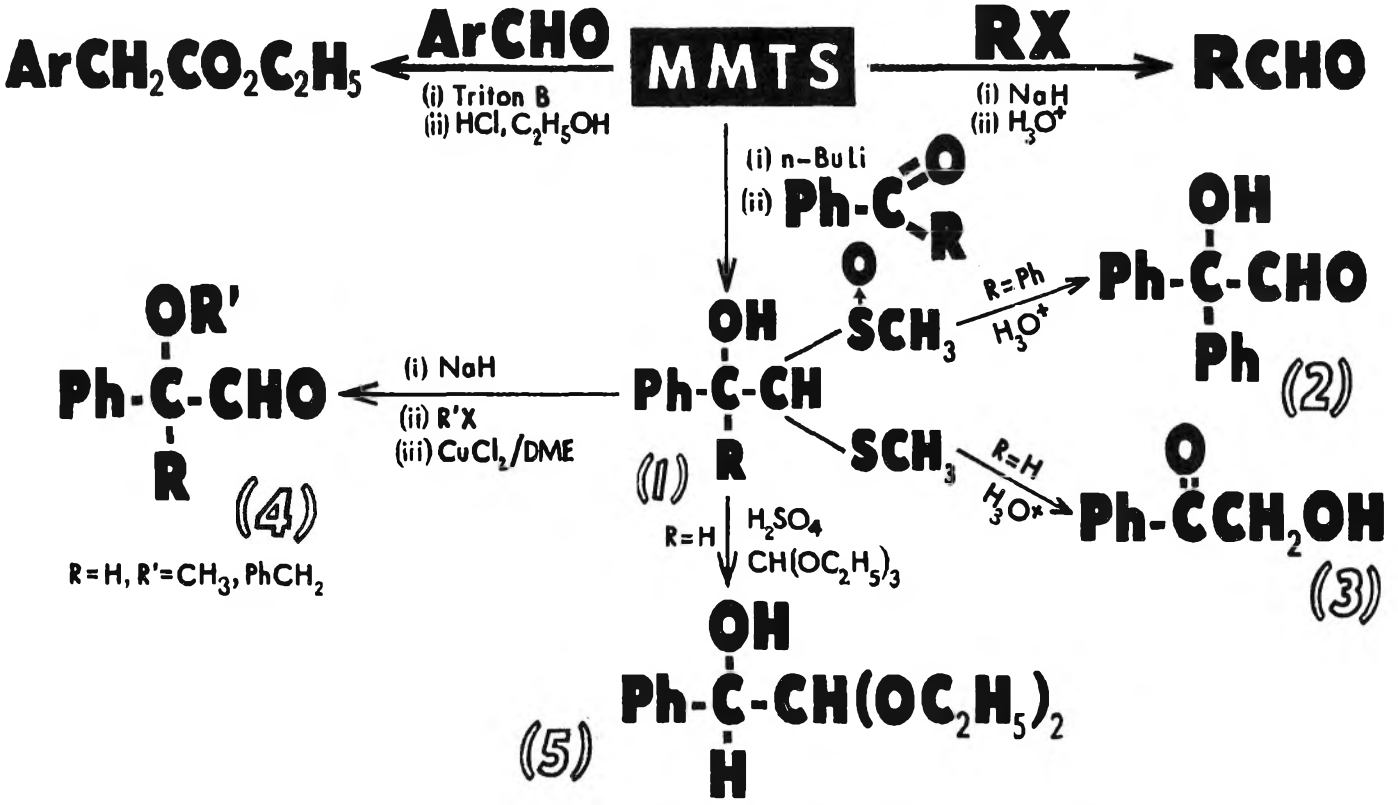
73A

METHYL METHYLTHIOMETHYL SULFOXIDE

$(CH_3\overset{O}{\overset{\uparrow}{S}}CH_2SCH_3$, MMTS)

A versatile reagent for the preparation of aldehydes,[1] phenylacetic acids,[2] and α-hydroxyaldehydes.[3]



The carbanion derived from methyl methylthiomethyl sulfoxide (MMTS) and sodium hydride[1] reacts with alkyl halides to give aldehyde dimethyl mercaptal S-oxides which are readily hydrolyzed with a catalytic amount of sulfuric acid to produce the corresponding aldehydes[1] in excellent overall yield. Phenylacetic esters are obtained[2] from the reaction of MMTS and an aromatic aldehyde in the presence of Triton B followed by cleavage in an alcohol containing acid.

α-Hydroxyaldehyde dimethyl mercaptal S-oxides (**1**) are prepared[3] by reacting the carbanion of MMTS, generated by butyllithium, with ketones. Various types of α-hydroxyaldehydes, which undergo thermal degradation and acid catalyzed isomerization to hydroxyacetophenones,[4] are obtained from these derivatives. For example, acid hydrolysis of the benzophenone adduct in THF yields diphenylglycolaldehyde (**2**) whereas, under the same conditions the benzaldehyde adduct gives α-hydroxyacetophenone (**3**). Methylated or benzylated derivatives (**4**) of phenylglycolaldehyde are produced by treating the protected hydroxy compounds with cupric chloride in dimethoxyethane (DME). Conversely the diethyl acetal (**5**) of phenylglycolaldehyde is produced by the reaction of the benzaldehyde adduct with triethyl orthoformate and a few drops of sulfuric acid.

1,3-Dithiane also may be used to prepare aldehydes and ketones[5]; however, MMTS is clearly the superior reagent because the intermediate S-oxides are more easily hydrolyzed.

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4. S. M. McElvain, S. B. Mirviss and C. L. Stevens, **J. Amer. Chem. Soc., 73,** 3807 (1951).
5. (a) E. J. Corey and D. Seebach, **Angew. Chemie Int. Ed.,** 4, 1075, 1077 (1965).
   (b) For a review see: D. Seebach, **Synthesis,** 17 (1969).

15,787-2	1,3-Dithiane	12g-$8.50; 25g-$14.15; 100g-$44.00
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