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THE JOURNAL OF Organic Chemistry

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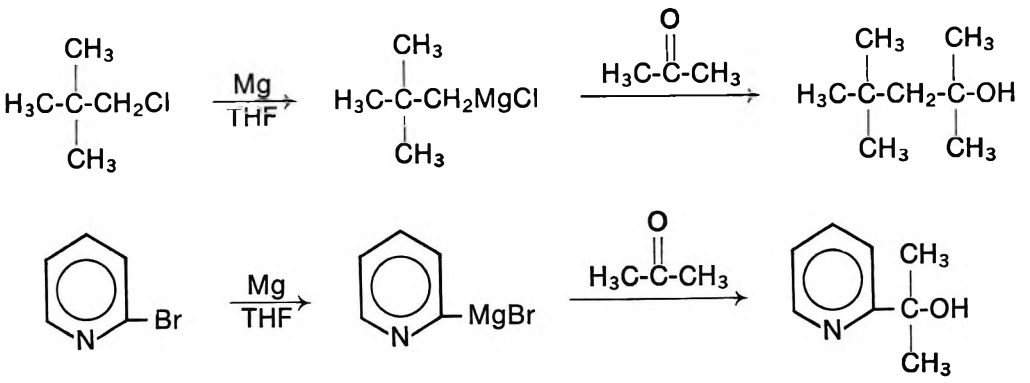

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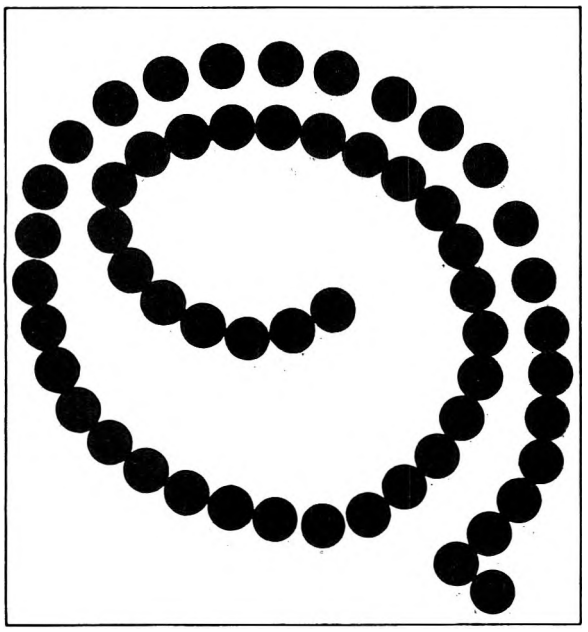

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NOTES

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THE JOURNAL OF Organic Chemistry®

VOLUME 37, NUMBER 11

JUNE 2, 1972

A General Conversion of Phenols to Anilines[1a]

ROBERT A. SCHERRER*[1b] AND HELGA R. BEATTY

Research Laboratories, Parke, Davis & Company, Ann Arbor, Michigan 48106

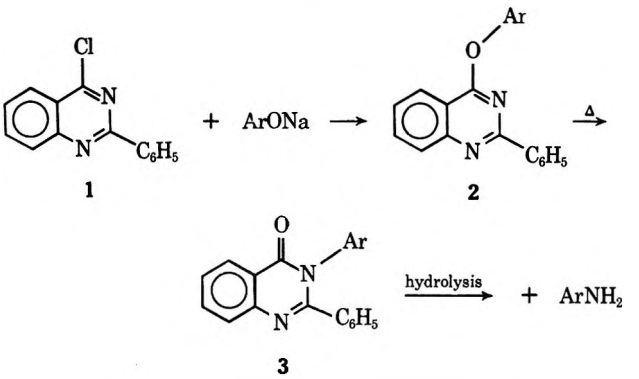
Received October 19, 1971

The rearrangement of 4-aryloxy-2-phenylquinazolines (2) at 275–325° to 3-aryl-2-phenyl-4(3*H*)-quinazolinones (3) has been utilized to convert phenols to anilines. The aniline produced on hydrolysis of 3 has the same substitution pattern as the 4-aryloxy group of 2 and, hence, the phenol from which the latter is made. By this procedure aniline (71%), 2,4-dichloroaniline (64%), 2,3,6-trimethylaniline (70%), and 4-nitroaniline (42%) have been prepared. The thermal rearrangements of 2-methyl-4-phenoxyquinazoline (14) and 4-phenoxyquinazoline (15) are also described.

While most anilines may be readily transformed to the corresponding phenol by way of a diazonium salt, the reverse path interrelating these two large classes of compounds has remained severely restricted. Two general approaches have been used for the conversion of a phenol into the corresponding aniline: a direct reaction with ammonia[2–5] requiring temperatures of the order of 450°, and an indirect method in which the phenolic ring is dearomatized, treated with ammonia or a derivative, and rearomatized. These methods are limited in scope. Some alkylphenols may be transformed to anilines by way of *o*- or *p*-quinol acetates[6–9] or 4-alkyl-4-fluorocyclohexadienones[10] and their reaction products with 2,4-dinitrophenylhydrazine or benzylamine. Some phenols may be converted to cyclohexenones, and oximes therefrom dehydrated to anilines.[9,11] The well-known Bücherer reaction of phenols with ammonium sulfite is generally limited to naphthols and hydroxy- and aminophenols.[12,13] Electronegatively substituted phenols, such as 2,4-dinitrophenol, and their oxygen derivatives, constitute special cases in which the oxygen function is more readily replaced.[14,15]

We wish to report a procedure we feel to be fairly general for the conversion of aromatic hydroxy compounds to the corresponding amine. It involves the sequence outlined in Chart I. The key step is the

CHART I[a]



[a] Ar: a, C_6H_5; b, 2,4-$Cl_2C_6H_3$; c, 2,3,6-$(CH_3)_3C_5H_2$; d, 4-$NO_2C_6H_4$.

thermal rearrangement of a 4-aryloxy-2-phenylquinazoline (2) to a 3-aryl-2-phenyl-4(3*H*)-quinazolinone (3). The rearrangement rate depends on the aryl substitution, but, in general, useful rates are obtained in the temperature range of 275–325°. Hydrolysis of the resulting quinazolinone gives the aniline having the same substitution pattern as the starting phenol. An advantage of this sequence over the direct method is that the phenol, the reacting nitrogen function, and the aniline are "protected" in the thermal step from side reactions which might occur with other substituents. By this procedure aniline hydrochloride has been obtained from phenol in 71% overall yield. Other ani-

(1) (a) Presented in part at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963, Abstracts, p 33Q. (b) Riker Research Laboratories, 3M Center, St. Paul, Minnesota 55101.

(2) V. Merz and P. Müller, *Chem. Ber.*, **19**, 2901 (1896).

(3) E. Briner, P. Ferrero, and E. de Luserna, *Helv. Chim. Acta*, **7**, 282 (1924).

(4) R. S. Barker, Belgian Patent 635,927 (1964); *Chem. Abstr.*, **61**, 13237*f* (1964).

(5) N. S. Kozlov and L. F. Akhmetshina, *Zh. Obshch. Khim.*, **25**, 485 (1955); *Chem. Abstr.*, **50**, 3336*h* (1956).

(6) E. Hecker and E. Walk, *Chem. Ber.*, **93**, 2928 (1960).

(7) E. Hecker, *ibid.*, **92**, 3198 (1959).

(8) H. Budzikiewicz, F. Wesseley, and O. S. Ibrahim, *Monatsh. Chem.*, **95**, 1396 (1964).

(9) A. M. Gold and E. Schwenk, *J. Amer. Chem. Soc.*, **81** 2198 (1959).

(10) E. Hecker and M. Hopp, *Justus Liebigs Ann. Chem.*, **692**, 174 (1966).

(11) F. M. Beringer and I. Ugelow, *J. Amer. Chem. Soc.*, **75**, 2635 (1953).

(12) N. L. Drake, *Org. React.*, **1**, 105 (1942).

(13) A. Rieche and H. Seeboth, *Justus Liebigs Ann. Chem.*, **638**, 57 (1960).

(14) E. Y. Spencer and G. F. Wright, *Can. J. Res.*, **24B**, 204 (1946).

(15) V. A. Lavrischchev, V. L. Plakidin, and A. E. Kretov, *Zh. Obshch. Khim.*, **30**, 3064 (1960); *Chem. Abstr.*, **55**, 18646*h* (1961).

lines prepared are 2,4-dichloroaniline (64%) and 2,3,6-trimethylaniline (70%) as hydrochlorides and *p*-nitroaniline (42%). Since our initial report[1a] Morrow and coworkers[16] have described the use of this method for the conversions of 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one and estrone to the 1-amino and 3-amino derivatives in 67 and 58% yields. Conrow and Bernstein[17] obtained the 3-amino analog of estrone in 67% yield compared with a 10% yield by a dearomatization sequence. Several variations of this procedure using other quinazolines will be described.

Discussion

As outlined in Chart I, this aniline synthesis consists of three steps: (1) preparation of a 4-aryloxy-2-phenylquinazoline; (2) thermal rearrangement to a 3-aryl-2-phenyl-4(3*H*)-quinazolinone; and (3) hydrolysis of the quinazolinone to give the aniline. These steps will be discussed in order.

Preparation of Aryloxyquinazolines.—The aryloxyquinazolines may be obtained in high yield by condensation of a sodium phenoxide with 4-chloro-2-phenylquinazoline in an inert solvent such as dimethylacetamide or diethylene glycol dimethyl ether (diglyme). The salt is conveniently prepared with sodium hydride. Conrow and Bernstein[17] used potassium carbonate in acetone to prepare the ether of estrone in 95% yield. The crude aryl ethers (2) may be used directly in the next step. The aryloxyquinazolines prepared in this study are listed in Table I.

TABLE I

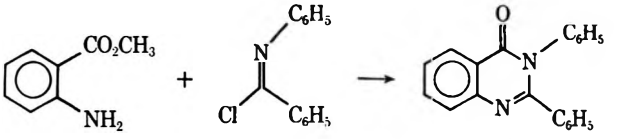
4-ARYLOXY-2-PHENYLQUINAZOLINES

Compd	Mp, °C	Yield, %	Formula[c]
2a	119–120[a]	70	$C_{20}H_{14}N_2O$
2b	177–178[a]	82	$C_{20}H_{12}Cl_2N_2O$
2c	146–147[a]	84	$C_{22}H_{20}N_2O$
2d	218.5–219.5[b]	69	$C_{20}H_{13}N_3O_3$

[a] Recrystallized from *n*-heptane. [b] Recrystallized from benzene. [c] Satisfactory analytical values (±0.3% for C, H, N) for all compounds were reported: Ed.

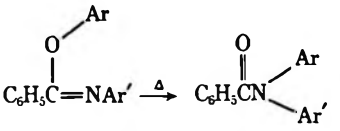
Aryloxyquinazoline Rearrangement.—The second step in this sequence is a thermally induced 1,3-O to N aryl migration around the quinazoline ring. This type of rearrangement was first observed by Chichibabin and Jeletzky.[18] By passing 2-phenoxyquinoline and 2-phenoxypyridine through a tube heated at a *dull red heat* (*i.e.*, above 700°) they were able to isolate *N*-phenylcarbostyril and *N*-phenyl-α-pyridone, respectively, in unspecified yields. This rearrangement has not attracted attention but it appears to be quite general. We have applied it to a number of heterocyclic systems, including 2-aryloxyquinolines,[19,20] 2-aryloxylepidines,[20] and 2-aryloxy-4(3*H*)-quinazolinones.[21] A double rearrangement takes place with 2,4-diaryloxyquinazolines[19,21,22] (**19**) and 3,6-diaryloxypyridazines.[23] Hey and Moynehan[24] have reported the rearrangement of 9-aryloxyphenanthridines to 10-aryl-9-phenanthridones at 350–360°.

The rearrangement product from 4-phenoxy-2-phenylquinazoline was proven to be **3a** by comparison with an authentic sample prepared according to Levy and Stephen[25] from methyl anthranilate and *N*-phenylbenzimidoyl chloride.

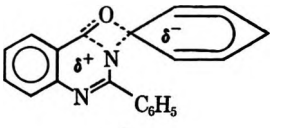


3a

The Chichibabin rearrangement bears a formal resemblance to the Chapman rearrangement of aryl *N*-arylbenzimidates to *N*,*N*-diarylbenzamides.[26] The factors which influence the latter rearrangement have been studied by Chapman[27a] and by Wiberg and Rowland,[27b]



and recently reviewed by Schulenberg and Archer.[27c] They seem to apply as well to the Chichibabin rearrangement.[28] They include the findings that electron-withdrawing groups and ortho substitution on the migrating aryl ring aid the rearrangement. Both reactions follow first-order kinetics. These data imply an intramolecular nucleophilic displacement of the incipient amide oxygen by the imine nitrogen in a four-membered transition state **4**.



4

The 4-aryloxy-2-phenylquinazoline (**2**) may be rearranged neat, but the reaction is generally cleaner when run in an inert solvent such as heavy mineral oil.[29] The course of the rearrangement is conveniently followed by infrared or ultraviolet spectroscopy.

The first-order course of the reaction is illustrated by the rate data in the Experimental Section. By a rough estimate, the rate doubles for a 10° rise in temperature in the 300° range. This is about the same as found for the Chapman rearrangement.[27b] The large decrease

(16) (a) D. F. Morrow and M. E. Butler, *J. Org. Chem.*, **29**, 1893 (1964); (b) D. F. Morrow and R. M. Hofer, *J. Med. Chem.*, **9**, 249 (1966).

(17) R. B. Conrow and S. Berstein, *Steroids*, **11**, 151 (1968).

(18) A. E. Chichibabin and N. P. Jeletsky, *Chem. Ber.*, **57**, 1158 (1924). We propose that this 1,3 O to N aryl rearrangement to a heterocyclic nitrogen be called the Chichibabin rearrangement.

(19) R. A. Scherrer, C. V. Winder, and F. W. Short, Abstracts, Ninth Annual Medicinal Chemistry Symposium, Minneapolis, Minn., June 1964, p 11i.

(20) R. A. Scherrer, U. S. Patent 3,238,201 (1966); *Chem. Abstr.*, **64**, 17614b (1966).

(21) R. A. Scherrer, German Patent 1,190,951 (1965); *Chem. Abstr.*, **63**, 4209d (1965).

(22) P. F. Juby, T. W. Hudyma, and M. Brown, *J. Med. Chem.*, **11**, 111 (1968).

(23) Unpublished work by the authors.

(24) D. H. Hey and T. M. Moynehan, *J. Chem. Soc.*, 1563 (1959).

(25) P. R. Levy and H. Stephen, *ibid.*, 985 (1956).

(26) A. W. Chapman, *ibid.*, **127**, 1992 (1925).

(27) (a) A. W. Chapman, *ibid.*, 1743 (1927); (b) K. B. Wiberg and B. I. Rowland, *J. Amer. Chem. Soc.*, **77**, 2205 (1955); (c) J. W. Schulenberg and S. Archer, *Org. React.*, **14**, 1 (1965).

(28) These conclusions come from this work and rearrangements in other systems as well.[19-21,23]

(29) An attempt to rearrange 4-(*p*-nitrophenoxy)-2-phenylquinazoline in heavy mineral oil at 275° led to decomposition products including the formation of water. There was also some decomposition when the reaction was run neat, probably owing to free-radical reactions involving the nitro group.[30]

(30) E. G. Janzen, *J. Amer. Chem. Soc.*, **87**, 3531 (1965).

in ultraviolet absorption at about 260 mμ in going from 2 to 3 (Δε of about 25,000) is useful in quantitatively following the rearrangement. It is apparently due to hindrance to coplanarity of the 2-phenyl group in 3 resulting from introduction of the 3 substituent. A distinct difference in the infrared absorption spectra of the Chichibabin rearrangement products (C=O) compared with the starting ethers makes this a simple qualitative tool to use in following the rearrangement. (This is not true of the carbonyl region for the Chapman rearrangement.)

The half-times for the rearrangement of **2a–d** to **3a–d** are listed in Table II as an aid in estimating the required conditions for other aryl derivatives. The rates were determined by uv for reactions run neat, but did not seem out of line with the gross observations on larger scale rearrangements run in mineral oil. In estimating half-times for other aryl substitution it should be kept in mind that ortho substitution on the migrating aryl ring is favorable, presumably because it reduces the entropy of activation for the rearrangement by restricting rotation of the *O*-aryl group in the ground state.[27] All these data in comparison with the Chapman reaction are consistent with the fact that the aniline produced has the same substitution as the starting phenol.

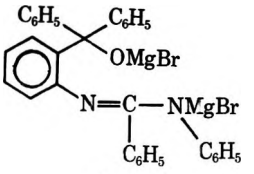
TABLE II

3-ARYL-2-PHENYL-4(3*H*)-QUINAZOLINONES

Compd	Estd rearr half-time,[a] min (°C)	Mp, °C[b]	Formula[d]
3a	60 (325) 175 (308)	158–158.5[c]	$C_{20}H_{14}N_2O$
3b	35 (315)	128–129	$C_{20}H_{12}Cl_2N_2O$
3c	35 (315)	124–125	$C_{23}H_{20}N_2O$
3d	15 (295)	226–228	$C_{20}H_{13}N_3O_3$

[a] Neat. [b] Recrystallized from aqueous ethanol. [c] Lit.[25] mp 158°. [d] Satisfactory analytical values (±0.3% for C, H, N) for all compounds were reported: Ed.

Hydrolysis Step.—The hydrolysis is carried out by either of two procedures (Chart II). The mildest consists of an alkaline hydrolysis to the presumed amidine intermediate **5** (and tautomer) which is considerably more resistant to further base hydrolysis. Acidification in most cases readily liberates the aniline with the formation of 2-phenyl-4*H*-3,1-benzoxazin-4-one (**6**). The formation of **6** indicates a participation by the carboxyl group in the hydrolysis of **5**, since acidification of sodium *o*-benzamidobenzoate merely gives the free acid. This closely parallels the finding[31] that the reaction product of **3a** and excess phenylmagnesium bromide, **9**, gives the oxazine **10** and aniline on acidification.



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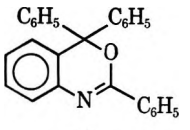
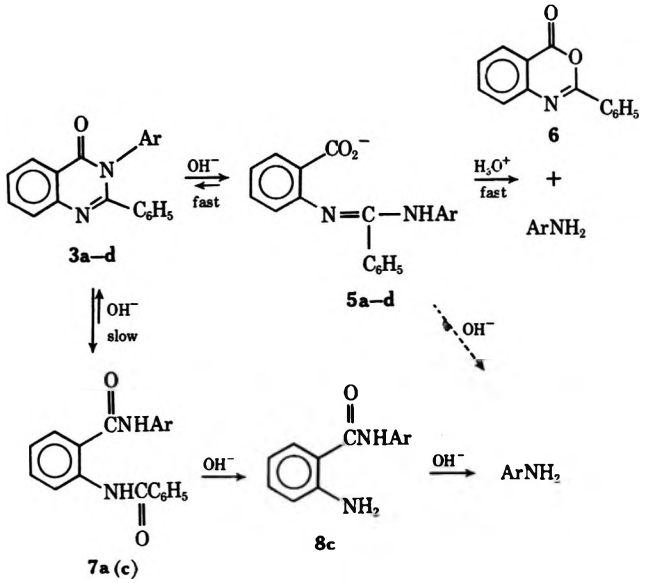


10

When Ar is 2,3,6-trimethylphenyl, **5** recyclizes to **3c** on acidification. Recyclization also occurred, but to a lesser extent, in the preparation of 1-amino-4-methylestra-1,3,5(10)-trien-17-one.[16a]

An alternative procedure for hydrolysis is to heat **3** with potassium hydroxide in ethylene glycol until completion. The mineral oil mixture from the rearrangement step may conveniently be treated directly in such a manner. The first three anilines in Table III were obtained in the overall yields indicated using this procedure.

CHART II[a]



[a] a to d same as Chart I.

TABLE III

$ArNH_2$ FROM ArOH

Ar	Derivative	Mp, °C	Yield from ArOH, %	Formula[g]
C_6H_5	Hydrochloride	193.5–196.5[a,b]	71.6	C_6H_8NCl
2,4-$Cl_2C_6H_3$	Hydrochloride	235–242[a,c]	64	$C_6H_6Cl_3N$
	p-Toluenesulfonamide	126–127[d]		$C_{13}H_{11}Cl_2NO_2S$
2,3,6-$(CH_3)_3$-C_6H_2	Hydrochloride	245–249[a]	70.4	$C_9H_{14}NCl$
	Acetamide	190–191[e]		$C_{11}H_{15}NO$
	p-Toluenesulfonamide	126.5–128.5		$C_{16}H_{19}NO_2S$
4-$NO_2C_6H_4$		144–145.5[f]	42	$C_6H_6N_2O_2$

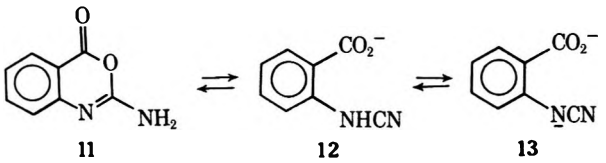
[a] Determined in an evacuated capillary. [b] Lit.[41] mp 198°. [c] A simultaneous melting point on authentic hydrochloride gave mp 230–240° (evacuated capillary). [d] Lit.[39] mp 126°. [e] A. Huender, *Recl. Trav. Chim. Pays-Bas*, **34**, 1 (1915), gives mp 187°. [f] Lit.[41] mp 148°. [g] Satisfactory analytical values (±0.3% for C, H, N) for all compounds were reported: Ed.

It is possible that alkaline hydrolysis to anilines proceeds entirely *via* **7**. The interconversion of **5a** and **3a** and the formation of **7a** under alkaline conditions is described in the Experimental Section. The alkaline hydrolysis of 2-aminobenzoxazin-4-one (**11**) to 2-ureidobenzoic acid has been shown to proceed exclusively by attack of hydroxide and water on the carbonyl of **11**, even though species **12** and **13** exist under the hydrolysis conditions.[32] Other cyclizations involving carboxylate anions are described by Hegarty.[32c] In

(31) A. Mustafa, *et al.*, *J. Amer. Chem. Soc.*, **77**, 1612 (1955).

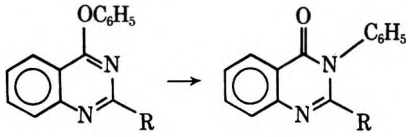
(32) (a) A. F. Hegarty and T. C. Bruice, *ibid.*, **92**, 6561 (1970); (b) *ibid.*, **92**, 6568 (1970); (c) *ibid.*, **92**, 6575 (1970).

the hydrolysis of **3c**, **8c** was isolated as an intermediate. No satisfactory acid hydrolysis conditions for **3** were found.



11 **12** **13**

Other Quinazolines.—The Chichibabin rearrangement was also carried out using 2-methyl-4-phenoxyquinazoline (**14**) and 4-phenoxyquinazoline (**15**) to



14, R = CH_3 **16**, R = CH_3
15, R = H **17**, R = H

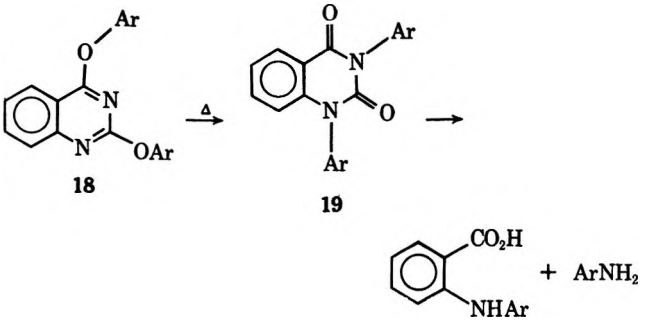
determine if either of these offered advantages over the 2-phenyl series. It was considered possible that the rearrangement could be faster in one of these series, depending on the importance of steric and electronic factors in the transition state. The relative rates of rearrangement of the three 2-substituted 4-phenoxyquinazolines (2-phenyl:2-methyl:2-hydrogen) were found to be 1:1.7:0.5 at 308° (neat, in evacuated ampoules). The steric effect of a substituent in the 2 position of the quinazoline is probably minimized by the geometry of the transition state (**4**), which requires the migrating ring to be perpendicular to the plane of the quinazoline.

The 2-phenyl series, of the three, is the preferred one for the conversion of phenols to anilines. In addition to a rate advantage in the Chichibabin rearrangement of the 2-phenyl series over the 2-unsubstituted series, the former appears to be cleaner, as judged by lack of darkening. In the 2-methyl series a red-orange by-product was obtained in the rearrangement step. A side reaction is also indicated by the rate studies. The apparent rate of rearrangement of the 2-methyl series appeared to fall off with time as determined from the ratio of starting material to product by gas chromatography. In duplicate experiments this apparent rate ranged from an initial half-time of 105 min to a half-time of 360 min after 200 min of reaction time. This seems best explained by a loss of quinazolinone to a nonvolatile by-product rather than by postulating a higher order rearrangement. It should be pointed out that special care must be taken in the preparation of the 4-chloro-2-methylquinazoline to avoid chlorination of the methyl group.[33,34] A by-product having a persistent nauseating odor is also formed in this chlorination.

In spite of the drawbacks, the 2-methyl series would be useful for the preparation from phenols of 3-aryl analogs of the sedative methaqualone,[35] 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone, when the required arylamine is not available. Use of an inert solvent in the rearrangement step could lessen the extent of by-product formation.

The double Chichibabin rearrangements[21,22] of 2,4-diaryloxyquinazolines **18** to 2,4-quinazolinediones **19** (Chart III) were run primarily to obtain the *N*-aryl-

CHART III[a]



18 **19**

[a] Ar: **e**, 2,3-xylyl; **f**, 2,6-dichloro-3-tolyl.

anthranilic acids resulting on hydrolysis, but also provided in each case the aniline corresponding to the starting phenol. Juby[22] obtained 2,6-dichloro-*m*-toluidine in 77% yield from **19f** and the latter in 75% yield from **18f**. The rearrangement in this series is slower than for the corresponding 4-aryloxy-3-phenylquinazoline such that we estimate[1a,23] that a 25° higher temperature is required to obtain a comparable reaction rate.

The aniline synthesis described here should lend itself to the preparation of ^{15}N anilines since the required quinazoline-3-^{15}N derivative should be readily obtainable (by way of reaction of isatoic anhydride or 2-phenyl-4*H*-3,1-benzoxazin-4-one with $^{15}NH_4OH$).

Experimental Section[36]

4-Chloro-2-phenylquinazoline (**1**).—This material was obtained by the sequence benzoylanthranilamide to 2-phenyl-4-(3*H*)-quinazolinone[37] to **1**.[38] It is now available from the Aldrich Chemical Co. under the name "AM-ex-OL."

4-Phenoxy-2-phenylquinazoline (**2a**).—Phenol (10.0 g, 0.106 mol) was added in portions to a cooled suspension of 5.1 g (0.112 mol) of 53% sodium hydride (dispersed in mineral oil) in 35 ml of dry diglyme. When hydrogen evolution subsided, 24.0 g (0.10 mol) of 4-chloro-2-phenylquinazoline was added. The temperature of the mixture rose to 75°. The mixture was heated to 110° for 10 min, then cooled and poured onto ice and water. The dense granular product, 29.8 g, had mp 112–116°. Recrystallizations from aqueous ethanol and *n*-heptane gave 20.9 g (70%) of 4-phenoxy-2-phenylquinazoline as white needles: mp 119–120°; λ_{max} 287 and 257 mμ (ε 16,700 and 34,500); $\nu_{max}^{CCl_4}$ 1625, 1395, 1380, 1205, and 935 cm^{-1}, not in the spectrum of the isomeric quinazolinone.

Other 4-Aryloxy-2-phenylquinazolines (Table I).—The method described for the 4-phenoxy derivative was used. The condensations were run on a 0.05-mol scale under the following conditions: **2b**, 45 min at 130–150°; **2c**, 1.5 hr at 165°; **2d**, 7 hr at 165°. Two grams of each aryloxyquinazoline was recrystallized for analysis and yield.

(33) H. C. Scarborough, B. C. Lawes, J. L. Minielli, and J. L. Compton, *J. Org. Chem.*, **27**, 957 (1962).

(34) R. F. Smith and R. A. Kent, *ibid.*, **30**, 1312 (1965).

(35) K. H. Boltze, H. D. Dell, H. Lehwald, D. Lorenz, and M. Rüberg-Schweer, *Arzneim.-Forsch.*, **13**, 688 (1963).

(36) Melting points are corrected; reaction temperatures are uncorrected. Ultraviolet spectra were determined in methanol on a Cary Model 11 spectrophotometer, infrared spectra were obtained on a Beckman IR-7 or IR-9 spectrophotometer, and nmr spectra were obtained in deuteriochloroform on a Varian A-60 spectrometer. Gas–liquid phase chromatography was run on a Model 810 F & M chromatograph.

(37) (a) R. Anschütz, O. Schmidt, and A. Greiffenberg, *Chem. Ber.*, **35**, 3480 (1902); (b) H. Stephen and G. Wadge, *J. Chem. Soc.*, 4420 (1956).

(38) M. Endicott, E. Wick, M. L. Mercury, and M. L. Sherrill, *J. Amer. Chem. Soc.*, **68**, 1299 (1946).

2,3-Diphenyl-4(3*H*)-quinazolinone (3a). A. From 2a.—Five grams of 4-phenoxy-2-phenylquinazoline was heated under nitrogen in a 50-ml round-bottom flask equipped with a magnetic stirrer and thermometer. The flask was heated with a mantle. After 50 min at 325° the rearrangement was estimated by infrared to be about 50% complete. Heating was continued for a total of 130 min at 325°. Two recrystallizations from aqueous ethanol gave 3.0 g (60%) of 2,3-diphenyl-4(3*H*)-quinazolinone as white needles: mp 158–158.5°; λ_{max} 278 and 229 mμ (ε 12,050 and 31,800); λ_{min} 257 mμ (ε 8900); $\nu_{max}^{CCl_4}$ 1694 (s) and 1270 cm^{-1} (m). This product was identical with that prepared under B by the infrared and ultraviolet spectra and mixture melting point.

B. By the Method of Levy and Stephen.[25]—A solution of 32.0 g (0.212 mol) of methyl anthranilate and 21.5 g (0.10 mol) of *N*-phenylbenzimidoyl chloride in 45 ml of dry dimethylformamide was prepared. After an initial exothermic reaction the solution was allowed to stand overnight at room temperature, then was heated for 10 min at about 100°. The latter heating period was required to complete cyclization of the intermediate. Dilution with ethanol and water precipitated the product, which was recrystallized from aqueous ethanol to give 20.7 g (69.5%) of **3a**, mp 158.5–159° (lit.[25] mp 158°).

Anal. Calcd for $C_{20}H_{14}N_2O$: C, 80.51; H, 4.73; N, 9.39. Found: C, 80.37; H, 4.56; N, 9.33.

Other 3-Aryl-2-phenyl-4(3*H*)-quinazolinones (Table II).—A 2.00-g sample of the aryloxy derivative was heated neat to determine an effective rearrangement temperature. This sample was purified for analysis by chromatography and recrystallization.

Preparation of Anilines (Table III). A. Single-Stage Alkaline Hydrolysis Procedure. Aniline.—4-Phenoxy-2-phenylquinazoline from 5.00 g of phenol (16.3 g, mp 114–117.5°) was heated in 30 ml of heavy mineral oil under nitrogen for 4 hr at 320–325°. The mixture was transferred to a larger flask with the aid of 160 ml of hot ethylene glycol. After addition of 32 g of 85% potassium hydroxide it was heated under nitrogen at 125–138° for 9.5 hr. Dilution with water, extraction with ether, and treatment of the washed and dried ether solution with hydrogen chloride gas gave 5.23 g (76%) of aniline hydrochloride as tan needles, mp 191–194° (evacuated capillary). Sublimation of 270.1 mg of this material at 130–140° (22–27 mm) gave 254.6 mg of aniline hydrochloride, mp 193.5–196.5° (evacuated capillary); identity was verified by mixture melting point and infrared comparison with authentic aniline hydrochloride, Eastman White Label, mp 197–198°. This corresponds to a yield of 71.6% from phenol.

2,4-Dichloroaniline.—This compound was prepared in the same manner as aniline. The infrared spectrum of the hydrochloride was identical with that of an authentic sample prepared from Eastman White Label base. Vapor phase chromatography of the crude dichloroaniline indicated a single volatile component identical in retention time with authentic 2,4-dichloroaniline (6-ft ethylene glycol succinate column, 175°). In addition the *p*-toluenesulfonanilide, mp 126–127°, was in agreement with the literature value,[39] 126°.

2,3,6-Trimethylaniline.—The crude ether **2c** obtained from 10.0 g of 2,3,6-trimethylphenol (Aldrich Chemical Co.) was heated in two volumes of mineral oil at 320° for 3.5 hr. Hydrolysis in 250 ml of ethylene glycol with 50 g of potassium hydroxide for 20 hr at 140° gave mostly 2-amino-2′,3′,6′-trimethylbenzanilide (**8c**), which crystallized from the mixture on cooling. This anilide had mp 136.5–137° (benzene–hexane); λ_{max} 330 and 250 mμ (ε 4780 and 10,600); $\nu_{max}^{CCl_4}$ 3510 (w), 3460 (w), 3365 (w), 1670 (s), 1560 (w), and 1250 cm^{-1} (m).

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.55; H, 7.13; N, 11.02. Found: C, 75.96; H, 7.26; N, 10.90.

The crude product mixture of anilide plus some aniline was further hydrolyzed by heating in 70 ml of ethylene glycol containing 14 g of sodium hydroxide and 14 g of potassium hydroxide for 48 hr at 145°. (These conditions approach the limits of durability of a magnetically stirred Pyrex flask.) The washed and dried ether extract of the mixture was treated with hydrogen chloride gas to give 7.48 g of 2,3,6-trimethylaniline hydrochloride as a white solid, mp 241–248° (evacuated capillary), and a second crop, 1.93 g, mp 236–244° (evacuated capillary). Sublimation of 124.8 mg at 110–140° (20 mm) gave 117.4 mg of sublimate, mp 245–249° (evacuated capillary), for a 70.4% yield from 2,3,6-trimethylphenol. The infrared spectrum of the free base compares well with the published spectrum.[40] Other derivatives are listed in Table III.

B. Two-Stage Alkaline and Acid Hydrolysis Procedure.—These results suggest the presence of intermediate **5** and document the formation of **6**.

***p*-Nitroaniline.**—The rearranged product from 10.00 g of crude 4-(*p*-nitrophenoxy)-2-phenylquinazoline was heated for 30 min in 100 ml of ethanol containing 20 g of 50% sodium hydroxide. A *sample* of the solution remained clear on dilution with water, suggesting **5d**, but gave a precipitate on acidification. This precipitate consisted of 2-phenyl-4*H*-3,1-benzoxazin-4-one (**6**, CCl_4 soluble) and *p*-nitroaniline (CCl_4 less soluble), identified by their infrared spectra. To facilitate work-up, the main hydrolysis mixture was acidified with 12 *N* hydrochloric acid, kept at 40–50° for 10 min to hydrolyze the benzoxazinone, and then made alkaline again and concentrated to near dryness. Dilution with 200 ml of water gave a granular solid which was extracted several times with ether and with hot water to obtain 3.55 g of crude *p*-nitroaniline. Recrystallization from water afforded 1.81 g of yellow needles, mp 144–145.5° (lit.[41] mp 148°), 42% yield from *p*-nitrophenol. The structure of the aniline was further substantiated by its ultraviolet and infrared spectra.

Aniline.—A solution of 7.0 g of 2,3-diphenyl-4(3*H*)-quinazolinone in 100 ml of 80% ethanol containing 18 g of sodium hydroxide was heated at reflux for 10 hr, after which only a 13% yield of aniline could be extracted from the water-diluted alkaline reaction mixture. The alkaline solution was then acidified and extracted with ether to obtain 3.6 g of white needles, mp 108–113°, consisting of about 10% benzoylanthranilic acid and 90% 2-phenyl-4*H*-3,1-benzoxazin-4-one (**6**). The benzoxazine was purified by extraction of an ether solution with sodium bicarbonate and recrystallization from cyclohexane, mp 117.5–119.5°, undepressed by admixture with an authentic sample (lit.[42] mp 123°). The infrared spectrum of **6** has strong characteristic absorption at 1773 cm^{-1} in CCl_4.

The acidic aqueous solution from which **6** was extracted was made alkaline and extracted twice with ether to obtain an additional 23% of aniline as the hydrochloride.

Recyclization of Amidine 5a to 3a.—Potassium hydroxide (2.0 g, 85% pellets) was added to a solution of 1.00 g of **3a** in 10 ml of ethylene glycol at 120°. The solution was heated for 30 min at 110°, then poured into 200 ml of water. There was obtained by filtration 0.38 g of 2-benzamidobenzanilide (**7a**), mp 244–267° (lit.[37a] mp 279°), confirmed by comparison of the infrared spectrum with that of an authentic sample.[37] When the alkaline filtrate, presumed to contain **5a**, was heated on a steam bath for 15 min there was obtained a flocculent precipitate, 0.46 g of **3a**, mp 156–157°, verified by its infrared spectrum. If the alkaline filtrate is acidified without heating one obtains 2-phenyl-4*H*-3,1-benzoxazin-4-one (**6**) and aniline.

2-Methyl-4-phenoxyquinazoline (14).—4-Chloro-2-methylquinazoline[33] (15.0 g, 0.084 mol) was treated with 1 equiv of sodium phenoxide in the general manner outlined for the 2-phenyl series. Recrystallizations from *n*-hexane and aqueous ethanol afforded 13.6 g (69%) of **14**: mp 69.5–70.5° (lit.[43] mp 71–71.5°); λ_{max} 313, 303, 279, and 220 mμ (ε 4040, 4220, 6590, and 51,100); $\delta_{TMS}^{CDCl_3}$ 2.63 ppm (2-CH_3). The strong absorption at $\nu_{max}^{CHCl_3}$ 1625, 1375–1385, and 1205 cm^{-1} is lost on rearrangement.

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.43; H, 5.18; N, 11.88.

2-Methyl-3-phenyl-4(3*H*)-quinazolinone (16).—A solution of 1.0 g of 2-methyl-4-phenoxyquinazoline in 2 ml of heavy mineral oil was heated under nitrogen in a Wood's metal bath at 308–311° for 3 hr. Chromatography (Florisil) gave 0.22 g of recovered starting material (C_6H_{12}:C_6H_6, 1:1) and 0.57 g of **16** (C_6H_6 and C_6H_6–Et_2O, 10:1). A red-orange by-product followed closely and partly overlapped with **16**. Recrystallization gave 0.22 g of **16** as light orange crystals, mp 145–146° (lit.[37a] mp 147°), undepressed on mixture with authentic material with which it compared in other physical and spectral properties. Compound **16** has λ_{max} 316, 305, 264, and 225 mμ (ε 2930, 3680, 9250, and 1490); $\nu_{max}^{CHCl_3}$ 1680 (s) and 1280 cm^{-1} (m); $\delta_{TMS}^{CDCl_3}$ 2.22 ppm (2-CH_3). In glpc on a 6-ft SE-30 column at 250°, **16** had

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(40) M. Dolinsky, J. H. Jones, C. D. Ritchie, R. L. Yates, and M. A. Hall, *J. Ass. Offic. Agr. Chem.*, **42**, 709 (1959).

(41) "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1965.

(42) D. T. Zentmyer and E. C. Wagner, *J. Org. Chem.*, **14**, 967 (1949).

(43) K. W. Breukink, L. H. Krol, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **76**, 401 (1957).

a retention time of 7 min compared with 4.2 min for 2-methyl-4-phenoxyquinazoline.

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25;- H, 5.12; N, 11.86. Found: C, 76.42; H, 5.24; N, 11.73.

4-Phenoxyquinazoline (15).—This compound was prepared in the same manner as **2a** from 8.00 g of 4-chloroquinazoline.[38] Recrystallizations from cyclohexane–*n*-hexane and aqueous ethanol gave 7.74 g (71%) of 4-phenoxyquinazoline: mp 72.5–74° (lit.[44] mp 78–79°); λ_{max} 310, 299, 263, and 219 mμ (ε 4160, 4000, 5850, and 48,700); $\nu_{max}^{CCl_4}$ 1625 (s), 1385 (s), and 1220 cm^{-1} (broad, m) not found in **17**. The nmr signal at $\delta_{TMS}^{CDCl_3}$ 8.82 (2 H) was absent in the spectrum of the rearranged product.

Anal. Calcd for $C_{14}H_{10}N_2O$: C, 76.65; H, 4.53; N, 12.61. Found: C, 75.82; H, 4.62; N, 12.73.

3-Phenyl-4(3*H*)-quinazolinone (17).—A solution of 2.00 g of 4-phenoxyquinazoline in 4 ml of heavy mineral oil was heated under nitrogen at 321 ± 3° for 5 hr. A combination of recrystallizations and chromatography (Florisil) yielded 1.18 g (59%) of **17** as white needles, mp 137–137.5° (lit.[45] mp 136–136.5°), undepressed on mixture with, and comparable in spectral and physical properties to, purchased quinazolinone (Aldrich Chemical Co.), and 0.21 g of recovered starting material. The ultraviolet spectrum of **17** has λ_{max} 303, 277, 267, and 225 mμ (ε 3740, 7820, 8500, and 35,200); the infrared spectrum has $\nu_{max}^{CCl_4}$ 1698 (s), 1615 (s) and 1300 cm^{-1} (m) not found in 4-phenoxyquinazoline. In glpc on a 6-ft SE-30 column at 250°, **17** had a retention time of 6 min compared with 4.1 min for 4-phenoxyquinazoline.

Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.53; N, 12.61. Found: C, 75.76; H, 4.52; N, 12.74.

Relative Rearrangement Rates of 2a, 14, and 15.—In order to avoid differences in reaction temperature owing to the volatility of **14** and **15**, the rearrangements were run in sealed evacuated ampoules. Three 100-mg portions of each aryl ether were sealed in 6-mm tubing at 10–15-mm nitrogen pressure. The tubes were bundled in groups of three and immersed in a silicone oil bath maintained at 308 ± 3°.

A. **Compound 2a and 3a.**—At 257 mμ, **2a** has an E_1^1 of 1155 and **3a** an E_1^1 of 298. The following calculated values (E_1^1 minus 298) at 257 mμ for various times were obtained: 0 time, 857; 55 min, 699; 130 min, 508; and 255 min, 324. From these values the half-time at 308° was determined to be 175 min. A duplicate determination at 309 ± 2° gave a half-time of 185 min.

B. **Compound 14 to 16.**—A rate study at 308 ± 3° gave the following values for the percentage of **14** as determined by glpc: 55 min, 68.5%; 130 min, 50.4%; and 255 min, 36%. In a duplicate determination at 309 ± 2° the following values were obtained: 5 min, 94%; 50 min, 71%; 110 min, 56%; 175 min, 44%; and 225 min, 40%. If a first-order reaction is assumed, the values for the first 50 min correspond to a half-time of 105 min, and the values at 175 min and 225 min to a half-time of 360 min. The apparent deviation from first-order kinetics may be due to loss of **16** to a nonvolatile by-product.

C. **Compound 15 to 17.**—Gas–liquid phase chromatography gave the following values for the percentage of **15**: 55 min, 88%; 130 min, 77%; 255 min, 58%. These values correspond to a reaction with a half-time of 325 min or about 0.5 times the rate for the conversion of **2a** to **3a**.

Registry No.—**2a**, 18600-27-6; **2b**, 34281-52-2; **2c**, 34281-53-3; **2d**, 18600-28-7; **3b**, 34280-97-2; **3c**, 34280-98-3; **3d**, 34280-99-4; **6**, 1022-46-4; **8c**, 34297-91-1; **14**, 34297-92-2; **15**, 16347-97-0; **16**, 2385-23-1; **17**, 16347-60-7; 2,4-dichloroaniline HCl, 29084-76-2; 2,3,6-trimethylaniline HCl, 34297-93-3; 2,3,6-trimethylaniline *p*-toluenesulfonamide, 34297-94-4.

Acknowledgment.—The authors wish to thank Mr. C. E. Childs and his staff of our Microanalytical Department for elemental analyses and glpc work, Dr. J. M. Vandenbelt and his staff of our Physical Chemistry Department for the spectral data, and Messrs. H. D. Troutman and N. Jenesel for the synthesis of intermediates.

(44) J. S. Morley and J. C. E. Simpson, *J. Chem. Soc.*, 1354 (1949).
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α-Azocarbinols. The Synthesis and Some Reactions of 3-Hydroxypyrazolines[1]

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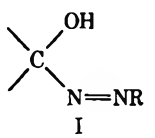
3-Hydroxy-1-pyrazolines, cyclic examples of α-azocarbinols, have been synthesized by hydrolysis or hydrogenolysis of 3-acetoxy-1-pyrazolines. These carbinols undergo both acid- and base-catalyzed ring opening to give ketones. The acid reactions produce both saturated and unsaturated ketones while the base reactions yield only saturated ketones but principally those of rearranged carbon skeleton. The carbinols may be esterified and etherified under closely controlled conditions.

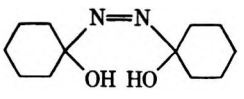
The geminal juxtaposition of an azo linkage and a hydroxyl group (I) produces a chemical structure whose



I

properties will depend upon the interplay of competing factors. Thus α-azocarbinols might resemble cyanohydrins in that they are adducts of carbonyl compounds and diazenes. From this point of view they would be expected to be unstable in basic solution and to avoid carbonium ion intermediate reactions. On the other hand, they might be viewed as diaza allylic alcohols and thus to show unusual reactivity toward electrophilic reagents.

Little is known about these compounds because it is only recently that some have been reported. The first example, 1,1′-dihydroxyazocyclohexane (**1**), was reported in 1963.[2] This compound was relatively un-



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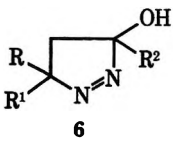
stable, reverting to cyclohexanone with loss of diimide.

Recently, Hünig has generated α-azocarbinols by two methods: the action of base on alkoxydiazenium

(1) This research was supported by grants from the Petroleum Research Fund and the National Science Foundation.

(2) E. Schmitz, R. Ohme, and E. Schramm, *Justus Liebigs Ann. Chem.*, **702**, 131 (1967).

TABLE I
3-HYDROXY-1-PYRAZOLINES



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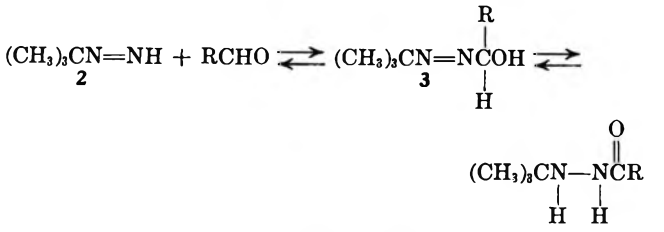
Compd[d]	R	R¹	R²	Bp (mp), °C (mm)	Yield, % Hyd	Yield, % $NaBH_4$	3,5-DNB[c] mp, °C
6a	CH_3	CH_3	CH_3	62–63 (0.5)	80.6	85.8	162–163
6b	CH_3	C_2H_5	C_2H_5	71–73 (0.25)	56.6	71.7	176–177
6c	$-CH_2(CH_2)_3CH_2-$		CH_3	*a*	55.0		206–208
6d	CH_3	CH_3	$CH_2{=}C(CH_3)_2$	*a*	4.6		
6e	CH_3	CH_3	C_6H_5	(95–98)[b]	84.0		
6f	CH_3	CH_3	H	*a*	64.3	56.3	

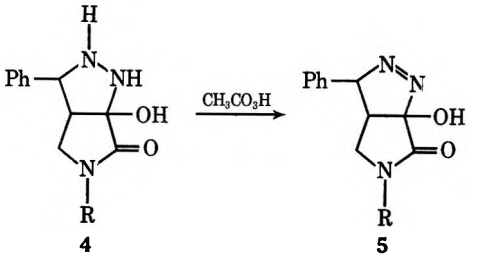
[a] Purified by column chromatography rather than distillation. [b] Recrystallized from hexane. [c] 3,5-Dinitrobenzoate ester. [d] Satisfactory analyses (±0.4% in C, H, and N) for 6a–f were reported with the following exceptions: 6a, calcd for N, 21.86, found for N, 20.94; 6b, calcd for C, 61.51, found for C, 60.54, and calcd for N, 17.93, found for N, 16.60; nitrobenzoates of 6a, calcd for C, 48.45, found for C, 49.79; 6b, calcd for C, 51.43, found for C, 52.11, and calcd for N, 15.99, found for N, 14.94; 6c, calcd for N, 15.46; found for N, 14.64.

salts,[3] and, more generally, the addition of diazenes to carbonyl compounds.[4] For example, addition of *tert*-butyldiazene (2)[4] to aliphatic aldehydes in aqueous solution reversibly yielded the corresponding α-hydroxyazo compounds **3**. These compounds could be distilled, but they slowly rearranged to the isomeric hydrazides.



R = H, CH_3, C_3H_7

A somewhat more complicated example was reported[5] recently wherein the oxidation of the α-hydroxyhydrazines **4** yielded the azocarbinols **5**.



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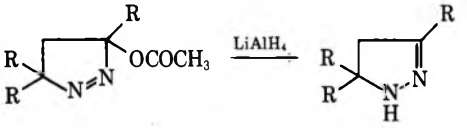
Because of the isolated structures which have so far been generated, it is not surprising that no consistent pattern of reactivity for these compounds is yet apparent. The Schmitz compound **1** was very unstable even undergoing attack by air. Hünig's compounds (**3**) behaved to some extent as unstable carbonyl adducts while the Southwick compound **5** gave typical pyrazoline reactions: thermal decomposition to cyclopropanols and acid-catalyzed dehydration to pyrazoles.

The oxidation of 2-pyrazolines with lead tetraacetate made available a wide variety of 3-acetoxy-1-pyrazolines.[6] Early attempts to convert these esters to the corresponding 3-hydroxypyrazolines were complicated by the competing acid- or base-catalyzed decomposition of these compounds to ketones.[7] Recently, we reported that this hydrolysis could be controlled to yield 3-hydroxypyrazolines,[8] compounds which contain functional group I. It is the purpose of this paper to detail the synthesis of these compounds, their acid- and base-catalyzed reactions, and their utility in organic synthesis.

Preparation (Table I).—Two methods of converting 3-acetoxypyrazolines to 3-hydroxypyrazolines were employed: hydrolysis with aqueous methanolic alkali at room temperature, and hydrogenolysis with sodium borohydride in methanol. Interestingly, lithium aluminum hydride, the more conventional hydrogenolysis reagent, could not be used because it reduced the acetoxypyrazolines to the original 2-pyrazoline.



Acetoxypyrazolines with a hydrogen atom at position 5 could not be converted to the corresponding hydroxypyrazolines because they aromatized to pyrazoles upon treatment with bases or sodium borohydride and underwent ring opening to ketones with acids. The hydroxypyrazolines were characterized by infrared spectra containing bands attributable to the hydroxyl group and the azo function (1555–1563 cm^{-1}). They could be stored for long periods of time in the refrigerator in the dark, but gradually decomposed upon storage under ordinary laboratory conditions. Apparently glass surfaces can catalyze some of the decomposition reactions discussed below since satisfactory analyses were difficult to obtain in a few cases.

Reactions. Acid Catalysis.—Attempts to dehydrate 3,5,5-trimethyl-3-hydroxypyrazoline (**6a**) using a variety of acidic catalysts failed to yield any of the known 3,5,5-trimethylpyrazolenine.[9] The carbinol also failed

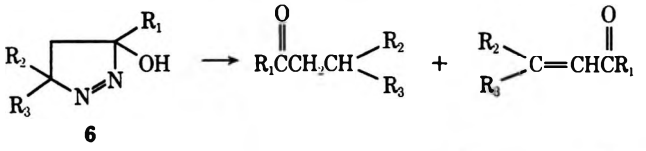
(3) S. Hünig and G. Büttner, *Chem. Ber.*, **104**, 1088 (1971).
(4) S. Hünig and G. Büttner, *ibid.*, **104**, 1104 (1971).
(5) P. L. Southwick, N. Latif, J. Klijanowicz, and J. G. O'Connor, *Tetrahedron Lett.*, 1767 (1970).
(6) J. P. Freeman, *J. Org. Chem.*, **29**, 1379 (1964).
(7) J. P. Freeman and J. L. Plonka, *J. Amer. Chem. Soc.*, **88**, 366 (1966).
(8) J. P. Freeman and C. P. Rathjen, *J. Chem. Soc. D*, 538 (1969).
(9) G. L. Closs, L. E. Closs, and W. Böll, *J. Amer. Chem. Soc.*, **85**, 3796 (1963).

to give a typical reaction with the Lucas reagent or with hydrobromic acid. On the basis of the products isolated under acidic conditions it is clear that carbonium ion formation from the tertiary carbinol does not compete effectively with ring-opening reactions.

The principal acid-catalyzed reaction was ring opening to produce ketones. In general, mixtures of saturated and unsaturated ketones were obtained with the former predominating. For example, pyrazoline **6a** yielded a mixture consisting of 93% methyl isobutyl ketone and 7% mesityl oxide (Table II).

TABLE II

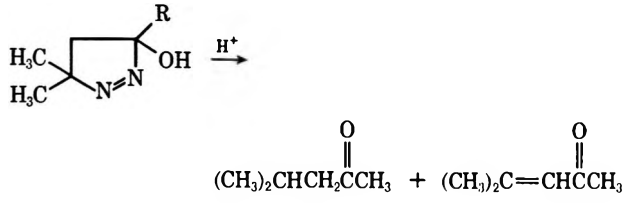
ACID-CATALYZED RING OPENING



6

			Rel yield, %[a]	
			Satd	Unsatd
R_1	R_2	R_3	ketone	ketone
CH_3	CH_3	CH_3	93	7
C_2H_5	C_2H_5	CH_3	100	
CH_3	$-CH_2(CH_2)_2$	CH_2-	100	
$CH{=}C(CH_3)_2$	CH_3	CH_3	98	2
C_6H_5	CH_3	CH_3	95	5
H	CH_3	CH_3	100	

[a] Calculated on the basis of reacted starting material.



A scheme to account for these products is shown in Scheme I. It is not necessary that different products arise from protonation of alternative nitrogens, since it is possible that carbonium ions **7** and **8** could equilibrate, with ion **7**, the precursor of the major products, predominating because of its greater stability.

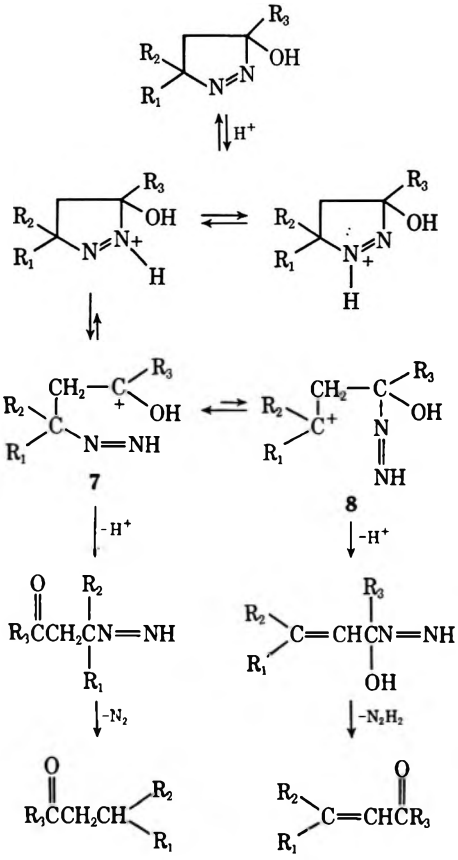
That diimide was in fact produced during these reactions was inferred from the detection of hydrazine, its disproportionation product, through azine formation with *p*-dimethylaminobenzaldehyde.[10]

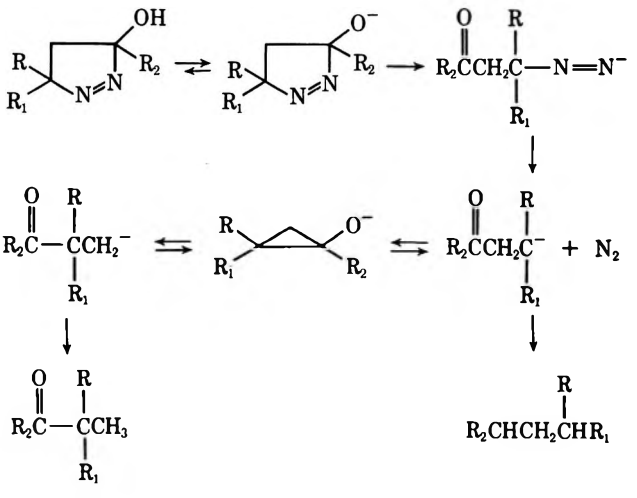
A remarkable feature of these reactions is that even under treatment with rather concentrated acids the pyrazolines survived for long periods. For example, up to 80% of **6a** could be recovered after a mixture of this carbinol and 50% methanolic HCl were heated under reflux for 1 hr. This is an extreme example, as the pyrazolines substituted at position 3 with groups other than methyl decomposed more rapidly, but it still indicates that this compound has a stability much greater than that exhibited by any other α-azocarbinol.

Base Catalysis. Cleavage.—Some years ago when the alkaline hydrolysis of 3-acetoxypyrazolines was first reported,[7] it was observed that ester hydrolysis was followed by ring opening to give a ketone of rearranged carbon skeleton. With the several carbinols now in hand this ring opening has been more closely examined. While the earlier results have been confirmed, it is clear that the intermediate alkoxide ions are far more stable to ring opening than had been realized. For example, compound **6a**, after it had been heated under reflux in methanol containing an equimolar amount of sodium hydroxide for 1 hr, was recovered to the extent of 94%. However, pyrazoline **6f** was much less stable and only 10% could be recovered under these conditions. In all cases rearranged ketones predominated in the mixtures obtained although the ratio varied with structure (Table III).

Although no new information on this point has been gathered, it still is believed that the structural rearrangement occurs after loss of nitrogen to produce cyclopropanoxide ions, which may open by alternative paths with the one giving the more stable carbanion favored.[7]

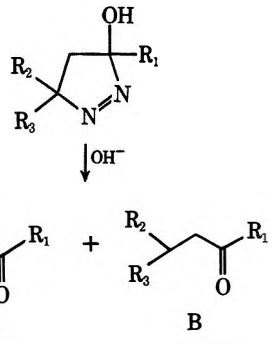
SCHEME I





(10) M. Pesez and A. Petit, *Bull. Soc. Chim. Fr.*, 122 (1947).

TABLE III
PRODUCTS OF ALKALINE DECOMPOSITION OF 3-HYDROXY-1-PYRAZOLINES[a]



A B

Substituents	Yield, % Unreacted starting material	Carbonyl products A	B
$R_1 = R_2 = R_3 = CH_3$	94.1	5.1	0.8
$R_1 = R_2 = CH_2CH_3$, $R_3 = CH_3$	71.4	12.6	6.0
$R_2, R_3 = c\text{-}C_5H_{10}$, $R_1 = CH_3$	17.6	34.2	27.1
$R_1 = CH{=}C(CH_3)_2$, $R_2 = R_3 = CH_3$	20.5	60.0	7.3
$R_1 = C_6H_5$, $R_2 = R_3 = CH_3$	59.5	20.3	16.7
$R_1 = H$, $R_2 = R_3 = CH_3$	10.2	60.0	19.6

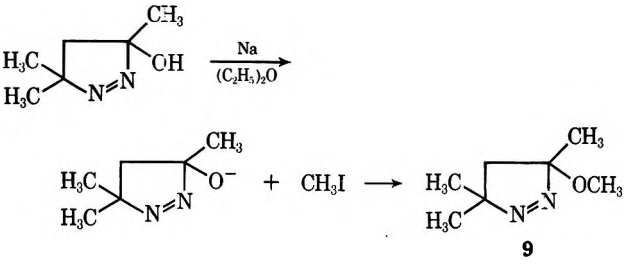
[a] Conditions: approximately 0.05 mol of pyrazoline was heated under reflux for about 1–2 hr with an equimolar amount of methanolic NaOH.

Ester and Ether Formation.—It proved to be possible to esterify the 3-hydroxypyrazolines using the Brewster technique[11] which employs the acid, benzenesulfonyl chloride, and pyridine. A wide variety of esterifications was not attempted but, merely to establish that the reaction was characteristic of these compounds, conversion to the corresponding 3,5-dinitrobenzoates was carried out. These solid esters were easy to isolate and purify. Pyrazoline **6a** could be reconverted in low yield to the parent acetate by treatment with acetic anhydride but this reaction failed with most of the other hydroxypyrazolines. Presumably steric hindrance to esterification allows other acid- or base-catalyzed reactions to compete.

Consistent with the previously described resistance of the hydroxypyrazolines to undergo acid-catalyzed reactions characteristic of tertiary alcohols, these 3,5-dinitrobenzoates failed to undergo solvolysis reactions. For example, they could all be recovered unchanged after heating under reflux in methanol. From the few experiments reported herein, we tentatively conclude that the azo linkage is deactivating with respect to carbonium ion formation, but this suggestion needs much experimental verification.

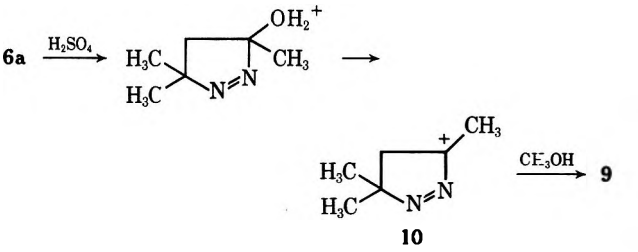
Ether formation was studied extensively with pyrazoline **6a**. While dimethyl sulfate and base could be used, the best procedure was to preform the sodium salt of the hydroxypyrazoline and treat it with methyl iodide.

It was also possible to prepare this ether by the classic acid-catalyzed method often used with tertiary



9

alcohols, that is, dissolution of the hydroxypyrazoline **6a** in concentrated sulfuric acid followed by mixing with methanol. Such a reaction may be interpreted as involving carbonium ion **10** and represents the only reaction where such an intermediate suggests itself. [A referee has suggested that this reaction may occur by interception of ion **7** (Scheme I) by methanol followed by loss of water and ring closure.]



10

As previously reported,[8] ether **9** could be converted to 1,2,2-trimethylcyclopropyl methyl ether by pyrolysis.[12]

Thermal Reactions.—While most of these hydroxypyrazolines could be stored at room temperature or below for relatively long periods with little decomposition and even distilled at low pressures in some cases, extended heating at high temperatures led to decomposition to ketonic products. Whether cyclopropanols were intermediates in these reactions was not determined, but it is known that these compounds are also converted to ketones thermally.[14]

Experimental Section

Preparation of 3-Acetoxy-Δ¹-pyrazolines.—The procedures previously described[6] were followed. Two previously unreported acetoxypyrazolines are described here. Both were rather unstable and could not be purified sufficiently for elemental analysis.

3-Acetoxy-3-methyl-5,5-pentamethylene-1-pyrazoline.—3-Methyl-5,5-pentamethylene-2-pyrazoline was prepared by the formic acid catalyzed cyclization of cyclohexanone acetone azine according to the method of Kost and Grandberg.[15] Acetoxylation according to the described procedure[6] yielded 3-acetoxy-3-methyl-5,5-pentamethylene-1-pyrazoline (51%): bp 32° (0.44 mm); ir (neat) 1745 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.78 (s, 3, $OCOCH_3$).

3-Acetoxy-3-isobutenyl-5,5-dimethyl-1-pyrazoline.—The 2-pyrazoline was synthesized from the reaction of hydrazine with phorone. Treatment of it with lead tetraacetate yielded the title compound: bp 89° (0.50 mm); ir (neat) 1737 (C=O), 1557 cm^{-1} (N=N); uv max (C_2H_5OH) 330 nm (ε 275); nmr ($CDCl_3$) δ 2.06 (s, 3, $OCOCH_3$).

(11) J. H. Brewster and C. J. Ciotti, *J. Amer. Chem. Soc.*, **77**, 6214 (1955).

(12) A recent report[13] of the conversion of hydrazones to α-azo ethers with iodine, methanol, and sodium acetate suggests a direct route from pyrazolines to ethers like **9**. A preliminary experiment to check the utility of this route may be found in the Experimental Section. Combined with the thermolysis reaction this reaction might provide a convenient route to cyclopropyl ethers.

(13) J. Schantl, *Tetrahedron Lett.*, 3785 (1970).

(14) C. H. Depuy, W. C. Arney, and D. H. Gibson, *J. Amer. Chem. Soc.*, **90**, 1830 (1968).

(15) A. N. Kost and I. I. Grandberg, *J. Gen. Chem. USSR*, **26**, 1925 (1956).

Preparation of 3-Hydroxypyrazolines (Table I). Hydrolysis Procedure.—A mixture of 10.0 g (0.059 mol) of 3-acetoxy-3,5,5-trimethylpyrazoline-1[6] and 30 ml of 5% methanolic sodium hydroxide was stirred at room temperature for 10 hr. It was diluted with water and carefully neutralized with 5% HCl. After extraction with ether, drying ($MgSO_4$), and concentration, distillation yielded 6.1 g (81%) of **3-hydroxy-3,5,5-trimethyl-1-pyrazoline**: ir (neat) 3378 (OH), 1560 cm^{-1} (N=N); nmr (neat) δ 1.32, 1.42, 1.58 (s, 3, CCH_3), 1.53 (m, 2, CH_2), 5.88 (s, 1, OH).

Hydrogenolysis Procedure.—A solution of 17.0 g (0.1 mol) of 3-acetoxy-3,5,5-trimethyl-1-pyrazoline in 100 ml of CH_3OH was added, dropwise and with stirring, to a solution of 37.85 g (1 mol) of sodium borohydride in 450 ml of CH_3OH. This mixture was heated under reflux for 1 hr, cooled, diluted with water, concentrated to half its volume, and extracted with five 50-ml portions of $CHCl_3$. The $CHCl_3$ extract was dried ($MgSO_4$), concentrated, and distilled to yield 11.0 g (86%) of 3-hydroxy-3,5,5-trimethyl-1-pyrazoline.

3-(3,5-Dinitrobenzoyloxy)-3,5,5-trimethyl-1-pyrazoline.—To a cold mixture of 1.65 g (0.0078 mol) of 3,5-dinitrobenzoic acid and 2.8 g (0.016 mol) of benzenesulfonyl chloride in 15 ml of pyridine was added 1.0 g (0.0078 mol) of 3-hydroxy-3,5,5-trimethylpyrazoline (6a). The mixture was stirred for 4 hr, poured into water, and filtered, and the residue was recrystallized from C_2H_5OH–C_6H_6 to give 0.7 g (28%) of the title compound, mp 162–163°.

3-Methoxy-3,5,5-trimethyl-1-pyrazoline. Procedure A.—An ether suspension of the sodium salt of 6a was prepared by adding 12.3 g (0.096 mol) of 6a to a suspension of 2.2 g of sodium in ether. This mixture was stirred at room temperature for several days to ensure complete reaction. Methyl iodide (28.4 g, 0.2 mol) was added dropwise and the mixture was heated under reflux for 24 hr. It was filtered, dried, and distilled to give 9.9 g (73%) of 3-methoxy-3,5,5-trimethylpyrazoline-1: bp 22° (0.25 mm); ir (neat) 1655 (N=N), 1201 cm^{-1} (COC); nmr ($CDCl_3$) δ 3.75 (s, 3, OCH_3), 1.40 (m, 2, CH_2), 1.46, 1.35, 1.27 (s, 3, CCH_3 groups).

Anal. Calcd for $C_7H_{14}N_2O$: C, 59.13; H, 9.92; N, 19.70. Found: C, 59.14; H, 9.95; N, 18.31.

Procedure B.—A 1.7-g (0.013 mol) sample of 6a was slowly added to 1.1 ml of cold, concentrated H_2SO_4. This solution in turn was added immediately to 5 ml of cold methanol. This solution was stirred for 15 min, diluted with water, and extracted with ether. The ether extracts were dried and distilled to yield 0.98 g (54%) of the methyl ether.

Procedure C.—A solution of 11.2 g (0.1 mol) of 3,3,5-trimethylpyrazoline in 100 ml of CH_3OH was added over a 2-hr period to a solution of 25.4 g (0.1 mol) of iodine and 27.2 g (0.2 mol) of sodium acetate in 600 ml of CH_3OH. The mixture was stirred at 25° for 2 hr, concentrated *in vacuo*, diluted with ether, and washed with water, $NaHSO_3$ solution, and saturated NaCl solution. The dried ether extracts were distilled to yield 4 g (28%) of the methyl ether. Mesityl oxide and pinacolone were also present in the product mixture.

1,1,2-Trimethylcyclopropyl Methyl Ether.—3-Methoxy-3,5,5-trimethyl-1-pyrazoline (1.75 g, 0.012 mol) was heated under reflux (~200°) until N_2 evolution ceased (6 hr). The residue was distilled to yield 0.58 g (42.5%) of the title compound, identical in all respects with an authentic sample:[16] bp 48–50° (150 mm); nmr (neat) δ 3.16 (s, 3, OCH_3), 1.30, 1.13, 1.05 (s, 3, CCH_3), 0.23 (m, 2, CH_2).

Ring-Opening Reaction of Hydroxypyrazolines. Acid Catalyzed.—The general procedure was to mix methanol solutions of the hydroxypyrazoline and methanolic HCl at room temperature and then to stir the mixture for various times at various temperatures. After the reaction period the mixtures were diluted with water, washed with base, and extracted with ether. The ether extracts were dried and distilled to remove the solvent; the residue was then subjected to gas chromatographic analysis. Silicone columns operating between 50 and 100° proved to be adequate for resolving the ketones and starting material. In all cases the columns were calibrated using authentic samples (Table II).

Base Catalyzed.—The general procedure was the same except that methanolic NaOH was employed (Table III).

Registry No.—**6a**, 22883-54-1; **6a** 3,5-DNB, 34277-62-8; **6b**, 34277-63-9; **6b** 3,5-DNB, 34277-64-0; **6c**, 34277-81-1; **6c** 3,5-DNB, 34281-09-9; **6d**, 34281-10-2; **6e**, 34281-11-3; **6f**, 34281-12-4; 3-acetoxy-3-methyl-5,5-pentamethylene-1-pyrazoline, 34281-13-5; 3-acetoxy-3-isobutenyl-5,5-dimethyl-1-pyrazoline, 34281-14-6; 3-methoxy-3,5,5-trimethyl-1-pyrazoline, 23019-13-8.

(16) C. H. DePuy and A. DeBoer, Abstracts, 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969, ORGN 62.

The Direct Alkylation of Pyridine 1-Oxides

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Received November 18, 1971

n-Butyllithium in inert nonprotic solvents abstracts a ring proton from the α position of pyridine 1-oxides to give a carbanion which can be trapped with aldehydes and ketones to give 2-(α-hydroxyalkyl)- and 2,6-di(α-hydroxyalkyl)pyridine 1-oxides. A chloro, ethoxyl, or methyl group at the 4 position is unaffected under these conditions, but a 2-methyl substituent undergoes proton abstraction morer eadily than does the C_6H. When a 3-methyl group is present it directs the entering hydroxyalkyl group to the 6 position, but 2,6-disubstituted derivatives are also formed. This orientation is discussed. The use of some bases other than butyllithium is described.

There are few methods available for the direct alkylation of pyridines and related systems, particularly since Friedel–Crafts alkylation is not possible with such π-deficient molecules. Other than high-temperature reactions, the most common modes of nuclear alkylation involve nucleophilic addition–eliminations with organometallic, and in particular organolithium, compounds and by the use of aldehydes and ketones in the Emmert reaction.[2a] More recently, the novel enamine-type alkylation of *N*-lithio-1,2-dihydropyridines has resulted in a useful route to 3-alkylpyridine derivatives.[2b] We now report a convenient method of effecting alkylations of pyridine 1-oxides which promises to have wide utility and to lead to compounds which would be otherwise tedious to prepare.[3]

Nuclear proton abstraction from substituted pyridines has only found sporadic application, this usually involving the formation of pyridyne intermediates.[4]

(1) University of Alabama.

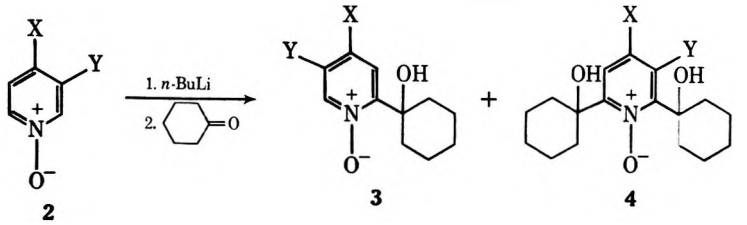
(2) (a) R. A. Abramovitch and J. G. Saha, *Advan. Heterocycl. Chem.*, **6**, 229 (1966); (b) C. S. Giam and J. L. Stout, *J. Amer. Chem. Soc.*, **93**, 1294 (1971).

(3) For preliminary communication, see R. A. Abramovitch, M. Saha, E. M. Smith, and R. T. Coutts, *J. Amer. Chem. Soc.*, **89**, 1537 (1967).

(4) (a) H. J. den Hertog and H. C. van der Plas, *Advan. Heterocycl. Chem.*, **4**, 121 (1965); (b) T. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, **4**, 543 (1965); T. Kauffmann and R. Wirthwein, *ibid.*, **10**, 20 (1971).

TABLE I

REACTION OF 2-LITHIOPYRIDINE 1-OXIDES WITH CYCLOHEXANONE

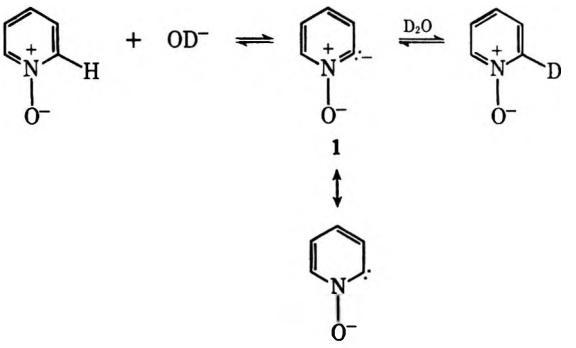


2 3 4

N-Oxide (2)	Conditions	Products, % 3	4
X = Y = H	*n*-BuLi, Et_2O, −65°	7.4	
X = Y = H	*n*-BuLi, THF–Et_2O (2:1 v/v), −65°	4.6	14.8
X = Y = H	*n*-BuLi, Et_2O, *a*	12.5	35.5
X = Y = H	LiOEt–EtOH		
X = Y = H	TlOEt–Et_2O or EtOH		
X = Y = H	$(Me_3Si)_2NNa$, C_6H_6, Δ	0.85	
X = Me; Y = H	*n*-BuLi, THF, −65°	21.1	27.3
X = Me; Y = H	*n*-BuLi, Et_2O, *a*	19.8	24.9
X = Cl; Y = H	*n*-BuLi, Et_2O, −100°		10.9
X = Cl; Y = H	*n*-BuLi, Et_2O, −65°	35.6	20.7
X = Cl; Y = H	*n*-BuLi, THF, −65°		10.5
X = Cl; Y = H	*n*-BuLi, Et_2O, −15°		13.2
X = Cl; Y = H	*n*-BuLi, Et_2O, 0°		7.3
X = OEt; Y = H	*n*-BuLi, Et_2O, −65°	3.7	12.5
X = OEt; Y = H	*n*-BuLi, THF, −65°	19.9	20.7
X = OEt; Y = H	NaH, THF, bp	7.5	
X = H; Y = Me	*n*-BuLi, THF–Et_2O (1:4 v/v), −65°	25.1	7.7
X = Y = Me	*n*-BuLi, THF, −65°	38.7	12.1
X = Y = Me	*n*-BuLi–TMEDA, THF, −65°	28.5	6.7
X = Y = Me	MeLi, THF, −65°	47.3	8.9
X = Y = Me	*n*-BuLi, Et_2O, −65°	56.3	15.6
X = Y = Me	$(Me_3Si)_2NNa$, C_6H_6, Δ	1.68	
X = Y = Me	$(Me_3Si)_2NNa$, THF, *a*	1.41	
X = Y = Me	$(Me_3Si)_2NNa$, THF, Δ	1.4	
X = Y = Me	$(Me_3Si)_2NLi$, Et_2O, *a*	4.0	(2.6)[b]
X = Y = Me	$(Me_3Si)_2NLi$, Et_2O, Δ	4.5	(3.3)[b]
X = Cl; Y = Me	*n*-BuLi, Et_2O, −65°	43.8	4.7
5	*n*-BuLi, −78°	6 (4.3%)	7 (19.6%)

[a] Room temperature. [b] 3-Methyl-4-(1-hydroxycyclohexylmethyl)pyridine 1-oxide.

It was expected[5] that base-catalyzed deprotonation of pyridine 1-oxides and pyridinium salts should occur much more readily than in pyridine themselves,[6] and that the C_2 H would be the most acidic proton; this prediction has been verified quantitatively.[5,7] If, indeed, base-catalyzed H–D exchange in pyridine 1-oxide did involve formation of an intermediate carbanion **1**; it might be possible to trap such a carbanion with appropriate electrophiles if it were generated in a nonprotic solvent. This has indeed been found to be the case, and we report here the use of aldehydes and ketones as the electrophiles, leading to α-hydroxy alkylated pyridine 1-oxides. In subsequent papers we shall consider reactions with other electrophiles.



The 2-pyridyl 1-oxide anions were conveniently generated by the addition of *n*-butyllithium to a solution of the *N*-oxide in ether or tetrahydrofuran at −65°, followed by the addition of the aldehyde or ketone. A number of other conditions were investigated and the results are summarized in Table I, but no attempt was made to optimize yields. When pyridine 1-oxide itself in a mixture of ether and tetrahydrofuran was treated

(5) R. A. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem. Commun.*, 55 (1967); R. A. Abramovitch and A. R. Vinutha, *J. Chem. Soc. B*, 131 (1971).

(6) J. A. Zoltewicz and C. L. Smith, *J. Amer. Chem. Soc.*, **88**, 4766 (1966).

(7) Base-catalyzed nuclear proton abstraction may be of importance in biological systems and could be involved in the appearance of an absorption maximum at 290 mμ when NAD^+ is treated with 0.17 *N* KOH or the rapid formation of a species absorbing at 282 mμ when 1-methylnicotinamide iodide is treated with 0.3 *N* KOH solution.[8] This had previously been attributed[8] to the formation of a charge-transfer intermediate between the pyridinium salt and OH^-. In preliminary studies we have shown that the change in the uv spectrum observed when nicotinonitrile methiodide is treated with aqueous base parallels the rate of H–D exchange with NaOD in D_2O.

(8) R. M. Burton and N. O. Kaplan, *Arch. Biochem. Biophys.*, **101**, 139 (1969). For an alternate explanation, see R. B. Martin and J. G. Hull, *J. Biol. Chem.*, **239**, 1237 (1964).

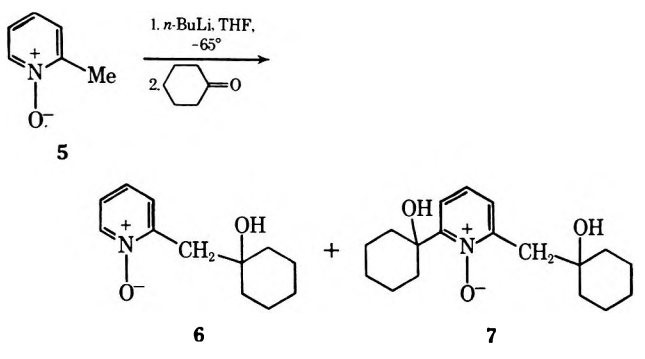
with *n*-BuLi at −65°, two products were obtained: 2-(1-hydroxycyclohexyl)pyridine 1-oxide (**3**, X = Y = H) (4.6%) and 2,6-di(1-hydroxycyclohexyl)pyridine 1-oxide (**4**, X = Y = H) (14.8%). The structures of the products were established mainly on the basis of microanalysis and infrared and nmr spectroscopy. **3** (X = Y = H) was found to be identical with an authentic sample prepared from 2-(1-hydroxycyclohexyl)-pyridine *via* 2-pyridyllithium and cyclohexanone. When this reaction was carried out in ether alone only **3** (X = H) was obtained in low yield.

The reaction of 4-picoline 1-oxide (**2**, X = Me; Y = H) with *n*-BuLi and then cyclohexanone gave both **3** (X = Me; Y = H) and **4** (X = Me; Y = H). No exchange of the otherwise active side-chain protons took place under these conditions, or even at room temperature, since no product derived from a 4-pyridylmethyl anion was observed (see below, however, for conditions under which such a product *was* formed from 3,4-lutidine 1-oxide). This is to be contrasted with the ready formation of 4-picolyllithium from 4-picoline and phenyllithium and indicates that under the present conditions the C_2 H proton is more acidic than the 4-methyl protons in 4-picoline 1-oxide. In all cases, some 2-*n*-butylpyridines and 1-butylcyclohexanol were detected but not analyzed further.

The case of C_2 H proton abstraction is further emphasized by the fact that the 2-pyridyl 1-oxide carbanion is formed preferentially even in the presence of substituents in **2** which normally undergo nucleophilic substitution or halogen–metal interconversion very readily, *e.g.*, X = Cl or OEt. Thus, the reaction of 4-chloropyridine 1-oxide with *n*-BuLi in ether and then with cyclohexanone gave **3** (X = Cl, Y = H) (35.6%), and **4** (X = Cl, Y = H) (20.7%). No evidence for the formation of any 1-oxido-4-pyridyllithium was found in any of the reactions studied in which a 4-chloro substituent was present in the *N*-oxide. A 4-ethoxyl group was similarly inert. The retention of both a 4-chloro substituent and of the *N*-oxide function in these products should make this reaction quite useful, since such a 4-chloro group is known to undergo nucleophilic aromatic substitution readily.

The physical constants of **3** and **4** are given in Table II.

The alkylation of 2-picoline 1-oxide (**5**) was investigated briefly. In contrast to the behavior of a 4-methyl group, the 2-methyl substituent was found to be more reactive than C_6–H toward proton abstraction by BuLi; thus, both 1-(1-oxido-2-pyridylmethyl)cyclohexanol (**6**) (4.3%) and α,6-di-(1-hydroxycyclohexyl)-2-methylpyridine 1-oxide (**7**) (19.6%) were obtained. **6** was identical with an authentic sample prepared from 2-picolyllithium and cyclohexanone followed by peracid N oxidation. As expected,[9] it was observed that in cases as those above where no substituents are present at the β and γ positions of the pyridine 1-oxide ring the C_3 H and C_4 H protons are not well resolved when the nmr spectra of the compounds in nonprotic solvents are determined.



5 **6** **7**

The reaction with a number of 3-methylpyridine 1-oxides with cyclohexanone was studied with a view of determining the effect of a 3-methyl group upon the orientation of the entering group. It has been established that in the addition–elimination of an organolithium compound to 3-picoline the main product formed is the 2,3 isomer. For example, with phenyllithium the ratio of 3-methyl-2-phenyl- to 5-methyl-2-phenylpyridine is 19:1,[10] and, indeed, the 3-methyl group *activates* C_2 toward nucleophilic attack. It was expected that this situation would not obtain in the present case since the transition states for the two reactions should be quite different. In the SNAr process, the highly reactive nucleophile attacks the α carbon atom in a direction perpendicular to the plane of the ring and the transition state is reached quite soon, before too much rehybridization has taken place (**8**) (*i.e.*, the transition state looks more like the ground state than the intermediate σ complex),[1,10] so that a 3-methyl group exerts very little, if any, steric hindrance to attack at C_2. On the other hand, proton abstraction from C_2 by base involves the approach of the base in line with the C_2–H bond and in the same plane as the *N*-oxide and 3-methyl group (**9**), so that the latter

8 **9**

might be expected to exert an appreciable steric effect in this case. It should be noted that there is no marked preference for C_2 H over C_6 H proton abstraction in the H–D exchange of 3-picoline methiodide with 0.1 *N* NaOD in D_2O at 26° ($k_{H\text{-}2}^{26°}/k_{H\text{-}6}^{26°}$ = 1.2)[5] and with 3-picoline 1-oxide the rates are almost identical.[11] On the other hand, *n*-butyllithium (tetramer or hexamer) is much bulkier than OD^-, and, even if the 2-lithio derivative is formed, its approach to the carbonyl group in cyclohexanone in the subsequent reaction will be sterically hindered by the groups flanking the carbanionic site.

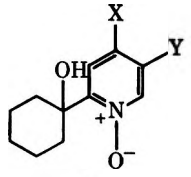
When 3-picoline 1-oxide in ether–tetrahydrofuran solution was treated with *n*-butyllithium followed by cyclohexanone, the main product formed was the 2-(1-hydroxycyclohexyl)-5-methyl derivative (**10**), and the 2,6-disubstituted compound (**11**) was the minor product. No 2-substituted compound unsubstituted at C_6 (**12**) was obtained in any of the alkylations studied here. An authentic sample of **10** was prepared from 2-bromo-5-methylpyridine.

The 3,4-disubstituted pyridine 1-oxides (**2**) studied behaved similarly on treatment with BuLi and then with an aldehyde or a ketone, giving either the 2α-

(9) R. A. Abramovitch and J. B. Davis, *J. Chem. Soc.*, *B*, 1137 (1966).
(10) R. A. Abramovitch and C. S. Giam, *Can. J. Chem.*, **40**, 213 (1962).
(11) R. A. Abramovitch and G. M. Singer, unpublished results.

TABLE II

PHYSICAL CONSTANTS FOR 2-(1-HYDROXYCYCLOHEXYL)PYRIDINE 1-OXIDES (3) AND 2,6-DI(1-HYDROXYLCYCLOHEXYL)PYRIDINE 1-OXIDES (4)[f]



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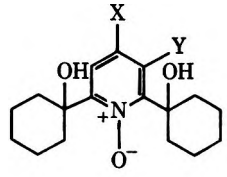
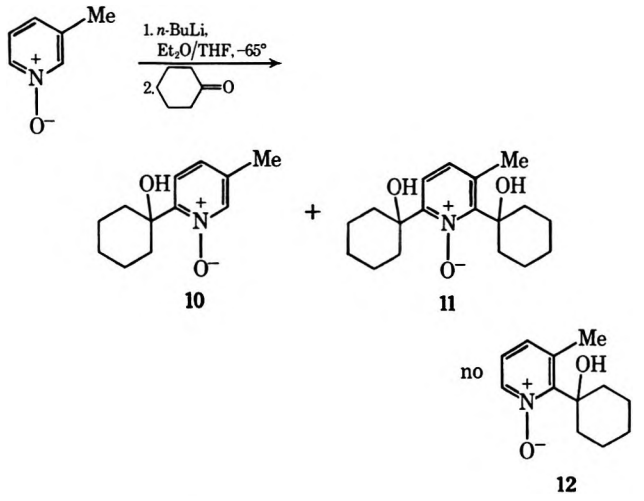


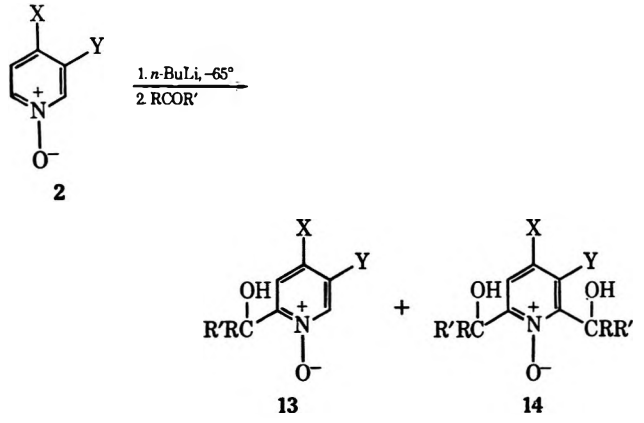
4

Registry no.	N-Oxide	Mp,[a] °C	Infrared spectrum, cm^{-1}	Nmr spectrum, τ: H$_3$	H$_4$	H$_5$	H$_6$	OH[e]	Aliphatic protons
34277-33-3	**3**, X = Y = H	93–94	3100 (s), 1296 (s), 1276 (w), 1237 (s), 1192 (s)	2.46–2.90[c]	2.46–2.90	2.46–2.90	1.82	2.44	7.40–9.00 (cyclohexyl)
17117-10-1	**4**, X = Y = H	158	3275 (s), 3180 (s), 1258 (m)	2.67[d]	2.67	2.67		2.74	7.50–8.65 (cyclohexyl)
17117-08-7	**3**, X = Me; Y = H	115	3130 (m), 1200 (s)	2.85[c]		2.96 ($J_{5,6}$ = 6 Hz)	1.93	2.17	7.68–8.85 (cyclohexyl), 7.66 (ArCH$_3$)
17117-09-8	**4**, X = Me; Y = H	198–199	3220 (s), 1125 (s)	2.90[c]		2.90		2.55	7.70–8.65 (cyclohexyl), 7.68 (ArCH$_3$)
34277-37-7	**3**, X = Cl; Y = H	113–114	3220 (w), 1276 (s)	2.70[c]		2.70	1.87	2.70	7.50–8.80 (cyclohexyl)
34277-38-8	**4**, X = Cl; Y = H	195	3260 (s), 1250 (s)	2.70[c]		2.70		3.01	7.50–8.65 (cyclohexyl)
17117-03-2	**3**, X = OEt; Y = H	128	3150 (m), 3040 (m), 1270 (m), 1220 (m), 1200 (w), 1155 (s)	3.10[c]		3.10	1.89	1.70	7.55–8.80 (cyclohexyl, –CH$_2$CH$_3$), 5.66-6.01 (–OCH$_2$CH$_3$)
17117-07-6	**4**, X = OEt; Y = H	166	3190 (s), 1270 (s), 1155 (s)	3.16[c]		3.16		2.18	7.55–8.70 (cyclohexyl, –CH$_2$CH$_3$), 5.68–6.03 (–OCH$_2$CH$_3$)
34277-41-3	**3**, X = H; Y = Me	123–125	3080 (m), 1265 (s), 1233 (s), 1193 (m), 1164 (s)	2.82[c]	2.82		1.96	2.40	7.50–8.90 (cyclohexyl, ArCH$_3$)
34277-42-4	**4**, X = H; Y = Me	138–139[b]	3600–3100 (s), 1260 (m), 1230 (w), 1208 (w), 1182 (m)		2.86[c]	2.86		1.40, 2.80	7.30–8.80 (cyclohexyl), 7.48 (ArCH$_3$)
17117-06-5	**3**, X = Y = Me	148–149	3140 (m), 1250 (s)	2.95[c]			2.10	2.18	8.10–8.87 (cyclohexyl), 7.87, 7.78 (ArCH$_3$)
34277-44-6	**4**, X = Y = Me	189–190	3320–3100 (m), 1260 (m), 1190 (s)			2.98[d]		1.57, 3.15	7.65–8.80 (cyclohexyl), 7.58, 7.48 (ArCH$_3$)
17117-04-3	**3**, X = Cl; Y = Me	161–165	3120 (m), 3015 (m), 1240 (m), 1160 (s)	2.83[d]			2.03	3.28	7.80–8.70 (cyclohexyl), 7.73 (ArCH$_3$)
34277-45-7	**4**, X = Cl; Y = Me	168–169	3340–3110 (m), 1263 (s), 1241 (s), 1215 (w), 1185 (s)			2.75[d]		2.01, 3.58	7.50–8.80 (cyclohexyl), 7.47 (ArCH$_3$)

[a] Recrystallized from acetone. [b] Recrystallized from methanol. [c] $CDCl_3$. [d] CCl_4. [e] OH exchanges with D_2O. [f] Satisfactory analytical values (±0.4% for C, H, N) for all compounds were reported: Ed.

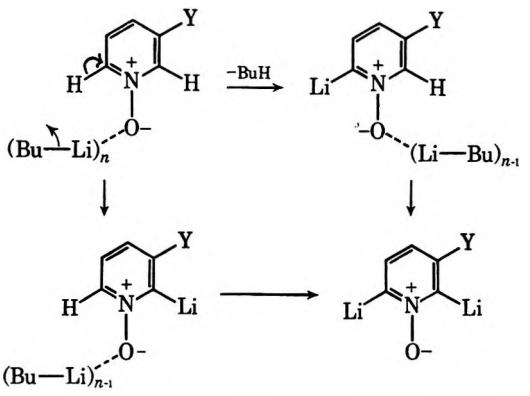


hydroxyalkyl 4,5-disubstituted compound (**13**) only or a mixture of the 2- and 2,6-di(α-hydroxyalkyl) derivatives (**14**). The question of the lack of formation of

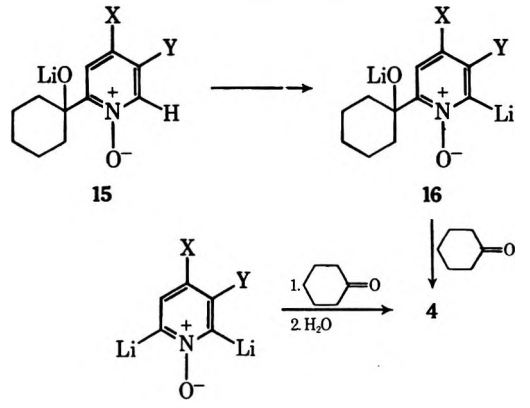


any 2-hydroxyalkyl 3-substituted derivatives in these reactions but the formation of 2,6-disubstitution product deserves discussion. Steric hindrance to approach in the plane of the ring of the bulky tetrameric or hexameric butyllithium, probably coordinated at the *N*-oxide oxygen, to the proton ortho to the methyl group would readily account for the preferential formation of **13**. The 2,6-disubstitution products **14** could then arise in a number of ways. The 2,6 dianion may first be formed (*cf.* *o*-dilithiobenzene[12]) and this then attacks the carbonyl compound. The question which comes to mind is why *no* 2-hydroxyalkyl derivative is formed if the 2,6 derivative is. If any 2-lithio 3-substituted 1-oxide were formed, one would expect some steric hindrance to its approach of the electrophilic carbonyl group, so that the latter might well be slower than that of the 6-lithio derivative, but not be forbidden as again the isolation of the 2,6 isomer testifies (proton abstraction leading to the cyclohexanone enolate anion and the pyridine 1-oxide may be favored over nucleophilic addition of the crowded anion to the carbonyl group). It is tempting to speculate that once the *N*-oxide-complexed butyllithium tetramer or hexamer has abstracted the proton from the 6 position the remaining complexed species may be less associated and hence less bulky, thus permitting an intramolecular approach to the C_2 H. This does not necessarily rule out the formation of some 2-lithio derivative initially, but the latter

(12) G. Wittig and F. Bickelhaupt, *Chem. Ber.*, **91**, 883 (1958).



would be expected to give the 2,6-dilithio derivative faster than would the 6-lithio compound, so that this fact, combined with the slower attack of the C_2 carbanion on the ketone when the latter is added, could account for the observation that no 2-monosubstituted derivative was formed in these cases. It is possible that with smaller electrophiles some 2 monosubstitution would be observed. Alternatively a dicarbanion may not be formed but the 6-monosubstituted anion **15** abstracts a proton from C_2 of another molecule to give **16**, this now reacting with more cyclohexanone to



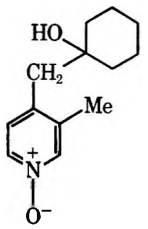
give **4**. An intramolecular proton abstraction can undoubtedly be ruled out on steric grounds. It is not clear why **15** might prefer to abstract a proton from the hindered 2 position rather than from a molecule of the unreacted *N*-oxide (some of which is always recovered). 1-Butylcyclohexyl oxide anion or cyclohexanone enolate anion could be the bases abstracting the C_2 H proton intermolecularly from **15** in the excess cyclohexanone present. None of these explanations appear to account for all the facts, but the evidence available from the use of halogens as electrophiles suggests that the dicarbanions are indeed formed, at least to some extent.[13] On the other hand, *both* possible 1-hydroxy-2-pyridinethiones were obtained on treatment of the lithio derivatives of 3,4-lutidine 1-oxide with sulfur, indicating that in this case both the 2- and the 6-lithio 3-substituted 1-oxides were formed,[13] which would be consistent with the first explanation proposed if sulfur is regarded as a smaller electrophile than cyclohexanone.

The effect of temperature upon the yields of products was studied briefly. In some cases, *e.g.*, pyridine 1-oxide in ether and cyclohexanone, it was found that warming the mixture to room temperature before the addition of cyclohexanone gave improved yields, while

(13) R. A. Abramovitch and E. E. Knaus, *J. Heterocycl. Chem.*, **6**, 989 (1969).

in others, *e.g.*, 4-chloropyyridine 1-oxide and cyclohexanone, the opposite was true. The addition of tetramethylethylenediamine (TMEDA) to the butyllithium solution did not improve the yields.

Sodium hydride and sodium bistrimethylsilylamide in benzene were not particularly effective as proton abstractors. Lithium bistrimethylsilylamide in ether was somewhat more effective, and in the reaction with 3,4-lutidine 1-oxide and cyclohexanone no 2,6-disubstitution product was formed. In addition to the 2-(1-hydroxycyclohexyl)-4,5-dimethyl derivative, however, there was obtained a small yield of 3-methyl-4-(1-hydroxycyclohexylmethyl)pyridine 1-oxide (**17**). Its



17

mass spectrum exhibited a parent ion peak at *m/e* 221 and an $(M - 18)^+$ ion at *m/e* 203 due to loss of water. The most important fragment arose from loss of the 3,4-dimethylpyridine 1-oxide ion ($C_7H_9NO^+$) to give a base peak at *m/e* 123. Interestingly, there was no $(M - 16)^+$ ion peak at *m/e* 205 which would have arisen from the loss of an oxygen atom from the molecular ion. The isolation of **17** provides the first example of a base-catalyzed proton abstraction of a 4-methyl proton in this study.

Lithium and thallous ethoxide, as well as potassium 2,6-di-*tert*-butylphenoxide, were completely ineffective as basic catalysts in this reaction.

Experimental Section

Melting points are uncorrected. In most cases only the main infrared bands are reported.

Starting Pyridine 1-Oxides.—3,4-Lutidine 1-oxide, prepared in 77.4% yield by the peracetic acid oxidation of 3,4-lutidine and purified by chromatography on alumina followed by recrystallization from acetone, had mp 138° (lit.[14] mp 128–130°).

Anal. Calcd for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.50; H, 7.44; N, 11.32.

4-Chloropyridine 1-oxide[15] (86%) had mp 181–182°, and 4-chloro-3-methylpyridine 1-oxide[16] (87%) had mp 119–120°.

2-(1-Hydroxycyclohexyl)pyridine 1-Oxide.—2-(1-Hydroxycyclohexyl)pyridine[17] (2.021 g) was oxidized with peracetic acid at 70–80° for 6 hr, with the addition of further amounts (2 ml) of 30% H_2O_2 every 12 hr. The product was purified by chromatography on a column of alumina and recrystallized from acetone, and was obtained as a solid (1.89 g, 86.4%).

2-(1-Hydroxycyclohexyl)-5-methylpyridine 1-Oxide.—2-(1-Hydroxycyclohexyl)-5-methylpyridine[18] (0.822 g) was oxidized with peracetic acid at 70° for 24 hr. The product was purified by chromatography on a column of alumina and recrystallized from acetone (0.513 g, 56.7%).

1-(1-Oxido-2-pyridylmethyl)cyclohexanol.—1-(2-Pyridylmethyl)cyclohexanol[19] (3.2 g) was oxidized with peracetic acid at 70° for 18 hr to give the *N*-oxide (3.1 g, 89.4%), mp 113–114° (acetone), ir (KBr) 3400–3200 (s, OH) and 1225 cm^{-1} (s, $^+NO^-$).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.25; N, 6.76. Found: C, 69.59; H, 8.16; N, 6.91.

Preparation of Pyridyl 1-Oxide Carbanions and Their Reactions with Aldehydes and Ketones. General Procedure.—To a stirred solution (or suspension) of the pyridine 1-oxide (0.007 mol) in anhydrous ether (or tetrahydrofuran) (40–60 ml) at −65° under dry N_2, *n*-butyllithium (0.96 g in hexane solution, 0.015 mol) was added dropwise. After stirring the solution for 15 min at that temperature, a solution of the aldehyde or ketone (0.015 mol) in anhydrous ether (or tetrahydrofuran) (10 ml) was added dropwise to give a dark red to brown solution. The reaction mixture was stirred for 1–3 hr at −65° and then allowed to warm to room temperature and decomposed with water (10 ml). The excess ether (or tetrahydrofuran) was evaporated *in vacuo*, and the products were isolated from the aqueous solution as described in individual cases.

Reaction of Pyridyl 1-Oxide Carbanion with Acetaldehyde.—Pyridine 1-oxide (1.90 g, 0.02 mol) in anhydrous tetrahydrofuran (70 ml) was treated with *n*-butyllithium (2.56 g in hexane, 0.04 mol) and then with acetaldehyde (1.76 g, 0.04 mol) at −65°. The orange viscous oil (2.6 g) obtained was chromatographed on a silica gel column (2.5 × 35 cm). Elution with benzene–ether (3:1, v/v) gave a brown aliphatic oil (0.198 g) which was not investigated further. Further elution with benzene–ether (3:1, v/v) and then ether gave **2,6-di(1-hydroxyethyl)pyridine 1-oxide** as a yellow oil (1.103 g, 30.1%), bp 127° (0.075 mm), which crystallized on standing to give a white solid: mp 70–72°; ir (neat) 3350 (s); nmr ($CDCl_3$) τ 8.47 (d, J = 6.5 Hz, 6, $-CHCH_3$), 4.76 (q, J = 6.5 Hz, 2, $-CHCH_3$), 4.18 (s, 2, OH, exchange with D_2O), 2.56 (s, 3, C_3H, C_4H, C_5H); mass spectrum no M^+ at *m/e* 183, *m/e* 165 (45, $M^+ - H_2O$).

Anal. Calcd for $C_9H_{13}NO_3$: C, 58.99; H, 7.15. Found: C, 58.45; H, 7.52.

Further elution with ether–methanol (4:1, v/v), and then methanol gave **2-(1-hydroxyethyl)pyridine 1-oxide** as a yellow oil (1.01 g, 36.3%), bp 110° (0.075 mm), which crystallized on standing: mp 97–98° (lit.[20] mp 97–99°); ir (KBr) 3350 (s) and 1225 cm^{-1} (s); nmr ($CDCl_3$) τ 8.47 (d, J = 6.5 Hz, 3, $-CHCH_3$), 4.76 (q, J = 6.5 Hz, 1, $-CHCH_3$), 4.02 (s, 1, OH exchanges with D_2O), 2.60–2.94 (m, 2, C_4H, C_5H), 2.46 (q, $J_{3,4}$ = 8 Hz, $J_{3,5}$ = 3 Hz, 1, C_3H), 1.85 ($J_{5,6}$ = 6 Hz, $J_{4,6}$ = 2 Hz, 1, C_6H); mass spectrum *m/e* 121 ($M^+ - H_2O$) (no M^+ ion at *m/e* 139 observed).

Reaction of 4-Chloro-3-methylpyridyl 1-Oxide Carbanion with Benzaldehyde.—4-Chloro-3-methylpyridine 1-oxide (1.00 g, 0.007 mol) was suspended in anhydrous ether (50 ml) and treated with *n*-butyllithium (0.96 g in hexane, 0.015 mol) and then with freshly distilled benzaldehyde (1.59 g, 0.015 mol) at −65° for 1 hr. The aqueous solution was acidified with dilute hydrochloric acid and then extracted with ether to remove any unreacted benzaldehyde. The acidic solution was made alkaline with 10% NaOH solution, and then extracted with $CHCl_3$ (3 × 75 ml). The dried (K_2CO_3) $CHCl_3$ extract was evaporated *in vacuo* to give a yellow-oil (0.824 g) which was distilled at 140° (0.03 mm) to give a yellow oil (0.593 g), trituration of which gave **4-chloro-2-(1-hydroxy-2-benzyl)-5-methylpyridine 1-oxide** (0.163 g, 9.4%): mp 134–135° (from acetone); ir (KBr) 3300–3100 (s), 1235 (s), and 1155 cm^{-1} (s); nmr ($CDCl_3$) τ 7.70 (s, 3, $ArCH_3$), 3.82 (s, 2, Ar_2CH- and OH, the latter exchanges with D_2O), 2.53 (m, 6, $-C_6H_5$, C_3H), 1.93 (s, 1, C_6H).

Anal. Calcd. for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.18; H, 4.89 N, 5.67.

Reaction of 3,4-Dimethylpyridine Carbanion with *n*-Butyraldehyde.—3,4-Dimethylpyridine 1-oxide (0.68 g, 0.007 mol) in anhydrous tetrahydrofuran (60 ml) was treated with *n*-butyllithium (0.96 g in hexane, 0.015 mol), and then with *n*-butyraldehyde (1.08 g, 0.015 mol) at −65° for 1 hr and worked up as above. The yellow oil obtained (0.988 g) was distilled at 122° (0.01 mm) to give a yellow oil (0.400 g) which, on trituration with ether, chromatography on alumina, and recrystallization from acetone, gave **(4,5-dimethyl-1-oxido-2-pyridyl)-*n*-propylcarbinol** (0.200 g, 14.7%): ir (KBr) 3250–3050 (s), 3000–2860 (s), 1260 (s), 1175

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(16) A. R. Katritzky, *J. Chem. Soc.*, 2404 (1956).

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(s), and 1135 cm^{-1} (w); nmr ($CDCl_3$) τ 7.90–9.30 (m, 7, C_3H_7), 7.83 (s, 3, $ArCH_3$), 7.75 (s, 3, $ArCH_3$), 5.08 [t, 1, $ArCH(CH_2)_2$], 4.00 (s, 1, OH, exchanges with D_2O), 2.88 (s, 1, C_3H), 1.99 (s, 1, C_6H).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.75. Found: C, 67.63; H, 8.93.

Reaction of Pyridyl 1-Oxide Carbanion with Acetone.—Pyridine 1-oxide (1.35 g, 0.015 mol) in anhydrous tetrahydrofuran (70 ml) was treated with *n*-butyllithium (1.92 g in hexane, 0.03 mol) and the mixture was treated with acetone (1.74 g, 0.03 mol) for 3 hr. The product was a brown oil which crystallized to give **2,6-di(1-methyl-1-hydroxyethyl)pyridine 1-oxide** (0.534 g, 17.8%): mp 118° (chromatographed on alumina and recrystallized from acetone); ir (KBr) 3300–3200 (s), 1266 (w), 1195 (s), 1168 (s), and 1150 cm^{-1} (m); nmr ($CDCl_3$) τ 8.40 [s, 12, 2 $>C(CH_3)_2$], 2.60 (s, 3, C_3H, C_4H, C_5H), 2.50 (s, 2, OH, exchanges with D_2O).

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11. Found: C, 62.40; H, 8.35.

4-(1-Hydroxycyclohexylmethyl)-3-methylpyridine 1-oxide had mp 217–219° (acetone); ir (KBr) 3240 (s), 1275 (s), 1185 (s), 1175 (s), and 1160 cm^{-1} (s).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65. Found: C, 70.35; H, 8.79.

Dimethyl (1-oxido-4,5-dimethyl-2-pyridyl)carbinol had mp 129° (acetone); ir (KBr) 3150 (s), 1250 (s), 1180 (s), and 1150 cm^{-1} (s); nmr ($CDCl_3$) τ 8.35 [s, 6, $>C(CH_3)_2$], 7.77 (s, 3, $ArCH_3$), 7.68 (s, 3, $ArCH_3$), 2.82 (s, 1, C_3H), 1.98 (s, 1, C_6H), 1.93 (s, 1, OH, exchanges with D_2O).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.00; H, 8.47; N, 7.89.

1-(1-Oxido-4,5-dimethyl-2-pyridyl)-1-phenylethanol had mp 141° (acetone); ir (KBr) 3200–3100 (w), 1245 (s), and 1155 cm^{-1} (s); nmr ($CDCl_3$) τ 8.17 (s, 3, $-CCH_3$), 7.82 (s, 3, $ArCH_3$), 7.70 (s, 3, $ArCH_3$), 2.70 (m, 6, C_3H, C_6H_5), 2.05 (s, 1, C_6H), 1.60 (s, 1, OH, exchanges with D_2O).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04. Found: C, 73.97; H, 7.17.

α,6-Di(1-hydroxycyclohexyl)-2-methylpyridine 1-oxide had mp 111° (acetone); ir (KBr) 3300–3100 (s), 1275 (m), and 1200 cm^{-1} (s).

Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91. Found: C, 70.83; H, 9.11.

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Registry No.—1-(1-Oxido-2-pyridylmethyl)cyclohexanol, 34277-46-8; 2,6-di(1-hydroxyethyl)pyridine 1-oxide, 34277-47-9; 2-(1-hydroxyethyl)pyridine 1-oxide, 34277-48-0; 4-chloro-2-(1-hydroxy-2-benzyl)-5-methylpyridine 1-oxide, 34965-48-5; (4,5-dimethyl-1-oxido-2-pyridyl)-*n*-propylcarbinol, 34277-50-4; 2,6-di(1-methyl-1-hydroxyethyl)pyridine 1-oxide, 34277-51-5; 4-(1-hydroxycyclohexylmethyl)-3-methylpyridine 1-oxide, 34277-52-6; dimethyl (1-oxido-4,5-dimethyl-2-pyridyl)carbinol, 34277-58-2; 1-(1-oxido-4,5-dimethyl-2-pyridyl)-1-phenylethanol, 34277-59-3; 2,6-di(1-hydroxycylcohexyl)-2-methylpyridine 1-oxide, 34277-60-6.

Ring-Opening Reactions of the Pyrazolo[1,2-*a*]pyridazin-6-one System[1]

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The ring-opening reactions of 8-phenyl-1,4-methano-1,4-dihydropyrazolo[1,2-*a*]pyridazin-6-one (**4**) and 1,4,8-triphenyl-1,4-dihydropyrazolo[1,2-*a*]pyridazin-6-one (**5**) in dilute hydrochloric acid and potassium hydroxide solutions were found to give 1- and 2-nitrogen-substituted pyrazol-3-one derivatives in high yield. The ring-opening reactions of **5** yielded 1-(1,4-diphenyl-1,3-butadienyl)-3-hydroxy-5-phenylpyrazole in potassium hydroxide solution, 1-(4-hydroxy-1,4-diphenyl-2-butenyl)-3-hydroxy-5-phenylpyrazole in hydrochloric acid, and the corresponding trichloroacetate in trichloroacetic acid. The ring opening of **4** in hydrochloric acid gave 1-(4-hydroxy-2-cyclopentenyl)-5-hydroxy-3-phenylpyrazole but no ring opening of **4** was observed in potassium hydroxide solution. The hydrogenated adduct, 8-phenyl-1,4-methano-1,2,3,4-tetrahydropyrazolo[1,2-*a*]-pyridazin-6-one, did not open under acidic or basic conditions.

The Diels–Alder reaction has been known to yield pyridazine derivatives since 1925.[4] The majority of work in this area from 1925 until 1960 has dealt with adducts of acyclic azodicarboxylates. Since 1960 a number of workers have reported adducts of cyclic acyl[5–7] and diacyl-cis-azo compounds.[8–11] Although the azodicarboxylate adducts have been shown to undergo a number of useful reactions,[12–15] investigations of the potentially more interesting adducts of cyclic azo compounds have not been pursued. The following is a report of some ring-opening reactions of pyrazol-3-one adducts to give N-substituted pyrazolin-3-ones.

The oxidation of a 3-substituted 2-pyrazolin-5-one (**1**) with lead tetraacetate gave the pyrazol-3-one ring system (**2**). When the oxidation was carried out in the presence of a diene the pyrazol-3-ones were trapped as Diels–Alder adducts (**3**).[6] The adducts **4** and **5** of cyclopentadiene and of 1,4-diphenylbutadiene, respectively, with 5-phenylpyrazol-3-one (**2**, R = C_6H_5)[6] were investigated in the course of this work.

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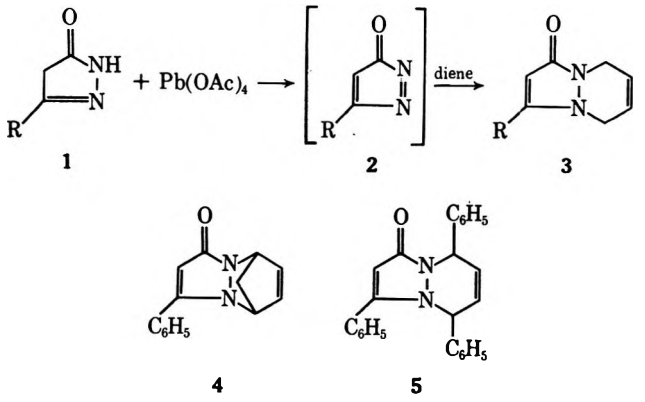
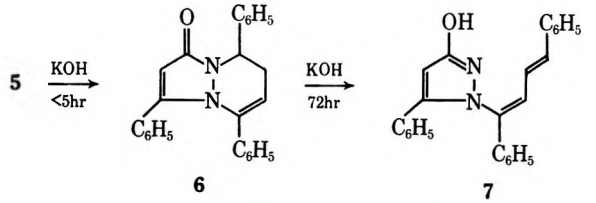


1 2 3 4 5

The 1,4-dihydropyrazolo[1,2-*a*]pyridazin-6-one ring system **3** contains both a *4-pyrazolin-3-one* and a *3,6-dihydropyridazine* moiety. The properties of the 4-pyrazolin-3-one ring system have not been investigated in much detail. Reactions carried out under acidic[16] and basic[17] conditions indicated that the ring system was stable to mild treatment. It has also been shown to be stable toward catalytic hydrogenation, as debenzylation of 1-benzyl-2,3-dimethyl-3-pyrazolin-5-one occurred rather than hydrogenation of the pyrazolinone ring.[16] The 3,6-dihydropyridazine ring system has been shown to undergo a number of reactions in the form of an ethyl azodicarboxylate adduct. Catalytic hydrogenation,[18] retro Diels–Alder reactions,[19] and acid-[20] and base-catalyzed[21] hydrolysis of *N*-acyl functions have been reported.

Results and Discussion

In this investigation it was found that widely different products were obtained from the alkaline and acidic reactions of the bicyclic system **3**. Further, all of the ring-opened products resulted from opening of the pyridazine rather than the pyrazolinone ring. Refluxing of **5** in 20% solution of potassium hydroxide in 80% aqueous ethanol results in rapid isomerization (<5 hr) of the pyridazine double bond to the 3 position (**6**) followed by slow ring opening (~72 hr) of this isomer to give the diene **7**. The isomer 1,4,8-tri-



6 7

phenyl-3,4-dihydropyrazolo[1,2-*a*]pyridazin-6-one (**6**) has an ultraviolet spectrum (Table I) which suggests that a styrene type chromophore [λ_{max}^{EtOH} 248 nm (ϵ 14,000), 282 (750), 291 (500)][22] is present along with the pyrazoline chromaphore of **5** (Table I). The mass spectrum of **6** showed intense peaks corresponding to loss of phenyl (*m/e* 273 and 77) and a peak at *m/e* 234 corresponding to $C_{16}H_{14}N_2$, probably a 3,6-diphenyldihydropyridazine. The mass spectrum of adduct **5** showed minor amounts of these fragments while cleaving primarily through a reverse Diels–Alder mechanism to give diphenylbutadiene (*m/e* 206). Each proton of the C-3 methylene group of **6** appeared as an eight-line pattern in the pmr spectrum with δ 2.63 (C_3H) and 3.08 ppm (C_3H') with the following coupling constants: J_{HH} = 17 (C_3H, C_3H'), 6.5 (C_3H, C_4H), 1 (C_3H, C_2H), 6.5 (C_3H', C_4H), and 3 Hz (C_3H', C_2H). The assignment of the pyridazine double bond of **6** to the two position was based primarily on the fact that it opened with cleavage of the ring at the amide nitrogen.

The difference in rates of isomerization of **5** to **6** and subsequent ring opening to **7** allowed complete isomerization of **5** to occur before the ring-opened product was detected. The ultraviolet spectrum of **7**, 1-(1,4-diphenyl-1,3-butadienyl)-3-hydroxy-5-phenylpyrazole, shows absorption at 335 and 238 nm (Table I) which may be attributed to the 1,4-diphenylbutadiene chromaphore [λ_{max}^{EtOH} 345 nm (ϵ 25,000), 328 (46,700), 314 (41,700), 232 (12,000)].[23] The pmr resonance for the 1-(1,4-diphenyl-1,3-butadienyl) vinyl protons on carbons 2, 3, and 4 appeared at 7.28, 6.68, and 7.03 ppm, respectively, with coupling constants J_{HH} = 9 (C_2H, C_3H), 1 (C_2H, C_4H), and 5 Hz (C_3H, C_4H). The mass spectrum of **7** showed intense peaks corresponding to loss of a styryl function (*m/e* 260 and 104) and a base peak at *m/e* 219 for $C_{16}H_{13}N$.

In order to determine that ring opening of **5** had occurred at the amide nitrogen, the ring-opened compound **7** was hydrogenated over palladium to give

TABLE I

ULTRAVIOLET ABSORPTION OF SUBSTITUTED PYRAZOLONES AND PYRAZOLES

Compd	Tautomeric form	Ultraviolet spectrum, nm (ϵ) 95% Ethanol	Cyclohexane
5	Oxo	245 (12,500)	245 (15,800)
6	Oxo	292 (10,200)	
		244 (24,700)	
7	Hydroxyl	335 (22,100)	
		255 (25,400)	
		sh 244 (3760)	
		238 (4380)	
7	Oxo		335 (34,600)
			267 (4120)
			sh 245 (4480)
			237 (5350)
8	Hydroxyl	sh 295 (2300)	
		254 (16,000)	
8	Oxo		307 (8000)
			265 (4100)
			sh 227 (8000)
9	Oxo	245 (9550)	245 (12,500)
10	Oxo	245 (6160)	244 (10,700)
4	Oxo	sh 305 (4500)	sh 326 (3780)
		271 (13,200)	257 (15,000)
11	Hydroxyl	300 (3860)	302 (7600)
		254 (18,800)	256 (18,500)
13	Hydroxyl	246 (11,800)	244 (7650)
14	Hydroxyl	255 (16,170)[a]	301 (12,190)
15	Oxo	256 (14,200)	

[a] Spectrum taken in water.

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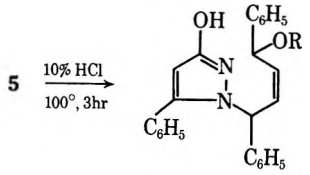
1-(1,4-diphenylbutyl)-3-hydroxy-5-phenylpyrazole (**8**) (*m/e* 368, $C_{25}H_{21}N_2O$). The ultraviolet spectrum of **8** was very similar to the model compound 1,5-diphenyl-3-hydroxypyrazole (**15**)[24] (Table I). The ultraviolet and infrared spectra of compounds **7** and **8** were influenced by solvent polarity. It appears that tautomerization between the hydroxyl form[25] (**7** as shown) and the oxo (amide O=CNH–) form occurs with the oxo form predominating in less polar solvents.

Acid-catalyzed ring opening of **5** occurred under somewhat milder conditions. Refluxing **5** in 10% hydrochloric acid for 13 hr yielded the ring-opened product 1-(4-hydroxy-1,4-diphenyl-2-butenyl)-5-phenyl-3-hydroxypyrazole (**9**), which was isolated and characterized as the monohydrate, $C_{25}H_{21}N_2O_3$. The chemical shifts of the side-chain methine and vinyl protons were similar and appeared as two broad peaks centered at 6.15 (2 H, $W_{1/2}$ = 3.5 Hz) and 6.19 ppm (2 H, $W_{1/2}$ = 4.0 Hz). The ultraviolet spectrum (Table I) showed no evidence of a styryl type chromophore, indicating that the pyridazine double bond did not migrate in the course of ring opening. The mass spectrum of **9** did not show a molecular ion at *m/e* 382, but did show a strong M − 18 peak at *m/e* 364. The fragmentation pattern of this ion was identical with that of **5**. This would indicate that loss of water from **9** occurs through ring closure to **5** rather than **6** or dehydration to **7**. Compound **9** was hydrogenated with loss of the benzylic hydroxyl group to give **8**, thus confirming that the position of ring attachment was the same as in compound **7**.



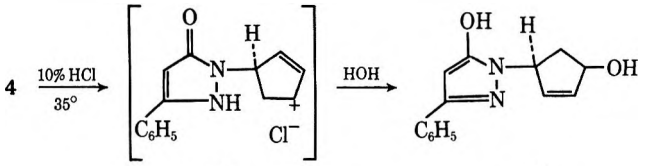
9

The product **9** can be viewed as resulting from nucleophilic displacement at the allylic–benzylic carbon which was bonded to the most electron-deficient nitrogen.[19] A bimolecular reaction was postulated, as unimolecular ring opening to give a carbonium ion at C-4 would be expected to lead to migration of the double bond into conjugation with the phenyl group. The same reaction pathway was followed on ring opening in trichloroacetic acid.

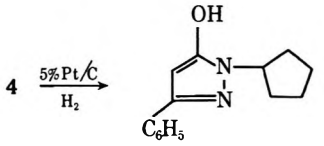
Heating **5** in trichloroacetic acid at 90° gave compound **10** ($C_{27}H_{21}N_2O_3Cl_3$), the trichloroacetate of **9**. The ultraviolet spectrum of **10** (Table I) was similar to that of **9** and showed two carbonyl absorptions at 5.65 and 6.10 μ in the infrared region for the trichloroacetate and pyrazolinone carbonyl groups, respectively. The methine and vinyl protons appeared as a broad, unsymmetrical peak between 6.00 and 6.14 ppm (4 H) in the pmr spectrum.

The trichloroacetate **10** underwent facile ring closure. Heating **10** at 117° gave the adduct **5** within 5 min. Attempts to hydrolyze **10** to **9** with 20% hydrochloric acid at 45° and with 20% potassium hydroxide at 80° yielded the ring closure product **5** and trichloroacetic acid. The facile ring closure of **9** in the mass spectrometer and of **10** on heating suggest that the double bond retained the cis configuration during ring opening, as this configuration should favor ring closure.

The two reaction pathways which led to ring opening of **5**, base-catalyzed double-bond migration followed by ring opening and acid-catalyzed nucleophilic displacement at the allylic carbon, should be effectively prevented by the 1,4-methano group of **4**. Nevertheless, the cyclopentadiene adduct **1** was found to open readily in acid solution. On stirring **4** with 10% hydrochloric acid for 5 hr, the ring-opened alcohol **11** was obtained (>90% yield). The ring strain of **4** and the stability of the hydroxypyrazole ring both facilitate unimolecular ring opening to the intermediate allylic cation **12**. The same N–C bond cleaved when **4** was hydrogenated over platinum to give 1-cyclopentyl-3-phenyl-5-hydroxypyrazole (**13**). The infrared and ultraviolet



12 **11**



13

spectra of **11** and **13** (Table I) were very similar to the reported values of 1-methyl-3-phenyl-5-hydroxypyrazole (**14**)[26] (Table I), thus indicating attachment of the alkyl group at the amide nitrogen as shown. The downfield resonance position of the methine hydrogens (δ >5 ppm) in the pmr spectrum of **11** indicates that they are both allylic. The mass spectrum of **11**, M^+ 242 (26% of *m/e* 160 = 100), shows ions from fragmentation of the cyclopentenol side chain (*m/e* 186, $M^+ - C_3H_4O$ and *m/e* 55, C_3H_3O); cleavage of the side chain (*m/e* 160 for phenylpyrazolinone and *m/e* 82 for cyclopentadienol ions) and subsequent fragmentation of these ions. The mass spectrum of **13** showed only two significant peaks, the molecular ion *m/e* 228 (22% of *m/e* 160 = 100) and *m/e* 160.

In contrast to the observed facile ring opening of the adduct **4**, no ring opening was observed with the hydrogenated derivative 8-phenyl-1,2,3,4-tetrahydro-1,4-methanopyrazolo[1,2-*a*]pyridazin-6-one (**16**).[6] Refluxing the hydrogenated adduct in 20% hydrochloric acid or in 20% potassium hydroxide solutions did not produce bond cleavage.

Base-catalyzed ring opening of the cyclopentadiene adduct **4** was also unsuccessful. Refluxing **4** in 20% potassium hydroxide solution for 100 hr under nitrogen led to partial decomposition of the adduct. The only identifiable compound isolated from this mixture was unreacted **4**.

Conclusion

The investigation of the acid- and base-catalyzed ring opening of the pyrazolo[1,2-*a*]pyridazine ring

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system has led to a number of interesting reactions and products. From the above data it appears that the pyridazine double bond was necessary to increase the reactivity of the ring system toward opening. After ring opening had occurred the resulting 1- or 2-substituted pyrazolin-5-ones underwent no further reactions under the conditions employed. A number of other pyridazine systems have been prepared[5,7,11] from *cis*-azodienophiles which may undergo ring opening through reaction pathways analogous to those presented here.

Experimental Section[27]

8-Phenyl-1,4-methano-1,4-dihydropyrazolo[1,2-*a*]pyridazin-6-one (4).—The title compound was prepared by the previously reported procedure.[6] The adduct was obtained in 70% yield and was recrystallized from cyclohexane to give the pure compound: mp 143–144° (lit.[6] mp 143–144°); pmr[28] ($CDCl_3$) δ 4.77 (s, C_1H), 5.75 (d, J = 5.5 Hz, C_2H, C_3H), 6.24 (d, C_3H), 5.15 (s, C_4H), 5.59 (s, C_7H), 7.43 (s, C_8 C_6H_5), 1.99 (d, J = 8 Hz, C_{1-4} methano CH, CH′), 2.99 (d, C_{1-4} methano CH′, CH).

1,4,8-Triphenyl-1,4-dihydropyrazolo[1,2-*a*]pyridazin-6-one (5).—The previously reported[6] general procedure for Diels–Alder reactions was followed. From a mixture of 0.05 mol of 1,4-diphenylbutadiene, 3-phenyl-2-pyrazolin-5-one, and lead tetraacetate was obtained 15.6 g (88%) of **5**. Recrystallization from cyclohexane–benzene mixtures gave the pure compound: mp 203–205° with darkening; pmr ($CDCl_3$) δ 5.12 (m, C_1H and C_4H), 6.78–7.47 (m, phenyl), 5.89 (m, C_2H and C_3H), 5.58 (s, C_7H); mass spectrum[29] *m/e* (rel intensity) 364 (72), 273 (13), 260 (2), 234 (9), 219 (8), 206 (100), 204 (91), 104 (13), 102 (40), 91 (49), and 77 (25).

Anal. Calcd for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.54; N, 7.68. Found: C, 82.31; H, 5.35; N, 7.81.

1,4,8-Triphenyl-3,4-dihydropyrazolo[1,2-*a*]pyridazin-6-one (6).—A mixture of 1.0 g (0.0027 mol) of **5** in a 20% solution of potassium hydroxide in 50% ethanol was refluxed for 5 hr. The mixture was then poured into 300 ml of cold water with rapid stirring to give 1.0 g of a white solid, **6**. Recrystallization from a cyclohexane–benzene mixture gave an analytical sample: mp 250–250.5°; pmr ($CDCl_3$) 6.98–7.55 (m, phenyl), 5.28–5.43 (m, C_2H and C_4H), 2.63 (octet, J = 17, C_3H, C_3H', J = 6.5, C_3H, C_4H, J = 1 Hz, C_3H, C_2H), 3.08 (octet, J = 6.5, C_3H', C_4H, J = 3 Hz, C_3H', C_2H), 5.61 (s, C_7H); mass spectrum *m/e* (rel intensity) 364 (88), 273 (100), 260 (3), 234 (35), 220 (52), 219 (40), 206 (12), 204 (78), 115 (96), 104 (98), 102 (40), 91 (41), 77 (100).

Anal. Calcd for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.54; N, 7.68. Found: C, 81.76; H, 5.61; N, 7.85.

1-(1,4-Diphenyl-1,3-butadienyl)-5-phenyl-3-hydroxypyrazole (7).—A mixture of 2.0 g (0.0054 mol) of **5** was refluxed in a 20% solution of potassium hydroxide in 80% ethanol for 72 hr. The mixture was then poured into 300 ml of cold water and neutralized with acetic acid to give 2.0 g of a white solid, **7**. Recrystallization from a benzene–95% ethanol mixture resulted in an analytical sample of the dihydrate, mp 217–218°. A recrystallization of **7** from a benzene–absolute ethanol mixture resulted in the nonhydrated form. The pmr assignments (DMSO-d_6) are δ 7.20–7.42 (m, phenyl), 6.12 (s, pyrazole C_4H), 7.82 (d of d, J = 9, C_2H, C_3H, J = 1 Hz, C_2H, C_4H), 6.68 (d of d, J = 15 Hz, C_3H, C_4H), 7.03 (d, C_4H); mass spectrum *m/e* (rel intensity) 364 (50), 273 (32), 260 (78), 234 (<3), 219 (100), 206 (9), 204 (32), 115 (80), 104 (41), 102 (7), 91 (59), 77 (56).

Anal. Calcd for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.54; N, 7.68. Found: C, 82.25; H, 5.54; N, 7.52.

Catalytic Hydrogenation of 7 to 1-(1,4-Diphenylbutyl)-5-phenyl-3-hydroxypyrazole (8).—To a slurry of 0.1 g of 5% palladium on charcoal catalyst in 10 ml of absolute ethanol was added a solution of 1.0 g (0.0027 mol) of **7** in 50 ml of absolute ethanol. The slurry was stirred at 1 atm under hydrogen for 25 hr at 27°. After uptake of hydrogen ceased at 130 ml, the catalyst was removed by filtration and the solvent was evaporated to give 1.0 g of **8**. Recrystallization from an ethanol–benzene mixture furnished an analytical sample: mp 114.5–115°; pmr (DMSO-d_6) δ 6.88–7.68 (m, phenyl and pyrazole C_4H), 5.25 (t, J = 7 Hz, C_1H, C_2H_2), 1.42–2.20 (m, C_2H_2 and C_3H_2), 2.60 (t, J = 7 Hz, C_4H, C_3H_2). The infrared spectra of **8** showed a considerable difference in chloroform and ethanol solutions. In chloroform, a strong peak at 5.9 μ was present but was not observed in ethanol. The mass spectrum included ions at *m/e* (rel intensity) 368 (19), 248 (100), 221 (13), 220 (12), 207 (8), 160 (40), 131 (25), 117 (35), 104 (44), 91 (62), 77 (27).

Anal. Calcd for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.49; N, 7.58. Found: C, 81.82; H, 6.73; N, 7.73.

Catalytic Hydrogenation of Compound 9 to 1-(1,4-Diphenylbutyl)-5-phenyl-3-hydroxypyrazole (8).—The above procedure for a catalytic hydrogenation was used with 0.5 g (0.0013 mol) of **9**. Hydrogen uptake stopped at 47 ml and 0.4 g (80%) of **8** was isolated. The product was shown to be **8** by means of its infrared spectrum, which was superimposable with the spectrum of the above sample (**8**).

1-(1,4-Diphenyl-4-hydroxy-*cis*-2-butenyl)-5-phenyl-3-hydroxypyrazole (9).—A mixture of 2.0 g (0.0054 mol) of **5** and 10% hydrochloric acid was refluxed and stirred for 13 hr. The mixture was cooled and filtered to give 2.0 g of a white solid **9**, mp 203–204°. Recrystallization from a benzene–95% ethanol mixture gave an analytical sample of the monohydrate: mp 203–205°; pmr ($CDCl_3$) δ 6.80–7.38 (m, phenyl), 6.67 (s, pyrazolone C_4H), 6.15–6.19 (m, C_1, C_2, C_3, and C_4 H's of butenyl side chain); mass spectrum *m/e* (rel intensity) 382 (0), 364 (76), 273 (10), 260 (2), 234 (1), 219 (8), 206 (80), 204 (72), 104 (25), 102 (100), 91 (90), 77 (45).

Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 6.99. Found: C, 75.28; H, 5.68; N, 6.86.

2-(1,4-Diphenyl-4-trichloroacetoxy-*cis*-2-butenyl)-3-phenyl-3-pyrazolin-5-one (10).—A mixture of 2.0 g (0.0054 mol) of **5** and 2.0 g of trichloroacetic acid was heated to 90° for 30 hr. The solution was poured into 300 ml of water with stirring to give 1.8 g (90%) of solid **10**. Recrystallization from benzene and cyclohexane gave an analytical sample: mp 117° dec with gas evolution; pmr ($CDCl_3$) δ 6.62–7.44 (m, phenyl), 5.71 (s, pyrazolone C_4H), 6.11 (m, C_1, C_2, C_3, and C_4 H's of butenyl side chain); mass spectrum ring closed thermally to **5**; ir 5.65 (ester C=O), 6.10 μ (pyrazolinone C=O).

Anal. Calcd for $C_{27}H_{21}N_2O_3Cl_3$: C, 61.43; H, 4.02; N, 5.31. Found: C, 61.38; H, 4.15; N, 5.17.

Acid-Catalyzed Ring Closure of 10.—A mixture of 0.6 g (0.0011 mol) of **10** and 15 ml of a 20% hydrochloric acid solution in an ethanol–water solvent was stirred at 45° for 30 hr. The reaction mixture was poured into 100 ml of water and neutralized with sodium carbonate. The solid which formed (0.5 g) was identified as **5** by means of its infrared spectrum which was superimposable with that of an authentic sample of **6**.

Base-Catalyzed Ring Closure of 10.—A mixture of 0.5 g (0.0011 mol) of **10** and 20 ml of a 20% potassium hydroxide solution in an ethanol–water solvent was heated to 80° for 1 hr. The reaction mixture was poured into 150 ml of water and neutralized with acetic acid. The solid which formed (0.5 g) was identified as **5** by means of its infrared spectrum, as in the acid-catalyzed closure.

1-(4-Hydroxycyclopent-2-enyl)-3-phenyl-5-hydroxypyrazole (11).—A mixture of 2.0 g (0.0090 mol) of **4** and 50 ml of 10% hydrochloric acid was stirred at 40° until homogeneous, *ca.* 10 hr. The reaction mixture was neutralized with sodium hydroxide to give 2.0 g of a white solid precipitate. Recrystallization from an ethanol–benzene mixture resulted in an analytical sample: mp 180–182°; pmr ($CDCl_3$) δ 7.25–7.75 (m, C_3 C_6H_5), 5.76 (s, pyrazole C_4H), 5.61 (m, J = 9, C_1H, C_5H, J = 5 Hz, C_1H, C_5H'), 5.78–6.28 (m, C_2H and C_3H), 5.15 (m, J = 7, C_4H, C_5H', J = 4 Hz, C_4H, C_5H), 2.63 (octet, J = 15 Hz,

(27) Boiling points and melting points are uncorrected. Microanalyses were performed by Alfred Berhardt, Mulheim, Germany, and Galbraith Laboratories, Inc. The infrared spectra were measured with a Perkin-Elmer Model 137 double-beam spectrophotometer. The ultraviolet spectra were measured on a Cary Model 14 spectrophotometer and the pmr spectra were obtained on a JOEL 4H-100 and Varian Model A-60 with deuteriochloroform and deuteriodimethyl sulfoxide as solvents and tetramethylsilane as an internal standard (TMS = 0.0 ppm). The mass spectrometer employed was an AEI MS-902.

(28) Pmr data follows the convention: pmr (solvent) δ in ppm downfield from TMS = 0.0 ppm (multiplicity, coupling constant in Hz when resolved, assigned proton, coupled proton). Integrated peak intensities are correct for the assigned proton.

(29) The mass spectral data is shown as the mass to charge ratio (*m/e*) with the intensity as the per cent of the base peak in parenthesis. The fragments reported are those considered important in comparison with other spectra reported herein and those peaks which have an intensity greater than 5% of the base peak.

C_5H, C_5H'), 3.08 (octet, C_5H'); the O and N are considered to be trans; mass spectrum m/e (rel intensity) 242 (26), 186 (22), 161 (98), 160 (100), 103 (90), 82 (46), 77 (49), 55 (19); ir 3.5–4.7 and 5.2–6.1 (H bond), 2.8 μ (OH).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.42; H, 5.79; N, 11.57. Found: C, 69.55; H, 5.93; N, 11.47.

1-Cyclopentyl-3-phenyl-5-hydroxypyrazole (13).—A mixture of 4.0 g (0.0018 mol) of **4** and 0.1 g of 5% platinum on charcoal was stirred in 95% ethanol under hydrogen at 1 atm and 23°. Hydrogen uptake ceased at 440 ml after 5 hr. After filtration of the catalyst and evaporation of the solvent, 3.8 g (95%) of the solid **13** was obtained. A recrystallization of the product from a benzene–ethanol mixture gave an analytical sample: mp 207–208°; pmr ($CDCl_3$) δ 7.20–7.84 (m, C_3 C_6H_5), 5.81 (s, pyrazole C_4H), 4.68 (m, cyclopentyl C_1H), 1.98 (m, cyclopentyl methylenes); mass spectrum m/e (rel intensity) 228 (22), 173 (73), 160 (100), 103 (7), 77 (7); ir 3.5–4.7 and 5.2–6.1 μ (H bond).

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.68; H, 7.02; N, 12.28. Found: C, 73.87; H, 6.82; N, 12.08.

8-Phenyl-1,4-methano-1,2,3,4-tetrahydropyrazolo[1,2-*a*]-pyridazin-6-one (15).—The title compound was prepared by the previously reported procedure,[6] mp 149–151° (lit.[6] mp 148–149°).

Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.34; H, 6.29; N, 12.39. Found: C, 74.30, H, 6.30; N, 12.60.

Registry No.—**4**, 14181-57-8; **5**, 34347-69-8; **6**, 34347-70-1; **7**, hydroxyl, 34347-71-2; **7**, oxo, 34347-79-0; **8**, hydroxyl, 34347-72-3; **8**, oxo, 34347-80-3; **9**, 34347-73-4; **10**, 34347-74-5; **11**, 34347-75-6; **13**, 34347-76-7; **14**, 34347-81-4; **15**, 14181-60-3.

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Mechanism of the Transformation of 2,4-Dihydroxy-1,4-benzoxazin-3-ones and 2-Hydroxy-2-methyl-4-methoxy-1,4-benzoxazin-3-one to 2-Benzoxazolinone

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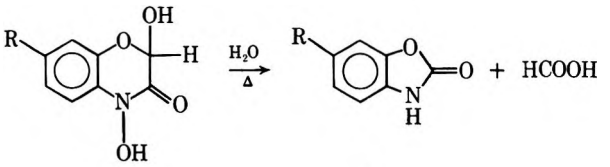
The formation of 2-benzoxazolinones from 2,4-dihydroxy-1,4-benzoxazin-3-ones and from 2-hydroxy-2-methyl-4-methoxy-1,4-benzoxazin-3-one is discussed. A previously proposed mechanism is criticized and a plausible mechanism is offered.

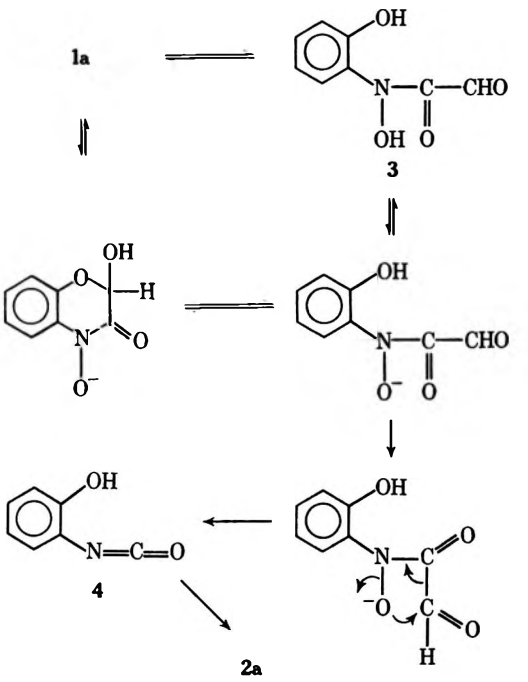
To date, the only reported hydroxamic acids from higher plants are those which are derivatives of 2,4-dihydroxy-1,4-benzoxazin-3-one (**1a**).[2] These compounds and products obtained from their rearrangement have been termed "Resistance Factors," since they are found in several varieties of crop plants and exhibit antifungal and insectistat properties.[3,4]



1 **2**

a, R = H
b, R = OCH_3

When **1** is heated in aqueous or alcoholic solution, the corresponding 2-benzoxazolinone (**2**) is rapidly formed with the liberation of formic acid, which has been established to arise from C-2.[5] The conversion of **1a** to **2a** was proposed to proceed *via* the isocyanate **4**.[6] This mechanism assigns no role to the phenolic hydroxyl group prior to the cyclization step (**4** → **2a**). Therefore, it would be assumed that isocyanate formation would occur independent of the presence of the phenolic hydroxyl function.



Under the conditions utilized for the formation of 2-benzoxazolinone (**2a**) from 2,4-dihydroxy-1,4-benzoxazin-3-one (**1a**), neither *N*-phenylglyoxylohydroxamic acid (**5**) nor *N*-phenyl-α,α-dichloroacetohydroxamic acid (**6**) gave the product expected from an isocyanate intermediate. *N*-Phenylglyoxylohydroxamic acid (**5**) could be transformed to aniline in 36% yield when it was refluxed with aqueous sodium bicarbonate solution, and a small amount of *sym*-diphenylurea (**7**) was isolated from *N*-phenyl-α,α-dichloroacetohydroxamic acid (**6**) after treatment with aqueous sodium hydroxide at room temperature. The products obtained would be

(1) Taken in part from the dissertation presented by M. D. Corbett, Nov 1970, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

(2) R. T. Coutts, *Can. J. Pharm. Sci.*, **2**, 27 (1967).

(3) S. D. Beck and E. E. Smissman, *Ann. Entomol. Soc. Amer.*, **54**, 53 (1961).

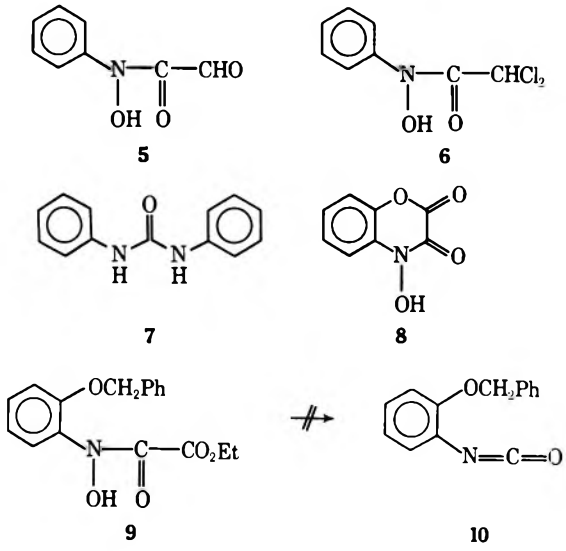
(4) J. A. Klun and T. A. Brindley, *J. Econ. Entomol.*, **59**, 711 (1966).

(5) E. Honkanen and A. I. Virtanen, *Acta Chem. Scand.*, **15**, 221 (1961).

(6) J. Bredenberg, E. Honkanen, and A. I. Virtanen, *ibid.*, **16**, 135 (1962).

expected to arise from the normal hydrolysis of hydroxamic acids.[7] These findings also indicate that the breakdown of the hydroxamic acid **5** requires more drastic conditions than those involved in the transformation of 2,4-dihydroxy-1,4-benzoxazin-3-one (**1a**) to 2-benzoxazolinone (**2a**).

The possibility that the phenolic hydroxyl of the ring-opened compound **3** or the ether oxygen of the parent compound **1** could participate in the rearrangement led to an investigation of other plausible mechanisms. It was found that the oxidized analog of **1a**, 4-hydroxy-1,4-benzoxazine-2,3-dione (**8**), also rearranged to the benzoxazolinone **2a**. Thus the hydroxamic acid **9**,[8] which can be considered to be an open-chain analog of **8** with the phenolic hydroxyl protected as an ether, was subjected to rearrangement conditions. This compound was stable to continuous heating at 70° in either water or ethanol and further demonstrates the need for a free phenolic hydroxyl to facilitate the reaction. The possibility that the ring oxygen in **1a** and **8** is only involved by its role in increasing the electron density at the hydroxamate nitrogen is eliminated by the failure of this reaction to proceed, since the phenolic ether would be expected to have an electronic effect similar to that of the free phenolic hydroxyl in **3**. If the only requirement for the transformation to occur is the attack of the hydroxamate hydroxyl on the carbonyl of the open-chain intermediate **3**, one could reasonably expect **9** to decompose in a similar manner to give products derived from the isocyanate **10**.



In order to ascertain the role of the N–O bond in the rearrangement, 2-methyl-2,4-dihydroxy-1,4-benzoxazin-3-one (**11**) and 2-methyl-2-hydroxy-4-methoxy-1,4-benzoxazin-3-one (**12**) were prepared by the sequences depicted in Schemes I and II, respectively.

The hydroxamic acid **11** was difficult to purify, since it decomposed readily to 2-benzoxazolinone (**2a**) as expected. However, its positive ferric chloride test, spectral characteristics, and hydrogenolysis to the lactam **16**, which is stable, gave proof for its structure. The rates of decomposition of **1a** and **11** appear to be similar.

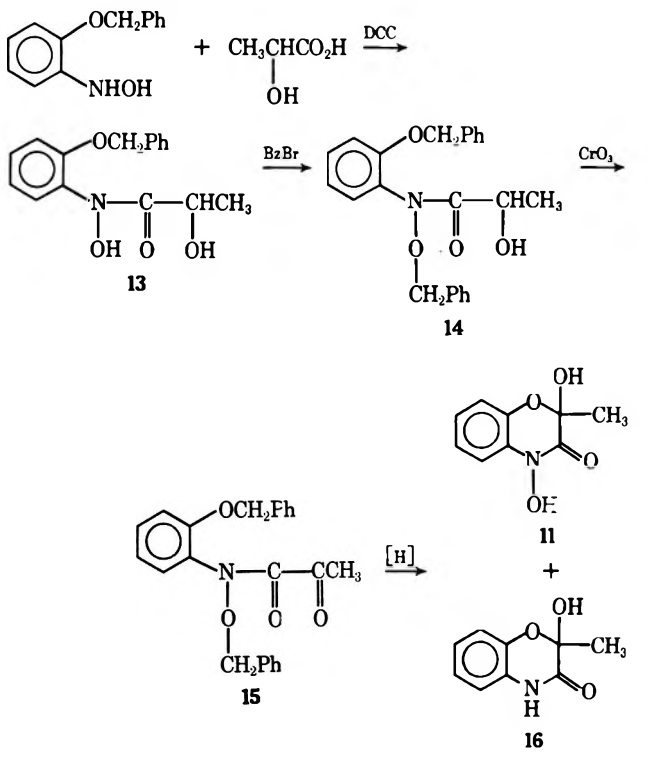
The lactam **16** was found to be stable to prolonged heating in hydroxylic solvents. This indicates that the hydroxamate oxygen is of definite importance to the decomposition reaction.

Heating the hydroxamate methyl ester **12** in water at 55° causes rapid decomposition to 2-benzoxazolinone (**2a**) with the loss of acetic acid. The decomposition of **12** followed first-order kinetics with a half-life of 24 min. This is a faster rate than that for the decomposition of **1a**.[6]

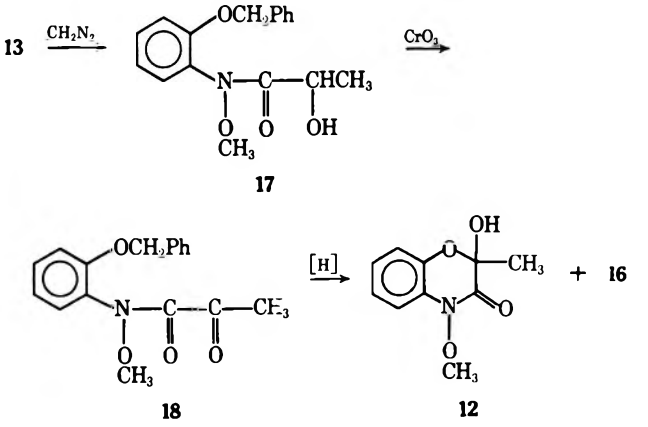
The decomposition of **12** to **2a** did not proceed *via* demethylation to **11**. This was established by the absence of color development when a concentrated ethanolic solution of **12** containing 2% ferric chloride was heated at 50°.

The observed stabilities of the hydroxamic acids **5**, **6**, and **9** indicates that a phenolic hydroxyl group is involved in the decomposition of **1a**, **11**, and **12** to **2a**. The necessity of the hydroxamic acid hydroxyl and a carbonyl group α to the hydroxamate system in order for the rearrangement to occur had been reported previously[6] and was supported by the results obtained in this investigation.

SCHEME I



SCHEME II



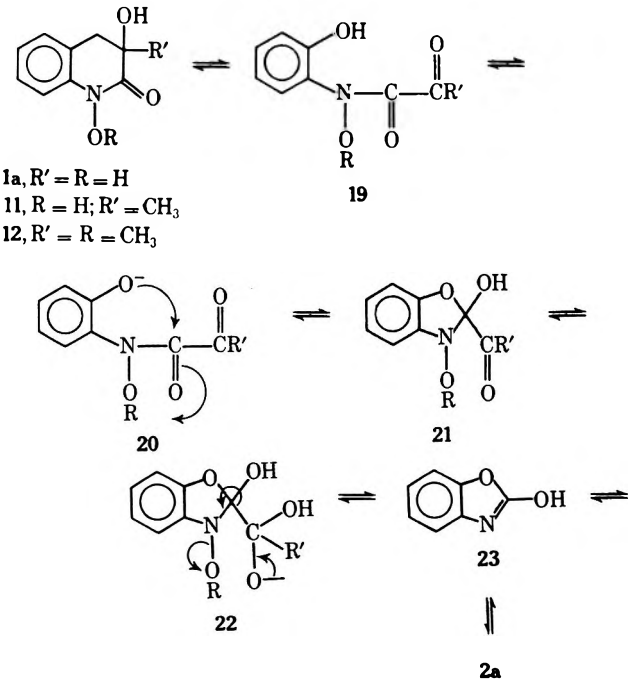
(7) P. A. S. Smith, "Open Chain Nitrogen Compounds," Vol. 2, W. A. Benjamin, New York, N. Y., 1966.

(8) E. E. Smissman and M. D. Corbett, *J. Org. Chem.*, **37**, 1847 (1972).

The observation which negates the mechanism proposed originally[6] is the fact that the methyl ester **12** undergoes decomposition to **2a** even more rapidly than do the free hydroxamic acids **1a** and **11**.

Based on the above findings a more plausible mechanism for this decomposition is offered (Scheme III).

SCHEME III



1a, R′ = R = H
11, R = H; R′ = CH_3
12, R′ = R = CH_3

19

20

21

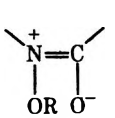
22

23

2a

In this mechanism, intermediate **21** is in equilibrium with the parent benzoxazine system through the open forms **19** and **20**. The equilibrium concentration of **21** would be expected to be quite low. The attack of hydroxide ion or water on the carbonyl carbon of **21** followed by the loss of an acid anion with a concomitant displacement of –OR from nitrogen in **22** would afford **23**, a tautomer of **2a**. Such a transformation is analogous to eliminative decarboxylation.

In. this mechanism no intermediate isocyanate is involved. The rate-determining step is the attack of hydroxide ion at the carbonyl group of **21**, followed by a rapid loss of an acid anion. The intermediate **21** is proposed as the rate-determining species, since it is observed that the methyl ester **12** decomposes more rapidly than **1a** or **11**. The concentration of **21** would be expected to be greater when R = methyl than when R = H, since there would be a lower contribution of the resonance form **24**. When R = H, this charge-



24

separated species is stabilized by intramolecular hydrogen bonding, whereas when R = methyl this cannot occur. The decreased contribution of resonance **24** would allow for increased interaction of the phenolic hydroxyl group with the hydroxamate carbonyl function to give **21**.

The hydroxyl or alkoxy group on the hydroxamate nitrogen serves only as a facile leaving group and not a nucleophilic function.

Further investigations of the kinetics of this decomposition with regard to the alkyl or aryl substituent at C-2 and the nature of the leaving group at N-4 are underway.

Experimental Section[9]

***N*-[*o*-(Benzyloxy)phenyl]lactohydroxamic Acid (13).**—To 85% lactic acid (6.3 g, 0.06 mol) dissolved in 20 ml of THF and cooled to −25° was rapidly added dicyclohexylcarbodiimide (14.4 g, 0.07 mol) in 30 ml of THF. The cold solution was stirred until a precipitate began to form, after which *o*-(benzyloxy)phenylhydroxylamine (6.0 g, 0.028 mol) in 40 ml of THF cooled to −25° was added in several portions in the course of 2 min. The mixture was stirred and cooled for 1 hr and allowed to warm to 25°. The mixture was filtered and the solid was washed with 100 ml of Et_2O. The combined filtrates were cooled by the addition of ice and extracted twice with 30 ml of ice-cold 5% NaOH. The combined base extracts were washed with 50 ml of Et_2O and carefully neutralized at 0° with 3 *N* HCl. This aqueous mixture was extracted twice with 50 ml of Et_2O. The combined Et_2O extracts were dried (Na_2SO_4) and the solvent was removed to give a dark oil which crystallized from Et_2O to give an amorphous gray solid. Recrystallization (Me_2CO–Et_2O) gave 2.5 g (29%) of **13** as a white, amorphous solid: mp 114.5–116.0°; violet color with $FeCl_3$ in EtOH; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.93; H, 6.25; N, 4.78.

***N*-[*o*-(Benzyloxy)phenyl]-*O*-benzyllactohydroxamic Acid (1).**—*N*-[*o*-(Benzyloxy)phenyl]lactohydroxamic acid (**13**, 4.6 g, 0.016 mol), benzyl bromide (3.1 g, 0.018 mol), and anhydrous K_2CO_3 (2.2 g, 0.016 mol) in 120 ml of Me_2CO were stirred under N_2 and heated to reflux for 6 hr. The solvent volume was reduced to 50 ml and the residue was shaken with 150 ml of Et_2O and 60 ml of H_2O. The ethereal solution was dried (Na_2SO_4) and the solvent was removed to produce an oil which crystallized from Et_2O to give 4.9 g (82%) of **14** as white crystals, mp 89.5–91.4°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.14; H, 6.30; N, 3.56.

***N*-[*o*-(Benzyloxy)phenyl]-*O*-benzylpyruvohydroxamic Acid (15).**—To *N*-[*o*-(Benzyloxy)phenyl]-*O*-benzyllactohydroxamic acid (**14**, 2.3 g, 0.006 mol) in 40 ml of Me_2CO cooled to 5° was added dropwise 8 *N* reagent[10] until the orange color of the oxidant persisted. Excess oxidant was destroyed by the addition of several milliliters of *i*-PrOH. The reaction mixture was combined with 100 ml of Et_2O and washed with 50 ml of H_2O, 50 ml of 5% $NaHCO_3$, and 50 ml of H_2O. The solution was dried (Na_2SO_4) and the solvent was removed to yield an oil which crystallized from EtOH to give 1.8 g (80%) of white needles, mp 86.5–88.0°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.59; H, 5.64; N, 3.73. Found: C, 73.28; H, 5.78; N, 3.38.

2,4-Dihydroxy-2-methyl-1,4-benzoxazin-3-one (11).—*N*-[*o*-(Benzyloxy)phenyl]-*O*-benzylpyruvohydroxamic acid (**15**, 0.75 g, 0.002 mol) was hydrogenated at 25° under 1-atm pressure in 30 ml of EtOH with 500 mg of 5% Pd/C as the catalyst. The reaction was stopped after the consumption of the theoretical amount of H_2 (0.004 mol). The catalyst was removed by filtration and the solvent was removed to give a thick oil. Chromatography on 40 g of silica gel gave **11** as the last component off the column. Removal of $CHCl_3$ gave a brown solid. Recrystallization (Et_2O–C_6H_6) yielded 20 mg (5.2%) of **11** as a white, amorphous solid, mp 132–135°, blue color with $FeCl_3$ in EtOH; spectral data are consistent with the assigned structure but the elemental analysis was not within the acceptable limits because of a small amount of an unknown colored contaminant

(9) Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Ir data were recorded on a Beckman IR-10 spectrophotometer and nmr data on Varian Associates A-60, A-60A, and HA-100 spectrometers (TMS). Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M 185 C, H, N analyzer, University of Kansas.

(10) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 144.

which could not be removed. Compound 11 could be converted to 16 by further hydrogenolysis.

Fractions immediately preceding those containing 11 yielded **2-hydroxy-2-methyl-1,4-benzoxazin-3-one** (16) as a brown solid. Recrystallization (EtOH–C_6H_6) gave fine white crystals (35 mg, 10%), mp 186.5–188°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.61; H, 4.99; N, 7.72.

***N*-[*o*-(Benzyloxy)phenyl]-*O*-methyllactohydroxamic Acid** (17).—Approximately 1.4 g (0.033 mol) of ethereal CH_2N_2 was generated and added to a solution of *N*-[*o*-(benzyloxy)phenyl]-lactohydroxamic acid (13, 2.0 g, 0.007 mol) in 50 ml of Et_2O which was cooled in an ice bath. The yellow solution was maintained at 0–4° until the evolution of N_2 ceased and the yellow solution was allowed to stand at 25° for 2 hr. Several drops of HOAC were added to the solution to ensure that all the CH_2N_2 had been destroyed. An additional 50 ml of Et_2O was added and the solution was washed with 20 ml of cold 5% NaOH and twice with 30 ml of H_2O. The solution was dried (Na_2SO_4) and the solvent was removed to give an oil which crystallized from 10 ml of Et_2O to give 1.8 g (85%) of 17 as white crystals, mp 86.5–88.0°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.64. Found: C, 67.61; H, 6.65; N, 4.84.

***N*-[*o*-(Benzyloxy)phenyl]-*O*-methylpyruvohydroxamic Acid** (18).—To *N*-[*o*-(benzyloxy)phenyl]-*O*-methyllactohydroxamic acid (17, 1.6 g, 0.0054 mol) in 20 ml of Me_2CO cooled to 5° was added dropwise 8 *N* Jones reagent until the orange color of the oxidant persisted. Excess oxidant was destroyed by the addition of several milliliters of *i*-PrOH. The reaction mixture was combined with 100 ml of Et_2O and washed with 80 ml of H_2O, 30 ml of 5% $NaHCO_3$, 40 ml of H_2O, and 30 ml of saturated NaCl solution. The organic solution was dried (Na_2SO_4) and the solvent was removed to give 1.2 g (92%) of 18 as an oil; spectral data are consistent with the assigned structure.

2-Hydroxy-2-methyl-4-methoxy-1,4-benzoxazin-3-one (12).—*N*-[*o*-Benzyloxy)phenyl]-*O*-methylpyruvohydroxamic acid (18, 1.2 g, 0.004 mol) was hydrogenated at 25° under 1-atm pressure with 500 mg of 5% Pd/C as the catalyst and 60 ml of 95% EtOH as the solvent. The reaction was stopped after the consumption of the theoretical amount of H_2 (0.004 mol). The catalyst was removed by filtration and the solvent was distilled to produce an oil which crystallized from C_6H_6 to give 0.40 g (40%) of 12 as a white solid. Recrystallization (Et_2O) gave white crystals, mp 119.0–121.5°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.23; H, 5.02; N, 6.55.

Degradation of *N*-Phenyl-α,α-dichloroacetohydroxamic Acid (6) and *N*-Phenylglyoxylohydroxamic Acid (5) under Basic Conditions. A. Preparation of *N*-Phenyl-α,α-dichloroacetohydroxamic Acid (6).—To a solution of 53 g (0.486 mol) of phenylhydroxylamine in 600 ml of anhydrous Et_2O was added in small portions 40 g (0.272 mol) of dichloroacetyl chloride in 75 ml of anhydrous Et_2O. The reaction temperature was maintained at 0–5° while the mixture was allowed to stand for 30 min after the last portion of acetyl chloride had been added. A dark precipitate was removed by filtration and the filtrate was extracted with 1 l. of 3% aqueous $NaHCO_3$. The Et_2O solution was dried ($MgSO_4$) and the solvent was removed to yield 55.8 g (93%) of a yellow solid. The product was recrystallized from a mixture of petroleum ether (bp 60–68°) and Et_2O to give long, white needles, mp 90.5–91°. The ferric chloride test gave an intense red color. Spectral data are consistent with the assigned structure.

Anal. Calcd for $C_8H_7NO_2Cl_2$: C, 43.66; H, 3.31; N, 6.37. Found: C, 43.91; H, 2.92; N, 5.89.

B. Preparation of *N*-Phenylglyoxylohydroxamic Acid (5).—To 250 ml of 1.5 *N* aqueous NaOH was added 13.20 g (0.06 mol) of *N*-phenyl-α,α-dichloroacetohydroxamic acid (6) at such a rate that the temperature did not rise above 30°. After standing for 2 hr the reaction mixture was extracted with 250 ml of Et_2O (ether extract I). The aqueous phase was acidified with 10% hydrochloric acid and extracted with 6 l. of Et_2O (ether extract II).

Ether extract II was concentrated until a precipitate started to form. The solution was cooled and the precipitate was filtered to yield 1.42 g (14.3%) of a white, crystalline material. The substance gave a positive ferric chloride test. Recrystallization (Et_2O) gave a product with mp 169.5–171°.

Anal. Calcd for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.05. Found: C, 58.28; H, 4.06; N, 8.30.

Ether extract I was extracted with 5% aqueous HCl. The neutral reaction products remained in the organic phase (ether extract Ia). The basic products were recovered from the aqueous phase by addition of 10% aqueous NaOH until basic and subsequent extraction with ether (ether extract Ib).

Ether extract Ia was evaporated to dryness. The residue consisted of 1.4 g of a brown oil which was purified by chromatography on a neutral aluminum oxide column (2.2 × 27.0 cm) with elution by the following solvent sequence: 100 ml of petroleum ether (fraction 1); 50 ml of petroleum ether (fraction 2); 75 ml of petroleum ether–C_6H_6 (1:1) (fraction 3); 50 ml of petroleum ether–C_6H_6 (1:1) (fraction 4); 100 ml of C_6H_6 (fraction 5); and 50 ml of Et_2O (fraction 6).

Fraction 2 was identified as nitrobenzene by reduction with tin and hydrochloric acid to aniline.

Fraction 3 was identified as azoxybenzene by its melting point and by reduction with magnesium and ammonium chloride to azobenzene.

Fraction 4 was characterized as azobenzene.

Fraction 6 was identified as *sym*-diphenylurea by mixture melting point and from its ultraviolet spectrum.

Ether extract Ib yielded 144 mg of yellow oil after evaporation of solvent. The product gave a crystalline derivative with benzoyl chloride, mp 157–158°, which caused no depression of melting point when mixed with benzanilide.

C. Degradation of *N*-Phenylglyoxylohydroxamic Acid (5) **in 5% Aqueous Sodium Bicarbonate Solution.**—Compound 5 (300 mg, 0.018 mol) was dissolved in 150 ml of 5% aqueous $NaHCO_3$ solution. The mixture was brought to boiling and water and steam-volatile materials were allowed to distil. The liquid volume was kept constant by gradual addition of water and a steady stream of nitrogen was through the apparatus during the reaction. The distillation was continued until all steam-volatile materials had been removed. Concentrated HCl was added to the aqueous suspension of the steam-volatile fraction until the HCl concentration reached 5%. The mixture was then extracted with 200 ml of Et_2O. The extract was dried ($MgSO_4$) and the solvent was removed. The residue consisted of 20 mg of yellow oil which was identified as nitrobenzene by reduction to aniline. The acidic, aqueous solution was made alkaline and extracted with 1 l. of Et_2O. The Et_2O solution was washed and dried and the solvent was evaporated to yield 61 mg (36%) of aniline, characterized as benzanilide.

Stabilities of Analogs in Hydroxylic Solvents.—Uv absorption spectra (Table I) were obtained on a Beckman Model DB recording spectrophotometer.

TABLE I

Compd	Solvent	Maxima, mμ	ε
11	H_2O	280	4700
		254	7300
16	H_2O	278	3800
		251	6900
12	H_2O	278	3300
		253	5800

No change in the uv spectra of compound 16 was observed after heating at 55° for at least 4 hr. The uv spectra of compounds 11 and 12 changed rapidly on heating to give a different absorption curve with maximum absorption at 270 mμ (2-benzoxazolinone λ_{max} = 270 mμ). 2-Benzoxazolinone (2a) was isolated from heated solutions of 11 and 12, and identified by comparison of its ir spectrum with that of authentic 2-benzoxazolinone (2a).

A kinetic analysis of the decomposition of 12 was performed at 40°. The decrease in absorption at 253 mμ was recorded for a period of 6 hr. The reaction follows first-order kinetics for the first 40 min in Sorenson's phosphate buffer (pH 7.0)[11] with a half-life computed to be 24 min.

Registry No.—2a, 59-49-4; 5, 34282-43-4; 6, 34282-

(11) K. Diem and C. Lentner, "Documenta Geigy," J. R. Geigy S. A., Basle, 1970, p 280.

44-5; **11**, 34282-45-6; **12**, 34282-46-7; **13**, 34282-47-8; **14**, 34282-48-9; **15**, 34282-49-0; **16**, 34282-50-3; **17**, 34282-51-4; **18**, 34282-52-5.

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The Syntheses of 4-Acylamido-1,4-benzoxazine-2,3-diones and 4-(*p*-Toluenesulfonamido)-1,4-benzoxazine-2,3-dione

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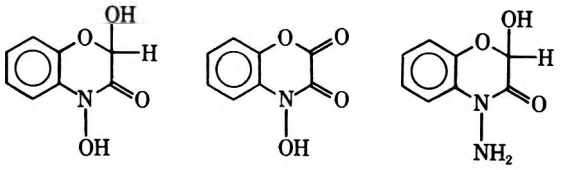
A general synthetic method for the synthesis of 4-acylamido-1,4-benzoxazine-2,3-diones (**8**) is described. Ortho-substituted hydrazines can be prepared by acid hydrolysis of the appropriate mesoionic sydnone. *o*-Benzyloxyphenylhydrazine hydrochloride (**4**) was prepared in this manner and acylated on the terminal nitrogen. The 1-(*o*-benzyloxyphenyl)-2-acylhydrazine (**5**) was treated with ethyl oxalyl chloride to give 1-(*o*-benzyloxyphenyl)-1-ethyloxalyl-2-acylhydrazine (**6**) which on hydrogenation afforded **8**. The synthesis of 4-(*p*-toluenesulfonamido)-1,4-benzoxazine-2,3-dione (**20**) was accomplished by the addition of sodium *p*-toluenesulfinite to the diazonium salt prepared from *o*-benzyloxyaniline. The resulting diimide **17** was reduced to the corresponding hydrazine **18**, which was treated with ethyl oxalyl chloride to afford 1-(*o*-benzyloxyphenyl)-1-ethyloxalyl-2-(*p*-toluenesulfonyl)hydrazine (**19**). This compound on hydrogenolysis of the benzyl protecting group cyclized to give **20**.

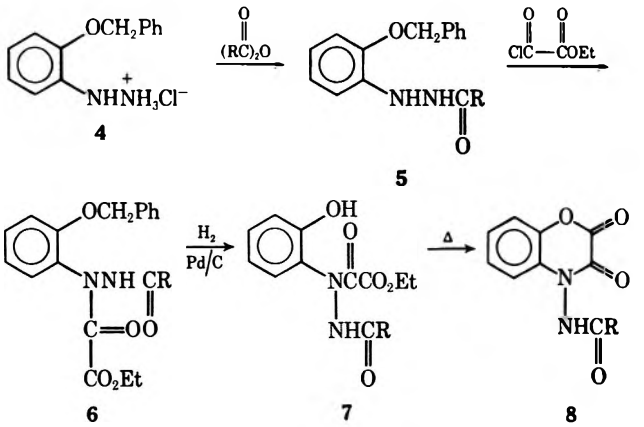
In view of the interesting chemistry and biological activity of the naturally occurring hydroxamic acids having the basic structure 2,4-dihydroxy-1,4-benzoxazin-3-one (**1**),[2-4] a study of the 4-amino analogs **3** and their derivatives was initiated.



1 **2** **3**

The preparative procedure utilized the acylation of *o*-benzyloxyphenylhydrazine (**4**) with either acetic anhydride or trifluoroacetic anhydride to afford the monoacylhydrazides **5a** and **5b**. The monoacylation of phenylhydrazines with anhydrides has been shown to occur at the terminal nitrogen.[5] The treatment of **5a** and **5b** with ethyl oxalyl chloride afforded the diacyl hydrazides **6a** and **6b**, respectively. Hydrogenolysis of **6a** produced a single product as determined by tlc analysis on silica gel. A crystalline compound, **8a**, was obtained when the oil produced by the hydrogenolysis of **6a** was heated in benzene. The nmr spectrum of the oil is consistent with structure **7**.

In the above sequence *o*-benzyloxyphenylhydrazine (**4**) was required as a starting material. *o*-Benzyloxyaniline hydrochloride (**9**) was prepared and converted to the corresponding diazonium salt, but the conventional method for the reduction of diazonium salts utilizing stannous chloride was found to be inapplicable in this case. Ek and Witkop[6] have also reported an unsuccessful attempt to reduce this diazonium salt



4 **5** **6** **7** **8**

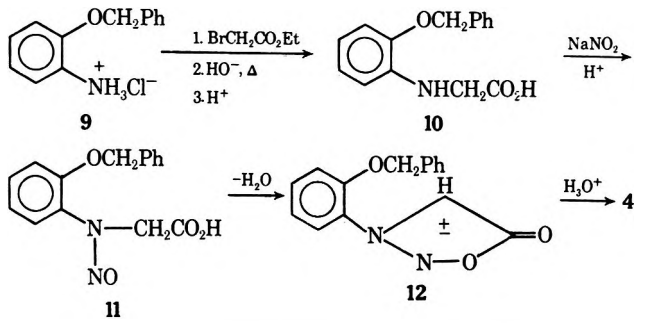
a, R = CH_3
b, R = CF_3

by the stannous chloride method, but Clerc-Bory[7] reported that this method gave a 72% yield of the desired product. Clerc-Bory also reported the melting point of this material to be 191°, which is 43° higher than the melting point of the product we obtained by an alternate route. Utilizing stannous chloride we also obtained a material melting at 191° but it would not undergo acylation with acetic anhydride.

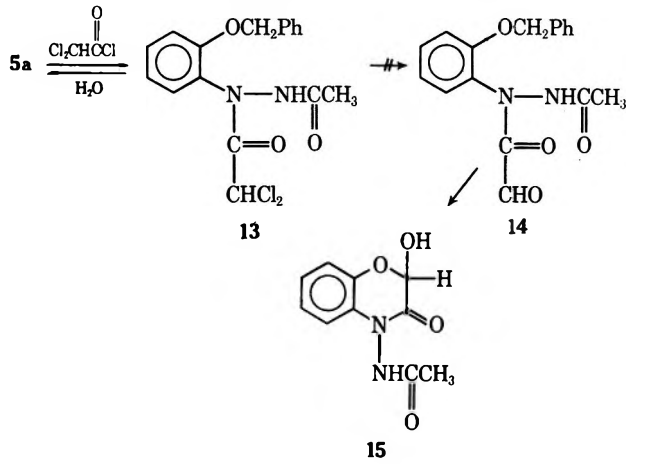
The acidic hydrolysis of mesoionic sydnones provided an alternate route for the preparation of ortho-substituted hydrazines.[8,9] 3-(*o*-Benzyloxyphenyl)sydnone (**12**) was prepared in good yield by cyclization of the nitroso intermediate **11**. This cyclization was found to proceed readily with the use of trifluoroacetic anhydride, while other dehydrating agents gave lower yields of **12**.[10] The hydrolysis of **12** with hot aqueous hydrochloric acid was accompanied by considerable tar formation, but, when dioxane–water was employed as the solvent, hydrolysis proceeded rapidly at room temperature with a minimum of decomposition.

The hydrazides **8** are the amino analogs of 4-hydroxy-1,4-benzoxazine-2,3-dione (**2**) which has properties

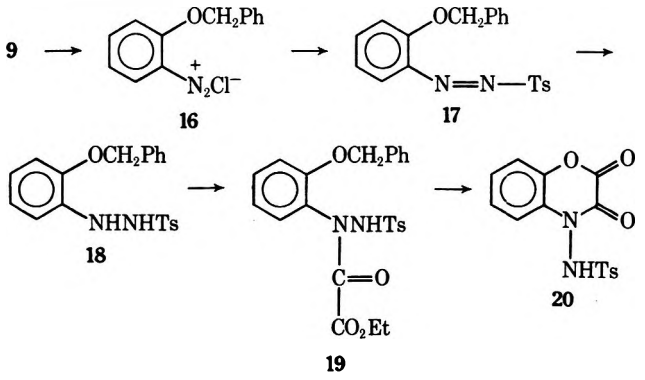
(1) Taken in part from the dissertation presented by M. D. Corbett, Nov 1970, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.
(2) A. I. Virtanen and P. K. Hietala, *Acta Chem. Scand.*, **14**, 499 (1960).
(3) J. A. Klun and T. A. Brindley, *J. Econ. Entomol.*, **59**, 711 (1966).
(4) G. L. Lammoureux, R. H. Shimabukuro, H. R. Swanson, and D. S. Frear, *J. Agr. Food Chem.*, **18**, 81 (1970).
(5) P. A. S. Smith, "Open Chain Nitrogen Compounds," Vol. 2, W. A. Benjamin, New York, N. Y., 1966.
(6) A. Ek and B. Witkop, *J. Amer. Chem. Soc.*, **76**, 5579 (1954).
(7) M. Clerc-Bory, *Bull. Soc. Chim. Fr.*, 337 (1954).
(8) L. B. Kier and E. B. Roche, *J. Pharm. Sci.*, **56**, 149 (1967).
(9) S. Aziz, A. F. Cockerill, and J. G. Tillett, *J. Chem. Soc. B*, 416 (1970).
(10) W. H. Nyberg and C. C. Cheng, *J. Med. Chem.*, **8**, 531 (1965).



similar to those of the hydroxamic acid **1**. An attempt to prepare the amino analog (**15**) of 2,4-dihydroxy-1,4-benzoxazin-3-one failed because it was not possible to convert the diacylhydrazide **13** to the aldehydic diacylhydrazide **14**. Under hydrolytic conditions, cleavage of the dichloroacetyl function in **13** occurs preferentially to regenerate **5a**. Currently, selective reduction of **8a** to yield **15** is being investigated.



An attempt to extend the above successful sequence (**4** → **8**) to the preparation of 4-(*p*-toluenesulfonamido)-1,4-benzoxazine-2,3-dione (**20**) met with little success, as the acylation of **4** with *p*-toluenesulfonyl chloride to give **18** proceeded in very low yield. An alternate synthesis of **18** was developed based on the known nucleophilic addition of *p*-toluenesulfinic acid to a diazonium salt.[11]



The diimide **17** formed readily at low temperatures when *p*-toluenesulfinic acid was added to a solution of the diazonium salt **16**. Reduction of **17** with zinc dust and acetic acid produced the desired tosyl hydrazine **18** in excellent yield. The hydrogenolysis of the benzyloxy group in **18** utilizing palladium-on-carbon catalyst failed due to apparent poisoning of the catalyst. The acylation of **18** with ethyl oxalyl chloride produced **19**, which underwent hydrogenolysis readily to give the desired 4-(*p*-toluenesulfonamido)-1,4-benzoxazine-2,3-dione (**20**).

(11) R. W. Hoffman, *Chem. Ber.*, **98**, 222 (1965).

Experimental Section[12]

***o*-Benzyloxyacetanilide.**—This procedure is similar to that of Ek and Witkop,[6] but these workers did not isolate the title compound.

o-Hydroxyacetanilide (60.4 g, 0.40 mol), benzyl bromide (68.4 g, 0.40 mol), and anhydrous K_2CO_3 (54.8 g, 0.40 mol) in 500 ml of Me_2CO were heated to reflux under N_2 for 12 hr. The solvent volume was reduced to about 300 ml and the residue was combined with 800 ml of C_6H_6 and washed with 100 ml of 5% NaOH, 300 ml of H_2O, and 100 ml of saturated NaCl solution. The C_6H_6 solution was dried (Na_2SO_4) and the solvent volume was reduced until solid material began to appear. Recrystallization (C_6H_6–Et_2O) gave 80.5 g (84%) of small white plates, mp 114.0–115.5°; spectral data are consistent with the assigned structure.

***o*-Benzyloxyaniline Hydrochloride** (**9**).—*o*-Benzyloxyacetanilide (80.5 g, 0.35 mol) in 400 ml of MeOH saturated with HCl was heated to reflux for 2 hr. The solvent was distilled at atmospheric pressure until a solid began to form. The mixture was allowed to cool and 500 ml of Et_2O was added. The mixture was cooled and the solid was collected by filtration and washed with 200 ml of Et_2O. The solid was stirred with 300 ml of Et_2O and collected and dried to give 60.7 g (78%) of fine white needles, mp 205–208°; spectral data are consistent with the assigned structure. This material must be stored below 10° to prevent decomposition. This procedure is more convenient than that previously reported.[6,13]

Ethyl *N*-(*o*-Benzyloxyphenyl)glycinate.—*o*-Benzyloxyaniline hydrochloride (**9**, 35.4 g, 0.15 mol) and anhydrous NaOAc (24.6 g, 0.30 mol) were mixed in 60 ml of absolute EtOH. To this stirred suspension was added ethyl bromoacetate (25.2 g, 0.15 mol). This mixture was stirred under an N_2 atmosphere and heated to reflux for 5 hr. The reaction mixture was combined with 150 ml of C_6H_6 and washed with 150 ml of H_2O and 50 ml of saturated NaCl solution. The organic solution was dried (Na_2SO_4) and the solvent was removed *in vacuo* to give a light brown oil, which was used immediately in the next reaction due to its instability. Spectral data are consistent with the assigned structure.

***N*-(*o*-Benzyloxyphenyl)glycine** (**10**).—Crude ethyl *N*-(*o*-benzyloxyphenyl)glycinate (theory 0.15 mol) was stirred in 90 ml of 10% EtOH containing NaOH (9.0 g, 0.225 mol) under an N_2 atmosphere. The mixture was heated to reflux for 30 min and the resultant orange solution was neutralized with 6 *N* HCl to give an oil. The suspension of the oil in H_2O was stirred and cooled until it solidified. The solid was collected by filtration and dissolved in 100 ml of EtOH. Crystallization was achieved by the addition of 30 ml of H_2O, followed by cooling for several hours. The solid was collected by filtration and recrystallized from Et_2O–petroleum ether (bp 60–68) to yield 26.4 g (69%) of **10** as fine white needles, mp 119–121°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.83; H, 6.03; N, 5.70.

***N*-(*o*-Benzyloxyphenyl)-*N*-nitrosoglycine** (**11**).—*N*-(*o*-Benzyloxyphenyl)glycine (**10**, 12.8 g, 0.05 mol) was stirred in 100 ml of MeOH and treated with 10 ml of 5 *N* HCl to effect dissolution. The solution was cooled to 0° with an ice bath and treated with $NaNO_2$ (3.45 g, 0.05 mol) dissolved in 40 ml of H_2O in the course of 15 min. The solution was stirred and cooled for an additional 30 min, after which the green solution was combined with 200 ml of C_6H_6. The C_6H_6 solution was washed twice with 100 ml of H_2O and dried (Na_2SO_4). The solvent was evaporated to 50 ml of total volume for use in the next reaction. The nitroso compound **11** can be isolated by further evaporation of the sol-

(12) Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Ir data were recorded on a Beckman IR-10 spectrophotometer and nmr data on Varian Associates A-60, A-60A, and HA-100 spectrometers (TMS). Microanalyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind., and on an F & M 185 C, H, N analyzer, University of Kansas.

(13) A. Sieglitz and H. Koch, *Ber.*, **58B**, 78 (1925).

vent *in vacuo* to a total of 30 ml. Crystals formed when the solution was cooled and the solid was collected by filtration. Recrystallization twice from C_6H_6 gave yellow needles, mp 93.5–95.0°; positive Lieberman nitroso reaction; the spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.78. Found: C, 63.28; H, 5.13; N, 9.95.

***N*-(*o*-Benzyloxyphenyl)sydnone (12).**—A crude concentrated C_6H_6 solution of *N*-(*o*-benzyloxyphenyl)-*N*-nitrosoglycine, 11 (theory 0.05 mol) was combined with 100 ml of anhydrous Et_2O, cooled to 10°, and treated with 25 g of trifluoroacetic anhydride in portions of several grams each. The solution was allowed to warm to 25° and the solvent volume was reduced to about 70 ml with a stream of N_2. Crystals formed and the mixture was cooled. The solid was collected by filtration and recrystallized (C_6H_6–Et_2O) to yield 7.6 g (57% from 10) of 11 as white plates, mp 93.0–94.5°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.06; H, 4.61; N, 10.68.

***o*-Benzyloxyphenylhydrazine Hydrochloride (4).**—*N*-(*o*-Benzyloxyphenyl)sydnone (12, 10.0 g, 0.037 mol) was stirred at 25° under an N_2 atmosphere in 200 ml of 67% dioxane in H_2O containing 0.52 equiv of HCl for 4 hr. The solvent was removed *in vacuo*, and the residue was dried under high vacuum. The solid residue was dissolved in a minimal amount of hot absolute EtOH. Crystallization was effected by adding ten volumes of Et_2O to the solution and cooling. The solid was collected and recrystallized (EtOH–Et_2O) to give 7.0 g (73%) of 4 as a gray solid, mp 144–145° dec; spectral data are consistent with the assigned structure. Compound 4 is unstable and can only be stored for several days with cooling.

1-(o-Benzyloxyphenyl)-2-acetylhydrazine (5a).—*o*-Benzyloxyphenylhydrazine hydrochloride (4, 1.25 g, 0.005 mol), acetic anhydride (0.6 g, 0.005 mol), and anhydrous NaOAc (1.1 g, 0.011 mol) in 25 ml of anhydrous Et_2O were stirred for 10 hr at 25°. The mixture was combined with 100 ml of C_6H_6 and washed with 50 ml of H_2O, 50 ml of 0.1 *N* HCl, 50 ml of H_2O, and 30 ml of saturated NaCl solution. The organic solution was dried (Na_2SO_4) and the solvent was removed to give an oil which crystallized from Et_2O to give 1.0 g (77%) of 5a as white plates, mp 130.0–131.5°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 69.96; H, 6.27; N, 11.19.

1-(o-Benzyloxyphenyl)-1-dichloroacetyl-2-acetylhydrazine (13).—1-(*o*-Benzyloxyphenyl)-2-acetylhydrazine (5a, 2.04 g, 0.008 mol), anhydrous $NaHCO_3$ (0.84 g, 0.01 mol), and dichloroacetyl chloride (1.2 g, 0.008 mol) were stirred in 60 ml of anhydrous C_6H_6 for 2 hr at 25°. The reaction mixture was combined with 200 ml of C_6H_6 and washed with 100 ml of H_2O and 50 ml of saturated NaCl solution. The C_6H_6 solution was dried (Na_2SO_4) and the solvent was removed *in vacuo* to produce a solid material, which was recrystallized (C_6H_6) to give 2.5 g (86%) of 9 as a white powder, mp 147–149°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{17}H_{16}N_2O_3Cl_2$: C, 55.60; H, 4.39; N, 7.63. Found: C, 55.35; H, 4.48; N, 7.73.

1-(o-Benzyloxyphenyl)-1-ethyloxalyl-2-acetylhydrazine (6a).—1-(*o*-Benzyloxyphenyl)-2-acetylhydrazine (5a, 2.3 g, 0.009 mol), anhydrous $NaHCO_3$ (0.9 g, 0.01 mol), and ethyl oxalyl chloride (1.36 g, 0.01 mol) in 60 ml of C_6H_6 were stirred for 1 hr at 25°. The reaction mixture was combined with 100 ml of Et_2O and washed twice with 30 ml of H_2O and once with 30 ml of saturated NaCl solution. The organic solution was dried (Na_2SO_4) and the solvent was removed *in vacuo* to give a thick oil (2.1 g, 70%); spectral data are consistent with the assigned structure.

4-Acetamido-1,4-benzoxazine-2,3-dione (8a).—Crude 1-(*o*-benzyloxyphenyl)-1-ethyloxalyl-2-acetylhydrazine (6a, 2.1 g, 0.006 mol) was hydrogenated at 25° under 1-atm pressure with 200 mg of 5% Pd/C as the catalyst and 50 ml of EtOAc as the solvent. When the uptake of H_2 stopped, the catalyst was removed by filtration and the solvent was removed *in vacuo* to give an oil. The oil was dissolved and heated in C_6H_6 until a solid had formed. The C_6H_6 solution was cooled and the solid was collected by filtration. Several more crops were collected by heating the mother liquor until more solid formed. The solid fractions were combined and recrystallized (Me_2CO–C_6H_6) to give 0.9 g (45%) of 8a as small white crystals, mp 240–242°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.85; H, 3.70; N, 12.89.

1-(o-Benzyloxyphenyl)-2-trifluoroacetylhydrazine (5b).—*o*-Benzyloxyphenylhydrazine hydrochloride (4, 5.0 g, 0.02 mol), anhydrous $NaHCO_3$ (3.4 g, 0.04 mol), and trifluoroacetic anhydride (5.0 g, 0.024 mol) were stirred at 25° for 6 hr in 50 ml of anhydrous Et_2O. The reaction mixture was combined with 70 ml of C_6H_6 and washed twice with 70 ml of H_2O. The organic solution was dried (Na_2SO_4) and the solvent was removed to give an oil, which crystallized from Et_2O–petroleum ether to give 5.5 g (89%) of 5b. Recrystallization from C_6H_6–petroleum ether gave fine white crystals, mp 108–110°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{15}H_{13}N_2O_2F_3$: C, 58.07; H, 4.22; N, 9.03. Found: C, 57.80; H, 4.21; N, 9.26.

1-(o-Benzyloxyphenyl)-1-ethyloxalyl-2-trifluoroacetylhydrazine (6b).—1-(*o*-Benzyloxyphenyl)-2-trifluoroacetylhydrazine (5b, 3.1 g, 0.01 mol), anhydrous $NaHCO_3$ (1.0 g, 0.012 mol), and ethyl oxalyl chloride (1.5 g, 0.012 mol) were stirred at 25° for 12 hr in 50 ml of anhydrous C_6H_6. The mixture was combined with 100 ml of Et_2O and washed twice with 50 ml of H_2O. The organic solution was dried (Na_2SO_4) and the solvent was removed *in vacuo* to give an oil (3.0 g, 97%); spectral data are consistent with the assigned structure.

4-Trifluoroacetamido-1,4-benzoxazine-2,3-dione (8b).—Crude 1-(*o*-benzyloxyphenyl)-1-ethyloxalyl-2-trifluoroacetylhydrazine (6b, 3.0 g, 0.01 mol) was hydrogenated at 25° under 1-atm pressure with 200 mg of 5% Pd/C as the catalyst and 50 ml of EtOAc as the solvent. The reaction was allowed to proceed until 225 ml (0.01 mol) of H_2 had been taken up. The catalyst was removed by filtration and the solvent was removed *in vacuo* to give an oil which crystallized from Et_2O–petroleum ether to give 0.9 g (33% overall) of 8b as fluffy white crystals. An additional 0.6 g (22%) of 8b was obtained by the addition of more petroleum ether to the mother liquor of the first crop. Recrystallization from C_6H_6–petroleum ether gave a total of 1.3 g (50%) of 8b as a white solid, mp 217–220°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{10}H_5N_2O_4F_3$: C, 43.81; H, 1.84; N, 10.22. Found: C, 43.54; H, 1.66; N, 10.26.

1-(o-Benzyloxyphenyl)-2-(p-toluenesulfonyl)diimide (17).—*o*-Benzyloxyaniline hydrochloride (11.8 g, 0.05 mol) dissolved in 100 ml of MeOH and 100 ml of 3 *N* HCl was stirred and cooled to 0°. To this solution was added $NaNO_2$ (3.45 g, 0.05 mol) dissolved in 25 ml of H_2O in the course of 15 min. The solution was stirred and cooled for 15 min, after which it was cooled to −5°. The solution was adjusted to pH 5 with NaOAc (30 g in 150 ml of H_2O). A precooled (−5°) solution of sodium *p*-toluenesulfinite (8.9 g, 0.05 mol) in 150 ml of H_2O was added rapidly to this solution, resulting in the formation of solid lumps. The mixture was stirred and the lumps were disintegrated to a powder after stirring for 1 hr at −5°. The solid was collected by filtration and dissolved in 300 ml of C_6H_6. The C_6H_6 solution was washed with 100 ml of H_2O, 100 ml of 5% $NaHCO_3$ solution, and 100 ml of H_2O. The organic solution was dried (Na_2SO_4) and the solvent was removed *in vacuo* to give a solid which was recrystallized by dissolving in hot C_6H_6 and adding Et_2O to give 16.9 g (92%) of 17 as pale orange needles, mp 113–116°; the spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{20}H_{18}N_2O_3S$: C, 65.56; H, 4.95; N, 7.64. Found: C, 65.45; H, 4.68; N, 7.60.

1-(o-Benzyloxyphenyl)-2-(p-toluenesulfonyl)hydrazine (18).—1-(*o*-Benzyloxyphenyl)-2-(*p*-toluenesulfonyl)diimide (17, 14.6 g, 0.04 mol) was suspended and stirred in 250 ml of 95% EtOH at 0°. To this suspension was added 40 ml of HOAc, followed by Zn dust (13.4 g, 0.20 g-atom). The mixture was stirred and cooled for 1 hr, after which the ice bath was removed and stirring was continued for 1 hr. The thick suspension was filtered and the filtrate was saved. The filter cake was dispersed in 60 ml of EtOH and 20 ml of HOAc and heated on a steam bath for 15 min, then filtered. The filtrate was saved and the filter cake was treated twice more with hot HOAc in EtOH to give two more filtrates. The combined filtrates were treated with two volumes of H_2O and cooled to 5° for several hours. The solid was collected by filtration and recrystallized (90% EtOH) to give 9.7 g (66%) of 18 as pale yellow needles, mp 134–136°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{20}H_{20}N_2O_3S$: C, 65.20; H, 5.47; N, 7.60. Found: C, 65.48; H, 5.51; N, 7.64.

1-(*o*-Benzyloxyphenyl)-1-ethyloxalyl-2-(*p*-toluenesulfonyl)hydrazine (19).—1-(*o*-Benzyloxyphenyl)-2-(*p*-toluenesulfonyl)hydrazine (**18**, 3.6 g, 0.015 mol) and ethyl oxalyl chloride (1.5 g, 0.011 mol) were stirred and heated to 50° in anhydrous C_6H_6 containing $NaHCO_3$ (0.84 g, 0.01 mol) for 2 hr. The reaction mixture was combined with 50 ml of C_6H_6 and washed four times with 70 ml of H_2O and once with 50 ml of saturated NaCl solution. The C_6H_6 solution was dried (Na_2SO_4) and the solvent was removed to give a dark oil, which crystallized slowly from 10 ml of Et_2O. Recrystallization (Me_2CO–Et_2O) gave 2.0 g (44%) of **19** as white crystals, mp 113–114.5°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{24}H_{24}N_2SO_6$: C, 61.52; H, 5.16; N, 5.98. Found: C, 61.17; H, 5.30; N, 5.61.

4-(*p*-Toluenesulfonamido)-1,4-benzoxazine-2,3-dione (20).—1-(*o*-Benzyloxyphenyl)-1-ethyloxalyl-2-(*p*-toluenesulfonyl)hydrazine (**19**, 0.46 g, 0.001 mol) was hydrogenated at 25° under 1-atm pressure with 100 mg of 5% Pd/C as the catalyst and 40 ml of EtOAc as the solvent. The uptake of H_2 slowed appreciably after 0.001 mol had been consumed. The catalyst was removed by filtration and the solvent was removed *in vacuo* to give a solid which was recrystallized (C_6H_6) to give 0.20 g (63%) of an amorphous white solid, Recrystallization (Me_2CO–Et_2O) gave the same white solid, mp 200–202°; spectral data are consistent with the assigned structure.

Anal. Calcd for $C_{15}H_{12}N_2O_5S$: C, 54.21; H, 3.64; N, 8.43. Found: C, 54.11; H, 3.49; N, 8.75.

Registry No.—**4**, 34288-06-7; **5a**, 34288-07-8; **5b**, 34288-08-9; **8a**, 34288-09-0; **8b**, 34288-10-3; **10**, 34288-11-4; **11**, 34288-12-5; **12**, 34288-13-6; **13**, 34288-14-7; **17**, 34288-15-8; **18**, 34288-16-9; **19**, 34288-17-0; **20**, 34288-18-1; *o*-benzyloxyacetanilide, 34288-19-2.

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Heteroaromatic Fused-Ring Mesoionic Compounds. Sydno[3,4-*a*]quinoxalines[1]

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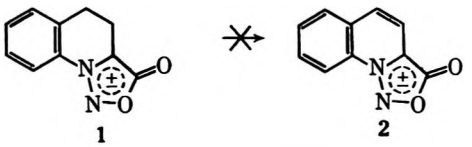
A number of derivatives of sydno[3,4-*a*]quinoxalines have been synthesized from 3-(*o*-nitrophenyl)sydnone. Incorporation of the five-membered mesoionic sydnone ring into a conjugated fused-ring heteroaromatic system produces compounds of enhanced stability toward thermal and aqueous acid-catalyzed decomposition. Susceptibility toward base-catalyzed reaction is increased. SCF molecular orbital treatments were found to be useful in predicting electronic absorption spectra, relative stability of tautomers, and the probable site of O alkylation.

Sydnones have been the most extensively studied member of mesoionic heterocyclic systems.[2] Classified as nonbenzenoid aromatic compounds, sydnones possess an unusual electronic structure characterized by an interplay of charge separation and electron delocalization. A large number of sydnone derivatives have been reported to date, many of which have been found to possess one or more of a wide variety of biological activities.[3] Despite this activity in sydnone chemistry, no conjugated heteroaromatic fused-ring sydnones have been reported.[4] Hammick and Voaden[5] have reported unsuccessful attempts to prepare sydno[3,4-*a*]quinoline (**2**) from 4,5-dihydrosydno[3,4-*a*]quinoline (**1**).



1 **2**

We wish to report the syntheses of a number of quinoxaline ring-fused sydnones. The effect upon the molecular properties of sydnones produced by this ring fusion were examined by quantum chemical and spectroscopic methods.

Results and Discussion

Despite the failures to prepare **2** and the absence of reported examples of heteroaromatic fused-ring sydnone derivatives, there is no apparent rationale to suggest a destabilizing influence effected by such a ring fusion. Stabilization achieved by such extended conjugation might be of practical significance, since many of the simple sydnones with potentially useful biological activities lack thermal stability and frequently darken upon exposure to light and air.[6]

The initial objective of this investigation was sydno[3,4-*a*]quinoxalin-4-one (**3**), chosen in part because of the electron-withdrawing effect upon the sydnone 4 position as depicted in the valence-bond representation **3b**. Electron-withdrawing substituents at C-4 in sydnones have been observed to enhance their stability, especially toward acid-catalyzed ring-opening hydrolysis.[7]

In order to estimate the perturbation of the sydnone π-electron system effected by this ring fusion, we have compared the results of semiempirical Pople–Parr–Pariser SCF–MO treatments of the π systems of *N*-phenylsydnone and **3**. For sydnones, the results of this type of treatment compare favorably with those obtained from CNDO/2 calculations.[8] The results of

(1) Taken in part from the M.S. Thesis of J. P. O'Donnell, SUNY/B, Sept 1971. Presented at the 3rd Northeast Regional Meeting of the American Chemical Society, Buffalo, N. Y., Oct 13, 1971.

(2) W. Baker and W. D. Ollis, *Quart. Rev., Chem. Soc.*, **11**, 15 (1959); F. H. C. Stewart, *Chem. Rev.*, **64**, 129 (1964).

(3) L. B. Kier and E. B. Roche, *J. Pharm. Sci.*, **56**, 149 (1967); E. Ackermann, *Pharmazie*, **22**, 537 (1967).

(4) M. Ohta and H. Kato in "Nonbenzenoid Aromatics," Vol. I, J. P. Snyder, Ed., Academic Press, New York, N. Y., 1969.

(5) D. L. Hammick and D. J. Voaden, *J. Chem. Soc.*, 3303 (1961).

(6) *N*-Methylsydnone darkens upon distillation at reduced pressure even in a short-path Kugelrohr distillation apparatus.

(7) F. H. C. Stewart, unpublished results cited in ref 2.

(8) F. P. Billingsley and J. E. Bloor, *Theor. Chim. Acta*, **11**, 325 (1968).

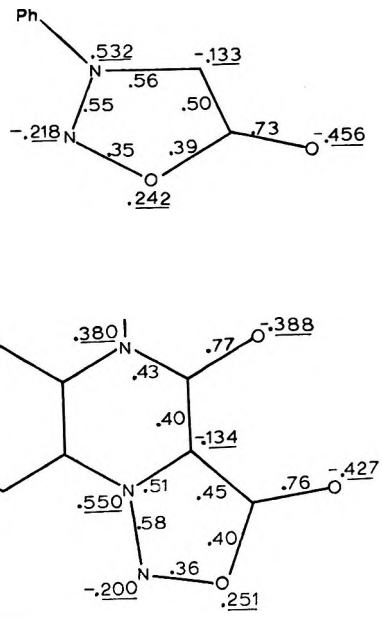
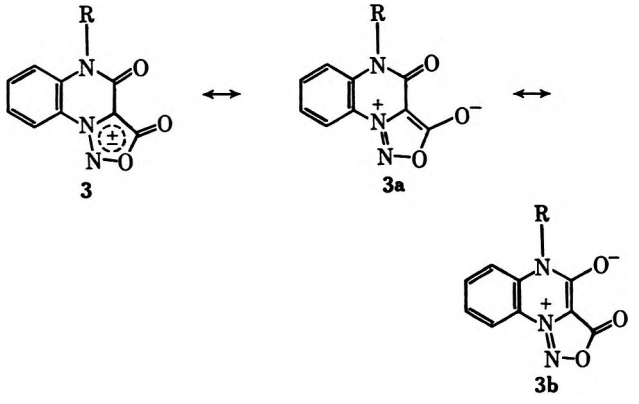


Figure 1.—VESCF π-MO calculated bond orders and charge densities for 3-phenylsydnone and sydno[3,4-*a*]quinoxalin-4-one.

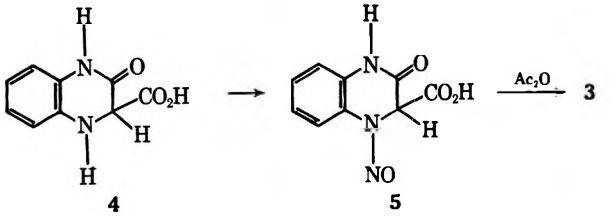


variable-electronegativity SCF calculations[9] are shown in Figure 1.

The electron deficiency of the sydnone N_3 atom increases in the fused system. The π-electron density of the exocyclic sydnone-ring oxygen decreases while the bond order for this oxygen–carbon bond increases. The near equality of bond orders for the two carbon exocyclic oxygen bonds implies nearly equal contribution of resonance structures **3a** and **3b**.

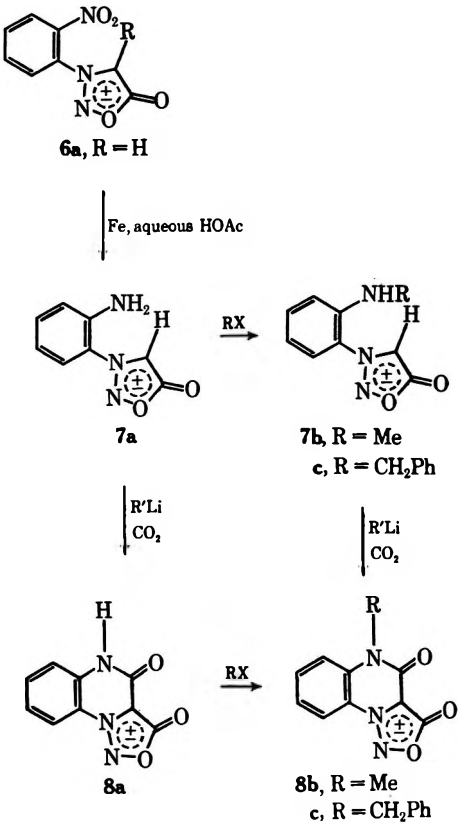
Two general synthetic routes leading to sydno[3,4-*a*]-quinoxalines were investigated. The first route, depicted in Scheme I, involves construction of the sydnone ring *via* a quinoxaline derivative. Such a route is attractive owing to the limited number of steps and the avoidance of synthetic manipulation of mesoionic intermediates.

SCHEME I



Quinoxalone **4** is available by catalytic hydrogenation of quinoxalin-2-one-3-carboxylic acid,[10] which in turn may be prepared from *o*-phenylenediamine and either mesoxalic acid or alloxan.[11] In spite of the apparent simplicity of this route, the difficulty encountered in the preparation of **5** by the nitrosation of **4** led to the adoption of the second route shown in Scheme II.

SCHEME II



3-(2′-Nitrophenyl)sydnone (**6a**) was prepared according to the procedure of Eade and Earl[12] by the cyclodehydration of *N*-nitroso-*N*-(2′-nitrophenyl)glycine. Metalation of **6a** using a variety of organolithium reagents (methyllithium, *n*-butyllithium, and *tert*-butyllithium) in various solvents (ether, THF, triethylamine, tetramethylethylenediamine) was investigated by quenching the reaction mixtures with D_2O and observing the intensity of the C-4 proton signal in the pmr spectrum of recovered sydnone. This procedure showed no evidence of metalation having occurred with **6a**, despite the general utility of this method in preparing 4-carboxyl derivatives of other sydnones.[13] Sydnone **6a** was brominated in aqueous ethanol, giving the 4-bromo derivative **6b** (R = Br). Metalation of **6b** was attempted under similar conditions followed by quenching with H_2O. No signal

(9) The method employed was similar to that used in previous treatments of mesoionic structures by K. Sundaram and W. P. Purcell, *Int. J. Quantum Chem.*, **2**, 145 (1968). A limited configuration interaction employing a triangularly generated matrix of 21 configurations was used to estimate singlet electronic transitions. Geometries were approximated from X-ray crystallographic data by H. Barnighausen, F. Jellinek, J. Munnik and A. Vos, *Acta Crystallogr.*, **16**, 471 (163).

(10) E. C. Taylor and M. J. Thompson, *J. Org. Chem.*, **26**, 3511 (1961).

(11) O. Kuhling, *Ber.*, **24**, 2363 (1891).

(12) R. A. Eade and J. C. Earl, *J. Chem. Soc.*, 591 (1946).

(13) C. V. Greco, M. Pesce, and J. M. Franco, *J. Heterocycl. Chem.*, **3**, 391 (1966); S. A. Zotova and V. G. Yashunskii, *Zh. Org. Khim.*, **1**, 2281 (1965).

corresponding to the C-4 proton of **6a** was observed in the crude product mixture.

Sydnone **6a** was reduced with iron in aqueous acetic acid to 3-(2′-aminophenyl)sydnone (**7a**). Use of an excess of methyllithium in either triethylamine or ether effected the desired metalation of the 4 position as judged by the amount of deuterium incorporation (*ca.* 95%) following D_2O quenching of the reaction mixture. Addition of this metalated intermediate to a Dry Ice–ether slurry gave, after evaporation of solvent, a water-soluble lithium salt. Acidification of an aqueous solution of this salt produced effervescence at pH 6 as the *N*-carboxylic acid group decarboxylated. At pH 1, **8a** precipitated following the apparent cyclodehydration of 3-(2′-aminophenyl)sydnone-4-carboxylic acid. The structural assignment of **8a** was supported by the disappearance of spectral evidence for the C-4 hydrogen of the sydnone ring (ν_{CH} 3190 cm^{-1}, δ 7.75) and the appearance of a strong absorption at 1675 cm^{-1} assigned to the quinoxalone lactam carbonyl; in addition the pmr multiplet of the aromatic protons undergoes a shift to lower field, as would be expected when the electron-releasing effect of the amino group is moderated. The remaining pmr signal appears at very low field, characteristic of a enolic or α-pyridone-like hydrogen.

The product **8a** can conceivably exist in any of three different tautomeric states, shown in Figure 2. The VESCF–MO treatment of the π systems of these tautomers would indicate that I is the most stable based upon π-electron delocalization energies. Also indicated are the three longest wavelength $\pi \rightarrow \pi^*$ singlet transitions. Since the predicted transitions differ substantially in their values and patterns, it was believed that they would be of assistance in structure assignment. The observed electronic absorptions of the product **8a** agree very closely with that predicted for the quinoxalone lactam tautomer (I). Supporting evidence for this assignment also comes from the spectral data for the N-alkylated derivatives of **8a**.

Alkylation of the sodium salt of **8a** in THF with alkyl halides or dimethyl sulfate was found to occur exclusively on nitrogen.[14] The structure of the alkylated product was indicated by the similarity of ir and uv spectra of **8a** with its methyl and benzyl derivatives, **8b** and **8c**. Confirmation of the site of alkylation was obtained by synthesis of **8b** and **8c** by metalation and carbonation of the corresponding 3-(2-alkylaminophenyl)sydnones, **7b** and **7c**.

O methylation was achieved by treatment of **8a** with an excess ethereal solution of diazomethane. Although N methylation usually predominates in the diazomethane methylation of quinoxalin-2-ones,[15] no corresponding product (**8b**) could be detected. The possibility exists of alkylation occurring at either of the two exocyclic oxygen atoms to give **9** or **10**.

The methyl derivative obtained from the reaction of **8a** and diazomethane was easily distinguished from **8b** *via* physical (melting point, tlc, and solubility in benzene) and spectral properties. It exhibited very strong absorption in the high-frequency region of carbonyl absorption (1800–1785 cm^{-1}) but lacked the

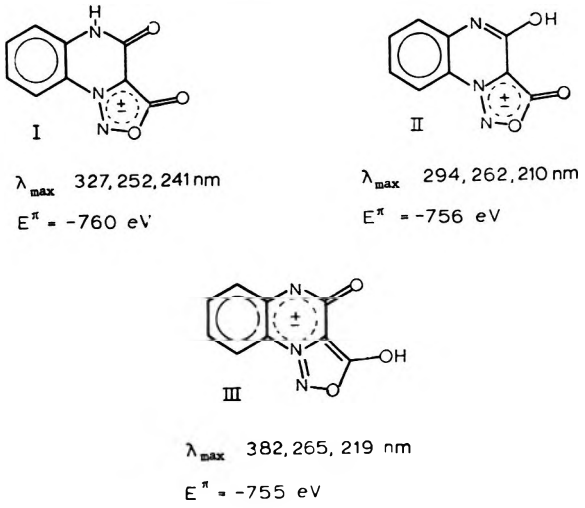
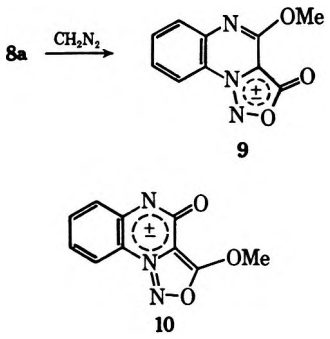


Figure 2.—VESCF π-MO calculated $\pi \rightarrow \pi^*$ singlet transitions and delocalization energies of the tautomers of sydno[3,4-*a*]-quinoxalin-4-one.



1675-cm^{-1} band observed for **8a**. This is consistent for structure **9**, since a high frequency, very intense carbonyl absorption is characteristic of sydnones.[16] From spectral data reported for quinoxalin-2-ones and several six-membered ring mesoionic systems, the anticipated carbonyl absorption of **10** would be likely to occur below 1700 cm^{-1}.[17]

The prominent parent molecular ion of **9** exhibits a very facile loss of NO followed by CO in a fashion identical with other sydnones[18] and sydno[3,4-*a*]-quinoxalines reported here (*vide infra*). Although the longest wavelength ultraviolet absorption of the product (376 nm) is close to that predicted for **10**, this band undergoes a 10-nm hypsochromic shift in water which suggests an $n \rightarrow \pi^*$ transition.

It is conceivable that O alkylation could occur at the sydnone exocyclic oxygen atom under kinetically controlled conditions. Potts has reported the O alkylation of 3-phenylsydnone with Meerwein's reagent.[19] However, INDO calculated total ($\sigma + \pi$) electron densities (Figure 3) indicate that the quinoxalone oxygen is substantially more electron rich and presumably more nucleophilic in spite of the reverse ordering based upon π-electron considerations alone (Figure 1). We have

(14) In DMF alkylation of the sodium salt of **8a** was found to produce both N- and O-alkylated derivatives.

(15) G. W. H. Cheeseman, *J. Chem. Soc.*, 1804 (1955).

(16) B. E. Zaitsev and Yu. N. Sheinker, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 407 (1962).

(17) G. W. H. Cheeseman, A. R. Katritzky, and S. ØKsne, *J. Chem. Soc.*, 3983 (1963); J. Honzl and M. Sorm, *Tetrahedron Lett.*, 333 (1969); L. Paoloni, M. L. Tosato, and M. Cignitti, *Theor. Chim. Acta*, **14**, 221 (1969).

(18) J. H. Bowie, R. A. Eade, and J. C. Earl, *Aust. J. Chem.*, **21**, 1665 (1968); R. S. Goudie, P. N. Preston, and M. H. Palmer, *Org. Mass Spectrom.*, **2**, 953 (1969); R. C. Dougherty, R. L. Foltz, and L. B. Kier, *Tetrahedron*, **26**, 1989 (1970).

(19) K. T. Potts, E. Houghton, and S. Husain, *Chem. Commun.*, 1025 (1970).

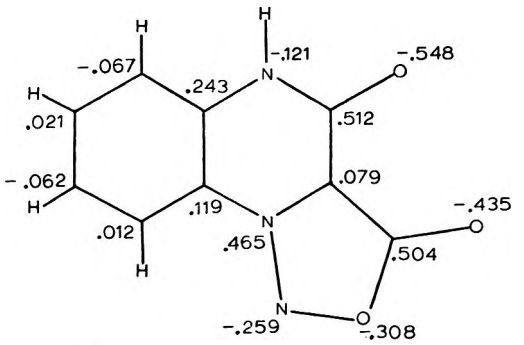
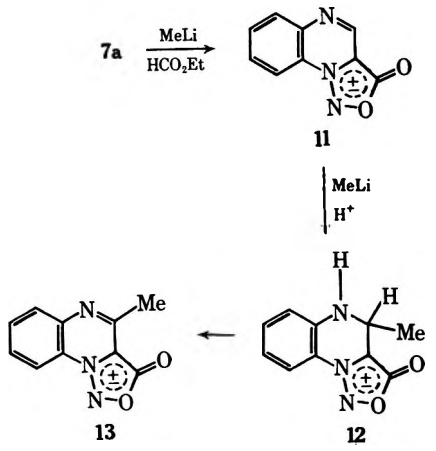


Figure 3.—INDO all-valence electron SCF net ($\sigma + \pi$) atom charges calculated for sydno[3,4-*a*]quinoxalin-4-one.

been unsuccessful in attempts to achieve O alkylation of the sydnone exocyclic oxygen *via* Meerwein's reagent. It is interesting to note that the INDO-calculated π-charge density of N-10 indicates the loss of 0.9 e, making this position extremely electron deficient.

If the metalated intermediate in Scheme II is treated with ethyl formate or ethyl orthoformate instead of CO_2, the parent sydno[3,4-*a*]quinoxaline (**11**) can be obtained. The use of an excess of methyllithium results in the formation of the 4,5-dihydro-4-methyl derivative **12**, which is easily air oxidized to 4-methylsydno[3,4-*a*]-quinoxaline (**13**). The reactivity of the 4,5 bond



toward nucleophilic addition provides a facile route for the preparation of 4-alkyl- or 4-aryl-substituted derivatives.

Sydnones are hydrolyzed in aqueous HCl to give substituted hydrazines, carboxylic acids, and carbon dioxide. For alkyl sydnones this reaction is facile and has been recommended for use in the preparation of difficulty accessible hydrazines.[4] Aryl sydnones are more resistant, requiring >0.1 *N* HCl and elevated temperatures ($k \sim$ *ca.* 10^{-6} sec^{-1}, 1 *N* HCl, 50°).[20] All of the sydno[3,4-*a*]quinoxalines exhibited great stability toward acid-catalyzed ring openings. For instance, **8a** was unchanged after 5 days at 80° in 0.8 *N* HCl as judged by spectrophotometric analysis and by recovery of unchanged starting material ($k \sim <10^{-7}$ sec^{-1}).

Garrett[21] has studied the rate of base-catalyzed ring opening of a number of alkyl- and aryl-substituted sydnones. Although sydnones are known to undergo ring opening in alkali to give *N*-nitroso carboxylate salts, as in previous studies we were unable to characterize these unstable products from the dilute solutions employed in kinetic studies. The product solutions, however, did give positive Liebermann tests for the *N*-nitroso group, in contrast to negative results obtained from the starting materials. Table I gives

TABLE I
RELATIVE RATES OF REACTIVITY OF SYDNONES IN 0.10 *N* KOH AT 39°

Compd	Relative rate[a]
8a	1
8b	22
14	29
9	153
13	283

[a] $k_{obsd} = 3.0 \times 10^{-5}$ sec^{-1} for **10a**.

the comparative results of the rate of disappearance of a representative selection of sydno[3,4-*a*]quinoxalines in aqueous alkali together with 3-phenyl-4-acetylsydnone (**14**). The rate of reaction of **8a** is comparable to that of previously reported simple sydnone derivatives.[21] The slower rate of reaction of **8a**, in comparison to the other listed compounds, is due to its conversion to an anion in base ($pK_a \sim 8.8$, determined spectrophotometrically). An electron-withdrawing substituent at the sydnone 4 position substantially increases the rate of ring opening, possibly by increasing the ease of nucleophilic attack at the sydnone pseudocarbonyl.[22]

The sydno[3,4-*a*]quinoxalines, in general, exhibited appreciably greater thermal stability. Compounds **11** and **13** are easily purified by sublimation (175–225°) while **8a** exhibits no sign of decomposition below its melting point, 307–308°. The normal sydnone pseudocarbonyl stretching vibration occurs at *ca.* 1740 cm^{-1}, while that for the sydno[3,4-*a*]quinoxalines occurs near 1790 cm^{-1}. The position of this intense absorption is sensitive to phase and concentration effects but nevertheless suggests an increase in the carbon–exocyclic oxygen bond order.

In conclusion, the sydno[3,4-*a*]quinoxalines have been found to exhibit increased thermal stability and resistance to acid-catalyzed ring opening. The properties of these fused-ring structures can be rationalized in terms of existing knowledge of the properties of the two-component ring systems. In this way they differ from the type of bicyclic mesoionic structures represented by the mesoionic purinone analogs[23] in which charge separation is formally required to involve both ring systems.

Experimental Section

Pmr spectra were obtained on a Varian T-60 spectrometer; chemical shifts are reported relative to TMS as an internal standard. Ultraviolet spectra were recorded on a Beckman Model DB spectrophotometer. Infrared spectra were obtained on a Perkin-Elmer Model 237 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. All melting points were determined with a Mel-Temp

(20) S. Aziz, A. F. Cockerill, and J. G. Tillett, *Tetrahedron Lett.*, 5479 (1968).

(21) The mechanism of this reaction has not been resolved. Garrett[22] suggests hydroxide ion attack at the divalent nitrogen while attack of the pseudocarbonyl group is favored by E. B. Roche and L. B. Kier, *Tetrahedron*, **24**, 1673 (1968).

(22) E. R. Garrett and P. J. Mehta, *J. Pharm. Sci.*, **56**, 1468 (1967); E. R. Garrett, *ibid.*, **53**, 42 (1964).

(23) R. A. Coburn, *J. Heterocycl. Chem.*, **8**, 881 (1971).

melting point apparatus and are uncorrected. Mass spectra were obtained by using a Hitachi Perkin-Elmer RMC-6 single focusing mass spectrometer.

3-(2'-Nitrophenyl)-4-bromosydnone (6b).—Sodium bicarbonate (2.0 g, 24 mmol) in water (25 ml) was added to a suspension of **6a** (0.7 g, 3.3 mmol) in ethanol (35 ml) at room temperature. Bromine (2.5 g, 15 mmol) in ethanol (25 ml) was added dropwise until the resultant cloudy solution became clear. The reaction was stirred for 20 min, followed by the addition of water (30 ml). The solvent was evaporated *in vacuo* at 50° and the resulting residue was washed with water and dried. Recrystallization from benzene–petroleum ether (bp 50–60°) gave 0.74 g of **8b** as light yellow crystals: mp 114–116° dec; ir (KBr) 1780 cm^{-1} (C=O); uv max (EtOH) 310 nm (ϵ 5577), 251 (15, 964); nmr (DMSO-d_6) δ 8.1 (m). This compound rapidly decomposed upon warming and darkened upon exposure to light and air. Satisfactory microanalysis was not obtained.

3-(2'-Aminophenyl)sydnone (7a).—A mixture of **6a** (1.0 g, 4.9 mmol) and 3.0 g of powdered iron was added to 60 ml of 2% acetic acid at 90°. The mixture was refluxed for 12 min and then chilled. Sodium bicarbonate (1.7 g, 0.023 mol) was added in small portions with stirring followed by filtration. The solid was washed with ice water (3 × 25 ml), air dried, and extracted with boiling tetrahydrofuran (4 × 20 ml). The combined extracts were evaporated *in vacuo* and the residue was recrystallized from THF–petroleum ether to yield 0.7 g (81%) of **7a** as light-yellow crystals: mp 136–137°; ir (KBr) 1750 cm^{-1} (C=O), 3400, 3500 cm^{-1} ($-NH_2$); uv max (EtOH) 302 nm (ϵ 6720), 233 (15, 960); nmr ($CDCl_3$) δ 4.54 (s, 2, $-NH_2$), 6.63 (s, 1, sydnone H), 7.18 (multiplet, 4, phenyl).

Anal. Calcd for $C_8H_7N_3O_2$: C, 54.23; H, 3.98; N, 23.72. Found: C, 53.97; H, 3.80; N, 23.59.

3-(2'-Methylaminophenyl)sydnone (7b).—To **7a** (1 g, 6 mmol) in anhydrous ethyl ether (100 ml) was added NaH (0.4 g, 57% in oil). After stirring for 10 min, methyl iodide (3 ml) was added and stirring was contined for 48 hr. The mixture was filtered and the residue was washed with ether (2 × 250 ml). The combined ether filtrate was evaporated *in vacuo*, giving 0.8 g of residue. This residue was taken up in methylene chloride–ethyl acetate (95:5) and placed on a silica gel (Woelm) column. Elution with the same solvent system gave 360 mg (32%) of **7b** as green crystals, recrystallized from benzene–hexane: mp 116–118°; ir (KBr) 3400 (NH), 3180 (sydnone CH), 1730 cm^{-1} (C=O); uv max (EtOH) 303 nm (ϵ 7350), 244 (16,200); nmr ($CDCl_3$) δ 3.1 (d, 3, J = 2.5 Hz, CH_3N), 5.0 (broad, 1, NH), 6.55 (s, 1, sydnone H), 7.1 (m, 4, aryl).

Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.74; N, 21.98. Found: C, 56.77; H, 4.76; N, 21.90.

3-(2'-Benzylaminophenyl)sydnone (7c).—A procedure identical with that used in the preparation of **7b** was employed using benzyl bromide (1.5 g), NaH (0.4 g, 57% in oil), and **7a** (1 g, 6 mmol). **7c** (641 mg, 40%) was obtained following elution column chromatography (silica gel) of the crude product mixture using methylene chloride–ethyl acetate (95:5). Recrystallization from benzene–hexane gave white crystals: mp 114–115°; ir (KBr) 3250 (NH), 3150 (sydnone CH), 1730 cm^{-1} (C=O); uv max (EtOH) 304 nm (ϵ 7480), 246 (16,400); nmr ($CDCl_3$) δ 4.4 (d, 2, J = 2.5 Hz, $PhCH_2$–), 5.4, (broad, 1, NH) 6.6 (s, 1, sydnone H), 6.7 (m, 4, aryl), 7.3 (s, 5, phenyl).

Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.41; H, 4.90; N, 15.71. Found: 67.69; H, 4.80; N, 15.55.

Sydno[3,4-a]quinoxalin-4-one (8a).—A solution of methyllithium (2.5 ml, 2.1 *M* in ether) was added dropwise to a suspension of **7a** (0.33 g, 1.86 mmol) in 3 ml of ether at −20° under a nitrogen atmosphere. After stirring for 1 hr the mixture was added to a Dry Ice–ether slurry. The reaction mixture was evaporated to dryness at room temperature and 20 ml of water was added. The pH of the solution was adjusted to 6 with concentrated HCl. The resulting precipitate was collected, giving 0.18 g, of starting material **7a**. The filtrate was acidified to pH 1 and the resulting precipitate was collected and washed with water. The product (0.12 g, 64% conversion) was recrystallized from THF–petroleum ether for analysis: mp 307–308°; ir (KBr) 3250 (NH), 1800 (sydnone C=O), 1675 cm^{-1} (lactam C=O); uv max (EtOH) 332 nm (ϵ 5640), 256 (15,600), 232 (22, 800); nmr (DMSO-d_6) δ 7.7 (m, 4, aryl), 11.7 (s, 1, NH).

Anal. Calcd for $C_9H_5N_3O_3$: C, 53.21; H, 2.48; N, 20.68. Found: C, 53.08; H, 2.41; N, 20.53.

5-Methylsydno[3,4-a]quinoxalin-4-one (8b). A. Preparation from 9b.—A solution of methyllithium (3.0 ml, 2.1 *M* in ether) was slowly added to **7b** (0.5 g, 2.6 mmol) in 10 ml of ether at −20° under a nitrogen atmosphere. After stirring for 1 hr the mixture was added to a Dry Ice–ether slurry. Acidification of the aqueous solution of the residue, obtained by evaporation of the ether slurry, resulted in a precipitate which was collected and washed with water. Recrystallization from benzene–hexane yielded 0.3 g (54%) of **8b**: mp 235–238° (sublimes); ir (KBr) 1790 (sydnone C=O), 1670 cm^{-1} (lactam C=O); uv max (EtOH) 342 nm (ϵ 5340), 262 (16,500), 235 (23,500); nmr (DMSO-d_6) δ 3.9 (s, 3, CH_3), 7.8 (m, 4, aryl).

Anal. Calcd for $C_{10}H_7N_3O_3$: C, 55.30; H, 3.25; N, 19.35. Found: C, 55.18; H, 3.25; N, 19.15.

B. By Alkylation of 8a.—To a solution of **8a** (0.3 g, 1.4 mmol) in anhydrous ether (200 ml) was added NaH (5 g, 57% in oil). After stirring for 10 min, dimethyl sulfate (0.3 ml. 2.4 mmol) was added to the reaction mixture and stirring was continued for 48 hr. The mixture was filtered and the residue was washed with THF (4 × 100 ml). The filtrate and washings were combined and the solvent was evaporated *in vacuo*. The residue was sublimed at 190° (1 mm), giving 50 mg of **8b**, mp 235–236°. This material was identical with that prepared by method A, as judged by comparison of ir and nmr spectra and by mixture melting point. Tlc (silica gel) examination of the crude product mixture showed only two spots, corresponding to starting material and isolated product. The solvent system employed, chloroform–tetrahydrofuran (95:5), was found to clearly separate **8b** and **9** (*vide infra*).

5-Benzylsydno[3,4-a]quinoxalin-4-one (8c). A. Preparation from 7c.—A procedure identical with that used in the preparation of **8a** and **8b** was employed to give **8c** (63%) after recrystallization from benzene–hexane: mp 213–214°; ir (KBr) 1785, 1675 cm^{-1} (C=O); uv max (EtOH) 338 nm (ϵ 6530), 262 (18,500), 235 (27,400); nmr ($CDCl_3$) δ 5.4 (s, 2, $PhCH_2$), 7.35 (m, 9, aryl).

Anal. Calcd for $C_{16}H_{11}N_3O_3$: C, 65.53; H, 3.78; N, 14.33. Found: C, 65.33; H, 3.83; N, 14.43.

B. By Alkylation of 8a.—A procedure identical with that employed in the methylation of **8a** was used with benzyl bromide as the alkylating agent. The product obtained (43%) exhibited identical ir and nmr spectra with those of **8c** prepared above. A mixture melting point exhibited no depression.

4-Methoxysydno[3,4-a]quinoxaline (9).—To a solution of **8a** (0.2 g, 0.98 mmol) in 15 ml of dimethylformamide–tetrahydrofuran (1:2) was added a distilled ethereal solution (50 ml, *ca.* 0.1 *M*) of diazomethane prepared from EXR-101. After standing overnight, the solvent was removed *in vacuo*. Tlc of the resulting residue revealed only two spots corresponding to starting material and product. The product spot exhibited a greater R_f than that of **8b**. The residue was taken up in benzene and the solution was filtered to remove insoluble starting material. Addition of hexane and cooling gave **9** as light yellow crystals (0.2 g, 92%): mp 183–185°; ir ($CHCl_3$) 1800–1785 cm^{-1} (doublet, C=O); uv max (THF) 376 nm (ϵ 4590), 355 (5270), 338 (4160), 322 (4500), 280 (13,300); uv max (H_2O) 364 nm (ϵ 4100), 345 (5100), 285 (14,000); nmr ($CDCl_3$) δ 4.18 (s, 3, OCH_3), 7.2–7.8 (m, 3, aryl), 8.2 (d, 1, aryl); mass spectrum (70 eV) *m/e* (rel intensity) 217 (28), 188 (27), 187 (95), 160 (16), 159 (50) 144 (50) 131 (30), 129 (100), 116 (37), 90 (63), 89 (38), 76 (24), 75 (25), 64 (30), 63 (27), 62 (26), 51 (28), 50 (37), 44 (21).

Anal. Calcd for $C_{10}H_7N_3O_3$: C, 55.30; H, 3.25; N, 19.35. Found: C, 55.22; H, 3.17; N, 19.11.

Sydno[3,4-a]quinoxaline (11).—A solution of methyllithium (15 ml, 2.1 *M* in ether) was slowly added to **7a** (2.5 g, 14 mmol) in 15 ml of anhydrous ether at −25° under a dry nitrogen atmosphere. After stirring for 1 hr, dry ethyl formate (1.04 g, 14 mmol) in anhydrous ether (15 ml) was slowly added. Following an additional 1 hr of stirring the reaction mixture was washed with aqueous ammonium chloride solution and the solvent was removed *in vacuo*. The residue was placed on a column of silica gel (Woelm, 100 g) and eluted with chloroform–hexane (95:5). There was obtained 1.1 g (42%) of **11** as white crystals purified by sublimation: mp 225–226° (sealed tube); ir ($CHCl_3$) 1790–1775 (vs doublet, C=O), 1585 cm^{-1} (s); uv max (EtOH) 369 nm (ϵ 7380), 352 (9480), 340 sh (7530), 290 (7550), 281 (7830), 250 sh (19,000), 241 (28,700); nmr ($CDCl_3$) δ 7.7–8.3 (m, 4, aryl), 8.9 (s, 1, C_4 H); mass spectrum (70 eV) *m/e* (rel intensity) 187 (15), 157 (44), 130 (15), 129 (100), 103 (7), 104 (73), 76 (19), 75 (26), 64.5 (10), 63 (10), 51 (26), 50 (25).

Anal. Calcd for $C_9H_5N_3O_2$: C, 57.72; H, 2.69; N, 22.46. Found: C, 57.52; H, 2.47; N, 22.18.

4,5-Dihydro-4-methylsydno[3,4-*a*]quinoxaline (12) and 4-Methylsydno[3,4-*a*]quinoxaline (13).—A solution of methyllithium (5 ml, 2.1 *M* in ether) was slowly added to a suspension of **7a** (0.3 g, 1.7 mmol) and anhydrous ether (5 ml) at −20° under a dry nitrogen atmosphere. The mixture was stirred for 1 hr and added to a solution of ethyl formate (0.5 g, 6.7 mmol) in ether (20 ml). After stirring for 1 hr, the mixture was extracted with aqueous ammonium chloride solution. The ether solution was dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The residue was taken up in methylene chloride and placed on a 15-g column of silica gel (Woelm). Elution with methylene chloride–ethyl acetate (95:5) yielded 26 mg of **13**, recrystallized from benzene–hexane: mp 160–162° (sublimes); ir (KBr) 1800 cm^{-1} (C=O); uv max (H_2O) 346 nm (ϵ 7320); nmr ($CDCl_3$) δ 2.9 (s, 3, CH_3), 7.8 (m, 4, aryl); mass spectrum (70 ev) *m/e* (rel intensity) 201 (16), 173 (9), 171 (25), 145 (23), 144 (56), 143 (100), 132 (11), 117 (42), 103 (10), 102 (44), 81 (10), 78 (22), 77 (21), 76 (34), 75 (21), 69 (20), 50 (25).

Anal. Calcd for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.20; H, 3.33; N, 20.44.

Further elution gave 20 mg of **12** which was recrystallized from benzene: mp 166–167°; ir (KBr) 1735 cm^{-1} (C=O); uv max (EtOH) 325 nm (ϵ 4580), 242 (25,700); nmr ($CDCl_3$) δ 1.54 (d, 3, CH_3), 4.5 (broad, 1, NH), 4.75 (q, 1, C_4 H), 6.6–7.9 (m, 4, aryl). This compound when exposed to air was slowly transformed to a substance identical in melting point and ir and nmr spectra with **13**. In solution this transformation was facile and **12** could be converted to **13** by shaking a solution of **12** in chloroform in a separatory funnel. The mass spectrum of **12** was identical with that of **13** when introduced *via* the glass inlet system.

Kinetic Procedures.—For alkaline hydrolsyes, a few drops of a master solution of the compound in ethanol were added to a cuvette containing aqueous KOH which had been brought to 39 ± 0.1° in the sample holder of a Gilford Model 2400 uv spectrophotometer by means of a circulating constant-temperature bath. Readings of optical density of the longest wavelength maximum were recorded until no perceptible change could be detected. Base concentrations ranged from 0.02 to 0.8 *N* with a minimum of three different values being used for each compound. Concentrations of sydnone were *ca.* 10^{-4} *M*. The apparent first-order rate constants were calculated by the method of least squares. For acid hydrolyses, 20 ml of a 10^{-3} *M* master solution of sydnone was added to 80 ml of 1.0 *M* hydrochloric acid solution maintained at 80°. Aliquots, which were quickly cooled, were taken over a period of 7 days to observe the decrease in optical density of the longest wavelength ultraviolet maximum.

Semiempirical SCF–MO Calculations.—The semiempirical self-consistent field π molecular orbital calculations were performed using QCPE program 167 which was modified to include the variable electronegativity procedure[9] and a Givens method of obtaining eigenvalues and eigenvectors. Repulsion integrals were obtained by the Mataga method and penetration integrals were neglected. Resonance integrals were evaluated by $B_{ij}^{SCF} = KS_{ij}(I_i + I_j)$ where S_{ij} is the overlap integral between atoms i and j and I is the ionization potential. The value of K was adjusted to reproduce the spectrum of 3-phenylsydnone (including CI) and was given the value 0.65.

The semiempirical all valence electron calculation was performed using the CNINDO program of Dobosh (QCPE 142). Only a limited number of geometries were investigated.

Registry No.—**6b** (R = Br), 14715-65-2; **7a**, 34315-02-3; **7b**, 34315-04-3; **7c**, 34315-05-4; **8a**, 11094-23-8; **8b**, 11094-25-0; **8c**, 11094-28-3; **9**, 11094-26-1; **11**, 11094-22-7; **12**, 11094-27-2; **13**, 11094-24-9.

Acknowledgment.—The authors are grateful to the SUNY/Buffalo Computing Center for their donation of computing services of a CDC 6400 computer. This investigation was supported by a training grant (5-T1-GM-55-08) from the Division of Medical Sciences, U. S. Public Health Services, Bethesda, Md.

Thiophene Analogs of Anthraquinone

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Six possible isomers resulting from the replacement of one or both benzene rings in 9,10-anthraquinone with thiophene rings have been synthesized: 4,9-dihydronaphtho[2,3-*b*]thiophene-4,9-dione (**1**), 4,9-dihydronaphtho[2,3-*c*]thiophene-4,9-dione (**2**), 4,8-dihydrobenzo[1,2-*b*:5,4-*b'*]dithiophene-4,8-dione (**3**), 4,8-dihydrobenzo[1,2-*b*:4,5-*b'*]dithiophene-4,8-dione (**4**), 4,8-dihydrobenzo[1,2-*b*:4,5-*c'*]dithiophene-4,8-dione (**5**), and 4,8-dihydrobenzo[1,2-*c*:4,5-*c'*]dithiophene-4,8-dione (**6**). Compound **6** was prepared by dechlorination of 1,3-dichloro-4,8-dihydrobenzo[1,2-*c*:4,5-*c'*]dithiophene-4,8-dione (**15**). The compounds **1**, **2**, **3**, **4**, **5**, and **15** were subjected to reduction by means of an equimolar mixture of aluminum chloride–lithium aluminum hydride. Compounds **3** and **4** show only reduction to the hydroquinone stage. Compounds **2** and **15** provide good yields of the corresponding dihydroaromatic systems, while **1** and **5** afford only moderate yields of the dihydroaromatic systems. These results are explained in terms of the position of keto–enol tautomerism in the corresponding anthrone–anthrol systems and the stability of the parent aromatic systems.

Two previous papers[2] report the synthesis of a series of thiophene analogs of anthrone which possess significantly different enolizabilities. It was found that substitution of a *b*-fused thiophene ring for one of the benzene portions of anthrone leads to an increase in the stability of the enol form, while a similar substitution of a *c*-fused thiophene ring promotes a decrease in the stability of the enol tautomer.

Replacement of one or both of the benzene rings in 9,10-anthraquinone by a thiophene ring gives rise to two isomeric naphthothiophenediones **1** and **2** and four isomeric benzodithiophenediones **3**–**6**. Of these, **1** has been known for some time,[3] while a brief, recent report[4] refers to a synthesis of **4**.

Synthesis of the Six Diones.—The known quinone 4,9-dihydronaphtho[2,3-*b*]thiophene-4,9-dione (**1**) was prepared in 75% yield by the cyclization of *o*-(2-thenoyl)benzoic acid under the influence of aluminum chloride in nitrobenzene following the method of Weinmayr.[3c] A direct pathway to 4,9-dihydronaptho[2,3-*c*]thiophene-4,9-dione (**2**) can be envisioned as

(1) NDEA Fellow, 1967–1970.

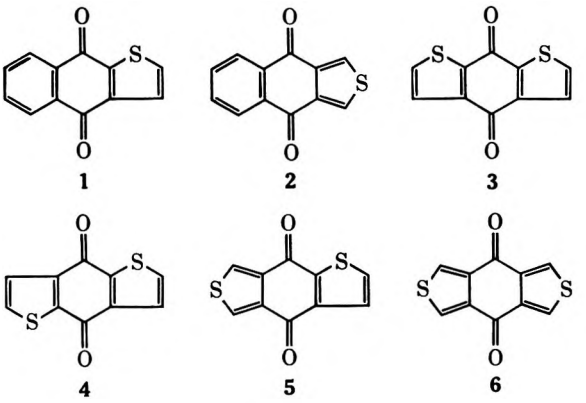
(2) D. W. H. MacDowell and J. C. Wisowaty, *J. Org. Chem.*, **36**, 3999, 4004 (1971).

(3) (a) W. Steinkopf and W. Butkiewicz, *Justus Liebigs Ann. Chem.*, **407**, 94 (1914); (b) R. Goncalves and E. V. Brown, *J. Org. Chem.*, **17**, 698 (1952); (c) V. Weinmayr, *J. Amer. Chem. Soc.*, **74**, 4353 (1952).

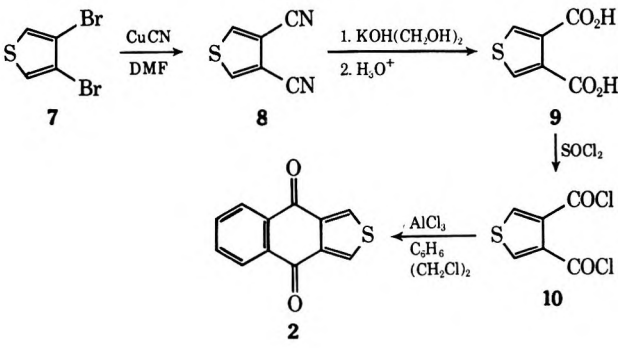
(4) D. W. Slocum and P. L. Gierer, *Chem. Commun.*, 305 (1971).

TABLE I

Dione	Color	Recrystn solvent	Mp, °C	$\nu_{C=O}$, cm^{-1} (KBr)	Uv (95% EtOH), λ_{max} (ϵ_{max})
1	Yellow	CH_3CO_2H	227–228	1660	248 (23,300), 253 (24,500), 283 (10,070), 334 (3060)
2	Yellow	CH_3CO_2H	277	1665	256 (43,900), 327 (2420)
3	Yellow	CH_3CO_2H	235–237	1640	236 (18,800), 293 (15,400), 334 (5400)
4	Yellow	CH_3CO_2H	258–260	1640	240 (15,300), 291 (13,280), 343 (4600)
5	Yellow	CH_3CO_2H	296–297	1640	258 (34,400), 283 (10,240), 329 (3960)
6	Yellow-orange	$C_2H_5CO_2H$	340	1655	259 (61,800)
15	Yellow	$CHCl_3$–CCl_4	208–209°	1670	261 (52,100), 327 (2840)



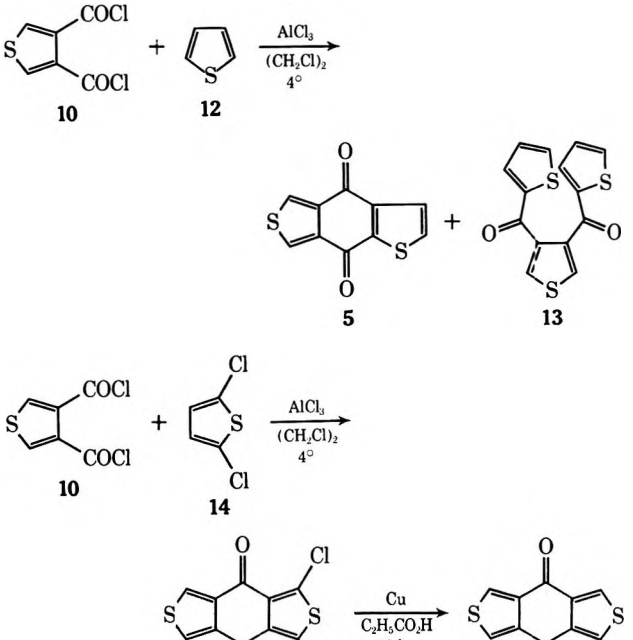
SCHEME I



utilizing thiophene-3,4-dicarboxylic acid as an intermediate as shown in Scheme I.

The transformation of 3,4-dibromothiophene (**7**) to the dinitrile **8** was accomplished by a modification of a method reported in the literature.[5] Hydrolysis of the dinitrile to the diacid **9** was best accomplished using potassium hydroxide in ethylene glycol in yields of 69–88%. The cyclic diacylation of benzene by means of **10** and aluminum chloride afforded the dione **2** in 42% yield accompanied by small amounts of other materials, the structures of which are under investigation at present.

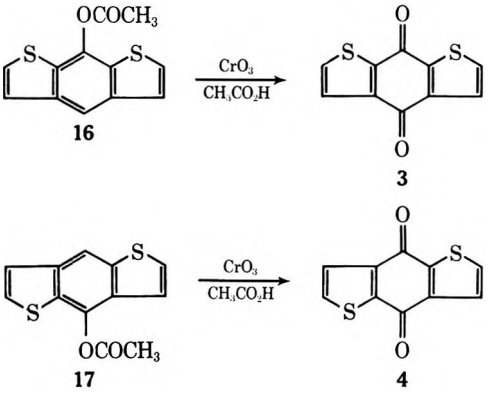
SCHEME II



Reaction of the diacid chloride **10** with thiophene (**12**) and aluminum chloride under similar conditions gave 4,8-dihydrobenzo[1,2-*b*:4,5-*c*']dithiophene-4,8-dione (**5**) in 37% yield along with a small amount of a white solid which was shown to be 3,4-bis(2-thenoyl)thiophene (**13**) (Scheme II). This method was also applied to the synthesis of **6**. When the acid chloride **10** was treated with 2,5-dichlorothiophene (**14**) in 1,2-dichloroethane, a 50% yield of 1,3-dichloro-4,8-dihydrobenzo[1,2-*c*:4,5-*c*']dithiophene-4,8-dione (**15**) was obtained. The dichlorodione **15** was dechlorinated by a suspension of copper metal in refluxing propionic acid[6] to give a 72% yield of 4,8-dihydrobenzo[1,2-*c*:4,5-*c*']dithiophene-4,8-dione (**6**). The diketone is a high-melting orange-yellow solid, very slightly soluble in most organic solvents.

The remaining isomers, 4,8-dihydrobenzo[1,2-*b*:5,4-*b*']dithiophene-4,8-dione (**3**) and 4,8-dihydrobenzo-[1,2-*b*:4,5-*b*']dithiophene-4,8-dione (**4**) were prepared from the known[2] acetoxy compounds 8-acetoxybenzo-[1,2-*b*:5,4-*b*']dithiophene (**16**) and 4-acetoxybenzo[1,-2-*b*:4,5-*b*']dithiophene (**17**) by oxidation with chromium trioxide in acetic acid. The yields of **3** and **4** were 79 and 54%, respectively (Scheme III).

SCHEME III

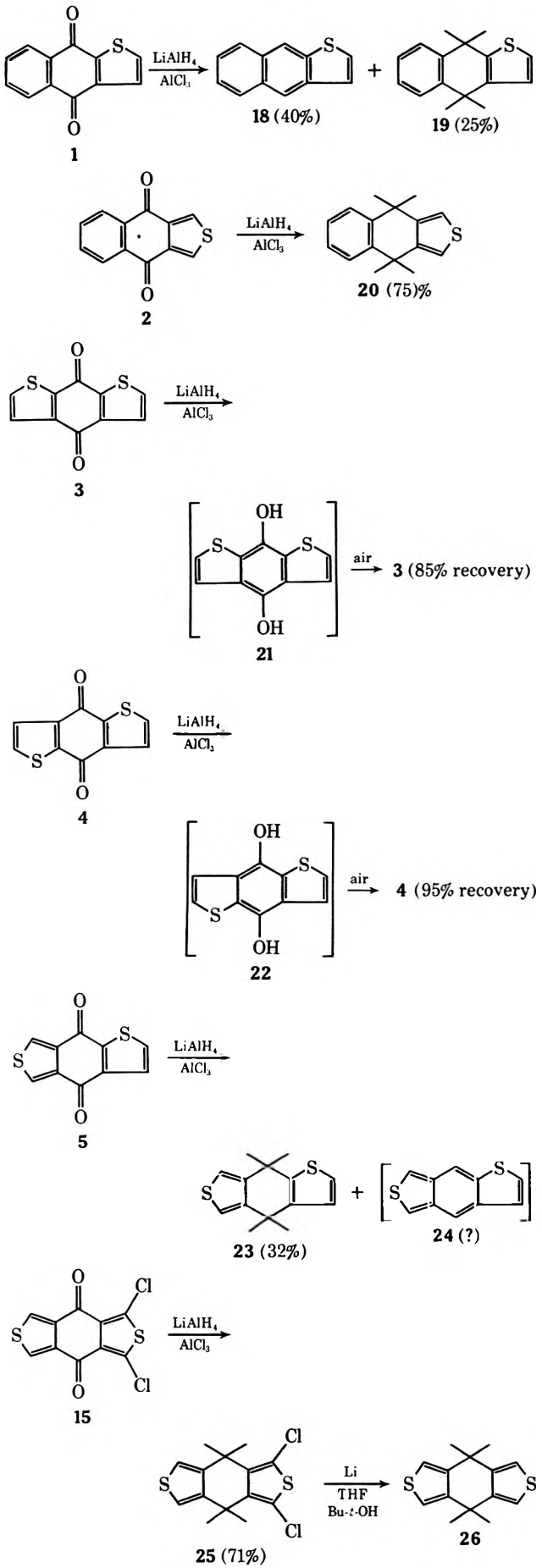


The properties of the aforementioned diones are collected in Table I.

(5) J. Morel, C. Paulmier, and P. Pastour, *C. R. Acad. Sci., Ser. C*, **266**, 1300 (1968).

(6) J. Skramstad, *Acta Chem. Scand.*, **23**, 703 (1969).

Scheme IV



Hydride Reduction of the Diones.—When ethereal suspensions of diones **1**–**5** and **15** were treated with an excess of an equimolar mixture of aluminum chloride and lithium aluminum hydride, reaction took place at the carbonyl functions. The products of reaction in each case were separated by chromatography on alumina using hexane as eluent and are shown in Scheme IV.

An examination of the reduction products seemed to place the diones into three separate classes: **3** and **4** show only reduction to the hydroquinone stage, **2** and **15** provide good yields of the respective dihydro compounds **20** and **25**, while **1** and **5** afford only moderate yields of the dihydro compounds **19** and **23**. A 40% yield of naptho[2,3-*b*]thiophene was also obtained from the reduction of **1**. The insolubility of **6** in ether necessitated the use of its dichloro derivative **15** in this study. As an additional structural proof, **25** was dechlorinated using lithium metal and *tert*-butyl alcohol in tetrahydrofuran solution[7] to 4,8-dihydrobenzo[1, 2-*c*:4,5-*c*′]dithiophene (**26**) in 53% yield.

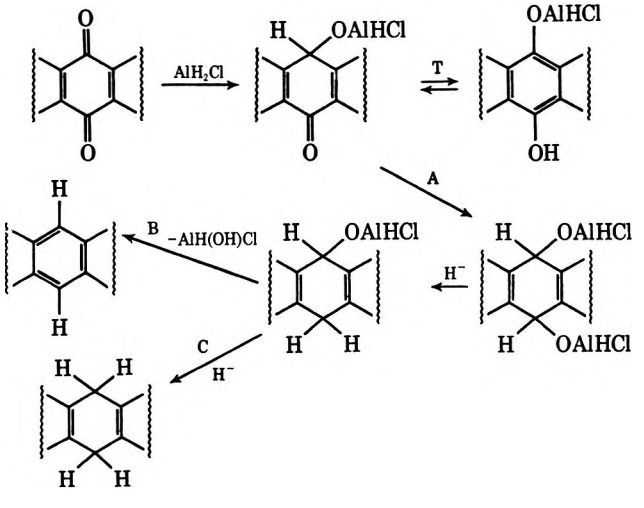
Discussion

When equimolar quantities of aluminum chloride and lithium chloride are mixed in ether, an acid–base reaction takes place, resulting in the formation of dihydridoaluminum chloride and lithium chloride.[8] The reaction

$$LiAlH_4 + AlCl_3 \longrightarrow LiCl + 2AlH_2Cl$$

of a quinone with this reducing mixture can be postulated to follow the general steps which are outlined in Scheme V.

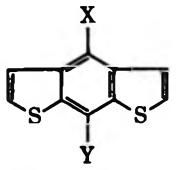
Scheme V



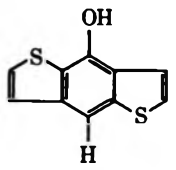
The four steps which determine product formation are designated A, B, C, and T. Step T involves the isomerization of the partially reduced quinone to a salt of the hydroquinone. Isomerization takes place only if step T is faster than the rate of attack at the second carbonyl function (step A). Since this transformation is in effect related to keto–enol tautomerism, the formation of the hydroquinone indicates a fast step T and also suggests a stable enol form in the corresponding keto–enol analogs. Therefore, the termination of the

(7) P. Bruck, *Tetrahedron Lett.*, 449 (1962).
(8) M. N. Rerick in "Reduction," R. L. Augustine, Ed., Marcel Dekker, New York, N. Y., 1968, p 3.

reduction of diones **3** and **4** at the respective hydroquinone stage is in agreement with the lack of ketone character in the benzodithiophene derivatives **27a,b** and **28**.[2]



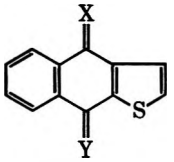
27a, X = OH; Y = H
b, X = H; Y = OH



28

The formation of an aromatic system is a result of step T and also step B. The isolation of only the product resulting from step C indicates a lack of driving force toward the formation of an aromatic system. Thus, the reduction of diones **2** and **15** to the corresponding dihydroaromatic compounds in good yield is not surprising, since it has been recently shown that naphtho[2,3-*c*]thiophene is a very unstable substance and could not be isolated.[9]

The reduction of dione **1** provides the products of both step B and step C, since the formation of naphtho[2,3-*b*]thiophene is a favorable process. Unlike the enol systems **27a,b** and **28**, the naphtho[2,3-*b*]thiophenones **29a,b** show considerable keto character,[2] hence an absence of the corresponding hydroquinone in the reaction mixture.



29a, X = O; Y = H_2
b, X = H_2; Y = O

The isolation of only the dihydro compound **23** from the reaction of dione **5** seems to indicate its similarity to diones **2** and **15**. However, a similarity to dione **1** can also be postulated by assuming the formation of benzo[1,2-*b*:4,5-*c'*]dithiophene (**24**). In order to resolve this ambiguity the preparation of **24** has been undertaken and will be the subject of a future publication.

Experimental Section[10]

Synthesis of 4,9-Dihydronaphtho[2,3-*b*]thiophene-4,9-dione (1).—A solution of *o*-(2-thenoyl)benzoic acid[11] (5.0 g, 22 mmol) and aluminum chloride (6.65 g, 50 mmol) in nitrobenzene (33 ml) was maintained at 130° for 18 hr and then allowed to cool. The nitrobenzene was removed by steam distillation and the black gummy residue was dissolved in hot benzene and run onto a column packed with neutral alumina. Elution with benzene (1000 ml) provided 3.85 g of yellow solid. Recrystallization from acetic acid afforded 3.45 g (75%) of the quinone: mp 227–228° (lit.[3c] 229–230°); uv max (95% C_2H_5OH) 248 mμ (ε 23,300), 253 (24,500), 283 (10,070), 334 (3060); ir (KBr) 1660 cm^{-1} (C=O); nmr (CF_3COOH) τ 1.63–2.44 (m).

Synthesis of 4,9-Dihydronaphtho[2,3-*c*]thiophene-4,9-dione (2). A. 3,4-Dicyanothiophene (8).—A stirred solution of 3,4-dibromothiophene (7) (242 g, 1 mol) and cuprous cyanide (260 g, 2.9 mol) in dry dimethylformamide (250 ml) was maintained at reflux for 4 hr. The dark mixture was then poured into a solution of hydrated ferric chloride (1000 g) in hydrochloric acid (1750 ml, 1.7 *M*) and maintained at 60–70° for 30 min. After the mixture had sufficiently cooled, methylene chloride (1250 ml) was added and the layers were separated. The aqueous phase was extracted four times with 1250-ml portions of methylene chloride. Each organic extract was washed successively with two 100-ml portions of hydrochloric acid (6 *M*), water, saturated sodium bicarbonate solution, and again with water. The individual portions were combined, dried ($MgSO_4$), and evaporated. The resulting slightly yellow solid was sublimed at 110° (0.1 mm) to give 100.6 g (75%) of white solid. Recrystallization from acetonitrile provided an analytical sample: mp 169–170° (lit.[5] 171°); ir (KBr) 2235 and 2240 cm^{-1} (CN); nmr (acetone-d_6) τ 1.50 (s).

Anal. Calcd for $C_6H_2N_2S$: C, 53.71; H, 1.50; N, 20.89; S, 23.90. Found: C, 53.65; H, 1.43; N, 20.76; S, 24.09.

B. Thiophene-3,4-dicarboxylic Acid (9).—A stirred solution of 3,4-dicyanothiophene (27.6 g, 0.21 mol) and potassium hydroxide (76.2 g, 1.36 mol) in ethylene glycol (300 ml) was refluxed for 4 hr and then allowed to cool, forming a yellow precipitate. The mixture was poured into water. The resulting solution was washed with ether (200 ml) and the aqueous phase was cooled in an ice bath and acidified with excess hydrochloric acid (12 *M*). The white precipitate was filtered and taken up in ether. The aqueous filtrate was extracted three times with 500-ml portions of ether. The ethereal solutions were combined, dried ($MgSO_4$), and evaporated, leaving a faintly yellow solid which was recrystallized from water to give 28 g (79%) of white needles, mp 227–229 (lit.[12] 230–231°), ir (KBr) 1690 cm^{-1} (acid C=O).

C. Thiophene-3,4-dicarbonyl Chloride (10).—A stirred suspension of thiophene-3,4-dicarboxylic acid (8.6 g, 50 mmol) in thionyl chloride (20 ml) was maintained at reflux for 1 hr. The dark solution was allowed to cool and the excess thionyl chloride was removed under reduced pressure. The residue was treated with two 10-ml portions of dry benzene, followed by the evaporation of each portion. The tan solid was dried in vacuum for 1 hr, and used without further purification.

D. 4,9-Dihydronaphtho[2,3-*c*]thiophene-4,9-dione (2).—A solution of the acid chloride 10 obtained above in dry 1,2-dichloroethane (50 ml) was added dropwise to a stirred suspension of aluminum chloride (15.0 g, 0.11 mol) in dry 1,2-dichloroethane (50 ml) maintained at 4°. The mixture was allowed to stir at 4° for 10 min and a solution of dry benzene (4 g, 51 mmol) in 1,2-dichloroethane (25 ml) was slowly added. The yellow suspension was allowed to stir at room temperature for 18 hr and was then poured into ice and hydrochloric acid (50 ml, 2 *M*). Chloroform (300 ml) was added and the mixture was shaken vigorously. The layers were separated and the aqueous layer was extracted with chloroform. The combined organic portions were washed with saturated sodium bicarbonate solution and with water, then dried ($MgSO_4$) and concentrated to 200 ml. The chloroform solution was run onto a column of neutral alumina followed by an additional 1500 ml of chloroform. The yellow residue, which remained after the solvent was evaporated, was recrystallized from acetic acid to give 4.5 g (42%) of the cyclic dione. An analytical sample was obtained by means of repeated recrystallization from acetic acid: mp 277°; uv max (95% C_2H_5OH) 256 mμ (ε 43,900) and 327 (2420); ir (KBr) 1665 cm^{-1} (C=O); nmr (CF_3COOH) τ 1.55 (s, 2 H, C_1 and C_3 protons) 1.63–1.96 (m, 2 H, C_5 and C_8 protons), 2.03–2.33 (m, 2 H, C_6 and C_7 protons).

Anal. Calcd for $C_{12}H_6O_2S$: C, 67.28; H, 2.82; S, 14.96. Found: C, 67.39; H, 2.81; S, 15.05.

Synthesis of 4,8-Dihydrobenzo[1,2-*b*:5,4-*b'*]dithiophene-4,8-dione (3).—A suspension of 8-acetoxybenzo[1,2-*b*:5,4-*b'*]dithiophene[2b] (10.45 g, 0.043 mol) and chromium(VI) oxide (~0.1 g) in glacial acetic acid was heated to 80° with stirring. The remainder of the chromium(VI) oxide (11.05 g, 0.11 mol) was added portionwise over a 5-min period. The dark solution began to reflux vigorously. Reflux was maintained for 5 min after the addition was completed and then hydrochloric acid (12 *M*,

(9) D. W. H. MacDowell, A. T. Jeffries, and M. B. Meyers, *J. Org. Chem.*, **36**, 1416 (1971).

(10) All temperatures are uncorrected. All elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded on a Beckman IR-8 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian HA-60 high resolution spectrometer as approximately 10% (weight–volume) solutions in solvents as specified using tetramethylsilane as an internal standard (τ 10). The ultraviolet spectra were determined in 95% ethanol on a Bausch and Lomb Spectronic 505 spectrometer.

(11) M. Rajsner, J. Metysova, and M. Protiva, *Collect. Czech. Chem. Commun.*, **34**, 468 (1969).

(12) J. Sice, *J. Org. Chem.*, **19**, 70 (1954).

20 ml) was added and the mixture was boiled for another 5-min period. The dark solution was diluted with water (200 ml) and cooled to 0°. The resulting precipitate was filtered, washed with water, and taken up in chloroform. The organic solution was washed with saturated sodium bicarbonate solution and with water, then dried ($MgSO_4$) and concentrated to give a yellow-green solid. This impure material was dissolved in benzene and chromatographed on neutral alumina using benzene as the eluent. Following concentration of the benzene solution, a yellow solid was obtained and subsequently recrystallized from acetic acid to give 7.45 g (79%) of the quinone. An additional recrystallization from acetic acid provided an analytical sample: mp 235–237°; uv max (95% C_2H_5OH) 236 mμ (ε 18,800), 293 (15,400), 334 (5400); ir (KBr) 1640 cm^{-1} (C=O); nmr (CF_3COOH) τ 2.13 (d, 2 H, $J_{2,3}$ = 5 Hz, C_2 and C_6 protons), 2.36 (d, 2 H, $J_{2,3}$ = 5 Hz, C_3 and C_5 protons).

Anal. Calcd for $C_{10}H_4O_2S_2$: C, 54.53; H, 1.83; S, 29.12. Found: C, 54.68; H, 1.95; S, 29.27.

Synthesis of 4,8-Dihydrobenzo[1,2-*b*:4,5-*b'*]dithiophene-4,8-dione (4).—A small quantity of chromium(VI) oxide (0.1 g) was added to a stirred suspension of 4-acetoxybenzo[1,2-*b*:4,5-*b'*]dithiophene (12.4 g, 0.05 mol) in glacial acetic acid (200 ml). The mixture was heated to 80° and the remainder of the chromium(VI) oxide (13.8 g, 0.14 mol) was added portionwise over a 3-min period, thus causing a vigorous reflux. The dark green solution was maintained at reflux for 10 min and then hydrochloric acid (12 *M*, 25 ml) was cautiously added. Work-up as for **3** yielded a granular yellow solid. Recrystallization from acetic acid provided 5.9 g (54%) of the quinone. Recrystallization from acetic acid afforded an analytical sample: mp 259–260°; uv max (95% C_2H_5OH) 240 mμ (ε 15,300), 291 (13,280), 343 (4600); ir (KBr) 1640 cm^{-1} (C=O); nmr (CF_3COOH) τ 2.08 (d, 2 H, $J_{2,3}$ = 5 Hz, C_2 and C_6 protons), 2.28 (d, 2 H, $J_{2,3}$ = 5 Hz, C_3 and C_7 protons).

Anal. Calcd for $C_{10}H_4O_2S_2$: C, 54.53; H, 1.83; S, 29.12. Found: C, 54.75; H, 1.88; S, 28.99.

Synthesis of 4,8-Dihydrobenzo[1,2-*b*:4,5-*c'*]dithiophene-4,8-dione (5).—The acid chloride **10**, which is described above, was dissolved in dry 1,2-dichloroethane (75 ml) and the resulting solution was added dropwise to a stirred suspension of aluminum chloride (14.6 g, 0.11 mol) in 1,2-dichloroethane (50 ml) which was maintained at 4°. The mixture was allowed to stir at 4° for 10 min after the addition had been completed. A solution of thiophene (5 g, 60 mmol) in 1,2-dichloroethane (25 ml) was slowly added to the cold mixture. The ice bath was removed and stirring was continued for 18 hr. The reaction mixture was then poured into ice and 2 *M* hydrochloric acid and shaken vigorously. Extraction with chloroform gave a red-brown solid, which was dissolved in chloroform and chromatographed on neutral alumina using chloroform as the eluent to give a yellow solid. Recrystallization from acetic acid gave 4.1 g (37%) of yellow plates. An additional recrystallization from acetic acid provided an analytical sample: mp 296–297°; uv max (95% C_2H_5OH) 258 mμ (ε 34,400), 280 (10,240), 329 (3960); ir (KBr) 1640 cm^{-1} (C=O); nmr (CF_3COOH) τ 1.50 (s, 2 H, C_5 and C_7 protons), 2.05 (d, 1 H, $J_{2,3}$ = 5 Hz, C_2 proton), 2.23 (d, 1 H, $J_{2,3}$ = 5 Hz, C_3 proton).

Anal. Calcd for $C_{10}H_4O_2S_2$: C, 54.53; H, 1.83; S, 29.12. Found: C, 54.46; H, 1.78; S, 29.05.

A similar experiment, in which the thiophene solution was more rapidly added to the acid chloride–aluminum chloride mixture, resulted in the formation and subsequent isolation of a small quantity of 3,4-bis(2′-thenoyl)thiophene (**13**) from the mother liquor of **5**. Recrystallization from benzene–hexane provided an analytical sample: mp 143–144°; ir (KBr) 1635 cm^{-1} (ketone C=O); nmr (acetone-d_6) τ 1.79 (s, 2 H, C_2 and C_5 protons), 2.06 (m, 2 H, $J_{4,5}$ = 5 Hz, $J_{3,5}$ = 1.3 Hz, C_5' protons), 2.23 (m, 2 H, $J_{3,4}$ = 3.6 Hz, $J_{3,5}$ = 1.3 Hz, C_3' protons), 2.79 (m, 2 H, $J_{4,5}$ = 5 Hz, $J_{3,4}$ = 3.6 Hz, C_4' protons).

Anal. Calcd for $C_{14}H_8O_2S_3$: C, 55.24; H, 2.65; S, 31.60. Found: C, 55.38; H, 2.58; S, 31.35.

Synthesis of 4,8-Dihydrobenzo[1,2-*c*:4,5-*c'*]dithiophene-4,8-dione (6). A. 1,3-Dichloro-4,8-dihydrobenzo[1,2-*c*:4,5-*c'*]-dithiophene-4,8-dione (15).—A solution of the acid chloride **10**, prepared as previously described from thiophene-3,4-dicarboxylic acid (20.6 g, 0.125 mol) and thionyl chloride (30 ml), in dry 1,2-dichloroethane (75 ml) was added dropwise to a stirred suspension of aluminum chloride (34 g, 26 mmol) in dry 1,2-dichloroethane (200 ml), which was maintained at 4°. The mixture was allowed to stir at 4° for 10 min and then a solution of 2,5-dichlorothiophene (19.0 g, 0.125 mol) in 1,2-dichloroethane (50 ml) was slowly added. The reaction mixture was stirred at room temperature for 18 hr and then poured into ice and 2 *M* hydrochloric acid (200 ml). Chloroform (300 ml) was added and the mixture was shaken vigorously. The layers were separated and the aqueous phase was extracted with chloroform (150 ml). The combined organic portions were washed with saturated sodium bicarbonate solution and with water, then dried ($MgSO_4$) and evaporated. The impure diketone was dissolved in a minimum amount of chloroform and run onto a column (25 × 6 cm) of neutral alumina. Elution with chloroform provided an initial dark red fraction which was discarded, followed by a slightly yellow fraction, which contained 17.25 g (50%) of the diketone. Repeated recrystallization from chloroform–carbon tetrachloride afforded an analytical sample: mp 208–209°; uv max (95% C_2H_5OH) 261 mμ (ε 52,100) and 327 (ε 2840); ir (KBr) 1670 cm^{-1} (C=O); nmr (CF_3COOH) τ 1.39 (s).

Anal. Calcd for $C_{10}H_2Cl_2O_2S_2$: C, 41.53; H, 0.70; S, 22.18; Cl, 24.52. Found: C, 41.35; H, 0.71; S, 21.95; Cl, 24.62.

B. 4,8-Dihydrobenzo[1,2-*c*:4,5-*c'*]dithiophene-4,8-dione (6).—A stirred suspension of 1,3-dichloro-4,8-dihydrobenzo[1,2-c:4,5-c′]dithiophene-4,8-dione (**12**) (3.2 g, 11 mmol) and copper powder (2.55 g, 0.04 g-atom) in propionic acid (100 ml) was maintained at reflux for 60 hr.[6] The hot solution was quickly filtered and allowed to cool. The crude product was filtered, washed with water, and recrystallized from propionic acid to give 1.75 g (72%) of yellow-orange plates. An additional recrystallization from chloroform provided an analytical sample: mp 340°; uv max (C_2H_5OH) 259 mμ (ε 61,800); ir (KBr) 1655 cm^{-1} (ketone C=O); nmr (CF_3COOH) τ 1.38 (s).

Anal. Calcd for $C_{10}H_4O_2S_2$: C, 54.53; H, 1.83; S, 29.12. Found: C, 54.71; H, 1.73; S, 28.97.

Reduction of 4,9-Dihydronaphtho[2,3-*b*]thiophene-4,9-dione (1).—A solution of aluminum chloride (10.0 g, 75 mmol) in absolute ether (50 ml) was added to a stirred suspension of lithium hydride (2.84 g, 75 mmol) in absolute ether (30 ml). The mixture was stirred for 15 min and then 4,9-dihydronaphtho[2,3-*b*]-thiophene-4,9-dione (4.0 g, 18.7 mmol) was added portionwise by means of Gooch tubing. The gray ethereal suspension was maintained at reflux for 2 hr. Ethyl acetate (30 ml) was added dropwise in order to decompose the excess hydride reagent. The reaction mixture was poured into ice and 2 *M* hydrochloric acid. The layers were separated and the aqueous phase was extracted with 50 ml of ether. The combined ethereal solution was washed with saturated sodium bicarbonate solution and with water, then dried ($MgSO_4$) and concentrated. The dark, gummy solid was dissolved in hot benzene and chromatographed on neutral silica gel. Elution with benzene–hexane (1:1) followed by concentration provided 2.3 g of white, solid material. The white solid was chromatographically separated on neutral alumina using hexane as the eluent. Two fractions were obtained: 4,9-dihydronaphtho[2,3-*b*]thiophene (0.84 g, 25%) [mp 105.5–106.5° (lit.[13] 104–105°); nmr ($CDCl_3$) τ 2.81 (s, 4 H, benzene), 2.88 (d, 1 H, $J_{2,3}$ = 5 Hz, C_2 proton), 3.10 (s, 1 H, $J_{2,3}$ = 5 Hz, C_3 proton), 5.78–6.17 (m, 4 H, $-CH_2-$)], followed by 1.36 g (40%) of naphtho[2,3-*b*]-thiophene [mp 192.5–194° (lit.[14] 192–193°); uv max (95% C_2H_5OH) 230 mμ (ε 32,600), 251 (57,400), 256 (57,700), 315 (3690), 327 (4910), 335 (5400), 351 (6440); nmr (CCl_4) τ 1.68 (s, 1 H, C_9 proton), 1.76 (s, 1 H, C_4 proton), 2.00–2.28 (m, 2 H, C_5 and C_8 protons), 2.45–2.73 (m, 4 H, C_2, C_3, C_6, and C_7 protons)].

Reduction of 4,9-Dihydronaphtho[2,3-*c*]thiophene-4,9-dione (2).—A solution of aluminum chloride (5.0 g, 37 mmol) in absolute ether (50 ml) was added to a stirred suspension of lithium aluminum hydride (1.42 g, 37 mmol) in absolute ether (50 ml). The mixture was stirred for 10 min and 4,9-dihydronaphtho-[2,3-*c*]thiophene-4,9-dione (2.0 g, 9.3 mmol) was added portionwise by means of a Gooch tube. The gray ethereal suspension was maintained at reflux for 2 hr. Ethyl acetate (20 ml) was dropwise added in order to decompose the excess reagent. Work-up was carried out as described in the reduction of **1**. The sticky yellow solid thus obtained was dissolved in hot hexane and chromatographed on neutral alumina. Hexane was employed as the eluent. Evaporation of the solvent left 1.3 g (75%) of 4,9-dihydronaphtho[2,3-*c*]thiophene as a white solid. Two recrystallizations from ethanol–water afforded an analytical

(13) W. Carruthers, *J. Chem. Soc.*, 4477 (1963).

(14) W. Carruthers, A. G. Douglas, and J. Hill, *ibid.*, 704 (1962).

sample: mp 74.5–75.5°; nmr (CCl_4) τ 2.92 (s, 4 H, benzene), 3.12 (s, 2 H, thiophene), 6.11 (s, 4 H, $-CH_2$).

Anal. Calcd for $C_{12}H_{10}S$: C, 77.37; H, 5.41; S, 17.22. Found: C, 77.53; H, 5.24; S, 17.35.

Reduction of 4,8-Dihydrobenzo[1,2-*b*:5,4-*b'*]dithiophene-4,8-dione (3).—A solution of aluminum chloride (10.0 g, 75 mmol) in absolute ether (50 ml) was added to a stirred suspension of lithium aluminum hydride (2.84 g, 75 mmol) in absolute ether (100 ml). The mixture was stirred for 5 min and then 4,8-dihydrobenzo-[1,2-*b*:5,4-*b'*]dithiophene-4,8-dione (4.0 g, 18.2 mmol) was added portionwise by means of Gooch tubing. The gray ethereal suspension was maintained at reflux for 2 hr, during which time all the quinone dissolved, forming a slightly green ethereal solution. Ethyl acetate (30 ml) was added dropwise in order to decompose the excess hydride reagent. The reaction mixture was poured into ice and 3 *M* sulfuric acid. The layers were separated and the aqueous phase was extracted with three 200-ml portions of ether. The combined ethereal solution was washed with saturated sodium bicarbonate solution and with water, then dried ($MgSO_4$) and allowed to stand for 18 hr. The solvent was removed to give 3.4 g (85% recovery) of starting quinone, identical melting point and mixture melting point with those of authentic material.

Reduction of 4,8-Dihydrobenzo[1,2-*b*:4,5-*b'*]dithiophene-4,8-dione (4).—A solution of aluminum chloride (5.0 g, 38 mmol) in absolute ether (100 ml) was added to a stirred suspension of lithium aluminum hydride (1.41 g, 38 mmol) in absolute ether (50 ml). The mixture was stirred for 5 min and the 4,8-dihydrobenzo[1,2-*b*:4,5-*b'*]dithiophene-4,8-dione (2.0 g, 9.1 mmol) was added portionwise by means of Gooch tubing. The gray ethereal suspension was maintained at reflux for 18 hr. A yellow-green ethereal solution resulted after all the quinone had dissolved. The excess hydride was decomposed by dropwise addition of ethyl acetate (35 ml). Work-up was achieved as described in the reduction of **3**. The solvent was removed to give 1.8 g (90% recovery) of the starting quinone, identical melting point and mixture melting point with those of authentic material.

Reduction of 4,8-Dihydrobenzo[1,2-*b*:4,5-*c'*]dithiophene-4,8-dione (5).—A solution of aluminum chloride (10.0 g, 75 mmol) in absolute ether (55 ml) was briskly run into a stirred suspension of lithium aluminum hydride (2.83 g, 75 mmol) in absolute ether (140 ml). Stirring was continued for 5 min and then 4,8-dihydrobenzo[1,2-*b*:4,5-*c'*]dithiophene-4,8-dione (4 g, 18 mmol) was added portionwise by means of Gooch tubing. The reaction mixture was maintained at reflux for 18 hr and then cooled. Ethyl acetate (50 ml) was added dropwise in order to decompose the excess reagent. Work-up was carried out as described in the reduction of **1**. The yellow, gummy solid thus obtained was washed six times with hot hexane (50 ml). The hexane fractions were combined, concentrated to 50 ml, and run onto a chromatography column which was packed with neutral alumina. Elution with hexane (500 ml) followed by evaporation of the solvent provided 1.1 g (32%) of 4,8-dihydrobenzo[1,2-*b*:4,5-*c'*]dithiophene as white flakes. Sublimation at 70° (0.1 mm) followed by several recrystallizations from pentane afforded an analytical sample: mp 106–107°; nmr (CCl_4) τ 3.0 (d, 1 H, $J_{2,3}$ = 5 Hz, C_2 proton), 3.12 (s, 2 H, C_5 and C_7 protons), 3.28 (d, 1 H, $J_{2,3}$ = 5 Hz, C_3 proton), 5.92–6.25 (m, 4 H, $-CH_2-$).

Anal. Calcd for $C_{10}H_8S_2$: C, 62.46; H, 4.19; S, 33.35. Found: C, 62.38; H, 4.16; S, 33.16.

Reduction of 1,3-Dichloro-4,8-dihydrobenzo[1,2-*c*:4,5-*c'*]dithiophene-4,8-dione (15).—A solution of aluminum chloride (18.5 g, 139 mmol) in absolute ether (75 ml) was briskly run into a stirred suspension of lithium aluminum hydride (5.30 g, 139 mmol) in absolute ether (50 ml). The reducing mixture was stirred for 10 min and then 1,3-dichloro-4,8-dihydrobenzo[1,2-c:4,5-*c'*]dithiophene-4,8-dione (10.0 g, 34.6 mmol) was added portionwise by means of Gooch tubing. The gray suspension was maintained at reflux for 2 hr. Sulfuric acid (3 *M*) was added dropwise in order to decompose the excess reagent. Work-up was carried out as described in the reduction of **1**. The impure product thus obtained was dissolved in hexane and chromatographed on neutral alumina. Hexane served as the eluent. Evaporation of the solvent left a white, crystalline solid, which was recrystallized from pentane to give 6.4 g (71%) of 1,3-dichloro-4,8-dihydrobenzo[1,2-*c*:4,5-*c'*]dithiophene (**25**) as white needles. An additional recrystallization from pentane provided an analytical sample: mp 100–101°; nmr (CCl_4) τ 3.02 (s, 2 H, thiophene), 6.24 (s, 4 H, $-CH_2-$).

Anal. Calcd for $C_{10}H_6Cl_2S_2$: C, 45.98; H, 2.32; Cl, 27.15; S, 24.55. Found: C, 46.05; H, 2.34; Cl, 26.99; S, 24.77.

4,8-Dihydrobenzo[1,2-*c*:4,5-*c'*]dithiophene (26).—A stirred suspension of 1,3-dichloro-4,8-dihydrobenzo[1,2-*c*:4,5-*c'*]dithiophene (**25**) (4.47 g, 17 mmol), *tert*-butyl alcohol (4 g, 54 mmol), and finely chopped lithium ribbon (0.7 g, 0.1 g-atom) was maintained at reflux under nitrogen for 2 hr. The mixture was allowed to cool and 95% ethanol was cautiously added in order to destroy the excess lithium metal. Water (100 ml) and ether (100 ml) were added and the mixture was shaken vigorously. The layers were separated and the aqueous phase was extracted with two 50-ml portions of ether. The combined ethereal solution was washed twice with water and dried ($MgSO_4$). The solution was evaporated and the residue was dissolved in hot hexane and chromatographed on neutral alumina using hexane as the eluent. The resulting solution was concentrated to 50 ml and allowed to cool. The white solid (1.75 g, 53%) thus obtained was recrystallized from hexane as long white needles: mp 143–144°; nmr (CCl_4) τ 3.12 (s, 4 H, thiophene), 6.12 (s, 4 H, $-CH_2-$).

Anal. Calcd for $C_{10}H_8S_2$: C, 62.46; H, 4.19; S, 33.35. Found: C, 62.55; H, 4.26; S, 33.55.

Registry No.—**1**, 4968-81-4; **2**, 33527-20-7; **3**, 33527-21-8; **4**, 32281-36-0; **5**, 33527-22-9; **6**, 33527-23-0; **8**, 18853-32-2; **9**, 4282-29-5; **10**, 33527-26-3; **13**, 33527-27-4; **15**, 33527-28-5; **25**, 33527-29-6; **26**, 33527-30-9; 4,9-dihydronaphtho[2,3-*b*]thiophene, 33608-30-9; naptho[2,3-*b*]thiophene, 269-77-9; 4,9-dihydronaphtho[2,3-*c*]thiophene, 33608-31-0; 4,8-dihydrobenzo[1,2-*b*:4,5-*c'*]dithiophene, 33527-31-0.

Acknowledgment.—The authors wish to thank Mr. Robert Smith for recording some of the nmr spectra reported in this paper.

Thiabenzenes. IX. The Rearrangement of 1-(*p*-Dimethylaminophenyl)-2,4,6-triphenylthiabenzene to Isomeric Thiopyrans

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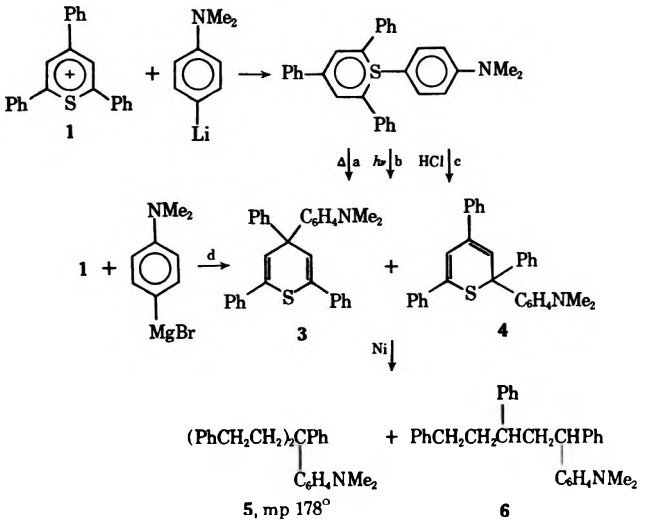
While 1-(*p*-dimethylaminophenyl)-2,4,6-triphenylthiabenzene (2) is much more stable than the analog without the *p*-dimethylamino group, it has been shown to produce a mixture of two isomeric thiopyrans, **3** and **4**, by heat, by light, or by acid. The same mixture of thiopyrans is produced directly by the reaction of 2,4,6-triphenylthiopyrylium ion with *p*-dimethylaminophenylmagnesium bromide. The mixed thiopyrans, **3** and **4**, were desulfurized by Raney nickel to a mixture of two amines, **5** and **6**, from which pure **5** was obtained.

An earlier report[2] of the synthesis of *p*-dimethylaminophenylthiabenzene (2) disclosed that this compound was crystalline, and, although its intense purple color slowly disappeared, 2 was much more stable than the analog without the *p*-dimethylamino group. It has now been possible to identify the main product from the decomposition of 2 in boiling benzene, on exposure to light at room temperature, or on treatment with ethereal hydrogen chloride as an amorphous mixture of the isomeric thiopyrans **3** and **4** (see Chart I).

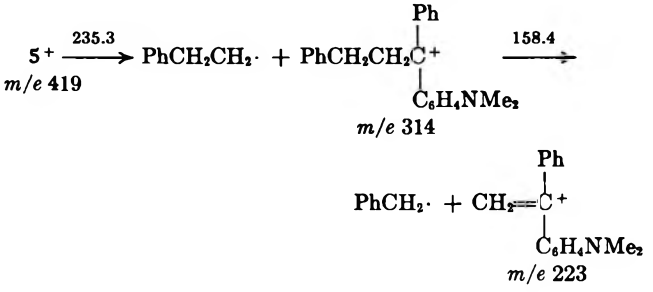
CHART I



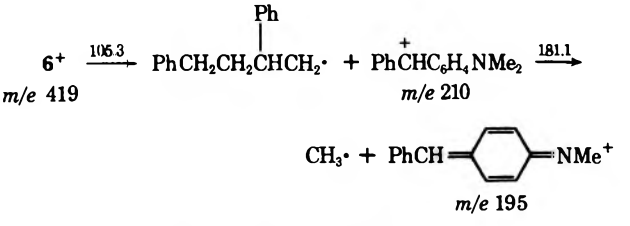
Because of the instability of the 1-phenyl analog of 2 with respect to rearrangement to the isomeric thiopyrans, it was never possible to be certain whether the isolation of the thiopyrans (rather than the thiabenzene) on treatment of **1** with phenyl Grignard reagents indeed may have proceeded through the thiabenzenes.[3] In view of the much greater stability of 2, we have investigated the reaction of **1** with *p*-dimethylaminophenylmagnesium bromide. This produced as the major product the orange-yellow mixture of thiopyrans, but again with temporary purple color indicating that at least some 2 may have been formed.

A conceivable alternate structure to the thiopyrans **3** and **4** for the rearrangement product, 1,3,5-triphenyl-*x*-(*p*-dimethylaminophenylmercapto)cyclopentadiene, was eliminated as the major component of the rearrangement mixture by the isolation of a good yield (1.8 g) of sulfur-free oily solid from Raney nickel desulfurization of 2 g of **3** + **4**. Only 18 mg of acid-soluble unidentified product was obtained; the cyclopentadiene isomer should have given over 500 mg of dimethylaniline in the acid extract. From the 1.8 g of oily solid, tlc gave 680 mg of a mixture of **5** and **6**. Recrystallization of this mixture gave pure crystalline **5**, mp 176–178°. The nmr, mass, ir, and uv spectra were in accord with the assigned structures. The methyl and methylene peaks in the nmr spectrum for the mixture of **5** and **6** indicated the ratio of the isomers to be about 3:1.

The mass spectra of **5** and of the mixture of **5** and **6** revealed metastable peaks, two of which (*m/e* 235.3 and 105.3, corresponding to $314^2/419$ and $210^2/419$, respectively) particularly support the structure assignments. The former is present in both and presumably arises from the parent molecular ion **5** by loss of a phenethyl group to give the carbenium ion (*m/e* 314), resonance stabilized by the amino group.



The second is present only from the mixture and corresponds to the loss of the alkyl group from the molecular ion **6** which leaves a similarly stabilized



carbenium ion (*m/e* 210). Both these primary metastable peaks are confirmed by the further fragmentations indicated (*m/e* 158.4 and 181.1, respectively).

The mixtures of **3** and **4** obtained by all four processes (a, b, c, and d) were amorphous (by X-ray) orange solids softening near 100°. They were purified by chromatography on alumina, but all efforts to separate them by crystallization or through their hydrochloride or picrate salts were unsuccessful in our hands. The

(1) Abstracted from the doctoral dissertation of Hooshang Pirelahi, 1971; supported in part by the National Science Foundation Grant No. GP-16236 and a grant from the Gulf Oil Company.

(2) C. C. Price, J. Follweiler, H. Pirelahi, and M. Siskin, *J. Org. Chem.*, **36**, 791 (1971).

(3) See, *e.g.*, G. Suld and C. C. Price, *J. Amer. Chem. Soc.*, **84**, 2090 (1962).

TABLE I

CHANGES IN ULTRAVIOLET SPECTRUM FOR 2 (2.4×10^{-5} *M*) IN CYCLOHEXANE ON EXPOSURE TO DAYLIGHT (UNDER N_2)

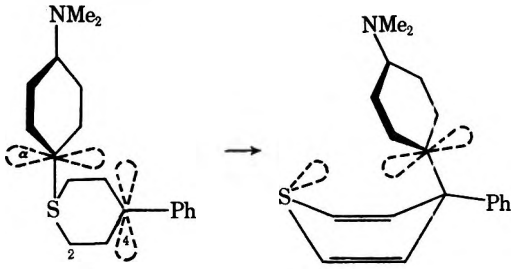
Time	λ_{max}	*A*[a]	λ_{max}	*A*	λ_{max}	*A*	λ_{max}	*A*	λ_{max}	*A*
0	534	0.270	357	0.322	311	0.630	271	0.600	231	0.490
10 min	534	0.261	357	0.318	311	0.620	271	0.637	231	0.479
1 hr	534	0.187	357	0.252	311	0.525	271	0.729		
3 hr	534	0.053	355[b]	0.131	310[b]	0.325	271	0.799		
5 hr	534	0.017	355[b]	0.120	310[b]	0.273	271	0.802		
7 hr	534	0.003	355[b]	0.098	310[b]	0.260	272	0.788		
9 hr					310[b]	0.254	272	0.753		
50 hr					310[b]	0.253	272	0.709	250[b]	0.570
7 days			350[b]	0.160			272	0.682	250[b]	0.590
14 days			350[b]	0.160	298[b]	0.350	272	0.673	250[b]	0.620

[a] Absorbance. [b] Point of inflection or shoulder.

infrared spectra in KBr for all four were clean and sharp and virtually identical. There were also no significant differences observed for the nmr or uv spectra.

The yields of the mixed thiopyrans from rearrangement were about 30% after chromatography. Examination of the changes in ultraviolet spectra during a photochemical rearrangement (Table I) reveals complete and rapid loss of the 534-nm band characteristic of 2 and intensification of absorbance at 272 nm. This latter band, corresponding to the λ_{max} at 275 nm for the mixture of **3** and **4**, subsequently decreases in intensity while a new absorbance at 250 nm develops, an absorbance not shown by the isolated mixture of **3** and **4**. The data in Table I thus suggest that, at least for the photochemical rearrangement, the low yield of the thiopyrans is due to formation of by-products, apparently by further reaction of the thiopyrans. This view is supported by the fact that route d gave a 70% yield of the **3** and **4** mixture, since, in this case, isolation was effected without exposure to "rearrangement" conditions.

Some comment on the ultraviolet spectra of the thiopyran mixtures is in order. We[3] have earlier reported that 4-methyl-2,4,6-triphenylthiopyran showed a single λ_{max} at 235 nm (log ϵ 4.45) while the 2-methyl isomer showed λ_{max} at 257 nm (log ϵ 4.32) and 347 (3.75). The mixtures of **3** and **4** showed λ_{max} 275 nm (log ϵ 4.45) and 395 (3.1–3.8). Presumably this red shift is due to "homoconjugation" effects of sulfur with the dimethylamino group. This would be normally expected in **4**, where sulfur–carbon homoconjugation over a single intervening saturated carbon is involved. It is somewhat less expected in **3**. However, the transition geometry for rearrangement of an aryl group from the sulfur in **2** to the 4 carbon in **3** would indicate that such orbital overlap may be possible.



2 **3**

The remarkable similarity between the mass spectra of **2** and of **3** + **4** (see Table II), and especially the *m/e* 152 peak, earlier[2] shown to be due to dimethylaminophenylmercapto cation, also suggests easy bonding of the *p*-dimethylaminophenyl group and sulfur in **3** (and **4**). The homoconjugation in **3** would be envisaged as electron donation from the electron-rich p orbital (in **3**) to a vacant 3d orbital on sulfur. The rearrangement would be envisaged as electron donation from the electron-rich p orbital on carbon 4 of the thiazbenzene ring **2** to the p orbital on the α carbon of the *S*-aryl ring. Enhanced electron density at carbon 4 (and carbon 2) would arise from ylide contributions to the thiabenzene ring structure. The rearrangement would then be enhanced by low electron density at the α carbon, offering an explanation for the marked differences in rate of rearrangement of the *S*-aryl group, depending on the para substituent: $Me_2N \ll CH_3 < H \ll Me_2NH^+$. The somewhat greater stability produced by a *p*-methyl group has been reported earlier.[2] The marked decrease in stability produced by a *p*-dimethylammonio group is inferred from the extremely rapid rearrangement induced by HCl.

TABLE II

MAJOR MASS SPECTRAL PEAKS FOR 2, 3, AND 4

m/e	2[a]	3 + 4[b]
445	14	6
368	10	3
325	4	2
304	8	9
294	24	8
215	13	7
209	12	4
191	5	9
167	1	5
165	6	8
153	52	53
152	100	100
137	8	11
136	13	16
121	9	10
120	12	14
109	7	9
105	13	52
91	10	8
77	12	30

[a] 120°, 50 eV. [b] 90°, 70 eV.

Experimental Section

Rearrangement of 2. A. Thermal.—A solution of 1.0 g (2.25 mol) of **2** in 120 ml of degassed benzene was refluxed overnight with stirring in an atmosphere of nitrogen. The color of

the solution remained purple for 1.5 hr. Benzene was then removed from the resulting orange-brown solution under reduced pressure and the residue was placed on a 250 × 32 mm column of Merck 71707 alumina in benzene. Developing the column with benzene resulted in a diffuse orange band which began to come off the column at 30% ether–70% benzene. The orange solution was collected through to 100% ether. Removal of solvent and triturating with petroleum ether (bp 30–60°) yielded 600 mg of dark orange solid which, after several recrystallizations from ethanol under nitrogen, furnished 375 mg (37.5% yield) of orange solid melting at 94–102°.

B. By Light.—A solution of 500 mg (1.12 mmol) of **2** in 800 ml of dry ether was left standing at room temperature with exposure to daylight in an atmosphere of nitrogen for 2 weeks. After this period, the purple color, which had been retained for 7 days, turned to orange. (In a parallel experiment in the dark, no visible change in purple color was observed after 5 weeks.) Removal of the solvent under reduced pressure and recrystallization from ethanol under nitrogen gave 192 mg (38.4% yield) of orange solid melting at 95–106°. Further treatments in ethanol or other common organic solvents failed to narrow the melting range.

C. By Acid.—To a purple solution of 2.910 g (6.5 mmol) of **2** in 100 ml of benzene and 200 ml of dry ether was added 116.5 ml of a 0.17 *N* ethereal solution of hydrogen chloride (19.8 mmol, 3 equiv) at 0° under nitrogen. A yellow solid precipitated immediately. (In another experiment, it was observed that this precipitate was soluble in the presence of excess hydrogen chloride gas.) The yellow suspension was stirred for 0.5 hr and then treated with 200 ml of 5% aqueous sodium hydroxide solution under nitrogen. The color of the organic layer changed from yellow to orange. After about 1 hr of stirring, the resulting orange ethereal solution was thoroughly washed with water and dried over anhydrous sodium sulfate overnight. Evaporation of the solvent under reduced pressure gave an orange solid (2.75 g). The solid was subjected to column chromatography on alumina, as had been the product of thermal rearrangement, and recrystallized from ethanol under nitrogen. The resulting orange solid weighed 720 mg (24.7% yield) and melted at 90–95°.

In a similar experiment, adding 0.105 *N* acetic acid in ether gave no change in spectrum, even with 55 equiv of excess acid.

Reaction of 1 with *p*-Dimethylaminophenylmagnesium Bromide (D).—To a yellow suspension of 6.36 g (0.015 mol) of **1** in 120 ml of dry ether, 80 ml (0.0672 mol) of 0.84 *M* *p*-(dimethylamino)phenylmagnesium bromide[4] (4.48 equiv) in THF was added at room temperature, under a nitrogen atmosphere over a 5-min period. An immediate reaction was indicated by formation of the characteristic purple color. The reaction mixture was stirred for 30 min and then placed in an ice–water bath. The reaction was quenched after 15 min with 100 ml of cold saturated ammonium chloride solution. The color changed from purple to wine red. Removal of the ice–water bath and stirring the reaction mixture for an additional 1 hr changed the color to orange-red, and stirring overnight changed the latter color to orange. The orange organic layer was washed, dried, and evaporated. The orange-brown residue was held for 48 hr at 0.01 mm, and 5.250 g of *N*,*N*-dimethylaniline was distilled over into the cold trap. The remaining glassy orange-brown solid was dissolved in 40 ml of ether, filtered from a few milligrams of greenish-yellow solid, cooled in an ice–water bath, and added dropwise to 500 ml of cold (0°) petroleum ether. The orange-yellow precipitate (5.2 g), mp 98–104°, was chromatographed over alumina as before to give 4.720 g (70.7% yield) of orange solid. Recrystallizations from ethanol under nitrogen afforded an orange solid which melted at 108–115°.

Anal. Calcd for $C_{31}H_{27}NS$: C, 83.59; H, 6.07; N, 3.15; S, 7.19. Found: (A) C, 83.43; H, 6.10; N, 3.11; S, 7.13; (B) C, 83.67; H, 6.15; N, 3.08; S, 7.12; (C) C, 83.37; H, 6.25; N, 2.90; S, 7.31; (D) C, 83.44; H, 6.04; N, 3.13; S, 7.05.

The ultraviolet spectra of the mixtures of **3** and **4** were run in 1–1.5 mg/100 ml EtOH showing λ_{max}, nm (log ϵ), as follows: (A), 275 (4.45), 395 (3.40); (B) 275 (4.43), 395 (3.58); (C) 275 (4.45), 395 (3.12); (D) 275 (4.46), 385 (3.79). The varying intensities of the longer wavelength absorbance presumably reflect the amount of isomer **4** in the mixture.

The infrared spectra (KBr) showed the following major bands, cm^{-1} (per cent absorbance): 700 (80), 760 (70), 815 (50), 950 (30), 1030 (40), 1195 (50), 1350 (55), 1440 (65), 1490 (60), 1500 (70), 1595 (80). All bands were sharp and essentially identical for all four samples.

Table III

Major Mass Spectral Peaks for **5** and the Mixture of **5** and **6**

m/e	**5**[a]	**5** + **6**[b]
419	31	50
314	100	82
223	69	62
210	63	100
194	6	18
165	8	23
121	7	23
105	6	12
91	33	59

[a] Broad peaks from metastable ions at *m/e* 235.3, 221, and 158.4. [b] Metastable ion peaks as for **5** plus *m/e* 181.1, 164, 131.2, and 105.3.

The nmr spectra (CCl_4) showed a slightly broadened singlet at δ 2.75 (6 H) and broad multiplets at δ 6–6.7 (4 H) and 6.77–7.77 (17 H). The multiplet at 6–6.7 (4 H), corresponds to the two vinylic protons on the thiopyran ring and the two aromatic hydrogens ortho to the dimethylamino group.

The mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6D spectrometer. Typical data are summarized in Table II. Detailed data are recorded.[1] The observed ratio of parent peak (P_{446} = 100) to P + 1 = 35.4 to P + 2 = 10.4 is very close to the calculated ratio from isotope abundances (100:35.1:10.4).

Reductive Desulfurization of the Isomeric Mixture of 3 and 4.—Raney nickel W-2 catalyst[5] (30 g) in ethanol was added to a solution of 2 g (4.5 mmol) of the isomeric mixture (A), in a small amount of benzene and 200 ml of ethanol. The mixture was refluxed with stirring for 6 hr. After cooling and removal of the catalyst by filtration, 100 ml of benzene was added to the filtrate and the solution was washed with water. The benzene layer was then extracted four times with a dilute solution of hydrochloric acid. The acid layer was made alkaline with a concentrated solution of sodium hydroxide and extracted several times with small portions of ether. The ether extract was washed with water and dried over anhydrous potassium carbonate. Evaporation of the ether solution under reduced pressure at room temperature gave only 18 mg of a light brown liquid whose thin layer chromatography on silica gel with trichloroethylene showed a mixture of unidentified components (R_f 0.84, 0.44, 0.15, 0.04, 0.00).

The benzene layer was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure furnished 1.80 g of a light yellow, oily solid which gave a negative test for sulfur after sodium fusion. The residue was subjected to preparative thin layer chromatography on silica gel with trichloroethylene and methylene chloride (30:70) as the solvent. Five 20 × 20 cm plates, with fluorescent indicator and a layer thickness of 2 mm, were used. Spots with R_f 0.86, 0.46, 0.17, 0.06, and 0.00 were identified under ultraviolet light. The major spot (R_f 0.46) was removed and extracted several times with small portions of methylene chloride. Removal of the solvent gave 680 mg of a yellow-white semisolid.

Anal. Found (semisolid): C, 86.24; H, 7.80; N, 2.83.

Recrystallization from *n*-hexane afforded a white, crystalline solid which melted at 176–178°.

Anal. Calcd for $C_{31}H_{33}N$: C, 88.78; H, 7.88; N, 3.34. Found (mp 178°): C, 88.62; H, 7.93; N, 3.10.

Attempts to separate the other isomer from the mother liquor by crystallization and thin layer chromatography on alumina or silica gel were unsuccessful.

The ultraviolet spectrum of the semisolid mixture (1.5 mg/100 ml EtOH) showed λ_{max} 258 and 300 nm, while the solid with mp 178° showed λ_{max} (log ϵ) 258 (4.27) and 300 (3.57). The infrared spectrum (KBr) of **5** showed the following major bands,

(4) T. C. Owen, *J. Chem. Soc.*, 465 (1961).

(5) R. Mozingo, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 181.

cm^{-1} (per cent absorbance): 700 (90), 755 (65), 810 (50), 1350 (50), 1450 (55), 1490 (60), 1520 (80), 1615 (65).

The nmr spectrum ($CDCl_3$) for the solid with mp 178° (**5**) showed a broadened singlet at δ 2.37 (8 H), a singlet at 2.90 (6 H), a doublet at 6.67 and 6.58 (2 H), and a multiplet at 7–7.4 (17 H). The doublet at δ 6.67 and 6.58 corresponds to the two aromatic hydrogens ortho to the dimethylamino group. The semisolid shows two broad bands at δ 0.90–1.05 (~2 H), and 1.25–1.40 (~2 H), which may be due to solvent impurities, as well as an extra methyl singlet at δ 2.83 and methylene absorbance at δ 2.25. Assuming that these latter are due to **6**, the ratio of **5** to **6** is about 3:1.

The mass spectral data are summarized in Table III. The observed ratio of parent peak (P_{419} = 100) to P + 1 = 34.3 and P + 2 = 5.6 is in good agreement with the ratios calculated from isotope abundances of 100:34.4:5.7.

Registry No.—**2**, 28278-49-1; **3**, 34347-83-6; **4**, 34347-84-7; **5**, 34347-85-8; **6**, 34347-86-9.

The Reactions of Dimethyl Diazomalonate with Divalent Sulfides

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Biscarbomethoxycarbene, generated photochemically from dimethyl diazomalonate, reacts with alkyl and aryl sulfides to form stable sulfonium biscarbomethoxymethylides. The reaction of the carbene with alkyl disulfides forms alkylthiomalonate as the major product instead of the sulfonium ylides. The triplet carbene, generated from benzophenone-photosensitized decomposition of the diazomalonate, also reacts with dimethyl sulfide to produce the sulfonium ylide. This ylide formation is considered to involve the fast intersystem crossing from the triplet to the singlet carbene in the presence of dimethyl sulfide. Copper salt catalyzed thermal decomposition of diazomalonate in alkyl or aryl sulfides produces sulfonium ylides in high yields.

Photochemically induced reactions of diazo compounds with various types of compounds containing heteroatoms have been studied extensively.[1-4] Most of these reactions have been proposed to proceed through ylide formation by reactions of carbenes derived from diazo compounds and this has been supported by the recent synthesis of sulfonium ylides by the reaction of highly electrophilic carbenes with alkyl sulfides.[5-7]

Previously, we reported in preliminary form that the photolysis and copper salt catalyzed thermal decomposition of dimethyl diazomalonate in neat dimethyl sulfide gave dimethylsulfonium biscarbomethoxymethylide, and we showed that the reaction may be useful for synthesis of such stable sulfonium ylides.[6,7]

This paper deals with the details of the reaction and some properties of the ylides thus prepared.

$$N_2CR_2 \xrightarrow{h\nu} :CR_2 \xrightarrow{R'SR'} R_2'\overset{+}{S}-\overset{-}{C}R_2$$

Several studies on the chemical behavior of triplet carbenes have documented that the most marked difference in the chemical nature between singlet and triplet carbenes is found in the stereochemistry of addition to olefins.[8-15]

Jones and coworkers have shown that direct photolysis of diazomalonate generates singlet biscarbomethoxycarbene, which adds to olefins in a stereospecific manner, while photosensitized decomposition generates the corresponding triplet carbene, which reacts with olefins to give nonstereospecific addition products.[16,17]

Now, it is not unreasonable to suppose that carbenes in the two different spin states may react in different ways with molecules containing heteroatoms; *i.e.*, the singlet carbene might react with such a molecule to afford ylide, whereas the triplet might not. From this viewpoint, the photosensitized reactions of diazomalonate in alkyl sulfides were also investigated.

Results and Discussions

Formation of Sulfonium and Sulfoxonium Ylides in the Reactions of Dimethyl Diazomalonate in Sulfides and Sulfoxides.—Photolysis of dimethyl diazomalonate in various alkyl and aryl sulfides was carried out in Pyrex tubes with a high pressure mercury lamp. The crystalline major products of the reactions were stable sulfonium ylides. Thus, the reaction of dimethyl diazomalonate with dimethyl sulfide gave in 88% yield dimethylsulfonium biscarbomethoxymethylide (**1**), ν_{CO} 1625 and 1675 cm^{-1}, δ ($CDCl_3$) 3.71 (s, -COOMe) and 2.89 (s, $-SCH_3$). The proton shift of the SCH_3 and the carbonyl shift are analogous to those observed in other sulfonium ylides[18] and suggest that the ylide **1** is strongly resonance stabilized by partici-

$$1 \longleftrightarrow (CH_3)_2\overset{+}{S}C(CO_2CH_3)=\overset{O^-}{\overset{|}{C}}OCH_3 \longleftrightarrow (CH_3)_2S=C(CO_2CH_3)_2$$

(1) J. Hine, "Divalent Carbon," The Ronald Press Co., New York, N. Y., 1964, p 135.
(2) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, p 95.
(3) J. I. G. Cadogan and M. J. Perkins, "The Chemistry of Alkenes," Wiley-Interscience, New York, N. Y., 1964, p 585.
(4) G. L. Closs, "Topics in Stereochemistry," Vol. 3, Wiley-Interscience, New York, N. Y., 1968, p 193.
(5) J. Dickmann, *J. Org. Chem.*, **30**, 2272 (1965).
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TABLE I

THE FORMATION OF SULFONIUM YLIDES[a]

$$N_2C(COR)_2 + R^1SR^2 \longrightarrow R^1R^2\overset{+}{S}-\overset{-}{C}(COR)_2$$

Ylide	R	R^1	R^2	Mp, °C	Ir (C=O), cm^{-1}	Nmr, ppm[b]	Photolysis,[c] %	Thermal reaction,[d]
1	OCH_3	CH_2	CH_2	169–170	1625, 1675	2.89 ($-SCH_3$)	88	75
2	OCH_3	C_2H_5	C_2H_5	150–151	1620, 1655	2.95, 1.30 ($-CH_2-$, $-CH_3$)	57	71
3	OCH_3	*i*-C_3H_7	*i*-C_3H_7	121–122	1625, 1685	4.14, 1.40 [$-CH-$, $-C(CH_3)_2$]	20	
4	OCH_3	CH_3	C_2H_5	144–145	1625, 1677	2.84 ($-SCH_3$)	40	48
5	OCH_3	CH_3	*n*-C_4H_9	121–123	1620, 1675	2.86 ($-SCH_3$)	56	50
6	OCH_3	CH_3	*tert*-C_4H_9	86–87	1620, 1640, 1672	2.90 ($-SCH_3$)	40	
7	OCH_3	C_2H_5	*n*-C_4H_9	93–94	1620, 1670	2.95 ($-SCH_2-$)	45	
8	OCH_3	CH_3	C_6H_5	126–127	1640, 1680	3.25 ($-SCH_3$)	40	83
9	OCH_3	CH_3	$CH_2C_6H_5$	157–159	1620, 1678, 1675	2.77 ($-SCH_3$)	39	56
10	OCH_3	C_6H_5	C_6H_5	127–128	1650, 1675	7.53 ($-SC_6H_5$)	12	85
11	OC_2H_5	CH_3	CH_3	134–135	1635, 1670	2.88 ($-SCH_3$)	87	
12	OC_2H_5	CH_3	*n*-C_4H_9	63–64	1620, 1672	2.87 ($-SCH_3$)	50	
13	OC_2H_5	CH_3	$CH_2C_6H_5$	128–129	1618, 1670	2.76 ($-SCH_3$)	15	
14	CH_3	CH_3	CH_3	166–167	1565, 1595	3.00 ($-SCH_3$)	52	
15	OCH_3	C_2H_5	$CH_2CO_2CH_3$	118–119	1620, 1673, 1745	3.10, 1.31[e] ($-SCH_2-$, $-CH_3$)	53	

[a] Satisfactory analytical data (±0.4% for C and H) were reported for all new compounds listed in the table: Ed. [b] Nmr signal of CO_2CH_3 generally appears in the range of 3.69 and 3.75 ppm, and $CO_2CH_2CH_3$ appears at 4.17 (q, OCH_2-) and 1.29 (t, $-CH_3$). [c] High pressure mercury lamp (3660 Å). [d] Copper sulfate catalyzed thermal reaction at 90°. [e] Nmr signals also appear at 3.66 (s, 3 H), 3.78 (s, 6 H), 3.95 (d, 1 H, J = 16.0 Hz), 4.68 ppm (d, 1 H, J = 16.0 Hz).

pation of sulfur d orbitals and two carbonyl groups. Similar types of reactions in a variety of monosulfides were applied to give sulfonium ylide in high yield (Table I). However, the yields of the ylides were not satisfactory in the reaction with aryl and high branched sulfides.

Thermal decomposition of diazomalonate in sulfides in the presence of copper sulfate or copper metal powder also gave the corresponding stable sulfonium ylides in high yields even in aryl sulfides.

Reactions of diazomalonate in sulfoxides were also studied. Irradiation of a solution of diazomalonate in sulfoxide carried out in a Pyrex vessel with a high pressure mercury lamp. The corresponding sulfoxonium biscarbomethoxymethylides, **16** and **17**, from dimethyl and diphenyl sulfoxides were obtained as pure colorless solids. Copper sulfate catalyzed thermal decomposition of diazomalonate also gave sulfoxonium ylides in better yields than did the photolysis. More sulfoxonium ylides from the thermal reaction of various diazo compounds with dimethyl sulfoxide were also reported recently.[19] Moreover, methyl oxomalonate could not be detected from the reaction mixture, and this suggests that the diazo compound interacts with the sulfur, not with oxygen.

$$[R_2\overset{+}{S}O\overset{-}{C}(CO_2CH_3)_2] \longrightarrow R_2S + O{=}C(CO_2CH_3)_2$$

$$N_2C(CO_2CH_3)_2 + RSR \longrightarrow O{=}\overset{R}{\underset{R}{S^+}}-\overset{-}{C}(CO_2CH_3)_2$$

	16, R = CH_3	17, R = Ph
hν	34%	12%
Thermal	42%	26%

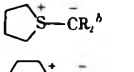
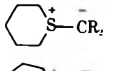
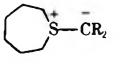
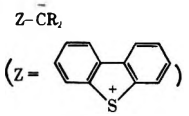
(19) F. Dost and J. G. Gosseleck, *Tetrahedron Lett.*, 509 (1970).

The formation of sulfonium and sulfoxonium ylides, together with data already reported,[16] clearly demonstrates that the direct irradiation of diazomalonate in solution probably produces biscarbomethoxycarbene in the singlet state. Thus, the electrophilic singlet carbene attacks the nonbonding electron pairs on sulfur giving ylide. This is direct evidence for the involvement of ylides in the reaction of carbenes with compounds containing heteroatoms.

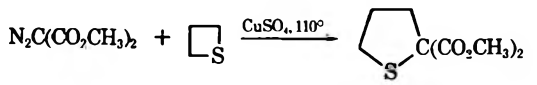
In the reaction of dimethyl diazomalonate with saturated cyclic sulfides, the corresponding sulfonium ylides were also obtained as stable colorless solids. Irradiation of dimethyl diazomalonate in pentamethylene sulfide gave 41% sulfonium ylide (Table II), but in thietane it did not give any sulfonium ylide because of the polymerization of thietane. On the other hand, copper-catalyzed thermal reaction of diazomalonate in thietane gave the insertion product of the carbene into

TABLE II

FORMATION OF CYCLIC SULFONIUM YLIDES IN THE REACTION OF DIAZOMALONATE WITH CYCLIC SULFIDES

Ylide[a]	Mp, °C	Ir (C=O), cm^{-1}	Photolysis, %	Thermal reaction, %
	*c*	1615, 1670	75[d]	23
	104–105	1620, 1675	41	90
	73–75	1610, 1670	11	61
	173–175	1655, 1675		68

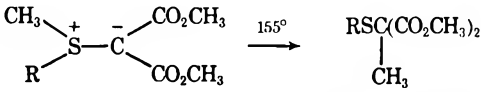
[a] Registry numbers are, respectively, 34281-98-6, 34281-99-7, 34282-00-3, 34297-79-5. [b] R = CO_2CH_3. [c] Oily product and it is difficult to recrystallize. [d] Yield of crude product.



18 (26%)

the carbon–sulfur bond. This ring expansion product is probably formed through the facile rearrangement of the intermediate sulfonium ylide.

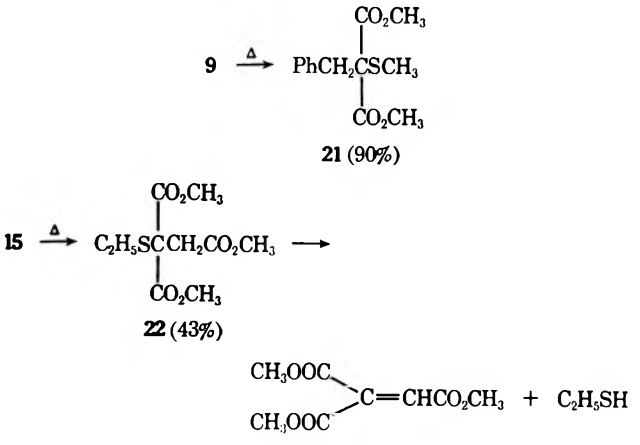
Pyrolysis of Sulfonium Ylides.—One of the many interesting properties of sulfonium ylides is their susceptibility to thermal cleavage of the dipolar sulfur–carbon bond to give the products of Stevens rearrangement or Hofmann-like elimination. When **1** was heated in sealed tubes at temperatures above 155° for >20 hr, the product in which the biscarbomethoxymethylene group was inserted into a methyl–sulfur bond was obtained.[20]



19, R = CH_3 (16%)
20, R = Ph (10%)

This example represents a Stevens-type rearrangement, involving the migration of a methyl group from a sulfonium center to an adjacent carbanionic carbon. Similar results were obtained in the thermal decomposition of other sulfonium ylides by heating in sealed tubes above 180°. These observations strongly support the proposal that the insertion of carboalkoxycarbene into the carbon–oxygen and carbon–nitrogen bonds in the reaction of ethers and amines with carboalkoxycarbene actually takes place through the rearrangement of oxygen and nitrogen ylides.[1,2,17] Recently on the basis of observations of chemically induced dynamic nuclear polarization (CIDNP) in the nmr spectrum of the product, the intervention of radical pair intermediates in the Stevens rearrangement has been suggested.[21–24]

The ylides **9** and **15** were converted into the rearranged products **21** and **22** by heating at 160°. The later ylide also gave the ethylenetricarboxylate, which may be formed by thermal elimination of mercaptan from **22**, since prolonged heating gave a larger amount



(20) W. Ando, T. Yagihara, and T. Migita, *Tetrahedron Lett.*, 1975 (1969).
(21) U. Schöllkopf, G. Ostermann, and J. Schossing, *ibid.*, 2619 (1969).
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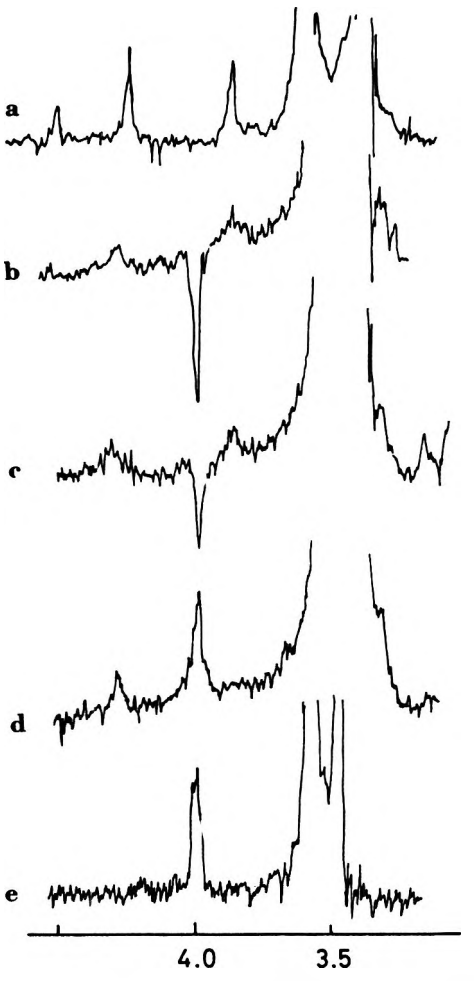
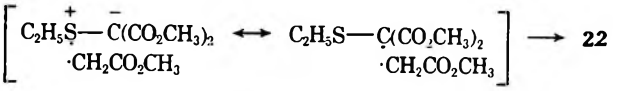
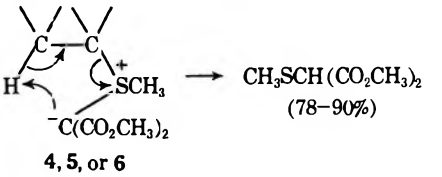


Figure 1.—CIDNP effect observed for β-methylene protons of the product **22** forming in thermolysis of **15**. Spectrum was taken at 60 MHz (δ, parts per million) with TMS as a lock signal: a, **15** (0 min); b, **15** (4.5 min); c, **15** (7.0 min); d, **15** (18.0 min); e, **22**.

of the ethylenic product. We have examined the formation of **22** in the rearrangement of **15** in diphenyl ether using nmr spectroscopy, scanning the region of the developing β-methylene singlet of the product **22** (Figure 1). Within 20 sec after inserting the sample into the probe heated at 160°, a CIDNP effect could be observed for ~9 min. These results are consistent with a mechanism involving homolytic cleavage from **15** yielding a radical pair intermediate, which collapses to **22**.



Thermal decomposition of **4**, **5**, and **6** at 180° gave dimethyl methylthiomalonate in 90, 84, and 78%



4, **5**, or **6**

yields, respectively, together with olefins. The eliminative decomposition of sulfonium ylides probably a cis elimination through a five-membered cyclic transition state. These observations give support to the

proposed ylide mechanism in the reaction of carboalkoxycarbene with ethers and amines bearing β hydrogens, which give similar elimination products.[1,2]

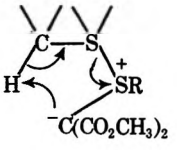
Pyrolysis of cyclic sulfonium ylides in Pyrex tubes was carried out at temperatures above 235° for 10 hr, but no decomposition or reaction products could be detected by gas chromatography. However, the sulfonium ylide from dibenzothiophene was pyrolyzed to give dibenzothiophene and dimethyl malonate.

Reactions of Dimethyl Diazomalonate in Alkyl Disulfides.—In the photolysis of dimethyl diazomalonate in disulfides, the expected sulfonium ylides were not isolable, in contrast to the case of the reactions in alkylmonosulfides. The photolysis of diazomalonate in dimethyl disulfide afforded the principal product, dimethyl methylthiomalonate (**23**) in 43.6% yield and the minor product, thioketal **24**, in 2.2% yield. Similar products were obtained in diethyl disulfide. The structures of these products were determined by comparison of ir and nmr spectra with those of authentic samples. The main products **23** and **25**

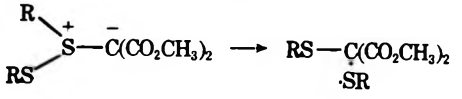
$$N_2C(CO_2CH_3)_2 + RSSR \xrightarrow{h\nu} RSCH(CO_2CH_3)_2 + (RS)_2C(CO_2CH_3)_2$$

23, R = CH_3 (44%) **24**, R = CH_3 (2.2%)
25, R = C_2H_5 (41%) (trace)

correspond to the β-elimination products from the corresponding sulfonium ylides. These can be postulated to form through ylide formation from the carbene and the disulfides, followed by α- or β-hydrogen abstraction concerted with heterolysis of S–S$^+$ bonds (mechanism I). The minor S–S bond insertion product can be regarded as a Stevens-type rearrangement product from an intermediate sulfonium ylide. The formation and recombination of a radical pair seems to be a higher plausible process because of the weakness of the S–S bond. However, supporting experimental evidence is not given (mechanism II).



(I)



(II)

In the reaction with di-*tert*-butyl disulfide, biscarbomethoxy-carbene gave three products only in small yields, although the reactions of di-*tert*-butyl disulfide with dichlorocarbene have been reported[25] to give selectively *tert*-butyldichloromethyl disulfide through the elimination of isobutylene from the intermediate sulfonium ylide.

$$N_2C(CO_2CH_3)_2 + (CH_3)_3CSSC(CH_3)_3 \xrightarrow{h\nu} (CH_3)_3CSCH(CO_2CH_3)_2 + (CH_3)_3CSSCH(CO_2CH_3)_2 + [(CH_3)_3CS]_2C(CO_2CH_3)_2$$

26 (6.2%) **27** (3.3%) **28** (13.2%)

Reactivity of Dimethyl Sulfide toward Carbene.—The relative reactivity of the sulfur atom in dimethyl sulfide toward the carbene was estimated from product distributions in the photolysis of dimethyl diazomalonate in mixtures of cyclohexene and dimethyl sulfide. The results are shown in Table III. Control experiments showed that the products are stable under the reaction conditions. The results indicate that biscarbomethoxycarbene reacts with dimethyl sulfide about six times as fast as with double bond of cyclohexene. In all cases, the sulfonium ylide was separated and weighed, and the reaction products from cyclohexene were determined by gas chromatography using an appropriate internal standard. The adducts to cyclohexene were found to be 7,7-dicarbomethoxynorcarane and dimethyl 2-cyclohexenylmalonate in the ratio of 2.1:1. Table IV shows the yields of the reaction products from the photolysis of dimethyl diazomalonate in equimolar mixtures of dimethyl sulfide and other nucleophiles. These observations suggest that dimethyl sulfide can be used as a more effective and convenient acceptor of negatively substituted carbenes than olefins when the sulfonium ylides are stable under the reaction conditions, because of the high reactivity of dimethyl sulfide and the ease of isolation of the ylide products. Biscarbomethoxycarbene reacts with dimethyl sulfide six–eleven times as fast as with olefins.

TABLE III

YIELD OF PRODUCTS FROM DIMETHYL DIAZOMALONATE IN CYCLOHEXENE AND DIMETHYL SULFIDE

Mole ratio of cyclohexene/sulfide	Products, %	
	Ylide 1	Adducts to cyclohexene[a]
1	61	15
2	49	25
5	36	41
∞	0	92

[a] 7,7-Dicarbomethoxynorcarane and dimethyl 2-cyclohexenylmalonate in the ratio of 2.1:1.

TABLE IV

YIELD OF PRODUCTS OF DIMETHYL DIAZOMALONATE IN EQUIMOLAR REACTANTS

Pair of reactants with dimethyl sulfide	Products, %	
	Ylide, 1	Adducts to the other
Cyclohexene	61	15[a]
2-Methyl-2-butene	49	8.5[b]
cis-4-Methyl-2-pentene	60	5[b]
Cyclopentadiene	44	
Methanol	78	10
Ethyl ether	73	12[c]

[a] Mixtures of olefin adduct and C–H insertion product. [b] Olefin adduct only. [c] Ethylene elimination product and C–H insertion product.

Photosensitized Reactions of Dimethyl Diazomalonate in Alkyl Sulfides.—Contrary to the earlier expectation, photosensitized decomposition of diazomalonate in dimethyl sulfide was found to give a considerable amount of the ylide. Irradiation of dimethyl sulfide solutions of dimethyl diazomalonate in the presence of benzophenone as a sensitizer was carried out with the high pressure mercury lamp and found to produce sulfonium ylide in 60–65% yields. The absolute yield of the sulfonium ylide **1** was estimated by relative sizes of the integrated nmr signal of the $-S^+CH_3$ (2.68 ppm in Ph_2CO and $CHCl_3$ solution)

(25) S. Searles, Jr., and R. E. Wann, *Tetrahedron Lett.*, 2899 (1965).

$$N_2C(CO_2CH_3)_2 + RSR + Ph_2CO \xrightarrow{h\nu} R_2\overset{+}{S}-\overset{-}{C}(CO_2CH_3)_2$$

1, R = CH_3 (60–65%)
2, R = C_2H_5 (40–43%)

of the ylide in the solution with respect to that of the CH_2 signal (4.50 ppm in Ph_2CO and $CHCl_3$ solution) from known amounts of dibenzyl ether added as an internal standard. In the photosensitized reaction of diazomalonate in di-*tert*-butyl sulfide, *tert*-butylthiomalonate, the elimination product of the corresponding sulfonium ylide, was obtained in 21% yield.

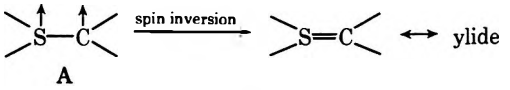
In alkyl disulfides, the photolysis of diazomalonate in the presence of benzophenone gave the same products obtained in the direct photolysis. These

$$N_2C(CO_2CH_3)_2 + RSSR + Ph_2CO \xrightarrow{h\nu} RSCH(CO_2CH_3)_2 + (RS)_2C(CO_2CH_3)_2$$

R = CH_3	32%	14%
R = C_2H_5	61%	Trace
R = $C(CH_3)_3$	5%	Trace

findings suggest that the photosensitized reaction of the diazomalonate can produce the sulfonium ylide in the dialkyl disulfides.

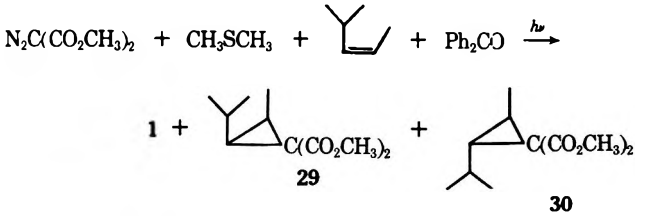
One might explain the unexpected ylide formation in the photosensitized decomposition of dimethyl diazomalonate in alkyl sulfides and disulfides by a process in which a triplet carbene attacks the sulfur atom producing the intermediate represented by formular A. Spin inversion of A leads to ylide formation.



A

Structure A requires the expansion of the valence shell on the sulfur atom to accomodate nine electrons. Such an attack on a sulfur atom by a triplet carbene has not been previously proposed. However, similar examples of such a shell expanded sulfur has been proposed on the basis of studies of the decomposition of *tert*-butyl *o*-(methylthio)perbenzoate[26] and of the copolymerization of vinyl sulfide.[27]

However, the additional information concerning the behavior of triplet carbene in dimethyl sulfide solution is available. The sensitized decomposition of dimethyl diazomalonate[28] in mixtures of dimethyl sulfide and *cis*-4-methyl-2-pentene gave cis- and trans-disubstituted cyclopropanes and the dimethylsulfonium biscarbomethoxymethylide (1) in yields shown in



29 30

Table V. It is noteworthy that, as the concentration of dimethyl sulfide increases, the ratio of the cis adduct to the trans isomer increases. This fact indicates that, in the reaction system diluted with dimethyl sulfide, the species attacking olefin reacts in a more stereospecific fashion than the triplet carbene derived by the photosensitized decomposition of the diazomalonate in olefin alone.

One may postulate a transition of carbene from triplet to singlet brought about by the presence of dimethyl sulfide. The singlet carbene thus formed will react with sulfide giving the sulfonium ylide, as well as with olefin in a stereospecific manner. However, there are a number of alternative explanations of these facts, and the question of even the gross mechanism is therefore still open.

Although detailed mechanism of participation of sulfide in the transition are not yet clear, the transition seems to require the presence of sulfide, since, when the reactants (olefin and diazomalonate) were diluted with other invert solvent such as Freon 113, no change in stereochemistry of addition was observed.

Sensitized reaction of diazomalonate in diethyl ether, which gave no product presumed to form from ylide precursor, showed that ethers are incapable of assisting the transition of the triplet to the singlet.

It is interesting to note that, as shown in Table VI, no change in stereochemistry of addition was observed when photolysis was carried out in the presence of di-*tert*-butyl sulfide, which does not afford the corresponding ylide even in the reaction with singlet carbene.[7] The triplet and singlet carbenes would hardly interact with a sulfur atom of di-*tert*-butyl sulfide because of steric hindrance caused by bulky *tert*-butyl groups.

TABLE V

PHOTOSENSITIZED DECOMPOSITION OF DIAZOMALONATE IN *cis*-4-METHYL-2-PENTENE AND DIMETHYL SULFIDE[a]

Molar ratio of olefin/sulfide	Products, %[b] 29	30
0.23	24.2	75.8
0.33	22.5	77.5
0.66	19.5	80.5
1.0	16.8	83.2
Olefin only	12.3	87.7

[a] Appropriate control experiments were performed. Under the reaction conditions there is insignificant isomerization of the solvent and the products are neither isomerized nor destroyed. [b] Sulfonium ylide 1 was also obtained in 40–65% yields and the yields of olefin adducts increase with olefin concentrations.

TABLE VI

PHOTOSENSITIZED DECOMPOSITION OF DIAZOMALONATE IN *cis*-4-METHYL-2-PENTENE AND DI-*tert*-BUTYL SULFIDE

Molar ratio of olefin/sulfide	Products, % Cis adduct 29	Trans adduct 30
0.09	9.5	90.5
0.34	9.5	90.5
1.0	10.5	89.5

Experimental Section

General.—Ir spectra were determined on a Japan Spectroscopic Co., Ltd, DS-21 instrument in chloroform, carbon tetrachloride, or neat. The nmr spectra were recorded on a Varian A-60D spectrometer using solutions in carbon tetrachloride or deuteriochloroform with internal tetramethylsilane (TMS) as standard. Chemical shifts are reported in parts per million (ppm) downfield from TMS, with the parentheses designating the multiplicity of the signals: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. The number immediately following the parentheses

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(28) Under the reaction conditions, the sensitizer absorbs ~98% of the incident light. The data are not corrected for small extent of contamination by the direct photolysis, as the relative quantum yields of the two processes are not known.

indicates the number of protons causing the signal. Samples of dimethyl diazomalonate were added to clean 10 × 100 mm Pyrex tubes. The tubes were then corked (nondegassed) and placed in a water cooled bath for irradiation. The light source was a 400-W Rikosha high pressure mercury lamp having the maximum output at 3650–3660 Å with low intensities at 3126–2132 Å. The photolyses were carried to the disappearance of diazo band in ir spectra. The solutions were analyzed on an Ohkura glpc with a calibrated 5 ft × 1/4 in. stainless steel column of 10% DC-710 and Carbowax 20M on C-22 firebrick. Peak areas were obtained by multiplying the height of the peak times the width at half-height. Absolute yields were then obtained relative to the area of the known amounts internal peak.

Materials.—The reagents [dimethyl, diethyl, and di-*tert*-butyl sulfides, dimethyl, diethyl, and di-*tert*-butyl disulfides, tetrahydrothiophene, and *cis*-4-methyl-2-pentene (contained <1% trans isomer)] were obtained commercially and purified by distillation before use. Methyl ethyl sulfide,[29] methyl *n*-butyl sulfide,[29] methyl *tert*-butyl sulfide,[29] methyl benzyl sulfide,[29] ethyl *n*-butyl sulfide,[30] methyl phenyl sulfide,[31] diphenyl sulfide,[32] thietane,[33] and cyclic sulfides[34] were prepared by known procedure as referenced. Dimethyl diazomalonate was prepared as follows. A solution of dimethyl malonate (26.4 g, 0.2 mol) and tosyl azide (39.4 g, 0.2 mol) in diethyl ether (200 ml) at 0° was treated with dry diethyl amine (20 ml, 0.2 mol).[35] The mixture was stirred for 1 hr at 0° and for a further 1 hr at room temperature. When solid was deposited, the mixture was treated with petroleum ether (bp <60°) and the solid was filtered off. Removal of solvent from the filtrate and distillation of the residue gave dimethyl diazomalonate, 50% yield, bp 60–61° (2 mm) [lit.[36] bp 63° (1 mm)], $\nu_{N=N}$ 2140 cm^{-1}, uv absorption maximum at 352 nm (ε 22).

Reactions of Dimethyl Diazomalonate in Alkyl and Aryl Sulfides. Formation of Stable Sulfonium Ylides.—Most of the dialkyl- and diarylsulfonium biscarbomethoxymethylides were prepared by the photolysis of dimethyl diazomalonate in the corresponding dialkyl and diaryl sulfides. For example, compound **1** was prepared in 88% yield by the photolysis of 0.52 g (3.3 mmol) of diazomalonate in 3 ml of dimethyl sulfide. **1** was obtained as pure white solid by decantating the unreacted dimethyl sulfide and washing the remaining solid with petroleum ether (bp 30–60°). The product easily dissolved in water and chloroform, but not in carbon tetrachloride or acetone. The dialkyl- and diarylsulfonium biscarbomethoxymethylides were often prepared with copper and copper salt catalyzed thermal decomposition of diazomalonate in the corresponding sulfides. For example, the stable diphenylsulfonium biscarbomethoxymethylide (**10**) was obtained when a solution of 1.02 g (6.6 mmol) of diazomalonate in 5 ml of diphenyl sulfide was heated at 90° for 5 hr in the presence of anhydrous cupric sulfate (20 mg). Chloroform was added and the undissolved materials were separated from the reaction mixture. After the chloroform was distilled off, the solid was recrystallized from ethanol to give the ylide in 85% yield. The nmr and ir spectra and other physical properties are recorded in Tables I and II.

Reactions of Dimethyl Diazomalonate in Sulfoxides.—Photolysis of 0.52 g (3.3 mmol) of diazomalonate in 3 ml of dimethyl sulfoxide, according to the procedure above, gave dimethylsulfoxonium biscarbomethoxymethylide (**16**) in 34% yield, which showed ir 1640 cm^{-1}; nmr ($CDCl_3$) 3.54 (s, 6 H) and 3.72 ppm (s, 6 H); mp 157–158°. *Anal.* Calcd for $C_7H_{12}O_5S$: C, 40.38; H, 5.77. Found: C, 40.80; H, 5.88. Cupric sulfate catalyzed thermal decomposition of diazomalonate in dimethyl sulfoxide, according to the procedure above, also gave the sulfoxonium methylide **16** in 42% yield. Photolysis of the diazomalonate in 2 ml of diphenyl sulfoxide was carried out in the same manner described above to give **17** in 12% yield, in contrast to the 26% yield in thermal reaction. **17** showed ir (CCl_4) 1680 cm^{-1}; nmr ($CDCl_3$) 3.40 (s, 6 H) and 7.77 ppm (m, 10 H); mp 196–197°. *Anal.* Calcd for $C_{17}H_{16}O_5S$: C, 61.44; H, 4.81. Found: C, 61.21; H, 4.78.

Reactions of Dimethyl Diazomalonate in Thietane.—Photolysis of diazomalonate in thietane was carried out with the high pressure mercury lamp. During the photolysis, white thin film was deposited on the glass wall of reaction tubes. After 40-hr irradiation, the ir band of the reaction mixture showed no decomposition of diazo compound. The white thin film on the glass wall was found to be the polymeric material from thietane. Thermal decomposition of diazomalonate in thietane was carried out in the presence of cupric sulfate at 110°. From the analysis by gas chromatography, one product (**18**) was isolated. **18** showed ir (CCl_4) 1735 cm^{-1}; nmr (CCl_4) 2.20 (m, 4 H), 3.15 (m, 2 H), 3.73 ppm (s, 6 H). *Anal.* Calcd for $C_9H_{12}O_4S$: C, 47.06; H, 5.92. Found: C, 47.33; H, 6.20.

Thermal Decomposition of Alkylsulfonium Biscarbomethoxymethylides.—The reaction described below exemplifies the general thermolysis of the sulfonium biscarbomethoxymethylides. Ylide **1** (0.32 g, 1.66 mmol) was sealed in 8 × 100 mm Pyrex tubes without degassing. The sample was heated at 200° for 20 hr in an oil bath. After complete decomposition of the ylide **1**, the reaction mixture was analyzed directly by gas chromatography. The structure of the product collected from the gas chromatography was determined by elemental analysis and the nmr and ir spectra. Ylide **1** gave **19**, dimethyl malonate, and dimethyl sulfide in 16, 15, and 10% yields, respectively. **19** showed ir (CCl_4) 1740 cm^{-1}; nmr (CCl_4) 1.62 (s, 3 H), 2.15 (s, 3 H), 3.75 ppm (s, 6 H). Ylide **8** gave **20** in 10% yield which showed ir (CCl_4) 1765 cm^{-1}; nmr (CCl_4) 1.54 (s, 3 H), 3.64 (s, 6 H), 7.32 ppm (m, 5 H). Ylide **9** gave **21** which showed ir (CCl_4) 1735 cm^{-1}; nmr (CCl_4) 2.12 (s, 3 H), 3.34 (s, 2 H), 3.74 (s, 6 H), 7.30 ppm (m, 5 H). Ylides **4**, **5**, and **6** gave dimethyl methylthiomalonate in 90, 84, and 78% yields, respectively. It was identified by the comparison of its physical properties with those of an authentic sample prepared by the irradiation of diazomalonate in methyl mercaptan: ir (CCl_4) 1750 cm^{-1}; nmr (CCl_4) 3.74 (s, 6 H), 3.91 (s, 1 H), 2.21 ppm (s, 3 H). *Anal.* Calcd for $C_5H_{10}O_4S$: C, 40.45; H, 5.62; S, 17.97. Found: C, 40.64; H, 5.67; S, 17.95.

Observation of CIDNP Effect on the Thermolysis of Ylide 15.—A solution of 10 mg of **15** and 0.5 ml of diphenyl ether in an nmr tube was sealed carefully. The nmr spectrum of this sulfonium ylide showed 1.31 (t, 3 H), 3.10 (q, 2 H), 3.66 (s, 3 H), 3.78 (s, 6 H), 3.95 (d, 1 H), 4.68 (d, 1 H). The sample tube was inserted into the probe heated at 160°, and one new nmr signal appeared as an emission line at 3.77 ppm after 20 sec. This new emission was observed for 9 min. The signal intensity decayed exponentially and the line width was approximately constant during the thermolysis. The final product from the thermolysis of ylide **15** was found to be **22**. **22** showed the following nmr spectrum in carbon tetrachloride: 1.24 (t, 3 H), 2.66 (q, 2 H), 3.72 (s, 3 H), 3.75 ppm [s + s, (6 + 2) H]. *Anal.* Calcd for $C_{10}H_{16}O_6S$: C, 45.45; H, 6.10. Found: C, 45.52; H, 5.98.

Reactions of Dimethyl Diazomalonate in Alkyl Disulfides.—The reaction described below is typical. Diazomalonate 0.35 g (2.2 mmol) was dissolved in 1.01 g (10.8 mmol) of dimethyl disulfide and then irradiated for 15 hr with a high pressure mercury lamp. The reaction products were analyzed directly by gas chromatography to give 44% **23** and 2.2% **24**. **23** was identified by comparison of its spectral data with that of an authentic sample. **24** showed nmr (CCl_4) 2.04 (s, 6 H), 3.78 ppm (s, 6 H). *Anal.* Calcd for $C_7H_{12}O_4S_2$: C, 37.50; H, 5.36. Found: C, 37.55; H, 5.09. The reaction of diazomalonate in diethyl disulfide gave 41% **25**, which showed ir (CCl_4) 1735 cm^{-1}; nmr (CCl_4) 1.27 (t, 3 H), 2.74 (q, 2 H), 3.78 (s, 6 H), 4.02 ppm (s, 1 H). *Anal.* Calcd for $C_7H_{12}O_4S$: C, 43.75; H, 6.29; S, 16.65. Found: C, 43.79; H, 6.34; S, 16.96.

The reaction of diazomalonate in di-*tert*-butyl disulfide gave three products, **26**, **27**, and **28**. **26** showed ir (CCl_4) 1735 cm^{-1}; nmr (CCl_4) 1.36 (s, 9 H), 3.76 (s, 6 H), 4.02 ppm (s, 1 H). *Anal.* Calcd for $C_9H_{16}O_4S$: C, 49.99; H, 7.27. Found: C, 50.23; H, 7.29. **27** showed ir (CCl_4) 1735 cm^{-1}; nmr (CCl_4 1.31 (s, 9 H), 3.74 (s, 6 H), 4.14 ppm (s, 1 H). *Anal.* Calcd for $C_9H_{16}O_4S_2$: C, 42.86; H, 6.34. Found: C, 43.06; H, 6.8. **28** showed ir (CCl_4) 1735 cm^{-1}; nmr (CCl_4) 1.33 (s, 18 H), 3.77 ppm (s, 6 H). *Anal.* Calcd for $C_{13}H_{24}O_4S_2$: C, 52.50; H, 7.50. Found: C, 52.33; H, 7.75.

Photolysis of Dimethyl Diazomalonate in a Solution of Di-

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methyl Sulfide and Cyclohexene.—Photolysis of 1.02 g (6.6 mmol) of diazomalonate in a solution of 9.32 g (0.15 mol) of dimethyl sulfide and 12.01 g (0.15 mol) of cyclohexene was carried out with the high pressure mercury lamp described above. After the diazo band disappeared from the spectrum of the reaction mixture, a known amount of internal standard (biphenyl) was added to the reaction mixture. A white precipitate formed when the reaction was over.

The solid was filtered to give 0.75 g (61% yield) of sulfonium ylide 1 which was identified by comparison of spectra with those of an authentic sample. The reaction mixture was then analyzed directly by gas chromatography. Two major peaks appeared which were found to be the adducts of biscarbomethoxycarbene to cyclohexene. One of them was identified as the adduct of carbomethoxycarbene with the C=C bond of cyclohexene which showed ir (CCl_4) 1735 cm^{-1}; nmr (CCl_4) 1.15 (m, 2 H), 1.85 (m, 8 H), 3.66 (s, 3 H), 3.76 ppm s, 3 H). *Anal.* Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.79; H, 7.45. The other product was identified as the insertion product of biscarbomethoxycarbene into the allylic carbon–hydrogen bond, which showed ir (CCl_4) 860, 1025, 1740 cm^{-1}; nmr (CCl_4) 1.83 (m, 7 H), 3.15 (d, 1 H), 3.66 (s, 6 H), 5.88 ppm (m, 2 H). *Anal.* Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.03; H, 7.58.

Photosensitized Reactions of Dimethyl Diazomalonate in Dialkyl Sulfides and Disulfides.—Dimethyl diazomalonate (220 mg) was added to dimethyl sulfide (700 mg) solution with 880 mg of benzophenone. Irradiation of the sample in Pyrex tubes for 40 hr provided a white solid, which was washed with petroleum ether (bp 30–60°) and identified as sulfonium ylide 1 by comparison with an authentic sample. The overall yield of 1 was determined by nmr spectroscopy through addition of dibenzyl ether as an internal standard. The formation of benzopinacol was also observed, but it was neglibible before decomposition of diazomalonate. Irradiation of diazomalonate was also performed in diethyl and di-*tert*-butyl sulfides solution containing benzophenone: 220 mg of dimethyl diazomalonate was dissolved in 1 ml of diethyl or di-*tert*-butyl sulfides and 800 mg of benzophenone and irradiated for 40 hr in a Pyrex tube. Although no significant precipitation could be observed in the solution, the nmr analysis indicated the formation of **2**. On the other hand ethyl or *tert*-butylthiomalonate from the thermolysis of corresponding sulfonium ylides was isolated by preparative gas chromatograph. These were identified by comparison of their spectra with those of authentic samples. When 100 mg of dimethyl diazomalonate in a solution of 300 mg of dimethyl disulfide and 165 mg of benzophenone was irradiated for 40 hr in Pyrex tubes, no corresponding sulfonium ylide formation could be observed. However, the product analysis by gas chromatography indicated the formation of alkylthiomalonate. It was identified by comparison of its spectra with those of authentic samples.

Photosensitized Reaction of Dimethyl Diazomalonate in Dimethyl Sulfide and *cis*-4-Methyl-2-pentene. Competitive Reactions.—Dimethyl diazomalonate (1 mmol) and 4.5 mmol of benzophenone were dissolved in weighed quantities of dimethyl sulfide and *cis*-4-methyl-2-pentene. The solution was irradiated for 40–50 hr until the diazo band in ir spectrum disappeared. The analyses for sulfonium ylide were performed on Varian A-60D nmr spectrometer after the solid that appeared in the reaction mixture was dissolved with deuteriochloroform. The relative integral heights of ylide S^+CH_3 to internal standard CH_2 of dibenzyl ether were compared to obtain the yield of ylide formation. The reaction mixture was concentrated and analyzed by gas chromatograph. Two main products were isolated and shown to be *cis*- and *trans*-cyclopropane derivatives, **29** and **30**, by comparison of their spectra with those of authentic samples.[16]

Registry No.—**1**, 17870-68-7; **2**, 24308-25-6; **3**, 24420-55-1; **4**, 24420-56-2; **5**, 24420-57-3; **6**, 24420-58-4; **7**, 34282-07-0; **8**, 24420-59-5; **9**, 24420-60-8; **10**, 24420-61-9; **11**, 14070-66-7; **12**, 34282-11-6; **13**, 34282-12-7; **14**, 7039-28-3; **15**, 33781-29-2; **16**, 24420-62-0; **17**, 24420-63-1; **18**, 34282-14-9; **22**, 34282-15-0; **24**, 34282-16-1; **25**, 24420-53-9; **26**, 34282-18-3; **27**, 34282-19-4; **28**, 34282-20-4; **29**, 34282-53-6; **30**, 34282-54-7; dimethyl diazomalonate, 6773-29-1; dimethyl methylthiomalonate, 24420-52-8.

Synthesis and Antifungal Properties of Dithiocarboxylic Acid Derivatives. II.[1] Novel Preparation of 2-Alkylamino-1-cyclopentene-1-dithiocarboxylic Acids and Some of Their Derivatives

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2-Methylamino-1-cyclopentene-1-dithiocarboxylic acid (II) can be obtained in low yield from cyclopentanone with carbon disulfide and methylamine; no other 2-alkylamino analogs can be synthesized. The amino group of 2-amino-1-cyclopentene-1-dithiocarboxylic acid (I) and that of its methyl ester (VII) can be substituted by the alkylamino group by an amine exchange reaction, yielding the corresponding 2-alkylamino-1-cyclopentene-1-dithiocarboxylic acid (II) or its methyl ester (III–V, VIII–XII), respectively. The structures, including tautomeric forms of the synthesized compounds, were proved by ir and nmr spectroscopy.

In previous research it was found that 2-amino-1-cyclopentene-1-dithiocarboxylic acid (I) synthesized by Takeshima and coworkers[3] exerts a marked antifungal action against various fungi.[4] The steric arrangement of the functional groups in this compound permits the formation of six-membered chelates with metals, which fact may be responsible for the biological activity, too. Chelation plays an important role in the action of several antifungal compounds, among which are the dithiocarbamates.[5–7]

For studying the structure–activity relationship within this group we attempted to prepare the *N*-alkyl and *S*-alkyl derivatives of I. Some of these compounds have been synthesized by Mayer and coworkers[8] by treating *N*-alkyliminocyclopentanes with carbon disulfide. To avoid the tedious preparation of *N*-alkyl-

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iminocyclopentanes by the reaction of 1,1-cyclopentanedithiol with aliphatic amines[8,9] we worked out a new synthesis of *N*-alkyl derivatives of I.

The attempted extension of the reaction of cyclopentanone, carbon disulfide, and ammonia[3] to amines succeeded only in case of methylamine; 2-*N*-methylamino-1-cyclopentene-1-dithiocarboxylic acid (II) was obtained in 25% yield. All other primary and secondary aliphatic amines yielded only the corresponding dithiocarbamates, except ethylenediamine, which yielded ethylenethiourea as a result of a well-known reaction.[10-12] Methylation of II by dimethyl sulfate gave the methyl ester (III).

In our search for other synthetic methods we found that *N*-alkyl derivatives of I can be prepared by means of amine exchange reaction. The reaction of I with methylamine, ethylamine, and butylamine gave the corresponding *N*-alkylcyclopentenedithiocarboxylic acids (II, IV, V) in fairly good yield. The melting point of the *N*-butylamino-1-cyclopentene-1-dithiocarboxylic acid was identical with that described by Mayer and Jentzsch.[6] The reaction of I with ethylenediamine resulted in the formation of 2,2′-*N*,*N*′-ethylenebis(amino-1-cyclopentene-1-dithiocarboxylic acid) (VI) even when ethylenediamine was used in excess. Attempts to react I with primary aromatic amines such as aniline and *p*-chloroaniline resulted in decomposition rather than formation of the expected product; secondary aliphatic amines as well as glycine failed to react.

Similar amine exchange reactions proceeded smoothly also when the methyl ester (VII) was used instead of the free acid (I). Thus the methyl esters of 2-methylamino- (III), 2-ethylamino- (VIII), 2-allylamino- (IX), and 2-cyclohexylamino-1-cyclopentene-1-dithiocarboxylic acid (X) were obtained by this way. Reaction of VII with ethylenediamine yielded both the β-aminoethylamino- (XI) and the ethylenebisamino derivative (XII). The N-acetylated product of XI (XIII) was prepared mainly for spectroscopic investigations. Sterically hindered primary aliphatic amines, such as *tert*-butylamine, diacetonamine, primary aromatic amines, and secondary aliphatic amines failed to undergo this reaction even on elevated temperature and prolonged reaction time.

The success of this reaction in aqueous media at room temperature raised the idea whether VII could undergo this reaction also in living organisms with side-chain amino groups on protein surfaces. We found, however, that glycine, glycylglycine, and ethyl glycinate used as simple model substances failed to react.

The usual conditions applied in equilibrium reactions, *e.g.*, the use of an excess of amine or removal of the ammonia formed, are necessary to obtain good yields. However, the reverse reaction was not observed by treatment with an excess of ammonia under similar conditions.

Compound III is highly resistant to alkaline hydrolysis but can be readily decomposed by acids, like the salts of dithiocarbamic acids and in sharp contrast to their esters which show a great stability in the presence of acids and are sensitive to alkaline agents.

The reaction of I and II with formaldehyde and diethylamine yielded the diethylaminomethyl esters (XIV, XV), respectively.

The structure and tautomeric form of the synthesized new compounds was proved by ir and nmr spectroscopy.

The nmr spectrum of compound II contains a two-proton signal of roughly quintet shape at 1.17 ppm due to the methylene group in position 4. The 3- and 5-methylene groups give two almost overlapping triplets at 2.75 ppm. This fact excludes the tautomeric structure IIa since the chemical shift of the 3- and 5-methylene motions should be rather different in this case because of the neighborhood of the C=N and methine group, respectively, and no triplet due to the 1-methyne can be detected in the spectrum. The *N*-methyl signal appears at 3.08 ppm as a doublet (J = 5 Hz), owing to the coupling with the NH proton which can be removed by addition of acid.[13] This proves unambiguously the presence of structure IIb, since in structure IIc, where the methyl signal could give a doublet in consequence of a syn and anti isomer, no collapsing to a singlet should occur by acid. The tautomer IIb has a chelate structure according to the large chemical shift of the NH proton (δ_{NH} 12.4 ppm).

In the ir spectrum (in KBr and in $CHCl_3$, respectively) of compound II no ν_{NH} band can be detected, being a further evidence of the chelate structure.[14] The ν_{SH} group gives a sharp maximum at 2550 cm^{-1} (2575 in $CDCl_3$), excluding its participation in an association structure. The most intense bands appear at 1610, 1510, and 1360 cm^{-1} which can be assigned to the group frequencies of the chelate structure and approach the character of the $\nu_{C=C}$, ν_{C-N}, ν_{NH}, and $\nu_{C=S}$ bands.[15]

All other N-substituted derivatives gave nmr spectra similar to that of compound II, proving the general validity of the tautomeric structure b.[16] The doublet of the *N*-methyl group in compound III and XV and the *N*-methylene multiplet in compound XII collapsed to a singlet by addition of acid. The same treatment resulted in a simplification of the *N*-methylene multiplets in compounds VIII, IX, XI, and XIII and of the *N*-methyne multiplet in compound X.

The elucidation of the tautomer structure of the compounds carrying no substituent on their nitrogen (I, VII, XIV) is more difficult. In the spectrum of I there are two separated signals due to acidic protons, one of them being shifted downfield (11.0 ppm), which is characteristic for chelates. Structure b can be valid in this case only if one proton of the NH_2 group is presumed to take part in the chelate, as this explains

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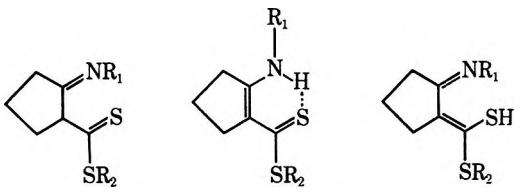
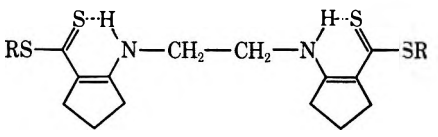
(15) The assignment of these bands as group frequencies is backed by the spectra of the deuterated compounds, where all three bands are shifted to lower wavenumbers, but these shifts (30, 50, and 5 cm^{-1}, respectively) are significantly smaller than those which should originate from XH and XD band frequencies, respectively.

(16) Tables and figures of ir and nmr values will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteeth St., N.W., Washington, D. C. 20036, by referring to code number JOC-72-1727. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.



a b c

Compd	R_1	R_2
I	H	H
II	CH_3	H
III	CH_3	CH_3
IV	C_2H_5	H
V	C_4H_9	H
VII	H	CH_3
VIII	C_2H_5	CH_3
IX	$CH_2CH{=}CH_2$	CH_3
X	cyclohexyl	CH_3
XI	$CH_2CH_2NH_2$	CH_3
XIII	CH_2CH_2NHAc	CH_3
XIV	H	$CH_2N(C_2H_5)_2$
XV	CH_3	$CH_2N(C_2H_5)_2$



VI, R = H
XII, R = CH_3

the nonequivalence of the two NH_2 protons. The tautomeric structure a (suggested by Takeshima, *et al.*,[5] for compound I) can be excluded, as the signal of the 1-methyne proton can be detected neither in the spectrum of compound I, nor in those of compound VII, or XIV. As the ir spectra of these compounds show strong similarity to those of the N-substituted derivatives (Table II),[16] it seems reasonable to suggest for them the same tautomeric structure b.

Experimental Section

Preparation of II from Cyclopentanone.—Cyclopentanone (4.2 g, 0.05 mol) was mixed with 31 g (0.2 mol) of 20% aqueous methylamine solution. After 2 hr the mixture was cooled to 5°, 4.6 g (0.06 mol) carbon disulfide was added in portions, and the reaction mixture was shaken for 2 hr. The precipitated yellow product was separated and washed with water. After drying it was suspended in 8 ml of acetic acid and warmed at 50° for several minutes; after the mixture cooled to room temperature, 20 ml of water was added. The yellow solid product was separated, washed with water, and dried, yield 2.2 g (25%), mp 122°. The product was recrystallized from methanol, yield 1 g (12%), mp 125.5°.

Anal. Calcd for $C_7H_{11}NS_2$: C, 48.51; H, 6.39; N, 8.08; S, 37.00. Found: C, 48.31; H, 6.27; N, 8.10; S, 36.74.

Preparation of II from I.—A solution of I (3.2 g, 0.02 mol) in 6 ml of 40% aqueous methylamine solution and 30 ml of methanol was refluxed for 3 hr. The solution was evaporated to dryness under diminished pressure, the residue was taken up in 70 ml of water and filtered, and the solution was acidified with 10% hydrochloric acid. The yellow solid product was separated, washed with water, and dried, yield 1.6 g. The crude product was recrystallized from methanol, mp 125.5°; there was no depression in melting point on admixture with II prepared by the previous method.

Preparation of IV from I.—I (6.3 g, 0.04 mol) and ethylamine (6.75 g, 0.15 mol) in 60 ml of methanol was refluxed for 3 hr. After the mixture cooled 180 ml of water was added and the mixture was filtered. To the filtrate 20 ml of acetic acid was added and the precipitated yellow product was separated by filtration, washed with water, and dried. The crude product was recrystallized from acetone, wt 6.0 g (80.0%), mp 111°.

Anal. Calcd for $C_8H_{13}NS_2$: C, 51.30; H, 7.00; N, 7.48; S, 34.23. Found: C, 51.37; H, 7.02; N, 7.15; S, 33.82.

Preparation of V from I.—I (6.3 g, 0.04 mol) and butylamine (7.3 g, 0.1 mol) in 60 ml of methanol was refluxed for 3 hr and the product was isolated as above, wt 5.5 g (63.9%), mp 90° (EtOH).

Anal. Calcd for $C_{10}H_{17}NS_2$: C, 55.77; H, 7.96; N, 6.50; S, 29.77. Found: C, 55.62; H, 7.96; N, 6.40; S, 29.75.

Preparation of VI from I.—A mixture of I (4.8 g, 0.03 mol), ethylenediamine (1.8 g, 0.03 mol), and 30 ml of methanol was refluxed for 4 hr. The precipitation of a yellow crystalline product began shortly. After cooling the product was separated, washed with methanol, and dried. The crystals (4.8 g) could not be purified by crystallization; they were taken up in a solution of 2.4 g (0.06 mol) of sodium hydroxide and 80 ml of water and filtered, the filtrate was acidified with 10% hydrochloric acid, and the yellow precipitate was separated, washed with water and dried, yield 1.6 g (31%), mp 145–147°.

Anal. Calcd for $C_{14}H_{20}N_2S_4$: C, 48.88; H, 5.85; N, 8.13; S, 37.22. Found: C, 47.76; H, 6.06; N, 7.31; S, 36.58.

Preparation of VII from I.—I (4.77 g, 0.03 mol) was dissolved in a solution of 1.2 g (0.03 mol) of sodium hydroxide in 50 ml of water; 3.9 g (0.03 mol) dimethyl sulfate was added in portions under cooling and vigorous stirring, with the temperature being kept below 20°. The brown product was then separated, dried (4.19 g), and recrystallized from 1:1 methanol–water, yield 3.3 g (63%), mp 77–79°.

Anal. Calcd for $C_7H_{11}NS_2$: C, 48.51; H, 6.39; N, 8.08; S, 37.00. Found: C, 48.13; H, 6.15; N, .30; S, 36.77.

Preparation of III from II.—II was methylated as described above. The crude product was recrystallized from 2-propanol, yield 58%, mp 143–144°.

Anal. Calcd for $C_8H_{13}NS_2$: C, 51.29; H, 6.99; N, 7.52; S, 34.23. Found: C, 51.27; H, 7.20; N, 7.74; S, 34.31.

Reaction of I and II with Diazomethane.—The acids I and II were treated with an excess of diazomethane in the usual way, with methanol being used as solvent. The methyl esters VII (76%) and III (81%) were identical with those described above.

No reaction took place when the methyl esters III and VII were treated on the similar way, indicating that both dithiocarboxylic acids undergo S-methylation but no N-methylation when diazomethane is used as the methylating agent. No other side reactions such as ring expansion or C-methylation were observed.

Preparation of III from VII.—A mixture of 3.46 g (0.02 mol) of V, 20 ml of 40% aqueous methylamine solution and 20 ml of methanol was shaken for 3 hr. The separation of yellow crystals began shortly after starting the reaction. The product was separated, washed with water and methanol, and dried; 3.5 g of crude product was obtained, which was recrystallized from methanol, yield 2.4 g (69%), mp 143–144°; no depression in melting point was found on admixture with III prepared by the previous method.

Preparation of VIII from VII.—A mixture of 3.46 g (0.02 mol) of VII, 3.8 g (0.06 mol) of 70% aqueous ethylamine solution, and 20 ml of methanol was refluxed for 3 hr. After cooling the yellow product was separated and washed with and recrystallized from methanol, yield 1.9 g (47%), mp 96–97.5°.

Anal. Calcd for $C_9H_{15}NS_2$: C, 53.69; H, 7.51; N, 6.96; S, 31.84. Found: C, 53.42; H, 7.73; N, 6.60; S, 32.01.

Preparation of IX from VII.—A mixture of VII (3.46 g, 0.02 mol), allylamine (3.42 g, 0.06 mol), and 20 ml of methanol was refluxed for 1 hr. After 24 hr, the lustrous yellow plates were separated and recrystallized from methanol, yield 2.9 g (67%), mp 63–65°.

Anal. Calcd for $C_{10}H_{15}NS_2$: C, 56.29; H, 7.08; N, 6.56; S, 30.05. Found: C, 56.23; H, 7.07; N, 6.26; S, 29.94.

Preparation of X from VII.—VII 3.46 g, 0.02 mol) VII was dissolved in 18 ml of cyclohexylamine. After 24 hr, water was added to the dark red solution until precipitation was complete. The yellow crystalline product was separated, washed with water, dried (3.6 g), and recrystallized from methanol, yield 1.9 g (37%), mp 84–86°.

Anal. Calcd for $C_{13}H_{21}NS_2$: C, 60.87; H, 8.65; N, 5.46; S, 25.00. Found: C, 61.31; H, 8.27; N, 5.55; S, 25.60.

Preparation of XI and XII from VII.—VII (3.46 g, 0.02 mol) was dissolved in 35 ml of methanol and 6 g (0.1 mol) of ethylene-

diamine was added. After 24 hr, the red solution gradually turned pale yellow; the precipitated yellow crystalline product (XII) was separated, washed with water, dried (0.6 g), and recrystallized from dioxane, yield 0.33 g (9%), mp 210–213°.

Anal. Calcd for $C_{16}H_{24}N_2S_4$: C, 51.56; H, 6.49; N, 7.51; S, 34.42. Found: C, 51.24; H, 6.61; N, 7.84; S, 34.58.

Water (120 ml) was added to the filtrate; the precipitated yellow crystals (XI) were separated, washed with water, and dried. The crude product (XI, 3.1 g) was recrystallized from 3:2 water–methanol, yellow plates, yield 2.1 g (48.5%), mp 94–95°.

Anal. Calcd for $C_9H_{16}N_2S_2$: C, 49.95; H, 7.45; N, 12.95; S, 29.63. Found: C, 50.15; H, 7.72; N, 13.20; S, 29.57.

Preparation of XIII from XI.—XI (3.24 g, 0.015 mol) was dissolved in 35 ml of dioxane and 1.5 g (0.015 mol) of acetic anhydride was added below 30°. The precipitated yellow acetate of XI was separated, washed with methanol and dried, 1.3 g; after repeated recrystallization from 1:2 dioxane–methanol the melting point was 119–122°.

The filtrate was diluted with water and yellow crystals were separated. The product was recrystallized from methanol–water (1:2) and identified as the N-acetylated derivative of XI (XIII), yield 1.0 g (25%), mp 130–132°.

Anal. Calcd for $C_{11}H_{18}N_2OS_2$: C, 51.10; H, 7.00; N, 10.84; S, 24.82. Found: C, 50.80; H, 6.82; N, 10.97; S, 24.31.

Preparation of XIV from I.—I (1.6 g, 0.01 mol) was dissolved in a solution of 0.73 g (0.01 mol) of diethylamine in 20 ml of water; 0.75 g (0.01 mol) of 40% aqueous formaldehyde was added to the solution. After 1 hr, the precipitated yellow product was separated, washed with water, and dried, yield 1.7 g (70%), mp 97–99°.

Anal. Calcd for $C_{11}H_{22}N_2S_2$: C, 54.0; H, 8.24; N, 11.46; S, 26.24. Found: C, 53.76; H, 8.33; N, 11.02; S, 25.86.

Preparation of XV from II.—II (1.73 g, 0.01 mol) was dissolved in a solution of 0.73 g (0.01 mol) of diethylamine in 20 ml of water; 0.75 g (0.01 mol) of 40% aqueous formaldehyde was added. The yellow product, which separated out immediately, was separated, washed with water, dried, and recrystallized from 1:2 water–ethanol, yield 1.5 g (58%), mp 72°.

Anal. Calcd for $C_{12}H_{22}N_2S_2$: C, 55.80; H, 8.59; N, 10.84; S, 24.83. Found: C, 55.71; H, 8.66; N, 11.10; S, 25.04.

The nmr spectra were recorded in $CDCl_3$ solution on a Varian A-60D instrument at 60 MHz, using TMS as internal standard. One drop of TFA was used for acidifying the probes. Ir spectra were recorded on a Perkin-Elmer 457 spectrometer in KBr pellets and in $CDCl_3$ solution (0.1 mol/l.), respectively.

Registry No.—Ib, 20735-33-5; IIb, 34281-24-8; IIIb, 34281-25-9; IVb, 34281-26-0; Vb, 34281-27-1; VIb, 34281-28-2; VIIb, 34281-29-3; VIIIb, 34281-30-6; IXb, 34281-31-7; Xb, 37297-90-0; XIb, 34281-32-8; XIIb, 34281-33-9; XIIIb, 34281-34-0; XIVb, 34281-35-1; XVb, 34281-36-2.

Acknowledgment.—We are indebted to Miss M. Fodor for the microanalyses. Thanks are due to Mrs. C. Méhesfalvi, Miss A. Bede, Mr. I. Echter, and Mr. A. Fürjes for valuable technical assistance.

Synthesis and Some Reactions of 3,3-Dimethoxycyclopropene[1,2]

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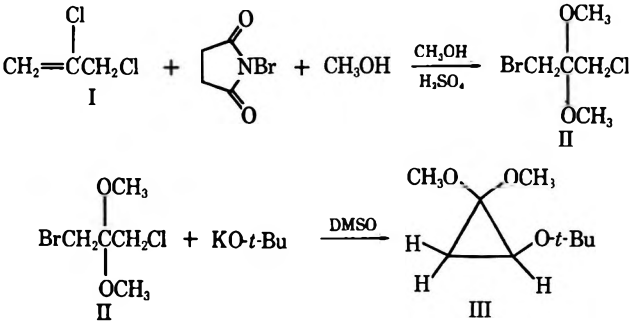
During the course of attempts to synthesize compounds potentially capable of intramolecular charge-transfer interaction, an easy and relatively simple procedure for the preparation of 3,3-dimethoxycyclopropene (IV) was developed. The starting material for this synthesis is the commercially available 2,3-dichloropropene (I). Reaction of I with methanol and *N*-bromosuccinimide, using an acid catalyst, yields 1-bromo-3-chloro-2,2-dimethoxypropane (II) in 33–40% yield. Reaction of II with potassium *tert*-butoxide (KO-*t*-Bu) in dimethyl sulfoxide (DMSO) led to 1,1-dimethoxy-2-*tert*-butoxycyclopropane (III) which has been identified and characterized by nmr, ir, mass spectroscopy, and elemental analysis. IV was considered to be an intermediate and subsequent attempts to isolate this compound were successful. Cyclization of II was achieved using KNH_2 in liquid NH_3. IV was obtained in yields up to 50% and its identity has been well established. When IV was hydrolyzed, cyclopropenone was obtained. Reaction of IV with 1,3-diphenylisobenzofuran gave the adduct V which was converted to 1,4-diphenyl-2-carbomethoxynaphthalene (VI) using trifluoroacetic acid. VI was identified by conversion to its known hydrazide derivative. IV dimerizes at room temperature to 3,3,6,6-tetramethoxytricyclo[3.1.0.0^{2,4}]cyclohexane (VII) which was characterized by its spectral properties and elemental analysis. Reaction of IV with anhydrous dimethylamine led to 1,1-dimethoxy-2-(dimethylamino)cyclopropane (VIII).

An easy and relatively simple procedure for the preparation of 3,3-dimethoxycyclopropene (IV) was developed during the course of attempts to synthesize compounds potentially capable of intramolecular charge-transfer interaction. The starting material for this synthesis is the commercially available 2,3-dichloropropene (I). Reaction of I with methanol and *N*-bromosuccinimide, using an acid catalyst, yields 1-bromo-3-chloro-2,2-dimethoxypropane (II) in 33–40% yield. Reaction of compound II with KO-*t*-Bu in DMSO led to 1,1-dimethoxy-2-*tert*-butoxycyclopropene (III), which has been identified and characterized by nmr, ir, mass spectroscopy, and elemental analysis. IV was postulated to be an intermediate in the formation of III and subsequent attempts to isolate this compound were successful. Cyclization of II was achieved using KNH_2 in liquid NH_3. IV was obtained in yields up to 50% and its identity has been well established.

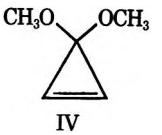


Formation of IV can be accounted for on the following basis.

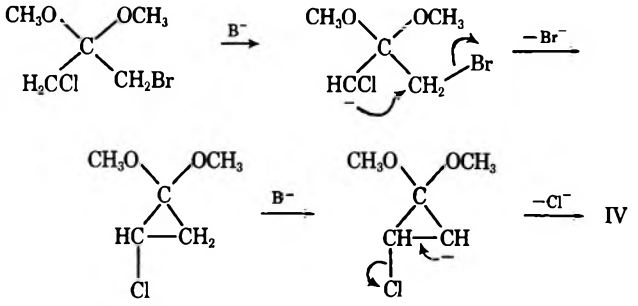
(1) We acknowledge the support of this work by the National Institutes of Health under Grant No. CA-06838.

(2) Presented before the Organic Division, 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970, No. 139.

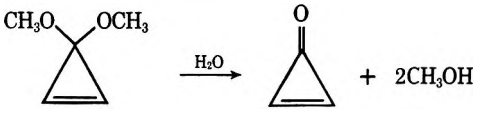
(3) To whom all correspondence should be addressed.



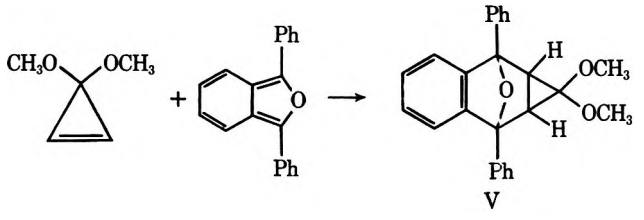
IV



When a pure sample of IV was hydrolyzed, cyclopropenone was obtained.

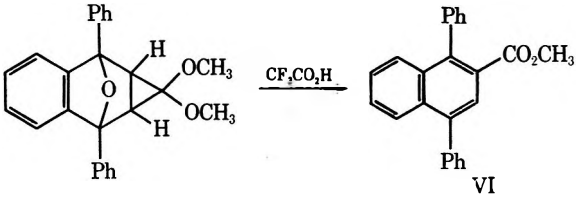


Reaction of IV with 1,3-diphenylisobenzofuran yielded the adduct V, which was then converted to the



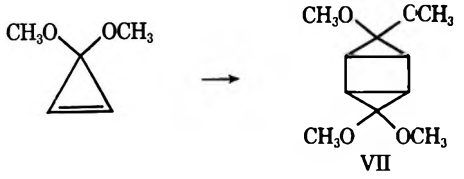
V

unexpected and previously unreported 1,4-diphenyl-2-carbomethoxynaphthalene (VI) by treatment with trifluoroacetic acid. The latter compound was identified by conversion to its known hydrazide derivative.



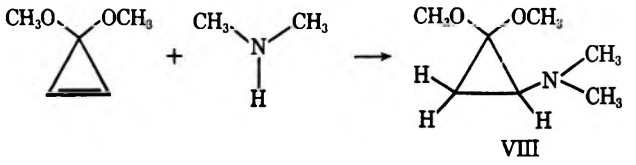
VI

When pure IV is allowed to stand at room temperature it is readily converted to the dimer VII, which was



VII

characterized by its spectral properties and elemental analysis. Reaction of IV with anhydrous dimethylamine led to 1,1-dimethoxy-2-(dimethylamino)cyclopropane (VIII).



VIII

Experimental Section

Preparation of 1-Bromo-3-chloro-2,2-dimethoxypropane (II).—This reaction should be carried out in a hood. To a three-necked, 1-l., round-bottom flask equipped with magnetic stirrer and condenser was added 300 ml of anhydrous methanol, 92 ml (1.0 mol) of 2,3-dichloropropene (I), and 2 drops of concentrated sulfuric acid. To this was added in small portions through the condenser 178 g (1.0 mol) of *N*-bromosuccinimide. After the final addition of *N*-bromosuccinimide, the reaction solution was stirred for 1 hr. Then 5 g of sodium carbonate was added to neutralize the acid catalyst. The reaction was stirred for 15 min longer.

The alcoholic solution was poured into an equal volume of water. The organic layer was removed, and the aqueous layer was extracted twice with pentane. The pentane extracts were combined with the original organic layer and were washed twice with an equal volume of water. The pentane solution was then dried over anhydrous magnesium sulfate, filtered, and placed in a 500-ml Erlenmeyer flask equipped with a rubber stopper. The flask was then cooled in a Dry Ice–isopropyl alcohol bath for 45 min. The pentane was then decanted from the white crystalline product. The product was redissolved in pentane and again frozen. Yields varied from 72 to 88 g (33–40%). II, mp 69.5–70.5°, gave a 2,4-dinitrophenylhydrazone, mp 118–119°, compared to mp 116–119° for the literature value for the 2,4-dinitrophenylhydrazone of 1-bromo-3-chloropropanone-2:[4] ir (CCl_4) 2960 (s), 2850 (s), 1445 and 1425 (s), 1295 and 1280 (s), 1205 and 1180 (s), and 1075 cm^{-1} (broad); nmr (CCl_4) τ 6.40 (s, 1), 6.54 (s, 1), an 6.75 (s, 3). The mass spectrum showed no parent peak but gave P − 31, P − 35, and P − 79 fragments with correct isotope effects.

Preparation of 3,3-Dimethoxycyclopropene (IV).—A dry 500-ml, three-necked, round-bottom flask equipped with a stirring bar, Dry Ice condenser, ammonia inlet, and nitrogen inlet was purged with dry nitrogen for about 5 min. The Dry Ice condenser was then filled with Dry Ice–isopropyl alcohol. A Dry Ice–isopropyl alcohol bath was placed under the flask. The nitrogen flow was reduced to a slow rate, and the condensation of ammonia was begun. After about 450 ml of ammonia had condensed, a small piece (0.5 g) of clean potassium metal was added to the ammonia. The Dry Ice–isopropyl alcohol bath was removed. A catalytic amount of ferric chloride was added to the ammonia solution. When the ammonia reached reflux temperature, the blue color of the dissolved potassium had been replaced by a gray color. The remainder of 11.7 g (0.30 mol) of clean potassium was added in about 0.5-g pieces at such a rate that the reflux rate was controllable. After the final addition of potassium, the color of the solution was gray.

At this point, 21.7 g (0.10 mol) of finely ground II was added very slowly. Care was taken to prevent the finely ground ketal from being blown out of the powder funnel by the rapid vaporization of ammonia. After the addition was completed, the entire reaction assembly was placed in a subzero reaction box thermostatically controlled at −50°. A nitrogen inlet reaching to the bottom of the reaction vessel was used for stirring. A gas outlet from the reaction extended to the hood. The reaction was maintained under these conditions overnight.

The next morning, the reaction vessel was removed from the cold box, and 10.8 g (0.20 mol) of ammonium chloride was added. As the ammonia evaporated, anhydrous ethyl ether was added to replace it. This evaporation process was accelerated by placing the reaction vessel in a heated methanol bath (*ca.* −10°). After most of the ammonia had evaporated, the solution was filtered to remove inorganic salts (if extensive decomposition has not occurred, the salts will be light in color). The ethereal solution was then subjected to *ca.* 50–80 mm with the vacuum being pulled through a reflux condenser maintained at *ca.* −20° and then through a Dry Ice trap. This process was hastened by warming the pot in a methyl alcohol bath. When the quantity of residue seemed to remain constant, the receiver was changed, and the coolant in the reflux condenser was removed. The pressure was then lowered to *ca.* 1–2 mm. Nmr was used to show the absence of ether in the distillate. Yields of IV varied from 4 to 5 g (40–50%). The product should be stored below 0°. The boiling range of the product was *ca.* 25–30° (25 mm); ir (CCl_4) 3000 (w), 2960 (m), 2940 (w), 2905 (w), 2830 (s), 1600 (m), 1450 (w), 1275 (s), 1200 (w), 1075 cm^{-1} (s); nmr (CCl_4) τ 6.77 (s, 6) and 2.23 (s, 2).

(4) A. Roedig, H. G. Kleppe, and G. Markl, *Chem. Ber.*, **95**, 1245 (1962).

Preparation of Cyclopropenone.—When a pure sample of IV was added to D_2O, it was immediately hydrolyzed to cyclopropenone and methyl alcohol, nmr (D_2O) τ 1.0 (s). The water solution of cyclopropenone was saturated with sodium chloride and extracted with methylene chloride. This was dried over magnesium sulfate: nmr (CH_2Cl_2) τ 1.0–1.1 (s); ir (CH_2Cl_2) 1870, 1835, and 1730 cm^{-1}. All of these spectral data agree with those reported by Breslow and Ryan.[5]

Preparation of 1,1-Dimethoxy-2-*tert*-butoxycyclopropane (III).—To 30 ml of dry dimethyl sulfoxide in a 50-ml round-bottom flask was added 2.17 g (0.01 mol) of II and 3.36 g (0.03 mol) of KO-*t*-Bu. The solution turned black quickly. It was stirred at room temperature under a drying tube overnight, after which it was poured into water and extracted several times with ether. (Trouble with emulsion formation was experienced). The ethereal solution was dried over anhydrous magnesium sulfate and filtered. The ether was removed by distillation at atmospheric pressure and the residue was distilled bulb-to-bulb at atmospheric pressure. The product was then chromatographed over silica gel using petroleum ether (bp 20–40°) as eluent. III was shown to be pure by vpc. The yield of clear, colorless product was *ca.* 0.8 g (50%): ir (neat) 3110 (w), 2990 (s), 2850 (s), 1450 (s), 1390 (m), 1365 (s), 1295 (s), 1220 (m), 1195 (w), 1150 (s), 1050 (s), 980 (m), and 880 cm^{-1} (m); nmr (CCl_4) τ 8.83–9 (m, 2), 8.74 (s, 9), 6.69 (s, 3), 6.55 (s, 3), and 6.69–6.78 (m, partially hidden, 1). The hidden proton at τ 6.69–6.78 was shown to exist by double resonance at this region while observing the other cyclopropyl protons at τ 8.83–9.30. The double resonance caused the high-field multiplet to collapse to an AB quartet. The mass spectrum did not give a parent peak but did give P − 57 for loss of *tert*-butyl radical. *Anal.* Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.20; H, 10.47.

Preparation of an Adduct between 1,3-Diphenylisobenzofuran and IV.—To a CCl_4 solution of IV (prepared from 0.01 mol of II) was added 2.7 g (0.01 mol) of 1,3-diphenylisobenzofuran. The reaction was allowed to continue for 1 week at room temperature. At the end of this time, the solvent was removed under vacuum. The residue was dissolved in hot methanol and allowed to cool. The solution was filtered, and the methanol was allowed to evaporate slowly at room temperature in a crystallization dish. The product (V) was isolated as clear hexagonal crystals: mp 140–141.5°; yield 1.1 g (30%); ir (KBr) 3070 (w), 3040 (w), 2940 (m), 2840 (w), 1600 (w), 1500 (w), 1450 (s), 1375 (s), 1340 (s), 1325 (w), 1305 (s), 1240 (s), 1190 (m), 1120 (s), 1090 (w), 1055 (s), 1015 (m), 995 (m), 975 (w), 900 (w), 860 (m), 800 (m), 760 (s), 700 cm^{-1} (s); nmr (CCl_4) τ 7.90 (s, 2), 7.02 (s, 3), 6.68 (s, 3), and 2.16–3.08 (m, 14). The mass spectrum gave a parent peak at *m/e* 370. *Anal.* Calcd for $C_{25}H_{22}O_3$: C, 81.06; H, 5.99. Found: C, 80.92; H, 6.00.

V was warmed with trifluoroacetic acid, which converted it to 1,4-diphenyl-2-methylnaphthoate. The ester was recrystallized from methanol to give a white crystalline solid: mp 162–162.5°; ir (CCl_4) 3080 (m), 3050 (w), 3005 (w), 2970 (m), 1730 (vs), 1600 (w), 1500 (w), 1440 (m), 1390 (m), 1350 (w), 1255 (s), 1230 (s), 1165 (m), 1130 (m), and 1120 cm^{-1} (m); nmr (CCl_4) τ 6.50 (s, 3), 2.84–2.33 (m, 14), and 2.26 (s, 1). The mass spectrum gave a parent peak at *m/e* 338 (also the base peak) and an intense peak at *m/e* 307 indicative of loss of $CH_3O\cdot$. *Anal.* Calcd for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36. Found: C, 85.26; H, 5.42. The hydrazide was prepared from the ester using hydrazine hydrate. The hydrazide had mp 174–176°, compared to the literature value of 179° for the hydrazide of VI.[6]

Dimerization of 3,3-Dimethoxycyclopropene.—A sample of 3,3-dimethoxycyclopropene was placed in a sublimator and left at room temperature for 6 days. During this time white crystals of a new product formed on the condenser and walls of the sublimator. The product was removed from the sublimator and then sublimed twice at 60° (1 mm): ir (CCl_4) 3060 (m), 3005 (m), 2970 and 2950 (s), 2910 (w), 2850 (m), 1440 (m), 1380 (s), 1220 (s), 1180 (m), 1110 (s), 1040 (s), 1010 cm^{-1} (m); nmr (CCl_4) τ 8.27 (s, 2), 6.72 (s, 3), and 6.65 (s, 3). The mass spectrum gave fragments at *m/e* 169, 154, and 126. The parent peak was not observed. These results show the product VII to be 3,3,6,6-tetramethoxytricyclo[3.1.0.$0^{2,4}$]cyclohexane. *Anal.* Calcd for $C_{10}H_{16}O_4$: C, 59.99; H, 8.06. Found: C, 59.62; H, 7.81.

Preparation of 1,1-Dimethoxy-2-dimethylaminocyclopropane (VIII).—To a small pressure bottle was added 1.0 g (0.01 mol) of IV, and 5 ml of dry dimethylamine was condensed into the bottle. The bottle was sealed and heated at 50° for 3 hr. The next day the dimethylamine was distilled from the product. The residue was then distilled at atmospheric pressure: bp 120–140°; yield 0.9 g (60%); ir (neat) 3100 (w), 3000 (w), 2950 (s), 2920 (w), 2840 (m, doublet), 2780 (m), 1660 (m), 1460 (s), 1280 (s), 1220 (s), 1160 (s), 1090 (s), 1060 and 1040 (s), 995 (m), 925 (m), and 880 cm^{-1} (m); nmr (CCl_4) τ 9.17 (m, 2), 8.28 (m, 1), 7.75 (s, 6), 6.77 (s, 3), and 6.63 (s, 3). The mass spectrum gave fragments at P − 1, *m/e* 144, and a base peak at P − 15, *m/e* 130. The hydrochloride had mp 157–159°; ir (KBr) 2760–2300 (ammonium salt), 3100 cm^{-1} (cyclopropyl). *Anal.* Calcd for $C_7H_{16}NO_2Cl$: C, 46.37; H, 8.71; N, 7.71; Cl, 19.52. Found: C, 46.28; H, 8.88; N, 7.71; Cl, 19.64.

Registry No.—II, 22089-54-9; II 2,4-DNP, 34219-71-1; III, 34219-72-2; IV, 23529-83-1; V, 34219-74-4; VI, 34219-75-5; VII, 34219-76-6; VIII, 34219-77-7; VIII HCl, 34219-78-8.

Acknowledgment.—The authors are grateful to Professor M. A. Battiste and Dr. C. A. Sprouse for many helpful discussions during the course of this work.

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The Reaction of Organozinc Compounds with Carbon Monoxide[1]

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Di-*n*-butylzinc and diisopropylzinc react with carbon monoxide at atmospheric pressure in the presence of potassium *tert*-butoxide to furnish, after hydrolysis, the corresponding acyloins. In the absence of the base, the two organozinc compounds are inert to carbon monoxide. Diphenylzinc absorbs only small amounts of carbon monoxide in the presence of potassium *tert*-butoxide and the only identified product is biphenyl. A possible mechanism for the base-promoted carbonylation of dialkylzinc compounds is presented.

The absorption of carbon monoxide by Grignard reagents was first observed by Vinay in 1908.[2] Since that date, the reaction has been studied in detail by a large number of workers using a variety of reaction conditions and catalysts. A host of products has been reported including trialkylcarbinols, ketones, olefins, and acyloins.[3] In contrast, the action of carbon monox-

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

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(3) (a) V. Egorova, *J. Russ. Phys. Chem. Soc.*, **46**, 1319 (1914); (b) F. Gottwalt Fischer and O. Stoffers, *Justus Liebigs Ann. Chem.*, **500**, 253 (1933); (c) W. L. Gilliland and A. A. Blanchard, *J. Amer. Chem. Soc.*, **48**, 410 (1926); (d) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, New York, N. Y., 1954, pp 910–1913.

ide on the closely related organozinc compounds has been mentioned only once. Fischer[3b] reported that phenylzinc bromide is inert to carbon monoxide at atmospheric pressure. We have completed a survey of the reaction of a variety of simple organozinc compounds with carbon monoxide with the results reported below.

Results

Reaction with Di-*n*-butylzinc.—Di-*n*-butylzinc was prepared by the reaction of activated zinc metal with *n*-butyl iodide. This compound does not absorb carbon monoxide at atmospheric pressure either in the absence of solvents or when dissolved in tetrahydrofuran, diglyme, ether, or benzene. However, the addition of an equivalent amount of potassium *tert*-butoxide to a diglyme solution of di-*n*-butylzinc promotes an absorption of 0.85 equiv of carbon monoxide which is complete in 3 hr at room temperature. Hydrolysis of the reaction mixture with dilute hydrochloric acid produces *n*-butane (1.1 equiv) and *n*-valeroin (0.35 equiv, glpc analysis).

A study of the effect of temperature and amount of base on the reaction of di-*n*-butylzinc with carbon monoxide is shown in Table I. The maximum yield of *n*-valeroin (42%, based on di-*n*-butylzinc) is obtained using 1 equiv of potassium *tert*-butoxide and a reaction temperature of $-15°$. At this temperature the reaction mixture remains nearly colorless throughout the absorption of carbon monoxide. At room temperature or above, the reaction mixtures usually turn black as absorption proceeds.

TABLE I

REACTION OF DI-*n*-BUTYLZINC (10 MMOL) WITH CARBON MONOXIDE IN DIGLYME SOLUTION (1 *M*) AT ATMOSPHERIC PRESSURE AND 25°

Potassium *tert*-butoxide, mmol	Carbon monoxide, mmol	*n*-Valeroin, mmol[a]	*n*-Butane, mmol[b]
20	9.9	4.0	10.0
10	8.5	3.5	11.0
5	3.6	1.2	16.0
1.5	1.4	0.6	18.5
10[c]	9.0	4.2	10.5

[a] Glpc analysis. [b] Measured by gas buret during acid hydrolysis. [c] Reaction at $-15°$.

A number of other bases were studied for their effect on the reaction. Triethylamine, pyridine, *N,N,N,N*-tetramethylethylenediamine, and sodium acetate do not promote the reaction with carbon monoxide in either diglyme or benzene solvents. Sodium methoxide promotes a slow uptake of carbon monoxide which stops after the absorption of 0.1 equiv. No products of the reaction could be identified.

Reaction with *n*-Butylzinc Iodide.—*n*-Butylzinc iodide was made by the addition of anhydrous zinc iodide to a solution of di-*n*-butylzinc in diglyme. This compound is inert to carbon monoxide at atmospheric pressure either with or without added potassium *tert*-butoxide.

Reaction with Diisopropylzinc.—Diisopropylzinc behaves similarly to di-*n*-butylzinc. In the absence of potassium *tert*-butoxide the compound is inert to carbon monoxide. In the presence of 1 equiv of the base, the compound absorbs 0.9 equiv of carbon monoxide at $-15°$ and atmospheric pressure. Hydrolysis with dilute hydrochloric acid produces isovaleroin (35%, glpc analysis).

Reaction with Diphenylzinc.—Diphenylzinc is inert to carbon monoxide at atmospheric pressure in the absence of a promoter. In the presence of an equivalent amount of potassium *tert*-butoxide, a slow absorption of 0.25 equiv of carbon monoxide occurs. Hydrolysis of the reaction mixture produces biphenyl (0.3 equiv) as the only identified product. The absence of benzoin in the hydrolyzed reaction mixture was established by glpc.

Discussion

In contrast to Grignard reagents, organozinc compounds are unreactive to carbon monoxide in the absence of a promoter. Presumably, this is due to the less polar nature of the zinc–carbon bond. Potassium *tert*-butoxide is an effective promoter for the reaction when present in stoichiometric amounts. It is possible that the function of the base is to coordinate to the zinc compound to furnish a species with greater carbanion character capable of transferring an alkyl group to carbon monoxide. The ability of base to

$$R_2Zn + K^{+}\,{}^{-}OC(CH_3)_3 \rightleftharpoons K^{+}R_2\bar{Z}n{-}OC(CH_3)_3$$

enhance the reactivity of organometallic compounds has been observed in many other cases.[4]

The results in Table I agree reasonably well with the partial stoichiometry shown by the following equation.

$$2R_2Zn + 2K^{+}\,{}^{-}OC(CH_3)_3 + 2CO \xrightarrow{H_3O^+} 2RH + R\overset{\overset{\large O}{\|}}{C}{-}\overset{\overset{\large OH}{|}}{C}HR$$

The reaction of Grignard reagents with carbon monoxide also produces acyloins,[3a] along with a variety of other products. The intermediacy of an acyl magnesium compound has been postulated to explain the formation of these compounds.[3b] An analogous mechanism for the potassium *tert*-butoxide promoted reaction of organozinc compounds with carbon monoxide is consistent with (although not demanded by) our results. From this mechanism, the dialkylzinc compound could furnish a maximum of 0.5 mol of acyloin.

$$2K^{+}R_2\bar{Z}n{-}OC(CH_3)_3 \xrightarrow{CO} 2K^{+}R{-}\underset{\underset{\large OC(CH_3)_3}{|}}{\bar{Z}n}{-}\overset{\overset{\large O}{\|}}{C}R \longrightarrow$$

$$2RZnOC(CH_3)_3 + R\overset{\overset{\large \bar{O}K^+}{|}}{C}{=}\overset{\overset{\large \bar{O}K^+}{|}}{C}R$$

On this basis, the observed yields of *n*-valeroin and isovaleroin are 84 and 70% of the theoretical maximum, respectively.

The potassium *tert*-butoxide promoted reaction of diphenylzinc with carbon monoxide proceeds differently from that of the dialkylzinc compounds. Benzoin is not formed and the only identified product is biphenyl. Presumably other organic products are

(4) *Cf.* C. G. Screttas and J. F. Eastham, *J. Amer. Chem. Soc.*, **87**, 1379 (1965).

formed which account for the slight uptake of carbon monoxide.

Experimental Section

Potassium *tert*-butoxide was obtained from MSA Research Corp. Diglyme was distilled from lithium aluminum hydride and stored under nitrogen. Glpc analyses were performed using a 6-ft SE-30 column (5.0% on Chromosorb W, DMCS treated).

Preparation of Di-*n*-butylzinc.—The procedure was essentially that described by Noller[5] except that a specially activated zinc–copper couple,[6] prepared by the treatment of granular zinc (20 mesh) with cupric acetate in glacial acetic acid, was used for the reaction with *n*-butyl iodide. The yield of di-*n*-butylzinc was 75–80%, bp 81–82° (9 mm).

Preparation of Diisopropylzinc.—Reaction of the activated zinc–copper couple with isopropyl iodide produced only modest yields (0–25%) of diisopropylzinc. Yields of 70–75% were obtained by the reaction of isopropylmagnesium bromide with anhydrous zinc iodide in ether solution followed by distillation under reduced pressure.

Preparation of Diphenylzinc.—Diphenylzinc was obtained by the reaction of phenyllithium with zinc iodide.[7]

Reaction of Di-*n*-butylzinc with Carbon Monoxide.—The following procedure is illustrative of the general technique. A dry 50-ml round-bottom flask equipped with magnetic stirring and septum inlet was connected to a gas buret filled with carbon monoxide, the system was flushed with carbon monoxide, and 30 ml (30 mmol) of a solution of potassium *tert*-butoxide in diglyme was injected. The flask was immersed in a cooling bath maintained at a temperature of −15° and stirring was initiated. Di-*n*-butylzinc (30 mmol, 5.28 ml) was injected by means of a syringe and the uptake of carbon monoxide was recorded. Complete absorbance of the gas required 3 hr. A total of 27 mmol of carbon monoxide was absorbed. The reaction mixture was quenched by adding it to 10 ml of cold 5 *M* hydrochloric acid. (Addition of the acid to the reaction mixture results in a lower recovery of the acyloin.) The volume of gas evolved corresponded to 30 mmol of *n*-butane. The clear solution was extracted with 50 ml of pentane and the organic phase was then washed with three 30-mmol portions of *n*-butane. The clear solution was extracted with 50 ml of pentane and the organic phase was then washed with three 30-ml portions of water to remove diglyme. Glpc analysis of an aliquot established the formation of 12.1 mmol of *n*-valeroin. The product was isolated by removal of the solvent and distillation under reduced pressure to obtain 1.77 g (10 mmol) of pure *n*-valeroin, mp 60° (0.5 mm), $n^{24.2}$D 1.4312 (lit.[8] $n^{26.6}$D 1.4298), mp of phenylosazone 126.5–127.5° (lit.[9] mp 127°).

Reaction of Diisopropylzinc with Carbon Monoxide.—The general procedure was identical with that described above for the reaction with di-*n*-butylzinc. Distillation produced isobutyroin, bp 70° (0.5 mm), $n^{23.8}$D 1.4178 (lit.[10] $n^{26.6}$D 1.4159), mp of phenylosazone 136–137° (lit.[11] mp 139–140°).

Registry No.—Carbon monoxide, 630-08-0; di-*n*-butylzinc, 1119-90-0; *n*-butylzinc iodide, 34219-54-0; diisopropylzinc, 625-81-0; diphenylzinc, 1078-58-6.

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Reduction of *gem*-Dihalocyclopropanes with Zinc

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Some *gem*-dihalocyclopropanes were reduced to monohalocyclopropanes with zinc powder in ethyl alcohol (or isoamyl alcohol) containing 10% of potassium hydroxide. The reduction of *gem*-dibromocyclopropanes led to a mixture of two geometrical isomers, with the *endo*-bromo (*syn*-bromo) isomer predominating. The reduction of *gem*-bromofluorocyclopropanes proceeded with complete retention of configuration at low temperatures (25–80°) but with some inversion at higher temperatures (130–140°). The extent of stereospecificity observed at higher temperatures was greater than those obtained for the tri-*n*-butyltin hydride reduction. These results were explained by postulating cyclopropyl anion intermediate involved in the proton abstraction step.

The reduction of *gem*-dihalocyclopropanes to monohalocyclopropanes has been effected by various reducing agents such as organotin hydride,[1] methylsulfinyl carbanion,[2] Grignard reagent,[3] chromium sulfate,[4] lithium or sodium in alcohol,[5] alkyllithium in alcohol,[6] and lithium aluminum hydride,[7] by catalytic hydrogenation,[8] or by electrochemical methods.[9]

Zinc in acetic acid has also been used as a means of reducing halocyclopropanes. 3,3-Dibromocyclopropane-*cis*-1,2-diacetic acid was partially dehalogenated to afford the corresponding monobromide in 50% yield.[10] Hodgkins and his coworkers[11] obtained 7-phenylbicyclo[4.1.0]heptane by reducing 7-chloro-7-phenylbicyclo[4.1.0]heptane with zinc in ethanol or in aqueous or glacial acetic acid. Annino and his coworkers[12] showed that the zinc metal reduction of optically active 1-bromo-2,2-diphenylcyclopropanecarboxylic acid or its methyl ester gave products of partially inverted configuration, whereas the reduction of its carboxylate anion or 1-bromo-1-methyl-2,2-

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diphenylcyclopropane proceeded with partial retention of configuration. They also showed that the reduction of isomers of 7-bromo-7-chlorobicyclo[4.1.0]heptane with zinc in ethanol–acetic acid resulted in exclusive removal of the bromine with predominant retention of configuration.[13]

Two mechanisms have been proposed for these reactions; one is the displacement of halogen as an anion by a two-electron transfer process leading to the formation of a carbanion, and the other is the one-electron displacement of halogen as an anion leading to a carbon radical which then either reacts with solvent to form the reduced product or adds another electron to form a carbanion intermediate.

This paper will describe the stereochemistry and the mechanism of the reduction of *gem*-dibromo- and *gem*-bromofluorocyclopropanes with zinc in an alcohol containing potassium hydroxide.

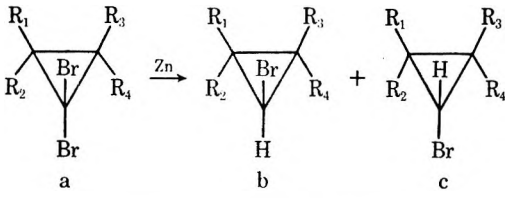
Results

Reduction of *gem*-Dibromocyclopropanes.—The *gem*-dibromocyclopropanes employed for the present study were 7,7-dibromobicyclo[4.1.0]heptane (Ia), 1,1-dibromo-2-phenylcyclopropane (IIa), and 1,1-dibromo-2,2,3-trimethylcyclopropane (IIIa). The reduction was effected by treating them with zinc powder in ethanol containing 10% of potassium hydroxide at 25 or 80°. The results are summarized in Table I.

TABLE I

REDUCTION OF *gem*-DIBROMOCYCLOPROPANES WITH ZINC IN ETHANOL CONTAINING 10% OF POTASSIUM HYDROXIDE

Compd reduced	Reaction temp, °C	Products	Yield, %	Isomer ratio (b/c)
Ia	25	Ib + Ic	30	2.6
Ia	80	Ib + Ic	70	2.9
IIa	25	IIb + IIc	36	2.5
IIa	80	IIb + IIc	66	2.6
IIIa	25	IIIb + IIIc	28	3.3
IIIa	80	IIIb + IIIc	40	5.3

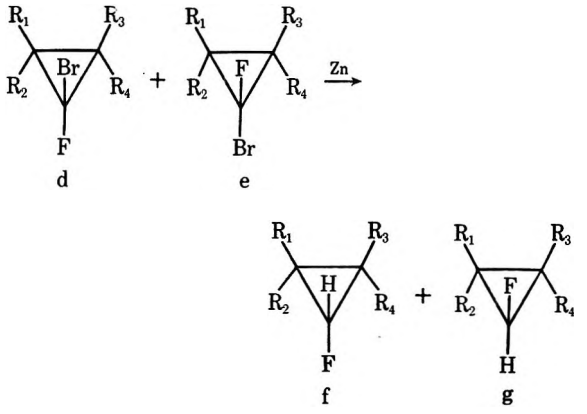


I, $R_1, R_3 = -(CH_2)_4-$; $R_2 = R_4 = H$
II, $R_1 = Ph$; $R_2 = R_3 = R_4 = H$
III, $R_1 = R_2 = R_3 = CH_3$; $R_4 = H$

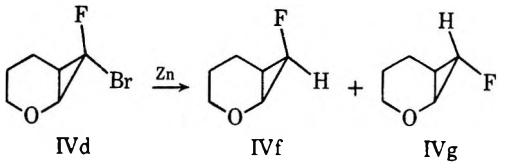
The reduction products were identified by comparing their proton nmr spectra with those of authentic samples. As is shown in Table I, the major component of the monobromocyclopropane thus obtained was the *endo*-bromo (*syn*-bromo) isomer (Ib, IIb, IIIb) with the bromine atom cis to the larger number of substituents.

Reduction of *gem*-Bromofluorocyclopropanes.—The *gem*-bromofluorocyclopropanes employed were 7-bromo-7-fluorobicyclo[4.1.0]heptane (Id and Ie), 1-bromo-1-fluoro-2-phenylcyclopropane (IId and IIe), 1-bromo-1-fluoro-2,2,3-trimethylcyclopropane (IIId and IIIe), and 7-*exo*-bromo-7-*endo*-fluoro-2-oxabicyclo[4.1.0]heptane (IVd). They were prepared by the reaction of the corresponding olefins with bromofluorocarbene as a mixture of two possible geometrical isomers (d and e). Their structural assignments were made by proton and fluorine nmr spectra. The isomer ratio (d/e) obtained for I, II, and III are given in the Experimental Section.

The treatment of a mixture of Id and Ie, IId and IIe, or IIId and IIIe with zinc under the same conditions as used for the reduction of *gem*-dibromocyclopropanes resulted in the selective reduction of the bromine to give an isomeric mixture of monofluorocyclopropanes (f and g).



The isomer ratio of the monofluorocyclopropanes thus formed (f/g) was generally very close to that of the starting *gem*-bromofluorocyclopropane (d/e), except for the reduction of IIId and IIIe.[14] These results strongly suggested the stereospecific nature of the reduction. The degree of stereospecificity was therefore examined by isolating each of the isomers (Id, Ie, IId, IIe, IIId, and IVd) pure and reducing them separately with zinc at 25, 80, and 135–140° in ethyl or isoamyl alcohol, to give the results shown in Tables II and III.



As is evident from Table II, the reductions of Id, Ie, IId, IIe, and IIId occurred essentially stereospecifically at 25 or at 80°, but with some inversion of configuration at 135–140°. The reduction of IVd, on the other hand, gave 4 and 9% of the inversion product (IVg) at 80 and 130°, respectively.

Table III also lists the results of the reduction of IVd with tri-*n*-butyltin hydride, a well-known radical reducing agent, at 130°; the relative amount of the inversion product was 39% when the reduction was

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(14) In the reduction of a mixture of IIId and IIIe at 80°, the isomer ratio of the reduction product (IIIf/IIIg = 7.8) was very different from that of the starting material (IIId/IIIe = 3.6). It must be due to the decomposition of IIIe under the reaction conditions before being reduced. When a mixture of IIId and IIIe was heated at 80° in ethanol containing 10% of potassium hydroxide, IIIe was decomposed with ring opening but IIId was recovered unchanged. The reduction of IIId proceeded stereospecifically at 80° to give only one isomer (IIIf) of retained configuration.

TABLE II

REDUCTION OF *gem*-BROMOFLUOROCYCLOPROPANE ISOMERS WITH ZINC

Compd reduced	Solvent	Reaction temp, °C	Retention product, %	Inversion product, %	Yield, %
Id	EtOH	25	100	0	65
Id	EtOH	80	100	0	83
Id	AmOH	135–140	97	3	85
Ie	EtOH	25	100	0	62
Ie	EtOH	80	100	0	80
Ie	AmOH	135–140	97	3	85
IId	EtOH	25	100	0	59
IId	EtOH	80	100	0	79
IId	AmOH	135–140	95	5	80
IIe	EtOH	25	100	0	62
IIe	EtOH	80	100	0	78
IIe	AmOH	135–140	96	4	78
IIId	EtOH	25	100	0	63
IIId	EtOH	80	100	0	76
IIId	AmOH	135–140	92	8	65

TABLE III

REDUCTION OF 7-*exo*-BROMO-7-*endo*-FLUORO-2-OXABICYCLO[4.1.0]HEPTANE (IVd)

Reducing agent	Reaction temp, °C	Retention product (f), %	Inversion product (g), %	Yield, %
Zn/EtOH–10% KOH	25	100	0	42
Zn/EtOH–10% KOH	80	96	4	68
Zn/*i*-AmOH–10% KOH	130	91	9	62
n-Bu_3SnH	130	61	39	80
n-Bu_3SnH/*i*-AmOH	130	42	58	72

effected without solvent and 58% when isoamyl alcohol was used as solvent.

Discussion

As was described in the preceding section, the reductions of Id, Ie, IId, IIe, and IIId proceeded with complete retention of configuration at low temperatures while inversion occurred to some extent (3–8%) at higher temperatures.

Since it has been fairly well established that cyclopropyl radical intermediates generally lead to products which reflect loss of configurational stability[15] whereas cyclopropyl anion intermediates often give products in which the original configuration is retained,[16] the present results may be explained by postulating that the reduction proceeds *via* cyclopropyl anions at lower temperatures and partially *via* cyclopropyl radicals at higher temperatures. However, as the α-fluorocyclopropyl radicals, which would be formed from these bromofluorocyclopropanes, are known to be capable of maintaining their configuration at low temperatures,[17] the retention of configuration at lower temperatures can also be rationalized by a radical process. On the contrary, the possibility of the formation of α-fluorocyclopropyl anions by a one-step two-electron transfer process can be ruled out in these reactions, because the corresponding cyclopropyl anions, if formed, must be protonated very rapidly in protic solvent[18] before any inversion can occur.[19]

The problem that is left unsolved is, therefore, whether the reduction product is formed by the direct reaction of the radical with solvent or by the addition of an electron to the radical followed by protonation. The reduction of 7-*exo*-bromo-7-*endo*-fluoro-2-oxabicyclo[4.1.0]heptane (IVd) and related compounds throws some light on distinguishing between these two possibilities.

As is shown in Table III, IVd gave 91% of the retention product when reduced with zinc at 130°, but only 61% when reduced with tri-*n*-butyltin hydride at the same temperature. A similar tendency has been observed in the reduction of 7-*exo*-bromo-7-*endo*-chlorobicyclo[4.1.0]heptane; the reduction with zinc led to a higher retention of configuration (95%)[13] than the reduction with tri-*n*-butyltin hydride (76%).[20] These results are best explained by assuming that cyclopropyl anions, rather than cyclopropyl radicals, are involved in the hydrogen abstraction step of the reaction.

The possibility that cyclopropyl radicals are true intermediates and abstract hydrogen from solvent at a faster rate than from tri-*n*-butyltin hydride may be excluded not only by the well-known high ability of organotin hydrides in hydrogen transfer reactions,[21] but also by the fact that the tri-*n*-butyltin hydride reduction of IVd proceeded with a higher degree of retention without solvent than in the presence of isoamyl alcohol.

The mechanism now proposed as the most plausible one for the zinc reduction of *gem*-bromofluorocyclopropanes is shown in Scheme I. Pyramidal cyclopropyl radicals are formed first by a one-electron transfer; the rate of their inversion is so slow at low temperatures that nearly all of them are converted to cyclopropyl anions by another one-electron transfer and then protonated rapidly to form the stereospecific reduction product. At higher temperatures, however, the inversion of cyclopropyl radicals can occur at a rate fast enough to compete with the addition of an electron, and hence the complete stereospecificity is lost.

The lower stereospecificity in the reduction of 7-*exo*-bromo-7-*endo*-fluoro-2-oxabicyclo[4.1.0]heptane (IVd), compared with that of 7-*exo*-bromo-7-*endo*-fluorobicyclo[4.1.0]heptane (Ie), may be ascribed to the effect of ring oxygen of increasing the rate of inversion, which has already been discussed in a separate paper.[17b]

The predominant formation of the *endo*-bromo (*syn*-bromo) isomers in the reduction of *gem*-dibromocyclopropane suggests that the attack by zinc metal at the less hindered C–Br bond of *gem*-dibromo compounds occurs more readily than at the more hindered C–Br

(15) D. E. Applequist and A. H. Perterson, *J. Amer. Chem. Soc.*, **82**, 2372 (1960); R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963); H. M. Walborsky, C.-J. Chen, and J. L. Webb, *Tetrahedron Lett.*, 3551 (1964); H. M. Walborsky, *Rec. Chem. Progr.*, **23**, 75 (1962).

(16) H. M. Walborsky, F. J. Impastato, and A. E. Young, *J. Amer. Chem. Soc.*, **86**, 3283 (1964); H. M. Walborsky and A. E. Young, *ibid.*, **86**, 3288 (1964); J. B. Pierce and H. M. Walborsky, *J. Org. Chem.*, **33**, 1962 (1968).

(17) (a) T. Ando, F. Namigata, H. Yamanaka, and W. Funasaka, *J. Amer. Chem. Soc.*, **89**, 5719 (1967); (b) T. Ando, H. Yamanaka, F. Namigata, and W. Funasaka, *J. Org. Chem.*, **35**, 33 (1970).

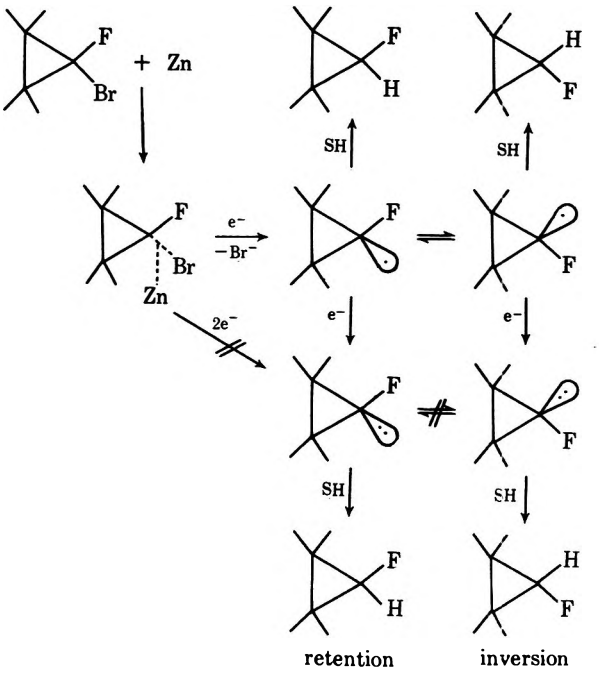
(18) H. M. Walborsky, A. A. Youssef, and J. M. Notes, *J. Amer. Chem. Soc.*, **84**, 2465 (1962); H. M. Walborsky and J. M. Notes, *ibid.*, **92**, 2445 (1970); J. M. Notes and H. M. Walborsky, *ibid.*, **92**, 3697 (1970).

(19) The assumption that α-fluorocyclopropyl anion does not invert at 135° under these conditions is not unreasonable, since α-fluorocyclopropyl radical is configurationally stable at 135°.[17]

(20) T. Ando, K. Kushima, H. Yamanaka, and W. Funasaka, unpublished results.

(21) L. Kaplan, *J. Amer. Chem. Soc.*, **88**, 4531 (1966).

SCHEME I



bond, and the resulting α-bromocyclopropyl radical abstracts an electron to form a carbanion which is then protonated stereospecifically. The possibility cannot be excluded that the attack by zinc occurs exclusively on the less hindered bromine and the resulting *endo*-bromo (*syn*-bromo) radical partially inverts its configuration before it abstracts an electron, since α-bromocyclopropyl radicals can invert very rapidly, relative to α-fluorocyclopropyl radicals, even at lower temperatures. This seems very unlikely, however, in view of the results of the reduction of pure isomers of *gem*-bromofluorocyclopropane, *i.e.*, the stereospecific reduction of the *endo*-bromine as well as the *exo*-bromine.

Experimental Section

Preparation of *gem*-Dihalocyclopropanes.—The *gem*-dibromocyclopropanes were prepared by the reaction of the corresponding olefins with dibromocarbene.[22] The *gem*-bromofluorocyclopropanes were obtained by the reaction of the corresponding olefins with bromofluorocarbene, generated by the reaction of bromoform with potassium *tert*-butoxide at −5 to −10°.

7-Bromo-7-fluorobicyclo[4.1.0]heptane (Id and Ie) was obtained in 44% yield (isomer ratio, Id/Ie = 1.8): bp 42.5–44° (6 mm); n^{20}D 1.4390; nmr, Id, δ_F 41 ppm (upfield from trifluoroacetic acid as external reference), J_{HF}^{cis} = 21 Hz; Ie, δ_F 76 ppm, J_{HF}^{trans} = 13 Hz (half-height width).

1-Bromo-1-fluoro-2-phenylcyclopropane (IId and IIe) was obtained in 37% yield (IId/IIe = 1.8): bp 71–72° (5 mm); n^{21}D 1.5350; nmr, IId, δ_F 44 ppm, J_{HMF}^{cis} = 17 Hz; IIe, δ_F 65 ppm, J_{HMF}^{trans} = 3 Hz (H_M denotes the hydrogen bonded to carbon atom with phenyl group).

1-Bromo-1-fluoro-2,2,3-trimethylcyclopropane (IIId and IIIe) was obtained in 33% yield (IIId/IIIe = 3.6): bp 52–53° (60 mm); n^{21}D 1.4403; nmr, IIId, δ_F 53 ppm, J_{HF}^{cis} = 23.5 Hz; IIIe, δ_F 70 ppm, J_{HF}^{trans} = 9 Hz (half-height width).

7-*exo*-Bromo-7-*endo*-fluoro-2-oxabicyclo[4.1.0]heptane (IVd) was obtained in 22% yield (the other isomer was decomposed under the distillation): bp 40–53 (12 mm); nmr, IVd, δ_F 87.3 ppm, J_{HF}^{trans} = 7.5 and 0 Hz.

Separation of Id and Ie, and of IId and IIe, was performed by preparative glpc (tricresyl phosphate at 100° and Apiezon Greese L at 120°). Isolation of pure IIId and IVd was achieved by heating an isomeric mixture of IIId and IIIe and of IVd and IVe (the isomer of IVd, small amount), respectively, with an excess of quinoline, followed by vacuum distillation. This treatment resulted in the decomposition of only one of the isomers, the other isomer being recovered unchanged.[23]

Reduction of *gem*-Dihalocyclopropanes.—The *gem*-dihalocyclopropane (0.5–1.0 g) was added to 10 ml of ethanol (or isoamyl alcohol) containing 1 g of potassium hydroxide and 3 g of zinc, and the mixture was stirred for 48 hr at 25°, 20 hr at 80°, or 12 hr at 135–140°. The reaction mixture was filtered, and 100 ml of water was added to the filtrate. The aqueous layer was extracted with ether. The organic layer and the ethereal extract were combined, washed with water, dried over sodium sulfate, and concentrated carefully *in vacuo* at room temperature. Glpc separation of the residue gave the geometrical isomers of monohalocyclopropanes and unchanged starting material.

Monobromocyclopropanes thus formed were identified by comparison of their ir spectra, proton nmr data, and retention times in glpc with those of authentic samples.[1] Monofluorocyclopropanes were also identified by ir, proton nmr, and fluorine nmr spectra, as well as by retention times in glpc.[17]

Registry No.—Ia, 2415-79-4; Id, 19144-90-2; Ie, 19144-91-3; IIa, 3234-51-3; IId, 32347-17-4; IIe, 32347-16-3; IIIa, 21960-71-4; IIId, 34217-06-6; IIIe, 34217-07-7; IVd, 34217-08-8; zinc, 7440-66-6.

(22) W. von E. Doering and A. K. Hoffmann, *J. Amer. Chem. Soc.*, **76**, 6162 (1954).

(23) T. Ando, H. Hosaka, H. Yamanaka, and W. Funasaka, *Bull. Chem. Soc. Jap.*, **42**, 2013 (1969).

Reaction of Trimethylsilyl Azide with Anhydrides and Imides. A New Uracil Synthesis *via* Nitrogen Insertion

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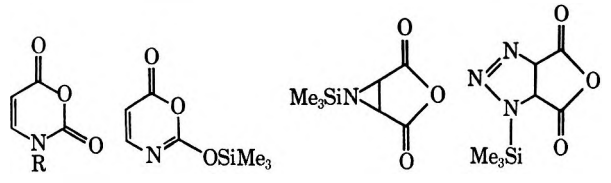
Trimethylsilyl azide reacts with maleic anhydride to give 1-trimethylsilyl-1,3-oxazine-2,4(6*H*)-dione (1) formed by cyclization of trimethylsilyl 2-isocyanatoacrylate which arises from a Curtius rearrangement of a maleic anhydride–silyl azide adduct. The analogous reaction with *N*-alkylmaleimides gives the cycloaddition product, 1-trimethylsilyl-4,5-dicarboximido-1,2,3-triazoline (18), which forms 2-aminomaleimides upon thermolysis. Application of the maleic anhydride reaction to *N*-butylisomaleimide (20) gave 3-butyluracil and a new entry into the pyrimidinedione ring system.

Organic azides are well known to behave as 1,3 dipoles toward a wide variety of olefinic[1] and polar unsaturated[2] linkages. Organometallic azides of tin[3] and silicon[4] appear to behave similarly. The reactions of maleic anhydride and *N*-phenylmaleimide with aryl azides are well documented, exhibiting Hammett ρ constants of -1.1 and -0.8, respectively. The rate constants for reaction with phenyl azide at 25° are respectively 72 and 2.8 $\times$ 10^{-6}.[1a] The reaction of trimethylsilyl azide with benzonitrile proceeded analogously to the reaction of phenyl azide with the latter substrate, affording after hydrolysis 5-phenyltetrazole and 3,5-diphenyltriazole.[4c] Typical conditions involve an extended reflux period in an excess of substrate.

Reactions of Trimethylsilyl Azide with Anhydrides.— The reaction of trimethylsilyl azide (TMSA) with maleic anhydride did not fit into this pattern. Admixture of the reactants gave rise to a vigorous evolution of nitrogen and a violent exotherm. With benzene as diluent the reaction was moderated, but at 50° rapid evolution of nitrogen was observed. When the reaction mixture was chilled colorless crystals, $C_7H_{11}NO_3Si$, were isolated whose spectral parameters were in accord with structure **1** or **2**. The presence of two



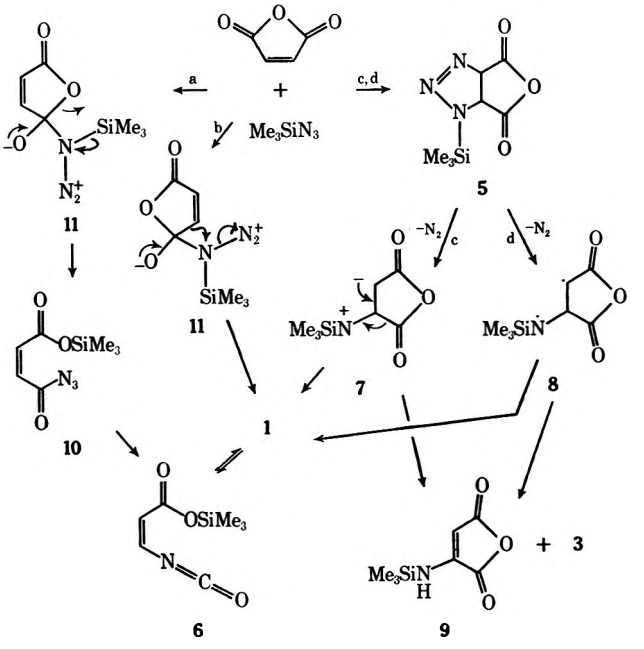
1, R = Me_3Si **2** **3** **5**

4, R = H

resonances in the olefinic region of the nmr spectrum definitely ruled out aziridine **3**, which might have been expected to be formed by thermolysis of an initially formed Δ^2-1,2,3-triazoline, *e.g.*, **5**.[5]

Since the ir spectrum of the crystals showed a medium band at 990 (SiN) and only weak absorbance at 1090 cm^{-1} (SiO), structure **1** is favored. Further work-up of the reaction mixture or, alternatively, exposure of **1** to moisture, gave 1,3-oxazine-2,4(6*H*)-dione (**4**), the *N*-carboxyanhydride of 2-aminoacrylic acid.

Thus the overall reaction involves the insertion of an –NH– moiety between the carbonyl and olefinic carbon atoms of maleic anhydride. At least four mechanisms (a–d) may be postulated for this transformation.



6 **9**

Path c and its radical analog d involve intermediates similar to those proposed by Huisgen[5] to obtain in the thermolysis of triazoline. By analogy to known pathways of triazoline decomposition,[5] **7** or **8** would be expected to cyclize to aziridine **3** or to enamine **9** *via* hydrogen migration. Such migration should be favored over acyl migration leading to **1**. Yellow products similar to **9** were isolated from the reaction of maleimides with TMSA, *vide infra*, and, since the present reaction mixture took on a deep orange coloration, the presence of **9** as a minor product is a distinct possibility.

Path b bears some analogy to a Schmidt reaction, such as the conversion of substituted benzoquinones to azepinones by treatment with sulfuric and hydrazoic acids,[6] but collapse of **11** to product *via* b, which requires alkenyl group migration, must be viewed as less favorable than conversion to **10** through C–O bond rupture. Path a then proceeds through Curtius rearrangement of acyl azide **10** to isocyanate **6** which should be facile in refluxing benzene. The cyclization of **6** to **1** finds analogy in the known equilibrium between silylated *N*-carboxyanhydrides and the open-chain

(1) (a) R. Huisgen, G. Szeimies, and L. Moebius, *Chem. Ber.*, **100**, 2494 (1967); (b) S. Patai, Ed., "The Chemistry of Alkenes," Interscience, New York, N. Y., 1964, pp 808–878.

(2) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565, 633 (1963).

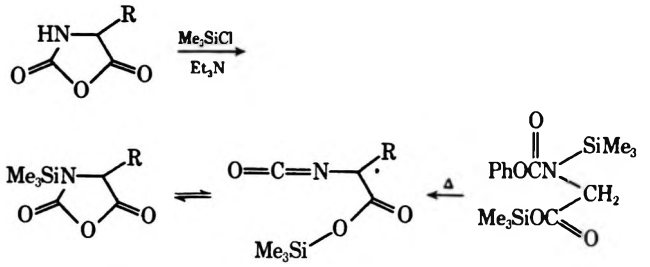
(3) P. Dunn and D. Oldfield, *Aust. J. Chem.*, **21**, 645 (1971).

(4) (a) L. Birkofer and P. Wegner, *Chem. Ber.*, **99**, 2512 (1966); (b) L. Birkofer, F. Müller, and W. Kaiser, *Tetrahedron Lett.*, 2781 (1967); (c) S. S. Washburne and W. R. Peterson, *J. Organometal. Chem.*, **21**, 427 (1970).

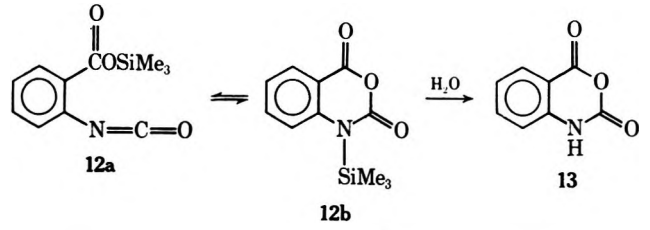
(5) G. Szeimies and R. Huisgen, *Chem. Ber.*, **99**, 491 (1966).

(6) D. Misiti, H. W. Moore, and K. Folkers, *Tetrahedron Lett.*, 1071 (1965).

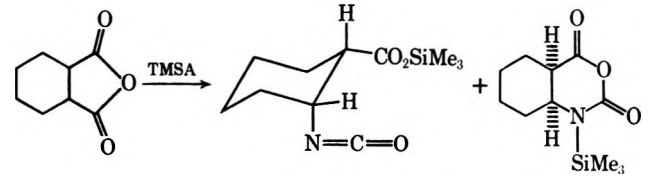
isocyanates.[7] That such an equilibrium exists was shown by production of the same mixture by either silylation of *N*-carboxyanhydrides or thermolysis of *N*-(phenoxycarbonyl)-*N*-(trimethylsilyl)amino carboxylates. That such an equilibrium between **1** and **6** exists is shown by the fact that a solution ir (but not a solid phase ir) of **1** shows an absorption at 2240 cm^{-1}.



In confirmation of the path a mechanism, we investigated the reaction of TMSA with other anhydrides. Phthalic anhydride, which could not react by path c or d, gave in 84% yield a clear liquid, **12**, which solidified on standing. The nmr spectrum of **12** showed two singlets (ratio of 1:4) in the region of Me_3Si resonances; the ir had both anhydride (1860, 1790 cm^{-1}) and isocyanate (2280 cm^{-1}) absorption. Treatment of **12** with aqueous ethanol afforded isatoic anhydride **13**



in 91% yield. Cyclohexane-*cis*-1,2-dicarboxylic anhydride gave a product with a similar ir spectrum, but the nmr showed a single Me_3Si resonance, a 1-proton signal at δ 2.41, an 0.8-proton signal at 4.20 indicative of a hydrogen adjacent to the strongly deshielding N=C=O group, and a 0.2-proton signal at 3.13 (HCNSi), implying the product to be a 1:4 mixture of *N*-trimethylsilyl *N*-carboxyanhydride and isocyanate. The δ 2.41 proton ($HCCO_2Si$) exhibited coupling constants of 11 and 4 Hz to the adjacent methylene group, implying that the CO_2Si group is equatorial. Succinic



anhydride gave, in 72% yield, trimethyl β-isocyanatopropionate. The ir showed no anhydride absorption and the nmr showed only two clean triplets and a Me_3Si singlet. This product was previously reported to exist exclusively in the isocyanate tautomer.[7]

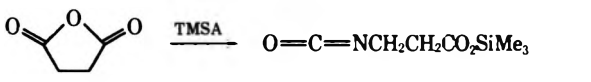
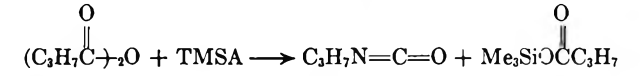


Table I summarizes the equilibrium positions for cyclic anhydrides. Nmr evidence points to the phthalic and hexahydrophthalic anhydride products existing predominately in the isocyanate form. Only in the maleic anhydride case, where the cyclized form (*N*-carboxyanhydride) is apparently crystalline and the open-chain (isocyanate) form is liquid, does the equilibrium favor an *N*-carboxyanhydride.

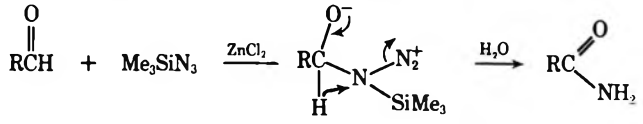
TABLE I
POSITION OF THE *N*-CARBOXYANHYDRIDE–ISOCYANATE EQUILIBRIUM

Anhydride	% product: *N*-Carboxyanhydride	% product: Isocyanate
Succinic	0	100
Hexahydrophthalic	20	80
Phthalic	20	80
Maleic	100	0

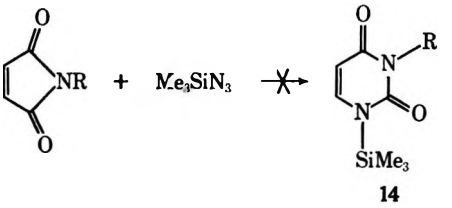
As final confirmation, the reaction of butyric anhydride with TMSA afforded in good yield trimethylsilyl butyrate and propyl isocyanate. Thus the possibility of using trimethylsilyl azide for the conversion of anhydrides to amines with one less carbon atom is opened up.



The mechanism involving an intermediate acyl azide, path a, is favored over path b. The reaction of TMSA with aldehydes and ketones, which must proceed by a mechanism analogous to path b, requires $ZnCl_2$ catalysis.[4b] As the present reactions proceed in the absence of Lewis acids, the direct rearrangement *via* path b is considered unlikely.



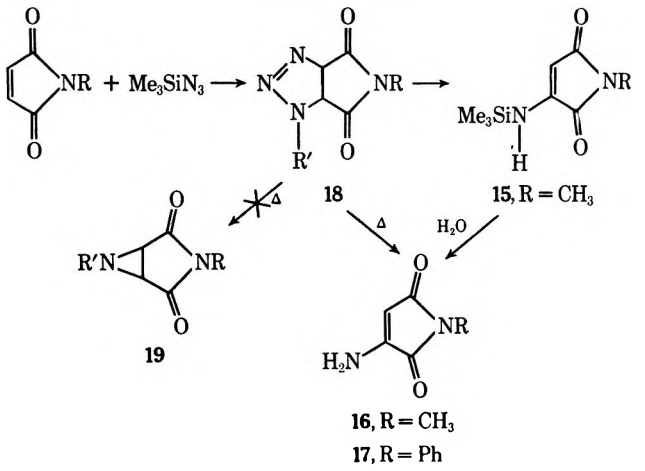
Reactions with Maleimides.—The facile reaction of TMSA with maleic anhydride held out the hope that a reaction with an N-substituted maleimide would afford an entry into the genetically important pyrimidinedione ring system. These hopes could not be realized. A reaction between *N*-methylmaleimide and TMSA in refluxing benzene over a 2-day period evolved no nitrogen but produced an intractable red tar. Switching to the higher boiling mesitylene solvent produced N_2 evolution and a yellow product (**15**, $C_8H_{11}N_2O_2Si$), which, from an nmr spectrum that showed a single unsplit olefinic proton, was clearly not 1-trimethylsilyl-3-methyluracil (**14**). Hydrolysis of **15** gave **16**, which was identified as *N*-methyl-2-aminomaleimide on the basis of the nmr spectrum, which showed a broad 2-proton signal (NH), and an unsplit olefinic proton. When the reaction of TMSA with *N*-methylmaleimide was carried out without solvent, **16** was isolated in lower yield.



(7) G. Greber and H. R. Kricheldorf, *Angew. Chem., Int. Ed. Engl.*, **7**, 942 (1968).

A similar reaction with *N*-phenylmaleimide in nonane (bp 145°) gave, after chromatography on alumina, a modest yield of *N*-phenyl-2-aminomaleimide (**17**).

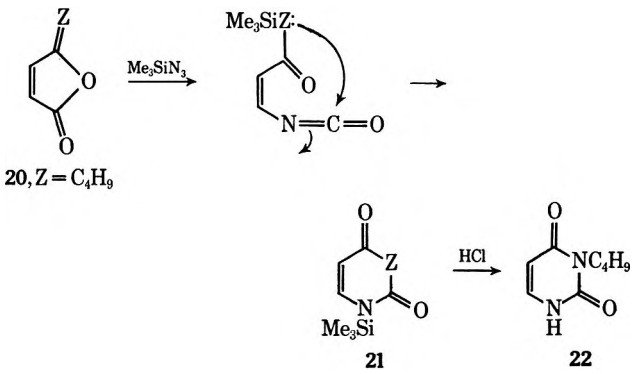
We suspected that the aminomaleimide products arose *via* thermal decomposition of triazoline **18**. Confirmation of this was found when TMSA and *N*-phenylmaleimide were allowed to react for 16 hr in refluxing xylene and produced **18** (R = Ph; R′ = H) after work-up with aqueous ethanol. Thermolysis (Ph_2O, 200°) and chromatography afforded **17** in 68% yield.



The reaction of trimethylsilyl azide with maleimides thus offers a convenient synthesis of aminomaleimides, previously available only *via* treatment of bromomaleimides with sodamide[8] or by ammonolysis of methoxymaleic acid.[9] The thermolysis of **18** (R = H; R′ = Me_3Si) leads to enamine structures and not to aziridines **19** which are found when **18** (R = Ph; R′ = Ar) is thermolyzed.[10] There is no reason to believe that **19** (R′ = Me_2Si) would be unstable had it been formed, for silylaziridines are well known,[11] and the reasons for nonformation of aziridines must lie in subtle facets of the radical character of triazoline decompositions.[5]

The rationale for the different courses taken by trimethylsilyl azide in its reactions with maleic anhydride and maleimides lies in two competing reactions: cycloaddition and acyl–heteroatom cleavage. With maleic anhydride, though cycloaddition to **5** is probably faster than cycloaddition of *N*-phenylmaleimide to **18**,[1a] cycloaddition to **5** can not compete with fast attack of azide to give **10** *via* acyl–oxygen cleavage. Acyl azides can be conveniently prepared from anhydrides,[12] but reactions of azides with imides are unknown; thus maleimides cycloadd silyl azide instead.

Synthesis of a Uracil.—We thought that, if we could couple the fast acyl–oxygen cleavage of maleic anhydride with a group (Z) that could reclose the six-membered ring through attack on the isocyanate group, other heterocycles might be accessible *via* this trimethylsilyl azide reaction. The biologically most important of these is the pyrimidinedione ring system of uracil (Z = NR), and the synthesis of 3-butyluracil was realized when *n*-butylisomaleimide (**20**), readily accessible in two steps from maleic anhydride and butylamine,[13] was allowed to react with TMSA in mesitylene at 110° for 16 hr. The silyl group was cleaved from **21** by treatment with dry HCl in ether, affording 3-butyluracil (**22**).



This method of uracil synthesis should be applicable to practically any 3-substituted derivative. In addition **21** should be a valuable intermediate for the synthesis of nucleotides and nucleosides, since the synthesis of 1-glucosyluracil has been accomplished by treatment of a glucosyl bromide with bis(trimethylsilyl)uracil.[14] The closure of the amido isocyanate to **21** rather than to an isouracil (exocyclic =NR) is probably merely a consequence of the preferred N-alkylation of amides under these conditions, but the detailed mechanistic steps in the conversion of **20** to **22** remain obscure at this time. Further studies on the mechanism of this synthesis of uracil derivatives are under investigation in these laboratories.

Experimental Section

General Comments.—All reactions with trimethylsilyl azide were carried out under purified nitrogen in an efficient hood. Ir spectra were determined on Perkin-Elmer Models 21, 137, 225, and 700 spectrophotometers, uv spectra on a Cary Model 14 spectrophotometer, nmr spectra as 15% solutions in $CDCl_3$ containing 2% TMS on Varian Model T-60, A-60, and XL-100-15 spectrometers. Chemical shifts are given in δ units (parts per million) downfield from internal TMS. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Trimethylsilyl azide was prepared as described by us previously.[15]

Reaction of Trimethylsilyl Azide with Maleic Anhydride.—Addition of 5.8 g (50 mmol) of trimethylsilyl azide to a solution of 50 mmol of maleic anhydride in 20 ml of C_6H_6 and warming the mixture 16 hr at 50° caused evolution of slightly more than 1 l. of N_2. Chilling the red solution to 5° caused separation of 1.4 g (15%) of **1**, mp 120–122° dec, identified by spectra as *N*-trimethylsilyl-1,3-oxazine-2,4(6*H*)-dione: ir (mull) 1770, 1730, 1630, 1255, 990, 845 cm^{-1}; nmr δ 0.48 (9 H, s, Me_3Si–), 5.68 (1 H, d, J = 8 Hz, HC=CN), 7.38 [1 H, d, J = 8 Hz, >C=C-(H)N] ppm.

(8) N. D. Heindel, V. B. Fish, and T. F. Lemke, *J. Org. Chem.*, **33**, 3997 (1968).

(9) A. Arai, M. Kado, I. Chiyomaru, *Yuki Gosei Kagaku Kyokai Shi*, **23**, 435 (1965); *Chem. Abstr.*, **63**, 6855 (1965). A. Arai and I. Ichikizaki, *Kobayashi Rigaku Kenkyushu Hokuku*, **13**, 52 (1963); *Chem. Abstr.*, **63**, 14382*c* (1965).

(10) A. Mustafa, S. M. A. D. Zayed, and S. Khattab, *J. Amer. Chem. Soc.*, **78**, 145 (1956); W. I. Awad, S. M. A. R. Omran, and F. Nageib, *Tetrahedron*, **19**, 1591 (1963).

(11) E. Ettenhuber and K. Rühlmann, *Chem. Ber.*, **101**, 3579 (1968); N. S. Nametkin, V. N. Perchenko, M. E. Kuzovkina, and I. A. Grushebeneko, *Dokl. Akad. Nauk SSSR*, **182**, 842 (1968).

(12) J. March, "Advanced Organic Chemistry," McGraw-Hill, New York, N. Y., 1968, p 341.

(13) T. M. Pyriadi and H. J. Harwood, *J. Org. Chem.*, **36**, 821 (1971).

(14) T. Nishimura and I. Iwai, *Chem. Pharm. Bull. (Tokyo)*, **12**, 357 (1964); *Chem. Abstr.*, **60**, 15968*b* (1964).

(15) S. S. Washburne and W. R. Peterson, Jr., *J. Organometal. Chem.*, **33**, 153 (1971).

Anal. Calcd for $C_7H_{11}NO_3Si$: C, 45.38; H, 5.99. Found: C, 45.83; H, 5.99.

Evaporation of the above filtrate caused separation of a red-brown taffy which was taken up in dry Et_2O. Addition of *n*-hexane caused precipitation of 2.9 g (52%) of 1,3-oxazine-2,4-(6*H*)-dione (**4**): mp 158–159° dec; ir (mull) 1780, 1700, 1208, 1112, 981, 770 cm^{-1}; nmr (DMSO-d_6) δ 5.59 and 7.75 (doublets, J = 7.5 Hz, olefinic H), 8.0–12.0 (1 H, broad, seen only in integration, >NH) ppm.

Anal. Calcd for $C_4H_3NO_3$: C, 42.49; H, 2.67; N, 12.39. Found: C, 42.70; H, 2.88; N, 12.10.

Reaction of TMSA with Phthalic Anhydride.—A mixture of 50 mmol each of phthalic anhydride and TMSA in 50 ml of C_6H_6, heated at reflux for 3 hr, evolved 1 l. of N_2. After removal by distillation of 40 ml of C_6H_6, the mixture was heated at reflux for 16 hr. Fractionation gave 9.9 g (84%) of clear liquid, **12**, bp 110–111° (0.1 mm), which solidified on cooling, mp 54–56°. The ir (CCl_4) (3000, 2950, 2280, 1860, 1775, 1695, 1610, 1575, 1480, 1350, 1310, 1280, 1255, 1080, 1045, 1010, 910, 850 cm^{-1}) and nmr [δ 0.38 ($Me_3SiN<$) and 0.45 (Me_3SiO-) (singlets, 9 H, ratio of 1:4), 7.1–7.4 (4 H, m) ppm] spectra implied the material to be an equilibrium mixture of trimethylsilyl 2-isocyanatobenzoate (**12a**) and *N*-trimethylsilylisatoic anhydride (**12b**), with the latter compound composing the crystalline phase.

Anal. Calcd for $C_{11}H_{13}NO_3Si$: C, 56.14; H, 5.57; N, 5.95. Found: C, 56.39; H, 5.29; N, 5.60.

Isatoic Anhydride.—Treatment of 3.0 g (13 mmol) of **12** with 20 ml of 95% EtOH gave a solution which was evaporated to dryness on the steam bath. The residue was recrystallized from ethyl acetate to give 2.2 g (91%) isatoic anhydride **13**: mp 250–252° (lit.[16] mp 243° dec; ir (mull) 1760, 1723 cm^{-1}

Reaction of TMSA with Cyclohexane-1,2-dicarboxylic Anhydride.—A solution of 23.1 g (0.15 mol) of cyclohexane-1,2-dicarboxylic anhydride (Aldrich) in 60 ml of mesitylene was treated with 0.13 mol of TMSA over 2 hr. After the mixture stirred for 3 hr at 145° (oil bath), volatiles were removed by evaporation at reduced pressure. Fractionation afforded 26.4 g (84%) of trimethylsilyl *cis*-2-isocyanatocyclohexanecarboxylate, bp 90–92° (0.02 mm). The ir (film) [2245 (s), 1850 (w), 1785 (m), 1710 (s), 1250, 1210, 1078, 1025, 942, 842 cm^{-1}] and nmr [δ 0.28 (9 H, s), 1.2–2.1 (8 H, m), 2.41 (1 H, d of t, J = 11, 4 Hz, $HCCO_2Si$), 3.13 (0.2 H, m, HCNSi), 4.20 (0.8 H, d of d, J = 5, 4 Hz, HCNCO) ppm] spectra implied the presence of a minor amount of the *N*-carboxyanhydride tautomer.

Anal. Calcd for $C_{11}H_{19}NO_3Si$: C, 54.74; H, 7.93; N, 5.80. Found: C, 55.38; H, 8.10; N, 5.68.

Reaction of TMSA with Succinic Anhydride.—A solution of 20 g (0.2 mol) of succinic anhydride in 100 ml of mesitylene was heated to 145° while 0.15 mol of TMSA was added over 2 hr. The mixture was stirred for 3 hr at 145°. After removal of volatiles, fractionation afforded 20.1 g (72%) of trimethylsilyl β-isocyanatopropionate: colorless oil; bp 59° (0.3 mm) [lit.[7] bp 56–57° (1 mm)]; ir (film) 2245, 1763, 1708, 1365, 1249, 1192, 883, 843 cm^{-1}; nmr δ 0.28 (9 H, s), 2.56 (2 H, t, J = 6.2 Hz), 3.50 (2 H, t, J = 6.2 Hz) ppm.

Reaction of TMSA with Butyric Anhydride.—Butyric anhydride (15.8 g, 0.1 mol, MC & B) in 30 ml of mesitylene was treated dropwise with 11.5 g (0.1 mol) of TMSA over 10 min. The mixture was stirred for 17 hr at 75° and evolved ~2 l. of N_2. The reaction flask was fitted with a 12-in. glass helices column. Fractionation gave 6.9 g (81%) of propyl isocyanate [bp 85–87°, ir spectrum (film) identical with that of an authentic sample] and 14.1 g (88%) of trimethylsilyl butyrate [bp 144–145° (lit.[17] bp 144°); ir (film) 2950, 1723, 1264, 1253, 1093, 947, 931, 848 cm^{-1}].

Reaction of TMSA with *N*-Methylmaleimide.—To a solution of 20 mmol of *N*-methylmaleimide in 40 ml of mesitylene was added 21 mmol of trimethylsilyl azide. The mixture, heated at reflux 56 hr, evolved 400 ml of N_2. The reaction mixture was filtered from 0.10 g of tan powder and fractionated to afford 2.3 g (58%) of 2-trimethylsilylamino-*N*-methylmaleimide (**15**): yellow oil; bp 85–87° (0.025 mm); mp 69–71°; ir (CCl_4) 3390, 3345, 1775, 1715, 1630, 1440, 1390, 1260, 1125, 1050, 1000 cm^{-1}; nmr δ 0.30 (9 H, s, Me_3Si), 2.90 (3 H, s, $CH_3N<$), 4.92 (1 H, s, HC=C<), 5.05 (1 H, broad, >NH) ppm.

Anal. Calcd for $C_8H_{14}N_2O_2Si$: C, 48.41; H, 7.13; N, 14.13. Found: C, 48.15; H, 6.96; N, 14.23.

2-Amino-*N*-methylmaleimide (**16**).—The silylated maleimide **15** was heated at reflux 5 min in 95% EtOH. Removal of volatiles by evaporation at reduced pressure and recrystallization from benzene–heptane afforded a quantitative yield of 2-amino-*N*-methylmaleimide: yellow crystals; mp 119–121°; ir ($CHCl_3$) 3570, 3455, 1775, 1715, 1660, 1465, 1380, 1240, 1135, 1045 cm^{-1}; nmr ($CDCl_3$) δ 2.82 (3 H, s) and 4.97 (1 H, s); nmr (DMSO-d_6) δ 2.75, 4.73, 7.1 (2 H, broad, $-NH_2$) ppm.

Anal. Calcd for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.73; H, 4.89; N, 21.97.

When *N*-methylmaleimide and TMSA were heated without solvent at 100° until refluxing ceased (2–3 hr) and then heated a further 56 hr at 145° (oil bath), and the reaction mixture was worked up with 95% ethanol as above, **16** was isolated in 43% yield, mp 118–120°.

Reaction of TMSA with *N*-Phenylmaleimide. A. In Xylene.—A mixture of 50 mmol each of TMSA and *N*-phenylmaleimide was heated at reflux for 16 hr in 25 ml of xylene (dried over sieves). The solvent was removed by evaporation at reduced pressure, and the residue was boiled with 50 ml of EtOH. Cooling and filtration afforded 10.0 g (93%) of 4,5-(*N*-phenyldicarboximido)-1,2,3-triazoline (**18**, R = Ph; R′ = H): mp 185°; ir (CCl_4) 3300, 1720, 1500, 1460, 1195 cm^{-1}; nmr (DMSO-d_6) δ 4.70 and 5.60 (doublets, J = 10 Hz, HCNSi and HCN=N), 7.08–7.59 (5 H, m), 11.50 (s, >NH) ppm.

Anal. Calcd for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.91. Found: C, 55.47; H, 3.79; N, 25.62.

B. In Nonane.—The reactants (50 mmol each) were heated at reflux for 20 hr in 125 ml of *n*-nonane (bp 145°), during which time N_2 was evolved and an orange oil beaded on the walls of the flask. Xylene (20 ml) was added; the mixture was cooled, then filtered, and evaporated to give an orange gum. Extraction of the gum with refluxing heptane and cooling of the extracts gave semicrystalline material which was chromatographed on Merck alumina. Elution of the yellow band with $CHCl_3$ afforded, after recrystallization from benzene–heptane, 2.0 g (21%) of 2-amino-*N*-phenylmaleimide (**17**): squat yellow needles; mp 112–113°; ir ($CHCl_3$) 3535, 3440, 1770, 1715, 1655, 1600, 1565, 1500 cm^{-1}; nmr δ 5.03 (1 H, s), 5.16 (2 H, broad, $-NH_2$), 7.35 (5 H, s) ppm.

Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.97; H, 4.15; N, 14.77.

17 Could also be prepared by thermolysis of **18**. A mixture of 1.5 g (7 mmol) of triazoline **18** and 25 ml of Ph_2O evolved N_2 when stirred for 30 min at 200°. After removal of 20 ml of solvent by distillation at reduced pressure and addition of 50 ml of Et_2O, filtration afforded 0.3 g (20%) of unreacted **18**. The filtrate was evaporated at reduced pressure to leave an orange gum which was chromatographed as above to give 0.70 g (68%) of **17**, mp 112–113.5°.

***N*-Butylisomaleimide.**—By the method of Pyriadi and Harwood,[13] *N*-butylmaleamic acid (from maleic anhydride and *n*-butylamine), acetyl chloride, and triethylamine gave 64% *N*-butylisomaleimide (**20**), bp 52° (1 mm), $\nu_{C=O}$ 1800 cm^{-1}.

Reaction of TMSA with *N*-Butylisomaleimide.—A mixture of 25 g (0.16 mol) of isomaleimide **20**, 18.7 g (0.16 mol) of TMSA, and 20 ml of mesitylene was stirred at 110° until N_2 evolution ceased (16 hr). Fractionation of the brown oil left by removal of the volatiles *in vacuo* gave 19.2 g (64%) of a yellow oil, bp 99–101° (0.08 mm), which solidified on standing to a waxy solid, 1-trimethylsilyl-3-*n*-butyluracil (**21**): ir (CCl_4) 3350, 3150, 3060, 1703, 1690, 1627, 1440, 1407, 1363, 1251, 1045, 842 cm^{-1}; nmr δ 0.44 (9 H, s), 0.92 (3 H, t), 1.2–1.5 (4 H, m), 3.82 (2 H, t, $-CH_2CH_2N<$), 5.60 (1 H, d, J = 7.5 Hz), 6.98 (1 H, d, J = 7.5 Hz, HC=CC=O) ppm.

Anal. Calcd for $C_{11}H_{20}N_2O_2Si$: C, 54.96; H, 8.39; N, 11.65. Found: C, 55.17; H, 8.20; N, 11.75.

A freshly distilled sample of the yellow oil showed $\nu_{N=C=O}$ (CCl_4) at 2225 (m) cm^{-1}, indicating the presence of some isocyanate, at least in fresh samples of **21**.

3-Butyluracil (**22**).—Anhydrous HCl was bubbled through an ether solution of **21** for 15 min. Removal of the Et_2O by evaporation *in vacuo* left a quantitative yield of yellow crystals, which after two recrystallizations from MeOH–H_2O afforded 80% 3-*n*-butyluracil (**22**): mp 150–151° (lit.[18] mp 152°); ir ($CHCl_3$) 3350, 3150, 3060, 1718, 1650, 1443, 1420, 808 cm^{-1}; nmr δ 0.94 (3 H, t), 1.1–1.95 (4 H, m), 3.92 (2 H, t), 5.76 (1 H, d, J = 8

(16) E. C. Wagner and M. F. Fegley, *Org. Syn.*, **27**, 45 (1947).

(17) H. H. Anderson, *J. Amer. Chem. Soc.*, **74**, 2371 (1952).

(18) W. Logemann, L. Caprio, and D. Artini, *Farmaco (Pavia), Ed. Sci.*, **12**, 586 (1957); *Chem. Abstr.*, **53**, 18052 (1959).

Hz), 7.20 (1 H, d, J = 8 Hz), 10.48 (1 H, broad, >NH) ppm; $\lambda_{max}^{H_2O}$ 257 nm (ϵ 6600), $\lambda_{max}^{HO^-}$ 287 nm (ϵ 10,000).

Anal. Calcd for $C_5H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.65. Found: C, 56.94; H, 7.04; N, 16.43.

Registry No.—**1**, 34314-62-0; **4**, 34314-63-1; **12a**, 34314-64-2; **12b**, 24314-65-3; **15**, 34314-66-4; **16**, 34314-67-5; **17**, 34314-68-6; **18** (R = Ph; R′ = H), 34314-69-7; **20**, 27396-39-0; **21**, 34314-71-1; **22**, 28-289-95-4; trimethylsilyl *cis*-2-isocyanoatocyclohexanecarboxylate, 34314-733; trimethylsilyl β-isocyanatopropionate, 21655-05-0; trimethylsilyl butyrate, 16844-99-8; TMSA, 4648-54-8.

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Dichloromaleimide Chemistry. I. Substituent Effects on Carbon-13 Nuclear Magnetic Resonance and Mass Spectra

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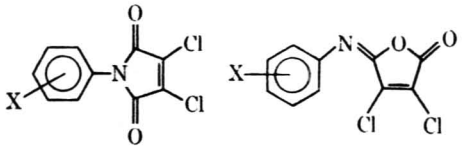
Eight *N*-aryldichloromaleimides (aryl = *p*-$MeOC_6H_4$, *p*-$PhOC_6H_4$, *p*-MeC_6H_4, *p*-PhC_6H_4, Ph, *p*-ClC_6H_4, *m*-ClC_6H_4, *p*-NCC_6H_4) were prepared from the appropriate aniline derivative and dichloromaleic andydride in HOAc.

Depending on the reaction conditions used, *N*-arylmaleimides or *N*-arylisomaleimides can be prepared from substituted anilines and maleic anhydride *via* the corresponding maleamic acids.[1]

Several authors have reported that the analogous reaction of substituted anilines with dichloromaleic anhydride produced *N*-aryldichloromaleimides **1**.[2] However, no evidence was presented to firmly establish that the products obtained were indeed the dichloromaleimides **1** and not the corresponding dichloroisomaleimides **2**.



1 **2**

a, X = *p*-OCH_3 **e**, X = H
b, X = *p*-OC_6H_5 **f**, X = *p*-Cl
c, X = *p*-CH_3 **g**, X = *m*-Cl
d, X = *p*-C_6H_5 **h**, X = *p*-CN

We have prepared a series of eight such imides from the appropriate aniline derivatives and dichloromaleic anhydride in acetic acid. It was not possible to make definitive structural assignments for the members (**a–h**) of this series using proton-nmr and mass spectrometry, elemental analysis, or ir spectroscopy, although the latter did favor **1a–h** over **2a–h**. Further structural proof was therefore sought using Fourier-transform, ^{13}C nmr spectroscopy. One would expect to find only *two* kinds of carbon atoms in the imide rings of **1** while *four* kinds would be expected in the isoimide rings of **2**.

It was found that each ^{13}C nmr spectrum showed two kinds of carbon atoms for the imide ring and the appropriate number and kind of carbon atoms in the *N*-aryl substituent (Table I). The C—Cl and C=O carbon atoms are little affected by remote substituents in the *N*-aryl ring and thus occur within very narrow ranges, 133.1–134.2 and 162.9–163.4 ppm, respectively. The former were readily distinguishable from nearby aromatic peaks because of their relatively low intensity resulting from a diminished nuclear Overhauser effect and the chlorine quadrupole broadening effect. It should be noted that these ranges are very close to the values for the corresponding kinds of carbon atoms in dichloromaleic anhydride, 135.9 and 159.7 ppm, respectively. These spectra leave little doubt that the correct structures are **1a–h**.

A most interesting substituent effect was observed for the aromatic carbon atoms attached to the imide nitrogens. An excellent correlation was found by plotting the ^{13}C chemical shifts of these carbon atoms against σ^+ for the substituents on the aromatic ring[3] (see Figure 1 and Table I); the correlation coefficient was 0.985.

It has recently been shown[4] that ^{13}C chemical shifts for aromatic ring carbon atoms do correlate quite well with calculated electron densities which, to some extent, are reflected by substituent parameters. It should be pointed out that a similar plot in the present example *vs.* σ gave a correlation coefficient of only 0.895. A similar difference in σ^+ and σ correlation coefficients was reported for the para carbons in monosubstituted benzenes.[4]

A study of the mass spectral rearrangements and cleavages of **1a–h** also proved to be very interesting. Reports have appeared in recent years indicating that a major path in the electron impact induced cleavage of N-substituted phthalimides and *N*-phenylmaleimide involved the loss of carbon dioxide from the molecular

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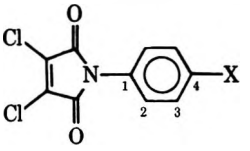
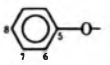
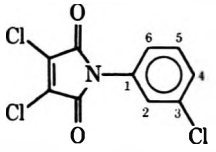
(2) (a) E. L. Martin, C. L. Dickinson, and J. R. Roland, *ibid.*, **26**, 2032 (1961); (b) G. H. F. Walker and F. R. Bradbury, U. S. Patent 2,962,504 (1960); (c) S. L. Shapiro, L. Freedman, and M. J. Karten, U. S. Patent 3,129,225 (1964); (d) M. J. Karten, S. L. Shapiro, E. S. Isaacs, and L. Freedman, *J. Org. Chem.*, **30**, 2657 (1965).

(3) Values for σ^+ taken from H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

(4) G. C. Levy, G. L. Nelson, and J. D. Cargioli, *Chem. Commun.*, 506 (1971).

TABLE I

ANALYTICAL DATA

Compd	X	^{13}C nmr chemical shifts[a] (probable assignments[b]) C-1	Other carbons	Mp, °C[c]	Lit. mp, °C
					
1a	$^{5}CH_3O$-	124.0	129.3 (2); 115.0 (3); 160.2 (4); 56.2 (5)	212–212.5	209–210[d]
1b		126.6	129.8, 130.9 (2, 7[e]); 119.3, 119.9 (3, 6[e]); 156.8, 157.8 (4, 5[e]); 124.8 (8)	183–183.5	*f*
1c	$^{5}CH_3$-	129.1	130.4 (2); 127.6 (3); 139.0 (4); 21.6 (5)	191–192	193–194[g]
1d		129.6	127.5, 128.0, 128.4 (2–8[e])	186.5–187	*f*
1e	H-	131.7	127.8, 129.4, 129.8 (2, 3, 4[e])	205–206	208[d]
1f	Cl-	134.0	129.5, 130.0, 130.8 (2, 3, 4[e])	214.5–215	210–216[d]
1h	^{5}-CN	136.3	128.2 (2); 134.6 (3); 111.8 (4); 119.1 (5)	229–230.5	*f*
					
1g	(Cl-)	134.0	126.5, 127.5, 129.5, 131.6, 133.7 (2, 3, 4, 5, 6[e])	181–182	183[d]

[a] Parts per million downfield from external TMS using DMSO-d_6 as solvent and internal standard. ^{13}C chemical shift of DMSO-d_6 from internal TMS was taken as 40.5 ppm. [b] Personal communications with G. C. Levy. [c] Recrystallization solvents: **1a**, chloroform + cyclohexane; **1b**, benzene + cyclohexane; **1c**, cyclohexane; **1d**, chloroform; **1e**, chloroform; **1f**, chloroform + hexane; **1h**, acetic acid; **1g**, acetic acid. [d] See ref 2c. [e] Not definite assignments. [f] A new compound for which satisfactory analytical data (±0.4% for C, H, and either N or Cl, or both) were reported. [g] See ref 2b.

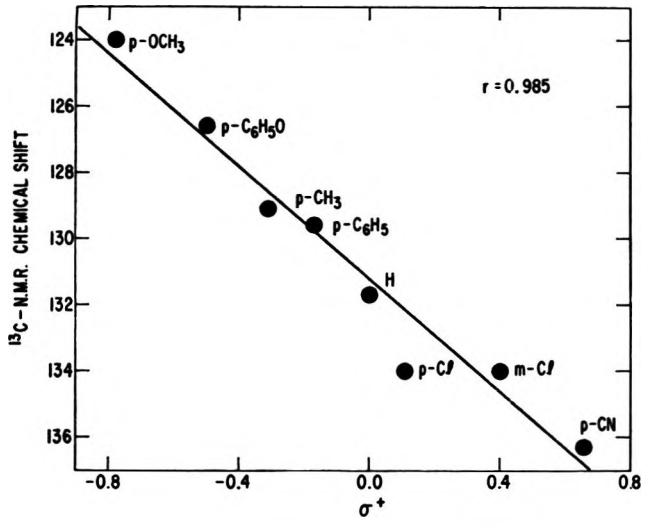


Figure 1.—Correlation of ^{13}C nmr chemical shift for the carbon bearing the imide nitrogen in **1a–h** with substituent parameters.

ions.[5] In view of these findings, we were surprised to find that the mass spectra of the *N*-aryldichloromaleimides (**1a–h**) showed no such $(M - CO_2)^+$ peaks at all (see Figure 2). On the other hand, each showed peaks representing the loss of CO_2 + Cl. This loss does not follow a regular pattern with respect to any substituent parameter (see Table II) and no Cl-, CO_2-, or CO_2-Cl-positive ions were present in any of these spectra. These facts are consistent with the rearrangement–cleavage mechanism proposed in Scheme I. Implied in the last decomposition step of this scheme is that the

TABLE II

SELECTED MASS SPECTRAL PEAK INTENSITIES FOR SUBSTITUTED *N*-PHENYLDICHLOROMALEIMIDES[a]

Substituent	Molecular ion	$(M - CO_2 - Cl)^+$	$(M - C_3Cl_2O)^+$	$(C_3Cl_2O)^+$	$\frac{(M - C_3Cl_2O)^+_{total}}{(C_3Cl_2O)^+_{total}}$[b]
p-OCH_3	100.0 (3)	9.9 (2)	53.0	3.6 (3)	8.41
	100.0 (3)	11.5 (2)	59.3	3.7 (3)	9.12
p-OC_6H_5	100.0 (3)	9.4 (2)	43.8	4.2 (3)	5.92
p-CH_3	100.0 (3)	24.4 (2)	67.0	7.1 (3)	5.40
	100.0 (3)	32.3 (2)	74.0	8.7 (3)	4.87
p-C_6H_5	100.0 (3)	13.7 (2)	72.0	2.2 (3)	18.45
	100.0 (3)	14.7 (2)	67.1	2.0 (3)	19.19
H	100.0 (3)	45.4 (2)	78.5	22.4 (3)	2.00
	100.0 (3)	79.2 (2)	87.5	28.3 (3)	1.77
p-Cl	100.0 (4)	35.6 (3)	81.0 (2)	32.5 (3)	1.91
	100.0 (4)	42.3 (3)	84.1 (2)	31.6 (3)	2.01
m-Cl	100.0 (4)	35.6 (3)	35.3 (2)	32.7 (3)	0.82
p-CN	100.0 (3)	38.9 (2)	30.9	38.9 (3)	0.45

[a] The number in parentheses next to intensity values indicates the number of peaks associated with the chlorine isotopic clusters (if present) for each ion. Intensities given are for the *all*-^{35}Cl peak of each cluster. Differences in the intensity values in two different spectra of a single compound are due to differences of as much as 50–100° in the source temperature of the mass spectrometer and to the use of two different source configurations during the course of this work. It should be noted that, when two ratios (last column) for the same compound were determined, they differed only slightly compared with those values for other compounds. [b] Total intensity for all peaks of $(M - C_3Cl_2O)^+$ cluster (when present) divided by total intensity for all peaks of $(C_3Cl_2O)^+$ cluster.

(5) (a) R. A. W. Johnstone, B. J. Millard, and D. S. Millington, *ibid.*, 600 (1966); (b) J. L. Cotter and R. A. Dine-Hart, *ibid.*, 809 (1966); (c) C. M. Anderson, R. N. Warrener, and C. S. Barnes, *ibid.*, 166 (1968); (d) T. W. Bentley and R. A. W. Johnstone, *J. Chem. Soc. C*, 2354 (1968); (e) J. L. Cotter and R. A. Dine-Hart, *Org. Mass Spectrom.*, **1**, 915 (1968).

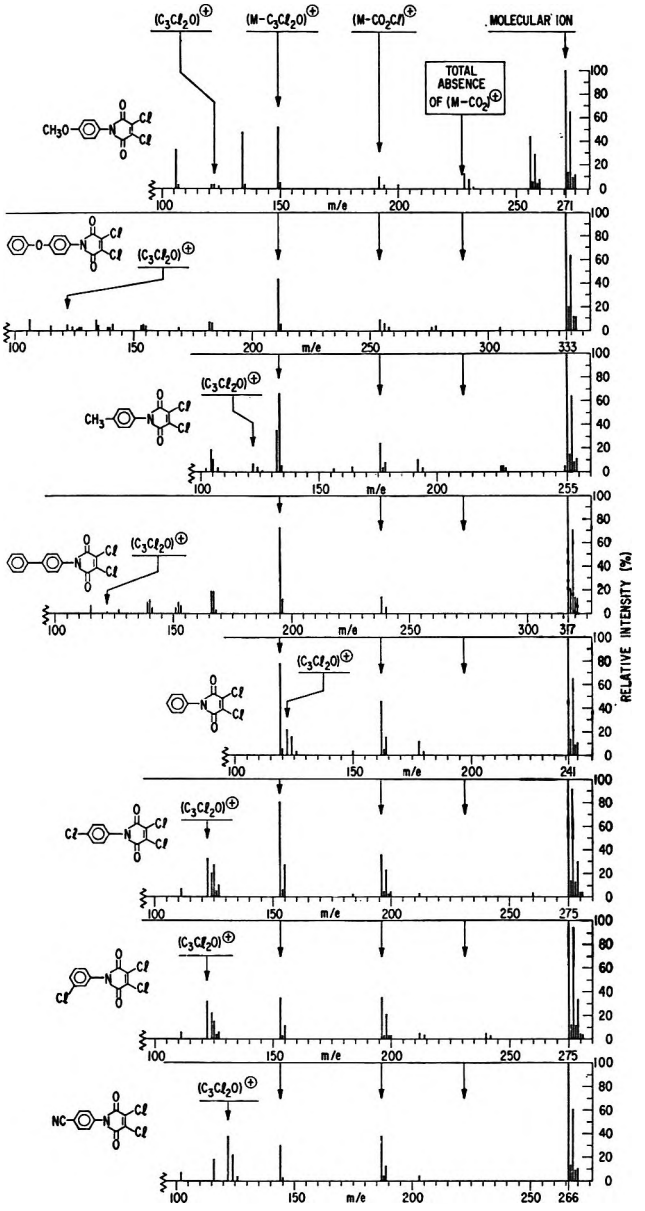
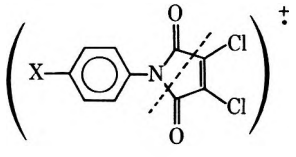


Figure 2.—Mass spectra of 1a–h.

loss of CO_2 and Cl are either concerted or so nearly so that no substantial amount of the $(M - CO_2)^+$ ion [or $M - Cl)^+$ ion] is formed.

The other most prominent cleavage observed in the mass spectra is shown by the dotted line in **3**. Both



3

the $(M - C_3Cl_2O)^+$ and the $(C_3Cl_2O)^+$ ions are observed in all cases and as the expected isotopic clusters (see Table II). The relative intensities of these two ions varied in a regular way depending on the nature of the substituent on the *N*-aryl group. Plotting the log of this ratio *vs.* σ^+ values gives a good straight line with a correlation coefficient of 0.982 (see Figure 3). Thus, the tendency for the charge to remain in the isocyanate half on cleavage depends on the electron-donating (or electron-withdrawing) effect of the ring substituent.

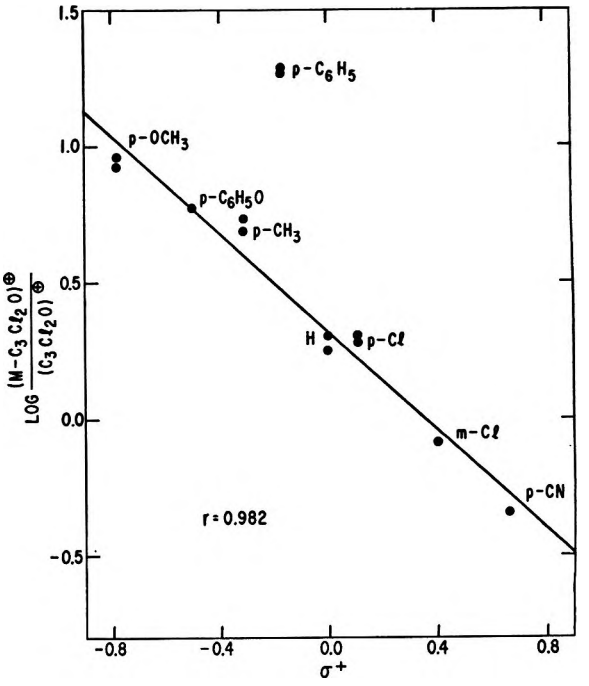
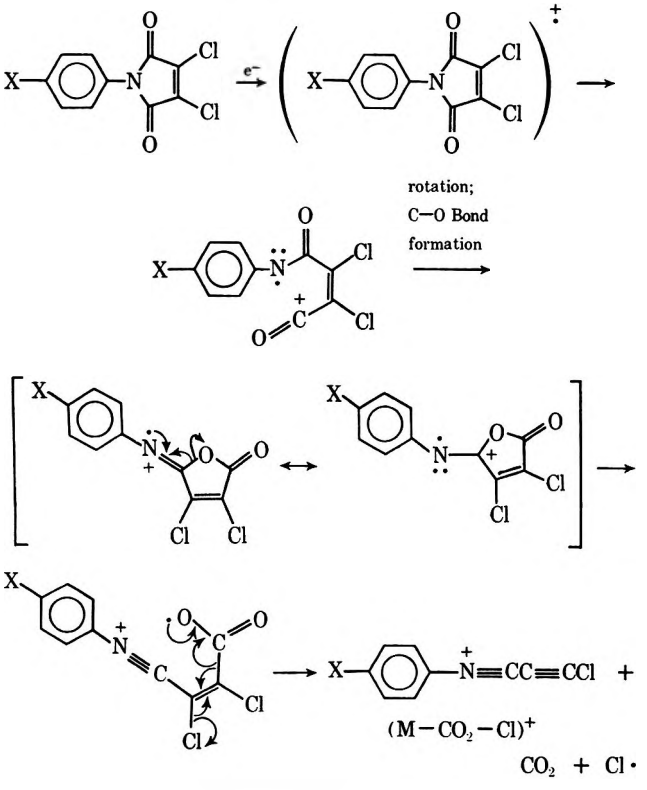


Figure 3.—Relation between the intensities of the $(M - C_3Cl_2O)^+$ and $(C_3Cl_2O)^+$ ions and the substituent parameters.

SCHEME I



(Substituent effects on relative ratios obtained in other mass spectral cleavages have been reported by several authors.[6]) The *p*-phenyl substituent of **1d** is quite unique, however, and apparently gives much more $(M - C_3Cl_2O)^+$ ions than would have been predicted. This may be the result of the formation of an unusually more stable ion than would have been expected from the σ^+ value of p-C_6H_5, a different ion from that pro-

(6) See, for example, (a) F. W. McLafferty and M. M. Bursey, *J. Amer. Chem. Soc.*, **90**, 5299 (1968), and references cited therein; (b) M. M. Bursey, *Org. Mass Spectrom.*, **1**, 31 (1968).

duced in the rest of the series, or other effects such as a different mode of cleavage for **1d**.[7] Indeed, considering these possible differences, it is remarkable that the other seven compounds gave as good a correlation as they did.

Experimental Section

All ^{13}C nmr spectra were recorded with a Varian Associates XL-100-15 nmr spectrometer utilizing complete ^{1}H decoupling at 100 MHz with simultaneous ^{13}C observation at 25.2 MHz. Mass spectra were recorded on a CEC 21-104 analytical mass spectrometer.

Each imide, **1a–h**, was prepared by adding the appropriate aniline derivative slowly (at ~25°) to an excess of the dichloromaleic anhydride in glacial acetic acid. After several hours of stirring at 25°, each system was refluxed for 1 hr and cooled. The products crystallized from the solution on cooling and were readily isolated and purified. Each gave the expected ^{1}H and ^{13}C nmr spectra and mass spectra and showed strong C=O absorption in the ir at ~1725 cm^{-1}. Other analytical data are given in Table I.

Registry No.—**1a**, 34379-53-8; **1b**, 34281-45-3; **1c**, 29244-55-1; **1d**, 34281-46-4; **1e**, 3876-05-9; **1f**, 29236-09-7; **1g**, 34281-49-7; **1h**, 34281-50-0.

Acknowledgments.—The authors are indebted to Dr. G. C. Levy and J. D. Cargioli for their assistance in interpreting the ^{13}C nmr spectra.

(7) Analogous behavior of the *p*-phenyl substituent has been noted before in another kind of correlation: M. M. Bursey and F. W. McLafferty, *J. Amer. Chem. Soc.*, **88**, 529 (1966).

Deuterium and Sulfur-34 Isotope Effects in the Thermal Decomposition of Some Cyclic Sulfones

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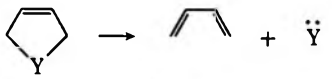
The k_H/k_D ratios in the decomposition of 2,5-dihydrothiophene-*2,2,5,5-d*$_4$ 1,1-dioxide (II) at 120° and 2,4-dimethyl-2,5-dihydrothiophene-*5,5-d*$_2$ 1,1-dioxide (IV) at 105° have been determined in the melt to be 1.094 ± 0.014 and 1.054 ± 0.019, respectively. The sulfur-34 isotope effect in the decomposition of the undeuterated analog of II has also been measured in the melt and in the diethylene glycol diethyl ether solution and $^{32}k/^{34}k$ ratio found to be 1.009 at 99.5°. Both deuterium and sulfur-34 isotope effects can well be accommodated by a concerted mechanism. The deuterium isotope effects are unusually small (about 3.3% per atom D extrapolated to room temperature). Possible explanations of this observation are mentioned.

The mechanism of addition of sulfur dioxide to conjugated acyclic dienes and the retro reaction, the thermal decomposition of cyclic sulfones, has been extensively studied. The two-step mechanism involving dipolar or diradical intermediates has been suggested mainly in earlier work,[1-5] though a concerted mechanism taking place in disrotatory manner has been also proposed.[6]

Woodward and Hoffman[7] predicted on the basis of orbital symmetry arguments that the concerted five-membered ring thermal fragmentation of the type

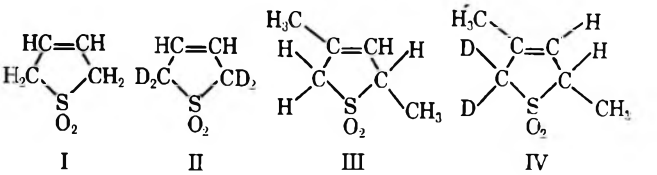


(Y can be SO_2, CO, NH, $\overset{+}{N}{=}\overset{-}{N}$, N–N=O) should be a disrotatory process. Experimental support for this prediction has been presented.[8,9] On the other hand, the photochemical SO_2 extrusion from sulfones occurs by concerted fragmentation[10] in a conrotatory manner, as also predicted by Woodward–Hoffman rules.[7]

We studied the effect of deuteration on the rate of thermal decomposition of sulfolene I (II) and its 2,4-dimethyl analog III (IV). The kinetic sulfur-34 isotope effect in the reaction of I has also been measured. The intent of this work was to gain additional information about the mechanism of these reactions with respect to the timing of the bond-breaking processes and the structure of the transition state.

Results

The kinetics of the thermal decomposition of I were previously studied.[2] We determined energy of activation, frequency factor, and entropy of activation as 33.2 kcal mol^{-1}, 7.1 × 10^{14} sec^{-1}, and 7.0 eu, which is in good agreement with published data (33.6 kcal mol^{-1}, 7.0 × 10^{14} sec^{-1}, and 8.9 eu).[2a,b] Using the sealed tube technique for the kinetic measurements, the rates of decomposition of I, of its tetradeuterated analog II, of 2,4-dimethyl-2,5-dihydrothiophene 1,1-dioxide (III) and of its deuterated analog IV, were determined.



I II III IV

(1) L. R. Drake, S. C. Stowe, and A. M. Partansky, *J. Amer. Chem. Soc.*, **68**, 2521 (1946).

(2) (a) O. Grummitt, A. E. Ardis, and J. Fick, *ibid.*, **72**, 5167 (1950); (b) O. Grummitt and H. Leaver, *ibid.*, **74**, 1595 (1952); (c) O. Grummitt and J. Splitter, *ibid.*, **74**, 3924 (1952); (d) O. Grummitt and A. L. Endrey, *ibid.*, **82**, 3614 (1960).

(3) R. C. Krug and J. A. Rignay, *J. Org. Chem.*, **27**, 1305 (1962).

(4) (a) L. K. Montgomery, K. Schueller, and P. D. Bartlett, *J. Amer. Chem. Soc.*, **86**, 622 (1964); (b) P. D. Bartlett, G. E. H. Wallbillick, and L. K. Montgomery, *J. Org. Chem.*, **32**, 290 (1967).

(5) T. J. Wallace, J. E. Hofmann, and A. Schriesheim, *J. Amer. Chem. Soc.*, **85**, 2739 (1963).

(6) W. L. Bailey and E. W. Cummins, *ibid.*, **76**, 1936, 1940 (1954).

(7) R. B. Woodward and R. Hoffmann, *ibid.*, **87**, 395 (1965); R. Hoffmann and R. B. Woodward, *ibid.*, **87**, 2046 (1965).

(8) (a) W. L. Mock, *ibid.*, **88**, 2857 (1966); (b) W. L. Mock, *ibid.*, **92**, 7610 (1970).

(9) D. McGregor and D. M. Lemal, *ibid.*, **88**, 2858 (1966).

(10) J. Saltiel and L. Metts, *ibid.*, **89**, 2232 (1967).

TABLE I
A TYPICAL KINETIC RUN. RATE OF DECOMPOSITION OF 2,5-DIHYDROTHIOPHENE 1,1-DIOXIDE AT 120 ± 0.15° [a]

Time, sec	HCl, ml	% Completion	$k \times 10^4$, sec^{-1}
0	27.62	0	
600	25.22	12.4	2.21
900	24.20	17.7	2.16
1200	22.98	24.0	2.30
1500	22.28	27.7	2.17
1800	21.38	32.4	2.18
2100	20.45	37.2	2.22
2400	19.62	41.5	2.24
3000	18.28	48.5	2.21
3600	17.32	53.3	2.13
4800	15.20	64.6	2.16
7200	12.64	77.8	2.10
24 hr	8.37	99.0	
		k_{av} = 2.19 ± 0.05[b]	

[a] The sealed tubes containing 0.0004 mol of the sulfone were broken and 15 ml of 0.0756 *M* NaOH was added. The excess of the base was titrated with 0.00411 *M* HCl. [b] Standard deviation of the mean.

Table I shows the results of a typical kinetic run (see Experimental Section).

Table II summarizes the results.

The rates of decomposition of compounds I and II were also measured in 1-butanol. At 116° k_H for I was found to be (1.34 ± 0.02) × 10^{-4}, and k_D for II (1.18 ± 0.04) × 10^{-4} sec^{-1} (uncertainties are standard deviation of the mean of seven kinetic measurements). The rate in 1-butanol is only slightly lower (for about 10%) than the rate in the melt, suggesting that the mechanism is unchanged. The deuterium isotope effect was found to be 13.6 ± 4.7%, which is not significantly different from the value obtained in the melt (9.4 ± 1.4%).

The sulfur-34 isotope effect in the decomposition of I was also determined. The reaction was carried out either in the melt or in diethylene glycol diethyl ether solution at 95.5°. One of the authors found that the isotope effect in the melt was 0.74 ± 0.19% (corrected for ^{18}O, 0.81%) and in diethylene glycol diethyl ether 0.81 ± 0.23% (corrected 0.89%). Another author, using a different mass spectrometer, determined the isotope effect in the melt as 0.90 ± 0.19% (corrected 0.97%). It can be concluded that the ^{34}S isotope effect is about 0.9%.

The maximum isotope effect for breaking a C–S bond can be calculated from Bigeleisen theory.[11] Assuming a C–S stretching frequency[12] of 700 cm^{-1}, the maximum isotope effect for decomposition of the hypothetical C–S molecule was calculated to be 1.28% at 99.5°.

Discussion

Experimental evidence[8,9] indicates that the thermally induced extrusion of sulfur dioxide from sulfolene is a concerted, disrotatory process. The orbital symmetry consideration[7] predicts that this concerted process is disrotatory. Our results can also be best accommodated by this reaction mechanism. Thus, the magnitude of rate deceleration brought about by two deuteriums in IV (5.4 ± 1.9%) is just about half of that for four deuteriums as measured with II (9.4 ± 1.4%). These results indicate that both carbons bound to sulfur in compounds I–IV are probably involved in the reaction transition state in a similar manner, which is in accord with a concerted mechanism. It should be pointed out that essentially the same experimental method has been used by Seltzer[13] in the study of the retrograde Diels–Alder reaction. Although the possibility of a two-step mechanism cannot be excluded on grounds of our results alone, the interpretation of the observed isotope effects in these terms is difficult.

Thus, if such a mechanism were operative, the attachment of a methyl group to one of the carbons bound to sulfur, as in III and IV, would be expected to result in the preferential prior cleavage of that C–S bond which gives rise to a secondary allyl radical. If this first step is rate determining, then the isotope effect observed with IV could be explained in terms of hyperconjugative electron release from the CD bonding orbitals to the neighboring allyl radical. Indeed, small secondary β-deuterium isotope effects have been observed in free radical reactions.[14] However, there is no evidence in the literature that such effects are transmitted through double bonds. Moreover, such β effects are significantly smaller than the corresponding α effects and could be expected to be further reduced if transmitted from a vinylogous position. Therefore it is difficult, if not impossible, to explain in terms of this mechanism the fact that the isotope effect observed with IV is just about one-half of that observed with II. Alternatively, a two-step mechanism with the second step rate determining can be considered. In this case the observed rate constant would be the product of the first step equilibrium constant times the second step rate constant. Ignoring the mentioned vinylogous β-deuterium effect, the observed isotope effect with IV is then due only to the kinetic α effect on the second step, while with II it is due to the product of α isotope effects on the first step equilibrium constant times that on the second step rate constant. If such were the case, the isotope effect with II could be expected to be larger than twice that measured with IV. Hyperconjugative electron release from CD bonds, if operative, would influence the reaction of II and IV in a similar manner and would therefore not change the above expectation.

The secondary deuterium isotope effect found in this work, which in case of a concerted mechanism can be considered as analogous to α effects in solvolyses reactions,[15] is surprisingly small (2.4% per deuterium atom at 120°). Using the equation $\ln (k_H/k_D)_{T_1} = T_2/T_1 \ln (k_H/k_D)_{T_2}$, the isotope effect per deuterium atom at 20° was calculated to be 3.3%, which is much less than usually observed.[16] There is ample evidence in the

(11) J. Bigeleisen and M. G. Mayer, *J. Chem. Phys.*, **15**, 261 (1947); J. Bigeleisen, *ibid.*, **17**, 675 (1949).

(12) W. O. George, R. C. W. Goodman, and J. H. S. Green, *Spectrochim. Acta*, **22**, 1749 (1966).

(13) (a) S. Seltzer, *J. Amer. Chem. Soc.*, **83**, 1861 (1961); (b) *Tetrahedron Lett.*, 457 (1962); (c) *J. Amer. Chem. Soc.*, **85**, 1360 (1963); (d) *ibid.*, **87**, 1534 (1965); (e) *ibid.*, **85**, 14 (1963).

(14) S. Seltzer and E. J. Hamilton, Jr., *J. Amer. Chem. Soc.*, **88**, 3775 (1966); T. Koenig and R. Wolf, *ibid.*, **89**, 2948 (1967); **91**, 2574 (1969).

(15) W. H. Saunders, Jr., S. Ašperger, and D. H. Edison, *ibid.*, **80**, 2421 (1958); K. Mislow, S. Borčić, and V. Prelog, *Helv. Chim. Acta*, **40**, 2477 (1957); A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Amer. Chem. Soc.*, **80**, 2326 (1958).

(16) A. Streitwieser, Jr., "Solvolytic Displacement Reaction," McGraw-Hill, New York, N. Y., 1962, p 173.

TABLE II

RATES OF THERMAL DECOMPOSITION OF COMPOUNDS I–IV

Compd	Atoms of D per molecule	Temp, °C	$k_H \times 10^4$, sec^{-1}	$k_D \times 10^4$, sec^{-1}	k_H/k_D
I	None	120 ± 0.15	2.21 ± 0.02[a]		
II	3.88	120 ± 0.15		2.02 ± 0.01[a]	1.094 ± 0.014
III	None	105 ± 0.10	3.34 ± 0.04[a]		
IV	1.95	105 ± 0.10		3.17 ± 0.02[a]	1.054 ± 0.019

[a] Standard deviation of the mean of five kinetic measurements.

literature[13e,17] that the magnitude of the α effect is correlated to the amount of bond breaking between the deuterated reaction center and the "leaving group" in the reaction transition state. Consequently, an obvious explanation of the observed reduced α effects would be that the reaction transition state is reactant-(sulfolene) like, with little C–S bond stretching. In this respect the measured primary sulfur-34 isotope effect is of interest. Unfortunately, the observed effect of 0.9% can give us only limited information on the extent of C–S bonds weakening in the transition state, since the maximum isotope effect for simultaneous breaking of both C–S bonds is not known.

The experimental value can only be compared with the maximum effect (1.3%) calculated for complete bond cleavage in a hypothetical C–S molecule, which is not a good model for the reaction studied.

It should be noticed that the sulfur-34 isotope effect in the elimination reaction of 2-phenylethyldimethylsulfonium ion with lyate ion[18] and the nitrogen-15 isotope effect in the elimination from the corresponding ammonium ion[19] are roughly $^1/_3$ of the maximum isotope effect for breaking a hypothetical C–S and C–N molecule, respectively. The corresponding α-deuterium isotope effect in ammonium salt is less than 2% per deuterium atom both in aqueous and ethanolic solutions.[20,21]

There are several other factors which, acting singly or in concert, could be responsible for the low α effects observed. Thus, the neighboring SO_2 dipole could influence the C–H (D) vibrational frequencies in sulfolenes, an inductive effect which would be operative in the ground state and largely lost in the transition state.[22] Another possible explanation seems to be in terms of steric hindrance of the C–H (D) bending frequencies.[24] Further, from the proposed geometry of the transition state[8,9] it appears that the reaction coordinate is not associated with a particular vibrational mode but with a combination thereof, which makes the evaluation of expected isotope effects difficult.

At present, it is not possible to make a clear-cut decision about the relative contribution of all these factors to the composite isotope effect observed.

Experimental Section

Materials.—**2,5-Dihydrothiophene 1,1-dioxide** (I) (Fluka) was purified by several recrystallizations from ethanol–ether solution, mp 63–64°.

2,5-Dihydrothiophene-*2,2,5,5-d*$_4$ 1,1-dioxide (II) was prepared according to the literature.[25] Nmr analysis showed 3.88 deuterium atoms per molecule.

2,4-Dimethyl-2,5-dihydrothiophene 1,1-Dioxide (III).—4-Methyl-1,3-pentadiene was first prepared following the published procedure.[26] The cyclization with SO_2 was carried out according to the literature[27] and 2,5-dihydrothiophene-2,2-dimethyl 1,1-dioxide should have been obtained. Nmr analysis showed that III was obtained in accordance with recent observation.[4b]

Anal. Calcd for $C_6H_{10}SO_2$: C, 49.29; H, 6.89; S, 21.93. Found: C, 49.49; H, 7.00; S, 22.16.

2,4-Dimethyl-2,5-dihydrothiophene-*5,5-d*$_2$ 1,1-dioxide (IV) was prepared by deuteration of the corresponding sulfone according to Cope's procedure.[25]

Kinetics.—The reactions in sealed tubes were carried out with about 0.0004 mol of the sulfone thermostated at 105 ± 0.10° or 120 ± 0.15° (or better) using an electronically controlled oil thermostat. At definite intervals the sealed tubes were cooled with liquid air and broken in excess of aqueous sodium hydroxide. Oxidation with 1% H_2O_2 converted sulfite to sulfate,[28] and the excess of base was titrated with hydrochloric acid.

When the reaction was carried out in the melt, the thermostated reaction vessel was evacuated to a pressure of 0.5 mm, and about 0.003 mol of the sulfone was introduced into the vessel. The vessel was closed and the change in pressure was measured on a mercury manometer.

Kinetic measurements in 1-butanol were carried out with specially dried solvent.[29] Sulfur dioxide was expelled from the reaction solution by a stream of highly pure nitrogen (carefully freed from carbon dioxide). SO_2 was absorbed in aqueous sodium hydroxide of pH 10. At that pH the absorption of SO_2 was complete and the interference of CO_2 from the atmosphere was negligible. The pH was kept constant with a 4 *N* NaOH solution using a pH-Stat.

The first-order rate constants were calculated with a computer using a least squares program.

Mass Spectrometry.—A Nier-type single collector mass spectrometer, produced at the Institute "Jožef Stefan," Ljubljana, Yugoslavia, and a single collector CSF M 500 (French) mass spectrometer were used. SO_2 was expelled from the reaction vessel by a stream of nitrogen, and butadiene was removed with P_2O_5. The low-temperature distillation using liquid air and Dry Ice removed traces of butadiene and carbon dioxide. Samples of SO_2 gas from the reaction carried out to about 2% completion

(17) V. J. Shiner, Jr., M. W. Rapp, and H. R. Pinnick, Jr., *J. Amer. Chem. Soc.*, **92**, 232 (1970); K. Humski, R. Malojčić, S. Borčić, and D. E. Sunko, *ibid.*, **92**, 6534 (1970); H. G. Bull, K. Koehler, T. C. Pletcher, J. J. Ortiz, and E. H. Cordes, *ibid.*, **93**, 3002 (1971).

(18) W. H. Saunders, Jr., A. F. Cockerill, S. Ašperger, L. Klasinc, and D. Stefanović, *ibid.*, **84**, 848 (1966).

(19) A. N. Bourns and P. J. Smith, *Proc. Chem. Soc.*, 366 (1964).

(20) S. Ašperger, L. Klasinc, and D. Pavlović, *Croat. Chem. Acta*, **36**, 159 (1964).

(21) The α-deuterium effect in sulfonium salt cannot be determined with certainty because of fast α-deuterium exchange: S. Ašperger, N. Ilakovac, and D. Pavlović, *J. Amer. Chem. Soc.*, **83**, 5032 (1961); *Croat. Chem. Acta*, **34**, 7 (1962).

(22) A complete vibrational analysis is available for the dimethyl sulfone molecule.[23] Indeed, in this compound the C–H bending modes occur at lower frequencies than in methyl groups of hydrocarbons, which could cause a lowering of the α-deuterium effect.

(23) W. R. Feairheller, Jr., and J. E. Katon, *Spectrochim. Acta*, **20**, 1099 (1964).

(24) There is evidence of strong steric interactions between substituents at C_3 and C_5 in the transition state. Thus cis-2,5-dimethylsulfolene decomposes at a temperature 50° to 90°[9] lower than the trans isomer. Such an interaction in sulfolenes I–IV would tend to *increase* the force constants for a bending vibration of the affected C–H (D) bonds. α effects are due to a *decrease* in this particular C–H (D) frequency which becomes an out-of-plane vibration in the sp^2-hybridized product.

(25) A. C. Cope, G. A. Berchthold, and D. L. Ross, *J. Amer. Chem. Soc.*, **83**, 3860 (1961).

(26) G. B. Backmann and Ch. J. Goebel, *ibid.*, **64**, 787 (1942).

(27) G. B. Backmann and R. E. Hatton, *ibid.*, **66**, 1513 (1944).

(28) E. Taylor and H. F. Johnstone, *Ind. Eng. Chem., Anal. Ed.*, **1**, 197 (1929).

(29) A. Vogel, "Practical Organic Chemistry," Longmans, London, 1959, p 168.

and to complete decomposition of the cyclic sulfone, respectively, were collected in a liquid air trap and purified on a vacuum line, and the $^{32}S/^{34}S$ mass ratios were determined as previously described.[30]

Nmr spectra were recorded on a Varian A-60A instrument.

Registry No.—I, 77-79-2; II, 20966-34-1; III, 10033-92-8; IV, 34206-55-8; deuterium, 7440-51-9; sulfur-34 isotope, 13965-97-4.

Acknowledgment.—The authors thank Professor Maurice Kreevoy and Professor Elliot N. Marvell for most helpful discussions. Thanks are due to Dr. J. Popović for help in measuring mass spectra.

(30) W. H. Saunders, Jr., and S. Ašperger, *J. Amer. Chem. Soc.*, **79**, 1612 (1957).

α-Phenylnitroxide Radicals from α-Phenylnitrones[1]

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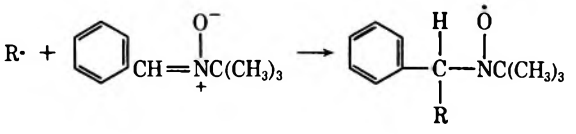
Irradiation of α-phenyl-*N*-*tert*-butylnitrone in benzene in the presence of some organometallic reagents traps short-lived radicals. The nitroxide radical formed is dependent on the amount of oxygen in solution. The inherent quality of α,*N*-diphenylnitrone to lose oxygen on irradiation allows only one of the above type nitroxide radicals. Nitroxide radicals are also formed when the phenylnitrones are irradiated in benzene containing alcohols. This reaction apparently does not proceed *via* the usual trapping mode. The reactions and structures of the nitroxides are discussed.

In a recent study we reported that α-phenylnitrones[2] on irradiation with ultraviolet light gave rise to *N*-benzoylnitroxide radicals.[3] The spin trapping characteristic of α-phenyl-*N*-*tert*-butylnitrone (PBN) has been dealt with in a number of papers.[4] In the spin trapping technique, a reactive free radical adds to PBN to produce a stabler nitroxide radical. The hyperfine splitting constants (hfsc's), from esr measurements, of the α-hydrogen and nitrogen atoms show slight variations with different trapped radicals, R·. This paper describes additional radicals arising from nitrones that we have detected under various conditions.



Results

Nitroxide Radicals from α-Phenyl-*N*-*tert*-butylnitrone.—When we irradiated, with ultraviolet light, benzene solutions of PBN to which organolead and -mercury compounds had been added, the esr signal obtained depended on the degree of deoxygenation of the solution. Incompletely deaerated solutions of PBN in benzene containing dimethylmercury, diethylmercury, triethyllead acetate, tetra-*n*-butyllead, or diphenylmercury yielded radicals whose hfsc's differed from those reported by Janzen and Blackburn,[5,6] but still showed the typical splitting pattern, a triplet of doublets, arising from a sharing of the odd electron between the nitrogen and α-hydrogen atoms. When fresh solutions were completely deaerated and then irradiated, the splitting constants agreed with the values reported. The splitting constants are listed in Table I. In the deoxygenated solutions, the radical which attached to the nitrone system was either a methyl, ethyl, *n*-butyl, or phenyl radical, depending on the radical source.[5,6] The hydrogen and nitrogen coupling constants which arose from incompletely deoxygenated solutions showed very little variation in value, which may indicate that a similar type of reactive species added to the nitrone function. We also observed that, when the totally deoxygenated solutions were irradiated briefly, for about 15 sec, the radicals detected were the ones with smaller hfsc's, shown in Table I. These signals were stable if the solutions were kept in the dark. On further irradiation, about 1–3 min, the nitroxide radicals with larger splitting constants were found. In partially deoxygenated solutions, the nitroxide with larger splitting constants was never observed, even after extended irradiation. Figure 1 shows the changes in the esr spectra during progressive stages of irradiation of a deoxygenated benzene solution of PBN containing diethylmercury. Figure 1b shows the esr signal as a mixture

TABLE I

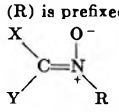
HYPERFINE SPLITTING CONSTANTS OF NITROXIDES FROM α-PHENYL-*N*-*tert*-BUTYLNITRONE[a]

Radical source	A^{N} [b]	A_{α}^{H} [b]	A^{N} [c]	A_{α}^{H} [c]	A^{N} [d]	A_{α}^{H}
$(CH_3)_2Hg$	13.74	1.99	14.79	3.73	14.82	3.60
$(CH_3CH_2)_2Hg$	13.80	1.97	14.68	3.25	14.62	3.33
$(CH_3CH_2)_3PbOAc$	13.75	1.95	14.54	3.30	14.50	3.35
n-Bu_4Pb	13.65	1.97	14.64	3.21	14.62	3.27
$(C_6H_5)_2Hg$	13.65	1.97	14.47	2.18	14.42	2.21
$(C_6H_5)_3CN{=}NC_6H_5$ [e]			14.48	2.17	14.43	2.18

[a] In benzene at room temperature. The splittings are in gauss. [b] Photolysis of incompletely deoxygenated solutions of PBN and radical source. [c] Photolysis of totally dexoygenated solutions of PBN and radical source. [d] Values from Janzen and Blackburn adjusted upwards by 4.4%.[6] [e] By thermal decomposition.

(1) Presented in part at the 9th National Meeting of the Society for Applied Spectroscopy, New Orleans, La., Oct 1970.

(2) In this paper the carbon substituents X and Y are prefixed by α, and the substituent on the nitrogen (R) is prefixed by N.



Hyperfine splitting constants from esr measurements referring to the hydrogen on the carbon atom are designated as A_a^H.

(3) A. L. Bluhm and J. Weinstein, *J. Amer. Chem. Soc.*, **92**, 1444 (1970).

(4) See E. G. Jantzen, *Accounts Chem. Res.*, **4**, 31 (1971), for a review of spin trapping including the nitrones and references thereto.

(5) E. G. Janzen and B. J. Blackburn, *J. Amer. Chem. Soc.*, **90**, 5909 (1968).

(6) E. G. Janzen and B. J. Blackburn, *ibid.*, **91**, 4481 (1969).

TABLE II

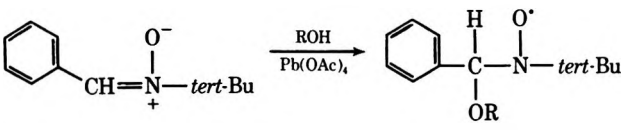
COMPARISON OF HYPERFINE SPLITTING CONSTANTS OF NITROXIDES BY IRRADIATION OF PBN IN BENZENE WITH ADDITIVES[a]

Additive	A^N	A_α^H	α-Carbon substituent on nitroxide radical	Registry no.
$(CH_3)_2Hg$[b]	14.79	3.73	CH_3	21894-27-9
$(CH_3)_2Hg$[c]	13.74	1.99	OX[e]	
$CH_3OH + Pb(OAc)_4$	13.76	2.00	OCH_3	34234-86-1
$CH_3OH + H_2O_2$	13.87	3.82	CH_2OH	34280-33-6
$(CH_3CH_2)_2Hg$[b]	14.68	3.25	CH_2CH_3	21894-28-0
$(CH_3CH_2)_2Hg$[c]	13.80	1.97	OX[e]	
CH_3CH_2OH	14.08	2.05	OCH_2CH_3	34280-35-8
$CH_3CH_2OH + Pb(OAc)_4$[d]	14.01	2.03	OCH_2CH_3	
$CH_3CH_2OH + H_2O_2$	14.07	3.12	$CH(CH_3)OH$	34234-87-2
n-Bu_4Pb[b]	14.64	3.21	*n*-Bu	21999-41-7
n-Bu_4Pb[c]	13.65	1.97	OX[e]	
n-BuOH	13.75	2.10	O-*n* Bu	34234-89-4
n-BuOH + $Pb(OAc)_4$[d]	13.82	2.00	O-*n*-Bu	
n-BuOH + H_2O_2	14.17	3.09	$CH(CH_2CH_2CH_3)OH$	34234-90-7
tert-BuOH	13.74	2.10	O-*tert*-Bu	34234-91-8
tert-BuOH + $Pb(OAc)_4$	13.79	2.01	O-*tert*-Bu	
tert-BuOH + H_2O_2	14.04	3.23	$(CH_2)(CH_3)_2COH$	34234-92-9

[a] In gauss at room temperature. [b] Completely deoxygenated. [c] Partially deoxygenated. [d] No irradiation necessary. [e] See Discussion.

of two radicals at an intermediate point of irradiation. Irradiation of the nitrone in the presence of 1′,1′,1′-triphenylbenzeneazomethane, a phenyl radical generator, yielded only one nitroxide radical independent of the degree of deoxygenation. Although we previously reported that irradiation of PBN in benzene yielded the *N*-benzoylnitroxide radical,[3] it was not prominent in the signals from solutions containing the reactive additives.

The value of the coupling constants from partially deaerated solutions of PBN and the above organometallics were found to be of the same order as found for PBN and scavenged alkoxyl radicals, as shown further on. When solutions of PBN in benzene to which 1% of an alcohol was added were irradiated, we observed splittings also of the same order as those from scavenged alkoxyl radicals. The alcohol concentration could be increased and the signal would still be observed, but in 100% alcohol no signal was observed. The alcohol-generated radical signals appeared very slowly on irradiation and were usually not strong. The higher instrumental modulation amplitudes used gave rise to broader signals. We examined benzene solutions of PBN in the presence of ethanol, ethanol and lead tetraacetate, and ethanol and hydrogen peroxide; and similar sequences with *n*-butyl alcohol and *tert*-butyl alcohol. The hfsc's are shown in Table II. From the solutions containing alcohols and lead tetraacetate, very strong signals appeared immediately. Forshult, Lagercrantz, and Torssell[7] used 2-methyl-2-nitrosobutanone-3 as a scavenger for alkoxyl radicals developed in the reaction of alcohols and lead tetraacetate. With PBN



as a radical trap we would expect an analogous reaction. The hfsc's for PBN with alcohol present and with alcohol plus lead tetraacetate are identical, and this has led us to believe that irradiation of nitrones in the presence of alcohols leads to the same nitroxide in which an alkoxyl group is attached at the α carbon. Additional evidence is given in this paper in the reaction of other nitrones and alcohols. Irradiation of a benzene solution of PBN containing only lead tetraacetate gave a weak esr signal with splittings about A^N 13.3 and A_α^H 1.9 G, which may be attributed to trapping of acetoxy radical.[6]

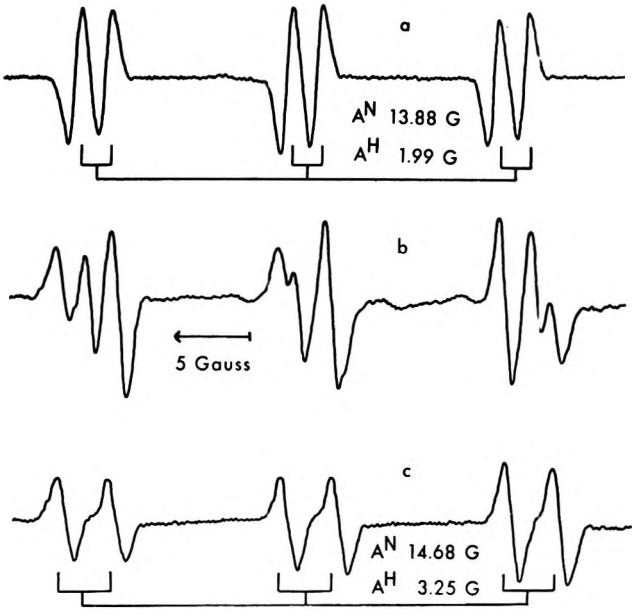


Figure 1.—α-Phenyl-*N*-*tert*-butylnitrone in benzene plus diethylmercury. Solution deoxygenated by argon flushing for 30 min: (a) after 30 sec irradiation with unfiltered high-pressure mercury lamp; (b) after 1.5 min irradiation; (c) after 2 min irradiation.

Hydroxyalkyl radical species have been generated and trapped by irradiation of solutions of alcohol, hydrogen peroxide, and 2-methyl-2-nitrosobutanone-3.[7] Utilizing this technique, we irradiated benzene solutions of PBN to which were added an alcohol and hydrogen

$$H_2O_2 \xrightarrow{h\nu} 2HO\cdot$$

(7) S. Forshult, C. Lagercrantz, and K. Torssell, *Acta Chem. Scand.*, **23**, 522 (1969).

$$HO\cdot + CH_3CH_2OH \longrightarrow H_2O + CH_3\dot{C}HOH$$

$$CH_3\dot{C}HOH + PBN \longrightarrow \text{(PBN-adduct)}$$

peroxide. The splitting constants obtained differed from the other nitroxide radicals in which R and RO were attached to the α-carbon position. These values for methanol, ethanol, and *n*-butyl and *tert*-butyl alcohols are also shown in Table II. The nitroxide radical arising from *tert*-butyl alcohol and hydrogen peroxide with PBN gave splitting constant values which differed from those obtained by trapping of the *tert*-butoxy radical generated in the presence of lead tetraacetate (Table II).

Nitroxide Radicals from α,*N*-Diphenylnitrone.—α,*N*-Diphenylnitrone (DPN) when employed as a radical scavenger gives more complex esr spectra due to the sharing of the odd electron with the *N*-phenyl protons. However, in most of our experiments, the signals were clean and well resolved, leading to good interpretations.

Although DPN would be expected to behave similarly to PBN, we noted some differences during our studies. For example, on irradiation of the nitrones in benzene without additives, the signal of the benzoyloxy radical from DPN developed rapidly and in good strength. In contrast, the photoxidation radical from PBN showed more sluggish development.[3] When solutions of DPN in benzene were irradiated in the presence of organomercury or -lead compounds, the signal observed was not dependent on the degree of deoxygenation, and was attributed to the trapping of either an alkoxyl or an alkylmetaloxyl group at the α position. The splitting constants, and those from thermal decomposition of 1′,1′,1′-triphenylbenzeneazomethane in DPN–benzene, are listed in Table III. The hfsc's for

TABLE III

HYPERFINE SPLITTING CONSTANTS OF NITROXIDES FROM α-PHENYL-*N*-PHENYLNITRONE[a]

Radical source	A^N	A^H[b] Ortho, para	Meta	α
$(CH_3)_2Hg$	10.57	2.49	0.90	1.60
$(CH_3CH_2)_2Hg$	10.60	2.57	0.86	1.64
$(CH_3CH_2)_3PbOAc$	10.65	2.56	0.85	1.64
n-Bu_4Pb	10.52	2.50	0.85	1.62
$(C_6H_5)_3CN{=}NC_6H_5$	10.62	2.64	0.90	3.57

[a] In benzene at room temperature. The splittings are in gauss. [b] Ortho, para, and meta H's from *N*-phenyl group.

nitrogen and ortho, para, and meta hydrogen atoms were of the same order of magnitude for the different additives. The α-hydrogen value, however, was much larger when the additive was a phenyl radical precursor, in which case it is proposed that the species trapped was the phenyl group. The α-hydrogen splittings observed with the organometallic additives were duplicated by irradiating DPN in benzene containing various alcohols and were attributed to a nitroxide with XO attached to the α-carbon atom. The nature of the XO group is discussed further on. In general, the α-hydrogen splittings for XO groups attached at the α-carbon position were about 1.6 G and for R about 3.6 G. This generalization is reinforced by the following work.

In the presence of alcohols containing lead tetraacetate, benzene solutions of DPN, without irradiation, yielded the same coupling constants as observed in DPN–benzene solution irradiated with only alcohols present. The coupling constants are shown in Table IV. We also observed that the hfsc's of the nitroxide arising from irradiation of the nitrone in benzene with *tert*-butyl hydroperoxide present were identical with those obtained with the nitrone in the presence of *tert*-butyl alcohol and *tert*-butyl alcohol plus lead tetraacetate. *tert*-Butyl hydroperoxide decomposes to give *tert*-butoxy and hydroxy radicals.

α-Alkyl substituted nitroxides, which we were unable to prepare by the reaction of DPN and organolead or -mercury compounds, as they could be with PBN, were obtained by two different procedures. The irradiation of organic carboxylic acids in the presence of lead tetraacetate proceeds through a radical process[8] according to the equation

$$RCOOH \xrightarrow[h\nu]{Pb(OAc)_4} R\cdot + CO_2$$

By this technique Forshult, Lagercrantz, and Torssell trapped alkyl radicals using nitroso compounds as scavengers.[7] When we irradiated a benzene solution of DPN to which was added acetic acid and lead tetraacetate, we obtained an esr signal with splittings A^N 10.67, $A_{o,p}^H$ 2.63 (3 H), A_m^H 0.93 (2 H), and A_α^H 3.60 G (1 H). This signal arises from the nitroxide radical with the methyl group joined to the α-carbon atom.

$$CH_3COOH \xrightarrow[h\nu]{Pb(OAc)_4} CH_3\cdot \xrightarrow{DPN} \text{(DPN-adduct)}$$

The experimental esr spectra and simulated stick patterns are shown in Figure 2 for the nitroxide radicals with α-methyl and α-methoxyl substituents. In another experiment, *n*-butyllithium was added to the benzene solution of DPN, followed by air oxidation.

$$n\text{-BuLi} + DPN \longrightarrow \text{(adduct)} \xrightarrow{O_2} \text{(nitroxide)}$$

This technique was used by Janzen and Blackburn to form α-alkyl substituted nitroxides from PBN and organolithium or Grignard reagents.[5,6] Previous reports demonstrated that Grignard reagents added to aldonitrones in a 1,3 manner.[9] The coupling constants from butyllithium and DPN were A^N 10.71, $A_{o,p}^H$ 2.71 (3 H), A_m^H 0.90 (2 H), and A_α^H 3.99 G (1 H). With phenyllithium we obtained A^N 10.61, $A_{o,p}^H$ 2.68 (3 H), A_m^H 0.90 (2 H), and A_α^H 3.59 G (1 H), which are the same values as obtained by the trapping of

(8) R. Criegee in K. Wiberg, "Oxidation in Organic Chemistry," Academic Press, New York, N. Y., 1965, Chapter 5.

(9) A. Angeli, L. Alessandri, and M. Aizza-Mancini, *Atti Accad. Naz. Lincei*, **20**, 546 (1910); *Chem. Abstr.*, **5**, 3403 (1911); G. E. Utzinger and F. A. Regenass, *Helv. Chim. Acta*, **37**, 1892 (1954).

TABLE IV

HYPERFINE SPLITTING CONSTANTS OF NITROXIDES FROM α-PHENYL-N-PHENYLNITRONE WITH ADDITIVES[a]

Additive	A^N	A^H[b] Ortho, para	meta	α	α-Carbon substituent	Registry no.
CH_3OH	10.74	2.58	0.97	1.62	OCH_3	34234-93-0
CH_3OH + $Pb(OAc)_4$	10.57	2.56	0.91	1.55	OCH_3	
CH_3CH_2OH	10.63	2.57	0.85	1.61	OCH_2CH_3	34234-94-1
CH_3CH_2OH + $Pb(OAc)_4$	10.52	2.61	0.80	1.64	OCH_2CH_3	
n-BuOH	10.52	2.53	0.90	1.62	O-*n*-Bu	34234-95-2
n-BuOH + $Pb(OAc)_4$	10.61	2.57	0.90	1.62	O-*n*-Bu	
tert-BuOH	10.57	2.50	0.98	1.49	O-*tert*-Bu	34234-96-3
tert-BuOH + $Pb(OAc)_4$	10.59	2.59	0.96	1.58	O-*tert*-Bu	
tert-BuOOH	10.57	2.50	0.95	1.49	O-*tert*-Bu	

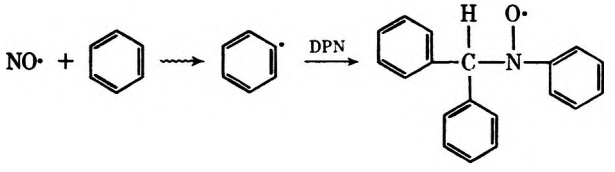
[a] In benzene at room temperature. The splittings are in gauss. [b] Ortho, para, and meta H's from *N*-phenyl group.

phenyl radicals from triphenylbenzeneazomethane (Table III).

When a benzene solution of DPN with phenol present was irradiated, we obtained an esr spectrum with couplings A^N 10.61, $A_{o,p}^H$ 2.64 (3 H), A_m^H 0.93 (2 H), and A_α^H 1.80 G (1 H). The α-hydrogen splitting was of the same order as found for the nitroxide with RO groups attached at the α-carbon atom, and suggests that the phenoxyl group was trapped.

We also irradiated DPN solution in the presence of ethanol and hydrogen peroxide, expecting the esr signal of the nitroxide formed by trapping $\cdot CH(OH)CH_3$, but the spectra were complicated by the large concentration of benzoyloxy radical which formed.

Other Reactions.—When nitric oxide was briefly bubbled through a solution of DPN in benzene, the esr signal showed splittings A^N 10.63, $A_{o,p}^H$ 2.62 (3 H), A_m^H 0.96 (2 H), and A_α^H 3.59 G (1 H), which were characteristic for phenyl radical scavenging. Apparently nitroxyl radical (NO·) abstracts a proton from the solvent, and the resultant phenyl radicals are



trapped. Treatment of PBN in an analagous manner yielded a strong signal characteristic of the benzoyloxy radical.

Most other substituted diphenylnitrones led to nitroxides analagous to those from DPN, when irradiated in the presence of alcohols, organolead, or -mercury reagents. For example, α-phenyl-*N*-*p*-chlorophenylnitrone with either ethanol or diethylmercury, in benzene, yielded on irradiation the esr spectra with splittings A^N 10.40, $A_{o,\alpha}^H$ 2.57 (3 H), and A_m^H 1.45 G (2 H). Under the same conditions α-(*p*-methoxyphenyl)-*N*-phenylnitrone gave A^N 10.70, $A_{o,p}^H$ 2.58 (3 H), A_m^H 0.90 (2 H), and A_α^H 1.65 G (1 H); and α-phenyl-α-deuterio-*N*-phenylnitrone gave A^N 10.64, $A_{o,p}^H$ 2.57 (3 H), and A_m^H 0.93 G (2 H). Splittings due to the deuterium atom were not resolvable. However, α-phenyl-α-cyano-*N*-phenylnitrone failed to give any signal when treated as above. Only on irradiation of a benzene solution with *tert*-butyl hydroperoxide added was a signal observed. This stable signal showed splittings A^N 11.19, $A_{o,p}^H$ 2.37 (3 H), and A_m^H 0.80 (2 H), and may be due to the trapping of the *tert*-butoxy radical.

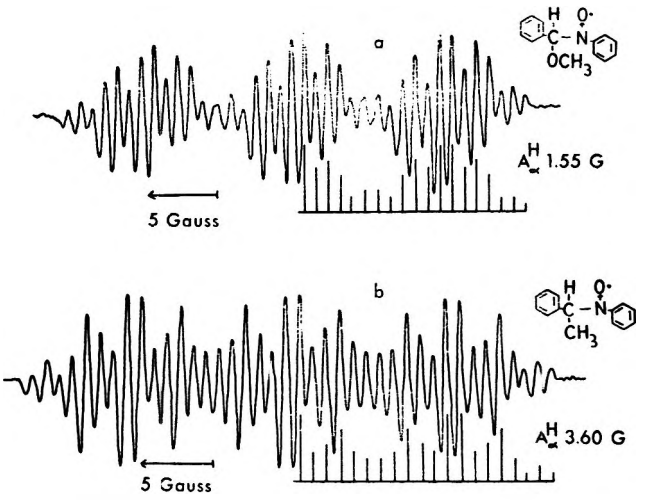
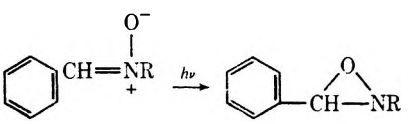


Figure 2.—Nitroxide radicals from α-phenyl-*N*-phenylnitrone. The stick patterns are based on coupling constants given in text: (a) from benzene solution containing methanol-lead tetraacetate; (b) from irradiation of benzene solution containing acetic acid and lead tetraacetate.

Discussion

In a deoxygenated solution of PBN in benzene containing the organometallics, Janzen and Blackburn established that alkyl radicals were generated and trapped by PBN.[6] We observed that the presence of oxygen changes the scheme of the reaction. As noted earlier, we were able to trap only the XO· radical with DPN and each organolead and -mercury compound, whereas with PBN two adduct radicals could be obtained. Partial deoxygenation gave rise to the XO adduct, while total removal of oxygen led to the trapping of R·. The difference observed is probably related to the stability of the oxaziranes which are primary intermediates formed on irradiation of nitrones.[10-12] The relative stabilities are indicated by the fact that the oxazirane from PBN can be isolated, whereas the oxazirane from DPN has been identified only at low temperatures.

We previously concluded that oxygen was evolved



R = phenyl, unstable
R = *tert*-butyl, stable

(10) M. J. Kamlet and L. A. Kaplan, *J. Org. Chem.*, **22**, 576 (1957).
(11) J. S. Splitter and M. Calvin, *ibid.*, **23**, 651 (1958).
(12) K. Shinazawa and I. Tanaka, *J. Phys. Chem.*, **68**, 1205 (1964).

during the irradiation of nitrones,[3] and other reports have indicated that irradiation of nitrones causes simple deoxygenation.[13-15] Thus, in the case of DPN, it may not be possible to completely void oxygen from solution owing to this decomposition of the oxazirane.

It also appears that this oxygen effect may be limited to the nitrones. Experiments using 2-methyl-2-nitrosobutanone-3 as a scavenger in poorly and well deoxygenated solutions led to the trapping of only one radical arising from alkyl radical scavenging.

We assign to these nitroxides formed from nitrones in partially oxygenated solutions a structure in which XO is attached at the α-carbon atom, and the XO group may be either an alkoxyl or an alkyl metal oxyl group. For example, with dimethylmercury additive, the XO may be either CH_3O or CH_3HgO. The splitting constants are almost identical with those found in the nitroxides with α-alkoxyl groups. However, differentiation between a nitroxide with an α-alkoxyl or α-alkyl metal oxyl group for the organometallic produced nitroxide is not feasible, since it is likely that either system would give splitting values of the same order. It is known that alkyl radicals react with other paramagnetic molecules, *e.g.*, oxygen, as follows[16]

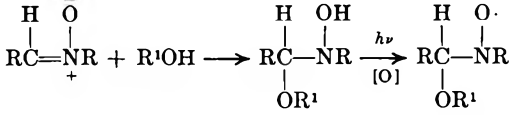
$$CH_3\cdot + O_2 \longrightarrow CH_3OO\cdot \xrightarrow{CH_3\cdot} CH_3OOCH_3 \longrightarrow CH_3O\cdot$$

and that a similar type of reaction apparently occurs in the case of organometallic radicals.[17]

$$MeHg\cdot + O_2 \longrightarrow MeHgOO\cdot \xrightarrow{MeHg\cdot} MeHgOOHgMe \longrightarrow MeHgO\cdot$$

Thus, either one of these oxygen-containing radicals could be trapped by the nitrone. It appears that this oxygen effect is seen only when nitrones are used as spin traps. Further work in this area is required to establish the structure of these nitroxides.

We assigned to those radicals formed by the irradiation of benzene solutions of the nitrones in the presence of alcohols, structures in which the alkoxyl group is joined at the α-carbon atom. The coupling constants obtained from PBN and DPN under these conditions are in good agreement with those obtained from the trapping of alkoxyl radicals generated by the treatment of alcohols with lead tetraacetate.[7] The nitroxides in which alkyl and hydroxyalkyl groups are attached to the α carbon give much different coupling constants (Tables I–IV). Reactions of alcohols irradiated in the presence of scavengers has not been previously noted in the literature, and this reaction, which leads to nitroxide radical, appears to be limited to nitrones. We have not been able to obtain characteristic esr signals from the irradiation of 2-methyl-2-nitrosobutanone-3 in benzene solution with alcohol present. The reaction of the nitrones with alcohols described is probably not a radical trapping process, but rather an initial addition of the alcohol across the reactive C=N→O site, followed by conversion to the nitroxide.



We have observed an oxidation similar to that proposed for the adduct when *N*-benzoylphenylhydroxylamine in benzene is irradiated. The reactivity of the aldonitrone species to 1,3-addition reactions has been noted in the literature.[18] The sluggishness of this reaction process with PBN as compared to DPN may be attributed to an inductive effect of the *tert*-butyl group, which would increase the electron density at the double bond and make the reaction site less attractive to the nucleophilic reagent.

The nitroxide formed by irradiation of a benzene solution of PBN with *tert*-butyl alcohol in the presence of hydrogen peroxide (Table II) is assigned the structure with $(-CH_2)(CH_3)_2COH$ joined at the α-carbon atom. The $(\cdot CH_2)(CH_3)_2COH$ radical is formed by abstraction of a β-hydrogen atom by $\cdot OH$ radicals and has been observed previously under similar conditions.[19]

The production and trapping of phenyl radicals by DPN in the presence of nitric oxide in benzene was shown to occur by examination of the hfsc's, which were identical with those obtained from DPN and 1′,1′,1′-triphenylbenzeneazomethane. Nitric oxide can behave as a radical quencher, but there is also evidence that nitric oxide will abstract hydrogen from stable molecules, and aryl radicals have been produced in the presence of nitric oxide.[20]

Experimental Section

Chemicals.—2-*tert*-Butyl-3-phenyloxazirane and α-phenyl-*N*-*tert*-butylnitrone were prepared as described by Emmons[21] and the α,*N*-diphenylnitrones according to the procedure of Wheeler and Gore.[22]

Dimethyl-, diethyl-, and diphenylmercury, triethyllead acetate, and tetra-*n*-butyllead were used as supplied by Alfa Inorganics. *n*-Butyllithium was obtained from Foote Mineral Co. and 1′,1′,1′-triphenylbenzeneazomethane was from Eastman Organic Chemicals.

Benzene was Baker and Adamson reagent redistilled and stored over sodium–lead alloy (dri-Na).

The alcohols were Spectrograde reagents used as supplied.

Generation and Measurement of Radicals.—Solutions of the nitrones approximately 0.05 *M* in benzene were always freshly prepared. To 1 ml of the nitrone solution in a small glass sample vial, a drop or a few crystals of the organometallic compound was added, the solution was mixed, and then a portion was transferred into a 2-mm i.d. quartz esr cell. Deoxygenation was effected by passing a fine stream of argon bubbles through the solution by means of a drawn-out glass capillary. In this paper a partially deoxygenated solution was one that was treated for 10 min, and a totally deoxygenated solution was subjected to a 30-min deaeration. Except as noted in the text, solutions were deaerated for 10 min.

The radicals formed from the nitrones in the presence of alcohols were obtained from 0.05 *M* solutions of the nitrone in benzene containing 1% of the alcohol. These solutions were deoxygenated for 10 min.

Irradiations of the solutions were carried out directly in a slotted cavity in the esr instrument, by exposing to the light of an un-

(13) L. Alessandri, *Atti Accad. Naz. Lincei*, **19**, 122 (1910); *Chem. Abstr.*, **5**, 276 (1911).

(14) H. Shindo and B. Umezawa, *Chem. Pharm. Bull.*, **10**, 492 (1962).

(15) M. Collonna, *Gazz. Chim. Ital.*, **91**, 34 (1961).

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filtered Bausch and Lomb SP 200-W super pressure mercury lamp for periods of 10 sec to 2 min. Spectra were measured at room temperature with a Varian V-4500 epr spectrometer equipped with a 9-in. magnet. Sweep rates were calibrated by the spectrum of *p*-benzosemiquinone in aqueous ethanol.

Registry No.—Nitroxide from DPN + phenol, 34234-97-4; nitroxide from DPN + $Ph_3CN{=}NPh$, 34234-98-5; nitroxide from α-phenyl-*N*-*p*-chlorophenylnitrone + EtOH, 34234-99-6; nitroxide from α-phenyl-*N*-*p*-chlorophenyl nitrone + dimethylmercury, 34235-00-2; nitroxide from α-(*p*-methoxyphenyl)-*N*-phenylnitrone + EtOH, 34235-01-3; nitroxide from α-(*p*-methoxyphenyl)-*N*-phenylnitrone + Et_2Hg, 34235-02-4; nitroxide from α-phenyl-α-deuterio-*N*-phenylnitrone + EtOH, 34235-03-5; nitroxide from α-phenyl-α-deuterio-*N*-phenylnitrone + Et_2Hg, 34235-04-6; nitroxide from α-phenyl-α-cyano-*N*-phenylnitrone + *tert*-butyl peroxide, 34235-05-7; nitroxide from PNB + Ph_2Hg, 21572-75-8; nitroxide from DPN + Me_2Hg, 34235-07-9; nitroxide from DPN + Et_2Hg, 34235-08-0; nitroxide from DPN + Bu_4Pb, 34288-72-7.

Hydrogen Abstraction by the *p*-Nitrophenyl Radical[1,2]

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The relative reactivities of a series of organic hydrogen donors were measured toward *p*-nitrophenyl radicals generated from *p*-nitrophenylazotriphenylmethane (NAT). The relative rate constants k_H for hydrogen abstraction from the donors are reported as k_H/k_{Cl} values, where k_{Cl} is the rate constant for chlorine abstraction from CCl_4. The problems in calculation of k_H/k_{Cl} values are discussed. Some ArH is produced from the $ArN{=}NCPh_3$ type initiators even in pure CCl_4 as solvent, and higher yields are produced at higher viscosities. It is shown that ArH is not a cage product. The ArH yields result from hydrogen abstraction from reactive hydrogen donors produced by the reaction of the ambident trityl radicals with radicals present in the system. These donors include XH from the reaction of trityl with Ar radicals and ZH from the reaction of trityl with a second trityl radical (see structures in paper). Two mechanisms are suggested to rationalize the viscosity effect; the more likely one assumes that XH is a cage product and, therefore, that higher yields of XH are produced at higher viscosities.

One of the most useful methods for probing the reactivity, polar nature, steric sensitivity, and other identifying features of free radicals is to measure their relative rate constants for hydrogen abstraction from a series of typical organic hydrogen donors. This approach has been used, for example, in studies of the phenyl radical,[4,5] aromatic radicals,[6a] the methyl radical,[6b] and the hydrogen atom.[7] A convenient method for determining such a series of relative rate constants involves generating the radical in a mixture of the hydrogen donor RH and carbon tetrachloride (eq 1 and 2). In this paper we report data obtained in this way for the phenyl and *p*-nitrophenyl radicals.

$$RH + Ar\cdot \xrightarrow{k_H} R\cdot + ArH \qquad (1)$$

$$CCl_4 + Ar\cdot \xrightarrow{k_{Cl}} CCl_3\cdot + ArCl \qquad (2)$$

These radicals were generated by thermolysis at 60° of the appropriate phenylazotriphenylmethane (PAT) type of intiator, PAT itself for the phenyl radical and NAT, $p\text{-}NO_2C_6H_4N{=}NCPh_3$, for the *p*-nitrophenyl radical. We previously reported[6a] some data for phenyl, *p*-bromophenyl, *p*-methylphenyl, and *p*-nitrophenyl, and Bridger and Russell[8] have reported extensive data for the phenyl radical. We here wish to clarify the cage chemistry of PAT-type initiators and also to report additional relative rate constants for hydrogen atom abstraction by the *p*-nitrophenyl radical.

Results and Discussion

The Cage Chemistry of PAT and NAT.—Cage processes have been particularly troublesome to identify[9-10] for PAT and similar initiators. Previously[6a] we presented data on the yield of nitrobenzene (ArH) from NAT. We showed that the extrapolated yield of ArH appeared to be finite (~3%) at infinite dilution of NAT, in agreement with earlier reports on PAT,[8,10a] and that the thermolysis of NAT in solvents of higher viscosity led to higher yields of ArH. These facts seemed to imply that ArH is a cage product. Arguments against ArH being a cage product are based on the observation that carbon disulfide or a solution of iodine in CCl_4 results in the elimination of ArH.[11,12] It is now clear that the implication of these scavenging experiments is correct and that ArH is not a cage product.

Our evidence indicating that ArH is not a cage product can be summarized as follows. (1) Using a new, more sensitive gas chromatograph, we have been able

(1) Reactions of Radicals. 42.

(2) This work was supported in part by a U. S. Public Health Service Grant GM-11908 from the National Institue of Health.

(3) (a) John Simon Guggenheim Fellow, 1970–1971; (b) postdoctoral student on an NIH grant, 1965; (c) Research Participant in an Atomic Energy Commission Research Participation Program, summer 1966.

(4) W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, Chapter 12.

(5) A. F. Trotman-Dickenson, *Advan. Free Radical Chem.*, **1**, (1965).

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(8) R. F. Bridger and G. A. Russell, *ibid.*, **85**, 3754 (1963).

(9) (a) E. L. Eliel, M. Eberhardt, O. Simamura, and S. Meyerson, *Tetrahedron Lett.*, 749 (1962); (b) D. H. Hey, M. J. Perkins, and G. H. Williams, *ibid.*, 445 (1963); (c) J. G. Garst and R. S. Cole, *ibid.*, 679 (1963); (d) G. A. Russell and R. F. Bridger, *ibid.*, 737 (1963).

(10) (a) W. A. Pryor and H. Guard, *J. Amer. Chem. Soc.*, **86**, 1150 (1964); (b) W. A. Pryor and K. Smith, *ibid.*, **89**, 1741 (1967).

(11) Figure 3 of ref 6a.

(12) It is possible that a trace (<0.1%) of ArH is formed under these circumstances, but the amount is too small to estimate accurately.

to show that graphs of the yield of ArH *vs.* initial concentration of PAT and NAT break sharply toward zero at very low concentrations (see Figure 1). (2) Iodine in toluene reduces the yield of ArH to <0.1%. Iodine or CBr_4 in CCl_4 reduces the yield of ArH to zero for NAT and for PAT, and this is true even when silicone oils are present as thickeners.

These facts establish that ArH is not a cage product. the production of ArH from PAT or NAT in pure CCl_4 and the increased yields of ArH at higher viscosity, therefore, must be explained. In addition, the question arises of whether there are any cage products from PAT. Any cage products which are formed are produced only in low yields; the data of Table I show that

TABLE I

SCAVENGING EXPERIMENTS WITH PAT AT 60°

		% yield			
Solvent	Scavenger	ArH	ArCl	ArX[a]	Total
CCl_4	0.12 *M* I_2	<0.5	11	79	90[b]
CCl_4	Variable I_2	<0.5	14	79	93[c]
Toluene	0.15 *M* CBr_4			88	
Toluene	Variable CBr_4			85	
CCl_4	0.15 *M* CBr_4	<0.5	6	90	96[d]
CCl_4	Variable CBr_4	<0.5	6	88	94[c]

[a] ArI or ArBr depending on whether I_2 or CBr_4 is the scavenger. [b] The total yield was studied for a range of PAT initial concentrations and was found to be approximately independent of this variable. [c] Using 0.05 *M* $[PAT]_0$, various scavenger concentrations were examined. The total yield was roughly independent of the initial scavenger concentration, although, of course, the product mixture changes drastically as the scavenger concentration is varied. [d] The yield of ArBr decreases as $[PAT]_0$ is increased, presumably owing to competition between trityl and CBr_4. This is the maximum value, obtained at 0.02 *M* $[PAT]_0$.

the recovery of Ar groups is always <100% but is very high.

Before consideration of these questions, one relatively trivial point needs clarification. There is a possibility that the spuriously low yields of ArI in scavenging experiments result from the radical-initiated destruction of ArI. We eliminated this by showing that reaction 3 occurs without loss of total organic iodide product (Table II).[13]

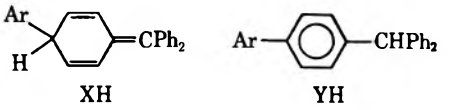
TABLE II

THE EXCHANGE OF IODIDE BY RADICALS IN CCl_4 AT 60°

	Concentrations, *M*			
	Expt 1		Expt 2	
Compd	Initial	Final	Initial	Final
PAT	0.0468	0	0.0508	0
Iodobenzene [PhI]	0	0.0016	0	0.0011
p-Nitroiodobenzene [ArI]	0.0095	0.0082	0.0095	0.0083
Total [iodine derivatives]	0.0095	0.0098	0.0095	0.0094

$$Ph\cdot + ArI \longrightarrow PhI + Ar\cdot \qquad (3)$$

It appears reasonable to assume that any cage products which are formed from PAT-type initiators result exclusively from the coupling of the Ar· and trityl radicals. Only radical disproportionation and combination reactions might be expected to compete with diffusion from the cage, and disproportionation is not possible for Ar· and trityl. The trityl radical is ambident[14] and can be expected to couple with Ar· radicals to give both $ArCPh_3$ and XH and, perhaps, the ortho analog of XH. If XH were formed, the aromatized derivative



XH YH

YH might be detectible by gas chromatography (gc). In fact, Table III shows that YH can be detected from

TABLE III

YIELDS OF COUPLING PRODUCTS IN THE PRESENCE AND ABSENCE OF SCAVENGERS[a]

	% yield	
Solvent	CPh_4	YH
CCl_4	1.5	0.51
$CCl_4 + I_2$[b]	0.70	0.28

[a] 0.0720 *M* PAT. [b] 0.104 *M* iodine initially.

PAT decompositions in pure CCl_4 both in the presence and the absence of iodine as scavenger. Ordinarily, this would be taken as *prima facie* evidence that XH is a cage product and that an additional amount is formed in free solution. However, in this case, the identification of $ArCPh_3$ and XH in the presence of a radical scavenger is not necessarily conclusive evidence that these products are produced in the cage because of the exceptional stability of the trityl radical.

Trityl is a stable radical and a good radical scavenger. In fact, this was why the PAT series of initiators were adopted for kinetic studies. It was hoped that trityl would "mop up" secondary radicals and prohibit chain processes,[6,8,9] and, in contrast with acetyl radicals, trityl does appear to serve this role.[15] An electron spin resonance (esr) study of PAT decompositions shows that trityl radicals reach a maximum concentration after 2 half-lives of PAT and that the concentration decreases quite slowly after that. The trityl concentration is still high after 4 half-lives, and the esr signal persists for months. The possibility exists, therefore, that coupling products from Ar· and trityl are formed in the presence of iodine because trityl is able to compete with iodine as a scavenger.[16] In addition, there is considerable evidence that PAT-type initiators decompose in two steps and that the aryldiazenyl radical is stable enough to diffuse from the cage.[17] This suggests

(13) After we had concluded this work, J. F. Bunnett and C. C. Wamser [*J. Amer. Chem. Soc.*, **88**, 5534 (1966)] published similar data which led to the same conclusion.

(14) Para coupling products from trityl radicals have previously been reported. (a) J. A. Kampmeier, R. P. Geer, J. A. Meskin, and R. M. D'Silva [*ibid.*, **88**, 1257 (1966)] identified *p*-$C_6H_5C_6H_4C(SC_4H_6)(C_6H_5)_2$, as well as tetraphenyl- and triphenylmethane, from the reaction of PAT with *tert*-butyl sulfide. (b) J. P. Lorand and P. D. Bartlett [*ibid.*, **88**, 3294 (1966)] isolated *p*-*tert*-$BuOC_6H_4CH(C_6H_5)_2$ from the decomposition of *tert*-butyl triphenylperacetate. (c) S. F. Nelson and P. D. Bartlett [*ibid.*, **88**, 137 (1966)] have shown that cumyl also is ambident and couples at the para position. (d) Also see H. Lankamp, W. T. Nanta, and C. MacLeon, *Tetrahedron Lett.*, 249 (1968); D. H. Hey, M. J. Perkins and G. H. Williams, *J. Chem. Soc.*, 110 (1965); D. H. Hey and R. Tewfik, *ibid.*, 2402 (1965).

(15) W. A. Pryor, U. Tonellato, D. L. Fuller, and S. Jumonville, *J. Org. Chem.*, **34**, 2018 (1969).

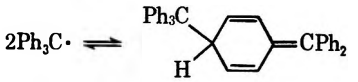
(16) The ratio of coupling at the center carbon to form $ArCPh_3$ and at the para position to give XH is roughly the same in the presence and absence of iodine, but this cannot be taken as evidence that the products are all formed in free solution. Ambident radicals undergo coupling at two positions with a similar ratio whether the reaction takes place in the cage or in free solution. See G. S. Hammond, C. S. Wu, O. D. Trapp, J. Warkentin, and R. T. Keys, *J. Amer. Chem. Soc.*, **82**, 5394 (1960).

(17) H. van Zwet and E. C. Kooyman, *Recl. Trav. Chim. Pays-Bas*, 1143 (1967).

that cage products should be formed only in low yields if at all.

In view of these facts, we suggest two different mechanisms to explain the ArH yields and viscosity dependence. The first assumes that both $ArCPh_3$ and XH are produced in the cage. If ArH *itself* is not a cage product, then the most obvious explanation of the increased yields of ArH at higher viscosities is to assume that the hydrogen donor which is the *precursor* of ArH is a cage product. Clearly, XH is a likely precursor. The cage yields of XH need not be large; we have presented evidence that a hydrocarbon hydrogen donor which is not unlike XH has an extraordinarily large transfer constant of the order of magnitude of those of thiols.[18]

The other mechanism, which can be formulated in two ways, allows the cage yield from PAT-type initiators to be zero, but assumes that the concentration of the unknown hydrogen donor is controlled such that its concentration increases at higher viscosity. One formulation envisions XH as the donor and postulates that the conversion of XH to YH is slower at higher viscosities. (It is clear that XH would have a much higher transfer constant than would YH.[18]) The second possibility uses ZH as the donor and postulates that the equilibrium[14d,19] between trityl radicals and ZH is shifted toward ZH at higher viscosities.



ZH

Thus, we can satisfactorily account for the formation of ArH in pure CCl_4, but we cannot formulate a unique mechanism which accounts for the viscosity dependence of the ArH yields. Of the two explanations for the viscosity effect which we have suggested, the mechanism which postulates that XH is the precursor to ArH and is a cage product has the advantage that it allows a straightforward interpretation of the production of YH and $ArCPh_3$ in the presence of scavengers (Table III). The mechanism which postulates that either a slower conversion of XH to YH or an equilibrium between trityl radicals and ZH increases the concentration of reactive hydrogen donors at higher viscosity is *ad hoc*. However, it has the advantage of being consistent with the assumption of zero cage yields from PAT-type initiators, an assumption which is attractive in view of the stability of $ArN_2\cdot$ radicals and the high yields of Ar fragments in our scavenging experiments (Table I). At present, we have no data which exclude either of these two mechanisms, but we favor the former. Although it is conceivable that the conversion of XH to YH is retarded by viscosity, there is no evidence that it is, and the equilibrium between ZH and trityl would more likely decrease the concentration of ZH at higher viscosities.

One further problem in the cage chemistry of PAT remains; it has been suggested that 9-phenylfluorene (9-PF) is a cage product from PAT.[8,9d] We could not detect this compound by gc analysis of decomposed solutions of PAT in CCl_4, even though the gc used in this work was sensitive enough to detect concentrations of 9-PF in standard solutions which would correspond to a yield of <0.1%. We conclude that 9-PF is neither a cage product nor a significant product in free solution in CCl_4 solvent.

(18) W. A. Pryor and J. H. Coco, *Macromolecules*, **3**, 500 (1970).

(19) A brief review is given by W. B. Smith, *J. Chem. Educ.*, **47**, 535 (1970).

Table IV

Yields of Nitrobenzene and *p*-Chloronitrobenzene and the Relative Rate Constants from the Thermolysis of 0.02 *M* *p*-Nitrophenylazotriphenylmethane

Hydrogen donor, RH (registry no.)	$[CCl_4]/[RH]$	% ArH	% ArCl	k_H/k_{Cl}[a]	$[ArH]_0$[b]
Heptane	3.9	56.35	25.32	8.1	3.9
(142-82-5)	31.0	19.12	58.20		
Octane	1.16	77.8	7.9	10.87	2.7
(111-65-9)	8.32	45.5	34.3		
	25.49	24.0	51.7		
	62.7	14.9	62.75		
3-Methylpentane	8.42	38.53	46.52	6.35	3.2
(96-14-0)	25.80	18.39	65.74		
	39.56	13.82	62.62		
	59.35	9.53	57.62		
2,3,4-Trimethylpentane	8.71	38.80	38.75	8.3	2.0
(565-75-3)	16.95	26.77	50.29		
	35.64	17.23	60.74		
	42.43	13.44	62.99		
	59.90	11.45	69.63		
2,3-Dimethylbutane	1.03	73.0	10.8	6.3	6.8
(79-29-8)	21.4	22.5	50.6		
	53.25	15.0	74.0		
Cyclohexane	1.50	70.0	10.2	9.5	3.7
(110-82-7)	7.99	43.8	34.0		
	9.80	41.5	40.0		
	29.4	21.9	58.4		
	63.8	13.6	61.0		
	66.4	13.5	65.0		
Cycloheptane	16.17	44.34	36.05	18.7	2.6
(291-64-5)	31.28	30.55	46.91		
	61.08	20.01	56.34		
Cyclooctane	24.71	45.62	29.7	26.9	1.8
(292-64-8)	32.77	36.65	42.87		
	41.15	31.67	45.3		
	61.59	24.04	51.34		
CCl_4		3.76	71.6		
(56-23-5)					

[a] From the slope of a plot of eq 5. [b] From the intercept of the plot of eq 5.

Calculation of k_H/k_{Cl} for PAT Initiators.—Edwards and Mayo[20] who originally used the CCl_4 method for determining relative rate constants, as well as Bridger and Russell[8,9d] and ourselves,[6a] observed the formation of some ArH-type products even when the solvent was pure CCl_4. Clearly, some ArH is produced from reactions other than eq 1, and a technique must be developed to correct for this spurious ArH yield.

Correction Factor.—The correction for the spurious ArH can be made by subtracting a correction factor, $[ArH]_0$, from the yield of ArH observed in CCl_4–RH mixtures. The equation is

$$\frac{k_H}{k_{Cl}} = \left(\frac{[ArH] - [ArH]_0}{[ArCl]}\right)R \qquad (4)$$

where R is the solvent ratio of $[CCl_4]/[R]$ and is assumed to be constant throughout a run. Russell[8,9d] suggested evaluating $[ArH]_0$ by using a standard concentration of PAT, measuring the ArH yield in CCl_4 at that concentration, and subtracting this yield from the total ArH yields in CCl_4–RH mixtures. (Edwards and Mayo[20] used an

(20) F. G. Edwards and F. R. Mayo, *J. Amer. Chem. Soc.*, **72**, 1265 (1950).

TABLE V

SUMMARY OF k_H/k_{Cl} VALUES FOR NAT IN VARIOUS SOLVENTS AT 60° [a]

Hydrogen donor, RH	k_H/k_{Cl}	$\pm\bar{X}$ [b]	No. of runs	$(k_H/k_{Cl})_{calcd}$ [c]
Alkanes and Alkylbenzenes				
Hexane	7.6	0.50	2	6.9
Heptane	8.4 [d]	0.42	3	8.5
Octane	10.3 [d]	0.29	7	9.7
Decane	12.8	0.60	2	11.7
2-Methylpentane	7.7		1	7.5
3-Methylpentane	8.0		1	7.5
2-Methylhexane	8.6	0.30	2	9.1
3-Methylhexane	8.8 [d]		1	9.1
2,5-Dimethylhexane	9.7		1	11.4
2,4-Dimethylpentane	5.2	0.16	4	9.8
2,3-Dimethylbutane	8.9 [d]	1.30	3	8.2
2,2,3-Trimethylbutane	6.2		1	4.9
2,3,4-Trimethylpentane	7.27 [d]	0.48	7	12.1
2,2,4-Trimethylpentane	2.77	0.53	4	6.4
2,2,3,3-Tetramethylbutane	1.33	0.47	3	1.33
1,4-Di-*tert*-butylbenzene	1.0		1	1.33
Diphenylmethane	6.7		1	
Triphenylmethane	16.1		1	
Indan	23.5		1	
Cyclopentane	8.85	0.05	2	
Cyclohexane	9.14 [d]	0.74	9	
Cycloheptane	18.35 [d]	0.74	4	
Cyclooctane	24.62 [d]	1.55	4	
Methylcyclohexane	13.9	0.88	3	
Alkenes				
1-Hexene	4.2	0.2	2	3.7
2-Hexene	14.5		1	10.8
3-Hexene	18.0	0.7	2	10.9
1-Heptene	10.35	0.25	2	10.3
2-Heptene	15.15	0.55	2	12.4
1-Octene	9.35	0.35	2	11.9
2-Octene	15.6		1	14.0
2-Methyl-2-butene	9.1		1	11.2
4-Methyl-1-pentene	6.4		1	9.4
2-Methyl-2-pentene	14.2		1	13.9
4-Methyl-2-pentene	5.75	0.15	2	
2,3-Dimethyl-2-butene	22.3		1	14.9
Cyclopentene	20.7		1	
Cyclohexene	30.3	0.54	3	
2,5-Dimethyl-2,4-hexadiene	19.4		1	
Haloalkanes				
1-Bromopropane	1.93		1	
2-Bromopropane	1.67	0.05	3	
Bromocyclopropane	0.32		1	
Bromoethane	0.75		1	
1-Bromobutane	2.53	0.12	3	
Methylene chloride	0.94	0.01	4	
Alkyl Sulfides				
Methyl phenyl sulfide	0.97		1	
Ethyl phenyl sulfide	5.1		1	
Isopropyl phenyl sulfide	8.0		1	
Heteroaromatics				
2-Methylpyrazine	0.32		1	
2-Methylpyridine	0.93	0.18	2	
2-Methylthiophene	1.5		1	
3-Methylthiophene	0.4		1	
Oxygen Compounds				
Ethyl acetate	0.8		1	
Methyl acetate	0.4		1	
Tetrahydrofuran	19.2	0.45	2	
tert-Butyl methyl ether	2.5		1	
Methanol	1.4		1	
3-Pentanone	5.2		1	
Dicyclopropyl ketone	1.1		1	
Nitrogen Compounds				
Nitromethane	0.05		1	
Nitroethane	0.43	0.02	2	
2-Nitropropane	0.6		1	
Hydrazobenzene	36.1		1	
Acetonitrile	0.23		1	
Methyl thiocyanate	0.16		1	
Miscellaneous Compounds				
Tetrahydrothiophene	32.1		1	
Tetramethylsilane	0.8		1	
Hexamethylbenzene	38.7	0.9	2	
Hexaethylbenzene	4.3	0.1	2	

[a] [NAT], 0.01–0.05 *M*. [b] The average error of the mean. [c] The $(k_H/k_{Cl})_{calcd}$ values were calculated from the reactivities of the appropriate carbon–hydrogen bonds (see text). [d] See Table IV for values obtained from a plot of eq 5.

analogous method.) This technique cannot be exact, since the value of $[ArH]_0$ should vary with the solvent as well as with the initial concentration of PAT. Solvents which are more reactive will scavenge more Ar· radicals, and the Ar· + T· reaction will produce a smaller yield of XH.

To reduce this uncertainty in $[ArH]_0$, and under the erroneous impression that ArH was a cage product, we previously used a method which involved the extrapolation of runs to zero PAT concentration.[6a] In practice, this is tedious since at least five runs must be made for each hydrogen donor studied; the Russell method often is used with only a single run.

We now wish to propose an alternative method for the evaluation of $[ArH]_0$. Rearrangement of eq 4

$$[ArH] = \frac{k_H[ArCl]}{k_{Cl}R} + [ArH]_0 \qquad (5)$$

gives 5, where k_H/k_{Cl} is the slope and $[ArH]_0$ is the intercept of a plot of [ArH] *vs.* [ArCl]/*R*. The correction factor, $[ArH]_0$, is determined by studying the competition reactions at a given $[NAT]_0$ and various ratios of $[CCl_4]/[RH]$. Table IV lists our new data for the results of competition studies for eight hydrogen donors with CCl_4. The mean $[ArH]_0$ is (3.3 ± 1.1)% [ArH] (excluding 2,3-dimethylbutane) at $(NAT)_0 = 0.02$ *M*. This $[ArH]_0$ is comparable with the 3.7% ArH obtained from thermolysis of 0.02 *M* NAT in pure CCl_4. The data of Table IV do indicate, however, that there is a significant variation in $[ArH]_0$. As expected, solvents with large relative values of k_H tend to give small correction values, although 2,3-dimethylbutane appears to be anomolous. Despite this indication that a separate value of $[ArH]_0$ should be evaluated for each solvent, the effort involved in determining data by this technique appears to be unjustified for the increased precision available. We, therefore, have chosen to use the Russell method in which the correction factor is taken to be the yield of ArH in CCl_4 for a given initial concentration of NAT. These values can be read from

Figure 1. Table IV shows that the error in k_H due to an erroneous correction factor should be <10%.

Selectivity of the p-Nitrophenyl Radical.—Table V summarizes the relative rate constants determined for numerous hydrogen donor solvents. The table also shows calculated values of k_H/k_{Cl} based on the assumption that the relative reactivity of the p-nitrophenyl radical toward primary, secondary, and tertiary alkyl hydrogens is 0.074, 0.805, and 3.67, respectively. The reactivity of a primary alkyl hydrogen was calculated using the k_H/k_{Cl} value of hexamethylethane and that for a secondary hydrogen was calculated using the data for all the normal alkanes and the previously calculated reactivity of primary hydrogens. Reactivity of a tertiary alkyl hydrogen was calculated using the data for monomethylalkanes. Normalization leads to a selectivity series of 1:10.9:49 for primary, secondary, and tertiary alkane hydrogens.

The relative reactivities of the primary and secondary allylic hydrogens are 1.24 and 2.63. Normalization relative to the primary alkyl hydrogen gives a series of 16.8 to 35.6 for primary to secondary allylic hydrogens. The sequence of relative reactivities for cycloalkyl hydrogens is cyclooctane > cycloheptane > cyclopentane > cyclohexane. This reactivity sequence is consistent with that for the methyl,[6b] phenyl,[8] chlorine,[21] and trichloromethyl[22] radicals.

Table VI summarizes the reactivities of primary hydrogen atoms α to various functional groups and the data show that most substituents have small effects on the reactivities of hydrogen atoms toward p-nitrophenyl radicals. Table VII compares the relative reactivities of the phenyl and p-nitrophenyl radicals. The p-nitrophenyl radical appears to be slightly more selective.

TABLE VI

RELATIVE RATE CONSTANTS FOR THE REACTION OF THE CARBON–HYDROGEN BONDS α TO FUNCTION SUBSTITUENTS AT 60°

Substituent Z in ZCH_3	Relative reactivity
Alkyl	(1)
Phenyl	7.7
Vinyl	17.2
Hydroxy	6.5
Cyano	1.1
Methoxycarbonyl	1.8
Nitro	0.3
Thiophenyl	4.4
Thiocyanate	6.9

Experimental Section

Material.—Alkanes from Phillips Petroleum Co. and Columbia Organic Chemical Co. were purified using columns filled with silver nitrate on alumina as reported by Murray and Keller.[23] Alkenes were purified by passing them through a column of alumina W200 basic. Tetrahydrofuran, 1-bromobutane, and 2-bromobutane were purified by the methods suggested by Wiberg.[24] CCl_4 was Spectrograde and was further purified by passing it through a column packed with silica gel. The azo compound was synthesized employing the method of Cohen and Wang.[25] Spectrograde benzene was purchased from Eastman Kodak Co. and used without further purification. Reagent grade nitrobenzene was distilled at 53° (1 Torr). Reagent grade nitrochlorobenzene was recrystallized twice from ethyl alcohol and dried in a vacuum oven, mp 82.8°.

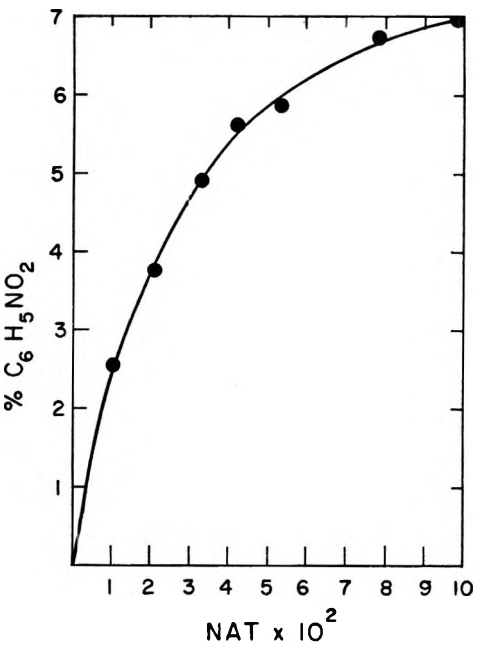


Figure 1.—Decomposition of NAT in carbon tetrachloride: effect of initial [NAT] on yields of nitrobenzene.

TABLE VII

RELATIVE REACTIVITIES OF VARIOUS TYPES OF CARBON–HYDROGEN BONDS TOWARD PHENYL AND NITROPHENYL RADICALS IN SOLUTION (RELATIVE TO THE α H ON TOLUENE)

Type of bond	Phenyl[a]	Nitrophenyl[b]
Primary alkyl	0.11–0.13	0.17
Secondary alkyl	1.01	1.8
Tertiary alkyl	4.8	8.3
Cyclopentane	1.15	2.1
Cyclohexane	1.0	1.7
Cycloheptane	1.8	2.9
Cyclooctane	2.0	4.6
Primary allylic	1.6	2.8
Secondary allylic	3.3	6.0
Tertiary allylic	13.3	
Cyclopentene (α)	9.7	10.4
Cyclohexene (α)	11.2	15.4
Toluene (α)	(1)	(1)
Ethylbenzene (α)	4.6	4.7
Cumene (α)	9.7	28.5
Diphenylmethane	7.7	7.6
Indan	8.0	11.7

[a] Reference 8. [b] Present work.

Procedure of Kinetic Runs.—A solution with a known ratio of hydrogen donor and carbon tetrachloride was prepared by weight. The NAT, 15.7 mg, was weighed into a 2-ml volumetric flask which was filled with the solution and then transferred to two 9-mm-o.d. Pyrex sample tubes. The ampoules were then degassed and sealed under vacuum and placed in a constant temperature bath at 60° for 10 half-lives (13 hr).[25] The samples were analyzed on a gas chromatograph equipped with a 6-ft, 0.25-in.-o.d. glass column packed with silicone XF-1150 (Nitrile) on Chromosorb W. The chromatograph was a Glowall 320 equipped with a flame-ionization detector, Varian Aerograph G-2010 recorder, and Disc Chart integrator. The experimental conditions follow: column temperature, 140°; detector temperature, 200°;

(21) G. A. Russell, *J. Amer. Chem. Soc.*, **80**, 4997 (1958).
(22) E. S. Huyser, H. Schimke, and R. L. Burham, *J. Org. Chem.*, **28**, 2141 (1963).
(23) F. C. Murray and R. N. Keller, *ibid.*, **34**, 2234 (1969).
(24) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill, New York, N. Y., 1960.
(25) S. C. Cohen and C. H. Wang, *J. Amer. Chem. Soc.*, **75**, 5504 (1953).

injection temperature, 200°; flow rate, ~30 cc/min. The relative retention for CCl_4, $C_6H_5NO_2$, p-$O_2NC_6H_4Cl$ was 1:20:24, respectively.

To determine the yield of $C_6H_4NO_2$ and p-$O_2NC_6H_4Cl$, standard solutions of $C_6H_5NO_2$ and p-$O_2NC_6H_4Cl$ dissolved in CCl_4 were prepared and stored in sealed 1-ml glass vials. These standards were analyzed in triplicate prior to and following the reaction samples.

Acknowledgments.—We wish to express thanks to Mr. W. R. Bushey, an undergraduate research participant at LSU 1967–1968, Dr. J. O. Schreck, a Postdoctoral Fellow on NIH Grant GM 11908 in 1966, and Dr. J. P. Stanley, a Postdoctoral Fellow on NIH Grant GM 11908 1968–1971, for significant contributions to this work. W. A. Pryor wishes to thank Professors W. F. Libby and M. Calvin for hospitality during the tenure of a John Simon Guggenheim Fellowship, 1970–1971.

Registry No.—NAT, 16186-97-3; PAT, 981-18-0; p-nitrophenyl radical, 2395-99-5.

Formation of Radical Anions from Vicinal Diamines and Strong Bases[1]

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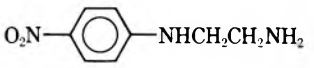
Ethylenediamine (EDA) reacts with butyllithium to form the pyrazine radical anion. On standing, in the presence of EDA and *N*-lithioethylenediamine, this radical is slowly converted to a dihydropyrazine radical. Other vicinal diamines were also found to yield pyrazine-type radicals when treated with strong base. The large amounts of hydrogen gas evolved during these reactions is attributed to loss of metal hydride from the metalated EDA.

In the course of the kinetic study of the reaction mechanism of the prototropic propargylic rearrangement of 3-hexyne with sodium amide in ethylenediamine (EDA) at room temperature,[3] the rate of rearrangement was found to be dependent on the time given to the interaction of sodium amide with EDA before introduction of the hexyne. The suspension of sodium amide in EDA gradually changes color from gray to purple to deep blue. Subsequent investigation by electron paramagnetic resonance (epr) revealed the presence of organic radicals in this and other reactions involving strong bases and vicinal diamines. Although further research has indicated that the rearrangement may not be related to the formation of these radicals,[4] the radicals themselves are of sufficient interest to warrant separate presentation.

Results

A. Detection of Radicals in Base-Treated Vicinal Diamines.—When strong bases [$NaNH_2$, $LiNH_2$, LiH, or butyllithium (BuLi)] are treated with excess EDA (a 10:1 molar ratio of diamine to base was commonly used) in a drybox at room temperature, intense blue solutions are obtained. Regardless of the base used, identical epr spectra resulted (Figure 1). The radical concentration was estimated to be 0.005 *M* by comparison with a standard solution of diphenylpicrylhydrazyl. Additional hyperfine structure was observed when tetrahydrofuran (THF) solvent was added to the EDA–BuLi mixture. Fully deuterated EDA, on treatment with BuLi, gave a five-line spectrum (Figure 2).

The reaction between EDA and BuLi results in a golden yellow color (no λ_{max} in the visible region 400–800 nm) if air is very carefully excluded using vacuum line techniques. Exposure to a trace of oxygen results in a gradual color change from yellow to purple (λ_{max} 585 nm) with little or no change in the epr signal. Extensive degassing does not reverse the color change. Excess oxygen, however, destroys the purple color as well as the radical signal. The radical signal can also be quenched by the addition of nitrobenzene, which results in formation of the nitrobenzene radical anion and *N*-(*p*-nitrophenyl)ethylenediamine (**1**).



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If either the yellow or the blue solution containing the radical (produced from EDA and BuLi) are allowed to stand for several days (under vacuum at room temperature) a different epr spectrum gradually develops (Figure 3).

Other diamines were also treated with strong base and examined by epr. The results are tabulated in Table I.

B. Formation of a Radical on Treatment of Pyrazine with Butyllithium.—Treatment of a dilute solution of

TABLE I

BASE-TREATED DIAMINES WHICH WERE ANALYZED BY EPR[a]

Diamine	Color	Epr signal
EDA	Blue[b]	Figure 1[c]
EDA-d_8	Blue	Figure 2
Propylenediamine	Red	Yes
N,N'-Dimethylethylenediamine	Green	Figure 4
2-Methyl-1,2-diaminopropane	Brown	Yes
N-Methylethylenediamine	Green	Yes
o-Phenylenediamine	Blue	Yes
cis-1,2-Diaminocyclohexane	Red-brown	Yes
trans-1,2-Diaminocyclohexane	Cloudy white	No
1,3-Diaminopropane	Cloudy white	No
N,N-Dimethylethylenediamine	Yellow	No

[a] A 10:1 molar ratio of diamine to BuLi was used. [b] The color is golden yellow if air is very carefully excluded. [c] Upon standing the spectrum gradually changes (Figure 3).

(1) Presented, in part, at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 28–April 2, 1971.

(2) Postdoctoral Research Associate, 1970–1971.

(3) J. H. Wotiz, W. E. Billups, and D. T. Christian, *J. Org. Chem.*, **31**, 2069 (1966).

(4) P. Barelski, Ph.D. Thesis, Southern Illinois University, 1971.

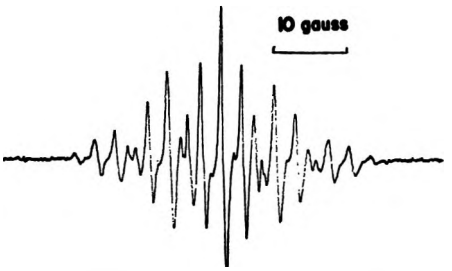


Figure 1.—First-derivative epr spectrum of radical formed from EDA and butyllithium.

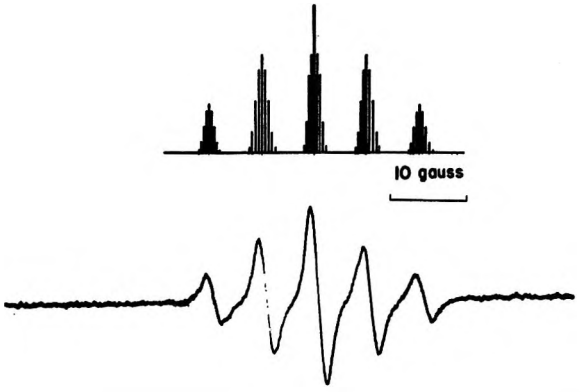


Figure 2.—First-derivative epr spectrum of radical formed from EDA-d_8 and butyllithium. The reconstruction refers to pyrazine-d_4 with a_N = 7.2 and a_D = 0.4.

pyrazine in THF ($\sim 10^{-2}$ *M*) with BuLi resulted in a yellow solution (no λ_{max} in the visible region) which gave the epr spectrum shown in Figure 5. This solution also turned blue on exposure to a trace of air.

C. Evolution of Hydrogen Gas on Treatment of Vicinal Diamines with Base.—Considerable amounts of hydrogen gas were evolved during the reaction between EDA and strong base. These and other results are given in Table II.

TABLE II

GASEOUS PRODUCTS FROM THE REACTION OF VICINAL DIAMINES WITH STRONG BASES[a]

Reactants		Products		
BuLi	EDA	Butane	H_2	NH_3
1	15	0.9	0.2	0
1	1	0.8	0.4	0.05
1	0.8	0.7 (.05)[b]	0.4 (0.1)[b]	0 (.02)[b]
$NaNH_2$	EDA			
1	10		0.02	0.2
1	1		0.06	0.1
BuLi	DMEDA[c]			
1	1	0.9	0 (0.2)[b]	0

[a] All data are in molar ratios. [b] Data in parentheses refers to the additional gas evolved after heating to 110° for 2 hr. [c] Refers to *N,N'*-dimethylethylenediamine.

D. Reaction of EDA with Alkali Metals.—EDA was refluxed over sodium metal and then distilled. The distillate as analyzed by vpc showed EDA plus eight other peaks. Piperazine and diethylenetriamine were identified by comparison with authentic samples. Pyrazine was identified, as a product, by vpc retention time and nmr.

When EDA was refluxed over lithium metal a purple solution developed which gave an epr spectrum identical

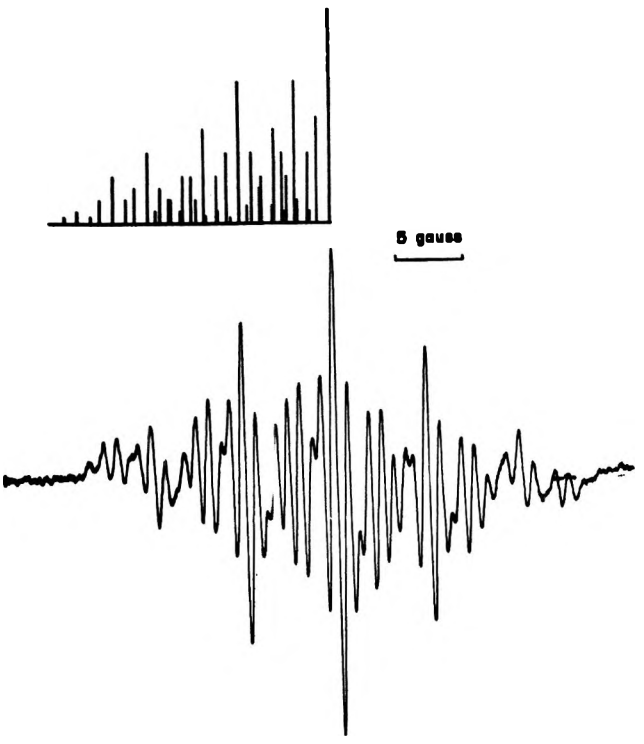


Figure 3.—First-derivative epr spectrum of radical formed in butyllithium–EDA after 1 week. The reconstruction refers to dihydropyrazine with a_N = 6.6, a_H = 2.4 (four equivalent), and a_H = 1.0 (two equivalent).

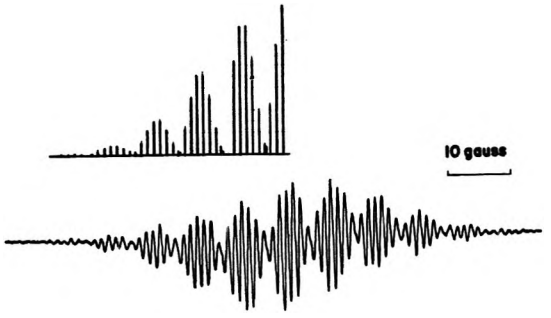
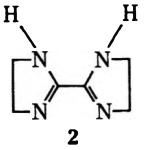


Figure 4.—First-derivative epr spectrum from reaction of *N,N'*-dimethylethylenediamine with butyllithium. The reconstruction refers to *N,N'*-dimethyldihydropyrazine with a_N = 6.7, a_H (methyl) = 6.7, a_H (ring) = 1.0, and a_{Li} = 1.0.

with that shown in Figure 1. A white solid, identified as bis(Δ^2-2-imidazolinyl) (2) was isolated from this reaction.



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Discussion

Radicals Formed in EDA.—The initially detected radical formed in the reaction of EDA with strong base (or lithium metal) is the pyrazine radical anion. Relative peak intensities and spacings (Figure 1) may be satisfactorily described as the result of hyperfine interaction of the unpaired electron with two equivalent nitrogen atoms (a_N = 7.3 G) and four equivalent hydrogen atoms (a_H = 2.7 G). We reduced pyrazine in THF with potassium metal and obtained an epr spectrum which was essentially identical with that ob-

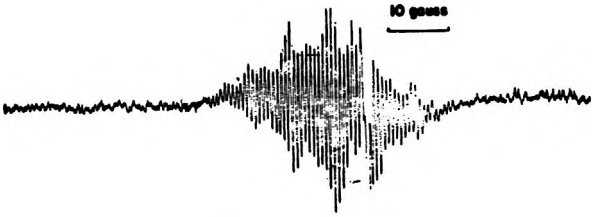


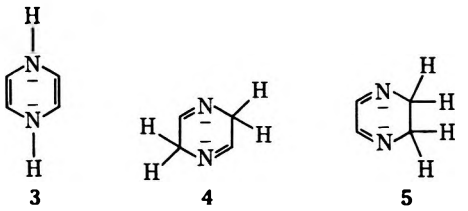
Figure 5.—First-derivative epr spectrum resulting from the reaction of butyllithium with pyrazine in THF.

tained from base treated EDA (literature values:[5] a_N = 7.22 G, a_H = 2.66 G). Furthermore, treatment of fully deuterated EDA with BuLi resulted in an epr spectrum (Figure 2) consistent with the perdeuterated pyrazine radical anion (a_N = 7.3 G, a_H (theoretical) = 0.4 G).

Generally aromatic radical anions are generated either by alkali metal reduction or by electrolytic reduction.[6] However, Russell and coworkers[7] have reported on the generation of radical reduction products in reactions between carbanions or organometallics and neutral unsaturated compounds. For example, phenazine[8] was reduced to its radical anion by treatment with potassium *tert*-butoxide in dimethyl sulfoxide. Similarly, we have found that pyrazine can be conveniently reduced with butyllithium in THF (see Figure 5 for the epr spectrum). This spectrum shows the additional quartet hyperfine structure from the alkali metal (a_{Li} = 0.7 G) as reported by Carrington and Santos-Veiga.[5] This additional hyperfine structure was also observed when THF solvent was added to the blue EDA–BuLi mixture containing the pyrazine radical.

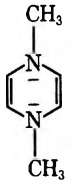
The pyrazine radical, when generated from EDA and butyllithium, is not stable. A different epr spectrum (Figure 3) was obtained after the EDA–BuLi mixture had been allowed to stand at room temperature under vacuum for 1 week. This observation was reproducible, starting with either the blue or the yellow EDA–BuLi mixture. The new spectrum is consistent with a pyrazine nucleus to which two additional equivalent hydrogens have been added (a_N = 6.6 G, two equivalent; a_H = 2.4 G, four equivalent; a_H = 1.0 G, two equivalent). Two interpretations were considered. Since hydrogen gas is evolved during the reaction, a weak interaction between hydrogen gas and the pyrazine radical was suggested. However, the bulk of the hydrogen gas is evolved during the first hour of the reaction; yet the new radical is not observed until after several days. Also, five freeze–pump–thaw cycles did not alter the epr spectrum. The favored interpretation, then, is that the new signal is due to the radical anion of a dihydropyrazine (**3**, **4**, or **5**).

Radicals from Other Vicinal Diamines.—The complex spectrum resulting from the reaction of butyllithium and propylenediamine could be due to a mixture of 2,6-dimethylpyrazine radical anion[9] and 2,5-dimethylpyrazine radical anion.[9] This is consistent with the observation that pyrazine is formed from the EDA (also, see below). Two propylenediamine molecules could combine to form 2,6-dimethylpyrazine and/or 2,5-dimethylpyrazine.



3 **4** **5**

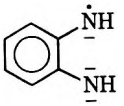
The spectrum initially observed from *N*,*N*′-dimethylethylenediamine and strong base (Figure 4) is consistent with the radical anion of *N*,*N*′-dimethyldihydropyrazine (**6**) (a_N = 6.7 G, two equivalent; a_H (methyl) = 6.7 G, six equivalent; a_H (ring) = 1.0 G, four equivalent; a_{Li} = 1.0 G, one). This radical would be completely analogous to the radical anion (**6**) of **3**.



6

Other vicinal dimaines (see Table I) also gave epr spectra when treated with butyllithium. These were not sufficiently resolved (or were too complex) to permit interpretation. Apparently, diamines which are vicinal (1,3-diaminopropane gave no epr signal) and which involve only primary or secondary amino groups (*N*,*N*-dimethylethylenediamine gave no epr signal) are required for formation of these pyrazine-type radicals. Interestingly, the cis isomer of 1,2-diaminocyclohexane gave an epr signal, whereas the trans isomer did not.

Russell and coworkers[8] assigned the radical obtained from *o*-phenylenediamine and potassium *tert*-butoxide in dimethyl sulfoxide as **7**.



7

The Origin of Pyrazine.—Since epr spectroscopy is a very sensitive technique, one must always be concerned with the possibility of impurities in the materials used. In particular, pyrazine was suspected as an impurity in EDA. However, no pyrazine could be detected in the starting EDA using vapor phase chromatography and nmr. The limit of sensitivity for both techniques was approximately 0.001 *M*. The radical (prepared from a 10:1 molar ratio of EDA to BuLi) concentration was estimated to be 0.005 *M* by comparison with a standard solution of diphenylpicrylhydrazyl (the accuracy of this technique is believed to be ±50%).

To confirm that pyrazine was being produced from the EDA, a EDA–BuLi mixture was quenched with nitrobenzene. The recovered EDA was found to contain pyrazine in a concentration of 10^{-2} to 10^{-3} *M* (detected both by vpc and nmr). Hence, small quantities of pyrazine (the yield was around 0.02%) are formed when EDA reacts with butyllithium. Pyra-

(5) A. Carrington and J. dos Santos-Veiga, *Mol. Phys.*, **5**, 21 (1962).

(6) R. S. Alger, "Electron Paramagnetic Resonance," Interscience, New York, N. Y., 1968, pp 265–272.

(7) G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Amer. Chem. Soc.*, **86**, 1807 (1964).

(8) G. A. Russell, R. Konaka, E. T. Strom, W. C. Danen, K. Chang, and G. Kaupp, *ibid.*, **90**, 4646 (1968).

(9) C. A. McDowell and K. F. G. Paulus, *Mol. Phys.*, **7**, 543 (1964).

zine was not detected when EDA was mixed only with nitrobenzene.

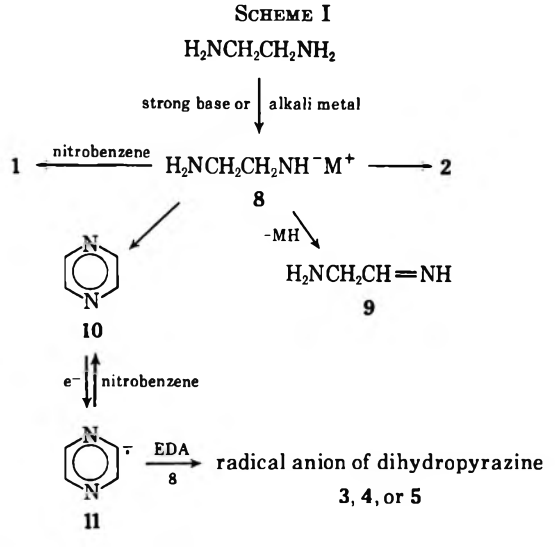
The formation of pyrazine may be a problem if extremely pure EDA is required. The recommended[10] and commonly used preparation of anhydrous EDA involves as a final step, the distillation from sodium metal. We found significant amounts of pyrazine ($\sim 10^{-2}$ *M*) in EDA which had been refluxed for 36 hr over sodium and then distilled. Pyrazine (bp 115.5°) and EDA (bp 116.5°) cannot be effectively separated by ordinary distillation.

Color Changes.—The observation of a deep blue coloration on treatment of EDA with sodium amide has been reported by other workers.[11] We have observed that a trace amount of air is required for the development of this color from the initially formed yellow solutions. A similar color change was noted when the pyrazine radical (prepared by reaction of pyrazine in THF with BuLi) was exposed to air.

Heterocyclic radical anions frequently dimerize.[12,13] Ward[12] was unable to prepare the pyridine radical anion in 1 2-dimethoxyethane owing to its rapid dimerization. Schmulbach, Hinckley, and Wasmund[13] observed that a yellow solution of pyridine radical anion (in pyridine solvent) changes to an intense blue color on standing This they attributed to formation of 4,4′-bipyridyl radical anion. We, however, observed little or no change in the pyrazine radical signal accompanying the color change. The exact structure of the chromophore responsible for the blue color remains a mystery.

Mechanistic Aspects.—We feel that the chemistry involved in the reaction of EDA with strong base or alkali metal can be, at least in part, explained according to Scheme I.

SCHEME I

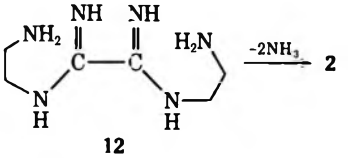


The initial step in the reaction almost certainly involves the formation of **8**. In fact, *N*-lithioethylenediamine has been prepared and isolated from the reaction between EDA and lithium metal powder.[14] This compound has been found useful as a metalating agent,[14,15] as a catalyst in the rearrangement of olefins[16-18] and acetylenes,[4] and as a reagent which dehydrogenates cyclic dienes.[16,17] Product **1** might arise as a result of nucleophilic attack, by **8**, at the para position of nitrobenzene. However, since electron transfer from **8** to nitrobenzene is probably diffusion controlled, a radical coupling is more likely.

The evolution of significant amounts of hydrogen gas most likely results from the loss of metal hydride (which reacts with EDA to produce hydrogen gas and more **8**) from **8**.[19] This would be completely analogous to the loss of lithium hydride on the thermal decomposition of alkyllithium compounds (*e.g.*, butyllithium decomposes into 1-butene and LiH on heating to 100°).[20] Two pieces of evidence require that the hydrogen gas arise from the EDA and not from the butyllithium. First, the evolution of butane is nearly quantitative and no butene is observed. Second, the use of perdeuterated EDA yields only D_2.

The product, **9**, resulting from loss of metal hydride, is an aldimine. Aldimines of the type RCH=NH are not stable.[21]

The imidazole derivative, **2**, has been reported previously from the reaction of lithium metal with EDA.[22] However, these workers reported that the presence of hydrocarbons, such as tetralin or isopropylbenzene, were required for the formation of that product. We obtained **2** in the absence of hydrocarbon. Woodburn and O'Gee[23] obtained **2** from the reaction of EDA with cyanogen at 0°. They proposed **12** as a precursor. In light of the preceding observations, it is not hard to visualize a process leading to **2** (or **12**) involving **8** and **9** as precursors.



12

The mode of formation of pyrazine from **8** and/or **9** would be largely spectulation at this time.[24] Its reduction to **11** most likely involves the transfer of an electron from **8** to **10**, analogous to that described by Russell.[7]

$$10 + 8 \longrightarrow 11 + H_2NCH_2CH_2\dot{N}H$$

The further reduction of **11** to a dihydropyrazine radical is not surprising. There is some evidence in the literature that hydrocarbon radical anions (*e.g.*, naphthalene radical anion) undergo partial ring satura-

(10) L. M. Mukherjee and S. Bruckenstein, *Pure Appl Chem.*, **13**, 419 (1966).
(11) J. C. Warf and V. Gutmann, *Inorg. Nucl. Chem. Lett.* **6**, 583 (1970).
(12) R. L. Ward, *J. Amer. Chem. Soc.*, **83**, 3623 (1961).
(13) C. D. Schmulbach, C. C. Hinckley, and D. Wasmund, *ibid.*, **90**, 6600 (1968).
(14) O. F. Beumel, Jr., and R. F. Harris, *J. Org. Chem.*, **28**, 2775 (1963).
(15) O. F. Beumel, Jr., and R. F. Harris, *ibid.*, **30**, 814 (1965).
(16) L. Reggel, S. Friedman, and I. Wender, *ibid.*, **23**, 1136 (1958).
(17) B. S. Tyagi, B. B. Ghatge, and S. C. Bhattacharyya, *ibid.*, **27**, 1430 (1962).
(18) P. Kaspar, unpublished results.
(19) Some hydrogen gas could result during the formation of pyrazine from EDA. However, the amount of gas given off is considerably more than can be accounted for in this way.
(20) W. H. Glaze, J. Lin, and E. G. Felton, *J. Org. Chem.*, **31**, 2643 (1966).
(21) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. 1, W. A. Benjamin, New York, N. Y., 1965, p 291.
(22) L. Reggel, J. P. Henry, and I. Wender, *J. Org. Chem.*, **26**, 1837 (1961).
(23) H. M. Woodburn and R. C. O'Gee, *ibid.*, **17**, 1235 (1952); H. M. Woodburn and J. R. Fisher, *ibid.*, **22**, 895 (1957).
(24) H. G. Viehe (personal communication) has suggested a mechanism involving reaction of a vicinal enediamine with the corresponding saturated diamine forming a tetrahydropyrazine structure. See A. Halleux and H. G. Viehe, *J. Chem. Soc. C*, 1726 (1968), for a discussion of the chemistry of vicinal enediamines.

tion owing to attack by solvent.[25] A sequence involving protonation of **11** (by EDA) followed by a one-electron reduction, another protonation, and a final one-electron reduction would lead to the required radical anion. This sequence is similar to that proposed for the Birch reduction.[26] Experiments involving reduction of dihydropyrazines, if stable, would be desirable to unambiguously confirm the radical assignments.

Experimental Section

Instrumentation.—First-derivative epr spectra were obtained using a Varian 4502-15 epr spectrometer with 100-kcps field modulation. Magnetic field settings and scan rates were obtained from the Varian Mark II Field Unit. Visible spectra were recorded with a Beckman DK-1A spectrophotometer. Nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as internal standard. Ir spectra were obtained on a Beckman Model IR-5A spectrophotometer. Mass spectra were determined using a CEC 21-104 mass spectrometer. The gas–liquid partition chromatographic data were obtained on a Varian-Aerograph Model 1800 chromatograph linked to a Varian Aerograph Model 20 recorder. A 10 ft × 0.25 in. aluminum column packed with 10% DC 710 silicone–10% KOH on Chromosorb W was used.

Epr Solutions.—Most solutions were prepared using a vacuum line (mercury diffusion pump, mechanical oil vacuum pump, liquid nitrogen trap) capable of producing a vacuum of 10^{-3} mm. In general, the solutions were prepared by vacuum transferring the diamine to the epr apparatus containing the strong base (cooled with liquid nitrogen). The epr apparatus consisted of a reaction flask equipped with a stopcock, for attachment to the vacuum system, and a side arm with a $\overline{\S}$ $^{7}/_{25}$ ground-glass joint to which a quartz epr tube was attached. Just above the $\overline{\S}$ $^{7}/_{25}$ joint was a sintered-glass filter. After the base and diamine had reacted (about 1 hr was allowed), a portion of the mixture was filtered into the epr tube and the spectrum was recorded. All spectra were recorded at room temperature.

The concentration of the radical, generated by reaction of a 10:1 molar ratio of EDA to butyllithium, was estimated by comparison with a solution of diphenylpicrylhydrazyl. Comparison of peak heights for the overmodulated spectra at identical instrumental settings indicated a radical concentration of 5×10^{-3} M.

Chemicals.—Ethylenediamine (Aldrich or Matheson Coleman and Bell) was distilled from sodium with a minimum of refluxing (bp 116–117°) and stored over "Linde" type 4A Molecular Sieve. The solvent was vacuum transferred from sodium before use. No impurities could be detected in the EDA prepared in this manner. The perdeuterated EDA was custom prepared by Merck Sharp and Dohme and was twice distilled from butyllithium before use. Commercial *N,N'*-dimethylethylenediamine (Aldrich) was found to contain ~8% 1,4-dimethylpiperazine as determined by vpc and mass spectral analysis. This diamine was purified by distillation (bp 119–120°) on a spinning-band column. *o*-Phenylenediamine (Matheson Coleman and Bell) was recrystallized from hot water and dried in a vacuum desiccator (mp 102–103°). Propylenediamine, 2-methyl-1,2-diaminopropane, *N*-methylethylenediamine, 1,3-diaminopropane, and *N,N*-dimethylethylenediamine (all from Aldrich) were distilled from sodium prior to use. The cis and trans isomers of 1,2-diaminocyclohexane (Aldrich) were separated according to the literature.[4,27]

Nitrobenzene (Fisher) was distilled prior to use. Tetrahydrofuran (Matheson Coleman and Bell) was distilled from a potassium hydroxide activated alumina mixture and stored over sodium. Lithium hydride (all from Matheson Coleman and Bell), sodium amide (Robert's Chemicals Inc.,), and butyllithium (1.5 M in hexane, Foote Mineral) were used as received. Pyrazine (Wyandotte) was vacuum sublimed before use.

Reactions of Diamines with Strong Bases.—These reactions were carried out on the vacuum line by vacuum transferring the diamine to the reaction flask containing the strong base. When butyllithium was used, the hexane solvent was removed prior to the addition of diamine. Generally, a 10:1 molar ratio of diamine to strong base was employed. A typical reaction sequence is described below.

Butyllithium (10 ml, 1.5 M) was placed in a 50-ml round-bottomed flask in a drybox (nitrogen gas, P_2O_5 desiccant). The flask was attached to the vacuum line and the bulk of the hexane was distilled from the solution. To this concentrated butyllithium (cooled with liquid nitrogen) was vacuum transferred 10 ml of dry EDA which had been degassed by two freeze–pump–thaw cycles. Gases were evolved, as the mixture was gradually allowed to warm to room temperature, and a golden yellow solution resulted. A small amount of material remained undissolved. Exposure to a trace of air gradually resulted in a deep purple color.

Determination of Gaseous Products.—The gases evolved during the reaction between butyllithium and vicinal diamines were hydrogen and butane. The butane was identified by ir (10-cm cell) and mass spectrometry. The hydrogen gas was identified by mass spectrometry. Quantitative data was obtained by using a calibrated vacuum manifold (volume determined with carbon dioxide) and a mercury manometer. The hydrogen and butane were separated with liquid nitrogen.

Reaction of EDA with Alkali Metals.—EDA (150 ml) was added to a dry three-neck flask fitted with reflux condenser, sodium hydroxide drying tube, and nitrogen inlet tube. The system was flushed with nitrogen and 0.3 g of freshly cut sodium was added. The surface of the metal turned blue. Hydrogen was evolved on heating. After 1 day of stirring and refluxing, the sodium was completely consumed. The dark viscous brown mixture was distilled to dryness leaving a black tar which was soluble in hot water. The distillate as analyzed by vpc showed EDA (major component) plus eight other peaks. Piperazine and diethylenetriamine was identified by retention times of the known compounds. Pyrazine was identified by retention time and nmr.

EDA (20 ml) was put into a dry 250-ml flask fitted with a magnetic stirring bar, reflux condenser, and drying tube. The system was flushed with nitrogen, and lithium wire (1.0 g) was added. The mixture turned dark blue, was refluxed for 24 hr, and then was distilled to dryness. Analysis of the distillate by vpc showed no pyrazine, piperazine, or diethylenetriamine; only EDA and an unidentified smaller peak with a longer retention time. The nonvolatile residue was quenched with water, and a water-insoluble white solid was filtered out and recrystallized from methanol: yield 4.2 g; mp 305–310°; mass spectrum *m/e* 138 (decomposes slowly around 300° without melting,[22] *m/e* 138[22]); ir (Nujol) 3.15 (N—H) and 6.48 μ (C=N).

Generation of Pyrazine Radical Anion from Pyrazine.—The pyrazine radical anion was prepared by reduction of a 10^{-3} M solution of pyrazine in THF with potassium metal (a_N = 7.2 G, a_H = 2.7 G; see ref 6, pp 265–272, for a general description of the technique used). The pyrazine radical anion was also prepared by vacuum transferring 15 ml of 10^{-2} M pyrazine in THF to 0.015 mol of butyllithium (a_N = 7.2 G, a_H = 2.7 G, a_{Li} = 0.7 G). In both cases initially the color of the solution was golden yellow.

Quenching of the Radical with Nitrobenzene.—To a purple solution made from 10 ml of 1.5 M butyllithium and 10 ml of EDA was vacuum transferred 0.5 ml of nitrobenzene. An exothermic reaction resulted and the color changed from purple to brownish-red. The new epr spectrum was due to the nitrobenzene radical anion [a_N = 12.2 G, a_H (para) = 3.8 G, a_H (ortho) = 3.7 G, and a_H (meta) = 1.1 G]. The EDA, which had been vacuum transferred to another flask, was found to contain a trace amount of pyrazine as determined by vpc (column 90°, injector 150°, flow 80 ml/min, EDA retention time 10.5 min, pyrazine retention time 19.5 min) and nmr (δ 8.57). No pyrazine could be detected in a sample of the starting EDA.

In another experiment, the quenched EDA–BuLi mixture was taken up in 20 ml of water and extracted with 30 ml of ether. The ether layer was dried and condensed to a volume of about 5 ml. The yellow crystals, which formed after the ether extract had been allowed to stand for 2 days, were recrystallized from absolute ethanol: mp 138–140° (lit.[28] mp 144° for 1),

(25) G. J. Hoijtink and P. J. Zandstra, *Mol. Phys.*, **3**, 371 (1960).

(26) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 65.

(27) A. I. Smith, U. S. Patent 3,163,675 (1964); *Chem. Abstr.*, **62**, 7656*f* (1965).

(28) J. P. Fourneau and Y. deLestrange, *Bull. Soc. Chim. Fr.*, 827 (1947).

nmr ($CDCl_3$, δ) 8.1 (d, 1 H, J = 9 cps), 6.6 (d, 1 H, J = 9 cps), 3.2 (m, 4 H), 1.4 (m, 3 H); mass spectrum m/e (rel intensity) 181 (16), 152 (73), 151 (48), 135 (37), 105 (100), 65 (40), 50 (38), 44 (84), and 40 (81).

Registry No.—1, 6332-77-0; 2, 934-03-2; 6 (radical anion), 11089-69-3; EDA, 107-15-3; EDA-d_8, 34281-22-6; DMEDA, 108-00-9; pyrazine radical anion, 11089-67-1; pyrazine radical anion-d_8, 11089-66-0; dihydropyrazine radical anion, 11089-68-2; nitrobenzene, 98-95-3; butyllithium, 109-72-8; sodium, 7440-23-5; lithium, 7439-93-2; nitrobenzene radical anion, 15753-78-3; pyrazine, 290-37-9; hydrogen, 1333-74-0.

Anodic Oxidations. VII. The Reaction Mechanism in the Electrochemical Oxidation of *N,N*-Dimethylformamide in Acetic Acid and in Methanol

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The anodic oxidation of *N,N*-dimethylformamide has been studied in methanol and in acetic acid, with fluoroborates, nitrates, and acetates as the supporting electrolytes. The operation of two oxidation mechanisms has been demonstrated. In the one, the primary reaction is an electron transfer from the amide to give a cation radical. In the other, the initiating reaction is an electron transfer from nitrate ion to give a nitrate radical. With a nitrate salt as the supporting electrolyte, both mechanisms operate, and the conditions under which each occurs have been defined.

There is evidence that, in acetic acid containing acetate ion, *N,N*-dimethylamides oxidize at a lower potential than acetate ion.[1,2] and the first step in the oxidations to form *N*-acetoxymethyl-*N*-methylamides is an electron transfer from the amide substrate. Nevertheless, when these reactions are run at constant current for preparative purposes, the coulombic efficiencies are low, and a significant portion of the charge passed is used in the Kolbe oxidation of acetate ion to give ethane and carbon dioxide.[1b]

The anodic oxidation of *N,N*-dimethylamides in alcohols, with nitrate salts as supporting electrolytes, is a good method for preparing *N*-alkoxymethyl-*N*-methylamides.[1c] However, there is uncertainty as to the mechanism. Current–potential curves, during electrolysis, support discharge of nitrate ion as the initiating reaction,[1c] but cyclic voltammetric curves show very similar peak potentials for *N,N*-dimethylformamide and for nitrate ion, suggesting that the amide and the anion oxidize simultaneously.[3]

The present research was undertaken to resolve some of these uncertainties. The anodic oxidation of *N,N*-dimethylformamide in both alcohols and acetic acid was studied using quaternary ammonium fluoroborates as the supporting electrolytes. Since the fluoroborate anion is known to oxidize at very high potentials,[4] it is certain that, in these systems, the amide oxidation is initiated either by direct oxidation of the amide or by oxidation of the solvent. For comparison purposes, these oxidations were also studied with quaternary ammonium nitrates as the supporting electrolytes.

Results

The electrochemical preparation of *N*-alkoxymethyl-*N*-methylformamides, using ammonium nitrate as the supporting electrolyte, has been described.[1c] In comparable oxidations, with a quaternary ammonium fluoroborate as the supporting electrolyte, the yields of product, isolated by distillation, varied from 60 to 90%. In a similar experiment in methanol, with sodium methoxide as the supporting electrolyte, the coulombic yield of *N*-methoxymethyl-*N*-methylformamide was 15%. In acetic acid the coulombic yield of isolated *N*-acetoxymethyl-*N*-methylformamide was >50% with a fluoroborate electrolyte but only 5.3% with sodium acetate as the supporting electrolyte.

The experiments compiled in Table I were carried out to obtain more accurate data on coulombic yields and to compare the reactions in the presence of fluoroborates with those using nitrates as supporting electrolytes. The solutions electrolyzed contained 0.05 mol of the supporting electrolyte, 0.13 mol of *N,N*-dimethylformamide and 140 ml of either acetic acid or the appropriate alcohol. The amount of charge passed was in every case 0.112 F, and the products formed were determined by vpc.

To elucidate the reaction mechanisms in these systems, the interdependence of the electrode potential and the electric current for the anodic oxidation of *N,N*-dimethylformamide was studied by potentiostatic steady-state measurements and by cyclic voltammetry. As was anticipated, electrooxidations in the presence of the fluoroborate anion proved the most straightforward in mechanism. The polarization curves shown in Figure 1 correspond to the steady-state behavior of the electrolyte (tetrabutylammonium fluoroborate in methanol) (curve a) and of added dimethylformamide at two different concentrations (curves b and c). In the absence of added dimethylformamide, the oxidation of methanol is self-inhibiting, and the current density remains low (i < 10 mA cm^{-2}) until the oxidation of

(1) (a) S. D. Ross, M. Finkelstein and R. C. Petersen, *J. Amer. Chem. Soc.*, **86**, 2745 (1964); (b) *J. Org. Chem.*, **31**, 128 (1966); (c) *J. Amer. Chem. Soc.*, **88**, 4657 (1966).

(2) L. Eberson and K. Nyberg, *ibid.*, **88**, 1686 (1966).

(3) C. K. Mann and K. K. Barnes, "Electrochemical Reactions in Nonaqueous Systems," Marcel Dekker, New York, N. Y., 1970, Chapter 9. The values given in Table 9-7 of this chapter for the peak potentials for the oxidation of aliphatic amides are in error and should all be higher by 0.6 V (private communication from Professor C. K. Mann).

(4) M. Fleischmann and D. Pletcher, *Tetrahedron Lett.*, 6255 (1968).

TABLE I

ANODIC OXIDATION OF *N,N*-DIMETHYLFORMAMIDE AT CONSTANT CURRENT

Solvent	Supporting electrolyte	Current, A	Product	Coulombic yield, %
Methanol	Tetraethylammonium fluoroborate	2.0	$HCON(CH_3)CH_2OCH_3$	100
Methanol	Tetraethylammonium nitrate	2.0	$HCON(CH_3)CH_2OCH_3$	88.4
Ethanol	Tetra-*n*-butylammonium fluoroborate	1.0	$HCON(CH_3)CH_2OC_2H_5$	90.0
Ethanol	Tetraethylammonium nitrate	1.0	$HCON(CH_3)CH_2OC_2H_5$	61.4
1-Butanol	Tetra-*n*-butylammonium fluoroborate	0.5	$HCON(CH_3)CH_2OC_4H_9$	87.5
1-Butanol	Tetraethylammonium nitrate	0.5	$HCON(CH_3)CH_2OC_4H_9$	62.3
Acetic acid	Tetra-*n*-butylammonium fluoroborate	0.5	$HCON(CH_3)CH_2OOCCH_3$	54.5
Acetic acid	Tetraethylammonium nitrate	1.0	$HCON(CH_3)CH_2OOCCH_3$	68.6

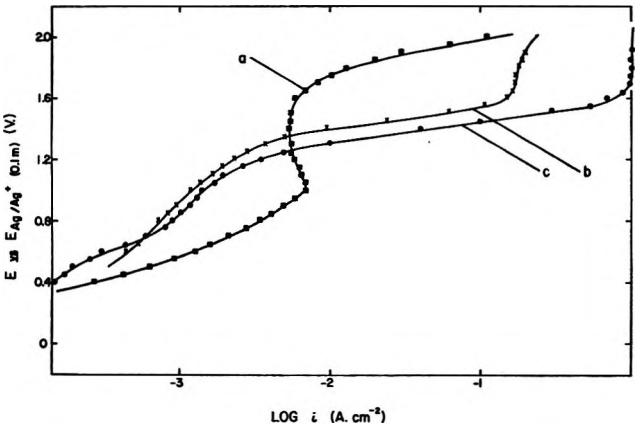


Figure 1.—Potentiostatic, steady-state polarization curves obtained at a platinum electrode in a solution of 0.33 *M* tetra-*n*-butylammonium fluoborate in methanol: curve a, electrolyte alone; curve b, electrolyte containing 0.25 *M* *N,N*-dimethylformamide; curve c, electrolyte containing 1.25 *M* *N,N*-dimethylformamide.

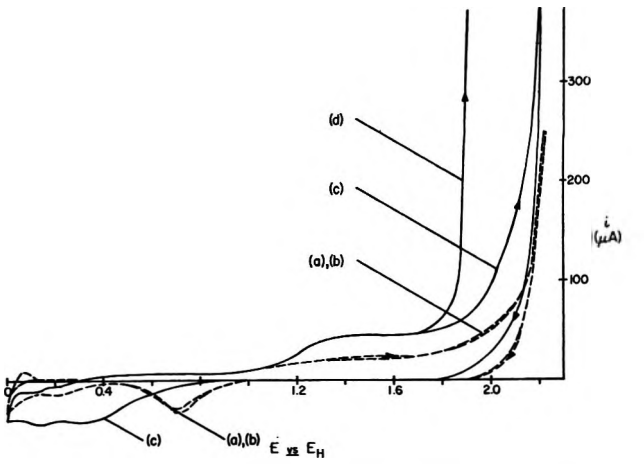


Figure 2.—Current–potential curves obtained by cyclic voltammetry at a scan rate of 50 mV sec^{-1} at a platinum electrode in a solution of 1.0 *M* potassium acetate in glacial acetic acid: curve a, electrolyte alone; curve b, electrolyte containing approximately 0.1 *M* *N,N*-dimethylformamide; curve c, electrolyte containing approximately 4 *M* *N,N*-dimethylformamide; curve d, electrolyte containing approximately 4 *M* *N,N*-dimethylformamide and 0.06 *M* anisole.

the fluoroborate anion becomes a significant Faradaic process, *i.e.*, at potentials more anodic than 1.8 V *vs.* *E*, $Ag|Ag^+$ (0.1 *M*). The addition of dimethylformamide suppresses the oxidation of methanol, and the amide itself is oxidized at potentials appreciably less anodic than those required to oxidize the fluoroborate anion.

The Tafel slope of 125–130 mV/decade of current, obtained from the steady-state log (current) *vs.* potential curves for the oxidation of dimethylformamide in methanol, and the observed electrochemical reaction order, $(d \log i/d \log C_r)E = 1$, where C_r is the bulk concentration of the amide, are consistent with an electrode reaction in which the rate-determining step is an irreversible one-electron transfer process.

The results of cyclic voltammetric studies of the oxidation of dimethylformamide in 1.0 *M* potassium acetate in acetic acid are shown in Figure 2. Curve a is the current–potential relation obtained for the electrolyte alone. The anodic sweep shows a large increase in current at $E > 2.1$ V *vs.* E_H (hydrogen reference electrode) due to the onset of the Kolbe oxidation of acetate ion. Addition of 0.1 *M* dimethylformamide (curve b) did not affect the anodic trace, and there is no indication that the amide is oxidized at potentials less anodic than 2.1 V *vs.* E_H, *i.e.*, the region of potential at which the Kolbe reaction also occurs. However, at high concentrations of the amide, *e.g.*, 4.0 *M* (curve c), the currents in the potential region, 2.0–2.4 V, are significantly larger, and this increase is attributable to oxidation of dimethylformamide. In contrast, the addition of a small amount of anisole[5] brought about a large increase in the current at potentials less anodic than 1.95 V *vs.* E_H (curve d).

The potentiostatic, steady-state polarization behavior of a solution of tetraethylammonium nitrate in methanol, containing tetra-*n*-butylammonium fluoroborate as the supporting electrolyte, is shown as curve b in Figure 3. The linear (Tafel) behavior in the potential region, 1.2–1.6 V *vs.* *E*, $Ag|Ag^+$ (0.1 *M*), corresponds to the electrooxidation of the nitrate anion. By comparing curve c in Figure 1 with curve b in Figure 3, it can be seen that, with 0.33 *M* nitrate ion and 1.25 *M* dimethylformamide, the oxidation of nitrate ion is a significant reaction in spite of the larger concentration of the amide. For the purpose of comparison it is instructive to define an "oxidation potential" as that potential at which the steady-state current is 10 mA cm^{-2}. The results for 0.33 *M* fluoroborate ion, 0.25 *M* dimethylformamide, 1.25 *M* dimethylformamide, and 0.33 *M* nitrate ion are 1.75 V, 1.40 V, 1.32 V, and 1.24 V, (V *vs.* *E*, $Ag|Ag^+$ (0.1 *M*), respectively.

The results of cyclic voltammetric studies in acetonitrile are shown in Figure 4. A current–potential curve obtained at a platinum electrode in a solution of 0.33 *M* tetra-*n*-butylammonium fluoroborate is shown as curve a. It can be seen that, within the chosen range of potentials [0 to 2.5 V *vs.* *E*, $Ag|Ag^+$ (0.1 *M*)],

(5) The half-wave potential for anisole oxidation in 0.5 *M* sodium acetate in acetic acid, as reported by Eberson and Nyberg,[2] is 1.67 V *vs.* sce.

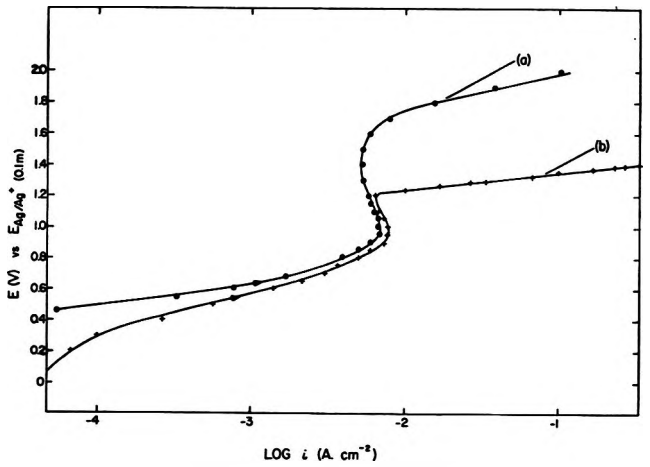


Figure 3.—Potentiostatic, steady-state polarization curves obtained at a platinum electrode in a solution of 0.33 *M* tetra-*n*-butylammonium fluoroborate in methanol: curve a, electrolyte alone; curve b, electrolyte containing 0.33 *M* tetraethylammonium nitrate.

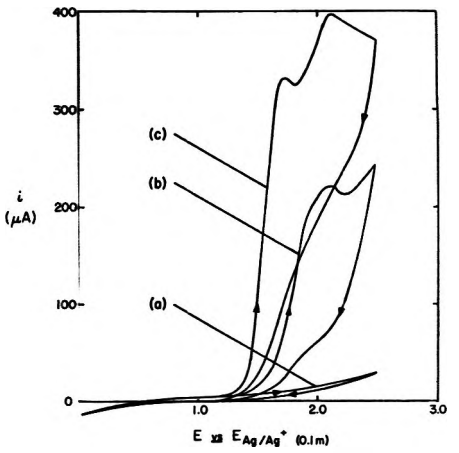


Figure 4.—Current–potential curves obtained by cyclic voltammetry at a scan rate of 100 mV sec^{-1} at a platinum electrode in a solution of 0.33 *M* tetra-*n*-butylammonium fluoroborate in acetonitrile: curve a, electrolyte alone; curve b, electrolyte containing ~0.05 *M* *N*,*N*-dimethylformamide; curve c, electrolyte containing ~0.05 *M* *N*,*N*-dimethylformamide and ~0.05 *M* tetraethylammonium nitrate.

no significant Faradaic process occurs prior to the oxidation of the anion of the supporting electrolyte.

The effect of adding dimethylformamide (concentration ≃0.05 *M*) is shown in curve b, where the currents over the potential range, 1.8–2.4 V, correspond almost entirely to oxidation of the amide. Analysis of a series of current–voltage curves obtained at various scan rates indicated an irreversible, diffusion-controlled reaction, and at fast scan rates ($dE/dt > 2$ V sec^{-1}), there was no evidence of a reduction peak.

Tetraethylammonium nitrate was then added to the solution (concentration ≃0.05 *M*), and the resulting current–potential profile (curve c) showed two peaks, corresponding to the oxidation of the anion and of dimethylformamide. The peak potential for the oxidation of nitrate ion occurred at a potential 0.4 V less anodic than that for the amide. Owing to distortion of the current–voltage curves in cases of consecutive peak currents,[6] it is difficult to correlate the peak current corresponding to the oxidation of dimethylformamide with that obtained in curve b.

The implications of the foregoing electrochemical experiments for the reaction mechanisms involved were further explored by carrying out appropriate electrolyses of *N*,*N*-dimethylformamide at controlled potential. The first experiment was designed to confirm the fact that constant current oxidations in methanol, with a fluoroborate electrolyte, were also at an essentially constant potential and one lower than that required for oxidation of the fluoroborate anion. The oxidation was carried out at 1.65 V *vs.* Ag|Ag$^-$ (0.1 *M*) in a methanol solution that was 0.5 *M* in tetra-*n*-butylammonium fluoroborate and 1.0 *M* in the amide and the coulombic yield of *N*-methoxymethyl-*N*-methylformamide was 100%, the same as that observed in the constant current experiment.

The constant current oxidation of the amide in acetic acid with tetra-*n*-butylammonium fluoroborate as the supporting electrolyte is at a potential which involves simultaneous oxidation of both the substrate and the fluoroborate anion. In a typical experiment (Table I), the coulombic yield of the product, *N*-acetoxymethyl-*N*-methylformamide, was 54.5%. When the oxidation was run at a constant potential of 1.6 V *vs.* Ag|Ag$^+$ (0.1 *M*), oxidation of the fluoroborate anion was avoided, and the coulombic yield of product increased to 89.5%.

Finally, dimethylformamide was oxidized in a methanol solution, 0.13 *M* in tetraethylammonium nitrate and 0.052 *M* in the amide, at a constant potential of 1.55 V *vs.* Ag|Ag$^+$ (0.1 *M*). The electrochemical measurements indicate that, at this potential and at these relative concentrations of amide and nitrate ion, no more than 15% of the charge passed is used for direct oxidation of the amide. Nevertheless, the coulombic yield of *N*-methoxymethyl-*N*-methylformamide was 71.9%. Since at least 85% of the charge passed in this experiment is used in oxidizing nitrate ion to nitrate radical, it follows that the mechanism in which the nitrate radical is formed in the primary step can lead to the normal amide oxidation product in relatively high yield.

Experimental Section

Materials.—DPI, White Label *N*,*N*-dimethylformamide was distilled from calcium hydride and a middle cut, bp 51° (16 mm), was used. Spectroquality acetonitrile from Matheson Coleman and Bell was used without purification. ACS reagent grade glacial acetic acid and ACS reagent grade methanol, both from Allied Chemical, were used without purification. The preparation of tetraethylammonium nitrate has been described.[7] Tetraethylammonium fluoroborate was prepared by the procedure given by Moe.[8] Tetra-*n*-butylammonium fluoroborate was prepared by adding with magnetic stirring an excess of 48–50% fluoroboric acid to a dilute aqueous solution of tetra-*n*-butylammonium bromide. The product, which precipitates immediately, was crystallized first from methanol–water and then from 2-propanol–ether, yield 86%, mp 160–162°.

Constant Current Electrolyses.—The same equipment was used both for those experiments in which the objective was to isolate the oxidation product and for the electrolyses in which the amount of product obtained was determined analytically. The electrolysis cell consisted of a water-jacketed, 200-ml beaker, fitted with a magnetic stirring bar, a thermometer, and a Teflon cover to which were attached two platinum electrodes, 0.025 cm thick, 2.5 cm wide, immersed to a depth of 7 cm and at a separa-

(6) P. Delahay, "New Instrumental Methods in Electrochemistry," Interscience, New York, N. Y., 1954, p 129.

(7) S. D. Ross and M. M. Labes, *J. Amer. Chem. Soc.*, **79**, 4155 (1957).

(8) N. S. Moe, *Acta Chem. Scand.*, **19**, 1023 (1965).

tion of 2 cm. Current was supplied by a voltage regulated dc power supply.

Where the objective was to isolate the oxidation product, a mixture of *N*,*N*-dimethylformamide (75 ml, 0.97 mol), a quaternary ammonium fluoroborate (0.05 mol) and 75 ml of the alcohol or acetic acid was electrolyzed at constant current, enough charge being passed to oxidize no more than half of the amide. The products were isolated by distillation and their identities were verified by comparing their retention times on vpc with the retention times of authentic samples.[1c]

For the experiments in which the products formed were determined by vpc, the solutions electrolyzed contained 0.05 mol of the supporting electrolyte, either a fluoroborate or a nitrate, *N*,*N*-dimethylformamide (0.13 mol), and 140 ml of either acetic acid or the appropriate alcohol. The amount of charge passed was in every case 0.112 F.

To prepare the reaction mixtures for vpc analysis, the solvent was first removed with the water pump using a water bath at 50° or below. Dry ether (400 ml) was added. The mixture was cooled, and the quaternary ammonium salt which precipitated was filtered. The ether was removed, and the residue was made up to 25 ml with acetone for analysis.

Electrochemical Measurements.—A two-compartment cell was used for all electrochemical measurements. The reference electrode was connected to the main compartment by a Luggin capillary, which terminated close to the study electrode. A closed, solution-sealed stopcock was used to separate effectively the two compartments yet allow electrolytic contact between them.

In all experiments and with all three solvents, methanol, acetic acid, and acetonitrile, the concept of a constant ionic medium in forming liquid junctions with the reference electrode was employed. Hence, the electrolyte, solvent plus supporting electrolyte, was always common to both the main and the reference electrode compartments, and silver perchlorate, to give a solution containing 0.1 *M* silver ion, was added only to the reference electrode compartment.[9] It should be noted that comparisons of voltammetric or steady-state polarization data should only be made within the same solvent, since the reference electrode is then constant within experimental error.[10,11] Attempts to refer all the measured potentials to a particular aqueous reference electrode, *e.g.*, the normal hydrogen electrode or the standard or saturated calomel electrode, lead to some uncertainty in the results. Butler[10] has pointed out that the potential difference between the $Ag|Ag^+$ electrode in acetonitrile and an aqueous saturated calomel electrode is dependent on such factors as the nature of the supporting electrolyte, the nature of the salt bridge, and even on whether or not a salt bridge is used.

Conventional circuitry was used for both the steady-state measurements and cyclic voltammetry. A Wenking potentiostat, Model No. 68FRO.5, provided the potential control, and potentials were measured with a Keithley Electrometer, Model No. 610A. A Wavetek function generator was used to superimpose the triangular wave required for cyclic voltammetry, and both single-scan and multiscan techniques could be used. The transient currents were passed through a calibrated resistor, and the resulting potential differences were recorded on an oscilloscope (Tektronix 501) or on a high impedance XY recorder (Hewlett-Packard Model No. 7030 AM). Some of the voltammetric studies were carried out using a Princeton Applied Research Model 170 electrochemistry system.

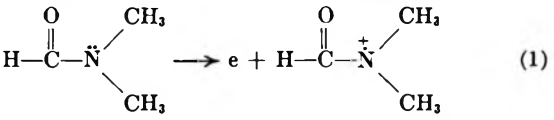
Controlled Potential Electrolyses.—These were carried out in the cell used for the electrochemical measurements, but the working electrode was of larger surface area (geometric area approximately 3 cm^2). The cell was jacketed with a copper coil, through which water was circulated, to control the temperature. The potential was controlled with the Princeton Applied Research electrochemistry system, and the total charge passed during an electrolysis was determined by the weight of copper deposited in a copper coulometer, connected in series with the auxiliary electrode. The amount of product formed was determined by vpc analysis after work-up of the reaction mixtures in the manner described for the constant current electrolyses.

Analysis by Vpc.—The vpc analyses were carried out with a Perkin-Elmer Model 154B vapor fractometer using helium as the carrier gas. The column used was a Perkin-Elmer large-diameter Golay column of 0.06-in. i.d. and 300-ft length, in which the stationary phase was Ucon polyglycol LB 550-X. The unknown solutions were compared with standards prepared from the identified components.

Discussion

In a methanol solution of a quaternary ammonium fluoroborate, it is possible to observe some anodic oxidation of methanol, but the reaction is self-inhibiting, and the current densities involved are small until the potential at which fluoroborate anion is oxidized is attained.[12]

The addition of *N*,*N*-dimethylformamide further inhibits the methanol oxidation, and the amide is oxidized at potentials appreciably lower than those required to oxidize fluoroborate ion. The electrochemical reaction order in the amide and the Tafel slope over the potential region of amide oxidation are consistent with an electrode reaction in which the rate-determining step is an irreversible, one-electron transfer. For the oxidation of *N*,*N*-dimethylformamide, it is highly probable that this transfer occurs in the primary step and results in a cation radical as shown in eq 1.



(1)

In the oxidation of dimethylformamide in acetic acid, with tetra-*n*-butylammonium fluoroborate as the supporting electrolyte, the electrochemical evidence again supports an irreversible, one-electron transfer as the rate-determining step. In this solvent an electrolysis at constant current can attain an anode potential high enough to permit oxidation of fluoroborate ion, and a controlled potential electrolysis, which prevents this side reaction, results in a higher coulombic yield of *N*-acetoxymethyl-*N*-methylformamide.

Cyclic voltammetric studies of the oxidation of dimethylformamide in 1.0 *M* potassium acetate in acetic acid afford no evidence that the amide is oxidized at a potential significantly less anodic than that at which the Kolbe reaction occurs, and the results indicate that the amide and acetate ion oxidize simultaneously. Since the initial acetate ion oxidation products, acetoxy and/or methyl radicals, do not lead to oxidation of the amide, the poor coulombic yields observed in this system are explained.

Potentiostatic, steady-state polarization studies of solutions of tetraethylammonium nitrate and of *N*,*N*-

(9) When a solution of tetraethylammonium perchlorate (0.1 *M*) in acetonitrile was used as the common electrolyte, the change in the potential difference between an $Ag|Ag^+$ (0.1 *M*) electrode placed in the reference electrode compartment and an $Ag|Ag^+$ (1.0 *M*) electrode placed in the main compartment was only 5 mV after 36 hr. Diffusion of silver ion to or from the separated compartment is, therefore, negligible within the time of the electrochemical measurements or controlled potential electrolyses.

(10) J. Butler, *Advan. Electrochem. Electrochem. Eng.*, **7**, 77 (1970).

(11) G. Charlot, J. Badoz-Lambling, and B. Tremillon, "Electrochemical Reactions," Elsevier Publishing Co., Amsterdam, The Netherlands, 1962, Chapter 13.

(12) The oxidation of methanol in both neutral and basic solution can give rise to methoxy radicals by the reactions i and ii. In neutral solution,

$$CH_3OH \rightarrow e + H^+ + CH_3O\cdot \quad \text{(i)}$$

$$CH_3O^- \rightarrow e + CH_3O\cdot \quad \text{(ii)}$$

e.g., in the reaction with tetraethylammonium fluoroborate as the supporting electrolyte, the oxidation of methanol is of no consequence, since the coulombic yield of amide oxidation product is 100%. In basic solution, *e.g.*, with sodium methoxide as the supporting electrolyte, oxidation of methoxide ion is an important reaction, and the coulombic yield of *N*-methoxymethyl-*N*-methylformamide is only 15%. In this system, the initially formed methoxy radicals are relatively ineffective in attacking the amide, and formaldehyde is probably the major oxidation product.

dimethylformamide demonstrate that nitrate ion is oxidized at a lower anodic potential than the amide. This conclusion is also supported by the results of cyclic voltammetric studies in acetonitrile.

The steady-state currents at constant potentials for oxidation of nitrate ion and the amide are such that, when the ratio of the two concentrations, $C_{amide}/C_{NO_3^-}$, is 3, the two oxidations proceed at nearly equal rates. When the ratio is 0.3, ~90% of the charge passed goes into oxidation of nitrate ion. For 90% of the charge to go into amide oxidation, the ratio would have to be ~30.

In a controlled potential experiment, with the initial ratio, $C_{amide}/C_{NO_3^-}$, such that at least 85% of the charge passed was going into nitrate oxidation, the coulombic yield of *N*-methoxymethyl-*N*-methylformamide was 71.9%. It, therefore, follows that oxidation of nitrate ion can initiate a sequence of reaction steps that leads ultimately to the amide oxidation product. The first step in this sequence must necessarily be that shown in eq 2, and this reaction has also been proposed by Mann.[13] Reasonable subsequent steps are eq 3–5.

$$NO_3^- \longrightarrow e + NO_3\cdot \qquad (2)$$

$$NO_3\cdot + H{-}\underset{\underset{O}{\|}}{C}{-}N(CH_3)(CH_3) \longrightarrow HNO_3 + H{-}\underset{\underset{O}{\|}}{C}{-}N(CH_2\cdot)(CH_3) \qquad (3)$$

$$H{-}\underset{\underset{O}{\|}}{C}{-}N(CH_2\cdot)(CH_3) \longrightarrow e + H{-}\underset{\underset{O}{\|}}{C}{-}N(CH_2^+)(CH_3) \qquad (4)$$

$$H{-}\underset{\underset{O}{\|}}{C}{-}N(CH_2^+)(CH_3) + CH_3OH \longrightarrow H{-}\underset{\underset{O}{\|}}{C}{-}N(CH_2OCH_3)(CH_3) + H^+ \qquad (5)$$

The above sequence constitutes an over-all ECEC reaction, in which nitrate ion functions as a catalyst, which is consumed in eq 2 but regenerated in eq 3.[14]

When the initial electron transfer is from the amide, the primary step is that shown in reaction 1, and possible subsequent reactions are 6, followed by 5. The over-all sequence is EEC. Reaction 6 has been written

$$H{-}\underset{\underset{O}{\|}}{C}{-}\overset{+}{N}(CH_3)(CH_3) \longrightarrow e + H^+ + H{-}\underset{\underset{O}{\|}}{C}{-}N(CH_2^+)(CH_3) \qquad (6)$$

as a concerted reaction involving the simultaneous transfer of a proton to a base and an electron to the anode. It is possible that eq 6 involves two discrete steps, a proton transfer followed by a separate electron transfer, in which case the over-all sequence is ECEC.

Registry No.—*N*,*N*-Dimethylformamide, 68-12-2; methanol, 67-56-1; ethanol, 64-17-5; butanol, 71-36-3; acetic acid, 64-19-7; tetraethylammonium fluoroborate, 429-06-1; tetraethylammonium nitrate, 1941-26-0; tetra-*n*-butylammonium fluoroborate, 429-42-5; nitrate radical, 34236-35-6.

(13) R. R. Rao, S. B. Mulliken, S. L. Robinson, and C. K. Mann, *Anal. Chem.*, **42**, 1076 (1970).

(14) G. Cauquis and D. Serve [*C. R. Akad. Sci., Ser. C*, **262**, 1516 (1966)] have proposed the electrochemical oxidation of nitrate ion to give the nitronium ion. The nitronium ion could abstract a hydride ion from the methyl

$$NO_3^- \rightarrow e + NO_2^+ + {}^1/_2O_2\cdot$$

group of the amide and thus lead to the observed *N*-methoxymethyl-*N*-methylformamide. A corollary of this mechanism is that oxidation of the amide is accompanied by conversion of the quaternary ammonium nitrate to a nitrite. Since the nitrate can be recovered unchanged from the present reactions, this mechanism is eliminated.

The Crystal and Molecular Structure and Absolute Configuration of *d*-Spiro[3.3]heptane-2,6-dicarboxylic Acid at −160°

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The crystal and molecular structure of *d*-spiro[3.3]heptane-2,6-dicarboxylic acid or *d*-Fecht acid, $C_9H_{12}O_4$, at −160° has been solved by conventional X-ray diffraction methods. The dimensions of the monoclinic cell are a = 8.486, b = 7.609, c = 6.928 Å; β = 93.25°; space group $C2$, Z = 2. The structure was refined by least-squares techniques, R = 0.056 and R_w = 0.062 for 2314 independent reflections. From a determination of the absolute configuration by use of the anomalous scattering of oxygen and carbon, a strong indication was obtained that *d*-Fecht acid has the *R* configuration shown in Figure 1. The molecules have twofold symmetry. The four-membered rings are puckered with a dihedral angle of 152.6°, resulting in an approximate equatorial position of the carboxylic acid groups. The bond lengths and angles in the ring range from 1.539 to 1.564 (0.0013) Å and from 88.0 to 88.9 (0.08)°, respectively. The C–C–C angles at the central spiro carbon atom vary from 114.8 to 126.2°.

The isolation and identification of *dl*-spiro[3.3]heptane-2,6-dicarboxylic acid or Fecht acid was first reported by Fecht[2a] in 1907. The resolution of the acid in its optical antipodes was achieved by Backer and Schurink[2b] in 1928 by fractional crystallization of the brucine salts.

Recently the acid has aroused interest as a suitable starting material for the synthesis of optically active 2,6-disubstituted spiro[3.3]heptane derivatives.[3] A knowledge of the absolute configuration of Fecht acid would establish the absolute configuration of this whole series of compounds. Wynberg and Houbiers[3] on the basis of ORD and CD measurements and making use of the application of Lowe's rule[4] to the spiro[3.3]-

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(2) (a) H. Fecht, *Chem. Ber.*, **40**, 3388 (1907); (b) H. J. Backer and H. B. J. Schurink, *Proc. Kon. Ned. Akad. Wetensch.*, **37**, 38 (1928); *Rec. Trav. Chim. Pays-Bas*, **50**, 921 (1931).

(3) H. Wynberg and J. P. M. Houbiers, *J. Org. Chem.*, **36**, 834 (1971).

(4) G. Lowe, *Chem. Commun.*, 411 (1965).

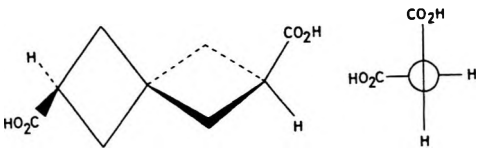

Figure 1.—*R*-(+)-Spiro[3.3]heptane-2,6-dicarboxylic acid with the notation of R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia* 12, 81 (1956); *Angew. Chem.*, **78**, 417 (1966).

heptane system assigned the *R* configuration (see Figure 1) to the dextrorotatory Fecht acid. Wynberg and Hulshof[5] in later work confirmed this assignment using ORD and CD spectra in concentrated sulfuric acid.

In order to obtain additional physical evidence in support of this conclusion and to determine the conformation of the acid, its crystal structure has been determined by means of X-ray diffraction.

Experimental Section

Crystals were grown from a solution of analytically pure *d*-spiro[3.3]heptane-2,6-dicarboxylic acid in acetone, optical purity of the compound 90%, $[\Phi]_{578}$ +7.8°. The geometry of the crystals (monoclinic sphenoidal) and their Weissenberg photographs showed the compound to be monoclinic. The space group was unequivocally found to be $C2$ (no. 5 in International Tables[6]) from the systematic absences (hkl absent for $h + k \neq 2n$) and the fact that the compound exhibits optical activity and a piezoelectric effect. The unit cell dimensions were obtained from zero layer line Weissenberg photographs taken at −160°, calibrated at room temperature with NaCl reflection spots [λ(Cu Kα_1) = 1.54051, λ(Cu Kα_2) = 1.54433, a (NaCl) = 5.6396 Å]. The crystallographic data are a = 8.486 (2) Å, b = 7.609 (3) Å, c = 6.928 (2) Å; β = 93.25 (2)°; unit cell volume 446.7 Å^3; Z = 2, μ (Mo Kα) = 1.16 cm^{-1}; ρ_{exptl} = 1.35 g cm^{-3} (flotation); ρ_{calcd} = 1.37 g cm^{-3}.

The intensities of *d*-Fecht acid were collected at low temperature (−160°) with an automatic Nonius single-crystal diffractometer (Zr filtered Mo radiation), the θ-2θ scan method being used. Deviations from linearity of the scintillation counting equipment were kept below 1% by the use of attenuation filters. For 2314 independent reflections (out of the 2441 measured up to sin θ/λ = 1.0778 Å^{-1}), the measured intensity was larger than zero. Corrections were made for intensity changes in the primary beam (by use of reference intensities), for the Lorentz and polarization effects, and for absorption. The latter corrections were calculated according to the Busing and Levy scheme.[7]

From the fact that the general position in $C2$ is fourfold and Z = 2, it could be concluded that the molecules have to lie at the twofold axes in the crystal. First the approximate arrangement of the carbon and oxygen atoms in the centrosymmetrical [010] projection was found from a three-dimensional Patterson synthesis sharpened according to the method of Jacobson, Wunderlich, and Lipscomb.[8] After refinement of this projection the y coordinates of the "heavy" atoms could be deduced from the Patterson map.

The positions and anisotropic temperature factors of the "heavy" atoms were refined with a least-squares program working in block diagonal approximation.[9] After some cycles the hydrogen atoms could be found from a difference Fourier map (hydrogen not included in F_c). In the final cycles of the refinement each hydrogen atom was given a fixed position at 1.00 or 1.08 Å, respectively, from its neighboring oxygen or carbon atom, the directions of O–H and C–H being taken from the previous refinement cycles. Isotropic refinement was used for their temperature factors. The weighting scheme $w = [w_c^{-1} +$ $0.0009|F_o|^2]^{-1}$ was applied, w_c being the weight based on counting statistics. Corrections for extinction were not necessary. The scattering factors for carbon and oxygen were taken from Doyle and Turner[10] and that of hydrogen from Stewart, Davidson, and Simpson.[11]

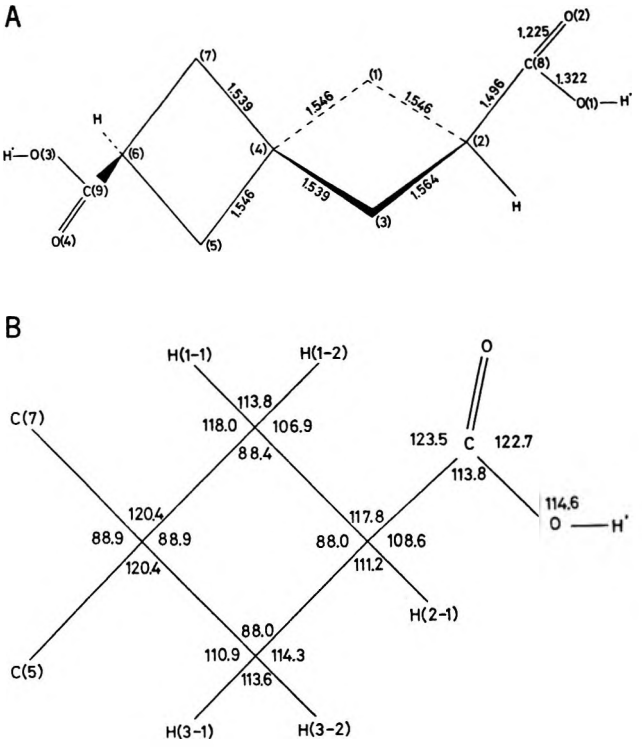

Figure 2.—Molecular geometry. The molecule has twofold symmetry. C(1) is related to C(5), C(3) to C(7), etc. A, bond lengths, standard deviation 0.0013 Å; B, bond angles, standard deviation for angles not involving hydrogen 0.08°. The bond angles omitted in the figure are C(4)-C(1)-H(1-2) = 109.9°, C(2)-(C3)-H(3-1) = 108.5°, C(2)-C(1)-H(1-1) = 116.9°, C(4)-C(3)-H(3-2) = 118.7°, C(1)-C(2)-H(2-1) = 113.5°, C(3)-C(4)-C(7) = 126.2°, C(3)-(C2)-C(8) = 116.7°, C(1)-C(4)-C(5) = 114.8°.

At the end of the refinement $\langle w|\Delta F|^2\rangle$ did not show systematic variations with $|F|$. The index $R = [\Sigma|\Delta F|^2/\Sigma|F|^2]^{1/2}$ and the corresponding weighted index R_w decreased to 0.056 and 0.062, respectively. The final atomic parameters[12] have been calculated with the standard deviations by the least-squares program. Analysis of the thermal parameters[12] according to Cruickshank[13] showed that the molecule is not a rigid body. The bond lengths and angles given in Figure 2 and Table I (B) are therefore not corrected for libration effects.

Discussion

Absolute Configuration.—The molecule given in Figure 2 (for coordinates, see ref 12) has the *R* configuration proposed by Wynberg and Houbiers[3] for *d*-Fecht acid. To check whether this configuration is correct, Weissenberg photographs about the c axis were taken with both Cu (layers 0, 1, and 2) and Cr (layers 0, 1, 2, and 3) radiation. A nice cylindrical crystal with a diameter of 0.2 mm was used. For

(5) H. Wynberg and L. A. Hulshof, unpublished results.

(6) "International Tables for X-Ray Crystallography," Vol. I, Kynoch Press, Birmingham, England, 1952, p 81.

(7) W. R. Busing and H. A. Levy, *Acta Crystallogr.*, **10**, 180 (1957).

(8) R. A. Jacobson, J. A. Wunderlich, and W. N. Lipscomb, *ibid.*, **14**, 598 (1961).

(9) D. W. J. Cruickshank in "Computing Methods and the Phase Problem in X-Ray Crystal Analysis," Pergamon Press, Oxford, 1961.

(10) P. A. Doyle and P. S. Turner, *Acta Crystallogr., Sect. A*, **24**, 390 (1968).

(11) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).

(12) Listings of structure factors, atomic coordinates, and anisotropic temperature factors will appear following these pages in the microfilm edition of this volume of the 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-72-1767. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(13) D. W. J. Cruickshank, *Acta Crystallogr.*, **9**, 757 (1956).

Table I
Results of the CNDO/2 Calculations

A. Models Used

	α, deg	β, deg	Energy, eV
Model 1	114.8	127.3	0
Model 2	120.0	120.0	1.38
Model 3	108.0	132.0	1.59

B. Calculated Bond Orders and Observed Bond Lengths

Bond	ΣP_σ	ΣP_π	Length, Å
C(1)–C(2)	1.777	0.267	1.546
C(2)–C(3)	1.777	0.265	1.564
C(3)–C(4)	1.773	0.249	1.539
C(4)–C(1)	1.765	0.243	1.546

some weak reflections there appeared to be very small differences between the intensities of the Bijvoet pairs[14] *hkl* and $h\bar{k}l$. The crystal used (weight *ca.* 0.007 mg) was definitely proved to consist of the *d* form by dissolving it in concentrated sulfuric acid (0.018 ml) and by measuring its CD spectrum. The spectrum was found to be the same as that observed for *d*-Fecht acid in the same solvent[5] ($[\theta]_{188}$ −3000, $[\theta]_{212}$ + 1050, Dichrographe II, Jouen).

Starting from the coordinates and thermal parameters[12] and using the anomalous scattering factors given by Cromer and Liberman[15] for the carbon and oxygen atoms, we calculated the intensities of the reflections *hkl* and $h\bar{k}l$. For five pairs obtained with Cr radiation and three pairs obtained with Cu radiation the difference was calculated to be larger than 3%. Visual estimations made by different persons showed that for 75% of the cases the observed intensity order corresponded with the calculated one. It can thus be concluded that the present X-ray work gives a reasonable support for the earlier proposed *R* configuration for *d*-Fecht acid.

Conformation.—This first X-ray diffraction structure determination of a simple spiran type compound shows that the four-membered rings of the molecules are not planar. The molecule is shown in Figure 2. The observed dihedral angle between the planes of C(1)-C(2)-C(3) and C(1)-C(4)-C(3) is 152.6°. This value lies close to the value of 147° observed for cyclobutane in the gaseous phase[16] (for a further discussion of four-membered rings observed in crystal structures, see Greenberg and Post[17] and Adman and Margulis[18,19]). Due to the nonplanarity the atoms C(2), C(4), and C(6) of the spiro system show a left-handed helicity for the observed *R* configuration, as could be seen from a Newman projection. The bending of the planes is such that the carbon atoms of the carboxyl groups are in a more equatorial position than for a planar four-membered ring. The angle between the plane through the carboxyl group and the best plane through the four-membered ring is 64.4°, while the angle between the planes through the carboxyl groups at the 2 and 6 position of the spiro[3.3]heptane system is 32.9°. It is further noteworthy that the angles C(1)–C(4)–C(5) (α = 114.8°) and C(3)–C(4)–C(7) (β = 126.2°)

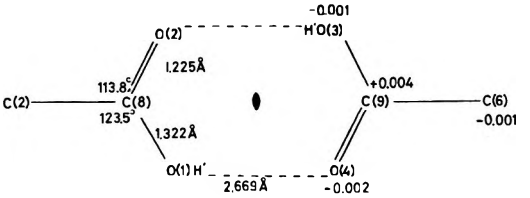

Figure 3.—The hydrogen bonding system viewed along the *b* axis. The asymmetric position of the hydrogen atoms was clearly shown by the $[F_o - F_c(C, O)]$ map. Each of the CCOOH groups lies in a plane, which makes an angle of 73.6° with the twofold axis. For distances to the plane, see the right-hand side of the figure.

differ considerably. Smaller differences are observed between the C–C bond lengths in the four-membered ring (see Figure 2).

By using the stereochemical information given above, for *d*-Fecht acid the *R* configuration is predicted by Klyne's sector rule for carboxylic acids.[20,21] This indicates that in this particular case the conformation in the crystals will not differ too much from that in solution, where the optical activity is measured. It should be noted, however, that in other cases (see, *e.g.*, Adman and Margulis[19]) the conformation of four-membered rings can be influenced to a considerable extent by the intermolecular interactions in the crystals.

Packing of the Molecules.—The structure in [010] projection (Figure 4)[12] shows that the carboxyl groups of successive molecules are linked by asymmetric hydrogen bridges, in such a way that linear arrays of molecules along [101] are formed. The geometry of the hydrogen bonding system is given in Figure 3. The neighboring carboxyl groups in Figure 3 are related by a twofold axis. As far as we know this has not been observed before for similar hydrogen bonding systems. The general rule that the carboxyl groups are related by an inversion center or pseudoinversion center cannot be obeyed by the present crystal because of the optical activity of the molecules.

CNDO Calculation.—To check whether the observed differences between the angles α and β, and between the C–C bond lengths of the four-membered ring, can be expected for a free Fecht acid molecule, CNDO/2 calculations[22] have been done. A standard CNDO/2 program was modified for this work by Dr. D. Kracht. Because of memory restrictions of the TR-4 computer the carboxyl groups of Fecht acid were replaced by hydroxyl groups, C–O(H) = 1.427 Å. The shape of the four-membered rings was slightly changed in order to give all C–C bonds a length of 1.5457 Å. With these rings three models were constructed, having twofold symmetry and the values for α and β mentioned in Table I (A). The CNDO/2 calculations showed that the value for α, 114.2°, for which the energy is minimal, −0.01 eV, lies surprisingly close to the experimental value of 114.8°. The $\Sigma P\sigma$ and $\Sigma P\pi$ bond orders of the C–C bonds, calculated for model 1, are compared with the observed bond lengths in Table I(B). We see that the differences in the bond orders are very small and not consistent with the observed bond lengths, although it is interesting to notice that there is a qualitative agreement for the bonds C(3)–C(4) and C(4)–

(14) J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel, *Nature (London)*, **168**, 271 (1951).
(15) D. T. Cromer and D. Liberman, *J. Chem. Phys.*, **53**, 1891 (1970).
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(17) B. Greenberg and B. Post, *Acta Crystallogr., Sect. B*, **24**, 918 (1968).
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(20) J. D. Renwick and P. M. Scopes, *J. Chem. Soc. C*, 1949 (1968).
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(22) J. A. Pople and G. A. Segal, *J. Chem. Phys.*, **44**, 3289 (1966).

C(1). Further attempts to explain the differences between the bond lengths will be made.

Registry No.—(+)-*R*-Spiro[3.3]heptane-2,6-dicarboxylic acid, 27259-78-5.

Acknowledgment.—The authors are greatly indebted to Mr. J. F. Kleibeuker of the Department of Physical Chemistry, Rijksuniversiteit, Groningen, for the CD measurements, Dr. D. Kracht for his contribution to the CNDO calculations, Dr. J. L. de Boer for his valuable comments, Dr. J. P. M. Houbiers of the Department of Organic Chemistry, Rijksuniversiteit, Groningen, for the preparation of the *d*-Fecht acid used in this work, and Dr. G. J. Visser for his considerable contribution to this work.

Electrophilic Bromination of Aromatic Conjugated Olefins. I. Evaluation of a Competitive Path Mechanism in Bromination of Trans-Monosubstituted Stilbenes[1a]

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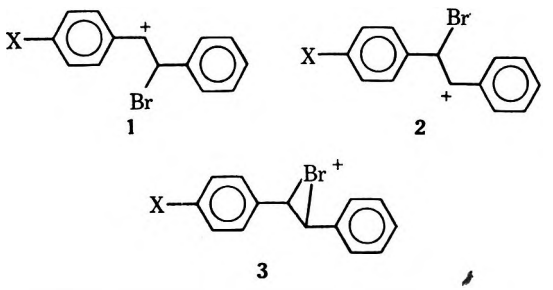
The bromine addition to monosubstituted stilbenes, $XC_6H_4C_xH{=}C_yHC_6H_5$, is treated as a reaction that can take place at two discrete centers C_x and C_y passing *via* C_x^+ and C_y^+ carbonium ion intermediates. The free-energy relationship for stilbenes whose substituents vary from *p*-hydroxy to *p*-nitro, and whose rate constants cover six powers of ten, is markedly curved. It corresponds to the equation, $\log (k/k_0) = \log [(k_x + k_y)/k_0] = \log (10^{\rho_\alpha \sigma^+} + 10^{\rho_\beta \sigma})$, where ρ_α is the reaction constant when the incipient carbonium center is C_x in the α position with respect to the substituted ring and ρ_β for the C_y center and where ρ_α and ρ_β are -5.0 and -1.5, respectively. It is shown that the bromination of *p*-methoxy- and *p*-hydroxystilbenes proceeds exclusively *via* the C_x path, whereas *p*-methyl, *m*-methyl, and *p*-chloro compounds involve this path only to the extent of 95, 65, and 35%, respectively. For *m*-chloro to *p*-nitro derivatives, only the C_y path is significant. These results are consistent with the regioselectivity of the nucleophilic attack of the solvent on the intermediates. The intermediate of the C_x path is clearly the free carbonium ion C_x^+, whereas in the intermediate of the C_y path, bromine participation cannot be excluded on the basis of kinetic data alone. The stereochemical and regiochemical analysis does not provide conclusive evidence either. Nevertheless, these latter data suggest that a free carbonium ion structure is the more likely.

For the bromination of styrenes, linear free-energy relationships, $\log k/k_0 = \rho\sigma^+$, were reported by Dubois, *et al.*, for electron-releasing substituents[1b,c] and by Yates, *et al.*, for electron attractors.[2] The value of ρ, -4.3 in methanol, -4.5 in acetic acid, compared with that of *tert*-cumyl chlorides,[3] -4.8, indicates that the benzylic carbon atom bears the charge in the transition state and neither the β carbon nor the bromine is concerned in the delocalization of the charge. The absence of bromine bridging in the transition state and consequently in the intermediate would lead to the absence of stereoselectivity in these solvents. However, in acetic acid, some stereoselectivity is observed in the bromination of the *cis*- and *trans*-β-methylstyrenes. This was explained[2] not by bromine bridging but by hindrance to free rotation in the carbonium ion, due to association with a bromine anion in an intimate ion pair. Thus, even when the ring bears a strongly electron-withdrawing substituent, the intermediate is an α-arylcarbonium ion, rather than a β-arylcarbonium or a bromonium ion where the destabilizing influence of the substituent would be minimized.[4]

It was, therefore, interesting to examine a system in which any carbonium ion formed would necessarily have both α- and β-aryl substituents. The charge distribution might then be expected to depend markedly on the electron-donating or electron-attracting character of the substituent. The present kinetic analysis[6] of the bromination of planar trans stilbenes was undertaken with this problem in mind.

The bromination of an unsymmetrical trans stilbene could generate three limiting intermediates, **1**, **2**, and **3**,



in which the charge is located on the α-aryl, the β-aryl carbon, or the bromine, respectively. For each one, there is a corresponding transition state, resembling each intermediate rather closely, since for bromination[7], the transition state structure has been shown to be nearer the intermediate than the ground state. Then the kinetic effect of X would be expected to be

(1) (a) Also regarded as part XXX of "Reactivity of Ethylenic Compounds: Bromination." Part XXIX: E. Brienvenue-Goetz, J. E. Dubois, D. W. Pearson, and D. L. H. Williams, *J. Chem. Soc. B*, 1275 (1970). (b) J. E. Dubois and A. Schwarcz, *Tetrahedron Lett.*, 2167 (1964). (c) M. Ropars, Ph.D. Thesis, CNRS, No. AO 2640, 1968, Paris.

(2) J. H. Rolston and K. Yates, *J. Amer. Chem. Soc.*, **91**, 1469 (1969); J. A. Pincock and K. Yates, *Can. J. Chem.*, **48**, 2944 (1970).

(3) Y. Okamoto, T. Inukai, and H. C. Brown, *J. Amer. Chem. Soc.*, **80**, 4972 (1958).

(4) In bromination of nonplanar 1,1-diphenylethylenes,[5] where two rings exert their influence on the same olefinic carbon, a dependence between the ring orientation and the electronic character of the substituent is observed; the more electron-releasing ring lies preferentially in the plane of the incipient carbonium ion, the other being turned out of this plane.

(5) E. D. Bergmann, J. E. Dubois, and A. F. Hegarty, *Chem. Commun.*, 1616 (1968).

(6) Preliminary communication: M. F. Ruasse and J. E. Dubois, *Tetrahedron Lett.*, 1163 (1970).

(7) F. Garnier, R. H. Donnay, and J. E. Dubois, *J. Chem. Soc. D*, 829 (1971).

different for each structure. The relative stabilities and the relative importance of these intermediates will depend on the electronic character of the substituent. In cases where the three intermediates contribute, the relationship log $k/k_0 = f(\sigma)$ would not be linear. However, we expected that, by choosing conditions where one intermediate is overwhelmingly predominant, the substituent effects on each can be defined separately. It will then be possible to determine the contribution of each structure in the bromination of any stilbene.

The intermediate bromonium ion **3** is not expected to play a major role if the brominations are carried out in methanol. In fact the stereoselectivity, and therefore the bromonium character of the intermediate, depends on solvent polarity.[8] In nitrobenzene, whose dielectric constant is similar to that of methanol, the observed stereoselectivity is probably due to a competition between the rotation of the free carbonium ion and the nucleophilic attack of the counterion rather than to rotational hindrance by bromine bridging. It is reasonable, therefore, to discuss the kinetic results, first of all, without considering bromine participation in our model.

Kinetic Results.—The rate constants for the bromination of 12 trans-monosubstituted stilbenes, measured in methanol (0.2 *M* NaBr) at 25°, are given in Table I.[9-13] Depending on the substituent, the rate constants vary over about eight powers of ten. As expected for an electrophilic reaction, the electron-releasing groups accelerate the bromination and the electron-attracting groups slow it. However, the rate is much more affected by electron donors than by electron attractors. For instance, the acceleration by the *p*-methoxy susbstituent is a factor of 2000, and the retardation by the *p*-nitro group, whose absolute value of σ^+ equals that of *p*-methoxy, is only 30. Thus no linear relationship of the type log $k/k_0 = \rho\sigma$ exists, neither with Brown's σ^+ nor with Hammett's σ constants.[14] In Figure 1, log k is plotted against σ^+ for the electron-donating substituents and against σ for the electron attractors. The free-energy relationship is markedly curved. The choice of the substituent constants will be justified later: we shall show that the reactivity depends predominantly on σ^+ for strong electron-donating substituents and on σ for strong electron attractors.

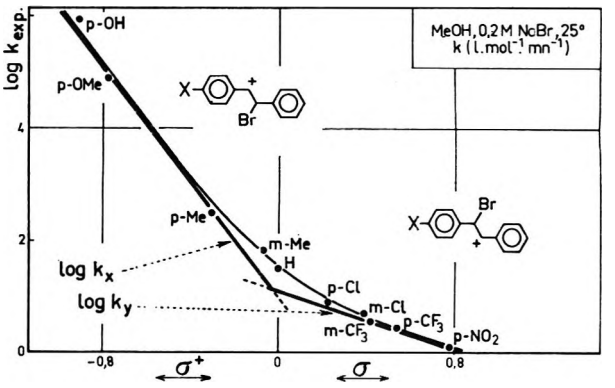


Figure 1.—Reactivity–structure relationship for monosubstituted stilbenes. The linear correlations of log k_x and log k_y corresponding to the C_x and C_y paths, are the tangents to the curved relationship for the overall reactivities.

In methanol, two brominating species, Br_2 and Br_3^-, act, making composite the overall rate constant. Owing to the complexity and uncertainty of the "Br_3^- mechanism,"[2,18] an exact assessment of structural effects can only be made from k_{Br_2}. Dubois and Huynh[19] have demonstrated that the overall rate constants can be used in free-energy relationships when Q, the $k_{Br_2}/k_{Br_3^-}$ ratio, in methanol is greater than or equal to 16. This ratio, measured by the usual method[13,23] for the most reactive compound **1**, for the unsubstituted stilbene **6**, and for the least reactive one **12** (see Table I), has values equal to 20, 43, and 17, respectively[19b] and is therefore in the acceptable range. Moreover, log $k_g = 0.99 \log k_{Br_2} - 1.16$ (see Table VI).

Thus the curvature of the $\rho\sigma$ relationship can be attributed neither to peculiar resonance effects nor to competition between the bromine and "tribromide ion" attack. Another special feature of the mechanism of the stilbene bromination must be sought to elucidate these kinetic data.

Free-Energy Relationships for Electrophilic Reactions at Two-Carbon Centers.—In protic solvents, the bromination of unsaturated compounds proceeds *via* an Ad_EC_1 mechanism[20] whose rate-determining step is the transformation of the π complex into an ionic intermediate by Br–Br bond rupture and carbon–bromine σ-bond formation.

In brominations where the intermediate is a bro-

(8) (a) R. E. Buckles, J. L. Forrester, R. L. Burham, and T. W. McGee, *J. Org. Chem.*, **25**, 24 (1960); (b) G. Heublein, *J. Prakt. Chem.*, **31**, 84 (1966).

(9) J. E. Dubois, P. Alcais, and G. Barbier, *J. Electroanal. Chem.*, **8**, 359 (1964).

(10) J. E. Dubois and G. Mouvier, *C. R. Acad. Sci.*, **255**, 1104 (1962).

(11) J. E. Dubois and F. Garnier, *Spectrochim. Acta*, **23A**, 2279 (1967).

(12) R. P. Bell and E. N. Ramsden, *J. Chem. Soc.*, 161 (1958).

(13) J. E. Dubois and E. Bienvenue-Goetz, *Bull. Soc. Chim. Fr.*, 2086 (1968).

(14) The nonlinearity of the $\rho\sigma$ relationship could be the result of different resonance effects in stilbene bromination and in solvolysis, the defining reaction of σ^+ constants.[15] It should be possible, then, to correlate the reactivities using the Yukawa–Tsuno equation,[15] log $k/k_0 = \rho(\sigma + R\Delta\sigma^+)$, where ρ is the usual reaction constant and R is a constant which measures the resonance effects. The application of this relationship to our data leads to a rather poor correlation (correlation coefficient, r = 0.975) and provides very improbable parameters, $\rho = -1.94$ and $R = 3.05$. For comparison, styrene bromination[1,2] gives $\rho = -4.30$ and $R = 1.00$. If the lessening of the ρ value, −4.3 to −1.9, could be interpreted in terms of a greater charge delocalization in stilbenes than in styrenes, the R value of 3.05 would be far and away the highest known value for reactions involving analogous benzylic cations.[16,17] Clearly two parameters give a better correlation than one, but the results of applying the Yukawa–Tsuno correlation to our data are ludicrous in terms of the values of ρ and R. Such multiparameter correlations can be very misleading if the apparent ρ and R values are not examined critically.

(15) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

(16) Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Jap.*, **32**, 965 (1959).

(17) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, 1963, p 211; Y. Yukawa, Y. Tsuno, and M. Sawada, *Bull. Chem. Soc. Jap.*, **39**, 2274 (1966); A. P. G. Kieboom and H. Van Bekkum, *Recl. Trav. Chim. Pays-Bas*, **88**, 1424 (1969).

(18) X. Q. Huynh, Ph.D. Thesis, CNRS, no. AO 5884, Paris, June 1971, and references cited therein.

(19) (a) X. Q. Huynh and J. E. Dubois, *Bull. Soc. Chim. Fr.*, 1436 (1968). (b) As seen here, there is no monotonic relationship between the Q ratio and the reactivity. This is additional evidence for the complexity of the mechanism of the attack by "tribromide ion." Detailed investigations of this problem have been published.[19c] For alkenes and allylic compounds, Dubois and Huynh show that a plot of reactivity log k_{Br_2} against the "catalytic coefficient B" ($B = a + 1/Q$, a being the additional term accounting for the medium salt effects) leads to a curve with inversion of slope. We have concluded that the term "k_{Br_2}" involves at least two competing mechanisms: electrophilic attack by Br_3^- on the substrate and nucleophilic assistance by Br^- of the dissociation of the charge transfer complex between bromine and olefin, the former mechanism acting predominantly at high olefin reactivity and the latter at low reactivity. (c) J. E. Dubois and X. Q. Huynh, *Tetrahedron Lett.*, 3369 (1971).

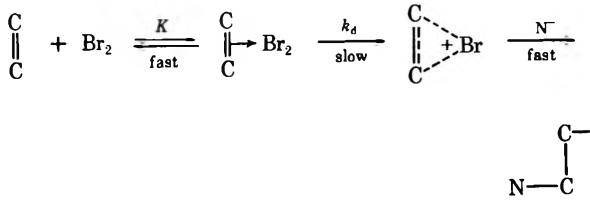
(20) F. Garnier and J. E. Dubois, *Bull. Soc. Chim. Fr.*, 3797 (1968).

TABLE I

RATE CONSTANTS FOR THE BROMINATION OF MONOSUBSTITUTED TRANS STILBENES

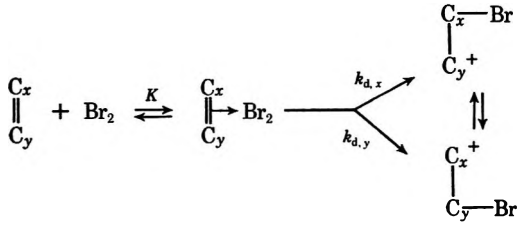
Registry no.	No.	X	k_2, M^{-1} min^{-1} [a]	Relative rates	Kinetic method[b]
838-95-9	1	p-NMe_2	2.2×10^8	6,850,000	A
6554-98-9	2	p-OH	8.5×10^5	26,000	B
1694-19-5	3	p-MeO	7.8×10^4	2,390	B
1860-17-9	4	p-Me	2.9×10^2	8.9	C
14064-48-3	5	m-Me	63	1.9	C
103-30-0	6	H	32.7	1.00	D
1657-50-7	7	p-Cl	7.8	0.23	E
13041-70-8	8	p-Br	8.2	0.25	E
14064-43-8	9	m-Cl	5.2	0.16	E
891-70-3	10	m-CF_3	3.4	0.104	E
1149-56-0	11	p-CF_3	2.5	0.076	E
1694-20-8	12	p-NO_2	1.05	0.032	E

[a] All rate constants measured in methanol (0.2 M NaBr) at 25° are averages of at least three determinations, with agreement between runs usually within 2%. [b] A, couloamperometry (ref 9); B, coulometric concentrostat (ref 10); C, potentiometry (ref 12); D, spectrometry (ref 11); E, amperometric titrations (ref 13).

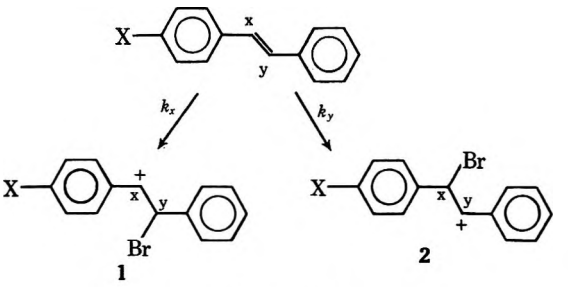


monium ion, the absence of accurate data[21] on the geometry and on the bond hybridization does not allow us to predict to what extent the entering bromine chooses between the two olefinic carbons. Kinetic results for such brominations, that of alkenes for instance,[22] have been interpreted without distinguishing the two carbonds which act, to all intents and purposes, as a single center.

In brominations where the intermediate is postulated as a carbonium ion, the entering bromine must choose either one of two olefinic carbons for σ bonding. There exists, then, two modes of dissociation of the initial π complex, leading to two discrete intermediates. The occurrence of an equilibrium between the C_x^+ and C_y^+ ions cannot be deduced from the kinetic data, since this equilibrium modifies only the third step: fast nucleophilic attack of the solvent or the bromide anion.



For the interpretation of the structural effects, the simplified scheme is sufficient if the rate-determining step is not reversible. The irreversibility of this step has been shown by the effect of added bromide ion on the rate.[23] The rate dependence on bromide ion concentration is consistent with the formation of the less reactive Br_3^-, and it follows the usual equation: $k_g(1 + K[Br^-]) = a + b[Br^-]$.



$$k = k_x + k_y \qquad (1)$$

For a reaction at two independent centers,[24] the measured rate constant is the sum of two partial rate constants, k_x and k_y (k_x is the rate constant of the C_x path leading to the carbonium ion C_x^+). We assume[28] that each partial rate constant obeys the Hammett equation. Then, the effect of X, which may be directly conjugated to the incipient carbonium ion **1**, is expressed as $\rho_\alpha\sigma^+$; the effect of X on **2**, transmitted by CHBr, will be given by $\rho_\beta\sigma$. The reaction constant ρ_α represents the effect of the substituent on the ring in the α position with respect to the charged center, *i.e.*, the C_x atom in this case of monosubstituted stilbenes, and ρ_β for substituents in the β position. For the C_x path,

(21) R. D. Bach and H. F. Henneike, *J. Amer. Chem. Soc.*, **92**, 5589 (1970).

(22) (a) J. E. Dubois and G. Mouvier, *Bull. Soc. Chim. Fr.*, 1441 (1968); (b) J. E. Dubois and E. Bienvenue-Goetz, *ibid.*, 2094 (1968).

(23) (a) P. D. Bartlett and D. S. Tarbell, *J. Amer. Chem. Soc.*, **58**, 466 (1936); (b) J. E. Dubois and F. Garnier, *Bull. Soc. Chim. Fr.*, 4512 (1967).

(24) Some examples of this type of reaction at two centers have been investigated; in particular, the protonation of azobenzenes,[25] examined by Jaffé and Wepster, where the difference between the two ρ values is so small that the $\rho\sigma$ relationship is approximately linear, and the reactions of *N*-phenylglycines[26] and 2,2′-bipyridyls[27] that their authors have not recognized as such.

(25) (a) H. H. Jaffé and R. W. Gardner, *J. Amer. Chem. Soc.*, **80**, 319 (1958); (b) M. A. Hoefnagel, A. Van Been, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **88**, 569 (1969).

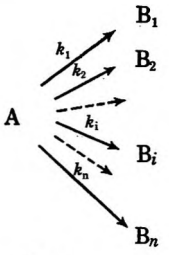
(26) A. Bryson, N. R. Davies, and E. P. Serjeant, *J. Amer. Chem. Soc.*, **85**, 1933 (1963).

(27) R. A. Jones, B. D. Roney, W. H. F. Sasse, and K. O. Wade, *J. Chem. Soc. B*, 106 (1967).

(28) This mechanistic scheme corresponds to a particular case of n competitive reactions whose rate constants, k_i for the ith reaction, depend on structural parameters p_i. The free-energy relationship which relates the overall reactivity, $\log k$ to the different structural parameters p_i, is a function such as

$$\log k = f(p_1, \ldots, p_n) \text{ with } k = \sum_{i=1}^{n} k_i \qquad (1)$$

If the partial reactivity for the ith reaction depends on the parameters p_i, $\log k_i = f_i(p_1, \ldots, p_n)$, the general relation 2 is inextricable.



$$\log k = \log\left[\sum_{i=1}^{n} \exp f_i(p_1, \ldots, p_n)\right] \qquad (2)$$

However, given, as is possible for the stilbene bromination, that the ith reaction depends on a single parameter, $\log k_i = f_i(p_i)$ (3), *i.e.*, postulating the structural independence of the reaction paths, the relation 2 becomes

$$\log k = \log[\exp f_1(p_1) + \exp f_2(p_2) + \ldots + \exp f_n(p_n)] \qquad (4)$$

Making the limits apparent, this equation is to be written

$$\log k = \sum \log k_i + \varphi(p_1, \ldots, p_n)$$

where φ is a nonlinear term which equals 0 when one of the partial rate constants predominates overwhelmingly.

$$\log (k_x/k_0) = \rho_\alpha \sigma^+ \quad (2)$$

$$\log (k_y/k_0) = \rho_\beta \sigma \quad (3)$$

the proper substituent constant is the Brown's σ^+, while for the C_y path, the substituent constant is the Hammett's σ. In the latter case, the substituted ring is insulated from the carbonium ion center by the bromomethylene group, hindering the transmission of most of the resonance effects. In the same way, it can be assumed that ρ_α is greater than ρ_β since the substituents are nearer the ionic center in the intermediate **1** than in the intermediate **2**.

With these assumptions, substituting 2 and 3 in eq 1, we developed the following relationship.

$$\log (k/k_0) = \log [(k_x + k_y)/k_0] = \log (10^{\rho_\alpha \sigma^+} + 10^{\rho_\beta \sigma}) \quad (4)$$

The solution of this equation, which relates nonlinearly the overall reactivities to the two structural parameters σ and σ^+, cannot be obtained directly. When $k_x \gg k_y$ or $k_y \gg k_x$, *i.e.*, when one of the exponential terms of the relationship 4 is negligible with respect to the other one, the reactivity becomes a linear function of a single parameter. Thus we can write the free-energy relationship in the form

$$\log (k/k_0) = \rho_\alpha \sigma^+ + \rho_\beta \sigma + \varphi(\sigma,\sigma^+)$$

where $\varphi = 0$ when one of the linear term $\rho_i\sigma_i$ predominates overwhelmingly. This nonlinear term does not express an interaction between k_x and k_y, but the fact that the partial rate constants are additive and not the free energies ($\log k \neq \log k_x + \log k_y$). This mathematical treatment of electrophilic additions with two carbonium ion intermediates requires two distinct transition states[29] for each path C_x and C_y. In extreme cases where $k_x \gg k_y$ or $k_y \gg k_x$, the reaction passes through a unique transition state since the other one is strongly disfavored, but, when k_x and k_y are in the same range, the two transition states coexist and there is not a single transition state whose charge would be distributed between the carbon centers. Thus this model for addition reactions is very similar to the electrophilic aromatic substitution[30] where partial rate constants for the ortho, meta, and para centers are derived from the overall rate constants, $k_g = 2k_o + 2k_m + k_p$. In these reactions, partial rate constants are measured from the overall rate constants and from the ratio of substitution products. Here we shall propose for addition reactions a treatment which makes possible the direct evaluation of partial rate constants from the overall rate constant only.

With a general relationship such as eq 4, the usual reactivity–structure diagram, $\log k = f(\sigma)$, is not really meaningful, since only for extreme cases does the reactivity depend on a single constant. In Figure 1, the reactivities of electron-releasing substituted stilbenes are plotted against σ^+ and that of electron-withdrawing ones against σ. The curve obtained in this way tends asymptotically to the straight lines log k_x and log k_y when σ^+ and σ are remote from zero. These asymptotes represent the partial free energies for each pathway C_x and C_y. At $\sigma = 0$, they intersect, while the experimental curve passes 0.3 l.u. beyond the intersection point, since at this point $10^{\rho_\alpha \sigma^+} = 10^{\rho_\beta \sigma} = 1$.

Reaction Constants, ρ_α and ρ_β, for the Bromination of Stilbenes.—In order to determine if the general free-energy relationship (eq 4) for the two-center reactions is suitable to the stilbene bromination in methanol, we must firstly evaluate the parameters ρ_α and ρ_β. ρ_α can be calculated from compounds for which k_x is the preponderant partial rate constant, *i.e.*, $\rho_\alpha \sigma^+ \gg \rho_\beta \sigma$ according to eq 2 and 3. This condition can be realized for strongly electron-releasing substituents where $\sigma^+ \gg \sigma$, if $\rho_\alpha - \rho_\beta$ is not very large. Conversely, ρ_β could be obtained from strongly electron-attracting substituents but only if $\rho_\alpha - \rho_\beta$ is sufficiently large, since for these $\sigma \simeq \sigma^+$. Then we have to determine for what substituents it is reasonable to assume the neglect of one of the two partial rate constants.

When the *trans*-β-methylstyrene is substituted by a *p*-methoxy group, the stereoselectivity, which measures the extent of bromine bridging, is entirely destroyed, even for the bromination in the apolar methylene chloride.[31] The intermediate is then a free benzylic carbonium ion. The similarity of the kinetic effect of this *p*-methoxy substituent on styrene, *trans*-β-methylstyrene, and stilbene (Table II) shows that the charges

TABLE II

IDENTITY OF THE KINETIC EFFECT OF THE *p*-METHOXY SUBSTITUENT ON THE BROMINATION OF AROMATIC OLEFINS, IN METHANOL (0.2 *M* NaBr) AT 25°

Compd	log (k_{MeO-4}/k_H)
Styrene	3.20
trans-β-Methylstyrene	3.48
Stilbene	3.38

in the transition state are similar for the three compounds, *i.e.*, on the carbon atom in the α position with respect to the substituted ring. Therefore, when X = *p*-MeO and even more for *p*-hydroxy and *p*-dimethylamino, k_x is much greater than k_y and the experimental rate constant equals directly k_x so that the free-energy relationship becomes linear: $\log k_{exp} = \rho_\alpha \sigma^+ + \log k_0$. The σ^+ value for the *p*-dimethylamino group being uncertain,[15] ρ_α is only evaluated from compounds **2**, **3**, and $\mathbf{6}_{corr}$. $\mathbf{6}_{corr}$ corresponds to the unsubstituted stilbene (**6**) whose rate constant is corrected as follows. For this compound, k_x equals k_y. Then from eq 4, $k_0 = 0.5k_6 = k_{6corr}$. ρ_α obtained from these three compounds is in the range of −5.

An estimation of ρ_β could be possible from ρ_α if the transmission factor for the bromomethylene group, CHBr, were known. In the bromination of alkenes[32] in methanol, the transmission factor of inductive effects

(29) Another explanation for the nonlinearity of the free-energy relationship can be a continuous change in the structure of a single transition state rather than two discrete alternatives. In the latter case, for all the compounds the complete charge is localized on a unique atom and the substituent makes variable the relative importance of the C_x and C_y intermediates. If the reaction proceeds through a single transition state, the charge is distributed among the C_x and C_y atoms, the fraction of charge on each depending on the substituent. Such a situation would be different from a bromoniumlike transition state by the absence of charge on the bromine atom. At present, it is not possible either kinetically or by product analysis to distinguish between these possibilities: one or two transition states. It has turned out that the treatment in terms of competitive paths provides a satisfactory understanding of kinetics and product data, and we have preferred it on account of its simplicity.

(30) H. C. Brown and L. Stock, "Advances in Physical Organic Chemistry," V. Gold, Ed., Academic Press, New York, N. Y., 1963, p 55.

(31) R. C. Fahey and H. J. Schneider, *J. Amer. Chem. Soc.*, **90**, 4429 (1968).

(32) E. Bienvenue-Goetz, J. E. Dubois, D. W. Pearson, and D. H. Williams, *J. Chem. Soc. B*, 1275 (1970).

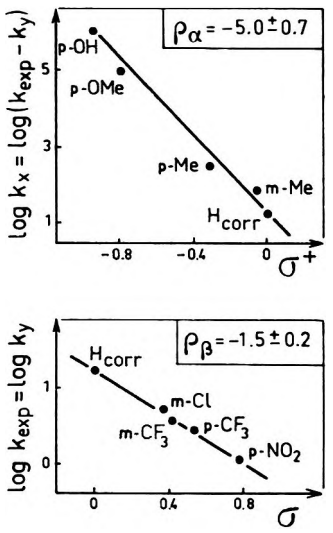


Figure 2.—Determination of the reaction constants.

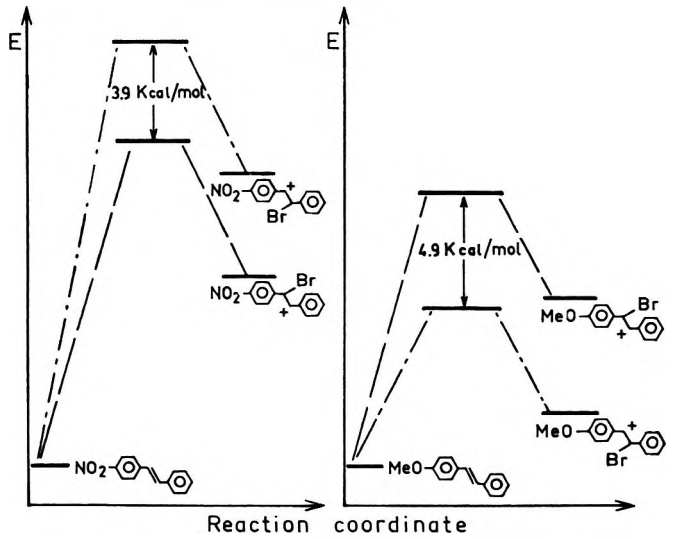


Figure 3.—Energy differences between the paths C_x and C_y of the brominations in methanol of 4-MeO and 4-NO_2 stilbenes.

by a methylene was found to be 0.42. The more general value, 0.50, of this coefficient has been estimated by McGowan.[33] Thus, if we assume that this factor for the bromomethylene group is near that of methylene, ρ_β is unlikely to be greater than 0.5 ρ_α. Furthermore, for strongly electron-attracting substituents, σ is approximately equal to σ^+ and positive. Then $\rho_\beta\sigma$, which is $\log k_y/k_0$, will not exceed the half value of $\rho_\alpha\sigma^+$, which is $\log k_x/k_0$. Since these logarithmic values are both negative, k_x can be neglected. For instance, if $\rho_\alpha = -5$, $\rho_\beta = -2.5$, for the *p*-trifluoromethyl stilbene, $k_x = 0.009$ and $k_y = 0.7$. From the compounds **9**, **10**, **11**, **12**, and $\mathbf{6}_{corr}$ (Figure 2), a precise value[34] of ρ_β (−1.5) is obtained by application of the equation $\log k_{exp} = \rho_\beta\sigma + \log k_0$. This value of ρ_β allows the calculation of k_y and $k_{x\ calcd} = k_{exp} - k_y$ for all the compounds; ρ_α is obtained[34] from compounds **2**, **3**, **4**, **5**, and $\mathbf{6}_{corr}$ using $\log k_{x\ calcd} = \rho_\alpha\sigma^+ + \log k_0$ (2′), $\rho_\alpha = 5.0$.

From these values of the two reaction constants ρ_α and ρ_β of each pathway, the partial rate constants k_x and k_y can be calculated from the general relationship,

(33) J. C. McGowan, *J. Appl. Chem.*, **10**, 312 (1960).

(34) The correlation coefficients are 0.995 for ρ_α as well as for ρ_β. The absolute errors (t test) for a 95% confidence level are ±0.7 and ±0.2 for ρ_α and ρ_β, respectively.

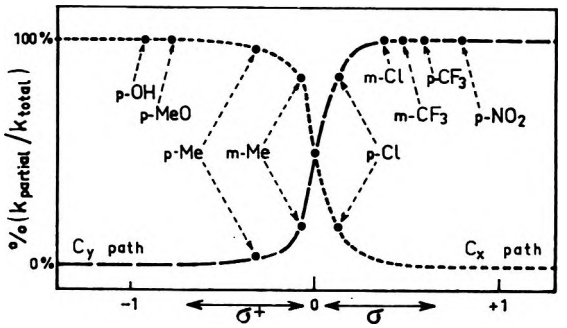


Figure 4.—Respective contribution of the C_x and C_y paths in the stilbene bromination.

TABLE III

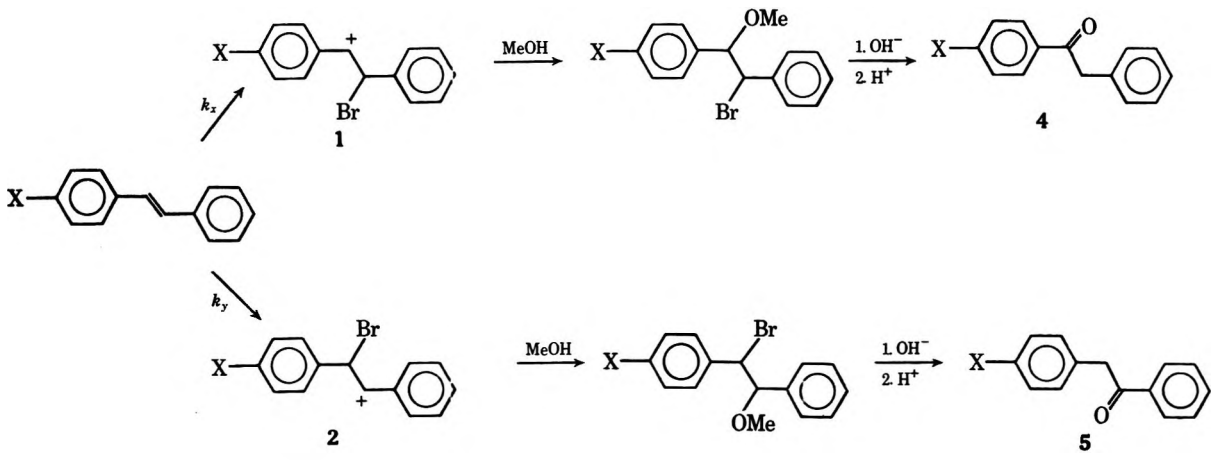
CALCULATED OVERALL AND PARTIAL RATE CONSTANTS OF THE BROMINATION OF MONOSUBSTITUTED STILBENES

X	log k_x[a]	log k_y[a]	log k_{calcd}[b]	Δ[c]
4-OH	5.78+	1.80	5.78 ± 0.6	−0.15
4-OMe	5.06+	1.65	5.06 ± 0.5	0.17
4-Me	2.69	1.50	2.73 ± 0.2	0.26
3-Me	1.48	1.35	1.72 ± 0.04	−0.08
H	1.13	1.24	1.49 ± 0.12	−0.02
4-Cl	0.55	0.87	1.05 ± 0.06	0.16
4-Br	0.37	0.87	1.00 ± 0.05	0.09
3-Cl	−0.90	0.67+	0.68 ± 0.07	−0.04
3-CF_3	−1.49	0.58+	0.58 ± 0.08	0.04
4-CF_3	−1.95	0.41+	0.41 ± 0.12	−0.02
4-NO_2	−2.81	0.05+	0.05 ± 0.16	0.02

[a] log k_x and log k_y calculated from eq 2 and 3. + This path predominates. [b] $k_{calcd} = k_x + k_y$. [c] Average $\Delta = \log k_{calcd} - \log k_{exp}$.

for all the stilbenes (Table III). The energy differences between the paths C_x and C_y, calculated from the equation $\Delta\Delta G^{\ddagger} = RT\ (\ln k_x - \ln k_y)$, give an approximate evaluation of the energy differences between the ions C_x^+ and C_y^+. The value obtained in this way is slightly underestimated, since the transition state is near the intermediate but not identical. For the ions derived from the *p*-methoxystilbene, the C_x^+ intermediate is favored by approximately 5 kcal/mol over the C_y^+ one in methanol. Conversely, for the *p*-nitrostilbene, the C_y^+ is more stable than the C_x^+ by about 4 kcal/mol (Figure 3). In another way, the respective values of k_x and k_y indicate the importance of paths C_x and C_y followed by each stilbene. Figure 4 shows how the importance of C_x and C_y depends on the value of σ_X^+ and σ_X, chosen as a convenient structure index.

Partial Rate Constants and Regioselectivity Analysis.—Although the evaluation of ρ_α and ρ_β allows for accurate calculation of the overall rate constants, this agreement alone would not verify our initial hypothesis, since ρ_α is obtained from ρ_β, so that the linearity of eq 2′, $\log (k_x/k_0) = \rho_\alpha\sigma^+$, might only be due to the optimization of successive calculations. Thus a verification, independent of the kinetic data, must be found. As a consequence of the mathematical treatment, the relative importance of the C_x and C_y paths has been calculated (Figure 4). The reaction products derived from the nucleophilic attack of the solvent on the intermediates of each path must be different, since C_x leads to the carbonium ion **1** which, when trapped by methanol, is converted into a methoxybromo compound, a positional isomer of the other compound obtained by the C_y path. The regioselectivity, $\geq C_x$-OMe/



$\geq C_y$–OMe, must be equal to the ratio k_x/k_y, provided that the ratio of methoxy bromides to dibromide is the same for C_x and C_y paths.[35a]

The regioselectivity was measured by chromatographic analysis of the two stable and known isomeric ketones **4** and **5**, derived from the methoxy bromides by successive treatment in basic and acidic media. The dibromide, which represents approximately 20 to 25% of the products,[23a] leads under these conditions to three compounds (tolane and dibromo olefins) whose retention times differ sufficiently from those of the ketones to produce no difficulty in the analysis.

The agreement between the ratio $k_x/(k_y + k_x)$ and the percentage of the C_x attack (Table IV) tends to confirm the validity of the initial hypothesis on two competitive paths in the rate-determining step. Moreover, since k_x and k_y measure directly the regioselectivity, either no equilibrium exists between the C_x and C_y intermediates, or the equilibrium constant is equal to k_x/k_y. Thus, from the regiochemical results, the question of the presence or the absence of an equilibrium between the two intermediates in the kinetic scheme can only be answered partially.

TABLE IV
AGREEMENT BETWEEN THE REGIOSELECTIVITY OF THE NUCLEOPHILIC ATTACK OF THE SOLVENT ON THE INTERMEDIATES AND THE RELATIVE IMPORTANCE OF THE C_x AND C_y PATHS

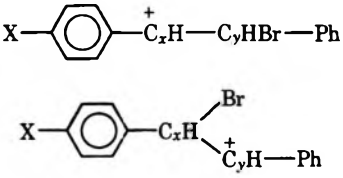
	MeOH attack[a] on		—Partial rate constants[b]—	
Stilbene	C_x, %	C_y, %	$k_x/(k_x + k_y)$, %	$k_y/(k_y + k_x)$, %
p-Me	97	3	95	5
p-Cl	34	66	35	65
m-Cl	0	100	0	100
m-CF_3	0	100	0	100

[a] Ratio of the ketones 4 and 5, measured by CPV after treatment of the bromination products; % C_x is measured to 2%. [b] Calculated from the results of Table III.

The regiochemistry also seems to confirm the carbonium ion structure of the intermediates. However, if the site of nucleophilic attack of the solvent on a carbonium ion is obvious, it is not possible to predict the regioselectivity of this attack on a bromonium ion which depends on the polar and steric effects of the substituents.[35b] Thus the agreement between the regioselectivity and the kinetic scheme does not necessarily imply the carbonium ion structure of the intermediates.

Structure of the Intermediates.—As a first approximation and to simplify the kinetic model, we have assumed that the intermediates of each pathway were carbonium ions. This assumption provides an accurate mathematical treatment of the kinetic data, but a more elaborate analysis must be carried out in order to determine the real structure of each intermediate, *i.e.*, to determine whether the bromine does or does not participate in the stabilization of the transition states and the intermediates.

The value of ρ_α, −5.0, is the same as that of many other reactions with benzylic carbonium ion intermediates: for example, methanolysis of *tert*-cumyl chlorides,[3] −4.8; bromination of styrenes, −4.3 in methanol,[1] −4.5 in acetic acid;[2] bromination of phenyl acetylenes,[36] −5.0. ρ_α tends to be reasonably accepted as the reaction constant for a bromination *via* an α-C_6H_4X carbonium ion intermediate. Concerning the value of ρ_β, −1.5, much lower than that of ρ_α, not enough is yet known to decide with the same certainty whether the intermediate of the C_y path is a β-aryl carbonium or bromonium ion, since the attenuation of the ρ value means mainly that the substituent and the charged center are more removed in the C_y path intermediate than in the C_x one.



In order to distinguish between the two possible structures of the C_y path intermediate, a comparison of these results on stilbene bromination with those obtained from reactions whose intermediate is a bromo-

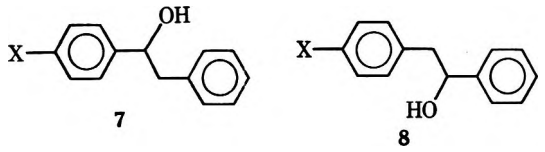
(35) (a) Obviously for a given pathway, if both intermediates are free carbonium ions, bromide ion attacks at the same site as methanol, independently of the magnitude of the ratio dibromide/methoxy bromide. However, if these ratios are different in each pathway, the overall regioselectivity would not be in agreement with the ratio k_x/k_y. The competition between bromide ion and methanol in attack of the bromination intermediate depends qualitatively[35b] on steric and inductive effects. Between attack on intermediate **1** or **2**, there is no difference in steric hindrance. Differences in inductive effects would be important only if the substituent is a strong electron donor or attractor. Since competition between intermediates **1** and **2** is possible only if the substituent is of weak electronic character (4-Me or 4-Cl), there are only small differences between inductive effects governing the competitive attack of bromide ion and methanol. This argument seems to be justified by the results (Table IV). (b) J. M. Chrétien, Ph.D. Thesis, CNRS, No. AO 5748, 1971, Orléans, France.

(36) J. A. Pincock and K. Yates, *Can. J. Chem.*, **48**, 3332 (1970).

nium or a β-aryl carbonium ion should be sought for more informations.

For the bromination of alkenes where a bromonium intermediate is strongly established,[35,37] a reaction constant ρ^* is reported:[20] ρ^* (bromonium) = −3.05. An analogous correlation between the reactivities of the stilbenes from which ρ_β has been obtained and the Taft's σ^* of the aryl groups[38] gives a ρ_β^* = −2.63, a value fairly near this ρ^* (bromonium). This agreement only confirms that the charge and the substituent are in the same relative position, *i.e.*, in β position, in the bromination of alkenes and in that of stilbenes substituted by strongly electron-attracting groups.

For anchimerically unassisted reactions whose intermediates are β-aryl carbonium ions, reaction constants are found to be near −1.00: *e.g.*, acetolysis of 1-aryl 2-propyl tosylates,[39] −0.71; solvolysis in aqueous ethanol of benzyl dimethyl carbinyl chlorides,[40] −1.11. A better analogy for stilbene bromination is to be found in the acid-catalyzed dehydration of 1,2-diaryl ethanols[41] where the rate-determining step is the formation of the olefin from carbonium ions derived from 1-aryl 2-phenyl ethanols **7** and 1-phenyl 2-aryl ethanols **8**.

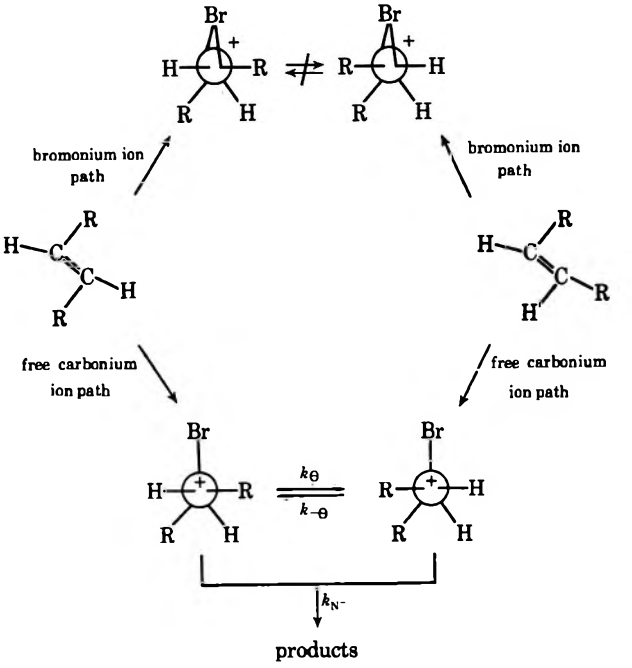


Thus in dehydration the two ions, α-aryl and β-aryl carbonium ions, are generated in independent reactions and there does not exist any ambiguity regarding the significance of the structural effects. The rate constants for the reaction of the alcohols **7** are correlated by σ^+ (ρ_7^α = −3.77) and these for the alcohols **8** by σ (ρ_8^β = −1.00). The similarity of the transmission factors $\rho_8^\beta/\rho_7^\alpha$ = 0.27 for dehydration and ρ_β/ρ_α = 0.30 for bromination could provide support for a free carbonium structure in the C_γ path of the bromination, as in dehydration of alcohols **8**. However, since numerous parameters of the two reactions are very different,[42] this agreement may be fortuitous and may signify only that the charge is localized on the β atom with respect to the substituted ring.

It is evident that, with ρ values alone, it is impossible to argue conclusively that bromine bridging is absent in the transition state leading to the C_γ intermediate.

However, in methanol, as we have already noted, a carbonium structure is to be preferred, owing to the stereochemical results.[8] Moreover, the regiospecificity of the 3-CF_3 stilbene, which reacts only *via* the C_γ path, cannot be clearly understood in terms of a bromonium ion. Regiospecificity is observed for a bromonium ion[33] only when bulky groups bounded to an olefinic carbon atom prevent the nucleophilic attack on this site. In stilbenes, the steric hindrance does not vary, and it is unlikely that polar effects alone could be so powerful as to direct entirely the opening of a bridged ion.

The stereoselectivity of the reaction provides generally better evidence for intermediate structure. A bromination *via* a bromonium ion must be stereospecific (100% anti adduct), but *via* a free carbonium ion the syn/anti adduct ratio depends on the relative rates of rotation of the ion, k_θ, and of the attack of the nucleophile, k_{N^-}, or on the conformational equilibrium if $k_\theta \gg k_{N^-}$. Approximate measurements of this dependence can be obtained from the ratio of syn/anti products derived from the pair of cis and trans olefins which lead to the same intermediate when free from bromine bridging.[2] For the unsubstituted cis and trans stilbenes, this measure has been carried out in several solvents.[8] It appears that, for the trans stilbene, the syn adduct goes from 5% when the intermediate is nearest the bromonium (in carbon disulfide) to 20% only for the nearest free carbonium ion (in methyl trichloroacetate). The relative rates, k_θ and k_{N^-}, or the equilibrium constant, $K_\theta = k_\theta/k_{-\theta}$, are such that the form **9**, which would be also the locked conformation of the bromonium ion, is preferred. The stereoselectivity of the attack on a bromonium ion is, therefore, very similar to that on a carbonium ion. Thus the stereochemical investigation of any dependence of



(37) R. C. Fahey, *J. Amer. Chem. Soc.*, **88**, 4681 (1966).

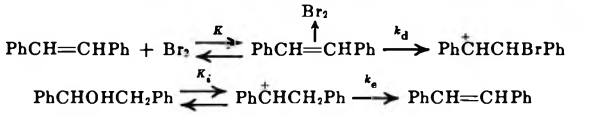
(38) R. W. Taft, "Steric Effects in Organic Chemistry," S. M. Newman, Ed., Wiley, New York, N. Y., 1956, p 556.

(39) C. J. Lancelot and P. Von Ragué Schleyer, *J. Amer. Chem. Soc.*, **91**, 4291 (1969).

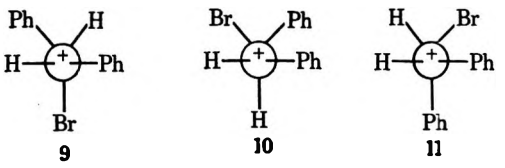
(40) A. Landis and C. A. Van der Werf, *ibid.*, **80**, 5277 (1958).

(41) D. S. Noyce, D. R. Hartter, and F. B. Miles, *ibid.*, **90**, 3794 (1968).

(42) The intervention of a preequilibrium step in the two reactions makes composite the experimental rate constants, $k_{exp}^{bromat} = Kk_d$ and $k_{exp}^{dehydr} = K_i k_e$. In bromination it has been claimed[21] that the structural effects af-



fect essentially the preequilibrium step. In dehydration, substituent effects on the deprotonation of the carbonium ion would lead to a positive reaction constant; since the global ρ is negative, these effects would act essentially also on the preequilibrium step. Thus, if the structural effects are operative on the nonrate-determining first step rather than on the step involving the formation or the destruction of the carbonium ions, comparison of ρ values may be unsuitable to determine the structure of the C_γ path intermediate. Moreover, the reaction media are very different, aqueous sulfuric acid in one case, methanol in the second. However, this latter difference can be minimized in comparing preferentially to the ρ values, the ratios $\rho_8^\beta/\rho_7^\alpha$ and ρ_β/ρ_α, which represent the damping factors for the transmission of substituent effects by methylene or bromomethylene groups, respectively.



9 10 11

the structure of the intermediate upon substituent character would necessitate the analysis of small variations of the syn/anti ratio and the measurement of conformational equilibria of the carbonium ions C_x^+ and C_y^+, from pairs of cis- and trans-substituted stilbenes.

To avoid this tedious stereochemical analysis for the determination of the structure of the C_y path intermediate, we have investigated another more direct method, extending the two competitive path scheme to the treatment of bromination kinetics of stilbenes with substituents in both rings. The results of this study will be presented in a forthcoming paper.

However, even if the structure of one of the two intermediates cannot be clearly defined, it appears from this analysis of the bromination of trans-monosubstituted stilbenes in methanol that a two competitive path mechanism leads to a rational approach of the addition reactions at two discrete centers.

Experimental Section

Synthesis of Stilbenes.—Trans-unsubstituted stilbene and the *p*-hydroxy stilbene are commercially available. The other stilbenes were prepared by methods F, G, H, and K (Table V), described below.

TABLE V

SYNTHESIS OF MONOSUBSTITUTED STILBENES

X	Synthesis method	Mp, °C	Ref
p-NMe_2	F	149–150	*b*
p-OH	*a*	192–193	*c*
p-OMe	G	137	*d*
p-Me	F	120	*d*
m-Me	F	47–48	*e*
H	*a*	125	*f*
p-Cl	F	130	*g*
p-Br	F	140	*d*
m-Cl	H	73–74	*h*
m-CF_3	H	66–67	*i*
p-CF_3	H	132–133	*i*
p-NO_2	J	155–156	*c*

[a] Commercially available. [b] M. Syz and H. Zollinger, *Helv. Chim. Acta*, **48**, 517 (1965). [c] H. Veschambre and A. Kergomard, *Bull. Soc. Chim. Fr.*, 336 (1966); 2846 (1967). [d] Reference 45. [e] J. I. G. Cadogan, E. G. Duell, and P. W. Inward, *J. Chem. Soc.*, 4165 (1962). [f] W. Schlenk and E. Bergmann, *Justus Liebigs Ann. Chem.*, **463**, 116 (1928). [g] Reference 43. [h] F. Bergmann, J. Weizman, and D. Shapiro, *J. Org. Chem.*, **9**, 408 (1944). [i] C. S. Wood and F. B. Mallory, *ibid.*, **29**, 3373 (1964).

Method F.—The aryl benzyl carbinols were prepared by condensation of benzylmagnesium chloride with the substituted benzaldehyde, as described by House.[43] The subsequent dehydrations were made with phosphoric anhydride in cold benzene.

$$C_6H_5CH_2MgCl + XC_6H_4CHO \longrightarrow C_6H_5CH_2CHOHC_6H_4X$$

$$C_6H_5CH_2CHOHC_6H_4X \xrightarrow{P_2O_5} C_6H_5CH{=}CHC_6H_4X$$

(43) H. O. House, *J. Amer. Chem. Soc.*, **77**, 3070 (1955).

Method G.—*trans*-*p*-Methoxystilbene was obtained from *trans*-*p*-hydroxystilbene by methylation with dimethyl sulfate in aqueous alkali solution following the conventional procedure.[44]

Method H.—The aryl diazonium salts were condensed with styrene in the presence of cupric chloride as described by Tashckuk and Dombrovskii[45] and led to the aryl phenyl chloroethanes, which were dehydrohalogenated in pyridine to the corresponding stilbenes.

$$XC_6H_4N_2Cl - C_6H_5CH{=}CH_2 \longrightarrow XC_6H_4CH_2CHClC_6H_5$$

$$XC_6H_4CH_2CHClC_6H_5 \xrightarrow{\text{pyridine}} XC_6H_4CH{=}CHC_6H_5$$

Method J.—*trans*-*p*-Nitrostilbene was obtained by decarboxylation of the *p*-nitrophenylcinnamic acid.[46]

Kinetic Method.—The stilbenes were purified by column chromatography on alumina with petroleum ether (bp 40–65°) or mixtures of benzene and petroleum ether and by further recrystallizations in appropriate solvents. Purity was checked by thin layer chromatography.

Methanol and sodium bromide were treated as previously described.[22]

Five kinetic methods were used to measure the rate constants: couloamperometry[9] for constants greater than 10^6 l. mol^{-1} min^{-1}; coulometric concentrostat[10] for constants in the range 10^3–10^6 l. mol^{-1} min^{-1}; potentiometry[12] for constants in the range 30–10^3 l. mol^{-1} min^{-1}; spectrometry[11] for the parent stilbene; amperometric titrations[13] for the rate constants between 1 and 15 l. mol^{-1} min^{-1}.

Measurement of the *Q* Ratio.—The second-order rate constants were measured at various sodium bromide concentrations (Table VI). The values of $k_g[1 + K(Br^-)]$, where K is the tribromide

TABLE VI

	k_g, l. mol^{-1} min^{-1}		
(NaBr), *M*	4-NMe_2	4-NO_2	H[a]
0.2	224 × 10^6	1.05	32.7
0.1	316 × 10^6	1.34	48.5
0.05	426 × 10^6	1.91	78.2
k_{Br_2}	312 × 10^7	11.9	655
Q	20	17	43

[a] Reference 23b.

equilibrium constant (177 in methanol at 25°[23b]), were plotted against (Br^-), the bromide ion concentration. The slope of the linear regression equals $Kk_{Br_3^-}$, and the intercept is k_{Br_2}.

Measurements of the Regioselectivity.—A slight excess (10%) of bromine was added to 200 ml of a solution of stilbene (10^{-3} *M*) in methanol, 0.2 *M* NaBr. This solution was kept over 1 hr or one night, depending on the rate of the bromination. After removal of the most of the solvent under reduced pressure at room temperature, the solution was diluted with water and extracted carefully with ether. The extracts were washed with a hyposulfite solution and then with water. After evaporation of ether, 100 ml of a 5% methanolic sodium hydroxide solution was added to the residue and the solution was refluxed for 3 hr and then cooled. The solution was concentrated under vacuum to about 50 ml, and acidified with 1 *M* sulfuric acid. The acidic solution was kept for 1 hr and extracted with three portions of 50 ml of ether. The organic layer was washed with water, dried, concentrated, and analyzed by vpc. The analysis was carried out on a Varian AE 1400 apparatus, on a 10 ft 10% SE-30 at 180–200° depending on the nature of the substituent. Ketones, tolan, and bromo olefins were identified by comparison of their retention time with those of authentic samples. Quantitative results were obtained from areas of the peaks after standardizing the response of the detector. The values of Table IV are the average values of three experiments. The error is about 2%.

The bromination experiments can be carried out in excess of stilbene and the dehydrohalogenations can be made by adding the alkali solution directly to the reduced solution of the bromination.

(44) G. S. Hiers and F. D. Hager, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 2nd ed, 1941, p 58.

(45) K. G. Tashchuk and A. V. Dombrovskii, *J. Org. Chem. URSS.*, **1**, 2034 (1965).

(46) R. H. Wiley and N. R. Smith, *Org. Syn.*, **33**, 62 (1953).

However, in this way stilbene is present in the product mixtures and the chromatographic analysis is consequently less accurate, because its retention time is similar to that of the corresponding ketones.

Acknowledgments.—We are grateful to Dr. J. S. Lomas, Professor K. Yates, and Professor B. M. Wepster for helpful and critical discussions.

Steric Crowding in Organic Chemistry. II. Spectral and Conformational Properties of Highly Substituted Phenylcarbinols[1]

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A series of highly substituted aryl carbinols ArCOHRR′ (2–14) has been prepared. The hydroxyl stretching frequencies of the alcohols in CCl_4 were measured and, although multiple bands were observed in some cases, the spectra were interpreted in terms of a predominant conformation with the oxygen in the plane defined by the carbinol carbon and the aromatic ring. The first overtone of the hydroxyl stretching frequency in the near-infrared showed the same multiple bands. The downfield chemical shift of the hydroxyl protons on addition of DMSO was examined. The magnitude of this shift was smaller in the more crowded compounds. The ρ values for the effect of para substituents on the chemical shifts are about 0.5 for all series examined and are insensitive to the size of attached groups. The effect of tris(dipivalomethanato)europium on the chemical shifts was examined, and the shifts of the aromatic protons were correlated with the distance and angle dependence of the pseudocontact shift equation. The geometries of the Eu complexed alcohols were interpreted in terms of a predominant conformation with a coplanar arrangement of the aryl–C–O–Eu atoms.

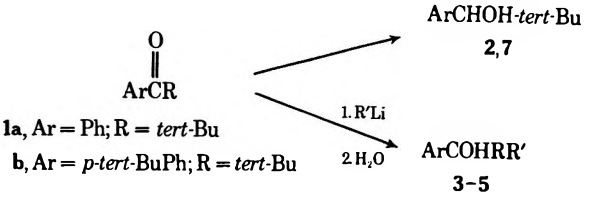
α-Phenylcarbinols display multiplicity in their hydroxyl stretching frequencies in the infrared which has been interpreted in terms of the conformations of the molecules.[3] The nmr chemical shift of the hydroxyl proton of phenylcarbinols in dimethyl sulfoxide (DMSO) solution has also been used as a probe for examining the structures of the carbinols,[4] and the nmr spectra of α-aryldi-*tert*-butylcarbinols have been related to their conformational properties.[5]

The present investigation was designed to examine the role of very bulky substituents on the spectroscopic properties of α-arylcarbinols. The accompanying paper[6] considers the spectral properties and reactivity of ferrocenylcarbinols. The reactivity of the aryl compounds will be presented elsewhere.[7]

Results

A series of highly substituted arylcarbinols (**2–5**, **7**) were prepared by reduction, or by addition of the appropriate alkyllithium to *tert*-butyl aryl ketones (**1a**, **b**) (Table I).

Phenyldi-*tert*-butylcarbinol (**6**) was prepared by the addition of phenyllithium to di-*tert*-butyl ketone to minimize 1,6-conjugate addition to the para position of **1a**, a reaction often observed in the reaction of **1a** with organometallic reagents.[3e,8] Similarly, phenyl-*tert*-butylneopentyl- and phenyldineopentylcarbinols (**8** and **9**) and their derivatives having a para substituent on the phenyl ring (**10–14**) were prepared by the addition of the corresponding aryllithium to *tert*-butyl neopentyl and dineopentyl ketones, respectively.



Hydroxyl stretching frequencies for the alcohols were measured for CCl_4 solutions and are summarized in Table I. The frequencies for compounds **2–7** were measured for 0.4 and 0.04 *M* solutions. At the higher concentration intramolecular hydrogen bonds around 3500 cm^{-1} could also be observed for **2–4**. The frequencies for compounds **8–15** were measured for 0.004 *M* solutions. The frequency reported for **6** is somewhat improved over that reported previously.[3e] Compound **6** also showed near-infrared absorption frequencies at 7117 and 7060 cm^{-1} with relative intensities 5 and 3, respectively, for either 0.13 *M* or 0.03 *M* solutions in CCl_4.

The nmr spectral parameters of the carbinols in various solvents are also given in Table I. The influence of the concentration of DMSO in CCl_4 on the hydroxyl chemical shift of **2** is given in Table II. Plots of the hydroxyl chemical shifts of the para-substituted aryldineopentylcarbinols and the aryl-*tert*-butylneopentylcarbinols in DMSO *vs.* the σ parameters of the substituents were linear, with ρ values of 0.50 and 0.47, re-

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(2) (a) University of South Carolina; (b) National Science Foundation Summer Undergraduate Research Participant, 1971; (c) Shionogi Research Laboratory, Osaka, Japan.

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(5) (a) G. P. Newsoroff and S. Sternhell, *ibid.*, 2539 (1967); (b) R. E. Gall, D. Landman, G. P. Newsoroff, and S. Sternhell, *Aust. J. Chem.*, **25**, 109 (1972).

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(7) H. Tanida and H. Matsumura, unpublished work.

(8) (a) C. Cottrell, R. C. Dougherty, G. Fraenkel, and E. Pecchold, *J. Amer. Chem. Soc.*, **91**, 7545 (1969); (b) G. Fraenkel and E. Pecchold, *Tetrahedron Lett.*, 4821 (1969); 153 (1970); (c) R. Calas, J. Dunogues, J.-P. Pillot, C. Biran, and N. Duffaut, *J. Organometal. Chem.*, **25**, 43 (1970).

TABLE I

SPECTRAL PARAMETERS OF ARYLCARBINOLS, ArCOHRR'

Compd	Ar	R	R'	ν_{max}, cm^{-1} [a]	Solvent	Nmr, δ: OH	Aromatic	*tert*-Bu	CH_2R	Other
2	Ph	H	*t*-Bu	3619	CCl_4	1.76	7.12	0.84		4.18 (CHOH)
					DMSO	5.08[e]	7.25	0.89		4.24 (CHOH)[e]
3	Ph	Me	*t*-Bu	3625 (sh)	CCl_4	2.0	7.4 (m)	0.89		1.52 (Me)
				3611	DMSO	4.58	7.2 (m)	0.86		1.50 (Me)
4	Ph	Et	*t*-Bu	3615	CCl_4	1.47	7.2 (m)	0.88	1.8–2.4 (m)	0.63 (Me)[d]
					DMSO	4.24	7.3 (m)	0.80		0.60 (Me)[d]
5	Ph	*i*-Pr	*t*-Bu	3624 (sh)	CCl_4	1.36	7.1 (m)	0.91	2.5 ($CHMe_2$)[f]	0.57, 1.09 ($CHMe_2$)[d]
				3612						
					DMSO	4.09	7.2 (m)	0.88		0.58, 1.10 ($CHMe_2$)[d]
6	Ph	*t*-Bu	*t*-Bu	3644 (5)	CCl_4	1.72	7.4 (m)	1.07		
				3617 (3)	DMSO	4.16	7.4 (m)	1.02		
7	*p*-*t*-BuPh	H	*t*-Bu	3620	CCl_4	1.97	7.2 (m)	0.84, 1.30		4.19 (CHOH)
					DMSO	4.98[e]	7.2 (m)	0.90, 1.33		4.22 (CHOH)[e]
8	Ph	*t*-Bu	Np[h]	3641	CCl_4	1.53	7.3 (m)	0.77, 0.85	1.88, 2.10[g]	
					DMSO	3.93	7.3 (m)	0.72, 0.80	1.83, 2.07[g]	
9	Ph	Np	Np	3640.5	CCl_4	1.45	7.3 (m)	0.70	1.71, 1.88[g]	
				3630 (sh)	DMSO	4.02	7.3 (m)	0.65	1.70, 1.87[g]	
10	*p*-Anis	*t*-Bu	Np	3640	$CDCl_3$	1.67	6.80, 7.35[b]	0.78, 0.87	1.90, 2.10[g]	3.80 (OMe)
					DMSO	3.83	6.80, 7.35[b]	0.73, 0.80	1.80, 2.02[g]	3.73 (OMe)
11	*p*-Anis	Np	Np	3641	CCl_4	1.40	6.70, 7.23[b]	0.70	1.59, 1.93[g]	3.75 (OMe)
				3632 (sh)	DMSO	3.90	6.78, 7.35[b]	0.68	1.77[c]	3.72 (OMe)
12	*p*-ClPh	*t*-Bu	Np	3641	CCl_4	1.55	7.18, 7.37[b]	0.78, 0.85	1.88, 2.08[g]	
					DMSO	4.00	7.26, 7.47[b]	0.77, 0.85	1.87, 2.07[g]	
					Pyridine		7.38, 7.68[b]	0.93, 0.98	2.23, 2.67[g]	
13	*p*-ClPh	Np	Np	3638	CCl_4	1.43	7.19, 7.35[b]	0.72	1.65, 1.92[g]	
				3629 (sh)	DMSO	4.15	7.25, 7.49[b]	0.68	1.80[c]	
					Pyridine		7.38, 7.67[b]	0.83	1.97	
14	*p*-F_3CPh	*t*-Bu	Np	3641.5	CCl_4	1.63	7.54[c]	0.77, 0.87	1.92, 2.14[g]	
					DMSO	4.22	7.63	0.73, 0.82	1.88, 2.12[g]	
15	*p*-ClPh	Me	Me	3620 (5)	CCl_4	1.82	7.15, 7.35[b]			1.48 (Me)
				3607 (6)	DMSO	5.02	7.24, 7.56[b]			1.43 (Me)
					Pyridine		7.39, 7.71[b]			1.67 (Me)

[a] CCl_4 solutions. [b] A'A'XX' quartets. Reported as δ, which was calculated with approximate J = 9 Hz in all cases and using an equation for the difference of chemical shifts between protons A and X in an AX system: L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, pp 129, 130. [c] Broad singlet. [d] J = 7 Hz. [e] Doublet, J = 4 Hz. [f] Heptet, δ 2.50, J = 7 Hz. [g] Doublet, J = 15 Hz. [h] Neopentyl.

TABLE II

EFFECT OF DMSO ON THE HYDROXYL CHEMICAL SHIFT OF PhCHOH-*tert*-Bu (2)[a]

DMSO/2[b]	0.0	0.5	0.75	1.0	1.25	2.75	6.0	11.0	∞
δ (OH)[c]	1.76	2.92	3.28	3.52	3.72	4.12	4.52	4.70	5.08

[a] 0.5 *M* in CCl_4. [b] Mol of DMSO/mol of 2. [c] Relative to TMS.

spectively. The downfield shifts of the resonances resulting from addition of 0–0.5 mol of the paramagnetic shift reagent tris(dipivalomethanato)europium [Eu(DPM)$_3$] to **12**, **13**, and *p*-chlorophenyldimethylcarbinol (**15**) were determined, and plots of δ for the various protons *vs.* the concentration of the shift reagent were linear in all cases. The slopes of these plots are tabulated in Table III.

TABLE III

Eu(DPM)$_3$ SHIFT GRADIENTS OF RESONANCES[a]

Compd	Ortho H[b]	Meta H[b]	*tert*-Bu	*tert*-BuCH_2	Me
12	2.36	0.20	1.80, 1.68	4.16, 2.48	
13	4.84	0.62	2.26	6.96, 5.82	
15	11.16	2.42			14.54

[a] Shift gradient $\Delta\delta_i$ defined as parts per million downfield/mol of Eu(DPM)$_3$ per mol of carbinol. [b] Refers to the position ortho and meta to the carbinol group, respectively. The lowest field protons experience the largest shifts and are assigned to the ortho positions.

Discussion

The arylcarbinols in CCl_4 display maxima at a high-frequency region around 3640 cm^{-1}, and at a low frequency region around 3615 cm^{-1}. These regions were proposed some time ago[3a] to be characteristic of free and π-bonded hydroxyls; for example, benzyl alcohol has bands at 3632 and 3615 cm^{-1} which were assigned to these types. This viewpoint has been criticized[3b,4a] because the frequency shifts between rotational conformers in some saturated alcohols were equally as large as those in the aromatic cases.[9] Recent results[3c,d,f] for 1-tetralols and chroman-4-ols of known configuration have suggested that π bonding is still a viable explanation for the occurrence of stretching frequencies of benzyl alcohols in the range 3600–3620 cm^{-1}, but such interpretations must be viewed with skepticism.

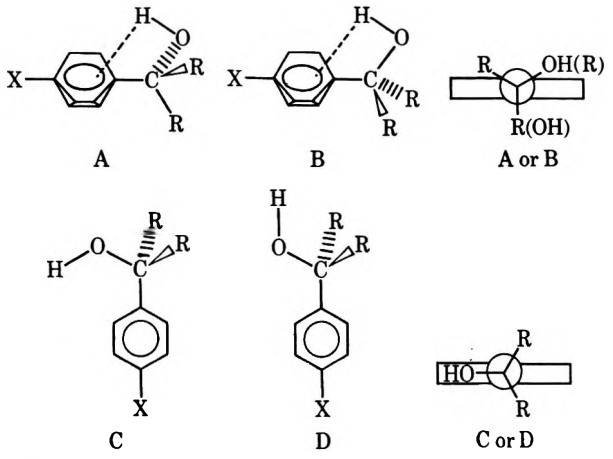
The first overtone of the hydroxyl stretching frequency occurs in the near-infrared region around 7100 cm^{-1} (1.4 μ). This absorption is perhaps more convenient for examination of multiplicity in the hydroxyl stretching frequency than the more usual infrared measurements, and such spectra of various 1,2-diphenylethanols have been interpreted in terms of both free and π-bonded hydroxyls.[3g] For **6** in CCl_4 we observe bands

(9) L. Joris, P. v. R. Schleyer, and E. Osawa, *Tetrahedron*, **24**, 4759 (1968).

at 7117 and 7060 cm^{-1}, relative intensities 5 and 3, respectively, corresponding to the 3644 and 3617 cm^{-1} bands in the infrared. However, the same caveat given above applies to the interpretation of these near-infrared absorptions as free and π-bonded hydroxyls.

Some possible conformations to be considered for the arylcarbinols are shown as structures A–D (Chart I).

CHART I



In structures A and B all three substituents are staggered around the plane of the phenyl ring, whereas in C and D the C–O bond lies in the plane of the phenyl ring. π bonding of the hydroxyl to the ring should be possible in A and B, although the hydroxyl hydrogen may point away from the ring and be unbonded in these conformations.

The hydroxyl group evidently forms rather strong complexes with DMSO of $Eu(DPM)_3$. Thus addition of DMSO to a CCl_4 solution of benzyl alcohol was observed[4a] to lead to shifts of the OH stretching frequency to 3440 cm^{-1}, and the data in Table II show a marked downfield shift of the hydroxyl resonance on addition of DMSO to a CCl_4 solution of **2**. Addition of $Eu(DPM)_3$ gives a linear change in chemical shifts with ratios of $Eu(DPM)_3$:alcohol up to 0.8.[10] The hydroxyl absorption is the only resonance markedly shifted by the addition of DMSO (Table I).

The nmr spectra of *p*-anisyldi-*tert*-butylcarbinols show a temperature variation of the aryl resonances ascribed to slow rotation around the aryl–carbinol bond,[5] and give the same behavior in a variety of solvents, including DMSO.[5] Apparently the conformation around the aryl–carbinyl bond is not significantly affected by the presence of DMSO or $Eu(DPM)_3$, which is reasonable in view of the reported[11] insensitivity of the effective size of the hydroxyl group of cyclohexanol upon complexation with DMSO.[11] It would seem that complexation of DMSO to the hydroxyl hydrogen, or $Eu(DPM)_3$ to the oxygen, might lead to a change in the rotational population around the C–O bond to accommodate the bulk of the added molecule, but the evidence on this point is only suggestive.

Sternhell and coworkers[5] have presented convincing evidence that conformations C and D are predominant (within the sensitivity of the nmr spectrometer) for the di-*tert*-butylcarbinols. Thus at lower temperatures the aromatic protons show nonequivalence of the ortho protons and nonequivalence of the meta protons, and this nonequivalence disappears at higher temperatures. This behavior is ascribed to slow rotation around the aryl–carbinol bond, so that the two sides of the molecule are unequally shielded at lower temperatures. The multiplet ir bands for **6** can be ascribed to the presence of C and D, rather than the presence of A or B, for this molecule as was suggested by one of us.[3e] The neopentyl compounds (**8**–**14**) show neither the nonequivalence of the two halves of the aromatic ring nor any strong ir bands at lower frequencies. Thus conformation D appears favored with these compounds, with a rapid rotation around the aryl–carbinol bond so that the two sides of the ring are equally shielded.

The lower frequencies observed with the less crowded compounds **2**–**5** and **15** suggest that these compounds do exist at least to some extent in CCl_4 solutions in conformations such as A or B with a degree of π bonding to the aromatic ring. Steric interactions would presumably be minimized in conformation A in compounds **2**–**5**, where the very large *tert*-butyl group would take the position furthest removed from the phenyl ring.

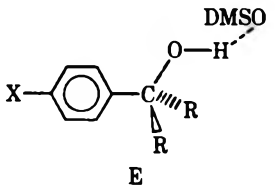
It is readily apparent from Table I that there is a trend in the chemical shifts of the hydroxyl protons in DMSO to higher fields with increasing bulk of the substituents. This is in accord with the trend reported by Ouellette and coworkers,[4a] who found δ values for benzyl alcohol, 1-phenylethanol, cumyl alcohol, and 3-methyl-2-phenylbutanol of 5.15, 5.12, 4.95, and 4.63, respectively. *cis*- and *trans*-1-phenyl-4-*tert*-butylcyclohexanols were reported to give shifts of δ 4.63 and 4.55, respectively.[3d] The strong dependence of chemical shift on the bulk of the alkyl groups suggests that the bonded dimethyl sulfoxide molecule is repelled by the substituents to weaken the complex. The δ values for phenyldi-*tert*-butylcarbinol (**6**), phenyl-*tert*-butylneopentylcarbinol (**8**), and phenyldineopentylcarbinol (**9**) are 4.16, 3.93, and 4.02, respectively, suggesting that **8** has the highest degree of steric crowding in the vicinity of the hydroxyl group. This is in accord with the fact that this system apparently formed the weakest complex with $Eu(DPM)_3$ [the smallest $Eu(DPM)_3$ shift gradient in Table III].

The values of ρ found for the aryldineopentyl and aryl-*tert*-butylneopentyl systems of 0.50 and 0.47, respectively, for the complexation with DMSO, may be compared with the values of 0.41, 0.45, 0.51, and 0.63 reported by Ouellette and coworkers[4a] for the substituted benzyl alcohols, 1-arylethanols, cumyl alcohols, and 3-methyl-2-phenylbutanols, respectively. The trend toward larger ρ values with increasing bulkiness of the groups noted in these latter series[4a] thus is probably only a random variation, as the present results with still larger substituents do not follow this pattern.

The large steric effect of the α substituents shows a rather severe interaction of the complexing DMSO molecule with these groups, but the absence of any steric effect in the *p*-*tert*-butyl substituted derivative **7** indicates that the complexing solvent is not closely associated with the benzene ring. These considerations suggest that conformation E is preferred for the complex, and that the effect of ring substituents on the strength of the hydrogen bond to DMSO is transmitted

(10) (a) J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, **93**, 641 (1971). (b) B. L. Shapiro, J. R. Hlubucek, G. R. Sullivan, and L. F. Johnson, *ibid.*, **93**, 3281 (1971).

(11) R. J. Ouellette, *ibid.*, **86**, 4378 (1964).



E

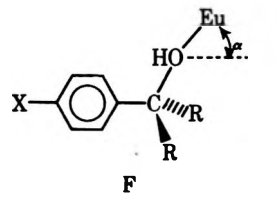
through the bonds of the molecule. This description differs from that proposed by Ouellette and coworkers,[4a] which included π bonding of the DMSO to the aromatic ring.

It has also been suggested[4a] that the H–C–O–H coupling in DMSO is influenced by the size of substituents on the carbinol carbon, in that primary alcohols (benzyl alcohols and ethanol) have couplings of 5.1–5.5 Hz, whereas 1-arylethanols have J = 4.0 Hz. However, the fact that compounds **2** and **7** also have J = 4.0 Hz establishes that the size of the 1-alkyl substituent does not affect the coupling constant, and suggests that the coupling constants probably reflect only the primary or secondary nature of the carbinol, and that all of the DMSO complexes have conformation E, or conformations related to E by rotation around the aryl–carbinol bond in the case of **2–5**, **7**, and **15**.

The Eu(DPM)$_3$-induced shifts are consistent with the usual[10b] pseudocontact shift dependence for a proton H_i (eq 1), where $\Delta\delta_i$ is the change in chemical

$$\Delta\delta_i = k(3\cos^2\theta_i - 1)R_i^{-3} \quad (1)$$

shift induced per mole, k is a constant for each compound and temperature, θ defines the H_iEuO angle, and R is the H_i–Eu distance. Using geometry F for the



F

complex, with the aryl–C–O–Eu system coplanar and rapid rotation around the aryl–C bond, the Eu can be located relative to the H_o and H_m protons of the ring. Use of an O–Eu distance of 3.0 Å and the ratio of the shift gradients $[\Delta\delta_o/\Delta\delta_m = (3\cos^2\theta_o)R_m^3/(3\cos^2\theta_m)\cdot R_o^3]$ from Table III gives calculated angles of α of 45, 61, and 67° for **15**, **13**, and **12**, respectively. Structures where the O–Eu distance and α increase simultaneously owing to repulsion of the bulkier alkyl groups are also consistent with the observed shifts.

Experimental Section

General.—Analyses were performed by the Bernhardt Mikroanalytisches Laboratorium, Elbach über Engleskirchen, West Germany, or Shionogi Research Laboratory. Routine infrared spectra were determined using Perkin-Elmer 137, 257, or 337 spectrophotometers and were calibrated against appropriate polystyrene bands. Hydroxyl stretching frequencies were measured with a Perkin-Elmer 621 or a JASCO-DS-403G grating spectrophotometer. Nmr spectra were measured with Varian A-60, A56/60D, or A-60A instruments with tetramethylsilane as an internal standard. Assignments of hydroxy peaks in carbon tetrachloride solution were confirmed by shaking with D_2O. Chemical shifts of hydroxyl protons in DMSO solution were determined using the published procedure.[4a] Melting points (capillary) and boiling points are not corrected. Mass spectra were obtained using a Perkin-Elmer Hitachi RMU instrument. Ultraviolet spectra were obtained with a Perkin-Elmer 202 spectrophotometer. Thin layer chromatography (tlc) was carried out on glass plates coated with silica gel with the solvents noted. Gas chromatography (glpc) was performed with a Varian Aerograph 90P-3 or a Hitachi Perkin-Elmer F6-D instrument and the columns and temperatures specified. Analytical data of the arylcarbinols are summarized in Table IV. Near-infrared measurements were made with a Cary 14 spectrophotometer.

TABLE IV

ANALYTICAL DATA FOR ARYLCARBINOLS

			—Calcd, %—			—Found, %—		
Compd	Formula	Mol wt	C	H	Cl	C	H	Cl
4	$C_{13}H_{20}O$	192.30	81.20	10.48		80.73	10.21	
5	$C_{14}H_{22}O$	206.33	81.50	10.75		80.88	10.81	
7	$C_{15}H_{24}O$	220.36	81.76	10.98		82.03	10.86	
8	$C_{16}H_{26}O$	234.38	81.99	11.18		82.22	11.17	
9	$C_{17}H_{28}O$	248.41	82.20	11.36		82.27	11.37	
10	$C_{17}H_{28}O_2$	264.39	77.22	10.67		76.99	10.56	
11	$C_{18}H_{30}O_2$	278.42	77.65	10.86		77.39	10.79	
12	$C_{16}H_{25}ClO$	268.82	71.48	9.37	13.19	71.49	9.40	13.46
13	$C_{17}H_{27}ClO$	282.84	72.18	9.62	12.54	72.30	9.55	12.47
14	$C_{17}H_{25}F_3O$	302.37	67.52	8.33	18.85 (F)	67.56	8.34	18.64 (F)

***tert*-Butyl Phenyl Ketone** (**1a**).—Pivalyl chloride (103 g, 0.883 mol) was placed in 200 ml of ether in a 1-l. three-neck flask, and phenylmagnesium bromide (350 ml of 3 M solution, 1.05 mol) in ether was added over 20 min with stirring and cooling in an ice bath. The solution was stirred for 6 hr while warming to room temperature, and then refluxed for 40 min. After work-up the infrared spectrum of the crude product revealed a ketone absorption at 1685 cm^{-1} and another band at 1710 cm^{-1}; so aqueous HCl was added and the solution was heated on the steam bath with rapid stirring for 5 hr. After work-up only the ketone absorption appeared in the ir; so the product was fractionally distilled through a 10-cm vacuum-jacketed column with a Nichrome spiral, giving 60.4 g (0.373 mol, 42%) of **1a**, bp 99–108° (13 Torr), which was 96% pure by glpc (10 ft × $^1/_8$ in. 20% DEGS on Chromosorb P, 165°).

Phenyldi-*tert*-butylcarbinol (**6**).[3e]—Phenyllithium (prepared from 0.127 mol of bromobenzene in ether) was added to di-*tert*-butyl ketone (18.1 g, 0.126 mol) in 100 ml of ether with stirring over 20 min at a rate to maintain reflux. The solution was stirred for 3 hr and half the solution was removed, poured into water, extracted with ether, and dried, and the solvent was evaporated. Glpc examination (10 ft × $^1/_8$ in. Carbowax 20M on Chromosorb P, 195°) of the product showed several short retention peaks, the major peak, and a long retention peak (equal to 10% of the major product) which had an identical retention time with **7**.

Distillation of the product failed to give pure material; so **6** was isolated by glpc (10 ft × $^3/_8$ in. Carbowax 20M on Chromosorb W, 225°). The remaining half of the reaction product above was added to 100 ml of toluene, the ether was distilled away under a stream of nitrogen, and the toluene solution was refluxed overnight. The product was isolated and found to have the same composition as the first portion by glpc analysis, consistent with the relative stability of the lithium alkoxide.[3e]

Phenylmethyl-*tert*-butylcarbinol (**3**)[12,13] was obtained from the reaction of **1a** with methyllithium in ether, bp 60–64° (0.25 Torr) [lit.[12] bp 128° (20 Torr)], and was purified by glpc (10 ft × $^3/_8$ in. Carbowax 20M on Chromosorb W, 215°).

Phenylethyl-*tert*-butylcarbinol (**4**) was obtained from the reaction of **1a** with ethyllithium in ether and purification of the product by glpc (10 ft × $^3/_8$ in. Carbowax 20M on Chromosorb W, 225°).

Phenylisopropyl-*tert*-butylcarbinol (**5**) was obtained from **1a** and isopropyllithium in pentane and was purified by glpc (10 ft × $^3/_8$ in. Carbowax 20M on Chromosorb W, 220°).

Phenyl-*tert*-butylcarbinol (**2**) was prepared by $NaBH_4$ reduction of **1a** followed by recrystallization from pentane at −10° and sublimation (120°, 25 Torr), mp 41.5–42.5° (lit.[14] mp 44–45°).

***tert*-Butyl *p*-*tert*-butylphenyl ketone** (**1b**) was prepared by the

(12) B. B. Corson, H. E. Tiefenthal, G. R. Atwood, W. J. Heintzelman, and W. L. Reilly, *J. Org. Chem.*, **21**, 584 (1956).

(13) J. Grimaud and A. Laurent, *Bull. Soc. Chim. Fr.*, 787 (1969).

(14) S. Winstein and B. K. Morse, *J. Amer. Chem. Soc.*, **74**, 1133 (1952).

reaction of *tert*-butylmagnesium chloride (0.35 mol) with *p-tert*-butylbenzoyl chloride (0.40 mol) in refluxing ether. After hydrolysis and recovery of considerable acid the product was distilled to give a center cut of **1b** (6.86 g, 0.0314 mol, 9%): bp 84–87° (0.4 Torr) [lit.[15] mp 103–106° (1 Torr)]; nmr (CCl_4) δ 1.32 (s, sharp, 18, both *tert*-Bu), 7.1–7.8 (m, 4, aromatic); nmr (benzene) δ 1.21 and 1.30 (each s, 9, *tert*-Bu), aromatic obscured. The higher boiling distillation fractions included a solid which could not be identified.

p-tert-Butylphenyl-*tert*-butylcarbinol (**7**) was obtained from the lithium aluminum hydride reduction of **1b**. After recrystallization from pentane at −25°, **7** was obtained as white prisms, mp 90–90.5°.

Preparation of Aryl-*tert*-butylneopentyl- and -dineopentylcarbinols.—*tert*-Butylneopentyl[16] and dineopentyl[17] ketones were prepared by the methods of Whitmore. Phenyllithium was made from lithium metal and bromobenzene in ether and *p*-anisyllithium, *p*-chlorophenyllithium, and *p*-trifluoromethylphenyllithium from *n*-butyllithium and the corresponding bromide. To a solution of the ketone in ether was added a solution of the aryllithium at about −20° under nitrogen atmosphere with vigorous stirring. After standing for 3 hr, the mixture was poured into an ice-cold aqueous ammonium chloride solution and extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and evaporated to give an α-arylcarbinol. Yields were satisfactory in the case of phenyl derivatives, those for the anisyl-, chlorophenyl-, and trifluoromethylphenyl compounds were not, and the carbinols were isolated from the reaction mixture by thin layer chromatography. All the carbinols thus obtained gave satisfactory analyses and ir and nmr spectra consistent with the structures: **8**, bp 85° (2 mm), 89% yield; **9**, bp 94° (2 mm), 83%; **10**, mp 77–78°, 31%; **11**, mp 63–64°, 44%; **12**, mp 77–78.5°, 40%; **13**, mp 103–104°, 31%; for **14**, mp 53–54°, 43%.

(15) D. E. Pearson, *J. Amer. Chem. Soc.*, **72**, 4169 (1950).

(16) F. C. Whitmore, J. S. Whitaker, W. A. Mosher, O. N. Breivik, W. R. Wheeler, C. S. Miner, Jr., L. H. Sutherland, R. B. Wagner, T. W. Clapper, C. E. Lewis, A. R. Lux, and A. H. Popkin, *ibid.*, **63**, 643 (1941).

(17) F. C. Whitmore, C. D. Wilson, J. V. Capinjola, C. O. Tongberg, G. H. Fleming, R. V. McGrew, and J. N. Cosby, *ibid.*, **63**, 2035 (1941).

Registry No.—**1a**, 938-16-9; **1b**, 22583-66-0; **2**, 3835-64-1; **3**, 21811-48-3; **4**, 34235-13-7; **5**, 34235-14-8; **6**, 15656-90-3; **7**, 34235-16-0; **8**, 34235-17-1; **9**, 34235-18-2; **10**, 34235-19-3; **11**, 34235-20-6; **12**, 34235-21-7; **13**, 34235-22-8; **14**, 34235-23-9; **15**, 1989-25-9; DMSO, 67-68-5; $Eu(DPM)_3$, 15522-71-1.

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Steric Crowding in Organic Chemistry. III. Spectral Properties, Conformations, and Reactivities of Highly Substituted Ferrocenylcarbinols[1]

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The preparation of a series of highly substituted ferrocenylcarbinols FcCRR'OH (**2–8**) has been accomplished. The hydroxyl stretching frequencies of the alcohols in CCl_4 solution showed bands in the region 3560–3583 cm^{-1} which were interpreted in terms of iron-bonded conformations, whereas bands at 3632 cm^{-1} were assigned to nonbonded conformations. Derivatives of the tertiary ferrocenyl carbinols could not be prepared, but the reactivity of the carbinols with acid to form cations was determined. *tert*-Butylferrocenylcarbinyl acetate (**10**) was prepared and found to undergo hydrolysis at a rate 4900 times as slow as methylferrocenylcarbinyl acetate. The depressed reactivity of **10** was attributed to steric hindrance of resonance stabilization.

The reactivity of α-arylcarbinols and their derivatives to form carbonium ions has been a topic of intensive investigation, particularly the electronic effect of substituents on the stability of the positive charge.[3,4] The stabilization by the ferrocenyl substituent is quite large,[4] but there has been considerable controversy as to whether the mode of stabilization by this group involves only hyperconjugative participation of bonding electrons[4h,i] or whether the nonbonding orbitals on iron are also significantly involved.[4a–d] The role of bulky substituents which prevent efficient overlap between the developing p orbital of the carbonium ion and the π system of the aromatic ring has also been examined in phenyl-substituted compounds.[5]

The spectroscopic properties of α-ferrocenylcarbinols have also been instructive regarding configurations and conformations of these compounds, as investigated by infrared[6a,b] and nmr[6c] measurements.

The present investigation was designed to elucidate the effect of very bulky substituents on the spectral properties and reactivity of α-ferrocenylcarbinols, and complements the investigation of the spectral proper-

(1) Part II: F. H. Hon, H. Matsumura, H. Tanida, and T. T. Tidwell, *J. Org. Chem.*, **37**, 1778 (1972).

(2) (a) National Science Foundation Summer Undergraduate Research Participant, 1971. (b) University of South Carolina.

(3) (a) E. A. Hill, M. L. Gross, M. Stasiewicz, and M. Manion, *J. Amer. Chem. Soc.*, **91**, 7381 (1969); (b) H. C. Brown and Y. Okamoto, *ibid.*, **80**, 4979 (1958); (c) W. S. Trahanovsky and D. K. Wells, *ibid.*, **91**, 5870, 5871 (1969).

(4) (a) E. A. Hill and J. H. Richards, *ibid.*, **83**, 3840, 4216 (1961); (b) D. W. Hall, E. A. Hill, and J. H. Richards, *ibid.*, **90**, 4972 (1968); (c) M. Cais, J. J. Dannenberg, A. Eisenstadt, M. I. Levenberg, and J. H. Richards, *Tetrahedron Lett.*, 1695 (1966); (d) D. S. Trifan and R. S. Bacskai, *ibid.*, No. 13, 1 (1960); (e) G. Gokel, P. Hoffmann, H. Klusacek, D. Marquarding, E. Ruch, and I. Ugi, *Angew. Chem., Int. Ed. Engl.*, **9**, 64 (1970); (f) M. J. A. Habib and W. E. Watts, *J. Chem. Soc. C*, 2552 (1970); (g) E. A. Hill, *J. Organometal. Chem.*, **24**, 457 (1970); (h) T. T. Tidwell and T. G. Traylor, *J. Amer. Chem. Soc.*, **88**, 3442 (1966); (i) T. G. Traylor and J. G. Ware, *ibid.*, **89**, 2304 (1967); (j) E. A. Hill and R. Wiesner, *ibid.*, **91**, 509 (1969); (k) J. Feinberg and M. Rosenblum, *ibid.*, **91**, 4324 (1969); (l) R. E. Davis, H. D. Simpson, N. Grice, and R. Petit, *ibid.*, **93**, 6688 (1971); (m) R. Gleiter and R. Seeger, *Helv. Chim. Acta*, **54**, 1217 (1971).

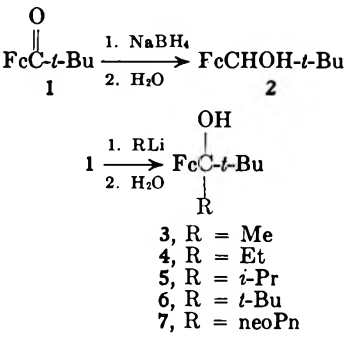
(5) (a) S. Winstein and B. K. Morse, *J. Amer. Chem. Soc.*, **74**, 1133 (1952); (b) G. Baddeley, J. Chadwick, and H. T. Taylor, *J. Chem. Soc.*, 2405 (1954); (c) J. Grimaud and A. Laurent, *Bull. Soc. Chim. Fr.*, 787 (1969).

(6) (a) D. S. Trifan and R. Bacskai, *J. Amer. Chem. Soc.*, **82**, 5010 (1960); (b) A. W. Baker and D. E. Bublitz, *Spectrochim. Acta*, **22**, 1787 (1966); (c) P. Reich-Rohrwig and K. Schlögl, *Monatsh. Chem.*, **99**, 2175 (1968).

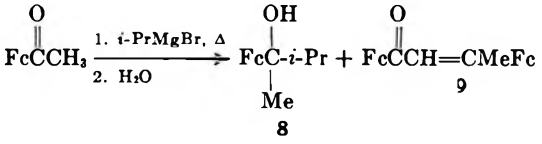
ties[1] and reactivities[7] of α-phenylcarbinols with bulky substituents.

Results

The *tert*-butylferrocenylcarbinols **2**–**7** were prepared either by reduction of *tert*-butyl ferrocenyl ketone (**1**) to give *tert*-butylferrocenylcarbinol (**2**) or by reaction of the appropriate alkyllithium with **1** (the ferrocenyl substituent is abbreviated Fc in this paper). Methylisopropylferrocenylcarbinol (**8**) was prepared by addition



of isopropylmagnesium bromide to acetylferrocene; the aldol product **9** was also obtained in this reaction.



The hydroxyl stretching frequencies of all the alcohols were measured in dilute solutions in carbon tetrachloride and are summarized in Table I. In selected cases

TABLE I

HYDROXYL STRETCHING FREQUENCIES OF FERROCENYLCARBINOLS (FcCRR'OH)[a,b]

Compd	R	R'	ν_{max},[a] cm^{-1}
2	*t*-Bu	H	3632 (sh)[c]
			3583
3	*t*-Bu	Me	3581
4	*t*-Bu	Et	3573
5	*t*-Bu	*i*-Pr	3573
6	*t*-Bu	*t*-Bu	3632 (4)
			3579 (1)
7	*t*-Bu	neoPn	3574
8	*i*-Pr	Me	3560

[a] CCl_4 solutions, 0.2 *M*, relative intensities in parenthesis. Unchanged on dilution. [b] For comparison, ferrocenylcarbinol, methylferrocenylcarbinol, and dimethylferrocenylcarbinol display hydrogen bonds to the upper π face of ferrocene at 3620, 3613, and 3608 cm^{-1}, respectively, and iron-bonded hydroxyls at 3576, 3575, and 3571 cm^{-1}, respectively. None of these compounds show clearly resolved free hydroxyls, but β-ferrocenylethanol displays a free band at 3632 cm^{-1}, and ferrocenylmethanol has a shoulder at 3635 cm^{-1} (ref 6a and D. S. Trifan, private communication). [c] Shoulder on 3583 cm^{-1} band.

these were examined over a tenfold concentration range and shown to be independent of concentration, although at higher concentrations intermolecular hydrogen bonds could be observed. The chemical shifts of the hydroxyl protons for the ferrocenylcarbinols were not determined in dimethyl sulfoxide solutions as was done for the corresponding phenyl compounds, because they were insufficiently soluble in DMSO for strong signals to be observed, and also because the signals were anticipated to fall in the region of the spectrum where the ferrocenyl hydrogens absorb.

The ferrocenyl compounds were examined for their reactivity in carbonium ion forming reactions. The conversion of **2** to the acetate **10** for solvolysis studies required refluxing with acetic anhydride–pyridine, in contrast to ferrocenylmethylcarbinol, which reacts at low temperature.[8] The rates of hydrolysis of **10** to reform **2** were measured in aqueous acetone and are summarized in Table II. Attempts to prepare acetates or

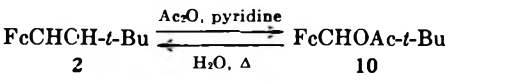


TABLE II

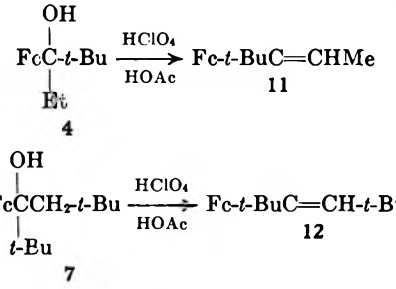
FIRST-ORDER RATE CONSTANTS FOR HYDROLYSIS OF α-ALKYLFERROCENYLCARBINYL ACETATES (FcCHROAc) IN 60:40 ACETONE–WATER

R	Temp, °C	k_1, sec^{-1}	k_{rel}	ΔH^*, kcal/mol	ΔS^*, eu
t-Bu	84.8	2.16×10^{-4}		20.9	−17
(**10**)	69.9	4.97×10^{-5}			
	54.5	1.29×10^{-5}			
	0[a]	1.69×10^{-8}	1.0		
Me[b]	0	8.35×10^{-5}	4.9×10^{3}	19.0[c]	−13[c]

[a] Extrapolated. [b] Reference 4a. [c] In 80% acetone.

methyl ethers of the tertiary alcohols **3** and **6** were uniformly unsuccessful, yielding the parent alcohols or olefins instead. The high stability of the tertiary ferrocenyl carbonium ions apparently renders these derivatives quite unstable.

Since derivatives suitable for solvolysis studies could not be prepared, the reactivities of the alcohols **4**–**7** were examined by reaction with 0.07 *M* perchloric acid in acetic acid. The corresponding olefins resulting from dehydration were formed from **4** and **7**; these olefins appeared to be single isomers by nmr but the stereochemistry around the double bond was not established.



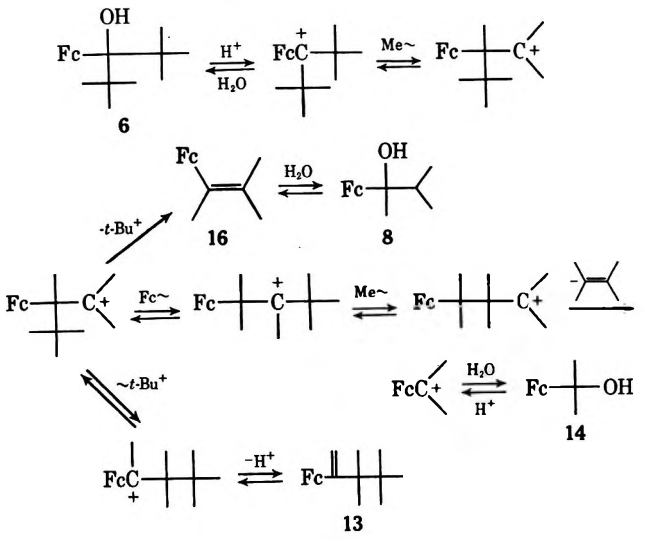
After about 30 min reaction time, **4** and **7** gave 20 and 51% recovered starting material, respectively, whereas the isopropyl compound **5** disappeared with a half-life of about 3 min under the same conditions. The product from **5** was an apparent mixture that could not be separated by column chromatography nor identified by spectral examination. Di-*tert*-butylferrocenylcarbinol (**6**) reacted completely within 1 min and gave a mixture which was separated by preparative thin layer chromatography and shown to consist of 2-ferrocenyl-3,3,4,4-tetramethyl-1-pentene (**13**), methylisopropylferrocenylcarbinol (**8**), and dimethylferrocenylcarbinol (**14**)

(7) H. Tanida, *et al.*, unpublished work.

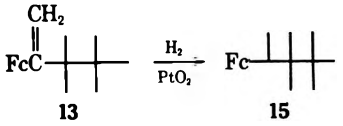
(8) F. S. Arimoto and A. C. Haven, Jr., *J. Amer. Chem. Soc.*, **77**, 6295 (1955).

CHART I

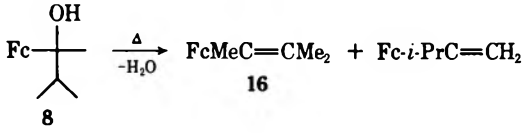
ACID-CATALYZED REARRANGEMENT OF DI-*tert*-BUTYLFERROCENYLCARBINOL (6)



(Chart I). The structure of **13** was established by spectral means and by hydrogenation to **15**, which also



displayed the expected spectral properties. Carbinol **8** from the reaction above was an oil identical with that prepared from acetylferrocene and isopropylmagnesium bromide. The compound could not be induced to crystallize, but on attempted distillation was dehydrated to the solid olefin **16** which was fully characterized.



Weak signals in the nmr of **16** showed that a trace of the isomeric 2-ferrocenyl-3-methyl-1-butene was probably also present.

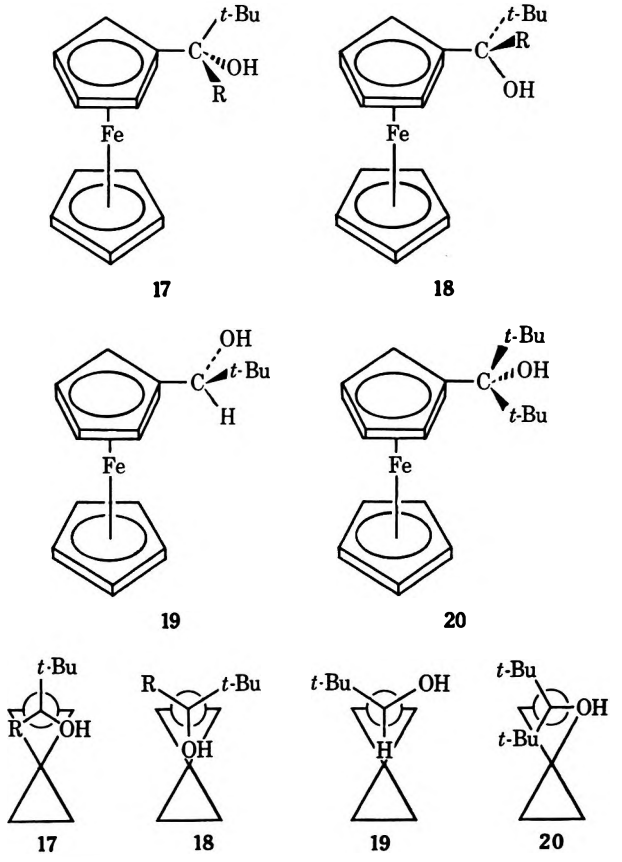
Discussion

The infrared spectra of the ferrocenylcarbinols all show a band at low frequency (3560–3583 cm^{-1}) in the region assigned to hydrogen bonding between the hydroxyl and nonbonding[6a,b] or bonding[9] orbitals of the iron. In the case of α-phenylcarbinols there is some question as to whether the infrared band which often appears in the region 3600–3625 cm^{-1} is due to an intramolecularly hydrogen bonded species or whether it arises from an unbonded rotamer.[1] The much larger shifts in the ferrocenyl derivatives leave little doubt that in these compounds such bonding does occur, probably in conformations such as **17** or **18** (Chart II). When R = H or *t*-Bu the nonbonded conformations **19** or **20**, respectively, are also significant. For compound **8** the isopropyl group is the largest substituent and occupies the position of the *tert*-butyl in **17** or **18**.

(9) J. C. Ware and T. G. Traylor, *Tetrahedron Lett.*, 1295 (1965).

CHART II

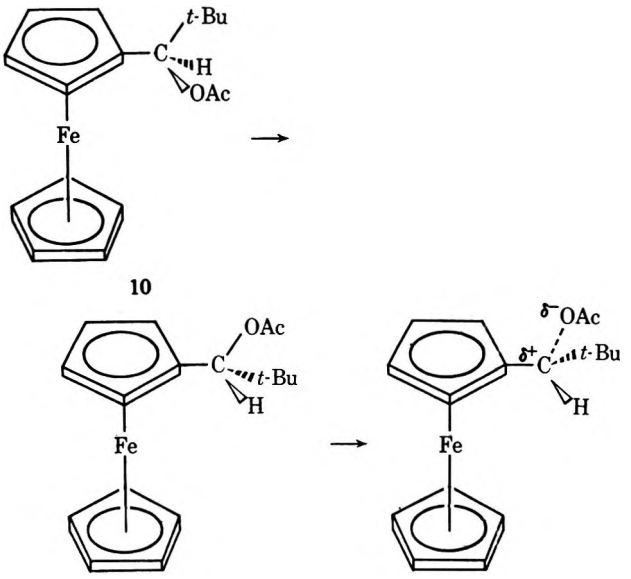
CONFORMATIONS OF FERROCENYLCARBINOLS



The solvolytic properties of *tert*-butylferrocenylcarbinyl acetate (**10**) (Table II) show a drastic decrease in first-order solvolysis rate relative to the methyl-substituted compound. The release of strain in an SN1 transition state for such a highly substituted derivative would have been expected to give a significantly accelerated rate; for example, di-*tert*-butylcarbinyl tosylate solvolyses 320 times faster than isopropyl tosylate in formic acid.[10] This steric acceleration decreases in more nucleophilic solvents, which give fast k_s reactions on isopropyl derivatives, but even in the highly nucleophilic aqueous solvents used for the ferrocene solvolyses the reactions consistently proceed with retention of configuration[4a,d,e] and surely involve a k_Δ process. Therefore, there is a rate-retarding effect for **10** of much more than the observed factor of 4900. This rate deceleration can be attributed to the steric repulsion of the *tert*-butyl by the ring in the transition state for exo departure of the acetate. This transition state suffers from the same unfavorable interactions which force the conformations **17** (or **18**) and **19** for the corresponding alcohol. Alternatively, the reaction might occur with endo departure of the leaving group, which is known to be less favorable in constrained systems by a factor of 2500.[4a,d] In the comparable phenyl compounds *tert*-butylphenylcarbinyl chloride is less reactive than methylphenylcarbinyl chloride in 80% ethanol at 50° by a factor of 490,[5a] which was attributed to steric interference of resonance by repulsion between the ortho hydrogens and the *tert*-butyl group.

The noticeable increase in reactivity of the ferro-

(10) S. H. Liggero, J. J. Harper, P. v. R. Schleyer, A. P. Krapcho, and D. E. Horn, *J. Amer. Chem. Soc.*, **92**, 3789 (1970).



cenylcarbinols with acid in the series **6** > **5** > **4** > **7** can be assigned to a driving force for reaction to form less crowded intermediates,[11] and a speculative scheme for the observed products from **6** is presented in Chart I. An overall decrease in steric strain could direct formation of the observed products, even though some of the intermediates appear to be unfavorable. Such multiple rearrangements and fragmentations have ample precedent in the literature.[7,11b,c]

Experimental Section

General.—Analyses were performed by the M. I. T. Microchemical Laboratory, the Meade Microanalytical Laboratory, Amherst, Mass., or the Bernhardt Mikroanalytisches Laboratorium, Elbach über Engleskirchen, Germany. Routine infrared spectra were determined using Perkin-Elmer 137, 257, or 337 spectrophotometers and were calibrated against appropriate polystyrene bands. Hydroxyl stretching frequencies were measured with a Perkin-Elmer 621 grating spectrophotometer. Nmr spectra were measured with a Varian A-60 instrument with tetramethylsilane as an internal standard. Assignments of hydroxy peaks in carbon tetrachloride solution were confirmed by shaking with D_2O. Melting points (capillary) and boiling points are not corrected. Mass spectra were obtained using a Perkin-Elmer Hitachi RMU instrument. Ultraviolet spectra were obtained with a Perkin-Elmer 202 spectrophotometer. Thin layer chromatography (tlc) was carried out on glass plates coated with silica gel with the solvents noted.

***tert*-Butyl Ferrocenyl Ketone** (1).—Ferrocene (40.0 g, 0.213 mol) and aluminum chloride (22 g, 0.16 mol) were placed in a dry 500-ml three-necked flask under nitrogen with 250 ml of 1,2-dichloroethane. The flask was cooled in an ice–salt bath, and pivalyl chloride (18.1 g, 0.150 mol) in 160 ml of 1,2-dichloroethane was dripped in over 25 min with stirring. The mixture was stirred for 100 min more while warming to room temperature and then was poured on ice, the layers were separated, the water layer was washed three times with 1,2-dichloroethane, and the combined organic layers were washed successively with 3 *N* HCl, 5% NaOH, and saturated NaCl. The solvent was distilled away and the residue was steam distilled. The distillate contained 11.7 g of ferrocene contaminated with **1** and the residue consisted of 27.5 g of red solid (0.1 mol, 68% based on pivalyl chloride). Two recrystallizations from 95% ethanol gave 20.3 g (0.0748 mol, 49.9%) of **1**, mp 91–93° (lit.[12] mp 92°, lit.[13] mp 91.5–92.5°), and further recrystallization from pentane at −25° gave red-orange needles: mp 93.4–93.8°; ir (CCl_4) 1665 (C=O), 1112, and 1010 cm^{-1} (monosubstituted ferrocene); nmr (CCl_4) δ 1.28 (s, 9, *t*-Bu), 4.08 (s, 5, unsubstituted cyclopentadienyl), 4.30 and 4.71 (each broad singlet, 2, substituted cyclopentadienyl); mass spectrum (70 eV) *m/e* 270 (molecular ion).

In later preparations CH_2Cl_2 was used as solvent and after removal of part of the residual ferrocene by steam distillation the product was purified by chromatography on Florisil with pentane–ether solvent.

Anal. Calcd for $C_{15}H_{18}FeO$ (270.16): C, 66.69; H, 6.72; Fe, 20.67. Found: C, 66.45; H, 6.88; Fe, 20.12.

Di-*tert*-butylferrocenylcarbinol (6).—*tert*-Butyllithium solution (115 ml of 1 *M* solution in pentane, Foote Mineral Co.) was dripped into a solution of **1** (20.3 g, 0.0752 mol) in 1.2 l. of pentane in a dry 2-l. three-necked flask under nitrogen. After 4 hr of stirring, the mixture was poured on ice and extracted with 5% $NaHCO_3$ and then NaCl solution. Removal of the pentane left 22.6 g of gummy red solid which after chromatography on Florisil with pentane–benzene and recrystallization from acetone at −70° gave 11.5 g (0.044 mol, 57%) of **6**, mp 65–72°. Recrystallization from pentane at −25° gave red prisms: mp 75.4–76.3°; ir (CCl_4) 3632 and 3579 cm^{-1} (OH); nmr (CCl_4) δ 1.11 (s, 18, *t*-Bu's), 1.48 (s, 1, OH), and 4.1 (m, 9, aromatic H); mass spectrum (70 eV) *m/e* 328 (molecular ion).

Anal. Calcd for $C_{19}H_{28}FeO$ (328.28): C, 69.52; H, 8.60; Fe, 17.01. Found: C, 69.66; H, 8.21; Fe, 17.32.

The later chromatography fractions of this preparation gave yellow solid which was recrystallized from acetone at −70° to give 0.54 g (0.002 mol, 3%) of *tert*-butylferrocenylcarbinol (**2**) as small yellow prisms: mp 89.1–90.2° (lit.[6b] mp 90°); ir (CCl_4) 3579 cm^{-1} (OH) (lit.[6b] ir 3631.5, 3582.8 cm^{-1}); nmr (CCl_4) δ 0.83 (s, 9, *t*-Bu), 1.78 (s, 1, OH), 3.93 (s, 1, HCO), and 4.1 (m, 9, aromatic); mass spectrum (70 eV) *m/e* 272 (molecular ion).

Anal. Calcd for $C_{15}H_{20}FeO$ (272.18): C, 66.19; H, 7.41; Fe, 20.52. Found: C, 66.56; H, 7.50; Fe, 20.10.

The reduction of **1** with $NaBH_4$ also gave **2**.

Preparation of Other Tertiary Ferrocenylcarbinols.—The tertiary alcohols derived from the addition of methyl, ethyl, isopropyl, and neopentyl groups to **1** were prepared in a manner similar to that above except that in these cases a solution of **1** in ether or pentane was added to excess alkyllithium in the same solvent in the flask in which it had been prepared. Alkyllithiums were prepared from methyl iodide and ethyl bromide in ether, and isopropyl and neopentyl chlorides in pentane.

Methyl-*tert*-butylferrocenylcarbinol (**3**) was obtained in 85% yield after one recrystallization from pentane. Chromatography on Florisil with pentane–ether and final recrystallization from hexane at −25° gave mustard-yellow crystals: mp 92–94° (lit.[13] mp 93.5–94°); ir (CCl_4) 3581 cm^{-1} (OH); nmr (CCl_4) δ 0.81 (s, 9, *t*-Bu), 1.52 (s, 3, Me), 1.70 (s, 1, OH), and 4.1 (m, 9, aromatic); mass spectrum (70 eV) *m/e* 286 (molecular ion).

Anal. Calcd for $C_{16}H_{22}FeO$ (286.20): C, 67.15; H, 7.75; Fe, 19.51. Found: C, 67.65; H, 7.75; Fe, 20.11.

Ethyl-*tert*-butylferrocenylcarbinol (**4**) was obtained in 80% yield after one recrystallization from pentane at −70° and recrystallization from hexane at −25° gave brown-orange prisms: mp 85.2–87.0°; ir (CCl_4) 3573 cm^{-1} (OH); nmr (CCl_4) δ 0.82 (s, 9, *t*-Bu), 1.18 (t, 3, J = 8 Hz, Me), 1.52 (s, 1, OH), 2.06 (quartet, 2, J = 8 Hz, CH_2), and 4.1 (m, 9, aromatic); mass spectrum (70 eV) *m/e* 300 (molecular ion).

Anal. Calcd for $C_{17}H_{24}FeO$ (300.23): C, 68.01; H, 8.06; Fe, 18.60. Found: C, 68.28; H, 8.14; Fe, 19.05.

Isopropyl-*tert*-butylferrocenylcarbinol (**5**) was obtained in 45% yield after one recrystallization from pentane at −70°, and recrystallization from hexane at −25° gave brown-orange prisms: mp 76.8–79.1°; ir (CCl_4) 3573 cm^{-1} (OH); nmr (CCl_4) 0.86 and 1.14 (each d, 3, J = 8 Hz, diastereotopic methyls of isopropyl), 1.04 (s, 9, *t*-Bu), 1.87 (s, 1, OH), 2.5 (m, 1, J = 8 Hz, CH), and 4.1 (m, 9, aromatic); mass spectrum (70 eV) *m/e* 314 (molecular ion).

Anal. Calcd for $C_{18}H_{26}FeO$ (314.26): C, 68.79; H, 8.34; Fe, 17.77. Found: C, 68.71; H, 8.29; Fe, 17.81.

***tert*-Butylneopentylferrocenylcarbinol** (**7**) was obtained in 56% yield after chromatography of the initially obtained red-black oil on Florisil with pentane–ether and one recrystallization from pentane. Recrystallization from pentane at −25° gave brown-orange prisms: mp 90.2–92.3°; ir (CCl_4) 3574 cm^{-1} (OH); nmr (CCl_4) δ 0.86 and 1.13 (each s, 9, *t*-Bu), 1.54 (s, 1, OH), 1.92 (s, 2, CH_2), and 4.1 (m, 9, aromatic).

Anal. Calcd for $C_{20}H_{30}FeO$ (342.30): C, 70.17; H, 8.83; Fe, 16.32. Found: C, 69.93; H, 8.51; Fe, 16.52.

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tert-Butylferrocenylcarbinyl acetate (10) was obtained by refluxing 1.0 g of 2 with 5 ml of pyridine and 2 ml of acetic anhydride overnight and then removing the solvent at 0.1 Torr. Sublimation of the black solid at 125° (0.15 mm) yielded 10 (0.91 g, 78%), which after recrystallization from pentane at −70° was small yellow crystals: mp 90.8–93.0°; ir (CCl_4) 1725 cm^{-1} (C=O); nmr (CCl_4) δ 0.79 (s, 9, *t*-Bu), 2.17 (s, 3, Me), 4.00 (m, 9, aromatic), and 5.50 (s, 1, HCO); mass spectrum (70 eV) *m/e* 314 (molecular ion).

Anal. Calcd for $C_{17}H_{22}FeO$ (314.22): C, 64.98; H, 7.06; Fe, 17.78. Found: C, 65.09; H, 7.01; Fe, 17.65.

Methylisopropylferrocenylcarbinol (8).—Acetylferrocene (2.0 g, 0.0088 mol) in 50 ml of ether was added to the Grignard reagent prepared from isopropyl bromide (12.5 g, 0.10 mol) and Mg (5 g, 0.2 g-atom) in 150 ml of ether. The solution was refluxed for 30 min, and worked up with aqueous sulfuric acid. The solvent was removed to give a 0.80 g of red oil (40% yield based on 8).

Chromatography on alumina with pentane–ether gave two fractions, the first being methylisopropylferrocenylcarbinol (8) as a red oil: ir (CCl_4) 3560 cm^{-1} (OH); nmr (CCl_4) δ 0.64 and 0.82 (each d, 3, J = 6.5 Hz, diastereotopic Me's of *i*-Pr), 1.38 (s, 3, MeCO), 1.75 (s, 1, OH), 1.4 (m, 1, -CH-*i*-Pr), 3.88 and 4.00 (each t, 2, J = 1.5 Hz, substituted cyclopentadienyl), and 4.08 (s, 5, unsubstituted cyclopentadienyl); mass spectrum (70 eV) *m/e* 254 (molecular ion minus water).

This compound was converted to the solid olefin 16 for analysis (*vide infra*).

The second fraction, after sublimation at 120° (0.1 Torr) and recrystallization from pentane, was identical with authentic 1,3-diferrocenylbut-2-en-1-one (9):[14] nmr (CCl_4) δ 2.46 (d, 3, J = 1 Hz, Me), 4.06 and 4.08 (each s, 5, unsubstituted cyclopentadienyls), 4.2–4.7 (m, 8, substituted cyclopentadienyls), 6.54 (m, 1, vinyl H).

Distillation of methylisopropylferrocenylcarbinol (8) at 100° (0.1 Torr) gave **2-ferrocenyl-3-methyl-2-butene (16)**, which after sublimation at 100° (0.1 Torr) was an orange solid: mp 46–48.5°; uv max (cyclohexane) 271 nm (ε 9100); nmr (CCl_4) δ 1.69 (br s, 6, $=CMe_2$), 1.98 (br s, 3, FcMeC=), 3.97 (s, 5, unsubstituted cyclopentadienyl), 3.9–4.1 (m, 4, substituted cyclopentadienyl) (weak absorptions at δ 1.08, 1.20, and 5.1 suggested the presence of <5% of the isomeric 1-isopropyl-1-ferrocenylethylene); mass spectrum (70 eV) *m/e* 254 (molecular ion).

Anal. Calcd for $C_{15}H_{18}Fe$ (254.16): C, 70.88; H, 7.14; Fe, 21.97. Found: C, 71.09; H, 7.41; Fe, 21.53.

Reaction of Di-*tert*-butylferrocenylcarbinol (6) in Acid.—A solution of 6 (0.70 g, 0.0021 mol) in 5 ml of acetic acid was added to 20 ml of 0.07 *M* perchloric acid solution (prepared by mixing 70% perchloric acid and acetic acid) with rapid stirring. The solution blackened immediately, and, after stirring for 1 min, was poured into excess $NaHCO_3$ solution and extracted twice with pentane. The pentane layer was washed with NaCl solution and evaporated, leaving a red oil which was chromatographed on silica gel with benzene to give three fractions. The first was 0.425 g (0.00137 mol, 65%) of a red oil identified as **2-ferrocenyl-3,3,4,4-tetramethyl-1-pentene (13)**: ir (CCl_4) 1610 (C=C), 1410 (triptyl[15]), and 905 cm^{-1} ($C=CH_2$); uv (cyclohexane) 272 nm (ε 8350); nmr (CCl_4) δ 0.83 (s, 9, *t*-Bu), 1.09 (s, 6, *t*-BuCMe_2), 3.91 and 4.13 (each t, 2, J = 1.5 Hz, substituted cyclopentadienyl), 3.96 (s, 5, unsubstituted cyclopentadienyl), 5.18 and 5.86 (each d, 1, J = 2 Hz, vinyl H); mass spectrum (70 eV) *m/e* 310 (molecular ion).

Hydrogenation of 13 (PtO_2 in acetic acid, 54 psi, 25°) and purification of the product by preparative tlc (benzene) gave **2,2,3,3-tetramethyl-4-ferrocenylpentane (15)** as a red oil: ir (CCl_4) 1410 cm^{-1} (triptyl[15]); nmr (CCl_4) δ 0.50 and 0.68 (each s, 3, diastereotopic Me's of -CMe_2-*t*-Bu), 0.88 (s, 9, *t*-Bu), 1.42 (d, 3, J = 7 Hz, CHMe), 2.46 (quartet, 1, J = 7 Hz, CHMe), 3.96 (s, 5, unsubstituted cyclopentadienyl), 3.8–4.0 (m, 4, substituted cyclopentadienyl); mass spectrum (70 eV) *m/e* 312 (molecular ion).

The second fraction from the chromatography of the reaction mixture from 6 was identified as 8 (0.091 g, 0.00033 mol, 16%) by comparison with the authentic material described above. The third fraction was identified as 14 (0.005 g, 1%) by comparison with authentic material prepared from acetylferrocene and methyllithium.

Preparative tlc of the reaction product from 6 with benzene gave R_f values for 13, 14, and 8 of 0.82, 0.47, and 0.14, respectively.

Reaction of Isopropyl-*tert*-butylferrocenylcarbinol (5) with Acid.—Under the conditions at which 6 (above) completely reacted in 1 min, 5 showed a slower conversion to a mixture of products. Thus at reaction times of 30 sec, 3 min, and 30 min there was recovered (by column chromatography on Florisil with pentane and ether–pentane mixtures) 75, 53, and 0% of starting material. The product was not identified but was apparently a mixture of olefins. The ir spectrum showed a C=C stretch at 1625 cm^{-1} and a terminal $=CH_2$ at 894 cm^{-1}, and the nmr also showed a vinyl methylene group (doublets, J = 2 Hz, at δ 5.1 and 5.6).

Reaction of Ethyl-*tert*-butylferrocenylcarbinol (4) with Perchloric Acid.—Treatment of 4 as above for 35 min and separation by column chromatography gave 20% recovered starting material and 68% of a red oil tentatively identified as **1-*tert*-butyl-1-ferrocenylpropene-1 (11)**: ir (CCl_4) 1625 cm^{-1} (C=C); nmr (CCl_4) δ 1.18 (s, 9, *t*-Bu), 1.81 (d, 3, J = 7.5 Hz, =CHMe), 4.0 (m, 9, ferrocenyl), 5.62 (q, 1, J = 7.5 Hz, =CHMe).

Reaction of *tert*-Butylneopentylferrocenylcarbinol (7) with Perchloric Acid.—Treatment of 7 as above for 30 min and separation by column chromatography gave 51% recovered starting material and 18% of a red solid identified as **1,2-di-*tert*-butylferrocenylethylene (12)**. Recrystallization from pentane at −25° gave red prisms: mp 95.2–95.8°; ir (CCl_4) 1580 cm^{-1} (C=C); nmr (CCl_4) δ 0.66 (s, 9, *t*-Bu), 1.61 (s, 9, *t*-Bu), 3.87 and 4.18 (each t, 2, J = 1.5 Hz, substituted cyclopentadienyl), 4.06 (s, 5, unsubstituted cyclopentadienyl), 5.47 (s, 1, =CH–).

Anal. Calcd for $C_{20}H_{28}Fe$ (324.29): C, 74.07; H, 8.70; Fe, 17.22. Found: C, 74.23; H, 8.73; Fe, 16.73.

Kinetics of Hydrolysis of *tert*-Butylferrocenylcarbinyl Acetate (10).—In a typical experiment 1.180 g (0.0038 mol) of 10 was dissolved in 75 ml of purified[16] acetone and 6 ml of aliquots of this material were added to each of 12 tubes containing 4 ml of water, which were then sealed. The tubes were placed on a constant-temperature bath at the appropriate temperature and agitated for 5 min while the acetate dissolved and the temperature equilibrated. Then a tube was removed for time zero, and others were removed at appropriate intervals. Liberated acetic acid was titrated to a phenol red end point with 0.1 *N* NaOH. The reactions gave reasonably good linear rate plots for 1–2 half-lives, although there was slight upward drift at long reaction times, particularly at the higher temperatures. This phenomenon is presumably due to reversal of the reaction from the dissociated ion or the carbinol. Such external return is a common feature in the reactions of α-ferrocenyl cations.[4h,17] At least two runs were made at each temperature, with a maximum deviation of ±7%.

Attempted Preparation of Methyl-*tert*-butylferrocenylcarbinyl Acetate.—A solution of methyllithium (0.014 mol) in ether was added to *tert*-butyl ferrocenyl ketone (1) (3.15 g, 0.012 mol) in refluxing ether, and then acetyl chloride (0.77 g, 0.0098 mol) was added. The solution was refluxed for 30 min and then evaporated, with successive removal of the precipitated white solid. The residue was chromatographed on Florisil with ether–pentane to give successively 1.38 g (44%) of material tentatively identified as **1-*tert*-butyl-1-ferrocenylethylene (21)**, 0.79 g (24%) of 3, and 0.37 g (12%) of 1. Purification of 21 by further chromatography gave a mobile red oil with the expected spectral properties but a poor analysis: ir (CCl_4) 1634 cm^{-1} (C=C); uv max (MeOH) 274 nm (ε 4,000); nmr (CCl_4) δ 1.12 (s, 9, *t*-Bu), 4.1 (m, 9, aromatic), and 5.28 and 5.66 (each d, 1, J = 2 Hz, $=CH_2$).

Anal. Calcd for $C_{16}H_{20}Fe$ (268.19): C, 71.86; H, 7.46; Fe, 20.67. Found: C, 72.72; H, 7.74; Fe, 19.71.

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Steric Crowding in Organic Chemistry. IV. Ultraviolet Absorption Spectra of Crowded Olefins

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The ultraviolet absorption spectra of a group of crowded olefins have been determined for both cyclohexane solutions (182 nm and above) and the vapor state (183 nm and above). Marked shifts in the $\pi-\pi^*$ absorption maximum to higher wavelengths were observed in 1,1-disubstituted olefins, cis-1,2-disubstituted olefins, and trisubstituted olefins. Neopentyl substituents caused the largest shifts. *cis*-1,2-Di-*tert*-butylethylene (in solution) is the only olefin which shows a maximum at higher wavelength for the cis relative to the trans isomer. An efficient Wittig synthesis of crowded 1,1-disubstituted ethylenes was developed.

The ultraviolet spectra of isolated olefinic double bonds have been investigated recently in several laboratories.[2-5] Together with previous work,[6] these studies have established that simple unstrained olefins have characteristic absorption maxima at 174–178 nm for monosubstituted olefins, 174–184.5 nm for *cis*-1,2-disubstituted olefins (the higher wavelength is characteristic of fatty acid esters, lower molecular weight hydrocarbons absorb at 174–182 nm) with the trans isomers typically 3–4 nm higher, 186–189 nm for 1,1-disubstituted olefins, 177–191 nm for trisubstituted olefins, and 187–191 nm for tetrasubstituted olefins.

The observed maxima are assigned to the π-bonding to π-antibonding ($\pi \rightarrow \pi^*$) transition which produces the intense N $\rightarrow$ V band.[7,8] Other absorption, of much lower intensity and apparently due to Ryberg transitions, occurs in some cases on the long-wavelength portion of the N $\rightarrow$ V band.[8-12] Recent reports give a detailed interpretation of the spectra of simple olefins.[8,11-13]

Polyolefins with homoconjugated double bonds, such as 1,4-pentadiene[6] and linoleic acid,[2] display the effects of delocalization of the double bonds with absorption maxima at higher wavelengths, and molar absorptivities 40% less than dienes with isolated double bonds. Cyclopropyl substituents also shift the absorption to higher wavelengths.[4]

The effect of angle strain on the ultraviolet absorption spectra of cyclic olefins has been examined in a variety of systems, including small-ring hydrocarbons,[14,15] steroids and terpenoids,[16] bicyclo[3.3.1]non-1-ene,[17] and highly strained olefins derived from natural products.[18]

Conjugated 1,3-dienes with bulky substitution on the double bond have also been examined and found to be twisted out of conjugation, giving a shift in the electronic spectrum to lower wavelength.[19] However, there has been no systematic investigation of the effects of bulky substitution on the ultraviolet absorption of noncyclic olefins; so to complement our previous studies on vibrational spectra of such compounds[20] we have examined the electronic absorption spectra of olefins **1–16** above 182 nm. The results are presented in Table I, together with selected data for reference.

Results and Discussion

All of the compounds utilized had been reported previously, but a modified general route to the pure 1,1-disubstituted olefins was also developed. This route was used for 2-ethyl-3,3-dimethyl-1-butene (**5**) and 2-isopropyl-3,3-dimethyl-1-butene (**6**) and involved the Wittig reaction in dimethyl sulfoxide at elevated temperatures. The procedure of Corey[21] involves generation of the methylsulfinyl carbanion from DMSO and NaH, and then formation of the phosphorane by addition of the phosphonium halide. The phosphorane reacts rapidly with most ketones at room temperature under these conditions, but we found that these conditions failed with ethyl *tert*-butyl ketone. However, use of longer reaction times and elevated temperatures gave apparently complete conversion to the desired olefins.

$$\text{no reaction} \xleftarrow[\text{DMSO, 25°}]{Ph_3P=CH_2} \text{Et-}t\text{-BuC(=O)} \xrightarrow[\text{DMSO, 80°}]{Ph_3P=CH_2} \underset{\mathbf{5}}{\text{Et-}t\text{-BuC(=CH}_2\text{)}}$$

Higher temperatures were unsuccessful with di-*tert*-butyl ketone, even at 150°, at which point the decomposition of the solvent becomes excessive.

Pyrolysis[20] or solvolysis[22] of the corresponding tertiary *p*-nitrobenzoates was used to prepare the trisubstituted olefins **14–16**.

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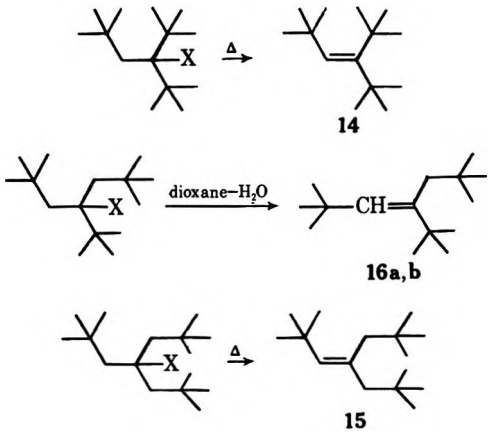
TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF OLEFINS[a]

1,1 Disubstituted	λ_{max}, nm (ϵ_{max})	1,2 Disubstituted	λ_{max}, nm (ϵ_{max})	Trisubstituted	λ_{max}, nm (ϵ_{max})
$Me_2C=CH_2$	188.2 (11,300)[b,c]	MeCH=CHMe		$MeCH=CMe_2$	177.5 (11,000)[b,f]
		trans	178.0 (13,000)[b]		
$MeEtC=CH_2$ (1)	186.0 (8,800)	cis	174.0 (16,000)[b]	MeCH=CMe-*t*-Bu	186.5 (11,750)
	188.3 (9,700)[b]			(trans) (12)	184.0[d]
Me-*i*-PrC=CH_2 (2)	186.5 (10,800)	*t*-BuCH=CHMe	184.5 (11,150)	*t*-BuCH=CMe_2 (13)	192.0 (10,050)
	187.0[d]	(cis) (9)	183.0[d]		193.5[d]
Me-*t*-BuC=CH_2 (3)	186.0 (10,850)	*t*-BuCH=CH-*t*-Bu		*t*-BuCH=C-*t*-Bu_2 (14)	194.5 (13,300)
	187.0[d]				191.0[d]
MeNpC=CH_2 (4)	191.0 (8,600)	cis (10)	185.5 (12,550)	*t*-BuCH=CNp_2 (15)	200.0 (9,650)[e]
	190.5[d]		183.0[d]		
Et-*t*-BuC=CH_2 (5)	186.0 (10,850)	trans (11)	184.5 (15,050)	*t*-BuCH=C-*t*-BuNp (16)	197.5 (10,500)
	188.0[d]		184.0[d]		198[d]
i-Pr-*t*-BuC=CH_2 (6)	188.5 (12,100)	*cis*-2-octene	181.5 (13,450)[e]		
	187.5[d]				
t-$Bu_2C=CH_2$ (7)	189.0 (11,650)	*trans*-2-octene	184.0 (10,450)[e]		
	189.0[d]				
$Np_2C=CH_2$ (8)	196.5 (7,900)				
	197.5[d]				

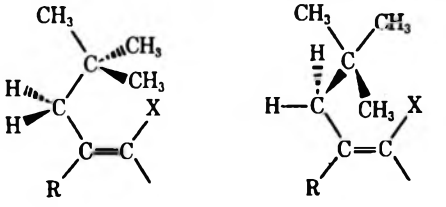
[a] Unless otherwise indicated results are for this work and were measured for cyclohexane solutions. Np = neopentyl. [b] Reference 6 (vapor). [c] We find 187.0 in cyclohexane solution and 184.0 and 188.0 (equal intensity) in the vapor. [d] Vapor spectrum. [e] Reference 2. [f] We observe a maximum at 187.0 (10,000), and ref 9 gives 188.7 (5800). Our vapor spectrum shows maxima at 183.0 > 185.5 > 191.5. [g] The vapor spectrum shows a series of maxima at 183.5, 185.5, 190.0, 197.0, 203.0, and 207.5, with the highest intensities at 183.5 and 185.5 nm.



X = *p*-nitrobenzoate

CHART I

CONFORMATIONS OF 1-ALKYL-1-NEOPENTYLETHYLENES



Inspection of molecular models suggests that the *tert*-butyl substituted olefins **6** and **7** suffer intramolecular steric crowding between the groups. This crowding apparently results in distortion of the double bond that is reflected in the spectra, which show augmentation of ϵ and a 2–3-nm bathochromic shift in λ_{max} relative to the unstrained **1–3** (this shift corresponds to 1.6–2.4 kcal/mol). The neopentyl-substituted compounds **4** and **8** show pronounced bathochromic shifts in λ_{max} of 5 and 10.5 nm, respectively. The models suggest that in neopentylethylenes the neopentyl group is significantly repulsed by any other substituent larger than hydrogen on the same olefinic carbon, so that the conformations shown in Chart I may tend to be favored, with the methyl groups close to the double bond.[23] Bond stretching and twisting may also occur, but the extent of these deformations cannot be specified.

The possible proximity of the methyl group and the π cloud suggests two sources of the bathochromic shifts in these compounds. There may be orbital interactions between the methyl groups and the π electrons of the double bond which change the energy levels of the ground and excited electronic states resulting in a net lowering of the energy of the transition. Alternatively, a nonbonding repulsion could distort the double bond and change the energy levels.

The 1,2-disubstituted ethylenes have generally lower wavelength absorption maxima and higher molar absorptivity than the 1,1-disubstituted compounds, with the trans compounds usually absorbing at longer wavelength than the cis isomers. This behavior has been analyzed in terms of the dipole moments of the molecules: olefins with dipole moments in the direction of the bond, such as 1,1-disubstituted compounds, absorb at longer wavelength, whereas if there is a component of the dipole moment perpendicular to the bond, as in cis-1,2-disubstituted olefins, the excitation energy is increased.[10]

cis-1-Methyl-2-*tert*-butylethylene (**9**) absorbs 3 nm higher than *cis*-2-octene, and *cis*-1,2-di-*tert*-butylethylene absorbs 1 nm higher (in solution) than the trans isomer. This is the only example of higher wavelength absorption of a cis relative to a trans isomer, but this effect is partly due to solvation effects, as the cis isomer does absorb at lower wavelength in the vapor.

The cause of the difference between the trisubstituted olefins **12** and **13** is not obvious on steric grounds. It is interesting, however, that Heathcock and Poulter[4a] observed the equivalent difference between the corresponding isopropyl derivatives, and classified it as a

(23) For a review of the properties of the neopentyl substituent see M. Montagné, *Bull. Soc. Chim. Fr.*, 347 (1970).

"special *gem*-dimethyl" effect. The model of tri-*tert*-butylethylene (**14**) indicates a highly crowded double bond with a strong twisting force, but the increase in λ_{max} is modest. The trisubstituted olefins with neo-

t-BuCH=CMe$_2$	*i*-PrCH=CMe$_2$
13, λ_{max} 192.0 (ϵ 10,050)	λ_{max} 191.0 (ϵ 10,200)
MeCH=CMe-*t*-Bu	MeCH=CMe-*i*-Pr
(trans) **12**, λ_{max} 186.5 (ϵ 11,750)	(trans), λ_{max} 186.5 (ϵ 10,000)

pentyl substituents (**15** and **16a**) show rather larger shifts, consistent with the behavior of the 1,1-disubstituted neopentylethylenes.

The patterns of behavior in the ultraviolet absorption are rather different from those of the vibrational spectra,[20] where the *tert*-butyl derivatives have much larger frequency shifts than the corresponding neopentyl derivatives; for example, **4**, **8**, and **15** absorb at 1640, 1635.5, and 1636 cm^{-1}, respectively, whereas **3**, **7**, and **14** absorb at 1638.5, 1615.5, and 1583 cm^{-1}, respectively.

Spectral information has recently become available on some highly distorted polycyclic olefins. Bicyclo[3.3.1]non-1-ene has a near-normal vibrational absorption (1620–1625 cm^{-1})[17] but a low-energy electronic absorption [206–207 nm (ϵ 7500–7000)].[17] A tetrasubstituted olefinic alcohol derived from katonic acid has Raman and ultraviolet absorptions at 1690 cm^{-1} and 224 nm (ϵ 5200), respectively.[18] Molecular models, and an X-ray crystallographic study in the latter case,[18] show these double bonds to be substantially deformed.

The geometries of the acyclic compounds considered in this report have not been experimentally determined, but two calculations have appeared[24,25] of the geometry of *cis*-1,2-di-*tert*-butylethylene (**10**). These agree on a value of 136° for the C=C–C angle of this compound. Neither of these calculations considered out-of-plane bond twisting, and only one[24] included bond stretching. The complete analysis of the properties of these crowded olefins in terms of their structures will require more experimental information on the molecular geometries and a more thorough theoretical evaluation of the relative contributions of in-plane bond bending, out-of-plane bond twisting, and bond stretching.

Experimental Section[26]

Elemental analyses were performed by the Bernhardt Mikroanalytisches Laboratorium, Elbach über Engleskirchen, Germany. Nmr spectra were measured on a Varian A-60 instrument with tetramethylsilane as an internal standard. Raman spectra were measured with a Cary 81 instrument equipped with a He–Ne laser source. Gas chromatography (glpc) was performed with a Varian Aerograph 90P-3 instrument and the columns and temperatures specified.

Source of Samples.—Compounds **1–4**, **8**, **9**, and **11–13** were obtained 98–99% pure from Chemical Samples Co., Columbus, Ohio. *cis*-1,2-Di-*tert*-butylethylene (**10**) was obtained by the selective hydrogenation[27] of di-*tert*-butylacetylene (Chemical Samples Co.) and was purified by glpc (10 ft × 3/8 in., DEGS on Chromosorb P, 110°, 75 ml/min He). Compounds **14–16** were prepared by pyrolysis or solvolysis of the corresponding *p*-nitrobenzoate esters[22] by the procedure reported previously.[20] 1,1-Di-*tert*-butylethylene (**7**) was prepared by the published procedure,[28] and compounds **5** and **6** were prepared by a modification of the Wittig reaction in DMSO[21] at elevated temperature.

Tri-*tert*-butylethylene (14)[20] was collected by glpc (10 ft × 3/8 in., 30% SE-52 on Chromosorb W column, 160°, 75 ml/min He): uv max (cyclohexane) 194.5 nm (ϵ 13,300); Raman (neat) 1583 cm^{-1} (C=C); nmr (CCl_4) δ 1.07, 1.09, and 1.22 (each s, 9, *t*-Bu) and 5.22 (s, 1, vinyl H); mass spectrum (70 eV) *m/e* 196 (molecular ion).

Anal. Calcd for $C_{14}H_{28}$ (196.38): C, 85.63; H, 14.37. Found: C, 85.79; H, 14.41.

1,1-Dineopentyl-2-*tert*-butylethylene (15)[22] was prepared by pyrolysis of trineopentylcarbinyl *p*-nitrobenzoate (7.70 g, 0.0196 mol) in a 100-ml round-bottom flask up to 220° (0.1 Torr). There was collected in a Dry Ice trap 3.1 g (0.0138 mol, 71%) of **15** pure by glpc: uv max (cyclohexane) 200.0 nm (ϵ 9650); Raman (neat) 1536 cm^{-1} (C=C); nmr (CCl_4) δ 0.88, 0.99, and 1.12 (each s, 9, *t*-Bu), 1.90 and 2.18 (each s, 2, –CH_2-*t*-Bu), and 5.05 (s, 1, vinyl H).

Anal. Calcd for $C_{16}H_{32}$ (224.33): C, 85.63; H, 14.37. Found: C, 85.55; H, 14.46.

1,2-Di-*tert*-butyl-1-neopentylethylene (16)[22] was prepared by solvolysis as previously reported[22] and separated by glpc (20 ft × 3/8 in. 30% FFAP on Chromosorb W column, 133°, 75 ml/min He) to give the cis and trans isomers. These were not differentiated but are designated as **16a** and **16b**. The compound of retention time 33 min, **16a**, constituted 87% of the total: uv max (cyclohexane) 197.5 nm (ϵ 10,500); Raman (neat) 1625 cm^{-1} (C=C); nmr (CCl_4) δ 1.00, 1.09, and 1.10 (each s, 9, *t*-Bu), 2.20 CH_2-*t*-Bu), and 5.31 (s, 1, vinyl H).

Anal. Calcd for $C_{15}H_{30}$ (210.41): C, 85.63; H, 14.37. Found: C, 86.04; H, 13.90.

The compound of retention time 47 min, **16b**, was 3% of the total: Raman (neat) 1622 cm^{-1} (C=C); nmr (CCl_4) δ 0.90, 0.97, and 1.07 (each s, 9, *t*-Bu), 1.95 (s, 2 H, CH_2-*t*-Bu), and 4.90 (s, 1, vinyl H). 2,3,5,5-Tetramethyl-3-neopentyl-1-hexene[22] had a retention time of 56 min and constituted 8% of the total.

2-Ethyl-3,3-dimethyl-1-butene (5) was obtained by treating 10.0 g (0.0880 mol) of ethyl *tert*-butyl ketone (Chemical Samples Co.) with the Wittig reagent (prepared by the published procedure)[21] obtained from 38.0 g (0.103 mol) of methyltriphenylphosphonium bromide and 0.100 mol of NaH at 80° for 24 hr. The product was distilled at 75° (pot) (40 mm) to give 7.24 g of liquid which by nmr and glpc analysis contained about 50% benzene. Separation by glpc (10 ft × 3/8 in. Carbowax 20M on Chromosorb W, 105°, 120 ml/min He) gave pure **5**: nmr (CCl_4) δ 1.01 (t, 3, J = 7 Hz, CH_2CH_3), 1.05 (s, 9, *t*-Bu), 2.03 (quartet, 2, J = 7 Hz, CH_2CH_3), and 4.60 and 4.78 (each singlet with fine structure, 1, C=CH_2).

2-Isopropyl-3,3-dimethyl-1-butene (6) was prepared and purified as above to give **6**: nmr (CCl_4) δ 1.00 (d, 6, J = 7 Hz, $CHMe_2$), 1.05 (s, 9, *t*-Bu), 2.35 (m, 1, $CHMe_2$), 4.65 (s, 1, vinyl H trans to *t*-Bu), and 4.73 (m, 1, J = 1 Hz, vinyl H *trans* to *i*-Pr).

Spectroscopy.—For determination of ultraviolet absorption spectra, an extended-range Beckman Model DK-2 spectrophotometer was employed as previously described.[2] Sample and reference cells were fused quartz and had path lengths of 0.01099 and 0.01004 cm (for solution spectra, useful to 182.0 nm) and 2.0 cm (for vapor spectra, useful to 183.0 nm). Solutions were prepared with Phillips Spectro Grade cyclohexane. Olefin samples, typically 4–6 mg, were weighed in sections of disposable 50-μl pipets on a Cahn electrobalance; the pipet section was weighed, partially filled with sample, reweighed, transferred to a 5-ml or 10-ml volumetric flask, and crushed under cyclohexane. Weighings of samples **1** and **2** may be inaccurate owing to their high volatility. Spectra of sample vapor in a nitrogen atmosphere were obtained by flushing the 2-cm cells with nitrogen, then allowing a small drop of sample to vaporize in the cell.

The CPK Atomic Models (Ealing Corporation) were used to construct molecular models.

Registry No.—**2**, 563-78-0; **3**, 594-56-9; **4**, 107-39-1; **5**, 18231-53-3; **6**, 20442-64-2; **7**, 5857-68-1; **8**, 141-

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70-8; **9**, 762-63-0; **10**, 692-47-7; **11**, 692-48-8; **12**, 598-96-9; **13**, 107-40-4; **14**, 28923-90-2; **15**, 34235-29-5; **16**, 34235-30-8; $Me_2C{=}CH_2$, 115-11-7; $MeCH{=}CMe_2$, 513-35-9; cyclohexane, 110-82-7.

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Micellar Effects upon the Reaction of the Tri-*p*-anisyl Carbonium Ion with Nucleophiles[1]

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Anionic micelles of sodium lauryl sulfate (NaLS) strongly catalyze the acid heterolysis of tri-*p*-anisylmethanol but do not affect the rate of attack of water upon the carbonium ion. Cationic micelles of cetyltrimethylammonium bromide (CTABr) and nonionic micelles of Igepal strongly inhibit the acid heterolysis but also do not affect the rate of attack of water upon the carbonium ion. Micelles of NaLS strongly inhibit the attack of hydroxide or azide ions upon the carbonium ion, and micelles of CTABr and Igepal weakly catalyze these reactions. Igepal decreases acidity as measured by H_0' and H_R.

One of the first kinetic studies of micellar catalysis and inhibition was that carried out by Duynstee and Grunwald on the alkaline fading of stable triphenylmethyl dye cations, *e.g.*, crystal violet.[2] Attack of the hydroxide ion upon the carbonium ion was inhibited by anionic and catalyzed by cationic micelles. These kinetic effects are readily explicable in terms of electrostatic interactions between the micelles and the initial and transition states.[3]

The equilibrium constant for carbonium ion formation from tri-*p*-anisylmethanol (ROH) in dilute acid is markedly increased by anionic micelles of sodium lauryl sulfate (NaLS) and decreased by cationic micelles of cetyltrimethylammonium bromide (CTABr),[8] and it was of interest to examine the forward and back reactions.

We have recently examined the kinetic salt effects upon the reaction of the tri-*p*-anisyl carbonium ion with water and related them to salt effects upon the H_R scale.[9,10] Our aim in the present work was to examine micellar effects upon the reactions shown in eq 1.

$$R^+ + H_2O \underset{k_b}{\overset{k_f}{\rightleftharpoons}} ROH + H^+ \qquad (1)$$

This investigation cannot be carried out using the triphenylmethyl dye cations because they are stable in water and hydroxylic solvents in the absence of added nucleophiles.[2,11] We were also interested in examining micellar effects upon the reactions of the relatively reactive tri-*p*-anisyl carbonium ion with hydroxide and azide ion for comparison with results obtained using the stable dyestuff cations in which the positive charge is delocalized into the amino-substituted aryl groups.[2]

Only ionic surfactants were used in the original work on micellar effects on acidity functions.[8] We have now extended these measurements to the uncharged micelles of Igepal, which is a nonylphenyl polyethylene oxide (mol wt 1403) and also measured the effects of Igepal upon the rates of nucleophilic attack upon the tri-*p*-anisyl carbonium ion.

Experimental Section

Materials.—The purification of the ionic surfactants has been described.[8] Igepal was kindly supplied by GAF Corp. and was used without purification. The carbonium ion was introduced as a solution of tri-*p*-anisylmethyl chloride (Aldrich) in dilute HCl. All solutions were made up using distilled deionized water, and were degassed before use.[9]

Kinetics.—The reactions with water were followed at 25.0° using a Durrum–Gibson stopped flow apparatus. A solution of the carbonium ion, R^+, in dilute HCl in one drive syringe was rapidly mixed with excess NaOAc in the other drive syringe.[9] The first-order rate constant, k_ψ, for attack of water upon R^+ was found to be 12.4 sec^{-1}, in good agreement with our earlier results.[9]

For experiments with hydroxide ion a slight excess of NaOH was used in one drive syringe, and for experiments with azide ion the acid was neutralized by a slight excess of hydroxide ion.[9]

Indicator Measurements.—The ionizations of tri-*p*-anisylmethanol and *p*-nitroaniline in Igepal were measured following general methods.[8,12]

Results

Indicator Measurements.—The ability of nonionic micelles of Igepal to reduce $-H_0'$ and $-H_R$ (Tables I and II) suggests that the base rather than the anilinium or carbonium ion is taken up by the micelles which protect it from the hydronium ion; and nonpolar organic solvents (except at high concentration) decrease acidity functions, in part by stabilizing the organic base.[11] Igepal has a terminal hydroxyl group which could react with the carbonium ion and thereby further reduce $-H_R$, but this reaction is probably not important because the rate of attack of water upon the carbonium ion is unaffected by Igepal (and the ionic micelles). How-

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TABLE I

EFFECT OF IGEPAL ON H_R

$10^4 c_D$, *M*	ΔH_R[a]
0.125	0.05
0.25	0.24
0.50	0.39
1.00	1.52

[a] Values relative to H_R in 0.05 *M* HCl at 25.0°.

TABLE II

EFFECT OF IGEPAL ON H_0'

$10^4 c_D$, *M*	$\Delta H_0'$[a]
6.25	0.02
12.5	0.04
25	0.08
50	0.18

[a] Values relative to H_0' in 0.1 *M* HCl at 25.0°.

TABLE III

EFFECT OF NaLS UPON THE WATER REACTION[a]

$10^3 c_D$, *M*	c_{OAc^-}, *M*	k_ψ, sec^{-1}
2.5	0.025	11.5
2.5	0.075	12.2
2.5	0.125	12.7
2.5	0.225	12.9
5.0	0.025	11.7[b]
5.0	0.075	12.0[b]
5.0	0.125	12.4[b]
5.0	0.225	12.2[b]

[a] At 25.0° with R^+ and NaLS and 0.05 *M* HCl quenched with NaOAc unless specified. [b] With 5.0×10^{-3} *M* NaLS in each drive syringe.

TABLE IV

EFFECT OF CTABr ON THE WATER REACTION[a]

$10^4 c_D$, *M*	c_{OAc^-}, *M*	k_ψ, sec^{-1}
2.5	0.075	11.7
2.5	0.125	11.5
2.5	0.225	11.5
2.5	0.475	12.7
5.0	0.075	13.6[b]
5.0	0.125	13.2[b]
5.0	0.225	14.0[b]

[a] At 25.0° with R^+ and CTABr and 0.05 *M* HCl quenched with NaOAc unless specified. [b] With 5×10^{-4} *M* CTABr in each drive syringe.

TABLE V

EFFECT OF IGEPAL ON THE WATER REACTION[a]

c_{OAc^-}, *M*	k_ψ, sec^{-1}
0.45	12.4[b]
0.013	12.7
0.065	11.5
0.20	12.7
0.45	12.7

[a] At 25.0° and 10^{-4} *M* Igepal with R^+, 0.05 *M* HCl and 2×10^{-4} *M* in one syringe and sodium acetate in the other. [b] In the absence of Igepal.

ever, Igepal is even more effective than CTABr at inhibiting the ionization of tri-*p*-anisylmethanol; *e.g.*, $\Delta H_R = 1.10$ in 7.5×10^{-4} *M* CTABr,[8] whereas it is 1.52 in 10^{-4} *M* Igepal (Table I). The effect of Igepal upon H_0' (Table II) is slightly smaller than that of CTABr for which $\Delta H_0' = 0.23$ in 5×10^{-3} *M* CTABr.[8]

Water Reaction.—Micelles do not affect the rate of attack of water upon the carbonium ion (Tables III–V). The rate constants are approximately, the same whether

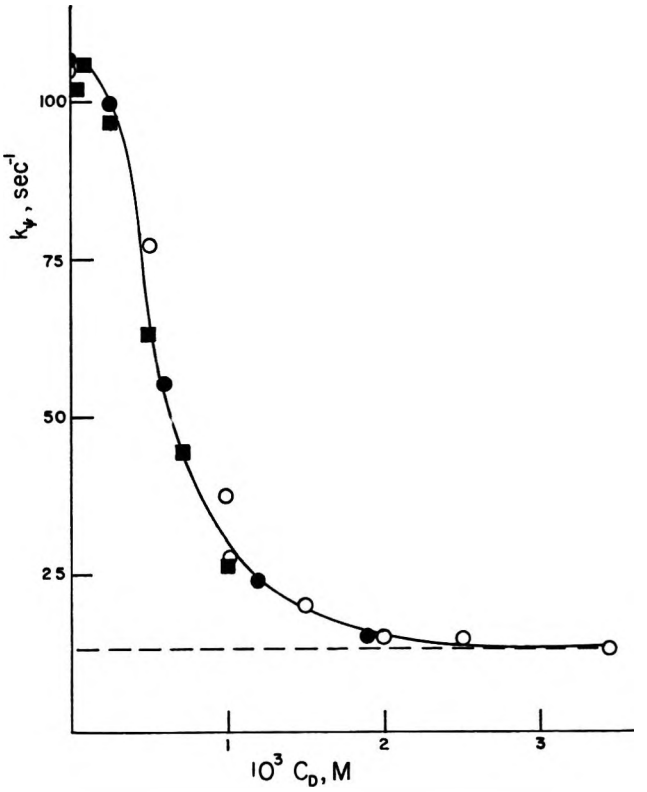

Figure 1.—Effect of NaLS upon the attack of 0.0145 *M* hydroxide ion on the tri-*p*-anisyl carbonium ion. The broken line is for reaction in the absence of hydroxide ion; ■, NaLS, R^+ and 0.1 *M* HCl in one drive syringe; ●, NaLS and OH^- in one drive syringe; ○, NaLS in both drive syringes.

the surfactant was in one or both drive syringes, suggesting that the reaction is much slower than the formation and disruption of the micelles and solute incorporation in them. As expected, acetate ion had little effect on k_ψ.[9,13] The ionization of the alcohol is markedly decreased by both Igepal and CTABr (Table I and ref 8) and we were forced to use them in low concentration ($2.5–5 \times 10^{-4}$ *M*) and even then the low concentration of carbonium ion reduced the accuracy of the rate measurements. Nonetheless the mean values in the presence of CTABr, $k_\psi = 12.8$ sec^{-1}, of Igepal, $k_\psi = 12.4$ sec^{-1}, and of NaLS, $k_\psi = 12.3$ sec^{-1}, are in good agreement with $k_\psi = 12.4$ sec^{-1} obtained in the absence of surfactant.

Reaction with Hydroxide Ion.—As expected, anionic micelles of NaLS protect the carbonium ion from attack by hydroxide ion. In the absence of surfactant, reaction with hydroxide ion is rapid,[9] but high concentrations of hydroxide ion have to be used to increase the reaction rate in the presence of 2.5–5 m*M* NaLS (Tables VI and VII and Figure 1). For concentrations of hydroxide ion below 0.03 *M* the value of k_ψ in 2.5–5 m*M* NaLS is very close to that of the spontaneous reaction of the carbonium ion with water (Tables III and VI and ref 9), and the rate enhancement at higher concentrations is probably caused by attack of hydroxide ion upon that small amount of carbonium ion which is not bound to the micelle. [The values of k_ψ in the absence of surfactant (Table VI) are calculated using $k_2 = 8200$ l. mol^{-1} sec^{-1}, for attack of OH^- upon the carbonium ion[9].]

This inhibition is observed at concentrations of

(13) E. A. Hill and W. J. Mueller, *Tetrahedron Lett.*, 2565 (1968).

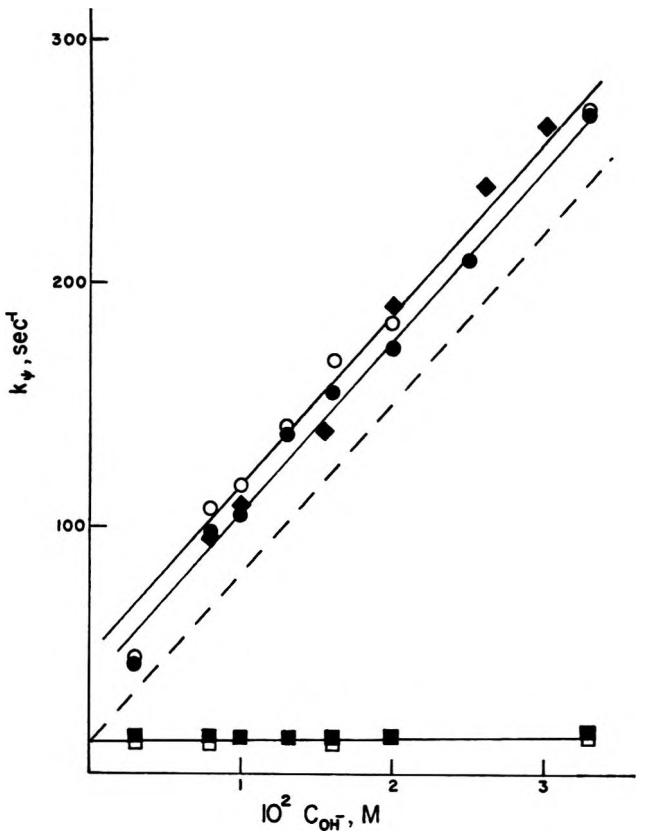

Figure 2.—Effect of surfactants on the reaction with hydroxide ion. The broken line is for reaction in the absence of surfactant; ■, 2.5×10^{-3} *M*; □, 5×10^{-3} *M* NaLS; ●, 5×10^{-4} *M*, ○, 10^{-3} *M* CTABr; ◆, 2×10^{-4} *M* Igepal.

TABLE VI
EFFECT OF HYDROXIDE ION UPON THE REACTION IN NaLS[a]

	10^3 c_D, *M*		
c_{OH^-}, *M*	0	2.5[b]	5.0[c]
0.003	37	15.4	12.9
0.008	79	15.0	13.1
0.010	95	15.2	
0.013	119	15.2	
0.016	145	15.2	14.0
0.020	177	15.4	
0.033	283	16.8	15.9
0.091	756	28.8	
0.100	833		27.6
0.225	1950	71.3	57.7
0.475	3900	198	

[a] Values of k_ψ, sec^{-1} at 25.0°; in the absence of OH^- k_ψ = 12.3 sec^{-1} in NaLS; values in the absence of NaLS are calculated.[9] [b] NaLS with NaOH. [c] NaLS in each syringe.

TABLE VII
EFFECT OF NaLS IN LOW CONCENTRATIONS ON THE HYDROXIDE ION REACTION[a]

10^4 c_D, *M*	k_ψ, sec^{-1}
	107
0.025	106
0.25	101
1.0	106[c]
2.5	96.9[b]
2.5	100
5.0	63.4[b]
5.0	77.0[c]

[a] At 25.0° in 1.45×10^{-2} *M* NaOH, R^+ in 0.05 *M* HCl in one syringe, NaOH + NaLS in the other. [b] R^+ and NaLS in one syringe. [c] NaLS in both syringes.

NaLS below the critical micelle concentration (cmc), but it is possible that micellization is induced by the carbonium ion.[14]

Equilibration of the carbonium ion with the anionic micelle must be relatively fast because k_ψ depends only slightly upon the way in which the solutions in the drive syringe are made up.

It was difficult to follow this reaction in the presence of CTABr and Igepal, which depress the acid ionization of the alcohol, but the kinetic effects of these surfactants are small (Figure 2). It is possible that we would have seen larger rate enhancements had we been able to use greater than 10^{-3} *M* CTABr. We note that Duynstee and Grunwald observed relatively large rate enhancements of the reaction of hydroxide ion with a number of stable triphenylmethyl dye cations by cationic micelles, but they were able to use relatively high surfactant concentrations.[2] The relatively small rate enhancements which we observe are understandable because electrostatic repulsions between a carbonium ion and a cationic micelle should oppose hydrophobic binding to the micelle and therefore hinder incorporation of the carbonium ion in the micellar pseudophase.

The small rate enhancement by Igepal (Figure 2) suggests that there is a small interaction between the carbonium ion and the nonionic micelles, possibly involving a base-catalyzed attack of the hydroxyl head groups of Igepal.

Reaction with Azide Ion.—Micellar effects upon the attack of azide ion upon the carbonium ion follow the pattern observed for the hydroxide ion reaction. Anionic micelles of NaLS suppress the reaction completely, but cationic micelles of CTABr and nonionic micelles of Igepal have little effect and the rate constants are similar to those found in water (Table VIII).

TABLE VIII
EFFECT OF SURFACTANTS UPON REACTION WITH AZIDE ION[a]

10^5 $c_{N_3^-}$, *M*	Surfactant			
	NaLS[b]	CTABr[c]	Igepal[c]	None[d]
1.25	14.3			180
1.55			159	200
2.35			210	240
2.5	13.7	267		250
2.5		292		
3.1			238	280
4.7			315	380
5.0	13.8	405		395
6.25			450	470
9.4			650	650
10.0	13.8	725		680
12.5			850	825

[a] Values of k_ψ, sec^{-1}, at 25.0° and 10^{-3} *M* NaOH and 0.025 *M* NaCl. [b] 5×10^{-3} *M* NaLS. [c] 5×10^{-4} *M* CTABr and Igepal. [d] Values of k_ψ in the absence of surfactant are from ref 9.

In water initial attack of azide ion gives an equilibrium mixture of the alkyl azide and the carbonium ion, and is followed by a slow conversion to the thermodynamically more stable tri-*p*-anisylmethanol.[9] The difference between the absorbance after the initial reaction is complete and that at time infinity gives the

(14) For NaLS, cmc = 6–9 × 10^{-3} *M* depending upon the method used.[15]
(15) P. Mukerjee and K. J. Mysels, "Critical Micelle Concentrations of Aqueous Surfactant Solutions," NSRDS–NBS, Washington, D. C., 1971.

amount of carbonium ion at the initial equilibrium, and $K_N \approx 7 \times 10^4$ l. mol^{-1} in water.[9]

$$ROH \underset{\text{slow}}{\overset{H_2O}{\longleftarrow}} R^+ + N_3^- \overset{K_N}{\rightleftharpoons} RN_3$$

A similar phenomenon is observed in CTABr, and the association constant, K_N, is slightly larger than in water (Table IX). (There is considerable uncertainty in these values of K_N because of the low initial concentration of R^+ in the presence of CTABr.)

TABLE IX

EQUILIBRIUM CONSTANT FOR THE FORMATION OF ALKYL AZIDE IN CTABr[a]

$10^5 c_{NaN_3}$, M	Absorbance	K_N, l. mol^{-1}
2.5	0.022	1.5×10^5
2.5	0.026	1.3×10^5
5.0	0.019	1.0×10^5
5.0	0.019	1.0×10^5
10.0	0.010	1.0×10^5
10.0	0.009	1.1×10^5

[a] At 25.0°. [b] At the initial "equilibrium;" the absorbance of R^+ before reaction is 0.108.

Igepal has little effect upon the rate constant for attack of azide ion (Table VIII) and in this system the initial reaction leads to complete disappearance of the carbonium ion. *i.e.*, K_N is very large. Nonionic micelles of Igepal should stabilize the alkyl azide relative to the carbonium and azide ions. Simple electrostatic considerations suggest that a cationic micelle should have little effect upon the equilibrium between the alkyl azide and the carbonium and azide ions, as is observed.

Discussion

Formation and Reaction of the Carbonium Ion.—For reaction 1, $K_a = k^f/k^b$, and, because K_a, as measured by ΔH_R (the change in H_R) is very sensitive to added micelles (Table I and ref 8) whereas k^f is not (Tables III–V), the rate constant for the acid heterolysis of the alcohol is sharply increased by micelles of NaLS and decreased by micelles of CTABr and Igepal. These rate effects are shown in Table X calculated from k^f and k^b in water[9] and ΔH_R, for surfactant concentrations which are convenient for the measurement of ΔH_R (Table I). These micellar effects are in the direction generally observed for acid-catalyzed reactions.[5,6,16]

(16) M. T. A. Behme and E. H. Cordes, *J. Amer. Chem. Soc.*, **87**, 260 (1965); M. T. A. Behme, J. G. Fullington, R. Noel, and E. H. Cordes, *ibid.*, **87**, 266 (1965); R. B. Dunlap and E. H. Cordes, *ibid.*, **90**, 4395 (1968); C. A. Bunton and L. Robinson, *ibid.*, **91**, 6072 (1969).

TABLE X

MICELLAR EFFECTS UPON FORMATION OF THE CARBONIUM ION[a]

Surfactant	c_D, M	k_b, l. mol^{-1} sec^{-1}
NaLS	5×10^{-3}	1.8×10^6
CTABr	10^{-3}	3
Igepal	10^{-4}	3.8

[a] At 25.0°; in the absence of surfactant k^b = 79 l. mol^{-1} sec^{-1}; see ref 9.

Micelles of both CTABr and NaLS solubilize tri-*p*-anisylmethanol,[8] and this stabilization of the initial state should, of itself, reduce k^b. However, these initial state effects upon the alcohol are small compared with the overall effects upon k^b.

The absence of any effect of cationic micelles of CTABr upon k^f (the first-order rate constant for attack of water upon R^+) is readily understandable if most of the carbonium ion is in the aqueous phase rather than in the micellar pseudophase (but see ref 2). Igepal behaves similarly to CTABr in having no effect on k^f and decreasing k^b, suggesting that the alcohol can enter the nonionic micelle which protects it from the hydronium ion. There are a number of ion–molecule reactions which are inhibited by nonionic micelles.[6,17] The carbonium ion, on the other hand, must be in the aqueous phase or in the exterior of the nonionic micelle where it can be attacked by water.

Inhibition of anionic attack and analogy with other systems show that the tri-*p*-anisyl carbonium ion is taken up strongly by anionic micelles of NaLS, even though there is no effect upon k^f. If the bulk of R^+ is in the micellar pseudophase the relative stabilities of R^+ and the transition state are unaffected by incorporation in the micelles, suggesting that the carbonium ion is close to the water-rich micellar surface.

Reactions with Ionic Nucleophiles.—The micellar effects upon the reaction of the tri-*p*-anisyl carbonium ion with anions accord very well with earlier observations and can be rationalized in terms of dominant electrostatic interactions. The very marked inhibition by NaLS of anion attack upon R^+ shows that the carbonium ion must be taken up very strongly by anionic micelles, but into a region of the micelle where it is open to attack of water.

Registry No.—Tri-*p*-anisyl carbonium ion, 28550-87-0; NaLS, 2386-53-0; tri-*p*-anisylmethanol, 3010-81-9; water, 7732-18-5; CTABr, 57-09-0; hydroxide ion, 14280-30-9; azide ion, 14343-69-2.

(17) C. A. Bunton and L. Robinson, *J. Org. Chem.*, **34**, 773 (1969).

The Decomposition of Cumyl Peracetate in Nonpolar Solvents

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Cumyl peracetate decomposes in toluene by competing radical and ionic paths. The ionic reaction is catalyzed by added acid with a Brønsted coefficient of 0.56. In carbon tetrachloride the reaction is somewhat erratic but exhibits good first-order kinetics in the presence of added pyridine, which also slows down the reaction. In carbon tetrachloride without added pyridine or with only a small amount, the products are again characteristic of mixed ionic and radical reaction paths. In 0.1 *M* pyridine in CCl_4, the reaction appears to be entirely a radical process. Iodine traps radicals from the reaction in toluene, giving benzyl iodide, but also catalyzes the ionic reaction both in toluene and in carbon tetrachloride.

In nitrobenzene and in acetic acid, cumyl peracetate has been shown to give the ionic Criegee rearrangement exclusively, with very nearly quantitative yields of acetic acid, acetone, and phenol after hydrolysis.[1] In the present paper we wish to report the rather different behavior of cumyl peracetate in the nonpolar solvents toluene and carbon tetrachloride.[2]

The proportion of the reaction going by radical paths can be judged from the yield of carbon dioxide, supported by the yields of acetophenone or cumyl alcohol.

Results

Toluene.—In toluene at 100° the mean rate constant for the decomposition of cumyl peracetate is (3.43 ± 0.06) × 10^{-5} sec^{-1} for carefully degassed reaction mixtures, and approximately (3.13 ± 0.29) × 10^{-5} sec^{-1} for nondegassed reaction mixtures. Within the analytically convenient range 0.02–0.10 *M* the rate constant is insensitive to changes in the initial concentration of the perester. It is also insensitive to the presence of added pyridine or water or smooth Pyrex beads. Freshly crushed Pyrex, however, increased the rate constant by 40%. The reaction products are given in Table I. Phenyl moieties could be accounted for completely in this solvent.

The decomposition of 0.1 *M* cumyl peracetate in the presence of 0.01 *M* trichloroacetic acid in toluene at 100° gave a greatly increased yield (83%) of the Criegee rearrangement product, 2-phenoxypropene. The reaction is catalyzed by carboxylic acids in general, with a Brønsted α of 0.56 (based on acetic, chloroacetic, dichloroacetic, trichloroacetic, and β-chloropropionic acids). The decomposition of the perester (0.025 *M*) in toluene at 100° in the presence of 0.036 *M* I_2 consumed I_2 at a constant ratio of only 0.48 mol per mole of ester as the ester decomposed. The rate of disappearance of ester was about 5% greater in the presence of the iodine and was observed to decrease somewhat during the run. Benzyl iodide was a product.

The substitution of three deuterium atoms for hydrogen in the acetoxy moiety of the perester decreased the rate constant by only 7% and had little effect on the nature of the products. Substitution of six deuteriums in the methyl groups of the cumyloxy moiety again decreased the rate constant by only 7% and increased the yield of CO_2 from its original value of 75% to 82%.

TABLE I

PRODUCTS FROM THE DECOMPOSITION OF CUMYL PERACETATE[a,b]

Product	Solvent and concentration of added pyridine, *M*: Toluene, 0	CCl_4, 0	CCl_4, 5×10^{-4}	CCl_4, 0.1
Methane	80	75[g]	77	22
Carbon dioxide	75	79	*c*	93
Methyl chloride		30[g]	*c*	111
Acetophenone	32[f]	33[g]	33	59
Cumyl alcohol	35[f]	0	0	0
Bibenzyl	34			*h*
2-Phenoxypropene	25[d,e]	16[d]	12[d]	0
α-Methylstyrene	0	9	7	Trace

[a] At 100° and with 0.1 *M* initial perester. [b] Yields in per cent moles per mol of perester. [c] CO_2 plus CH_3Cl was 127%. [d] As phenol, after hydrolysis. [e] In the presence of 0.01 *M* trichloroacetic acid the yield of this product was increased to 83%. [f] A similar experiment with dicumyl peroxide at 100° in toluene gave 114% acetophenone and 81% cumyl alcohol. [g] A similar experiment with dicumyl peroxide in CCl_4 at 100° gave 43% CH_4, 71% CH_3Cl, and 132% acetophenone. [h] 42% hexachloroethane.

Carbon Tetrachloride.—In this solvent at 100° the rate of decomposition of cumyl peracetate is erratic. Individial runs usually show increasing first-order rate constants and the rate constants are appreciably higher for runs of higher initial concentration. For example, the value at 0.05 *M* is (4.68 ± 0.20) × 10^{-5} sec^{-1} compared with 4.9 × 10^{-5} sec^{-1} at 0.10 *M* and 5.5 × 10^{-5} sec^{-1} at 0.20 *M*. The products from degassed 0.1 *M* solutions at 100° are shown in Table I. Only 58% of the phenyl groups could be accounted for.

An experiment with cumyl peracetate hexadeuterated in the methyl groups of the cumyl moiety, in CCl_4 at 100°, gave substantial quantities of CD_4, CD_3H, CH_4, and CH_3D. An experiment with perester deuterated in all three methyl groups gave both CD_3H and CD_4.

Erratic kinetics for the decomposition of acid-sensitive peresters are not at all uncommon.[3] The usual procedure is to add pyridine, which often slows the reaction and simplifies the kinetics. Small amounts of pyridine added to solutions of cumyl peracetate in CCl_4 considerably reduced the rate constant and simultaneously improved the precision and fit of the first-order plots. As shown in Figure 1, the effect on the rate levels off at about 0.04 *M* pyridine and $k = 2.85 \times 10^{-5}$ sec^{-1}. The products (Table I) are not very much affected by 0.0005 *M* pyridine, although this amount

(1) V. A. Yablokov, V. A. Shuskunov, and L. V. Kolyaskina, *Zh. Obshch. Khim.*, **32**, 2174 (1962).

(2) F. E. Scrivener, Jr., Dissertation, Florida State University, 1970.

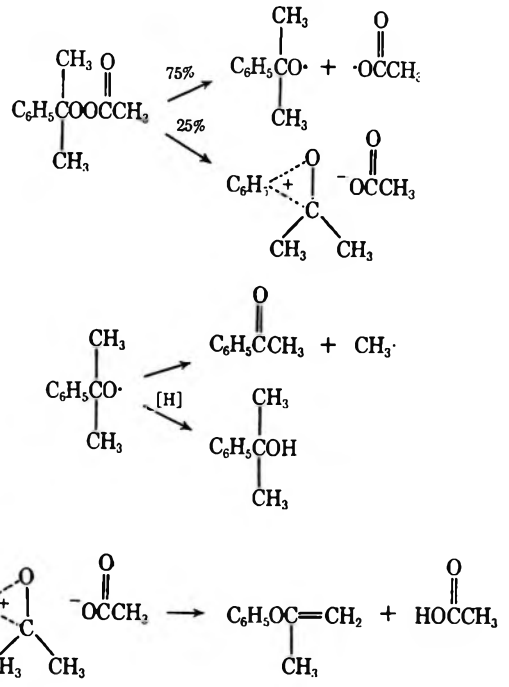
(3) (a) P. D. Bartlett and D. M. Simons, *J. Amer. Chem. Soc.*, **82**, 1753 (1960); (b) P. D. Bartlett and R. R. Hiatt, *ibid.*, **80**, 1398 (1958); (c) F. D. Greene, W. Adam, and G. A. Knudsen, Jr., *J. Org. Chem.*, **31**, 2087 (1966).

decreases the rate constant by about 15%. In 0.1 *M* pyridine, however, the products are quite different, while the rate constant is lower by about 35–40%.

Thiophenol, Koelsch's radical, and iodine were used unsuccessfully in an attempt to separate radical-induced and unimolecular components of the decomposition rate in CCl_4.[2,4]

Discussion

The decomposition of cumyl peracetate in toluene is clearly about 75% radical, judging from the yields of CO_2, acetophenone, cumyl alcohol, and bibenzyl. The remaining 25% is ionic, corresponding to the yield of the Criegee rearrangement–elimination product.



The yield of cumyl alcohol as opposed to acetophenone is greater in the decomposition of the perester than in the decomposition of dicumyl peroxide. This is reasonable in view of the higher concentration of hydrogen-donating radicals such as dimethylcyclohexadienyl in the decomposition of the perester. The major reaction giving cumyl alcohol is probably a disproportionation of the cumyloxy and dimethylcyclohexadienyl radicals, since attack of the latter radical on the perester should be at the less hindered and more electronegative peroxide oxygen of the acetoxy moiety.

The small isotope effects on the rate and on the product yields are consistent with a nonconcerted radical reaction in which the acetoxy radical decarboxylates in a second step. They are also consistent with a concerted ionic reaction in which the aliphatic protons of the cumyloxy moiety have at most only a weak hyperconjugative interaction with the developing positive charge.

The magnitude of the Brønsted α is close to that for the decomposition of several diacyl peroxides which also decompose in part by an ionic route in the absence of catalysts.[5]

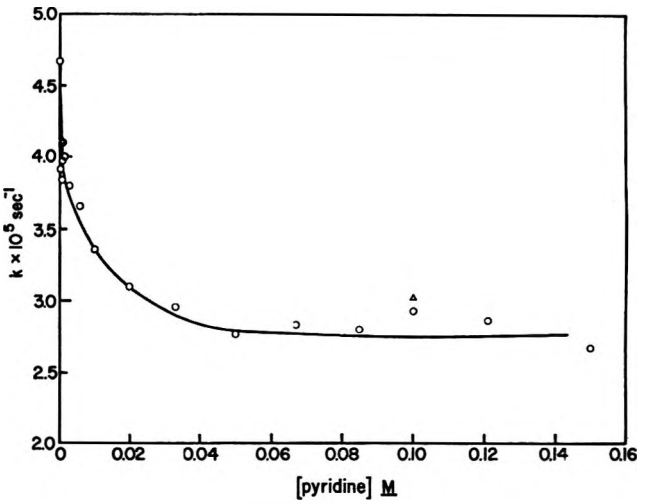


Figure 1.—Effect of added pyridine on the rate in CCl_4 at 100°. The initial perester concentration was 0.05 *M* except for the runs indicated by Δ (0.10 *M*).

The low uptake of iodine in the decomposition in toluene cannot be due entirely to cage recombination in view of the high yield of noncage products. It is probably due in part to the known inefficiency of iodine as a radical trap and in part to the ability of iodine to function as a Lewis acid, which might catalyze the ionic reaction. If catalysis of the ionic reaction did indeed occur, iodine must also have prevented some induced decomposition, since the total rate is not sufficiently enhanced to accommodate a greatly accelerated ionic process without some deceleration of the free-radical process.

The fast, erratic, and partly ionic reaction in CCl_4 is made slower, kinetically simpler, and almost entirely radical by adding 0.1 *M* pyridine. In previous examples,[3] the kinetic effect of pyridine has been attributed to quenching of acid catalysts, either adventitious or products of the decomposition reaction itself. In the present case a possible catalyst might be HCl formed by elimination from some minor product. We prefer this to the alternative explanation in terms of quenching of ionic or ion-pair chain carriers.

The other notable effect of added pyridine is the shift from methane to methyl chloride as the major isolable product of the reaction of methyl radicals. The isotope experiments in CCl_4 without added pyridine showed that the methyl radicals extracted their fourth hydrogen atoms from every conceivable source, both aromatic and aliphatic. In the presence of pyridine the methyl radicals appear to be more selective, reacting preferentially with the weaker C–Cl bonds of the solvent.

Experimental Section[2]

Cumyl Peracetate.—Commercial cumene hydroperoxide, purified *via* its sodium salt, was converted into the peracetate by treatment with acetyl chloride and pyridine in pentane at 0°.[1] The disappearance of perester in the kinetic runs was followed either by means of the carbonyl band at 1786 cm^{-1} or by iodometric titration. The titration procedure was essentially that of

(4) Cumyl peracetate plus iodine is stable in refluxing CCl_4 solution, but decomposes overnight at room temperature if *solid* I_2 is present. Besides phenol and acetic acid, one of the products of this reaction appears to be 2,4,4-trimethyl-1,4-benzopyran or an isomeric trimethyl-1,4-benzopyran.[2]

(5) (a) J. E. Leffler, *J. Amer. Chem. Soc.*, **72**, 67 (1950); (b) J. E. Leffler and A. A. More, *ibid.*, **94**, 2483 (1972).

Silbert and Swern,[6] a ferric chloride catalyzed reaction of the perester with sodium iodide. Since the reaction is not quantitative, a standardized analytical procedure must be carefully adhered to. The concentration of perester is a linear function of the volume of thiosulfate needed to titrate the iodine liberated, but the blank and the slope of the relationship differ somewhat from solvent to solvent.

Reaction Products.—Products were determined by means of standard gas analytical techniques and by gas–liquid chromatography. Chromatographic peaks were identified by retention time and by their infrared spectra using an attenuated total reflectance device.

(6) L. S. Silbert and D. Swern, *Anal. Chem.*, **30**, 385 (1958).

Registry No.—Cumyl peracetate, 34236-39-0; toluene, 108-88-3; CCl_4, 56-23-5; pyridine, 110-86-1.

Acknowledgment.—The authors wish to acknowledge support of this work by the Army Research Office, Durham, and in part by the Institute of Arthritis and Metabolic Diseases.

Synthesis of Hydroazulenes by Solvolytic Rearrangement of 9-Methyl-1-decalyl Tosylates[1]

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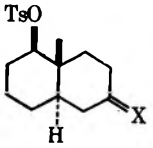
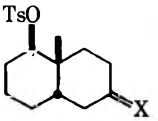
9-Methyl-1-decalyl *p*-toluenesulfonates **1**–**4** and **3**-*d* have been synthesized and their solvolyses studied. Trans-fused tosylates **1** and **2** yield predominantly hydroazulenes (**54**, **55**, **33**, and **36**). *cis*-Keto tosylate **3** yields predominantly the unrearranged octalones **13** and **15**. *cis*-Deoxy tosylate **4** yields substantial amounts of both rearranged products (hydroazulenes **33** and **36**) and unrearranged octalins **14** and **18**. No methyl-migrated rearrangement products are obtained in any case. Tosylates **1**–**4** undergo first-order acetolysis at 100° with relative rates of 1:319:10.8:352. *cis*-Keto tosylate **3** solvolyzes 1.55 times faster than its monodeuterated analog, **3**-*d*. The results are interpreted in terms of a mechanism involving rate-limiting ionization, without participation of the rearranging bond, to an intimate ion pair, which undergoes stereospecific rearrangement to yield hydroazulene or deprotonation to yield hydronaphthalene. With the *cis*-keto tosylate **3**, a conformation is available in which the initial ion pair may decompose with hydride participation to yield a new decalyl cation **58**, the immediate precursor of the unrearranged products

We have recently discussed a stereorational route to guaiazulenic sesquiterpenes which involves (a) construction of an appropriate decalinic intermediate, (b) establishment of the relative stereochemistry of the eventual guaiazulene using established conformational principles, and (c) solvolytic rearrangement of the intermediate to the required hydroazulene.[5] The route has been applied to the total synthesis of the sesquiterpenes bulnesol,[5,6] α-bulnesene,[5] and kessane.[6] As a prelude to that work, we studied, as model substances, the solvolysis of the 9-methyl-1-decalyl-*p*-toluenesulfonates **1**–**4**. In this paper we report the results of those preliminary studies.



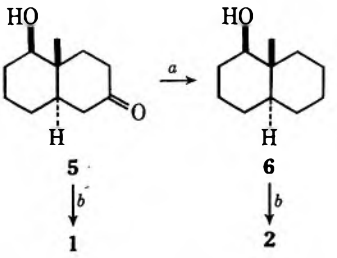
1, X = O
2, X = H_2



3, X = O
4, X = H_2

Synthesis of Tosylates 1–4.—The trans-fused tosylates **1** and **2** were synthesized from keto alcohol **5**[7] as outlined in Scheme I.

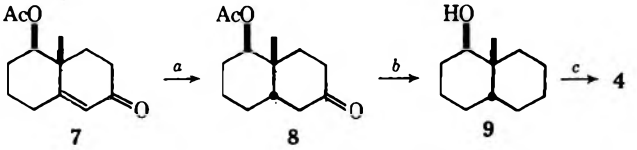
SCHEME I



[a] Wolff-Kishner reduction. [b] *p*-Toluenesulfonyl chloride, pyridine.

The *cis*-keto tosylate **3** was prepared by a route previously reported.[8] *cis*-Deoxy tosylate **4** was prepared from acetate **7**[9] as outlined in Scheme II.

SCHEME II



[a] H_2–Pd/$SrCO_3$. [b] Wolff-Kishner. [c] *p*-Toluenesulfonyl chloride, pyridine.

The configuration at the three centers of asymmetry in tosylates **1**–**4** follows from the methods of synthesis. Corroborative evidence is obtained from pmr spectroscopy. Recent observations of the proton signals adjacent to the *p*-toluenesulfonate group in the four isomeric 1-decalyl tosylates indicate a half-band

(1) Presented in preliminary form: (a) C. H. Heathcock, R. Ratcliffe, and C. Quinn, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 10, 1969; (b) C. H. Heathcock and R. Ratcliffe, *Chem. Commun.*, 994 (1968).

(2) Fellow of the Alfred P. Sloan Foundation, 1967–1969.

(3) National Institutes of Health Predoctoral Fellow, 1967–1970.

(4) Participant in a National Science Foundation Summer Research Program for High School Teachers, 1968.

(5) C. H. Heathcock and R. Ratcliffe, *J. Amer. Chem. Soc.*, **93**, 1746 (1971).

(6) M. Kato, H. Kosugi, and A. Yoshikoshi, *Chem. Commun.*, 185, 934 (1970).

(7) A. J. Birch, E. Pride, and H. Smith, *J. Chem. Soc.*, 4688 (1958).

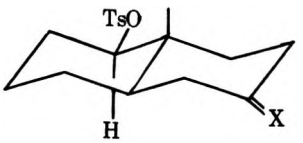
(8) C. H. Heathcock, R. A. Badger, and J. W. Patterson, Jr., *J. Amer. Chem. Soc.*, **89**, 4133 (1967).

(9) C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 2680 (1960).

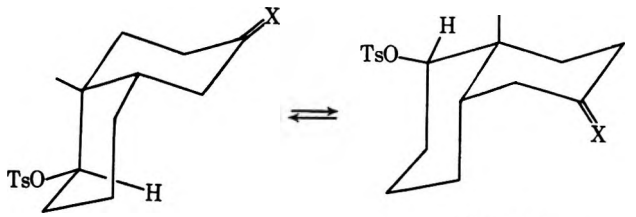
width of 18–20 Hz for an axial proton and 6 Hz for an equatorial proton.[10] An apparent exception, in which this resonance has a half band width of 13 Hz, was attributed to conformational equilibrium.

Similar results were obtained for tosylates **1**–**4**. Half band widths of 17–18 Hz for compounds **1**, **2**, and **4** are indicative of an equatorially disposed *p*-toluenesulfonate group, while the $W_{1/2}$ of 12 Hz for isomer **3** suggests a mixture of conformations.[10] The trans-fused tosylates **1** and **2** have available only a single low-energy conformation, in which the *p*-toluenesulfonate group is equatorial.

Analysis of the cis-fused tosylates **3** and **4** is complicated by conformational equilibrium. The observed $W_{1/2}$ of 17 Hz for compound **4** indicates a preponderance of conformation **4a**, whereas the value of 12 Hz for compound **3** suggests a more equal population of conformations **3a** and **3b**. For the *cis*-deoxy compound **4**, the steroid conformation **4a** should predominate to the extent that the *p*-toluenesulfonate grouping prefers an equatorial position.[11] Introduction of the carbonyl group brings the "3-alkyl ketone effect" into play,[12] thus reducing the energy of conformer **3b** relative to that of **3a**.[13]



1, X = O
2, X = H_2



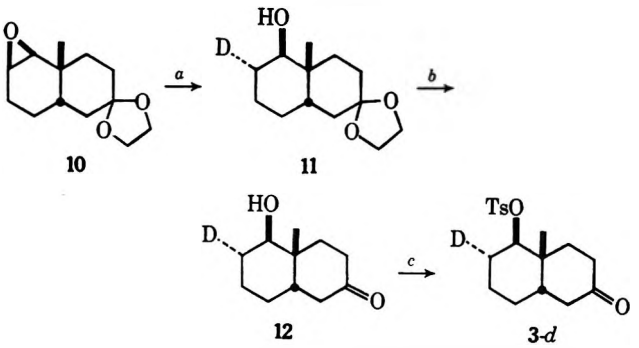
3a, X = O
4a, X = H_2

3b, X = O
4b, X = H_2

A deuterium analog of the *cis*-keto tosylate **3**, which was used subsequently for mechanistic studies, was synthesized from the known ketal epoxide **10**[8] as shown in Scheme III. Since epoxide **10** is known to suffer nucleophilic ring-opening at the less hindered position,[8] the structure of the deuterated tosylate may be assigned as **3**-*d*. Compound **12** was shown by mass spectrometry to contain 0.97 atom of deuterium per molecule.

Synthesis and Identification of Solvolysis Products.— Preliminary experiments showed that, although tosylates **1**–**4** undergo solvolysis to give only two or three major products in each case, several minor products are formed (*vide infra*). Since we planned to analyze our solvolysis mixtures by capillary glpc (see Experimental Section), we synthesized a number of possible products. Other solvolysis products were isolated and identified by a combination of spectroscopy and degradation. The presence of one solvolysis product was inferred from indirect evidence (*vide infra*).

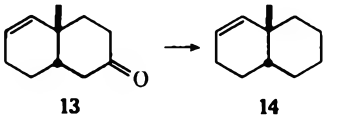
SCHEME III



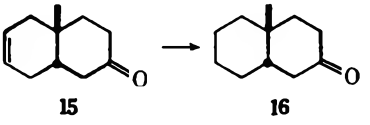
10 **11** **12** **3-*d***

[a] $LiAlD_4$. [b] H_3C^+. [c] *p*-Toluenesulfonyl chloride, pyridine.

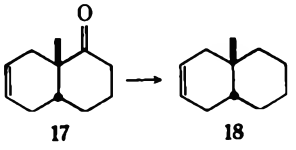
Octalone **13** was prepared as previously reported.[8] Wolff–Kishner reduction of **13** gave octalin **14**. Octalone **15**, which was isolated from a solvolysis of the *cis*-keto tosylate **3**, was shown to have an unrearranged skeleton by its hydrogenation to *cis*-decalone **16**.[14] The corresponding hydrocarbon, compound **18**, was prepared by Wolff–Kishner reduction of the known octalone **17**, the Diels–Alder adduct of 1,3-butadiene and 2-methylcyclohexenone.[15]



13 **14**

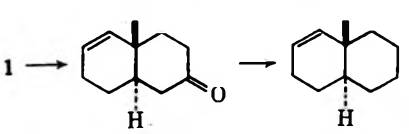


15 **16**



17 **18**

The trans-fused octalone **19** was prepared by refluxing *trans*-keto tosylate **1** with lithium chloride in dimethylacetamide. The crystalline octalone **19** is obtained in 70% yield. Wolff–Kishner reduction of octalone **19** yields the corresponding hydrocarbon **20**. Because of the severe treatment necessary to dehydro tosylate **1**,[16] and since the more stable location for a double bond in a *trans*-decalin is between carbons



19 **20**

(10) C. A. Grob and S. W. Tam, *Helv. Chim. Acta*, **48**, 1317 (1965).

(11) Jensen gives the *A* value of the *p*-toluenesulfonate group at −80° in CS_2–$CDCl_3$ as 0.515 ± 0.021 kcal/mol: F. R. Jensen, C. H. Bushweller, and B. H. Beck, *J. Amer. Chem. Soc.*, **91**, 344 (1969).

(12) W. Klyne, *Experientia*, **12**, 119 (1956).

(13) Allinger gives a value of 0.6 kcal/mol for the 3-alkyl ketone effect when the alkyl group is methyl: N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, **84**, 2201 (1962).

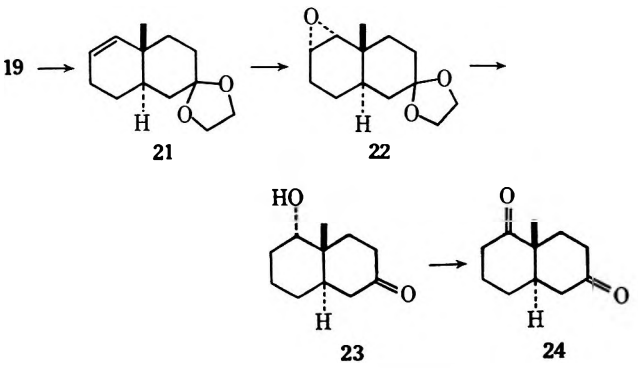
(14) W. G. Dauben, J. B. Rogers, and E. J. Blanz, *ibid.*, **75**, 6384 (1954).

(15) A. M. Gaddis and L. W. Butz, *ibid.*, **69**, 117 (1947).

(16) Compound **1** is recovered unchanged (98% recovery) after refluxing in pyridine for 48 hr. In contrast, isomer **3** undergoes smooth dehydrotosylation when refluxed in this solvent for 16 hr.[8]

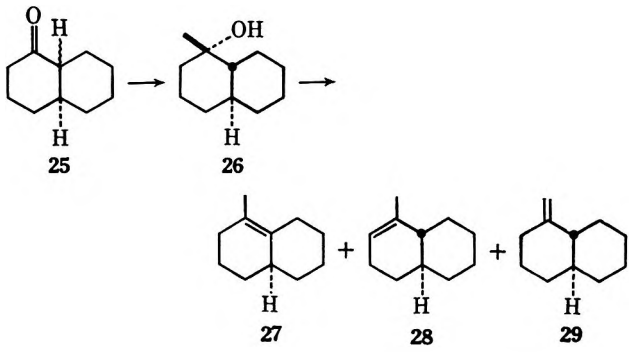
2 and 3,[17] we sought independent confirmation for structure **19**.[18]

Ketalization of **19** gives a crystalline dioxolane **21**, which is oxidized by *m*-chloroperbenzoic acid to obtain a single crystalline oxide, **22**, in 67% yield. That only one epoxide is formed is shown by pmr spectroscopy (a single angular methyl resonance at τ 9.07) and glpc. The assigned stereochemistry of the epoxide ring is based on the assumption that the *trans*-decalone **21** suffers predominant electrophilic attack from the less hindered face. Reduction of **22** with lithium aluminum hydride, followed by ketal hydrolysis, gives a ketol **23** (clearly different from ketol **5**) which is oxidized by Jones reagent[19] to the known diketone **24**.[7]

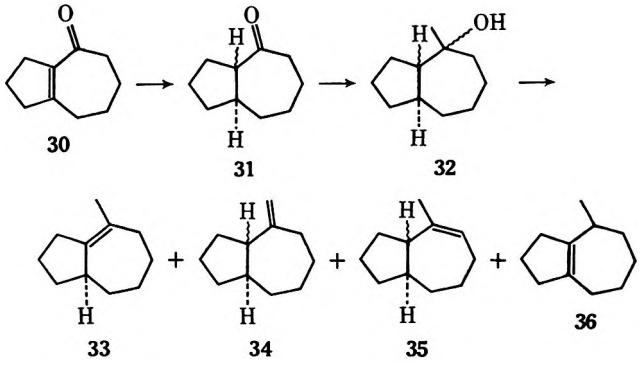


In order to examine the possibility of methyl-migrated decalinic products in the solvolysis mixtures, a mixture of 1-methyloctahydronaphthalenes was synthesized. Hydrogenation of 1-naphthol by the method of Meyers[20] affords a mixture of 1-decalols and 1-decalones. Oxidation of this mixture by Jones reagent,[19] followed by equilibration with aqueous sulfuric acid–benzene, yields a 9:1 mixture of epimeric 1-decalones (**25**) with the trans isomer predominating. Treatment of this mixture with methyllithium in ether gives, after chromatographic purification, the tertiary carbinol **26**. Treatment of alcohol **26** with phosphoryl chloride in pyridine affords a hydrocarbon mixture in 87% yield. Capillary glpc analysis reveals that the product is a mixture of four compounds in a ratio of 65:20:12:3. Analysis of the pmr spectrum, using the signals at τ 8.42 (vinyl methyl), 5.45 (exocyclic methylene), and 4.78 (endocyclic vinyl proton), indicates that the three major products are isomers **27** (65%), **28** (20%), and **29** (12%).

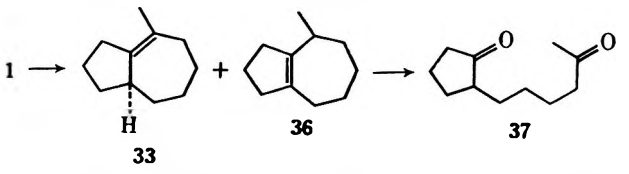
A similar mixture of 4-methyloctahydroazulenes was synthesized from the known enone **30**.[21] Lithium–ammonia reduction of **30** gives a 60:40 mixture of decahydroazulenones **31**, in which the more stable trans-fused isomer[22] is presumed to predominate. Treatment of **31** with ethereal methyllithium gives a



carbinol mixture **32**, which reacts with phosphoryl chloride in pyridine to give a hydrocarbon mixture. Capillary glpc analysis reveals that the mixture contains five components in a ratio of 72:15:10:2:1. The major dehydration product was obtained in a pure state by preparative glpc. It was assigned structure **33** on the basis of its pmr spectrum (vinyl methyl absorption at τ 8.37, no vinyl proton resonance) and the degradative evidence to be given below. The pmr spectrum of the crude dehydration product has absorption at τ 5.35 (exocyclic methylene) and 4.52 (endocyclic vinyl proton), attributable to compounds of type **34** and **35** (stereochemistry unknown). Coinjection experiments showed that the product formed in 2% yield is isomer **36** (*vide infra*).



Hydrocarbon **33** was also prepared and characterized in the following manner. Acetolysis of *trans*-keto tosylate **1** gives a mixture of four $C_{11}H_{16}O$ bicyclic keto olefins, in the ratio 78:10:7:5 (*vide infra*). Wolff–Kishner reduction of this mixture gives a mixture of four bicyclic $C_{11}H_{18}$ olefins in the same ratio. The major constituent of this mixture is identical, both spectrally and chromatographically, with the major product from the dehydration of **32**. Ozonolysis of the mixture yields a mixture of carbonyl compounds. The major product, purified by preparative glpc, was identified spectrally as **37**.



Hydrocarbon isomer **36** could not be separated from any of the solvolysis or dehydration mixtures in quantities sufficient for direct examination. Its structure was therefore deduced by the following method. A solvolysis mixture (bicyclic $C_{11}H_{18}$ olefinic), shown by isolation and glpc coinjection experiments to be a mix-

(17) (a) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **77**, 2505 (1955); (b) R. Bucourt, *Bull. Soc. Chim. Fr.*, 1262 (1963).

(18) There was actually a further reason to be anxious about the placement of the double bond in **19**. In the pmr spectrum of **19**, the two vinyl protons appear as a sharp singlet. In the cis series, isomer **18** has a sharp two-proton singlet in the vinyl region, but isomer **18** has complex absorption, with both protons clearly discernible as (roughly) tripled doublets.

(19) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(20) A. I. Meyers, W. Beuerung, and G. Garcia-Munoz, *J. Org. Chem.*, **29**, 3427 (1964).

(21) A. G. Anderson and J. A. Nelson, *J. Amer. Chem. Soc.*, **73**, 232 (1951).

(22) J. A. Marshall and W. F. Huffman, *ibid.*, **92**, 6358 (1970).

ture consisting of 78% **33**, 10% **20**, and 5% of another isomer (**36**), was treated with β-naphthalensulfonic acid in refluxing acetic acid. The isomerization was monitored by glpc analysis. After equilibrium had been achieved, the **33**:**20**:**36** ratio had changed from 78:10:5 to 28:14:52 (see Table II). Thus, isomer **36** is obtained at the expense of isomer **33**, and most probably has the same carbon skeleton. Since the pmr spectrum of the equilibrated mixture shows increased saturated methyl absorption at τ 9.08–9.20, corresponding decreased vinyl methyl absorption at τ 8.36, and no new vinyl proton absorption, we have assigned isomer **36** the indicated structure.

Solvolysis of Tosylates 1–4. Products.—Tosylates **1–4** were solvolyzed in buffered acetic acid. Keto tosylates **1** and **3** give mixtures of bicyclic $C_{11}H_{16}O$ keto olefins. Deoxy tosylates **2** and **4** give mixtures of bicyclic $C_{11}H_{18}$ olefins. In order to facilitate comparison, the keto olefin mixtures were submitted to Wolff–Kishner reduction before analysis. The hydrocarbon product mixtures were then analyzed by capillary glpc on two different columns (see Experimental Section). The results are shown in Table I.

TABLE I

ACETOLYSIS PRODUCTS FROM TOSYLATES 1–4[a]

	14	18	20	36	33	Other[b]
Retention time, min	6.20	6.30	6.39	7.12	7.38	
Rel retention time	0.84	0.85	0.87	0.96	1.00	
1	0	0	10	5	78	7 (3)
	0[c]	0[c]	14[c]	52[c]	28[c]	6[c] (2)
2	0	0	0	15	80	5 (2)
3	74	13	0	0	9	4 (2)
4	35	4	0	24	30	7 (2)

[a] Acetolyses were performed at 118° in glacial acetic acid containing 2 equiv of anhydrous KOAc. Keto olefins were reduced to hydrocarbons for analysis. The analyses were performed on a 150 ft × 0.01 in. SF 96 column at 105°. Composition was determined by peak heights ($W_{1/2}$ < 1 mm). [b] The number of unidentified compounds is given in parentheses. [c] Composition of the acid equilibrated mixture.

As shown in Table I, the major acetolysis products from the trans-fused tosylates are hydroazulene olefins. It is notable that the nonrearranged octalin **20**, which is obtained in 10% yield from *trans*-keto tosylate **1**, is not formed at all in the acetolysis of *trans*-deoxy tosylate **2**. Methyl-migrated octalins (*e.g.*, **27**, **28**, or **29**) cannot be detected in the product mixture from either of the trans-fused tosylates. Acetolysis of *trans*-deoxy tosylate **2** is remarkably clean, giving at least 95% of hydroazulene products **33** and **36**.

In the cis-fused series, the situation is much more complicated. The *cis*-keto tosylate **3** gives a total of 87% nonrearranged olefins (**14** + **18**) and only 9% of identifiable hydroazulene product. On the other hand, *cis*-deoxy tosylate **4** gives more rearranged (54%) than nonrearranged material (39%). Again, methyl-migrated products are not produced.

In order to test the effect of reaction conditions on the composition of the product mixtures, deoxy tosylates **2** and **4** were solvolyzed in various media, under various conditions. The results are shown in Table II.

Acetolysis of Tosylates 1–4. Kinetics.—The rates of solvolysis of tosylates **1–4** and tosylate **3**-*d* were determined in acetic acid at 100°. Kinetics were determined by potentiometric titration of the liberated acetic acid with sodium acetate.[23] The infinity titers, observed after at least 10 half-lives at the reaction temperature, were used to calculate first-order rate constants. The results are summarized in Table III. The observed rates are cleanly first order and, as shown in Table III by the small average deviations, are reproducible.

In Table IV, a comparison is made between the kinetic data obtained in this study and that for related compounds **38–42**. Since the substitution pattern at C-9 in tosylates **1–4** can be regarded as two alkyl groups, 2,2-dialkylcyclohexyl tosylates **40** and **41** are particularly suitable models. Comparison of the available data indicates that compounds **2**, **4**, **40**, and **41** solvolyze with nearly identical rates and demonstrates the suitability of the model. Recent studies have shown[24] that pinacolyl brosylate, which undergoes acetolysis three times faster than isopropyl brosylate,[25] solvolyzes in trifluoroacetic acid with rate-determining ionization to a tight ion pair. Similar arguments may be advanced for solvolysis of tosylates **40** and **41**, which are regarded as undergoing rate-determining ionization without participation, even though both yield mainly ring-contracted products.[26] Furthermore, tosylates **2** and **4** solvolyze only 10.3 and 3.2 times faster than their demethyl analogs **38** and **39**, respectively, and about three times faster than cyclohexyl tosylate (**42**). Although small rate increases (tenfold or less) have been attributed to neighboring-group participation,[27] such explanations must be regarded with caution. It appears that the slight rate enhancements found for tosylates **2** and **4** over compounds **38**, **39**, and **42** are the result of ordinary inductive contributions and steric effects.

Mechanistic Considerations.—The solvolysis of *trans*-deoxy tosylate **2** is illustrated in Scheme IV. Solvolysis is assumed to proceed by a slow unimolecular heterolysis to give the short lived "cationoid" species **43**. Since individuality is maintained, as evidenced by the absence of methyl-migrated products, this species probably exists as an intimate ion pair[28] with the departing tosylate anion. In addition, since the kinetic studies reveal no anchimeric assistance to ionization, the products are determined by rapid rearrangement to the thermodynamically more stable carbonium ion **44** (or ion pair) after the first transition state has been passed. It is an important feature of this reaction type that the migrating bond must be suitably placed trans and coplanar to the leaving group in order that the migrating electrons can attack the free lobe of the orbital at C-1 while the tosyl group may still be weakly bonded. Carbonium ion **44** can

(23) W. Winstein, E. Grunwald, and L. L. Ingraham, *J. Amer. Chem. Soc.*, **70**, 821 (1948).

(24) V. H. Shiner, R. D. Fisher, and W. Dowd, *ibid.*, **91**, 7748 (1969).

(25) (a) S. Winstein, B. K. Moore, E. Grunwald, K. C. Schreiber, and J. Corse, *ibid.*, **74**, 1113 (1952); (b) S. Winstein and H. Marshall, *ibid.*, **74**, 1120 (1952).

(26) Table IV, ref *e* and *f*.

(27) D. Bethell and V. Gold, *Quart. Rev., Chem. Soc.*, **12**, 173 (1958).

(28) For a discussion of intimate ion pairs, see J. L. Fry, G. J. Lancelot, L. K. M. Lam, J. M. Harris, R. C. Bingham, D. J. Raber, R. E. Hall, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 2538 (1970), and references cited therein.

TABLE II

SOLVOLYSIS OF TOSYLATES 2 AND 4 UNDER VARIOUS CONDITIONS[a]

Tosylate	Medium	Temp, °C	Time, hr	14	18	20	36	33	Other
2	Pyridine	120	5	0	0	0	4	42	54
	DMAC–LiCl	100	5	0	0	43	14	40	3[b]
	DMSO–$CaCO_3$	100	5	0	0	0	0	~40	~60
	$LiClO_4$–THF–$CaCO_3$[c]	80	5	0	0	0	11	7	82[d]
	80% aqueous EtOH	80	5	0	0	0	8	92	0
	HOAc–KOAc[e]	80	20	0	0	0	10	90	0
	HOAc–KOAc[e]	118	3.5	0	0	0	15	80	5
4	Pyridine[f]	120	17	78	5	0	0	17	0
	$LiClO_4$–THF–$CaCO_3$[c]	80	5	30[g]		0	35	28	9
	80% aqueous EtOH	80	5	57[g]		0	10	17	16
	HOAc–KOAc[e]	75	20	26[g]		0	10	35	29
	HOAc–KOAc[e]	118	3.5	39[g]		0	24	30	7

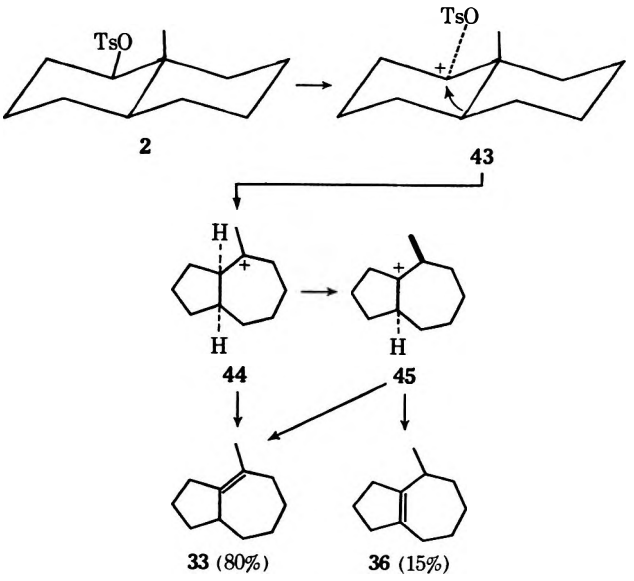
[a] The analyses were performed on a 200 ft × 0.01 in. SF 96 column at 80°. Composition was determined by disc integrator using internal n-$C_{11}H_{24}$ as standard. [b] Products analyzed on 500 ft × 0.03 in. Apeizon L (95%) + Ipegal 880 (5%) at 120°. [c] THF saturated with lithium perchlorate. [d] Seven unidentified volatile products. [e] Glacial acetic acid containing 2 equiv of anhydrous KOAc. [f] Products analyzed by glpc on a 10 ft × 0.25 in. FFAP on AW-DMCS Chromosorb P at 133°. [g] These peaks were insufficiently resolved for accurate division.

TABLE III

ACETOLYSIS RATES OF TOSYLATES 1–4 AND 3-d

Tosylate	Run no.	Temp, °C, ± 0.05	k, min^{-1} ± std dev	k_{avg}, min^{-1}	$t_{1/2}$, min
1	V-70	100.05	$3.59 \pm 0.10 \times 10^{-4}$		
	I-254	100.01	$3.63 \pm 0.09 \times 10^{-4}$	3.61×10^{-4}	1920
2	V-58	100.01	$1.18 \pm 0.04 \times 10^{-1}$		
	V-66	99.91	$1.11 \pm 0.03 \times 10^{-1}$	1.15×10^{-1}	6.0
3	V-28	100.01	$3.95 \pm 0.09 \times 10^{-3}$		
	V-51	100.01	$3.85 \pm 0.08 \times 10^{-3}$	3.90×10^{-3}	178
4	V-32	99.95	$1.25 \pm 0.03 \times 10^{-1}$		
	V-43	99.82	$1.29 \pm 0.04 \times 10^{-1}$	1.27×10^{-1}	5.5
3-d	V-74	100.02	$2.52 \pm 0.06 \times 10^{-3}$	2.52×10^{-3}	275

SCHEME IV



undergo direct deprotonation to give the major observed product of the reaction, or it can undergo a secondary hydride transfer to give a new tertiary carbonium ion **45**, which can deprotonate to yield either of the two hydroazulene double bond isomers.

In contrast to the situation for the trans compound, the *cis*-deoxy tosylate **4** has two conformations available to it, either of which may react (see Scheme V). The conformer with the tosylate moiety equatorial (**4a**) has the optimum geometry for bond migration, that is, an anti-coplanar relationship of the central bond and the tosylate group. Thus, rate-determining ionization to intimate ion pair **46**, followed by rapid skeletal reorganization, affords tertiary carbonium ions **47** and **48**. Deprotonation gives hydroazulenes **33** and **36**. On the other hand, the conformer with the tosylate group axial (**4b**) has the central bond and the tosylate group in a syn-clinical relationship, a conformation which would not undergo skeletal rearrangement. However, this conformer can react with participation of the axial β hydrogen to give carbonium ion **49** (or ion pair). Subsequent deprotonation gives octalins **14** and **18**. Alternative ionization to carbonium ion **50** is disfavored by the known propensity of conformations which have antiparallel carbon–hydrogen bonds, able to participate by hyperconjugation, and hence to initiate elimination and rearrangement reactions in concert with carbon–oxygen bond stretching, to solvolyze preferentially.[29]

If one assumes that rearranged products **33** and **36** arise *via* a transition state with the character of conformation **4a** and unrearranged products **14** and **18** arise *via* a transition state with the character of conformation **4b**, then one may perform a Winstein–Holness calculation[30] to arrive at specific rate constants for acetolysis of the equatorial and axial conformers **4a** and **4b**. Using Jensen's A value of 0.515 kcal/mol for the tosyl group,[11] the k_a/k_e ratio is found to be 1.5. Although tenuously based on extrapolation of the A value to 100°, the calculations do show a near equality of k_a and k_e, and support our hypothesis of no anchi-

(29) N. C. G. Campbell, D. M. Muir, R. R. Hill, J. H. Parish, R. M. Southam, and M. C. Whiting, *J. Chem. Soc. B*, 355 (1968).

(30) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955).

SCHEME V

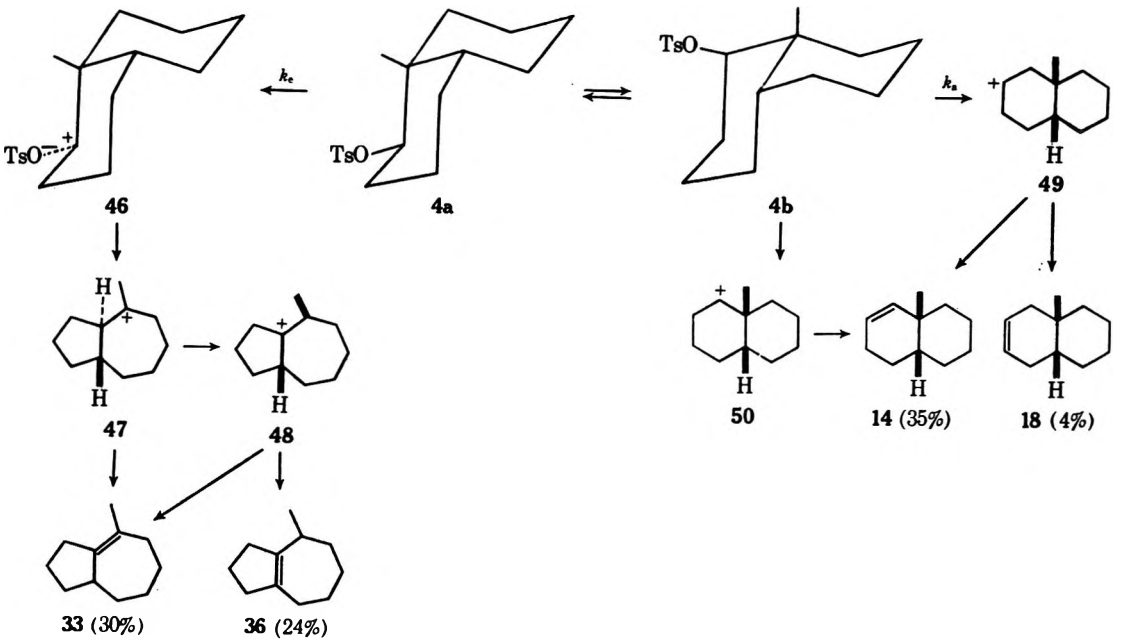
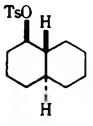
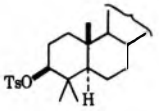


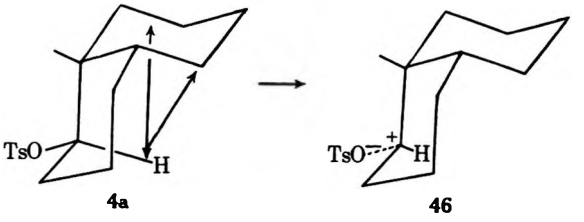
TABLE IV

RELATIVE RATES OF ACETOLYSIS AT 100°

Tosylate	No.	$10^4 k$, min^{-1}	k_{rel}	Ref
	1	3.61	1.0	
	3-*d*	25.2	7.0	k_3/k_D = 1.55
	3	39.0	10.8	
	2	1150	319	
	4	1270	352	
	38	112[a]	31.0	*c*
	39	397[b]	110	*d*
	40	1400[b]	388	*e*
	41	1110[b]	307	*f*
	42	412[b]	114	*g*

[a] Interpolated from data at other temperatures. [b] Extrapolated from data at other temperatures. [c] I. Moritani, S. Nishida, and M. Murakami, *J. Amer. Chem. Soc.*, **81**, 3420 (1959). [d] I. Moritani, S. Nishida, and M. Murakami, *Bull. Chem. Soc. Jap.*, **34**, 1334 (1961). [e] C. W. Shoppee and G. A. R. Johnston, *J. Chem. Soc.*, 3261 (1961). [f] A. P. Krapcho, J. E. McCullogh, and K. V. Nahabedian, *J. Org. Chem.*, **30**, 139 (1965). [g] H. C. Brown and G. Ham, *J. Amer. Chem. Soc.*, **78**, 2735 (1956).

meric assistance in the ionization step. If carbonium ion **47** were formed with participation in the rate-determining step, k_e would be expected to be much larger than k_a. The normal rate ratio for axial/equatorial tosylates is about 3. For example, k_a/k_e values of 2.7 and 3.3 have been observed for the axial and equatorial derivatives of 4-*tert*-butyl- and 3-*tert*-butylcyclohexyl toluenesulfonates at 75°,[30] and the axial *trans,trans*-2-decalyl *p*-toluenesulfonate solvolyzes more rapidly than the equatorial trans,cis-2 isomer at 75° by a factor of 3.1.[31] In our case, ionization of the equatorial conformer **4a** is sterically assisted by relief of two skew butane interactions, whereas only one such interaction is relieved in the transition of **4b** to **49**.



4a **46**

As can be seen from the data in Tables III and IV, the carbonyl group exerts a marked decelerating effect upon the reaction. The effect amounts to a factor of 319 in the case of the trans tosylates **1** and **2** and 33 in the case of the cis tosylates **3** and **4**. Remote substituents within a molecule may affect reactivity at a distant center by either polar or steric mechanisms. Furthermore, remote polar substituents may influence reactivity by electronic interaction transmitted through either the connecting atoms or interannular space. Examples of remarkably large effects of polar substituents at large distances from the reaction center have been observed in electrophilic additions to alkenes[32,33] and in various solvolytic systems.[34] Takeda, *et al.*, by demonstrating a good Hammett–Taft

(31) Table IV, ref c.

(32) (a) P. E. Peterson and G. Allen, *J. Org. Chem.*, **27**, 2290 (1962); (b) P. E. Peterson and G. Allen, *J. Amer. Chem. Soc.*, **85**, 3608 (1963); (c) P. E. Peterson, *Tetrahedron Lett.*, 181 (1963).

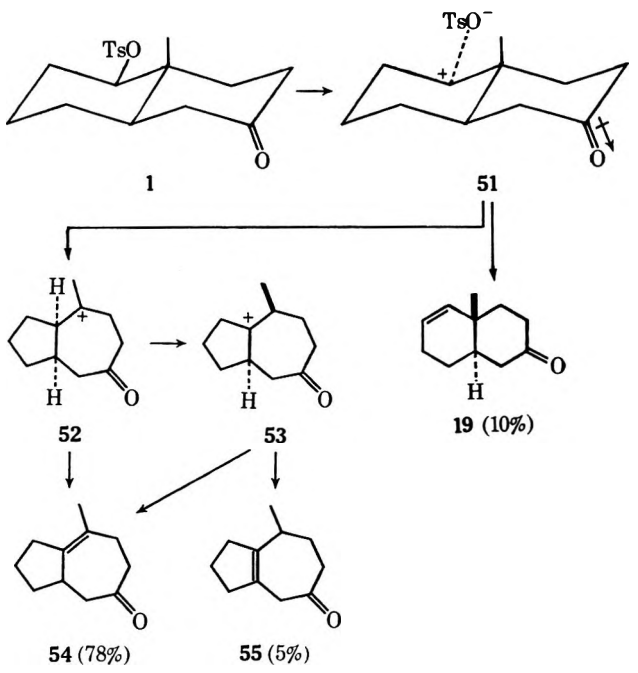
(33) (a) V. Schwarz, S. Hermanek, and J. Trojanek, *Chem. Ind. (London)*, 1212 (1960); (b) V. Schwarz, S. Hermanek, and J. Trojanek, *Collect. Czech. Chem. Commun.*, **26**, 1438 (1960); (c) V. Schwarz and S. Hermanek, *Tetrahedron Lett.*, 809 (1962).

(34) See, *inter alia*, (a) J. Mathieu, M. Legrand, and J. Valls, *Bull. Soc. Chim. Fr.*, 549 (1960); (b) R. Baker and J. Hudec, *Chem. Commun.*, 479 (1967); (c) K. Takeda, H. Tanida, and K. Horiki, *J. Org. Chem.*, **31**, 734 (1966).

$\rho^*\sigma^*$ correlation where σ^* was summed over all bond paths between substituent and reaction center, concluded that the dominant factor governing such effects is inductive.[34c] Noyce and coworkers have found very satisfactory agreement between the acetolysis rates of a series of 4-halocyclohexyl methansulfonates[35] and 4-cyano-*trans*-decalyl methanesulfonates[36] with the rates calculated using a field effect model. Their results indicate that "through the bond" inductive effects are, at best, of only minor importance.

The large rate effects observed in this study upon introduction of a keto group four carbon atoms removed from the reaction center are consistent with a field effect. Scheme VI illustrates the behavior of

SCHEME VI



the *trans*-keto tosylate **1**. Solvolysis proceeds by a slow rate-determining ionization to give intimate ion pair **51**, which is severely destabilized by interaction with the carbonyl dipole. Subsequent rearrangement to tertiary carbonium ion **52** places the electron-deficient center closer to the carbonyl group, with a resulting increase in the electrostatic repulsion. It is reasonable that this pathway becomes somewhat disfavored in the *trans*-keto series, and direct deprotonation of **51** now becomes competitive. We see 10% of the unrearranged octalone in this solvolysis, whereas no unrearranged product is observed in the *trans*-deoxy case.

As outlined in Scheme VII, the effect of the carbonyl group in controlling rate processes is particularly evident in the solvolysis of *cis*-keto tosylate **3**. Here we find only a small amount of rearranged products formed. Examination of Dreiding models reveals that the developing positive charge in conformer **3a** is closer to the positive end of the carbonyl dipole than it is in conformer **3b**. This increased electrostatic repulsion would raise the transition state for solvolysis of the equatorial tosylate to intimate ion pair **56**. Once formed, **56** should rapidly rearrange to more stable tertiary carbonium ion **57**, the precursor of **54**. Conformer **3b** solvolyzes with participation of the β axial hydrogen atom to give carbonium ion **58** (or ion pair) which subsequently undergoes deprotonation to octalones **13** and **15**. Hydride participation effectively increases the distance between the electron-deficient center and the positive end of the carbonyl dipole, thus decreasing the interannular electrostatic interaction and lowering the transition state for solvolysis of the axial tosylate. Since no such pathway is available to the *trans*-keto tosylate, we would expect it to solvolyze at a slower rate. Indeed, *cis*-keto tosylate **3** reacts 10.8 times faster than *trans*-keto tosylate **1**.

Our proposal that conformation **3b** reacts with hydride participation to give rearranged carbonium ion **58** directly is based on the observed deuterium isotope effect of 1.55 for tosylate **3**-*d*. Shiner and Jewett[37] observed a large axial β deuterium effect of 1.436 in the aqueous ethanolysis of brosylate **59**. Although originally ascribed to a hyperconjugative effect, subsequent studies[38] on tri- and tetradeuterated analogs of **59** showed a grossly noncumulative rate behavior best explained by neighboring hydrogen participation in the solvolytic transition state. Our value of 1.55 is consistent with the assumption that the deuterium atom is participating in the transition state leading to ion **58**-*d* (see Scheme VII). Further conformation of this proposal comes from a study of the products from the deuterium analog of the *cis*-keto tosylate. Octalones **13**-*d* and **15**-*d* retain 74 and 91–99%, respectively, of the original deuterium content.

Experimental Section

Melting points (Pyrex capillary) and boiling points are uncorrected. Infared spectra (ir) were recorded on Perkin-Elmer 137 and 237 spectrophotometers. Proton magnetic resonance spectra (pmr) were obtained on Varian A-60 and T-60 spectrometers. Line positions are given in the Tiers τ scale, with internal tetramethylsilane as standard; the multiplicity, peak areas, coupling constants, and proton assignments are given in parentheses. Consolidated 21-103c and Varian M-66 mass spectrometers provided the mass spectra. Gas–liquid partition chromatography (glpc) analyses were performed on Aerograph Models 204B, 90-P, and 600-D instruments. Elemental analyses were performed by the Microanalytical Laboratory, operated by the Department of Chemistry, University of California, Berkeley, Calif.

5β-Hydroxy-4aβ-methyl-3,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(1*H*)-one *p*-Toluenesulfonate (1).—To a solution of hydroxy ketone **5** (35.36 g)[7] in 120 ml of anhydrous pyridine was added a solution of *p*-toluenesulfonyl chloride (37.0 g) in 80 ml of pyridine. The solution was kept at room temperature for 21 hr, then poured into ice–water. The mixture was extracted with methylene chloride. The organic extracts were washed with cold 10% aqueous sulfuric acid, water, and saturated brine and dried over magnesium sulfate. Evaporation of the solvent left 62.8 g of an off-white solid. Five recrystallizations from ethyl acetate–pentane gave 25.77 g (39% yield) of analytically pure tosylate **1** as a white powder: mp 136–137°; pmr ($CDCl_3$) τ 8.93 (s, 3, angular Me), 7.55 (s, 3, aryl Me), 5.77 (broad m, 1, C-5 H), 2.42 (A_2B_2 with τ_A 2.20 and τ_B 2.63, 4, J_{AB} = 8.5 Hz, aryl H's).

Anal. Calcd for $C_{18}H_{24}O_4S$: C, 64.26; H, 7.19; S, 9.53. Found: C, 63.99; H, 7.10; S, 9.37.

The following *p*-toluenesulfonates were prepared by essentially the same procedure.

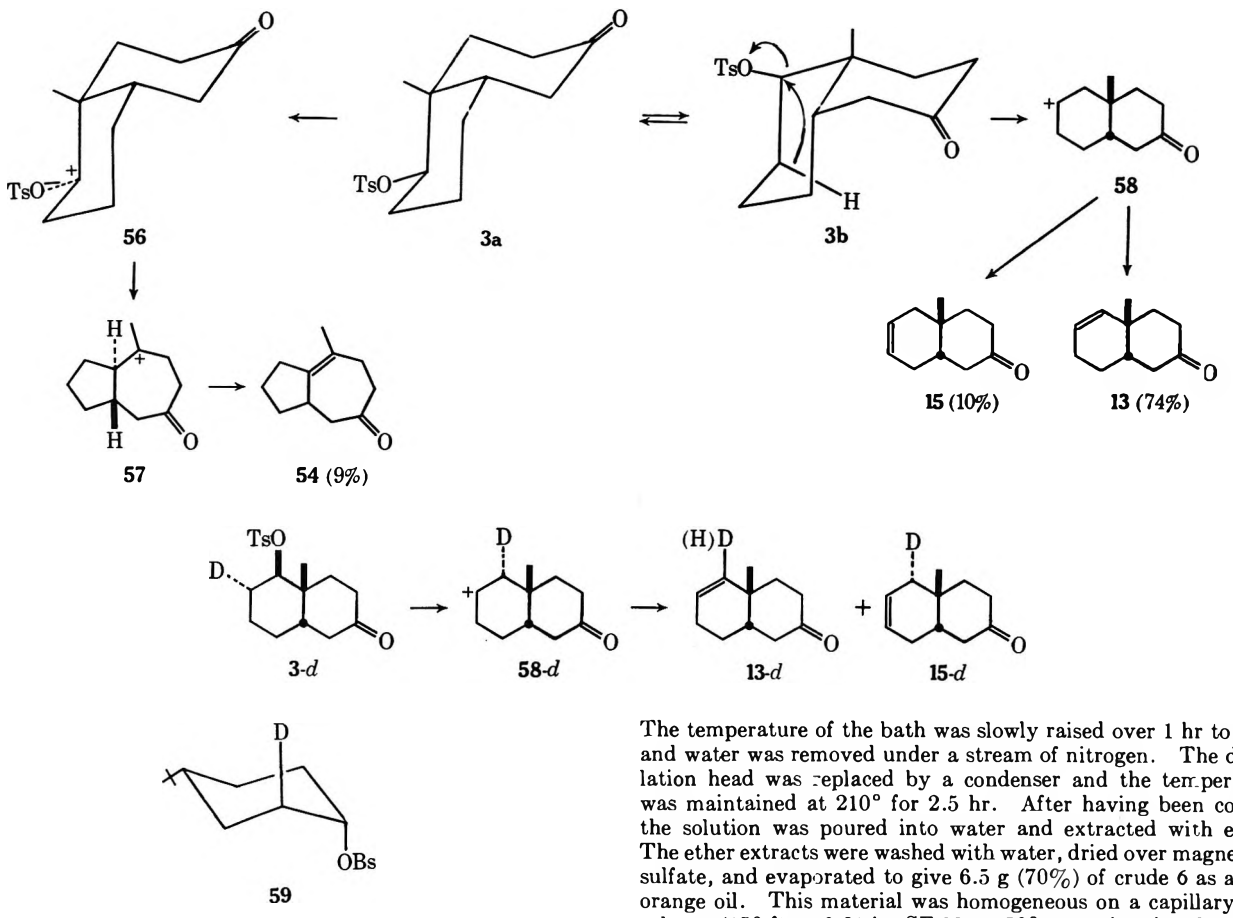
(35) D. S. Noyce, B. N. Bastian, P. T. S. Lan, R. S. Monson, and B. Weinstein, *J. Org. Chem.*, **34**, 1274 (1969).

(36) D. S. Noyce and B. E. Johnston, *ibid.*, **34**, 1252 (1969).

(37) V. J. Shiner and J. G. Jewett, *J. Amer. Chem. Soc.*, **86**, 945 (1964).

(38) V. J. Shiner and J. G. Jewett, *ibid.*, **87**, 1382 (1965).

SCHEME VII



8aβ-Methyl-4aα-decahydronaphth-1β-ol *p*-Toluenesulfonate (2).—From decalol 6 (1.68 g) there was obtained crude tosylate 2 (2.82 g). Several recrystallizations from ethyl acetate–pentane gave analytically pure 2 as fine, white needles: mp 95–102° dec; pmr ($CDCl_3$) τ 9.15 (s, 3, angular Me), 7.58 (s, 3, aryl Me), 5.76 (broadened t, 1, J = 7 Hz, C-1 H), 2.46 (A_2B_2 with τ_A 2.23 and τ_B 2.70, 4, J_{AB} = 8 Hz, aryl H's).

Anal. Calcd for $C_{18}H_{26}O_3S$: C, 67.04; H, 8.13; S, 9.95. Found: C, 66.79; H, 8.32; S, 9.72.

8aβ-Methyl-4aβ-decahydronaphth-1β-ol *p*-Toluenesulfonate (4).—Crude tosylate 4 (7.17 g) was obtained from decalol 9 (3.99 g). Several recrystallizations from ethyl acetate–pentane gave analytically pure 4 as white prisms: mp 63.0–64.2°; pmr (CCl_4) τ 9.07 (s, 3, angular Me), 7.56 (s, 3, aryl Me), 5.25 (broad m, 1, $W_{1/2}$ = 17 Hz, C-1 H), 2.52 (A_2B_2 with τ_A 2.30 and τ_B 2.74, 4, J_{AB} = 8 Hz, aryl H's).

Anal. Calcd for $C_{18}H_{26}O_3S$: C, 67.04; H, 8.13; S, 9.95. Found: C, 67.08; H, 8.18; S, 9.78.

In a subsequent run, the crude tosylate was recrystallized five times from ether to give analytically pure 4. This material had mp 80.2–81.4°, but in all other respects was identical with the material with mp 63.0–64.2°.

6α-Deuterio-5β-hydroxy-4aβ-methyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(1*H*)-one *p*-Toluenesulfonate (3-*d*).—From deuterated ketol 12 (1.26 g, 0.97 deuterium atoms per molecule by mass spectroscopy) there was obtained 2.06 g of tosylate 3-*d*. Three recrystallizations from ethyl acetate–pentane gave 1.356 g (60% yield) of analytically pure tosylate 3-*d* as a white, fibrous solid: mp 143–144.5°; pmr ($CDCl_3$) τ 8.88 (s, 3, angular Me), 7.55 (s, 3, aryl Me), 5.23 (d, 1, J = 7 Hz, C-5 H), 2.42 (A_2B_2 with τ_A 2.18 and τ_B 2.65, 4, J_{AB} = 8.5 Hz, aryl H's).

Anal. Calcd for $C_{18}H_{23}DO_4S$: C, 64.06; H, 7.14; S, 9.50. Found: C, 63.95; H, 7.05; S, 9.33.

8aβ-Methyl-4aα-decahydronaphth-1β-ol (6).—A solution of keto alcohol 5 (10.00 g)[7] and 70 ml of 85% aqueous hydrazine hydrate in 300 ml of freshly distilled diethylene glycol was heated under nitrogen at 120° (bath temperature) for 2.5 hr. After cooling the solution, 38.0 g of potassium hydroxide pellets was added and the condenser was replaced by a distillation head. The temperature of the bath was slowly raised over 1 hr to 210° and water was removed under a stream of nitrogen. The distillation head was replaced by a condenser and the temperature was maintained at 210° for 2.5 hr. After having been cooled, the solution was poured into water and extracted with ether. The ether extracts were washed with water, dried over magnesium sulfate, and evaporated to give 6.5 g (70%) of crude 6 as a pale orange oil. This material was homogeneous on a capillary glpc column (150 ft × 0.01 in. SF 96 at 150°, retention time 3.5 min). Distillation of the crude product [bp 69–73° (0.2 Torr)] gave 5.095 g (55% yield) of white crystalline alcohol 6, mp 40–48°. Recrystallization from hexane at −15° raised the melting point to 52–56°. The analytical sample was obtained by preparative glpc (10 ft × 1/4 in. SE-30 on Chromosorb W at 170°): pmr (CCl_4) τ 9.22 (s, 3, angular Me), 7.70 (s, 1, OH), 6.88 (broad m, 1, $W_{1/2}$ = 13 Hz, C-1 H).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.35; H, 12.05.

The low yield of crude decalol 6 obtained in this experiment is undoubtedly due to direct steam distillation of the product into the aqueous distillate. In a similar run starting with 20.0 g of keto alcohol 5, the aqueous distillate and reaction mixture were combined. Work-up gave 16.5 g (89% yield) of crude 6. This material was of sufficient purity for conversion to its tosylate.

5β-Acetoxy-4aβ-methyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(1*H*)-one (8).—A mixture of 29.2 g of acetoxy enone 7[5] and 3.0 g of 10% palladium on strontium carbonate in 200 ml of ethyl acetate was hydrogenated in a Parr apparatus. Hydrogen absorption was rapid and ceased after 30 min. The mixture was filtered and the filtrate was evaporated. Crystallization of the residue, 28.6 g of a pale yellow oil, from petroleum ether (bp 30–60°) at −20° afforded 28.0 g (95% yield) of crystalline keto acetate 8. A small portion of the product was recrystallized from petroleum ether to give the analytical sample: mp 50–51°; pmr (CCl_4) τ 8.87 (s, 3, angular Me), 7.98 (s, 3, acetoxy Me), 4.92 (broad m, 1, $W_{1/2}$ = 10 Hz, C-5 H).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.77; H, 9.05.

8aβ-Methyl-4aβ-decahydronaphth-1β-ol (9).—Keto acetate 8 was submitted directly to Wolff–Kishner reduction to obtain decalol 9. From 10.00 g of keto acetate 8, there was obtained 7.15 g of oily decalol. Distillation of this material from an oil-jacketed flask (0.3 Torr) and bath temperature of 80–90° afforded 6.61 g (88% yield) of 9 as a water-white oil: pmr (CCl_4) τ 9.10 (s, 3, angular Me), 7.62 (broad s, 1, OH), 6.30 (broad m, 1, $W_{1/2}$ = 14 Hz, C-1 H).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.58; H, 12.11.

Glpc analysis (150 ft × 0.01 in. SF 96 at 120°) of the distilled product gave one peak at a retention time of 7.4 min.

5β-Hydroxy-4aβ-methyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(1*H*)-one Ethylene Ketal and 6α-Deuterio-5β-hydroxy-4aβ-methyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(1*H*)-one Ethylene Ketal (11).—To a solution of 200 mg (0.89 mmol) of ketal epoxide **10**[8] in 6 ml of anhydrous tetrahydrofuran was added 17 mg (0.45 mmol) of lithium aluminum hydride. After refluxing the mixture for 19 hr, 0.1 ml of 5% aqueous potassium hydroxide was added and refluxing was continued for an additional 30 min. The mixture was cooled and filtered. The aluminum salts were washed with ether. The combined filtrates were dried over magnesium sulfate and evaporated to give 199 mg of a clear oil shown by capillary glpc (150 ft × 0.01 in. SF 96 at 147°) to consist of 4% starting material **10** and 96% of a ketal alcohol. Analytically pure ketal alcohol was obtained by preparative glpc (6 ft × 1/4 in. SF 96 on Chromosorb W at 190°): pmr (CCl_4) τ 9.08 (s, 3, angular Me), 6.16 (s, 4, ketal H's).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.72; H, 9.95.

Deuterated ketal alcohol **11** was prepared in a similar manner. Reduction of 3.00 g of epoxide **10** with 0.28 g of lithium aluminum deuteride gave 2.97 g (98%) of ketal alcohol **11**: pmr (CCl_4) τ 9.08 (s, 3, angular Me), 6.15 (s, 4, ketal Hs). The crude product was shown to be homogeneous by capillary glpc (150 ft × 0.01 in. SF 96 at 165°, retention time 10.0 min).

6a-Deuterio-5β-hydroxy-4aβ-methyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(1*H*)-one (12).—To a solution of 2.72 g of ketal **11** in 25 ml of acetone was added a mixture of 4 ml of water and 0.5 ml of concentrated sulfuric acid. After having been refluxed for 45 min, the solution was concentrated to 10 ml (reduced pressure) and poured into water. The resulting mixture was extracted with ether. The extracts were washed with saturated sodium bicarbonate solution and saturated brine, dried over magnesium sulfate, and evaporated. The product was 1.917 g (87.4% yield) of a clear oil which crystallized from ether–hexane at Dry Ice temperature to afford 1.27 g of ketol **12** as a white powder, mp 65–68°. The mother liquors were concentrated and crystallized from ether–petroleum ether at −10° to give an additional 0.16 g of crystalline ketol **12**. Recrystallization from ether gave analytically pure **12** as white clusters: mp 68–68.3°; pmr (CCl_4) τ 8.88 (s, 3, angular Me), 7.63 (s, 1, OH), 6.25 (broad m, 1, $W_{1/2}$ = 9.5 Hz, C-5 H).

Anal. Calcd for $C_{11}H_{17}DO_2$: C, 72.09; H, 10.45. Found: C, 72.25; H, 10.52.

The low-resolution mass spectrum peak intensities were determined for the peaks at *m/e* 182–184 of ketol **12** and at *m/e* 181–183 for the undeuterated analog. Analytical comparison of the data indicated 0.97 deuterium atoms per molecule of ketol **12**.

4aβ-Methyl-1,2,3,4,4a,7,8,8aβ-octahydronaphthalene (14).

A.—A solution of 1.42 g of *cis*-deoxy tosylate **4** in 15 ml of anhydrous pyridine was refluxed under nitrogen for 17 hr. The cooled solution was poured into ice–water and extracted with pentane. The extracts were washed with water, cold 10% aqueous sulfuric acid, and saturated brine and dried over magnesium sulfate. Evaporation of the solvent left 0.61 g (92% yield) of a hydrocarbon mixture. Glpc analysis (10 ft × 1/4 in. 10% FFAP on 60/80 AW-DMCS Chromosorb P at 133°) revealed the presence of three components: 78% octalin **14** (retention time 6.2 min), 5% (7.4 min), and 17% (8.4 min). Analytically pure **14** was obtained by preparative glpc: pmr (CCl_4) τ 9.01 (s, 3, angular Me), 4.92–4.33 (m, 2, olefinic H's).

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 87.84; H, 12.09.

Capillary glpc analysis [500 ft × 0.03 in. Apiezon L (95%) + Igepal 880 (5%) at 120°] of the analytical sample revealed the presence of one component with a retention time of 21.4 min.

B.—Olefin **14** was also prepared from enone **13** by Wolff–Kishner reduction, using conditions similar to those employed for the preparation of **6** and **9** (*vide supra*). From 0.57 g of enone **13**, there was obtained 0.36 g of octalin **14** as a clear liquid. The crude product exhibited ir and pmr spectra identical with those of the analytical material obtained in part A.

4aβ-Methyl-1,2,3,4,4a,5,8,8aβ-octahydronaphthalene (18).—Octalin **18** was prepared from enone **17**[15] by Wolff–Kishner reduction (*vide supra*). From 1.26 g of crude enone **17**, there was obtained 0.30 g of octalin **18** as a pale yellow oil; capillary glpc showed a single peak with a retention time of 22.2 min [500 ft × 0.03 in. Apiezon L (95%) + Igepal 880 (5%) at 120°]. The analytical sample was obtained by preparative glpc (10 ft × 0.25 in. 10% FFAP on 60/80 AW-DMCS Chromosorb P at 130°): pmr (CCl_4) τ 9.10 (s, 3, angular Me), 4.53 (m, 2, $W_{1/2}$ = 5 Hz, olefinic H's).

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 87.76; H, 11.99.

4aβ-Methyl-3,4,4a,7,8,8aα-hexahydronaphthalen-2(1*H*)-one (19).—A solution of 3.84 g of *trans*-keto tosylate **1** in 65 g of 10% lithium chloride in dimethylacetamide was stirred and refluxed under a nitrogen atmosphere for 2.5 hr. After having been cooled, the solution was poured into ice–water and extracted with ether. The extracts were washed with cold 10% aqueous hydrochloric acid, saturated sodium bicarbonate solution, water, and saturated brine, dried over magnesium sulfate, and evaporated. Distillation of the residue, 1.66 g, afforded 1.32 g (70% yield) of octalone **19** as small, white prisms, bp 50° (0.8 Torr). Several recrystallizations from pentane gave the analytical sample: mp 54–55°; pmr (CCl_4) τ 8.94 (s, 3, angular Me), 4.52 (s, 2, olefinic H's).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.25; H, 9.66.

The 2,4-dinitrophenylhydrazone melted at 172–173° after six recrystallizations from ethanol–ethyl acetate. The semicarbazone melted at 190–190.5° after three recrystallizations from methanol.

4aβ-Methyl-1,2,3,4,4a,7,8,8aα-octahydronaphthalene (20).—Octalin **20** was prepared from enone **19** by Wolff–Kishner reduction, using conditions similar to those employed for the preparation of alcohol **6** (*vide supra*). From 1.00 g of enone **19**, there was obtained 0.61 g (67%) of octalin **20** as a clear liquid.

The crude product was homogeneous on three capillary glpc columns; the retention times were 6.4 (150 ft × 0.01 in. SF 96 at 105°), 22.2 [500 ft × 0.03 in. Apiezon L (95%) + Igepal 880 (5%) at 120°], and 38.9 min [500 ft × 0.03 in. SF 96–50 (95%) + Igepal 880 (5%) at 100°]. The analytical sample ws obtained by preparative glpc (10 ft × 1/4 in. 10% FFAP on 60/80 AW-DMCS Chromosorb P at 120°): pmr (CCl_4) τ 9.13 (s, 3, angular Me), 4.65 (s, 2, olefinic H's).

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 87.78; H, 11.91.

4aβ-Methyl-3,4,4a,7,8,8α-hexahydronaphthalen-2(1*H*)-one Ethylene Ketal (21).—A mixture of 1.77 g of octalone **19**, 2.00 g of ethylene glycol, and 200 mg of 2-naphthalenesulfonic acid in 35 ml of benzene was refluxed under a water separator overnight. After having been cooled, the mixture was diluted with 40 ml of benzene and washed with 10% aqueous sodium bicarbonate and water. Evaporation of the dried solution (magnesium sulfate) left 2.14 g of a yellow oil. Crystallization from pentane afforded 1.64 g of ketal **21** as white needles, mp 38.9–39.3° (73% yield). The analytical sample was obtained by preparative glpc (5 ft × 1/4 in. 15% SF 96 on Chromosorb W at 182°): pmr (CCl_4) τ 9.12 (s, 3, angular Me), 7.97 (broad m, 2, C-7 H's), 6.22 (s, 4, ketal H's), 4.62 (s, 2, olefinic H's).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.95; H, 9.38.

4aβ-Methyl-5α,6α-oxido-3,4,4a,5,6,7,8aα-octahydronaphthalen-2(1*H*)-one Ethylene Ketal (22).—A solution of 1.70 g (9.24 mmol) of 85% *m*-chloroperbenzoic acid in 200 ml of chloroform was added dropwise to a stirring solution of 1.52 g (7.29 mmol) of ketal **21** in 100 ml of chloroform at 0°. The cooling bath was removed and the solution was stirred at room temperature overnight. Excess oxidant was destroyed by the addition of 35 ml of 20% aqueous sodium sulfite, followed by 2 hr of vigorous stirring. The phases were separated and the organic layer was washed with 10% aqueous sodium hydroxide and dried over magnesium sulfate. Evaporation afforded 1.61 g of crude epoxide **22** as a milky liquid. The crude product was homogeneous by glpc (5 ft × 0.25 in. 15% SF 96 on Chromosorb W at 182°). Crystallization from pentane gave 1.10 g of **22** as a white solid (67% yield). The analytical sample was obtained by preparative glpc: mp 55.0–56.9°; pmr (CCl_4) τ 9.07 (s, 3, angular Me), 7.43 (d, 1, J = 4 Hz, C-5 H), 7.08 (broad m, 1, $W_{1/2}$ = 10 Hz, C-6 H), 6.22 (s, 4, ketal H's).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.61; H, 8.96.

5α-Hydroxy-4aβ-methyl-3,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(1*H*)-one (23).—A solution of 0.95 g (4.23 mmol) of ketal epoxide **22** in 20 ml of anhydrous ether was added dropwise to a stirring suspension of 63 mg (1.65 mmol) of lithium aluminum hydride in 25 ml of ether. After stirring the mixture overnight,

excess hydride was destroyed by the addition of moist ether. The mixture was filtered, and the filtrate was washed with saturated sodium chloride solution and dried over magnesium sulfate. Evaporation of the solvent left 0.84 g of a clear oil. The pmr spectrum of this material revealed the presence of *ca.* 40% unreacted epxoxide. A solution of 0.79 g of the crude product in 20 ml of ether was added to a stirring suspension of 42 mg of lithium aluminum hydride in 25 ml of refluxing ether. The mixture was stirred at reflux for 3 hr and then at room temperature overnight. Excess hydride was destroyed by the addition of moist ether. The mixture was filtered, and the aluminate salts were extracted with boiling tetrahydrofuran. The combined ethereal and tetrahydrofuran solutions were washed with saturated salt solution and dried over magnesium sulfate. Evaporation of the solvent left 0.73 g of ketal alcohol as a clear oil: pmr (CCl_4) τ 9.17 (s, 3, angular Me), 6.20 (s, 4, ketal H's).

The crude ketal, 0.734 g, was dissolved in 25 ml of acetone. A solution of 0.5 ml of concentrated sulfuric acid and 2 ml of water was added, and the solution was refluxed for 30 min. The solution was then concentrated on a rotary evaporator, diluted with water, and extracted with ether. The dried extracts (magnesium sulfate) were evaporated to give 0.444 g (75% yield) of ketol **23** as a clear oil. The analytical sample was obtained by preparative glpc (10 ft × 0.25 in. 15% SF 96 on Chromosorb W at 200°): pmr (CCl_4) τ 8.98 (s, 3, angular Me), 6.82 (s, 1, OH), 6.53 (m, 1, $W_{1/2}$ = 5 Hz, C-5 H).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.61; H, 9.75.

Ketol **23** is clearly different from ketol **5**, as evidenced by ir and pmr spectroscopy and glpc mobility.

8aβ-Methyl-3,4,4aα,7,8,8a-hexahydronaphthalene-1(2*H*),6-(5*H*)-dione (24). A.—To a stirring solution of 1.01 g (5.5 mmol) of ketol **5** in 25 ml of acetone was added dropwise 1.53 ml of Jones reagent.[19] The mixture was diluted with water and extracted with ether. The dried extracts (magnesium sulfate) were evaporated to give 0.82 g (82.5% yield) of **24** as a yellow oil which crystallized from ether at Dry Ice temperature. Recrystallization from ether afforded the analytical sample as white plates: mp 57.7–59.0°; pmr (CCl_4) τ 8.70 (s, 3, angular Me).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.28; H, 9.15.

B.—A similar oxidation of 0.250 g of ketol **23** yielded 0.209 g (84.5%) of dione **24** as a yellow oil. Crystallization from ether–petroleum ether afforded material melting at 56.0–57.8°. This material exhibited identical ir and pmr spectra and glpc retention time (5.5 min, 150 ft × 0.01 in. SF 96 at 165°) as authentic **24** prepared in part A.

3,4,4aα,5,6,7,8,8aβ-Octahydronaphthalen-1(2*H*)-one and 3,4,4aα,5,6,7,8,8aα-Octahydronaphthalen-1(2*H*)-one (25).—Hydrogenation of 1-naphthol (10.00 g) by the method of Meyers[20] gave 9.12 g of a 9:1 mixture of 1-decalols and 1-decalones. Oxidation of 7.91 g of this mixture with Jones reagent[19] gave 7.36 g of a mixture of 1-decalones (**25**).

The crude decalone mixture was dissolved in 50 ml of benzene and treated with 5.0 ml of concentrated sulfuric acid and 30 ml of water. After stirring the two-phase mixture overnight, the benzene layer was separated and washed with water and saturated salt solution, dried over magnesium sulfate, and evaporated. Distillation of the residue, 6.97 g, afforded 6.45 g of 1-decalones **25** as a clear liquid, bp 50–51° (0.2 Torr). Glpc analysis (5 ft × 1/8 in. 20% FFAP on 60/80 Chromosorb W at 140°) revealed the presence of 90% *trans*-1-decalone (retention time 13.5 min) and 10% *cis*-1-decalone (12.5 min).

1β-Methyl-4aα,8aβ-decahydronaphth-1α-ol (26).—A solution of 5.96 g (39.1 mmol) of isomeric decalones **25** in 100 ml of anhydrous ether was treated with 75 ml of a 1.56 *M* methyllithium in ether solution. The solution was stirred at room temperature under a nitrogen atmosphere for 18 hr. Excess lithium reagent was destroyed by the careful, dropwise addition of 50 ml of water. The layers were separated and the ethereal phase was washed with water and saturated brine solution and dried over magnesium sulfate. Evaporation of the solvent left 5.41 g of a clear oil. This material contained a small amount of unreacted ketone, as evidenced by its ir spectrum and glpc trace.

The crude product, 5.32 g, was chromatographed on 150 g of activity III alumina, and eluted with petroleum ether–ether. Fraction purity was monitored by glpc (5 ft × 1/8 in. 20% FFAP on Chromosorb W at 140°). After a forerun of decalone-contaminated fractions, elution with 10% ether in petroleum ether and ether afforded 1.34 g of decalol **26** as a clear oil of greater than 96% isomeric purity. The analytical sample was obtained by preparative glpc (10 ft × 0.25 in. 10% FFAP on 60/80 AW-DMCS Chromosorb P at 180°): pmr (CCl_4) τ 8.78 (s, 3, C-1 Me), 7.95 (s, 1, OH).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.61; H, 11.75.

Dehydration of 1β-Methyl-4aα,8aβ-decahydronaphth-1α-ol (26).—To 503 mg of decalol **26** in 5 ml of anhydrous pyridine was added 810 mg of phosphorus oxychloride. The solution was heated in an oil bath maintained at 80° for 5 min, then allowed to cool to room temperature. After a total reaction time of 90 min, the solution was poured into a mixture of ice–water and extracted with pentane. The extracts were washed with cold 10% hydrochloric acid, saturated sodium bicarbonate solution, and saturated brine, and dried over magnesium sulfate. Evaporation of the solvent gave 389 mg (87% yield) of hydrocarbons as a clear liquid: pmr (CCl_4) τ 8.42 (s, olefinic Me), 5.45 (s, $=CH_2$), 4.78 (broad m, $=CH-$).

Glpc analysis [500 ft × 0.03 in. Apiezon L (95%) + Igepal 880 (5%) at 120°] revealed the presence of four components: 12% **29** (retention time 23.9 min), 3% (24.5 min), 65% **27** (25.4 min), and 20% **28** (26.6 min). The glpc assignments were confirmed by the pmr peak areas, which indicated a 12:73:15 ratio of hydrocarbons **29**, **27**, and **28**, respectively. An analytical sample of the hydrocarbon mixture was obtained by preparative glpc (10 ft × 0.25 in. 10% FFAP on 60/80 AW-DMCS Chromsorb P at 132°).

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 88.12; H, 12.09.

1,2,3,3aξ,6,7,8,8aα-Octahydroazulen-4-(5*H*)-one (31).—A solution of 2.01 g (13.4 mmol) of enone **30**[21] in 200 ml of anhydrous ether was added dropwise over a 15-min period to a stirring solution of 1.28 g (185 mg-atoms) of lithium in 500 ml of anhydrous ammonia (distilled from sodium). After the solution had been stirred for an additional 15 min, 12.0 g (225 mmol) of ammonium chloride was added in portions. The ammonia was allowed to evaporate under a stream of dry nitrogen. The resulting fine white powder was dissolved in water and extracted with ether. The combined extracts were washed with 5% aqueous hydrochloric acid, water, and saturated brine and dried over molecular sieves. Evaporation of the solvent left 1.87 g (92% yield) of isomeric ketones **31** as a clear oil; glpc analysis (150 ft × 0.01 in. Carbowax 20 M at 120°) revealed the presence of 60% trans-fused isomer (retention time 13.4 min) and 40% cis-fused isomer (14.6 min).

4-Methyl-3aξ,8aα-decahydroazulen-4-ol (32).—To a stirring solution of 1.71 g (11.2 mmol) of isomeric ketones **31** in 50 ml of dry ether, under nitrogen, and cooled in an ice bath, was rapidly added 20 ml of a 1.5 *N* methyllithium in ether solution. The resulting solution was stirred for 1 hr at 0°; then excess lithium reagent was destroyed by the careful addition of 25 ml of water. The layers were separated, and the ethereal phase was washed with saturated sodium chloride solution and dried over molecular sieves. The dried solution was cooled in an ice bath, treated with 10 ml of lithium reagent, stirred for 1 hr at 0°, and worked up to afford 1.48 g (78% yield) of tertiary alcohol **32** as a clear oil: pmr (CCl_4) τ 8.87 and 8.83 (singlets, C-4 methyls).

Dehydration of 4-methyl-3aξ,8aα-decahydroazulen-4-ol (32).—To 1.14 g (6.75 mmol) of alcohol **32** in 10 ml of anhydrous pyridine was added 1.81 g of phosphorus oxychloride. The solution was heated in a boiling water bath for 5 min, then allowed to cool to room temperature. After a total reaction time of 65 min, the solution was poured into ice–water and extracted with pentane. The extracts were washed with cold 10% hydrochloric acid, saturated sodium bicarbonate solution, and saturated salt solution, and dried over molecular sieves. Evaporation of the solvent afforded 828 mg (82% yield) of hydrocarbons as a pale yellow liquid: pmr (CCl_4) τ 8.37 (broad s, olefinic Me), 5.35 (broad s, olefinic H), 4.52 (broad m, olefinic H).

Glpc analysis [500 ft × 0.03 in. Apiezon L (95%) + Igepal 880 (5%) at 120°] of the hydrocarbon mixture revealed the presence of five components: 2% **36** (retention time 23.5 min), 1% (24.2 min), 72% **33** (24.8 min), 15% **35** (25.9 min), and 10% **34** (27.3 min). An analytical sample of the major hydrocarbon **33** was obtained by preparative glpc (10 ft × 0.25 in. 10% FFAP on 60/80 AW-DMCS Chromosorb P at 128°): pmr (CCl_4) τ 8.37 (broad s, olefinic Me).

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 87.89; H, 11.79.

Solvolysis of the *trans*-Keto Tosylate 1.—A solution of 10.00 g (29.8 mmol) of *trans*-keto tosylate 1 and 5.89 g (60 mmol) of potassium acetate in 250 ml of anhydrous acetic acid was refluxed under nitrogen for 48 hr. After having been cooled, the solution was added to 200 ml of 25% aqueous sodium hydroxide and 200 ml of crushed ice, and extracted with ether. The combined extracts were washed with saturated sodium bicarbonate solution and saturated brine, dried over magnesium sulfate, and evaporated. Distillation of the residue afforded 4.55 g (93% yield) of keto olefins as a pale yellow liquid: pmr (CCl_4) τ 8.97–8.83 (saturated methyls), 8.32 (broad 2, olefinic Me), 4.47 (s, olefinic H's).

Glpc analysis (150 ft × 0.01 in. SF 96 at 150°) of the product mixture revealed the presence of four components: 8% **55**, 75% **54**, and 17% of two unidentified compounds.

The dinitrophenylhydrazone of the major enone **54** melted at 156.2–157.0° after three recrystallizations from ethyl acetate–95% ethanol.

Anal. Calcd for $C_{17}H_{20}N_4O_4$: C, 59.27; H, 5.86; N, 16.28. Found: C, 59.38; H, 5.71; N, 16.41.

A portion of this material (1.98 g) was submitted to Wolff–Kishner reduction, using the conditions previously specified (*cf.* preparation of alcohol 6). The product (1.58 g, 86%) had pmr bands at τ 9.20–9.08 (saturated methyl), 8.36 (broad s, olefinic methyl), and 4.63 (s, olefinic hydrogens).

Glpc analysis (150 ft × 0.01 in. SF 96 at 105°) revealed the presence of six components: 10% **20** (retention time 6.4 min), 2% (6.8 min), 3% (7.0 min), 5% **36** (7.1 min), 78% **33** (7.4 min), and 2% (7.6 min).

To a solution of 104 mg of the hydrocarbon mixture in 5 ml of glacial acetic acid was added 10 mg of 2-naphthalenesulfonic acid. The resulting solution was refluxed under nitrogen for 19 hr. After cooling to room temperature, the solution was diluted with 4 ml of 25% aqueous sodium hydroxide and ice. The mixture was extracted with pentane. The extracts were washed with saturated sodium bicarbonate solution and saturated brine, dried over magnesium sulfate, and evaporated to afford 60 mg of a brown liquid. Capillary glpc analysis (150 ft × 0.01 in. SF 96 at 105°) revealed the presence of six hydrocarbons: 20% **20** (retention time 6.4 min), 2% (6.8 min), 4% (7.0 min), 43% **36** (7.1 min), 23% **33** (7.4 min), and 8% (7.5 min). Analysis of an aliquot obtained after 6.5 hr refluxing indicated 14% **20**, 52% **36**, 28% **33**, and 6% of two other components.

The pmr spectrum of the equilibrated mixture showed a considerable decrease in olefinic methyl absorption at τ 8.37 and a corresponding increase in saturated methyl absorption at τ 9.20–9.08, when compared to the spectrum of nonequilibrated hydrocarbons. Little change was observed in the olefinic hydrogen region of the spectrum.

2-(5-Oxohexyl)cyclopentanone (37).—Ozone was bubbled through a solution of 500 mg of olefins (derived from the *trans*-keto tosylate 1) in 20 ml of ethyl acetate at −40°. The ozone was generated by a Welsbach ozonater under the following conditions: air pressure of 8 psi, ozone flow rate of 0.01, and voltage at 65 V. The exhaust from the reaction flask was passed through an acidified aqueous potassium iodide solution. After 45 min of ozonation, the trapping solution turned deep purple, and the gas flow was stopped. To the solution of ozonides was added 200 mg of 10% palladium on carbon. The mixture was hydrogenated at room temperature and atmospheric pressure. Hydrogen uptake ceased after 2.5 hr. The mixture was filtered and the filtrate was dried over magnesium sulfate. Evaporation of the solvent at reduced pressure left 478 mg of a pale yellow oil shown by its ir and pmr spectra to consist mainly of dione **37**. Analytically pure **37** was obtained by preparative glpc (6 ft × 0.25 in. 10% FFAP on 60/80 AW-DMCS Chromosorb P at 190°): ir (CCl_4) 1738, 1718, 1153 cm^{-1}; pmr (CCl_4) τ 7.95 (s, 3, acetyl Me).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.58; H, 10.01.

Solvolysis of the *cis*-Keto Tosylate 3.—A solution of 10.00 g (29.8 mmol) of *cis*-keto tosylate **3** and 5.89 g (60 mmol) of potassium acetate in 250 ml of anhydrous acetic acid was refluxed under nitrogen for 6 hr. After normal work-up (see solvolysis of keto tosylate 1), the residue was distilled to obtain 4.04 g (84%) of keto olefins: pmr (CCl_4) τ 8.92 and 8.83 (singlets, angular methyls), 4.55–4.33 (m, olefinic H's).

Glpc analysis (150 ft × 0.01 in. SF 96 at 150°) of the product mixture revealed the presence of four components: 70% **13**, 15% **15**, 10% **54**, and 5% of an unknown compound.

Wolff–Kishner reduction of 1.01 g of this material (see preparation of alcohol 6 for conditions) gave 0.72 g (78% yield) of hydrocarbons: pmr (CCl_4) τ 9.10 and 9.00 (singlets, angular methyls), 8.98 (d, J = 7 Hz, secondary Me), 8.37 (broad s, olefinic H's).

The product mixture was analyzed on two capillary glpc columns. Column I (150 ft × 0.01 in. SF 96 at 105°) revealed the presence of five components: 74% **14** (retention time 6.2 min), 13% **18** (6.3 min), 2% (6.6 min), 2% (7.0 min), and 9% **33** (7.4 min). Column II [500 ft × 0.03 in. Apiezon L (95%) + Igepal 880 (5%) at 120°] revealed the presence of six compounds: 75% **14** (21.4 min), 13% **18** (22.2 min), 2% **36** (23.5 min), 4% (24.2 min), 4% **33** (24.8 min), and 2% **35** (25.9 min).

Solvolysis of the *cis*-Keto Tosylate 3-*d*.—A solution of 0.421 g (1.25 mmol) of tosylate **3-*d*** (0.97 atom of deuterium per molecule) and 0.229 g (2.54 mmol) of potassium acetate in 10 ml of anhydrous acetic acid was refluxed for 8 hr. After normal work-up (*vide supra*), there was obtained 0.168 g (82%) of a yellow oil.

Glpc analysis (150 ft × 0.01 in. SF 96 at 150°) of the crude mixture revealed the presence of four components: 69% **13-*d***, 12% **15-*d***, 13% **54-*d***, and 6% of an unknown compound.

A sample of the major octalone **13-*d*** was obtained by preparative glpc (10 ft × 0.25 in. 10% NPGS on 60/80 Chromosorb W at 185°). The pmr spectrum of this material was identical with that of the undeuterated analog **13** except for a diminished signal in the olefinic hydrogen region: pmr (CCl_4) τ 8.83 (s, 3, angular Me), 4.67–4.33 (m, *ca.* 1, olefinic H's). The low-resolution mass spectrum of the glpc purified octalone **13-*d*** exhibited a parent peak at *m/e* 165. Analysis of the relative intensities of the peaks at *m/e* 164–166 indicated 0.72 deuterium atoms per molecule (74% deuterium retention).

The crude solvolysis mixture, as well as the solvolysis products from the *cis*-keto tosylate **3**, were used for gas chromatograph–mass spectrometric analysis.[39] A comparison of the relative intensities of the peaks at *m/e* 164–166 for the deuterated octalones and at *m/e* 163–165 for the corresponding undeuterated compounds indicated 0.73 deuterium per molecule of **13** and 0.88–0.96 deuterium per molecule of **15** (91–99% deuterium retention).

Solvolysis of the *trans*-Deoxy Tosylate 2.—A solution of 1.00 g (3.09 mmol) of *trans*-deoxy tosylate **2** and 0.61 g (6.22 mmol) of potassium acetate in 25 ml of anhydrous acetic acid was refluxed under nitrogen for 3.5 hr. After normal work-up, there was obtained 0.37 g (89%) of pale yellow hydrocarbons.

The hydrocarbon mixture was analyzed on two capillary glpc columns. Column I (150 ft × 0.01 in. SF 96 at 105°) revealed the presence of four components: 3% (retention time 7.0 min), 15% **36** (7.1 min), 80% **33** (7.4 min), and 2% (6.4 min). Column II [500 ft × 0.03 in. Apiezon L (95%) + Igepal 880 (5%) at 120°] revealed the presence of five compounds: 2% (21.8 min), 14% **36** (23.5 min), 3% (24.2 min), 79% **33** (24.8 min), and 2% **35** (25.9 min).

Solvolysis of the *cis*-Deoxy Tosylate 4.—A solution of 1.59 g (4.92 mmol) of tosylate **4** and 0.96 g (9.75 mmol) of potassium acetate in 40 ml of anhydrous acetic acid was refluxed under nitrogen for 7.5 hr. After normal work-up, there was obtained 0.68 g (92%) of pale yellow hydrocarbons.

The hydrocarbon mixture was analyzed on three capillary glpc columns. Column I (150 ft × 0.01 in. SF 96 at 105°) revealed the presence of six components: 35% **14** (retention time 6.2 min), 4% **18** (6.3 min), 3% X (6.4 min), 4% (7.0 min), 24% **36** (7.1 min), and 30% **33** (7.4 min). Column II [500 ft × 0.03 in. Apeizon L (95%) + Igepal 880 (5%) at 120°] showed the presence of seven components: 28% **14** (21.4 min), 3% X (21.8 min), 3% **18** (22.2 min), 23% **36** (23.5 min), 4% (24.2 min), 36% **33** (24.8 min), and 1% **35** (25.9 min). Both columns I and II indicate the possible presence of the *trans*-octalin **20** (retention time 6.4 min on I and 21.8 min on II). This discrepancy was resolved by analysis on column III [500 ft × 0.03 in. SF 96–50 (95%) + Igepal 880 (5%) at 120°], which revealed the presence of seven components: 35% **14** (25.0 min), 3% **18** (25.4 min), 3% X (25.90 min), 4% (28.1 min), 25% **36** (28.5 min), 29% **33** (29.4 min), and 1% (30.4 min). *trans*-Octalin **20** (retention time 25.85 min) was not present. Com-

(39) We gratefully thank Dr. Jerry Han of the Department of Chemistry, University of California, Berkeley, Calif., for conducting this analysis.

pounds X and 20 were better resolved on column III at 100°, giving retention times of 38.9 and 39.3 min, respectively.

Kinetic Measurements. A. Anhydrous Acetic Acid.[40]—Anhydrous acetic acid was prepared by refluxing reagent grade glacial acetic acid with 10% acetic anhydride and a catalytic amount of concentrated sulfuric acid. After having been refluxed for 12 hr, the acetic acid was distilled through a 30-plate perforated-glass column and collected over the range 117–117.5°. The acetic acid was stored in a flask equipped with a siphon-type arrangement so that it could be removed using a positive pressure of dry nitrogen without exposing it to air.

B. **Titrations.**—Titrations of acetic acid solutions of *p*-toluenesulfonic acid with sodium acetate in acetic acid were accomplished potentiometrically on a Potentiograph E 336 (Metrohm Ltd., Herisau, Switzerland). The sodium acetate solution, approximately 0.05 *M*, was obtained by dissolving anhydrous, reagent grade sodium acetate in anhydrous glacial acetic acid and making the solution up to volume. The sodium acetate solution was standardized against 0.0527 *M* perchloric acid in acetic acid.

C. **Rate Measurements.**—Solutions 0.05 *M* in the compounds to be solvolyzed were made up at room temperature in a volumetric flask from a weighed portion of the tosylate and anhydrous acetic acid. About 3-ml portions of the solutions were sealed in 10 ml color-break ampoules (Kimble Neutraglas) under nitrogen and immersed in a 100° oil thermostat. The exact temperature of the bath was obtained from a Beckman thermometer which had been previously calibrated with a quartz thermometer (Hewlett-Packard, Inc., Quartz Thermometer No. 2801A). At suitable times an ampoule was removed and placed in a dewar of Dry Ice–isopropyl alcohol until all samples could be titrated together. Approximately 12 samples were taken during each run, spaced evenly over the first two to four half-lives. An additional one to three samples were taken for infinity points. The samples were brought to room temperature and opened. A 2-ml aliquot was removed with a Chaney syringe adjusted to deliver a constant volume. The 2-ml volume was standardized by weighing the volume of distilled water delivered by the syringe. Each aliquot was diluted to approximately 15 ml with glacial acetic acid and titrated potentiometrically.

Rate constants were obtained using a nonlinear least-squares computer program LSKIN1[41] which calculates the best value of the first-order rate constant. The infinity titer was treated as a fixed parameter. The standard deviations of the rate constants, as calculated by the computer, showed the precision of the measurements to be good, the error limits obtained generally being less than ±3% of the observed rate constants. Results are presented in Table III.

Registry No.—**1**, 22489-58-3; **2**, 34217-23-7; **3**-*d*, 34217-24-8; **4**, 34217-25-9; **6**, 34217-26-0; **8**, 34217-27-1; **9**, 34217-28-2; **10** ketal alcohol, 34217-29-3; **12**, 34217-30-6; **14**, 34217-31-7; **18**, 21789-58-2; **19**, 22489-59-4; **19** DNP, 34217-34-0; **19** semicarbazone, 34217-35-1; **20**, 22489-60-7; **22**, 34217-37-3; **23**, 34217-38-4; **24**, 34217-39-5; **25** (trans), 21370-71-8; **26**, 34217-41-9; **27**, 34217-42-0; **30**, 13031-01-1; **31** (trans), 5365-38-8; **32**, 34217-44-2; **33**, 22460-14-6; **37**, 15674-93-8; **54** DNP, 22460-13-5.

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(40) The procedure was adapted from the Ph.D. thesis of H. A. Hammond, "Studies of Acetolysis Rates of Arylmethyl *p*-Toluenesulfonates," University of California, Berkeley, Calif., 1966.

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Synthesis of 5- and 6-Fluorobenzo[c]phenanthrene by Photocyclization

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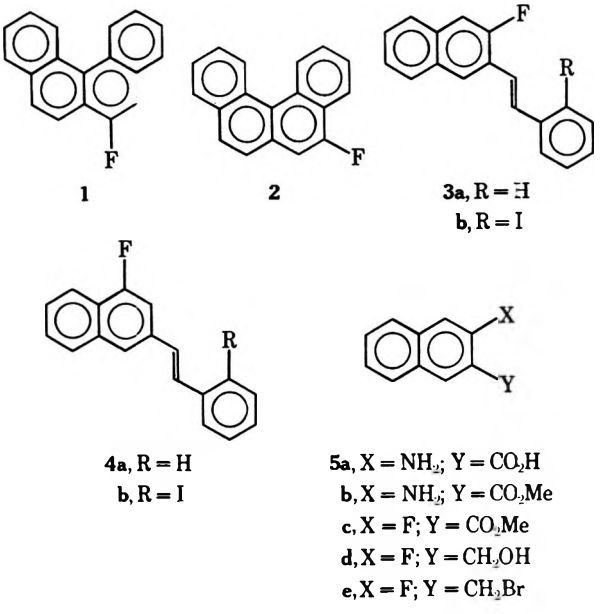
5- and 6-fluorobenzo[c]phenanthrene (**1**, **2**) were synthesized by photocyclization of the appropriately substituted 1-naphthyl-2-phenylethylenes. Various synthetic schemes for obtaining 1,3-disubstituted naphthalenes have been studied. The uv spectra of key compounds are tabulated.

Interest in fluoro analogs of polycyclic aromatic compounds stems from the hope that they may help evolve a model of chemically induced carcinogenicity.[1] We have synthesized the title compounds by photocyclization of the appropriately fluorinated diarylethylenes.[2-4]

An intrinsic expectation of the synthetic approach to **1** and **2** was that the photodehydrogenation or photocyclization step would occur on the 4 carbon of the naphthalene moiety. This expectation was bolstered by the statement[5] that the formation of phenanthrene moieties from stilbenelike compounds is possible if the sum of the free valence numbers in the first excited state (Σ Fr*) of the appropriate carbon is greater than 1.0.



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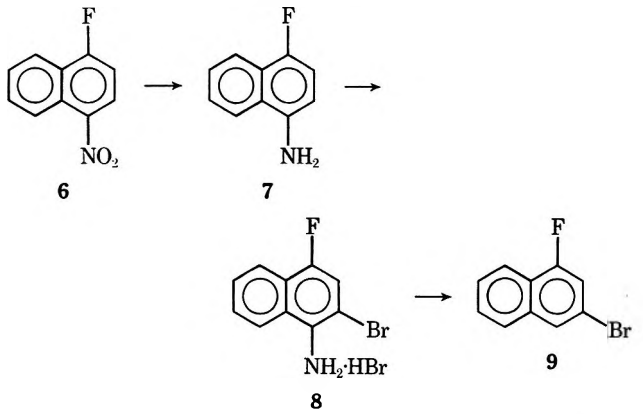
Such calculations were carried out and gave values of Σ Fr* = 1.169 (**3a**) and 1.173 (**4a**).

6-Fluorobenzo[*c*]phenanthrene (**1**) indeed was formed by the photolysis of either the ethylene **3a** or **3b**. Precursor **3a** gave yields ranging from 52% (without addition of I_2) to 82% (in the presence of the halogen), while **3b** gave >91%. Compounds **3a** and **3b** were obtained from 2-aminonaphthalene-3-carboxylic acid (**5a**), which was sequentially converted to **5e** by straightforward reactions. Horner–Wittig reaction of **5e** with either benzaldehyde or *o*-iodobenzaldehyde gave **3a** or **3b**.

Compound **2** proved to be much more difficult to obtain, since the overall yield in the multistep synthesis of the key compound 1-fluoro-3-bromonaphthalene (**9**) is very low. A number of pathways were explored.

Scheme I involved the reduction of 1-fluoro-4-nitro-

SCHEME I



naphthalene (**6**) to the amine, followed by bromination and deamination,[6] the latter step being particularly unrewarding.

Attempts to deaminate **7** by means of catalytic reduction of the diazonium fluoroborate, using rhodium complexes (RCTP and RCCP) in DMF, were unsuccessful.[7] On the other hand, the reduction of the diazonium fluoroborate of **8** with $NaBH_4$[8] did give **9** although in low yield (5–17%) depending on the solvent.

Scheme II started with the nitration of 1-aminonaphthalene. The 4-nitro *N*-acyl derivative (**10**) was brominated, deaminated, and reduced to 3-bromo-1-nitronaphthalene (**12**).[9–11] In the latter the nitro group was successively replaced by NH_2 (**13**) and F (**9**). The overall yield again was not satisfactory (2–3%).

Alternative syntheses leading to useful 1,3-disubstituted naphthalenes were explored. For example, reaction of 1-fluoro-4-nitronaphthalene (**6**) with NaCN (von Richter reaction)[12–14] gave a complex mixture of products. Ir examination of the many fractions obtained by hydrolysis and silica gel chromatography showed the loss of the NO_2 group and in some cases a new carbonyl band. However, it was not possible to isolate practical amounts of 1-fluoronaphthalene-3-

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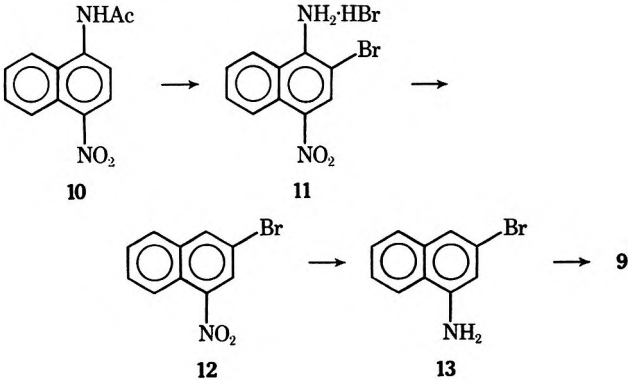
SCHEME II

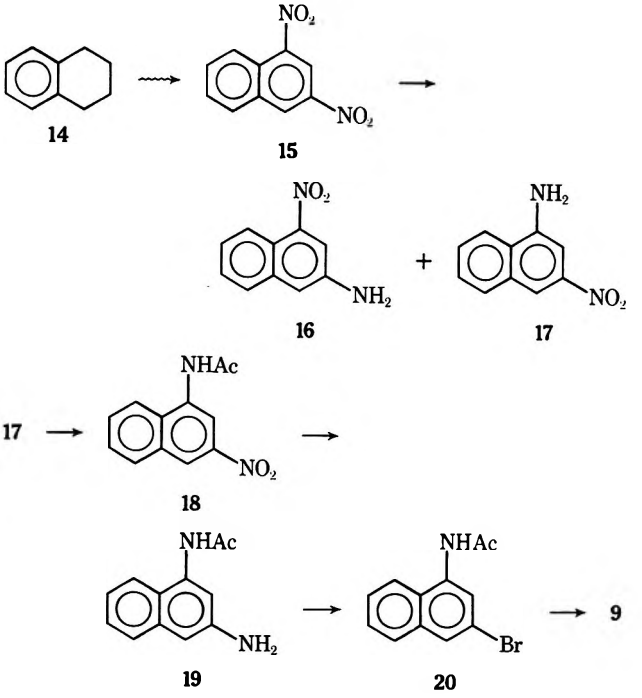


carboxylic acid (**22**). The inability of fluoronitrobenzenes to undergo the von Richter reaction has been remarked on.[10]

Our attempts to duplicate the reported procedure for the synthesis of 1-amino-3-cyanonaphthalene by fusion of sodium 1-aminonaphthalene-3-sulfonate[15] with potassium cyanide gave only traces of **15**.

A further synthesis of **9** was effected by a route starting from tetralin (Scheme III).[16–18] This procedure, too, gave only low yields (overall <1%).

SCHEME III



Altogether, the general unavailability of 1,3-disubstituted naphthalenes makes syntheses based on this type of compound extremely unpromising.

The sequence leading from **9** to compound **25** was similar to that used for the synthesis of **1**, with the exception that the Horner–Wittig reaction had to be replaced by the Michaelis–Arbuzov modification of this reaction. The photolysis of **4a**, when carried out under conditions identical with those for **3a**, gave ambiguous results. Apparently, only a portion of the material

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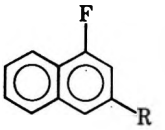
(18) H. H. Hodgson and E. R. Ward, *J. Chem. Soc.*, 1187 (1949).



9, R = Br **23**, R = CO_2Me
21, R = CN **24**, R = CH_2OH
22, R = CO_2H **25**, R = CH_2Br

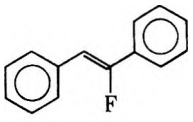
photocyclized to give **2**, as evinced by the uv spectrum. Compound **2** was successfully obtained, however, by the photolysis of **4b** in a Pyrex rather than a quartz vessel. As indicated by the uv spectrum (Table I), a

TABLE I
ULTRAVIOLET ABSORPTION PEAKS IN CYCLOHEXANE

Compd	λ_{max}, mμ ($\epsilon_{max} \times 10^{-4}$)
1	375 (0.068), 357 (0.067), 339 (0.045), sh 325 (0.35), 314 (0.86), 296 (1.2), 282 (4.70), 273 (4.1), sh 264 (2.4), 218 (3.1)
2	374 (0.070), 357 (0.081), sh 325 (0.41), 314 (0.80), 295 (1.2), 282 (4.0), 273 (3.6), sh 264 (2.4), 217 (5.0)
Benzo[c] phenanthrene	371 (0.019), 354 (0.029), 326 (0.65), 314 (1.1), 307 (1.2), 282 (8.2), 272 (6.6), sh 262 (2.6), 230 (2.6), 218 (4.6)
3a	sh 340 (1.4), 331 (3.1), 317 (3.5) sh 306 (2.4), 279 (3.5), 265 (3.5), sh 261 (2.2), 223 (3.0)
3b	sh 337 (0.25), 312 (0.37), sh 277 (0.52), 270 (0.57), 225 (0.85), 218 (0.9)
4a	354 (0.37), 340 (1.0), 327 (2.1), 317 (2.5), sh 305 (2.0), 284 (2.2), 274 (2.1), 253 (1.3), 227 (2.0)
4b	256 (0.68), 345 (0.15), 316 (3.1), 282 (2.7), 275 (2.7), 252 (2.1), 240 (2.2), 227 (3.3)
26	sh 315 (1.8), 300 (2.6), 290 (2.8), 233 (10.0), 226 (14.0), 220 (13.0)

dilute solution of **4a** also gave the desired compound **2** when irradiated in a quartz vessel.

The possibility of obtaining fluorophenanthrene systems directly by photolysis of suitable fluoro compounds of the stilbene type was attempted on α-fluorostilbene (**26**)[19] as a model. Even after irradiation of a solution



26

of **26** and iodine in cyclohexane with lamp wattages up to 250 V, no evidence of 9-fluorophenanthrene formation was observed.

MO calculations of **26** carried out subsequent to these experiments gave a value of $\Sigma F^* = 0.947$, clearly below the threshold value of 1.0 for successful photodehydrocyclization.[5]

Experimental Section

3-Fluoro-2-naphthoic Acid.—Commercial 3-amino-2-naphthoic acid (Schuchardt) was esterified using $SOCl_2$ and MeOH.[20] Diazotization and decomposition of the diazonium fluoroborate, followed by KOH hydrolysis, gave a 20% yield, mp 194–195°.

Anal. Calcd for $C_{11}H_7O_2F$: C, 69.5; H, 3.7; F, 10.0. Found: C, 70.0; H, 3.8; F, 10.3.

2-Fluoro-3-hydroxymethylnaphthalene (**5d**).—Esterification of the above acid followed by $LiAlH_4$–THF reduction gave crude **5d** (78% yield). Extraction with hot cyclohexane and recrystallization from CCl_4 gave tan crystals, mp 93–94°.

Anal. Calcd for $C_{11}H_9OF$: C, 75.0; H, 5.1; F, 10.8. Found: C, 75.3; H, 5.2; F, 10.6.

3-Bromomethyl-2-fluoronaphthalene (**5e**).—Reaction of **5d** with PBr_3 in benzene[2] gave, after chromatography on neutral alumina (benzene) and recrystallization from hexane, light tan needles, mp 87–88°.

Anal. Calcd for $C_{11}H_8FBr$: C, 55.3; H, 3.4. Found: C, 55.6; H, 3.5.

trans-**1-(2-Fluoro-3-naphthyl)-2-phenylethylene** (**3a**).—Horner–Wittig reaction of **5e** with benzaldehyde[2] gave, after chromatography on neutral alumina (cyclohexane), a 46% yield of **3a**. Recrystallization from hexane gave colorless plates, mp 136.5–138°.

Anal. Calcd for $C_{18}H_{13}F$: C, 87.1; H, 5.3; F, 7.6. Found: C, 87.3; H, 5.3; F, 7.3.

trans-**1-(2-Fluoro-3-naphthyl)-2-(*o*-iodophenyl)ethylene**(**3b**).—The same procedure as for **3a** gave a 52% yield when *o*-iodobenzaldehyde was used. Recrystallization from hexane gave needles, mp 91–92°.

Anal. Calcd for $C_{18}H_{12}FI$: C, 57.8; H, 3.2. Found: C, 57.6; H, 3.3.

6-Fluorobenzo[c]phenanthrene (**1**).[2]—A solution of 100 mg of **3b** in 200 ml of cyclohexane in a quartz tube was placed into a Rayonet photochemical reactor, fitted with 16 75-W, 2530-Å ultraviolet lamps. Nitrogen was bubbled through the solution. After 4 hr the reaction was complete (the solution had acquired a characteristic purple iodine color). The solvent was evaporated and the product was chromatographed on alumina (cyclohexane–benzene, 4:1) and recrystallized from hexane, mp 70–71°, yield 91%.

Anal. Calcd for $C_{18}H_{11}F$: C, 87.7; H, 4.5. Found: C, 87.4; H, 4.5.

Using precursor **3a** with 100 mg of iodine, a yield of 82% was obtained. Without the addition of I_2, the yield dropped to 52%.

3-Bromo-1-fluoronaphthalene (**9**).—This compound was synthesized as shown in Schemes I–III. The compound was effectively purified by silica gel chromatography (cyclohexane–benzene, 1:1). Tlc on silica gel G using cyclohexane–benzene (5:1) gave a spot, R_f 0.84. Vpc on a 1.5-m 15% DEGS column at 164° gave a well-separated peak after 23 min.

3-Cyano-1-fluoronaphthalene (**21**) was prepared from the 3-bromo compound[6] by treatment with $Cu(CN)_2$ in *N*-methylpyrrolidone.[2] Chromatography of the crude product on silica gel (benzene) followed by recrystallization in hexane gave colorless needles, yield 60%, mp 120–121° (lit.[6] mp 121–122°).

1-Fluoro-3-hydroxymethylnaphthalene (**24**).—Hydrolysis of **21** with H_2SO_4–HOAc gave the acid **22**, mp 186–189° (lit.[6] mp 189–191.5°). Esterification with diazomethane was followed by $LiAlH_4$ reduction as described for **5d**. Silica gel chromatography (EtOAc) gave the desired product, which was recrystallized from CCl_4, mp 63.5–64.5°.

Anal. Calcd for $C_{11}H_9OF$: C, 75.0; H, 5.1. Found: C, 74.7; H, 4.75.

3-Bromomethyl-1-fluoronaphthalene (**25**).—Using the same procedure as for **5e**, colorless crystals were obtained, after recrystallization from hexane, in 44% yield, mp 70–71°.

Anal. Calcd for $C_{11}H_8FBr$: C, 55.3; H, 3.4. Found: C, 55.7; H, 3.2.

trans-**1-(1-Fluoro-3-naphthyl)-2-phenylethylene** (**4a**).—The Horner–Wittig procedure on **25** gave poor yields of **4a**. Using the Michaelis–Arbuzov adaptation of this reaction,[21,22] 1.6 mmol of $(EtO)_2POH$ was mixed with 2.6 mmol of NaH and refluxed for 1 hr in 5 ml of toluene. The mixture was cooled and, after addition of 2.6 mmol of **25** in 5 ml of toluene, refluxed for 5 hr. Water and ether were added and the organic phase was separated, washed with dilute acetic acid and water, dried over $MgSO_4$, and distilled, bp 180–185° (1.5 mm), yield 54%. Treatment of this compound with equivalent amounts of benzaldehyde and NaOMe in DMF at 110° for 2.5 hr gave, after work-up and neutral

(19) E. D. Bergmann, I. Shahak, and J. Appelbaum, *Israel J. Chem.*, **6**, 73 (1968).

(20) A. Brenner, *Helv. Chim. Acta*, **36**, 1104 (1953).

(21) Houben-Weyl, "Methoden der Organischen Chemie," Vierte Auflage XII/1, Georg Thieme Verlag, Stuttgart, 1963, p 446.

(22) P. C. Crafts and G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **75**, 3379 (1953).

alumina chromatography (hexane), colorless crystals, 40% yield, mp 86–88°.

Anal. Calcd for $C_{18}H_{13}F$: C, 87.1; H, 5.3. Found: C, 87.3; H, 5.2.

trans-1-(1-Fluoro-3-naphthyl)-2-(*o*-iodophenyl)ethylene (4b).—Using the above procedure with *o*-iodobenzaldehyde, colorless needles were obtained, mp 85.5–86.5°.

Anal. Calcd for $C_{18}H_{12}FI$: C, 57.8; H, 3.2. Found: C, 57.5; H, 3.3.

5-Fluorobenzo[c]phenanthrene (2).—Photolysis of 4b in cyclohexane in a Pyrex reaction vessel gave the desired product after 3 hr, the solution having acquired a pink iodine color. The product was purified by chromatography on neutral alumina (cyclohexane–benzene, 3:1) and recrystallized from hexane, yield 80%, mp 57–59°.

Anal. Calcd for $C_{18}H_{11}F$: C, 87.7; H, 4.5. Found: C, 87.3; H, 4.8.

Photolysis of a solution of 4 mg of 4a in 100 ml of cyclohexane in a Pyrex reaction vessel gave a uv spectrum indicating that the photodehydrogenation reaction had occurred and that compound 2 was formed.

All uv spectra were run on a Unicam SP.800 spectrophotometer. The parameters used for the MO calculations were[23] $\alpha_F = \alpha_C + 2.3\beta$; $\alpha_{C'} = \alpha_C + 0.1\beta$; $\alpha_{CF} = 0.7\beta_{CC}$.

Registry No.—**1**, 34236-47-0; **2**, 34236-48-1; **3a**, 34280-38-1; **3b**, 34236-49-2; **4a**, 34236-50-5; **4b**, 34236-51-6; **5d**, 34236-52-7; **5e**, 34236-53-8; **24**, 34236-54-9; **25**, 34236-55-0; 3-fluoro-2-naphthoic acid, 712-70-9.

Acknowledgment.—Thanks are due to Dr. Jochanan Blum for his interest and for his discussions of some of the synthetic procedures. We also wish to thank Dr. A. Y. Meyer for carrying out the MO calculations.

(23) H. Berthod, personal communication.

Prostaglandins. IV.[1] A Synthesis of F-Type Prostaglandins. A Total Synthesis of Prostaglandin $F_{1\alpha}$

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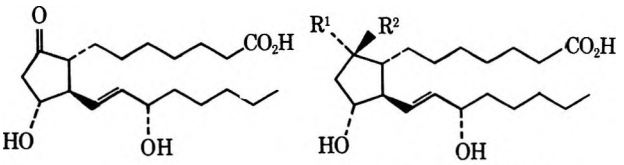
Received December 2, 1971

A seven-step total synthesis of eight racemic modifications of prostaglandin F_1 (12 and 13) is described in Chart I. The key steps are condensation of 3-oxoundecan-1,11-dioic acid with styrylglyoxal (5) to 9,12-dioxo-11-hydroxy-14-phenyltetradeca-13-enoic acid (6), cyclodehydration to 7, cleavage of the side chain to 8, selective reduction of the double bond to 9, and the Wittig reaction to 10 and 11. Borohydride reduction of 10 gives rise to *dl*-$PGF_{1\alpha}$ (12a), *dl*-$PGF_{1\beta}$ (12c), and their 15 epimers (12b and d), whereas borohydride reduction of 11 affords 11-epi-PGF_1s (13a–d). The stereochemistry of the four 11-epi-PGF_1 isomers was determined.

The prostaglandins,[2a–e] a family of oxygenated C_{20} fatty acids of widespread occurrence in animal tissues, exhibit a broad range of biological activities and presumably play an important role in sereral key processes.[2c,3] At present, the unavailability of a suitable natural source coupled with their potential drug utility has focused considerable attention toward the synthesis of these compounds and related analogs.

Prostaglandin $F_{1\alpha}$ (2, $PGF_{1\alpha}$) can be obtained along with $PGF_{1\beta}$ (3, a slightly predominant product) by borohydride reduction[4a,b] of natural PGE_1 (1). Similarly, *dl*-$PGF_{1\alpha}$ and *dl*-$PGF_{1\beta}$ were prepared[5a] by the borohydride reduction of racemic PGE_1, the latter having been synthesized by several independent methods.[5–9] Synthesis of the natural forms of 1 and 2 has been recorded by Corey and coworkers.[5c,e] The first direct total synthesis of *dl*-$PGF_{1\alpha}$ was reported by Just and Simonovitch[10] in 1967. Experimental details were not given in this communication, the pure compound was not isolated, and the reproducibility of these results was shortly thereafter questioned by Holden, *et al.*[11a] Subsequently, however, Just[11b] and Simonovitch, in colloboration with investigators from the Upjohn Co., described the experimental details for the isolation of the pure methyl esters of *dl*-$PGF_{1\alpha}$, $PGF_{1\beta}$, 8-epi-$PGF_{1\alpha}$, and 8-epi-$PGF_{1\beta}$. An efficient modification of this procedure with increased yield was reported by the Upjohn group.[7a,b]



1

2, R^1 = OH; R^2 = H
3, R^1 = H; R^2 = OH

(1) (a) Part III: M. Miyano, *J. Org. Chem.*, **35**, 2314 (1970). (b) A portion of this work was disclosed in preliminary form: M. Miyano and C. R. Dorn, *Tetrahedron Lett.*, 1615 (1969).

(2) (a) P. W. Ramwell, J. E. Shaw, G. B. Clarke, M. R. Grostic, D. G. Kaiser, and J. E. Pike, *Progr. Chem. Fats Other Lipids*, **9**, Part 2, 231 (1968); (b) S. Bergström, *Science*, **157**, 382 (1967); (c) S. Berström, L. A. Carlson, and J. R. Weeks, *Pharmacol. Rev.*, **20**, 1 (1968); (d) V. R. Pickles, *Nature (London)*, **224**, 221 (1969); (e) J. F. Bagli, *Annu. Rep. Med. Chem.*, 170 (1970).

(3) *Brit. Med. J.*, **4**, No. 5730, 253 (1970).

(4) (a) S. Bergström, L. Krabisch, B. Samuelsson, and J. Sjövall, *Acta Chem. Scand.*, **16**, 969 (1962); (b) J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, **34**, 3552 (1969).

(5) (a) E. J. Corey, N. H. Andersen; R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. Winter, *J. Amer. Chem. Soc.*, **90**, 3245 (1968); (b) E. J. Corey, I. Vlattas, N. H. Andersen, and K. Harding, *ibid.*, **90**, 3247 (1968); (c) E. J. Corey, I. Vlattas, and K. Harding, *ibid.*, **91**, 535 (1969); (d) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *ibid.*, **91**, 5675 (1969); (e) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *ibid.*, **92**, 397 (1970); (f) E. J. Corey, R. Noyori, and T. K. Schaaf, *ibid.*, **92**, 2586 (1970); (g) E. J. Corey, U. Koelliker, and J. Neuffer, *ibid.*, **93**, 1489 (1971); (h) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *ibid.*, **93**, 1491 (1971); (i) E. J. Corey, T. Ravindranathan, and S. Terashima, *ibid.*, **93**, 4326 (1971).

(6) H. Nugteren, H. Vonkeman, and D. A. van Dorp, *Recl. Trav. Chim. Pays-Bas*, **86**, 1237 (1967).

(7) (a) W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike, and J. L. Thompson, *J. Amer. Chem. Soc.*, **90**, 5895 (1968); (b) *ibid.*, **91**, 5372 (1969); (c) U. Axen, F. H. Lincoln, and J. L. Thompson, *Chem. Commun.*, 303 (1969).

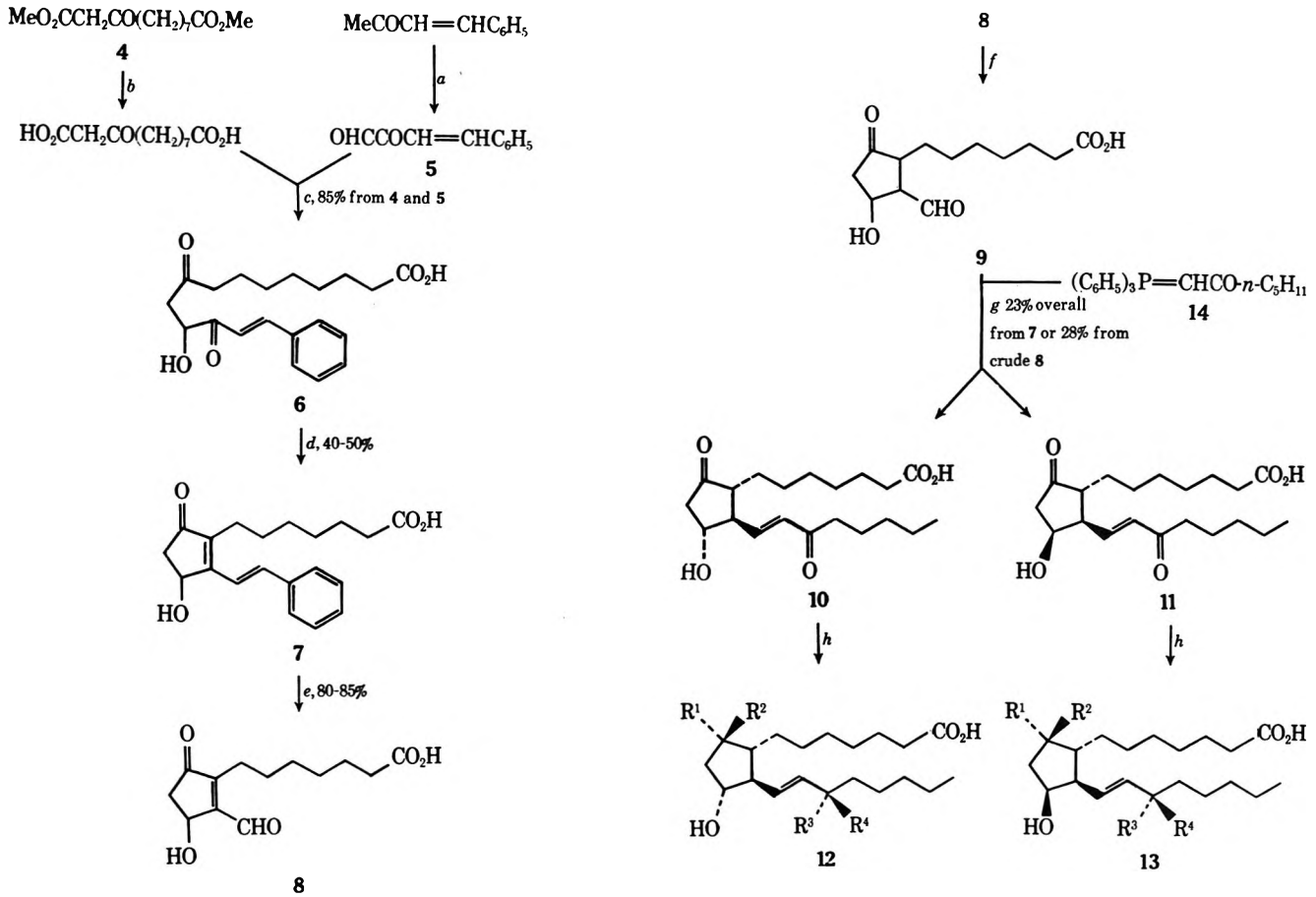
(8) N. Finch and J. J. Fitt, *Tetrahedron Lett.*, 4639 (1969).

(9) D. Taub, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, Z. S. Zelawski, and N. L. Wendler, *Chem. Commun.*, 1258 (1970).

(10) G. Just and C. Simonovitch, *Tetrahedron Lett.*, 2093 (1967).

(11) (a) K. G. Holden, B. Hwang, K. R. Williams, J. Weinstock, M. Harman, and J. A. Weisbach, *Tetrahedron Lett.*, 1569 (1968). (b) G. Just, C. Simonovitch, F. H. Lincoln, W. P. Schneider, U. Axen, G. B. Spero, and J. E. Pike, *J. Amer. Chem. Soc.*, **91**, 5364 (1969).

CHART I

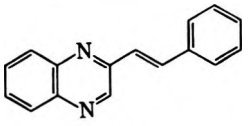


a, $R^1 = R^3 = OH$; $R^2 = R^4 = H$
b, $R^1 = R^4 = OH$; $R^2 = R^3 = H$
c, $R^2 = R^3 = OH$; $R^1 = R^4 = H$
d, $R^2 = R^4 = OH$; $R^1 = R^3 = H$

[a] Selenous acid in refluxing aqueous dioxane. [b] KOH in water at 5° for 72 hr. [c] Aqueous citrate buffer of pH 4.5–5.0 at room temperature. [d] Dilute KOH at room temperature. [e] 2 $NaIO_4$ in the presence of a catalytic amount of OsO_4 in aqueous dioxane. [f] Zinc powder in 2% acetic acid at 0° or in 8% phosphate buffer of pH 3.5 at 0°. [g] Two moles of *n*-hexanoylmethylene triphenylphosphorane in refluxing benzene containing dioxane. [h] Sodium borohydride in citrate buffer at 0°.

The object of this work was not merely the preparation of F_1 type prostaglandins, but also to develop an efficient general synthesis of new prostaglandin analogs having more selective biological activities. A sufficiently flexible synthetic route was sought which would afford the various PGF_1s (**12** and **13**) and might be extended to the synthesis of other important prostaglandins such as PGE_1 (**1**)[12] or dihydro-PGE_1.[13] A novel aspect of our seven-step scheme outlined in Chart I utilizes no protecting groups, but instead relies on a few carefully chosen reagents designed to achieve selective reactions in the presence of other reactive functional groups. Another unique feature of this scheme is that the relative stereochemistry at C-8, C-11, and C-12 of the final products (15-dehydro-PGE_1,[14a] PGE_1,[14a,c] and PGF_1[14b,c]) can be controlled by a single step, that is, reduction of **8** to **9**. This special situation offers an unusual opportunity to effect a stereospecific total synthesis of natural prostaglandins by modifying[12] the reduction step. All synthetic compounds described in this paper are racemic.

Synthesis and Determination of the Stereochemistry of the *dl*-15-Dehydro-PGE_1s (10, 11, and 18).—The starting material, styrylglyoxal (**5**), was readily prepared by the selenous acid oxidation of benzalacetone. Although the nmr spectrum of **5** revealed only a weak aldehyde proton signal (possibly due to the presence of polymeric forms), the structure was confirmed by the



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formation of styrylquinoxaline[15] (**15**) on brief treatment with *o*-phenylenediamine. Mild saponification of the dimethyl ester **4**[16] furnished 3-ketoundecan-1,11-dioic acid, which was condensed[17] with **5** in aqueous

(12) This has been acieved in these laboratories for the racemic substance and will be published in a subsequent paper.

(13) This was accomplished and is the subject of the accompanying communication: M. Miyano and C. R. Dorn, *J. Org. Chem.*, **37**, 1818 (1972).

(14) (a) The 8,12-cis forms can be isomerized to the trans isomers (see ref 4b and 25). (b) The configuration at C-15 of undesired isomers can be reversed by recycling either by formolysis and saponification (see ref 4b) or selective oxidation and reduction (see ref 5c). (c) See ref 5h for stereoselective reduction of 15 ketone.

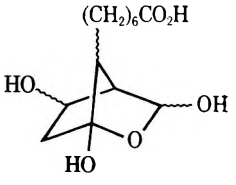
(15) (a) W. Ried and S. Hinsching, *Justus Liebigs Ann. Chem.*, **600**, 54 (1959); (b) J. K. Landquist and G. J. Stacey, *J. Chem. Soc.*, 2827 (1953).

(16) K. E. Arosenius, G. Ställberg, E. Stenhagen, and B. Tägtström-Eketorp, *Ark. Kemi, Mineral. Geol.*, **26A**, No. 19, 20 (1948).

(17) A similar condensation between pyruvic aldehyde and several 3-keto acids is well documented: M. S. Schechter, N. Green, and F. B. LaForge, *J. Amer. Chem. Soc.*, **71**, 3165 (1949).

buffer (pH 4.5–5.0) to afford the crystalline acid **6** in *ca.* 85% yield from the crude starting materials. The crystalline half potassium salt of **6** spontaneously precipitated from the reaction mixture as the condensation proceeded. It was absolutely necessary to *depolymerize* **5** (for instance, by briefly heating a methanolic solution to 60°) in order to obtain a satisfactory yield of **6**. Treatement of the hydroxy diketone **6** with dilute alkali effected cyclodehydration to the crystalline cyclopentenone derivative **7** in 40–50% yield. Periodate cleavage[18] of **7** in the presence of a catalytic amount of osmium tetroxide gave an 85% yield of the oily aldehyde **8**, which was characterized as the crystalline aldoxime and dioxime. The unsaturated aldehyde **8** was reduced to **9** with zinc in cold 2% aqueous acetic acid or in cold phosphate buffer of pH 3.5.

Since the nmr spectrum of **9** (mixture of stereoisomers) in deuteriochloroform or in deuteriodimethyl sulfoxide did not show the aldehydic proton, the aldehyde group is conceivably masked as hydrated lactol



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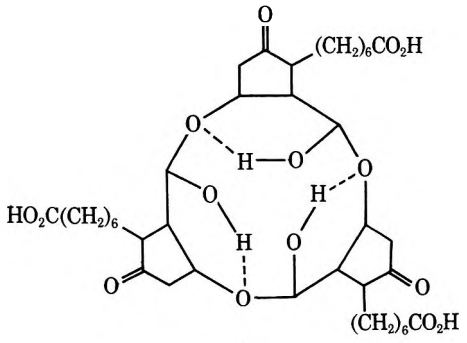
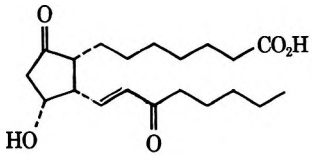


17

forms such as **16** or polymeric forms like **17**. The hydrated form **16** is unlikely to be the predominant species, since little water was formed in the subsequent Wittig condensation. In any event, compound **9** was too unstable to be fully purified and was used immediately in the next step. Apparently the saturated aldehyde derived some stabilization when mixed with (*n*-hexanoylmethylene)triphenylphosphorane (**14**)[19] and



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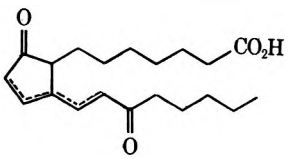

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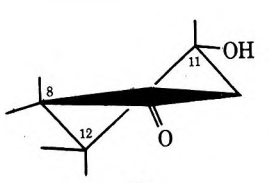
the Wittig reaction[20] produced oily 15-dehydro-PGE$_1$ (**10**, ~12% from **7**), crystalline 11-epi-15-dehydro-PGE$_1$ (**11**, ~12% from **7**), crystalline 12-epi-15-dehydro-PGE$_1$ (**18**, ~1.2%), and an oily dehydration product (**19**, ~12%). The product ratio is determined by the conditions of the zinc reduction rather than by the subsequent Wittig condensation. Thus, by zinc reduction of **8** in 2% acetic acid, **19** became one of the major products and **18** diminished to a negligible amount, while reduction in 8% phosphate buffer yielded little **19**.

The configurations of the 15-dehydro-PGE$_1$ stereoisomers were determined by nmr spectroscopy, mild base-catalyzed epimerizations, and further chemical transformations to the PGF$_1$s. The most stable conformation for **10**, **11**, **18**, and the fourth isomer, 8-epi-15-dehydro-PGE$_1$, is shown in Chart II with the

CHART II
THE MOST STABLE CONFORMATION OF "NATURAL" (**20**), 11-EPI- (**21**), 12-EPI- (**22**), AND 8-EPI-15-DEHYDRO-PGE$_1$ (**23**)



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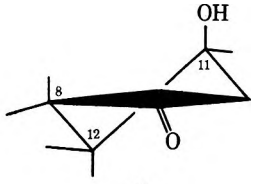

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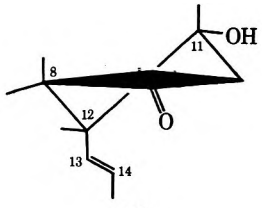

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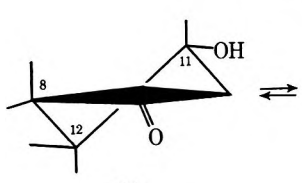
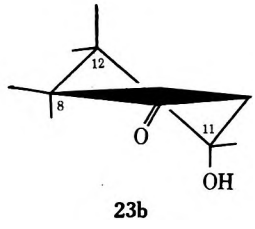


23a



23b

carbonyl group placed at the least puckered carbon[21–23] to minimize torsional energy and the half-chair conformation of the cyclopentanone ring taken to be more favorable than the envelope form.[22] It was also assumed that large equatorial substituents on the cyclopentanone ring are generally, but not necessarily, more stable than the corresponding axial orientations. For compounds **10**, **11**, and **18**, only one conformation (**20**, **21**, and **22**, respectively) is far more stable than the others; however, two equally plausible structures (**23a** and **23b**) may be written for the 8 epimer. The nmr signals of H-11 for **10** (higher field with larger coupling constants, typical for axial H), **11** (lower field with smaller coupling constants, suggesting equatorial H), and **18** (larger coupling constants, but lower field due to deshielding probably by the C-13–C-14 double bond) given in Table I are in good agreement with the conformations shown in Chart II. Furthermore, the olefinic proton signals (H-13,14) and the carbinol proton signal

(18) R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1958).

(19) P. F. Beal, III, J. C. Babcock, and F. H. Lincoln, *J. Amer. Chem. Soc.*, **88**, 3131 (1966).

(20) It was claimed that the tri-*n*-butylphosphorane gave better results (see ref 8) in a similar reaction.

(21) C. Altona, H. R. Buys, and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **85**, 973 (1966).

(22) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, p 200.

(23) O. Korver, *Recl. Trav. Chim. Pays-Bas*, **88**, 1070 (1969).

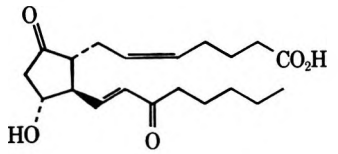
TABLE I

NMR SPECTRA OF 10, 11, 18, AND 24 IN DEUTERIOCHLOROFORM (60 MHz)

Compd	H-11, τ	H-13,[a] τ	$J_{12,13}$, Hz	H-14,[a] τ	$J_{13,14}$, Hz
24	5.56[b], 5.67, 5.82, 5.95	2.97, 3.10, 3.23, 3.36	7.5	3.58, 3.85	16
10	5.57[b], 5.70, 5.84, 5.96	2.97, 3.10, 3.23, 3.37	7.5	3.57, 3.84	16
11	5.46[c], 8.5 Hz[d]	2.77, 2.88, 3.03, 3.14	7.0	3.58, 3.85	16
18	5.40[c], ca. 24 Hz[d]	3.05, 3.22, 3.30, 3.48	10.0	3.59, 3.85	15.5

[a] H-14, H-13, and H-12 constituted an ABX pattern. [b] Broadened quartet. [c] Multiplet centered at value given. [d] Width between outer peaks.

(H-11) for **10** were indistinguishable from those of 15-dehydro-PGE_2 (**24**) prepared by a known procedure[24] from natural PGE_2. Final confirmation of the "natural"



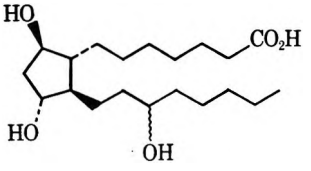
24

configuration for **10** was accomplished by reduction to *dl*-$PGF_{1\alpha}$ (**12a**) and *dl*-$PGF_{1\beta}$ (**12c**). In line with the 8,12-trans configuration, neither **10** nor **11** was epimerized by treatment with excess potassium acetate, the condition[4b,25] known to isomerize 8-epi-PGE_1 (8,12-cis) into PGE_1 (8,12-trans). On the other hand, mild treatment of **18** (8,12-cis) effected almost complete epimerization at C-8[26] to produce **11**, thus unequivocally establishing the configurations of **11** and **18**. Evidence for the absence of epimerization of the C-11 hydroxyl group (by reversed aldol followed by aldol cyclization) and of the C-12 hydrogen was demonstrated in these laboratories by deuterium exchange experiments which will be published elsewhere. To the best of our knowledge, **18** is the first compound of the 12-epi prostanoic acid series to be described in the literature.

Synthesis of *dl*-$PGF_{1\alpha}$ (12a), *dl*-$PGF_{1\beta}$ (12c), and Their 15 Epimers (12b,d).—The borohydride reduction of **10** was greatly dependent upon conditions; for example, sodium borohydride in cold methanol gave a significant amount of dihydro-PGF_1 compounds[27] along with the desired products (**12a–d**). The dihydro-PGF_1s were the major products from the tetraethylammonium borohydride reduction in methylene chloride, whereas only small amounts of these dihydro compounds were formed using potassium borohydride in aqueous buffer. In all cases, the crude reduction product was separated into two fractions by reversed phase partition chromatography.[4a] Rechromatography of the earlier fractions (mainly 9,11-trans glycols) on SilicAR CC-4[28] afforded pure *dl*-$PGF_{1\beta}$ (**12c**), mp 116° (lit.[5a,11b] mp 116.6 and 113–115°), and pure *dl*-15-epi-$PGF_{1\beta}$ (**12d**, glass[29]). Esterification of **12c** with diazomethane yielded *dl*-$PGF_{1\beta}$ methyl ester, mp 103–104° (lit.[7a,11b] mp 101–102°). The latter fractions (predominantly 9,11-cis glycols) from the partition column were chromatographed again to afford pure *dl*-15-epi-$PGF_{1\alpha}$ (**12b**), mp 61–62°,[29] and partially crystalline $PGF_{1\alpha}$ (**12a**) contaminated with **12d**. Crude **12a** was freed from impurities by boric acid impregnated dry column chromatography[30a,b] to furnish *dl*-$PGF_{1\alpha}$, mp 81° (lit.[5a] mp 81°), which was found[31] to be 48.6% as active on the smooth muscle of the rabbit duodenum as natural $PGF_{1\alpha}$ kindly provided by the Upjohn Co. The nmr spectra of synthetic **12a** and **12c** in deuteriomethanol were identical with the nmr spectra of natural $PGF_{1\alpha}$ and $PGF_{1\beta}$ prepared by a known procedure.[4a]

Synthesis and Stereochemistry of the Four 11-Epi-PGF_1s (13a–d).—Reduction of **11** with potassium borohydride afforded the desired products (**13a–d**) accompanied by dihydro 11-epi-PGF_1 isomers. The crude reduction mixture was separated by the reversed phase partition column[4a] followed by adsorption chromatography on SilicAR CC-4 to yield the pure isomers (**13a–d**), of which three are crystalline[29] (see Table V).

The cis,trans relationships between the C-9 and C-11 hydroxyl groups could be established by either nmr analysis or boric acid complex formation (see Tables II–IV and discussion below). A discussion of the nmr



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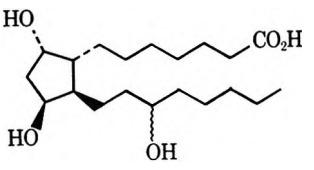


26

spectra of the dihydro compounds **25** and **26** (by-products from the aforementioned borohydride reduction of **10** and **11**, respectively) is informative, since the same general argument can be made for F-type prostaglandins. Complications arise from the nmr analysis of the PGF_1s, because these compounds do not assume "fixed" conformations, but exist as rapidly interconverting (pseudorotation[21]) conformational mixtures. Thus, compound **25** presumably pseudorotates rapidly among half-chair conformations such as **27**, **28**, and **29** and envelope conformations like **30** and **31** (X = H, Y = OH) (Chart III). From these conformations, it is readily seen that the carbinol H-9 and H-11 protons of **25** are predominantly axial, whereas H-9 and H-11 of

(24) E. Änggard and B. Samuelsson, *J. Biol. Chem.*, **239**, 4097 (1964).

(25) E. G. Daniels, W. C. Krueger, F. P. Kupiecki, J. E. Pike, and W. P. Schneider, *J. Amer. Chem. Soc.*, **90**, 5894 (1968).

(26) Since we are dealing with a racemic substance, 8,12-bisepi isomer is equivalent to the 11 epimer.

(27) A similar reduction of the $\Delta^{13(14)}$ bond has been recorded; see ref 5a.

(28) N. H. Andersen, *J. Lipid Res.*, **10**, 316 (1969).

(29) No melting point has been recorded in the literature.

(30) (a) This technique, developed in our laboratory, appears especially useful for separation of 9,11-*cis*- from 9,11-*trans*-hydroxy prostaglandin. (b) The methyl ester of *dl*-$PGF_{1\alpha}$ could be purified by boric acid impregnated thick layer chromatography (see ref 11b, p 5371). The crude *dl*-$PGF_{1\alpha}$ obtained by our synthesis could not be purified by the latter technique.

(31) Evaluated by Dr. J. H. Sanner of the Biology Department.

TABLE II

NMR SPECTRA OF 12a–d IN DEUTERIOMETHANOL (60 MHz)

Compd	$J_{9,10}$ and $J_{10,11}$, Hz	H-9, τ	H-10, τ	H-11, τ	H-15, τ	Diagnosis of cis, trans: By nmr	By boric acid complex
12a	Unequal	5.92[c]	*a*	6.12[b,d]	5.92	cis	cis
12b	Unequal	5.93[c]	*a*	6.17[b,d]	5.93	cis	cis
12c	6.5–7.0	6.00[d]	8.13[e] (triplet)	6.00[d]	6.14[b]	trans	trans
12d	6.5–7.0	6.05[d]	8.18[e] (triplet)	6.05[d]	6.17[b]	trans	trans

[a] Could not be located. [b] Approximate chemical shift; because of overlapping signals the exact position could not be located. [c] Quasiequatorial proton. [d] Quasiaxial proton. [e] Two protons were "equivalent."

TABLE III

NMR SPECTRA OF 13a–d IN DEUTERIOMETHANOL (60 MHz)

Compd	$J_{9,10}$ and $J_{10,11}$, Hz	H-9, τ	H-10, τ	H-11, τ	H-15, τ	Diagnosis of cis, trans: By nmr	By boric acid complex
13a	4.5	5.75[c]	8.00[d] (triplet)	5.75[c]	5.97	trans	trans
13b	4.5	5.75[c]	8.00[d] (triplet)	5.75[c]	5.92	trans	trans
13c	Unequal	6.20[b]	*a*	5.95[c]	5.95	cis	cis
13d	Unequal	6.25[b]	*a*	6.00[c]	6.00	cis	cis

[a] Could not be located. [b] Quasiaxial. [c] Quasiequatorial. [d] Two protons were "equivalent."

TABLE IV

NMR SPECTRA OF 25 AND 26 IN DEUTERIOMETHANOL (60 MHz)

Compd	$J_{9,10} = J_{10,11}$, Hz	H-9, τ	H-10, τ	H-11, τ	H-15, τ	Diagnosis of cis, trans: By nmr	By boric acid complex
25	6–6.5	5.95[a]	8.20[c]	5.95[a]	6.47	trans	trans
26	4.5	5.73[b]	8.02[c]	5.73[b]	6.43	trans	trans

[a] Quasiaxial. [b] Quasiequatorial. [c] Triplet; the two protons were "equivalent."

26 are essentially equatorial. As a consequence of this rapid pseudorotation, the H-10α and H-10β protons of **25** were equivalent by nmr spectrometry; they exhibited no geminal coupling and appeared as a triplet[32] due to equal couplings with H-9 and H-11 (see Table IV). Likewise, the H-10α and H-10β hydrogens of **26** also displayed "equivalence" and appeared as a triplet (Figure 1a). Upon irradiation of the H-9 and H-11 signals at τ 5.73, the H-10α and H-10β protons were decoupled to form a singlet (Figure 1b), while irradiation of the C-10 protons at τ 8.02 transformed the multiplet of H-9 and H-11 into a singlet ($W_{1/2}$ = 4 Hz, Figure 2). A careful examination of the nmr chart of **26** disclosed small coupling constants for $J_{8,9}$ and $J_{11,12}$ (0–2 Hz), suggesting a cis relationship for H-8 and H-9, as well as H-11 and H-12. Since H-10α and H-10β are "equivalent," the C-9 and H-11 hydroxyl groups must be trans, and this was confirmed by negative boric acid complex formation

(32) For a similar example, see N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "High Resolution NMR Spectra Catalog," Vol. 2, Varian Associates, Palo Alto, Calif., 1963, p 469.

TABLE V

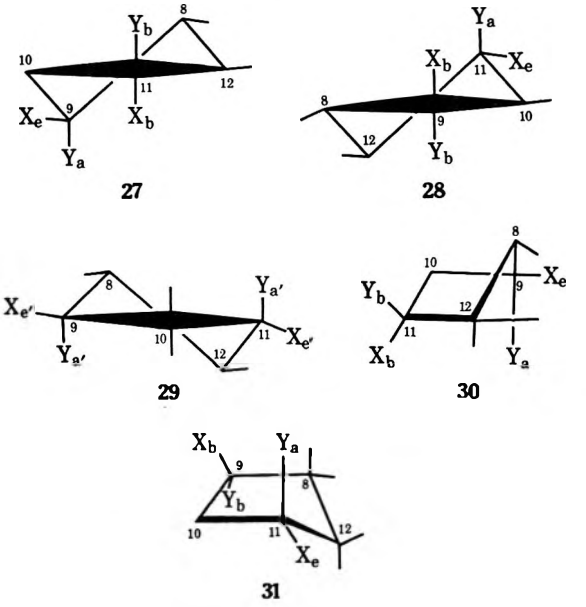
MELTING POINTS, IR SPECTRA, AND ELEMENTARY ANALYSES OF 12a–d, 13a–d, 25, AND 26

	Mp, °C	Found, % C	Found, % H	Ir (KBr), cm⁻¹ OH	Ir (KBr), cm⁻¹ C=O	Ir (KBr), cm⁻¹ C=C
dl-PGF$_{1\alpha}$ (12a)	81[d]	67.52	10.13[a]	3330	1716	967
12b	62[e]	67.85	10.25[a]	3400	1712	975
dl-PGF$_{1\beta}$ (12c)	116[f]	67.67	10.07[a]	3285	1720	978
12d	Glass[e]	67.41	10.17[a]	3330	1712	971[c]
13a	127.5[e]	67.11	10.25[a]	3300	1713	970
13b	108.5[e]	67.37	10.28[a]	3480, 3300	1713	982
13c	Glass[e]	67.26	10.34[a]	3360	1712	972[c]
13d	67.5[e]	67.72	10.05[a]	3350	1719	974
25	Glass[e]	67.15	10.59[b]			
26	100.5[e]	67.03	10.78[b]	3405, 3330	1705	None

[a] Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. [b] Calcd for $C_{20}H_{38}O_5$: C, 67.00; H, 10.68. [c] Neat. [d] Lit.[5a] mp 81°. [e] To the best of our knowledge, no melting point has been given in the literature. [f] Lit.[5a,11b] mp 116.4–116.8, 113.5°.

CHART III

STABLE CONFORMATIONS OF DIHYDRO-PGF$_{1\beta}$ (**25**, X = OH, Y = H) AND 11-EPIDIHYDRO-PGF$_{1\alpha}$ (**26**, X = H, Y = OH)[a]



[a] a, axial; b, bisectional; e, equatorial.

(Table IV). The "equivalence" of H-9 and H-11 (Figures 1 and 2, Table IV) dictates that the C-8 and C-12 side chains must also be trans, thus providing additional and independent evidence for the configuration of **11**.

The aforementioned nmr analysis of **25** and **26** can be applied to determine the cis,trans relationship of the C-9 and C-11 hydroxyl groups of **12a–d** as well as **13a–d**. In the trans glycols (**12c**, **12d**, **13a**, and **13b**) H-10α and H-10β appeared as triplets, whereas in the cis glycols (**12a**, **12b**, **13c**, and **13d**) they exhibited more complex patterns. In addition, the 9,11 cis,trans orientation could be ascertained by tlc; that is, the R_f values of the cis glycols are significantly increased on silica gel plates pretreated with boric acid, owing to transient formation of the boric acid complexes.[33] As

(33) For a similar observation, see (a) ref 11b, p 5371; (b) L. J. Morris, *Lipids*, **1**, 41 (1966); (c) *J. Chromatogr.*, **12**, 321 (1963).

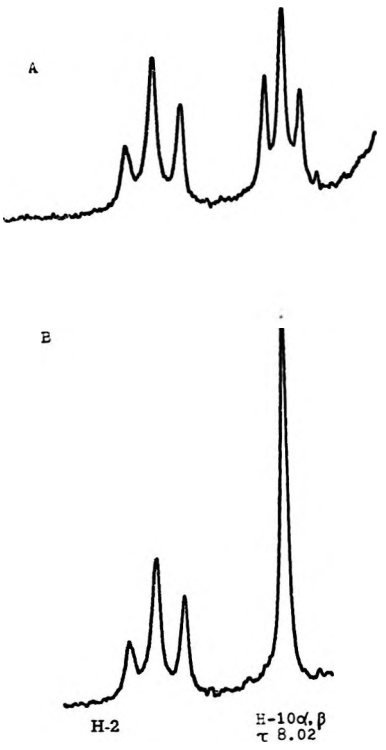
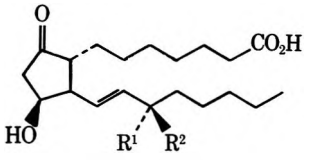


Figure 1.—Nmr signal (100 MHz, CD_3OD) of H-10α and H-10β of **26** before (A) and after (B) irradiating H-9 and H-11.

summarized in Tables II–IV, the nmr diagnosis is in good agreement with the boric acid complexing ability.

Finally, the stereochemistry at C-15 of **13a–d** was determined chemically by sodium borohydride reduction of *dl*-11-epi-PGE_1 (**32**)[5a,34] and *dl*-11,15-bisepi-



32, $R^1 = OH; R^2 = H$
33, $R^1 = H; R^2 = OH$

PGE_1 (**33**).[5a,34] Reduction of **32** afforded **13a** and **13c**, which must possess the "natural" configuration at C-15, whereas the isomer **33** produced the 15-epi compounds **13b** and **13d**.

All four 11-epi-PGF_1s (**13a–d**) have been mentioned in the literature.[28] Unfortunately, the method of preparation was not given. Furthermore, the only property described for these compounds was their relative mobilities on tlc and these were not consistent with our findings (**12b** > **13d** = **13b** > **12d** > **13c** > **12a** > **13a** > **12c**). We were therefore unable to compare our compounds with those previously reported.

Experimental Section

Melting points were taken on a Thomas-Hoover Unimelt in open capillaries and were not corrected. The nmr spectra were recorded at 60 MHz on a Varian A-60 and at 100 MHz on a Varian HA-100 nmr spectrometer in either $CDCl_3$ or CD_3OD, using TMS as an internal reference (τ 10.00). $W_{1/2}$ denotes peak width (hertz) at half-height. All uv spectra were determined in 1 mg % methanol solution.

Styrylglyoxal (5).—A solution of 106 g of benzalacetone and 100 g of selenous acid in 20 ml of water and 200 ml of dioxane in a 1-l. round-bottom flask was refluxed vigorously for 20 min. The reaction mixture was decanted while it was warm, concentrated, and distilled quickly to give 64.2–77.2 g (55–66%) of yellow crystalline **5**, bp 110–120° (2.5 mm), uv (MeOH) 295 mμ (ϵ 17,400).

(34) Prepared in these laboratories together with *dl*-PGE_1 (ref 12).

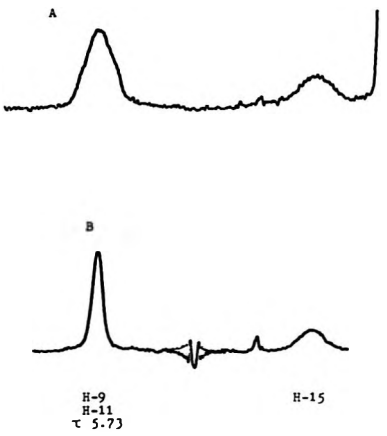


Figure 2.—Nmr signal (100 MHz, CD_3OD) of H-9 and H-11 of **26** before (A) and after (B) irradiating H-10.

2-Styrylquinoxaline (15).—A solution of 5.0 g of **5** and 3.4 g of *o*-phenylenediamine in 20 ml of ethanol was warmed on a steam bath and set aside overnight. Crystals (5.0 g, mp 106°) were collected and recrystallized from ethanol to give light brown needles, mp 106.5°.[15]

14-Phenyl-11-hydroxy-9,12-diketotetradeca-13-enoic Acid (6).—A cold solution of 38.2 g of dimethyl 3-oxoundecan-1,11-dioate (90–95% pure)[16] in 200 ml of 10% potassium hydroxide was refrigerated for 3 days. The alkaline solution was filtered through a wet filter to remove unsaponifiable oil (mostly dimethyl azelate contaminated in the starting β-keto ester), neutralized with concentrated citric acid to pH 4.9, and treated with 30 ml of 1.0 *M* citrate buffer (pH 4.8 prepared from citric acid and potassium hydroxide). To the undecanoate solution was added a solution of freshly depolymerized glyoxal, prepared by heating a mixture of 21.9 g of **5** in 50 ml of 50% aqueous methanol at 65–75° for 20 min and then diluting with 75 ml of methanol. The mixture was stirred at room temperature for 3 hr. The slightly exothermic reaction proceeded with evolution of carbon dioxide and the final pH of the reaction mixture was 6. Crystals were collected by suction, washed with water, and dried to give 37.6 g (76% based upon **5**) of the half potassium salt of **6**, mp 105°. The pure half potassium salt for analysis was obtained by recrystallization from methanol, mp 107.5°, uv (MeOH) 294 mμ (ϵ 22,500).

Anal. Calcd for $C_{40}H_{51}O_{10}K$: C, 65.73; H, 7.03. Found: C, 65.65; H, 7.01.

The ether extract of the mother liquor was washed with water, dried over sodium sulfate, and concentrated to yield 19.9 g of residue which gave rise to crystalline **6**. The latter was also obtained from the half potassium salt by shaking with ether and aqueous hydrochloric acid. Recrystallization from chloroform–ether afforded pure **6**: mp 81.5–83°; uv (MeOH) 294.5 mμ (ϵ 22,300); ir ($CHCl_3$) 2.84 (OH), 5.82 (C=O), 6.20 μ (C=O or C=C); nmr ($CDCl_3$) τ 2.19 (d, 1, J = 16 Hz), 2.97 (d, 1, J = 16 Hz,), 5.20 (t, 3, J = 5.5 Hz), 7.10 (d, 2, J = 6 Hz).

Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.34; H, 7.65.

2-Styryl-3-hydroxy-5-oxo-1-cyclopentene-1-heptanoic Acid (7).—To a stirred solution (21°) of 6.7 g of potassium hydroxide in 3 l. of distilled water was added a solution of 10.4 g of **6** in 125 ml of chloroform during 2.5 hr at 21–23°. The mixture was stirred at 23–25° for another 2 hr, 200 ml of saturated salt solution was added, and the reaction mixture was acidified with 10 g of oxalic acid dihydrate. The chloroform extract (total 1.2 l.) was washed with dilute salt solution, dried over sodium sulfate, and concentrated and the residue was recrystallized from benzene to give 4.1 g (42%) of **7**, mp 117°. An additional amount of **7** was obtained by chromatographing the mother liquor (4.3 g) on silica gel using benzene containing 2% acetic acid and increasing amounts (up to 60%) of ethyl acetate. The analytical sample was obtained by recrystallization from chloroform–ether: mp 118°; ir ($CHCl_3$) 2.66, 2.74, 2.82 (OH), 5.86 (C=O), 6.14 μ (C=O) or C=C); uv (MeOH) 325 mμ (ϵ 36,400); nmr ($CDCl_3$)

τ 4.76 (d of d, 1, J = 2 and 6 Hz), 7.11 (d of d, 1, J = 19 and 6 Hz), 7.65 (d of d, 1 J = 19 and 2 Hz).

Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.20; H, 7.57.

2-Formyl-3-hydroxy-5-oxo-1-cyclopentene-1-heptanoic Acid (8).—A mixture of 13.0 g of **7**, 17.8 g of sodium metaperiodate, 40 mg of osmium tetroxide, 55 ml of water, and 160 ml of dioxane was stirred in a stoppered flask filled with nitrogen for 4 hr at room temperature. The reaction mixture was diluted with 250 ml of dioxane, filtered to remove inorganic material, diluted with 500 ml of benzene, and extracted six times with 400 ml of 1% sodium chloride solution. The aqueous extracts were washed with 500 ml of benzene (the same benzene being used to wash the six extracts), saturated with sodium chloride, and extracted with ether. The ethereal extracts were combined, dried over sodium sulfate, and concentrated to give 8.3 g (82.5%) of crude **8** which was used for the subsequent step without purification (work-up procedure A): uv (MeOH), 228 mμ (ϵ 10,100); nmr ($CDCl_3$) τ −0.37 (s, 1, aldehyde), 4.76 (d of d, 1, J = 6 and 3 Hz), 6.33 (s, 3), 7.09 (d of d, 1, J = 19 and 6 Hz), 7.61 (d of d, 1, J = 19 and 2.5 Hz).

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.49; H, 7.75.

Two other work-up procedures for the above scale are given here. The aqueous extracts (6 × 400 ml of 1% sodium chloride) were concentrated to dryness *in vacuo* and the residue was extracted with ether. The ethereal solution was dried over sodium sulfate and concentrated to afford **8** (work-up procedure B).

The third and most convenient work-up was as follows. The reaction mixture was extracted repeatedly with ether and the ethereal dioxane solution was dried over sodium sulfate, concentrated, and dried at 70° (0.06 mm) for 5 min to remove benzaldehyde. The product obtained by the last procedure was contaminated with a small amount of **7** and benzaldehyde (work-up procedure C).

The dioxime was prepared in the usual manner and recrystallized from methanol–ethyl acetate: mp 184–185°; uv (MeOH) 278 mμ (ϵ 26,000); nmr (CD_3SOCD_3) τ 1.97 (s, 1, CH=N), 5.11 (broad d, 1, J = 5 Hz, CHO).

Anal. Calcd for $C_{13}H_{20}O_5N_2$: C, 54.92; H, 7.09; N, 9.85. Found: C, 54.97; H, 7.25; N, 9.27.

The aldoxime was prepared in the usual manner and recrystallized from ethyl acetate–chloroform and then from ether–chloroform: mp 111–112°; uv (MeOH) 273 mμ (ϵ 18,900); nmr (CD_3SOCD_3) τ 1.85 (s, 1, CH=N), 5.01 (broad d, 1, J = 5.5 Hz).

Anal. Calcd for $C_{12}H_{19}O_5N$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.68; H, 7.21; N, 5.17.

(*n*-Hexanoylmethylene)triphenylphosphorane (14).—A chloroform solution of the phosphonium chloride[19] was shaken with excess cold potassium carbonate solution, washed with dilute salt solution, dried over sodium sulfate, and concentrated. The residue was dissolved in benzene and the solvent was evaporated *in vacuo*. This was repeated once more to remove traces of chloroform. The residue was used for the subsequent condensations without further purification, nmr ($CDCl_3$) τ 6.41 (s, 1), 7.65 (t, 2, J = 7 Hz).

***dl*-15-Dehydro-PGE$_1$ (10), *dl*-11-Epi-15-dehydro-PGE$_1$ (11), and *dl*-12-Epi-15-dehydro-PGE$_1$ (18). A. Aqueous Acetic Acid Procedure 1.**—To a cold (2°) suspension of 20 g of zinc powder in 1.9 l. of 2% acetic acid was added with vigorous stirring 30.6 g of the crude unsaturated aldehyde **8** [prepared from 39 g (0.119 mol) of **7**] in 70 ml of tetrahydrofuran. The mixture was stirred under nitrogen with an additional 15 g of zinc powder for 1.5 hr at 2–3° and at the end of this period 1 l. of ether and 600 g of sodium chloride were added. The reaction mixture was filtered to remove excess zinc, which was washed with 200 ml of tetrahydrofuran. The cold filtrate was acidified with 6 g of tartaric acid and extracted with ether. The ethereal extracts (total of 3 l.) were washed with 1 l. of saturated sodium chloride solution, dried over sodium sulfate, concentrated *in vacuo*, and freed from traces of acetic acid under a nitrogen stream. The residue (26.3 g, crude **9**) was immdediately used for the condensation and refluxed with 90 g of phosphorane **14** in 200 ml of dioxane and 1.5 l. of benzene for 5 hr under nitrogen. The reaction mixture was concentrated *in vacuo*, dissolved in 1.5 l. of cold ether, and washed with 2 l. of cold 2.5% aqueous tartaric acid. Excess phosphorane **14** could be recovered from the tartaric acid washing by treatment with potassium carbonate followed by extraction with benzene. The ethereal solution containing acidic products and triphenylphosphine oxide was extracted repeatedly (5 × 200 ml) with chilled 3.5% potassium bicarbonate solution presaturated with carbon dioxide.[35] The cold bicarbonate extracts (total 1 l.) were acidified with 60 g of citric acid and the acidic product was taken up with ether. The ethereal extract was washed with 1% sodium chloride solution, dried over sodium sulfate, and concentrated *in vacuo* to afford 7.7 g of a mixture of **10**, **11**, and **19**. Repetitions of the bicarbonate extraction (5 × 200 ml) gave an additional 4.8 g. Further repetition of the bicarbonate extraction was very inefficient because the acidic products tended to remain in the ether layer, forming complexes with excess triphenylphosphine oxide. The ethereal mother liquor was then concentrated *in vacuo*, and the residue was dissolved in 30 ml of ether and treated with chilled bicarbonate solution.[35] Triphenylphosphine oxide crystallized out, thus forcing the acidic component to go into the aqueous phase. The chilled mixture was filtered to remove triphenylphosphine oxide, and another 2.9 g of material was obtained from the aqueous phase in the usual manner. Total amount of acidic material was 15.4 g (36% from **7**) which contained comparable amounts of **10**, **11**, and **19**, while 12.5–17 g of crystalline triphenylphosphine oxide was separated.

A mixture of 0.5 l. of Skelly B, 1 l. of benzene, 0.5 l. of methanol, and 0.2 l. of water was shaken and set aside. The lower phase was used to make the stationary phase of a partition column and the upper phase was used for elution. A portion (7.9 g) of the acidic product described above was chromatographed on a partition column made of 900 g of silica gel (Davison 923, 100–200 mesh) and 540 ml of the lower phase. After 2 l. of forerun containing **19** were discarded, fractions of 0.2 l were collected. Fractions 7–12 gave 2.0 g of **11**, fractions 13–18 gave 1.9 g of a mixture of **10** and **11**, and fractions 19–28 gave 1.4 g of **10**. The 11 epimer **11** was recrystallized from ether–pentane: mp 60°; uv max (MeOH) 228.5 mμ (ϵ 11,400); nmr ($CDCl_3$) τ 2.95 (q, 1, $J_{12,13}$ = 7 Hz, $J_{13,14}$ = 16 Hz, C-13 H), 3.72 (d, 1, $J_{13,14}$ = 16 Hz, C-14 H), 5.46 (m, 1, C-11 H).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.08; H, 8.89.

The *dl* natural isomer **10** was an almost colorless glass: uv max (MeOH) 228.5 mμ (ϵ 10,700); nmr ($CDCl_3$) τ 3.17 (q, 1, $J_{12,13}$ = 7.5, $J_{13,14}$ = 16 Hz, C-13 H), 3.70 (d, 1, $J_{13,14}$ = 16 Hz, C-14), 5.77 (m, 1, C-11 H).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.20; H, 9.16.

B. Aqueous Acetic Acid Procedure 2.—Crude aldehyde **8** (21 g, prepared from 27.8 g of **7**) was reduced with zinc and condensed with **14** in the usual manner (see A). After cooling, the reaction mixture was washed with 3 l. of cold 1% tartaric acid, washed with 0.7 l. of 2% sodium chloride, dried over sodium sulfate, and concentrated *in vacuo* to yield 26.2 g of brown gum. A portion (22.4 g) of this product was put on a column of 450 g of silicic acid (Mallinckrodt SilicAR CC-4, 100–200 mesh, packed using benzene), which was eluted with 3.3 l. of 10% ethyl acetate in benzene (dehydrated product **19** followed by triphenylphosphine oxide), 3 l. of 20% ethyl acetate in benzene (remaining triphenylphosphine oxide followed by **11**), and finally with 5 l. of 50% ethyl acetate–benzene (**11** and **10**). Thus 7.9 g (25.6%) of a mixture containing nearly equal amounts of **11** and **10** was obtained. Pure **11** and **10** were prepared by rechromatography of 6 g of the crude mixture on 600 g of SilicAR CC-4 washed with benzene and eluted with increasing amounts (10, 15, 20, 25, and 30%) of ethyl acetate. Pure **11** was obtained from the 25% ethyl acetate fractions while the 30% ethyl acetate fractions afforded a mixture of **11** and **10** followed by pure **10**.

C. Phosphate Buffer and "Magic Column" Procedure.[36]—A solution of 20 g of the crude aldehyde (**8**, prepared from 27 g of **7**) in 45 ml of tetrahydrofuran was added to 2 l. of cold phosphate buffer (8% sodium dihydrogen phosphate solution was acidified with phosphoric acid to pH 3.5) and stirred at 3–5° for 30 min. The zinc dust (35 g) was added portionwise and the mixture was stirred at 3–5° for 45 min. The reaction mixture (the final pH was 4.5) was filtered to remove zinc and the filter cake was washed with 50 ml of tetrahydrofuran. The filtrate was saturated with sodium chloride and extracted with ether (3 × 0.4 l.). The ethereal extracts were washed with saturated salt solution, dried over sodium sulfate and concentrated *in vacuo* to give crude **9** which was used immediately. The Wittig condensation with **14**

(35) Prepared by adding excess solid carbon dioxide to 3.5% potassium bicarbonate solution.

(36) Carried out by Mr. M. Stealey.

was carried out in the usual manner (see A). After cooling, the reaction mixture was washed with cold tartaric acid (see B) to recover excess 14 and concentrated to leave 22 g of residue which contained very little dehydration product 19 and was separated into 10, 11, and 18 by the "magic column" as described below.

A mixture of 1.5 l. of benzene, 0.5 l. of methanol, and 0.2 l. of water was shaken and set aside. The column consisted of 500 g of silicic acid (Mallinckrodt SilicAR CC-4, 100–200 mesh) and 300 ml of the lower phase solvent. This column can be used repeatedly (at least ten times) without recharging. The crude product (22 g) was chromatographed in four portions, each taking 3–4 hr and requiring 2 l. of the upper phase solvent. Triphenylphosphine oxide was eluted first followed by $HOCH_2$-$CH_2OCH_2CH{=}CHCOC_5H_{11}$, 11, 10, and 18, respectively. Mixture fractions were chromatographed once more on the same column, giving ultimately 1.5 g of crude $HOCH_2CH_2OCH_2CH{=}CHCOC_5H_{11}$, 2.3 g of 11 epimer 11, 1.4 g of a mixture of 11 and 10, and 3.39 g of 10 containing about 0.5 g of 12 epimer. Total yield of 10, 11, and 18 was 7.1 g (23% overall from 7). The last fraction was chromatographed on 300 g of CC-4. Elution with 33% ethyl acetate in benzene gave 1.34 g of pure 10, then a mixture of 10 and 18, and finally 0.50 g of 18. The latter was recrystallized from ether containing *n*-pentane to give 360 mg of the pure 18: mp 100–101°; uv max (MeOH) 226 mμ ε 12,300); nmr ($CDCl_3$) τ 3.28 (q 1, $J_{13,14}$ = 16, $J_{12,13}$ = 10 Hz, C-13 H), 3.72 (d, 1 $J_{13,14}$ = 16 Hz, C-14 H), 5.40 (m, 1, C-11 H).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.12; H, 9.36.

dl-**PGF$_{1\alpha}$**(**12a**), *dl*-**15-Epi-PGF$_{1\alpha}$** (**12b**), *dl*-**PGF$_{1\beta}$** (**12c**), and *dl*-**15-Epi-PGF$_{1\beta}$** (**12d**).—To 300 ml of cold (−5°) 2% aqueous sodium citrate was added a solution of 1.2 g of 10 in 20 ml of methanol. Five grams of potassium borohydride was added in several portions during 40 min while the reaction mixture was stirred at −5° and the pH was kept at about 8 by neutralizing with 10% citric acid. The reaction mixture was stirred for an additional 2 hr at −5° and then warmed to room temperature while the pH was continually adjusted to about 8. After excess borohydride was decomposed with acetone, the reaction mixture was acidified with citric acid to pH 4, saturated with sodium chloride, and extracted with ether. The ethereal extract was washed with dilute hydrochloric acid saturated with sodium chloride, washed with saturated salt solution, dried over sodium sulfate, and concentrated to give 1.5 g of a mixture of 12a–d.

The reduction product was chromatographed on a reversed phase partition column[4a] consisting of 60 g of hydrophobic Supercel and 60 ml of the stationary phase. After 0.4 l. of forerun, fraction 1 (1.6 l.) containing 12c and 12d was obtained, followed by fraction 2 (2.6 l.) containing 12a, 12b 25, and 9-epi-25. Fraction 1 was concentrated (0.7 g) and shaken with ether and 0.1% hydrochloric acid saturated with salt. The ethereal extract was washed with saturated salt solution, dried over sodium sulfate concentrated, and chromatographed on 40 g of SilicAR CC-4 (100–200 mesh) using ethyl acetate with increasing amounts of acetone. After a small amount of impurity (12b), 15-epi-PGF$_{1\beta}$ (12d, 213 mg) was eluted,[37] followed by a mixture fraction (12a, 12d) and finally by crystalline PGF$_{1\beta}$ (12c) which was recrystallized from ether to furnish 125 mg of 12c, mp 116°.[37] A portion (0.5 g) of fraction 2 from the reversed phase partition column was chromatographed on 40 g of SilicAR CC-4 using ethyl acetate containing increasing amounts of acetone. After the removal of fast-moving impurities (dehydration products, 25[37] and 9-epi-25), 85 mg of 15-epi-PGF$_{1\alpha}$ (12b) was eluted followed by 52 mg of a mixture fraction (12b, 12d) and finally 201 mg of crude PGF$_{1\alpha}$ (12a). The 15-epi-PGF$_{1\alpha}$ (12b) thus obtained gave rise to waxy crystals, mp *ca.* 60°, which could be recrystallized from ether at 0° with a significant loss to give needles melting at 62.5°.[37] The 15-epi-PGF$_{1\alpha}$ eluted from a CC-4 column was occasionally contaminated with a trace of 25, but was readily purified by a silver nitrate impregnated (5%) CC-4 column.

The crude *dl*-PGF$_{1\alpha}$ (12a) thus obtained was a sticky, crystalline mass which resisted crystallization, but could be purified by a boric acid impregnated column. Fifty grams of CC-4 was thoroughly mixed with 40 ml of 10% methanolic boric acid, and, after drying on a steam bath, the resulting silicic acid was further dried at 100° under reduced pressure (18 mm). The solvent system was the upper layer of 440 ml of ethyl acetate, 80 ml of acetic acid 60 ml of 2,2,4-trimethylpentane, and 400 ml of water. Crude 12a (60 mg) in 1 ml of solvent was put on a dry column of 6 g of boric acid impregnated CC-4 and eluted with the same solvent, and fractions of 2 ml were collected. Fractions 4–7 were combined and evaporated under a nitrogen stream, and the residue was taken up in ether. The ethereal solution was washed with saturated salt solution containing a few drops of hydrochloric acid, washed with saturated salt solution, dried over sodium sulfate, and concentrated. Recrystallization of the residue separated 13 mg of pure 12a, mp 81–82°.[37]

dl-**11-Epi-PGF$_{1\alpha}$** (**13a**), *dl*-**11,15-Diepi-PGF$_{1\alpha}$** (**13b**), *dl*-**11-Epi-PGF$_{1\beta}$** (**13c**),[38] *dl*-**11,15-Diepi-PGF$_{1\beta}$** (**13d**),[39] and **Dihydro-11-epi-PGF$_1$** (**26**).—To 500 ml of chilled (−5–0°) 2% sodium citrate solution was added 1.686 g of 11 in 50 ml of methanol. Potassium borohydride (7 g) was added portionwise during 1 hr while the reaction mixture was stirred at −5 to −3° and kept near pH 8 (phenolphthalein was used as internal indicator) by neutralizing with 10% citric acid. The cold bath was removed and the reaction mixture was stirred for 2 hr at pH 8–8.2. Excess borohydride was decomposed by acetone. The reaction mixture was diluted with ether, acidified with hydrochloric acid to pH 2.5, and saturated with sodium chloride. The ethereal extract was washed with 20% sodium chloride solution, dried over sodium sulfate, and concentrated to leave 1.812 g of colorless glass. Reversed phase partition chromatography[4a] on 100 g of hydrophobic Supercel was carried out and fractions of 100 ml were collected. Isomer 13a was concentrated in fractions 5–39, isomer 13b in fractions 26–50, isomer 13c in fractions 44–56, isomer 13d in 55–72, and the saturated compound 26 in 51–85. Fractions 9–35, on dissolution in methanol and treatment with acetone in the cold, gave rise to 150 mg of white crystals melting at around 146°. This substance 13a, containing inorganic material, was dissolved in a small amount of warm methanol and then shaken with ether and saturated sodium chloride solution containing a few drops of hydrochloric acid. The ethereal solution was washed with saturated sodium chloride, dried over sodium sulfate, and concentrated and the residue was recrystallized from ether to afford colorless crystals, mp 126.5–127°.[37] Fractions 36–43, 44–52, 53–60, and 61–72 were chromatographed separately on CC-4 columns using ethyl acetate with increasing amounts of acetone. Fractions enriched with 13b, 13c, 13d, and 26 were collected respectively. Fractions enriched by 13c were combined and recrystallized from ethyl acetate to give colorless crystals (98 mg), mp 66.5–67.5°.[37] Fractions enriched in 13b were combined and recrystallized from ether to give colorless crystals (188 mg) which were then recrystallized from ethyl acetate, mp 107.5–108.5°.[37] Fractions enriched with 26 were combined and recrystallized from ethyl acetate to give colorless crystals (117 mg), mp 99.5–100.5°.[37] Fractions enriched by 13d were combined (102 mg), chromatographed (ethyl acetate) on silver nitrate (5%) impregnated[40] CC-4, and rechromatographed on a boric acid (8%) impregnated dry column of CC-4 to give a colorless glass.[37]

Registry No.—**5**, 6784-05-0; **6**, 34407-34-6; **6** ($^1/_2$K salt), 34405-35-1; **7**, 34388-78-8; **8**, 34388-79-9; **8** dioxime, 34388-80-2; **8** aldoxime, 34388-81-3; **10**, 34402-60-3; **11**, 34388-82-4; **12a**, 17066-90-9; **12b**, 34388-84-6; **12c**, 20348-60-1; **12d**, 34402-61-4; **13a**, 34388-86-8; **13b**, 34388-87-9; **13c**, 34437-28-0; **13d**, 34388-89-1; **18**, 34388-90-4; **24**, 34388-91-5; **25**, 34388-92-6; **26**, 34388-93-7.

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(37) See Tables II–V for ir (KBr), nmr (CD_3OD), and elementary analyses.

(38) Equal to *dl*-9,11-diepi-PGF$_{1\alpha}$.

(39) Equal to *dl*-9,11,15-triepi-PGF$_{1\alpha}$.

(40) See purification of *dl*-PGF$_{1\alpha}$ (**12a**).

competent execution of column chromatographies, to Mr. B. Smith for preparative tlc, to the Special Synthesis group under the direction of Drs. W. M. Hoehn and J. Witt for some starting materials, and to Mr. M. H. Stealey for his skillful technical assistance. Thanks are due to Dr. F. B. Colton for helpful discussion on this work and revision of the manuscript. Styryl glyoxal (5) for large-scale preparation of compound 6 and 7 has been supplied by Dr. M. Scott, G. D. Searle & Co., High Wycombe, England, to whom thanks are due.

Prostaglandins. V.[1] Synthesis of *dl*-Dihydroprostaglandin E_1 and $\Delta^{8(12)}$-Dehydroprostaglandin E_1[2]

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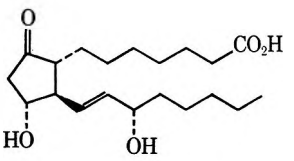
The facile synthesis of the new prostaglandin analogs, *dl*-$\Delta^{8(12)}$-dehydroprostaglandin E_1 (5) and its 15 epimer 6 is described (Chart I) which consists of a Wittig condensation of 3 with 19 to produce 4 followed by the selective reduction of the 15 ketone with borohydride. Hydrogenation of 5 afforded *dl*-dihydro-PGE$_1$ (7a) and *dl*-11,15-bisepidihydro-PGE$_1$ (8), while 6 gave rise to *dl*-15-epidihydro-PGE$_1$ (9) and *dl*-11-epidihydro-PGE$_1$ (10). Evidence concerning the stereochemical assignments for the above compounds is also presented. In addition, a new procedure for the large-scale preparation of the Wittig reagent, *n*-hexanoylmethylene triphenylphosphorane (19), is disclosed (Chart III). The key step is chlorination–decarboxylation of 3-oxooctanoic acid (16) to 17.

The prostaglandins[3] are characterized as a family of C_{20} fatty acids, and one of its members, dihydroprostaglandin E_1 (**7b**, dihydro-PGE$_1$), occurs naturally[4] as a biologically active metabolite[5] of prostaglandin E_1 (**1**, PGE$_1$). Beal, *et al.*,[6] prepared the ethyl ester of a diastereomeric mixture of the various racemic dihydro-PGE$_1$s. More recently two other research teams independently reported[7] the synthesis of a biologically active mixture (presumably **7a**, **8**, **9**, and **10**) of stereoisomers of dihydro-PGE$_1$.



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In this paper we report the synthesis of *dl*-$\Delta^{8(12)}$-dehydro-PGE$_1$ (**5**), *dl*-15-epi-$\Delta^{8(12)}$-dehydro-PGE$_1$ (**6**), and each of the four racemic modifications of dihydro-PGE$_1$ (**7a**, **8**, **9**, and **10**). This synthesis, an extension of our earlier work,[1] is outlined in Chart I. Unless specifically stated to the contrary, all compounds described in this paper are racemic.

The readily available unsaturated aldehyde (**3**)[1] reacted smoothly with the Wittig reagent (**19**)[6] in the presence of an equivalent amount of triethylamine to afford the dienedione **4** in 85% yield. It was evident that the newly formed double bond was trans, as is the case in the natural series, owing to the coupling constant (16.5 Hz) of H-13 and H-14.

Selective reduction of the 15 ketone was accomplished by excess sodium borohydride in aqueous media to produce an approximately 1:1 mixture of **5** and **6** in 70–85% yield. Evidence for the selective reduction of the 15 ketone was deduced from spectral data. First of all, the uv maxima of **5** and **6** at 276 mμ are consistent[8] with the observed value of 278 mμ for the known 11-deoxy analog, prostaglandin B_1 (**12**).[9] Secondly, the adsorption at 276 mμ is in good agreement with the calculated value[10a,c,d] of 272 mμ, but at variance with the theoretical value of 299 mμ for the alternative structure (**11**).[10b-d] The expected coupling between the olefinic protons of either **5** or **6** was not observed using a 60-MHz instrument and could barely be detected (about 16.5 Hz) in 100-MHz nmr spectra, probably due to the fact that H-13 and H-14 happened to exhibit almost identical chemical shifts. In sharp contrast, all of the *trans*-$\Delta^{13(14)}$-15-keto prostaglandins (with or without $\Delta^{8(12)}$ double bond) synthesized in these laboratories showed the typical A,B pattern ($J_{13,14}$ = 16–16.5 Hz) for the olefinic proton signals. It was very difficult to effect large-scale separation of **5** from **6** by conventional adsorption column chromatography because of the unexpected instability of these substances. However, it was discovered that partition column chromatography[11] using SilicAR CC-4 with a benzene–methanol–water system effected fairly good separation with little decomposition. The two stereoisomers (**5**

(1) Part IV: M. Miyano, C. R. Dorn, and R. A. Mueller, *J. Org. Chem.*, **37**, 1810 (1972).

(2) A portion of this work was disclosed in the preliminary communication: M. Miyano, C. R. Dorn, F. B. Colton, and W. R. Marsheck, *Chem. Commun.*, 425 (1971).

(3) For the review articles, see footnote 2 of part IV of this series.[1]

(4) E. Änggard and B. Samuelsson, *J. Biol. Chem.*, **239**, 4097 (1964).

(5) E. Änggard, *Acta Physiol. Scand.*, **66**, 509 (1966).

(6) P. F. Beal, III, J. C. Babcock, and F. H. Lincoln, *J. Amer. Chem. Soc.*, **88**, 3131 (1966).

(7) (a) D. P. Strike and H. Smith, *Tetrahedron Lett.*, 4393 (1970); (b) R. Klok, H. J. J. Pabon, and D. A. Van Dorp, *Recl. Trav. Chim. Pays-Bas*, **89**, 1043 (1970).

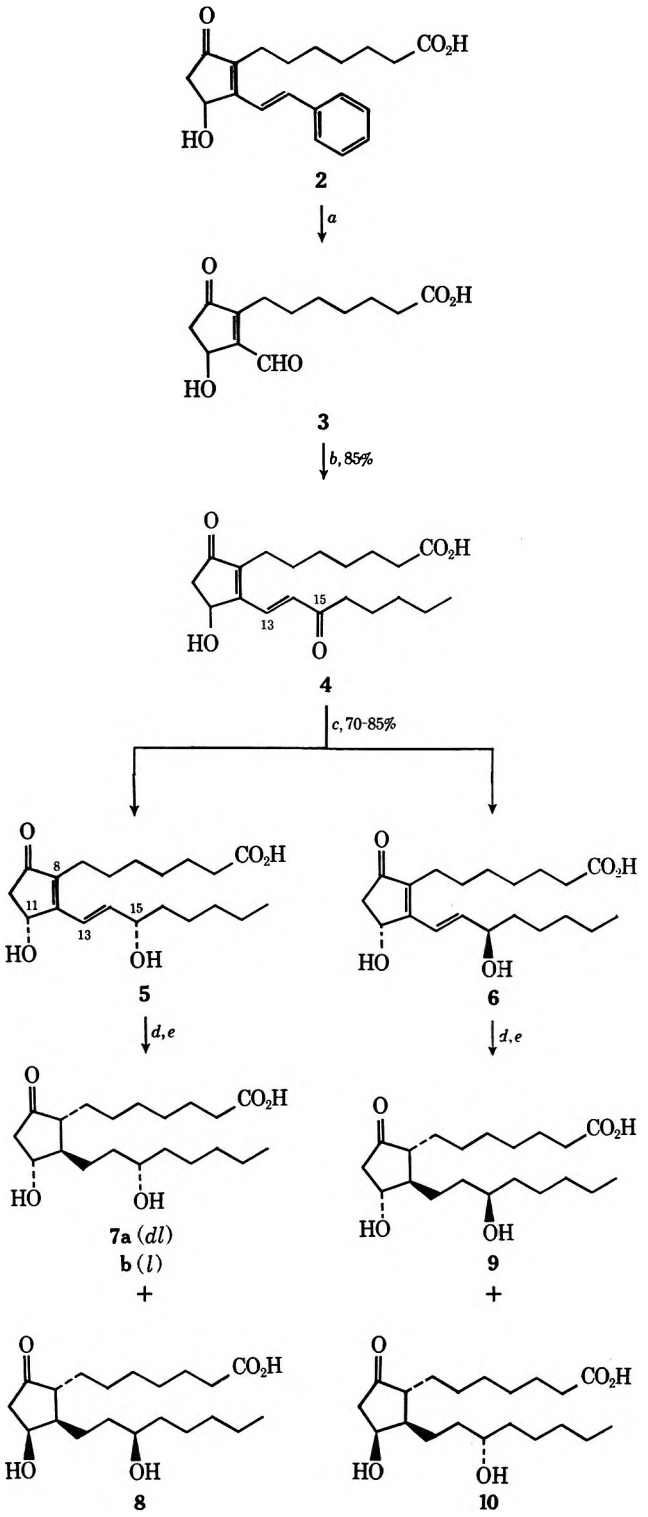
(8) The 11-hydroxy group exhibits a hypsochromic shift; see Table III of M. Miyano, *J. Org. Chem.*, **35**, 2314 (1970).

(9) S. Bergström, R. Ryhage, B. Samuelsson, and J. Sjövall, *J. Biol. Chem.*, **238**, 3555 (1964).

(10) (a) 202 (five-membered enone) + 30 (γ,δ double bond) + 10 (α substituent) + 12 (β substituent) + 18 (δ substituent) = 272; (b) 215 (aliphatic enone) + 30 (γ,δ double bond) + 18 (γ substituent) + 36 (two δ substituents) = 299; (c) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Macmillan, New York, N. Y., 1964, p 58; (d) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 19.

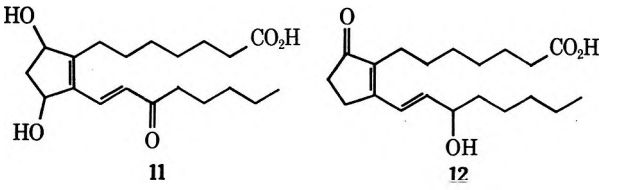
(11) See Experimental Section for **5** and **6**. Separation of 15-dehydro-PGE$_1$ from its 11 epimer (see ref 1) and separation of **7** from **8** as well as **9** from **10** (*vide infra*) were also carried out on the same column with little decomposition. Since the column can separate 2–5 g of a mixture in 4–5 hr, it may be considered a work-up procedure rather than a classical chromatography. The used column could be reused repeatedly without deterioration for as long as 6 months.

CHART I



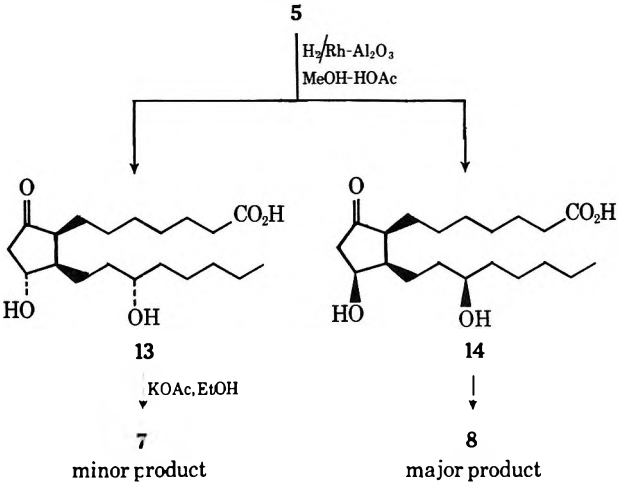
[a] $NaIO_4$, OsO_4; see ref 1. [b] $(C_6H_5)_3P{=}CHCO\text{-}n\text{-}C_5H_{11}$ and Et_3N in refluxing benzene. [c] Et_3N and $NaBH_4$ in water. [d] Hydrogenation over rhodium on alumina in methanol containing 0.5% of acetic acid. [e] KOAc in 95% EtOH at 25° for 4 days.

and 6) were spectroscopically indistinguishable except for a very slight difference in the nmr signals of the olefinic protons, but fortunately they displayed different chromatographic behavior on the partition column[11] (6 being less polar) or on tlc (5 being less polar, using silica gel with benzene–ethyl acetate–acetic acid, 25:25:1). Each isomer gave a crystalline oxime having a distinctive melting point and in addition 5 and 6 possessed different biological properties.[12] The stereochemistry of the 11- and 15-hydroxy groups was established by direct comparison of the racemic dihydro-PGE_1 (**7a**) obtained from hydrogenation of **5** with authentic dihydro-PGE_1 (**7b**) prepared from natural PGE_2.



The double bonds of **5** were saturated smoothly over rhodium on alumina in methanol containing acetic acid, whereas hydrogenation over palladium on carbon resulted mainly in hydrogenolysis of the 11-hydroxy group prior to the reduction of the $\Delta^{8(12)}$ double bond. In order to convert the 8,12-cis products into the more stable 8,12-trans isomers, the crude hydrogenation mixture was treated with excess potassium acetate in ethanol to effect epimerization[13] at C-8 to a mixture consisting predominantly of **7a** and **8**. Chromatography on the partition column[11] separated oily **7a** and crystalline **8** satisfactorily. Since the ratio of **7a** to **8** was about 2:5, hydrogenation must have occurred predominantly from the less hindered side of **5**, in other words, opposite the 11-hydroxy group, to afford **14** (8,12-cis), which in turn was isomerized to **8** (8,12-trans (Chart II). The formation of **7** may be rationalized by isomerization of **13**, the hydrogenation product from the more hindered side. Another product isolated from the column was 13,14-dihydro-PGA_1 (**15**),[7a] a dehydration product most likely formed during work-up. Likewise, the hydrogenation of **6** followed by the potassium acetate induced isomerization and partition chromatography afforded **10** as the major product together with a smaller quantity of **9**.

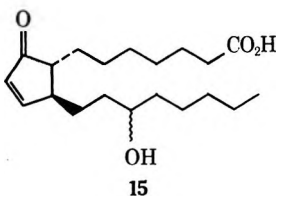
CHART II



The 100-MHz nmr spectra in deuteriochloroform

(12) Acute hypotensive activity on the anesthetized rat and activities of **5–10** on various smooth muscles were evaluate by Drs. L. P. Rozek and J. H. Sanner.

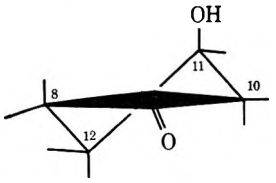
(13) For isomerization of 8-epi-PGE_1 (8, 12-cis) to PGE_1, see J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, **34**, 3552 (1969). For isomerization of 12-epi-15-dehydro-PGE_1 (8,12-cis) to 11-epi-15-dehydro-PGE_1 (8,12-trans), see ref 1.



15

clearly indicated that both **8** and **10** have the 11-hydroxyl in the β orientation (axial OH or equatorial carbonol H, see Chart III), since H-11 appeared at lower

CHART III
THE MOST STABLE CONFORMATION
(A HALF CHAIR) OF **8** AND **10**



field with smaller coupling constants (narrow multiplets, see Table I). On the other hand, **7a** and **9** ex-

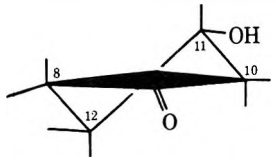
TABLE I
100-MHz NMR SPECTRA IN DEUTERIOCHLOROFORM

Compd	H-11, τ	$W_{1/2}$, Hz	H-15, τ	$W_{1/2}$, Hz
7a (synthetic)[a]	5.89	~17	6.35	15
8[b]	5.53	8.0	6.27	15
9[c]	5.89	~17	6.35	15
10[d]	5.54	8.0	6.36	15
7b (natural)[e]	5.89	~17	6.34	15

[a] Very similar to **9** but strong peak at τ 8.36. [b] Very similar to **10** but a peak at τ 8.32. [c] Two weak signals at τ 8.375 and 8.435 instead of strong peak at τ 8.36. [d] No peak at τ 8.32. [e] Identical with synthetic **7a**.

hibited the typical diaxial interaction of H-11 and H-10α (see Chart IV) with the carbinol protons at

CHART IV
THE MOST STABLE CONFORMATION
(A HALF CHAIR) OF **7a** AND **9**

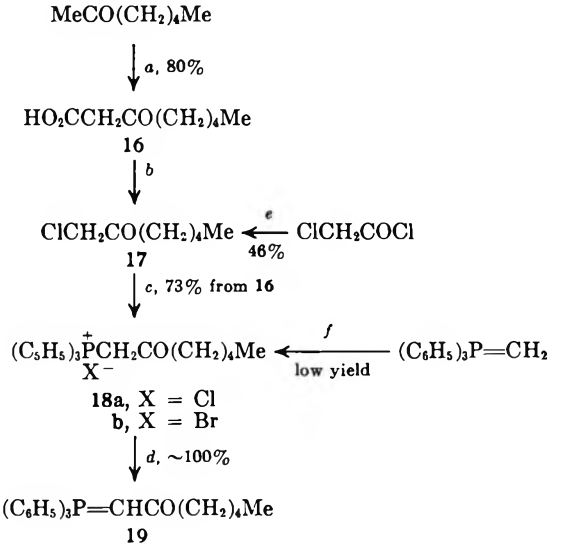


higher field having larger coupling constants (broad multiplets, see Table I). Furthermore, the nmr spectrum of **7a** was similar to that of **9**, but indistinguishable from that of dihydro-PGE_1 (**7b**) prepared by hydrogenation of natural PGE_2 (see Table I). The chromatographic behavior of the stereoisomers on tlc[14] as well as on the partition column[11] was consistent with[1] the assigned configuration at C-11; that is, the compounds having the axial hydroxyl group (**8** and **10**) migrated faster than the isomers bearing the equatorial hydroxyl group (**7a** and **9**). Lastly, the biological activities[12] of **7a** were in good agreement with the natural stereochemistry.

(14) Silica gel with either benzene–ethyl acetate–acetic acid (25:25:1) or the upper phase of ethyl acetate–acetic acid–2,2,4-trimethylpentane–water (11:2:3:10).

Although the Wittig reagent (*n*-hexanoylmethylene)-triphenylphosphorane (**19**) has been mentioned in the literature,[6] the compound was not characterized and the suggested preparative procedure (addition of *n*-hexanoyl chloride to triphenylphosphine methylene) invariably gave poor yields in our hands. To remedy this, we devised an efficient alternate scheme (see Chart V) for the kilogram-scale preparation of **19**.

CHART V



[a] Known procedure; see ref 15 and 16. [b] Sulfuryl chloride in methylene chloride at 25° followed by distillation. [c] Refluxing with triphenylphosphine in chloroform. [d] Shaking the chloroform solution of the phosphonium halide with aqueous carbonate. [e] *n*-Amylcadmium; see ref 17. [f] Known procedure; see ref 6.

Thus, the chlorination of readily available 3-ketooctanoic acid (**16**)[15,16] with sulfuryl chloride followed by distillation afforded 1-chloro-2-heptanone (**17**) which by displacement with triphenylphosphine was converted into the phosphonium chloride **18a** in 73% overall yield. The less satisfactory alternate route[17] to **17** involved the condensation of di-*n*-amylcadmium (prepared from *n*-amylmagnesium bromide *in situ*) with chloroacetyl chloride. Consistent yields could not be obtained and the **17** obtained by this procedure was contaminated with the corresponding bromo ketone.

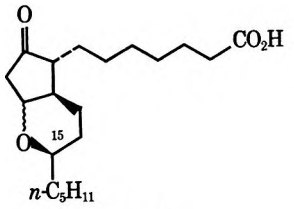
Upon prolonged refrigeration or warming in an isoosmotic phosphate buffer, a portion of **8** and **10** was transformed into **20** and **21**, respectively. It was also found that a mixture of **20** and **21** was formed in quantitative yield by chromatographing **15** (about a 50:50 mixture of 15 epimers) on a silicic acid column impregnated with silver nitrate. The nmr spectrum of **20** exhibited a typical axial H-15 at τ 6.69 (m, $W_{1/2}$ = 21 Hz) and a narrow multiplet for H-11 at τ 5.92 ($W_{1/2}$ = 7 Hz) which is consistent with cis conformation **20a**, but incompatible with the other cis conformation **20b** or the trans configuration **20c**. In contrast, the spectrum of 15α ether **21**[17a] revealed a broad multiplet for H-11 at

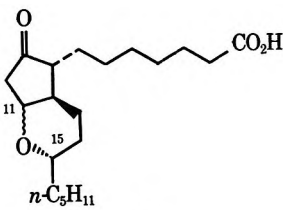
(15) S. B. Soloway and F. B. LaForge, *J. Amer. Chem. Soc.*, **69**, 2678 (1947).

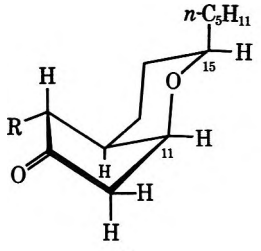
(16) R. Locquin, *Bull. Soc. Chim. Fr.*, **31**, 597 (1904).

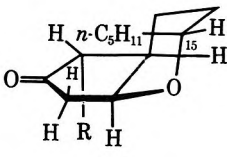
(17) S. Archer, M. J. Jackman Unser, and E. Frollich, *J. Amer. Chem. Soc.*, **78**, 6182 (1956).

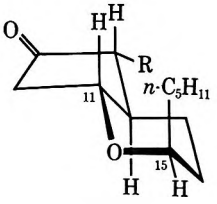
(17a) NOTE ADDED IN PROOF.—After this work had been completed the cyclic ether **21** was described in the literature: R. D. Hoffsommer, D. Taub, and N. L. Wendler, *Tetrahedron Lett.*, 4086 (1971).


20


21


20a


20b


20c

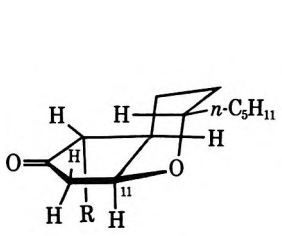
τ 6.23 ($W_{1/2}$ = 20 Hz) in addition to a somewhat broad multiplet representing H-11 at τ 5.67 ($W_{1/2}$ = 13 Hz), this pattern being compatible with the cis configuration **21a** or the trans configuration **21c**, but inconsistent with the other cis conformation **21b**. The remarkable downfield shift of protons H-11 and H-15 in compound **21** is more in line with the congested structure **21a** than with **21c**. Similar treatment (prolonged refrigeration) of natural dihydro-PGE$_1$ (**7b**) produced **21** (disregarding optical activity) exclusively, demonstrating that **21** has the 15α configuration. Whereas the nmr spectra of **5**, **7a**, and **8** were very similar to their respective 15 epimers **6**, **9**, and **10**, the nmr spectrum of **20** is quite different from its 15 epimer **21**, thus providing a reliable and probably general method for determining the stereochemistry of C-11 and C-15 in this series of compounds.

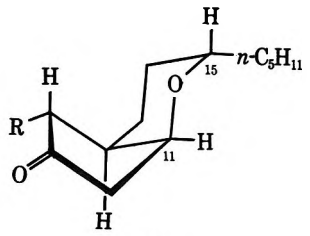
Experimental Section

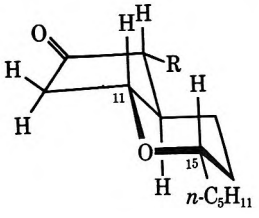
Melting points were taken on a Thomas-Hoover Unimelt in open capillary tubes and were not corrected. The nmr spectra were recorded at 60 MHz on a Varin A-60 and at 100 MHz on a Varian HA-100 nmr spectrometer in $CDCl_3$ using TMS as internal reference (τ 10.00). $W_{1/2}$ denotes peak width (hertz) at half-height. All uv spectra were determined in 1 mg % methanol solution.

Triphenyl 2-Keto-*n*-heptylphosphonium Chloride (18a).—A solution of 90 g of 3-ketooctanoic acid[15,16] in 360 ml of methylene chloride was treated dropwise at 25° with 82.3 g of sulfuryl chloride in 45 ml of methylene chloride. The mixture was stirred for 5 hr and allowed to stand at room temperature for 65 hr. The solvent was removed by distillation at atmospheric pressure and the residue was further distilled at 20 mm until the temperature of the vapor reached 65°. The pale yellow residue (83 g) contained at least 90% 1-chloro-2-heptanone[17] and was suitable for subsequent modification without further purification.

A solution 83 g of the crude chloro ketone and 180 g of triphenylphosphine in 650 ml of chloroform was refluxed for 3 hr and then allowed to stand overnight at room temperature. The solution was filtered to remove a small amount of insoluble material and the filtrate was concentrated *in vacuo*. The residue


21a


21b


21c

was dissolved in 700 ml of warm acetone, allowed to cool, and refrigerated overnight. Colorless inorganic-looking crystalline **18a** was obtained (170 g, 73%), mp 171°.

Anal. Calcd for $C_{25}H_{28}OClP$: C, 73.07; H, 6.87. Found: C, 72.77; H, 6.86.

Triphenyl 2-Keto-*n*-heptylphosphonium Bromide (18b).—A suspension of 214 g of methyl triphenylphosphonium *bromide* in 2 l. of ether was cooled in an ice bath and treated with 190 ml of 22% *n*-butyllithium in hexane under nitrogen. The ice bath was removed and the reaction mixture was stirred for 30 min, then poured into a cold stirred solution of 100 g of hexanoyl *chloride* in 500 ml of ether under nitrogen. The solvent was decanted and the residue was dissolved in chloroform washed successively with water, *hydrochloric* acid, and sodium *chloride* solution, dried over sodium sulfate, and concentrated to 600 ml. Crystals (44.9 g, the starting material) were removed by suction and the mother liquor was concentrated *in vacuo*. The residue (116 g) was dissolved in 20 ml of chloroform, diluted with cyclohexane to incipient turbidity, and allowed to stand at room temperature. Crystals (46.4 g, mp 179°) were collected and recrystallized from 30% ethanol, mp 196.5°; ir ($CHCl_3$) 5.84 μ (C=O).

Anal. Calcd for $C_{25}H_{28}OBrP$: C, 65.94; H, 6.20; Br, 17.55. Found: C, 65.84; H, 5.97; Br, 17.64.

***n*-Hexanoylmethylene(triphenyl)phosphorane (19).**—A chloroform solution of the phosphonium chloride or bromide was shaken with excess cold potassium hydroxide[18] solution, washed with dilute salt solution, and dried over sodium sulfate. The solvent was removed and the residue was dissolved in benzene. The solvent was evaporated *in vacuo;* benzene was added; and the evaporation was repeated to remove traces of chloroform. The residue was used for the subsequent condensation without further purification: nmr ($CDCl_3$, 60 MHz) τ 6.41 (s, 1), 7.65 (t, 2, J = 7 Hz). The compound crystallized on standing at room temperature.

9,15-Dioxo-11-hydroxyprosta-8(12),13-*trans*-dienoic Acid (4).—To a solution of **3** prepared from 13 g of **2** (work-up procedure C[1]) in 200 ml of dioxane was added a solution of 4.0 g of triethylamine in benzene. The mixture was concentrated *in vacuo* to remove the excess amine and finally dissolved in 210 ml of dioxane. A solution of **19** (prepared from 18 g of **18b**) in 450 ml of benzene was added and the mixture was refluxed under nitrogen for 18 hr. After cooling, the reaction mixture was concentrated and freed from triphenylphosphine oxide by dry column chromatography on 1.2 kg of silica gel containing 8% water using ethyl acetate as solvent. The desired material (**4**, 9.7 g,71% from **2** or 85% from **3**) migrated faster than triphenylphosphine oxide. The analytical sample was prepared by the second dry column chromatography on silica gel containing 8% water and 3% acetic acid using 4% methanol in benzene as solvent: uv (MeOH) 291 mμ (ϵ 21,900); nmr ($CDCl_3$, 60 MHz), - 2.46 (d, 1, J = 16 Hz), 3.07 (d, 1, J = 16 Hz), 4.85 (broad d, 1, J = 5.5 Hz).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.47; H, 8.69.

For a large scale preparation, the reaction mixture was dissolved in a small amount of ether and shaken vigorously with

(18) Potassium carbonate solution can be used in place of the alkali.

chilled potassium bicarbonate solution. As triphenylphosphine oxide crystallized out, the acidic product was transferred into the aqueous phase; the triphenylphosphine oxide was filtered off and the desired product was recovered from the bicarbonate solution.

The dioxime was prepared in the usual manner and recrystallized from ethanol: mp 211° dec; uv (MeOH) 307 mμ (ε 44,800), 319 (41,000); nmr (CD_3SOCD_3, 60 MHz) τ 3.24 (s, 2, olefinic H), 5.06 (d, 1, J = 5.5 Hz, C-11 H).

Anal. Calcd for $C_{20}H_{32}O_5N_2$: C, 63.13; H, 8.48; N, 7.36. Found: C, 63.47; H, 8.52; N, 7.65.

9-Oxo-11,15-dihydroxyprosta-8(12),13-*trans*-dienoic Acids (5 and 6).—Twelve grams of 4 was dissolved in 35 ml of ethanol and treated dropwise in the cold with a solution of 3.0 g of triethylamine in 275 ml of water. The mixture was stirred in an ice bath as 0.32 g of sodium borohydride in 32 ml of water was added dropwise. After stirring at approximately 10° for 25 min, the mixture was poured into excess aqueous citric acid and extracted three times with ether. The combined organic solutions were washed once with water, dried over anhydrous sodium sulfate, and concentrated to an oil (12 g).

A mixture of 1.5 l. of benzene, 0.5 l. of methanol, and 0.2 l. of distilled water was vigorously shaken in a separatory funnel. The stationary phase of the partition column consisted of 250 g of Mallinckrodt SilicAR CC-4 (100–200 mesh) and 250 ml of the lower phase solvent. The upper phase solvent was used for elution. The crude reduction product (2.5 g, mixture of approximately equal amounts of **5** and **6**) was dissolved in 50 ml of the upper phase solvent, placed on the partition column, and eluted. Fractions of 110 ml were collected. Fractions 21–30 contained 0.6 g of **6**, 31–33 gave 0.4 g of crude **6** contaminated by **5**, 34–35 gave 0.4 g of a mixture of **5** and **6**, and 36–42 produced 0.8 g of **5** in addition to a small amount of **6** and other impurities. Impure fractions were chromatographed on the previously used column without recharging. The same column could be used at least 20 times and still gave satisfactory separation. Although ordinary adsorption chromatography (SilicAR CC-4, benzene containing increasing amounts of ethyl acetate) effected partial separation of **5** (eluted first) and **6**, extensive decomposition took place on the column, whereas decomposition on the partition column was minimal. Since the stereoisomers **5** and **6** exhibited very similar ir, uv, and nmr spectra, the most convenient method to distinguish them was tlc (benzene–ethyl acetate–acetic acid, 25:25:1, silica gel plate); compound **5** migrated slightly faster than **6** (R_f 0.23 and 0.21, respectively) and both exhibited a yellow to green color on spraying with phosphomolybdic acid. *dl*-9-Oxo-11α,15α-dihydroxyprosta-8(12),13-*trans*-dienoic acid (**5**) was obtained as a colorless, viscous oil: uv (MeOH) 276 mμ (ε 28,200); nmr ($CDCl_3$, 100 MHz) τ 3.35 (2, broad s, J = 16–17 Hz, can barely be seen), 4.90 (1, broad d, H-11), 5.65 (1, m, H-15).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 67.97; H, 9.17.

The oxime was prepared in the usual manner and recrystallized from ethyl acetate: mp 113–115°; uv (MeOH) 276 mμ (ε 32,100); nmr (CD_3SOCD_3, 60 MHz) τ 3.65 (2, AB part of ABX), 5.20 (1, m, H-11) 5.90 (1, m, H-15).

Anal. Calcd for $C_{20}H_{33}O_5N$: C, 65.37; H, 9.05; N, 3.81. Found: C, 65.39; H, 9.01; N, 3.73.

***dl*-9-Oxo-11α,15β-dihydroxyprosta-8(12),13-*trans*-dienoic acid (6)** was also a colorless, viscous oil:[19] uv (MeOH) 276 mμ (ε 26,500); nmr ($CDCl_3$, 100 MHz) τ 3.43 (2, AB portion of ABX pattern, J_{AB} = 16–17 Hz, can barely be seen), 4.89 (1, broad d, H-11), 5.72 (1, m, H-15).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 67.52, 67.59; H, 9.03, 9.36.

The oxime was made in the usual manner and recrystallized from methanol–ether: mp 137–138.5°; uv (MeOH) 275.5 mμ (ε 31,600); nmr (CD_3SOCD_3 60 MHz), τ 3.66 (2, AB part of ABX pattern), 5.19 (1, m, H-11), 5.92 (1, m, H-15).

Anal. Calcd for $C_{20}H_{33}O_5N$: C, 65.37; H, 9.05; N, 3.81. Found: C, 65.18; H, 9.09; N, 3.69.

***dl*-Dihydro-PGE$_1$ (7a) and *dl*-11,15-Bisepidihydro-PGE$_1$ (8).**—A solution of 1.815 g of **5** in 226 ml of methanol containing 0.5% acetic acid was hydrogenated in the presence of 680 mg of 5% rhodium on alumina under 60–40 psi hydrogen at room temperature. After 4 hr the hydrogen uptake (120% of the calculated amount) ceased and the product exhibited no uv absorption. To the crude hydrogenation product were added 1.9 g of potassium bircarbonate in 65 ml of water, 31.5 g of potassium acetate, and 1.2 l. of ethanol. The homogeneous solution was set aside for 93 hr. The reaction mixture was concentrated *in vacuo*, dissolved in cold water, acidfied with citric acid to pH 4.0, and extracted with ether. The ethereal solution was washed with iced 1% sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. The residue was dissolved in 50 ml of ether and the solvent was stripped by a nitrogen stream. This procedure was repeated until the residue became completely free from acetic acid. The residue (1.5 g) was chromatographed on the partition column[11] made from 400 g of SilicAR CC-4 in the usual manner (see for **5** and **6**) and fractions of 100 ml were collected. Fractions 7–9 gave 266 mg of **15**, fractions 16–22 yielded 362 mg of crystalline **8**, fractions 23–24 gave 50 mg of a mixture of **7a** and **8**, and fractions 25–32 afforded 150 mg of **7a**. The *dl*-11,15-bisepidihydro-PGE$_1$ (**8**) thus obtained was free from any impurities and was recrystalized from ethyl acetate–Skelly B, mp 76–77°; for nmr ($CDCl_3$) see Table I.

Anal. Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.58; H, 10.25.

The purified *dl*-dihydro-PGE$_1$ (**7a**) thus obtained was chromatographed on 5 g of SilicAR CC-4 using 50% ethyl acetate in benzene. After 25 ml of forerun, fractions containing pure **7a** were collected as a colorless oil, nmr ($CDCl_3$, see Table I) identical with that of natural dihydro-PGE$_1$.

Anal. Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.34; H, 10.00.

***dl*-15-Epidihydro-PGE$_1$ (9) and *dl*-11-Epidihydro-PGE$_1$ (10).**—A solution of 1.454 g of **6** in 182 ml of methanol containing 0.5% acetic acid was hydrogenated and worked up in the same manner as for **7a** and **8**. The product (1.3 g) was chromatographed on the partition column[11] made from 400 g of SilicAR CC-4 in the usual manner (as for **5** and **6**). Fractions of 100 ml were collected Fractions 7–9 afforded 251 mg of **15**, 13–21 gave 362 mg of **10**, and 24–31 yielded crude **9**.

The *dl*-11-epidihydro-PGE$_1$ (**10**) thus obtained was essentially pure but was rechromatographed on 50 g of SilicAR CC-4 using 50% ethyl acetate–benzene. After 220 ml of forerun, pure **10** was eluted as a colorless oil; for nmr ($CDCl_3$) see Table I.

Anal. Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.66; H, 10.38.

The *dl*-15-epidihydro-PGE$_1$ (**9**) obtained from the partition chromatography was impure and was purified as follows. Fractions 24–26 from the partition chromatography were combined and rechromatographed on 5 g of CC-4 using 50% ethyl acetate–benzene and fractions of 12 ml were collected. Pure **9** (22 mg) was found in fractions 5–8. Fractions 27–31 of the partition chromatography were combined and rechromatographed on 5 g of CC-4 to give 38 mg of **9** as a colorless oil; for nmr ($CDCl_3$) see Table I.

Cyclic Ether 20.—A solution of 84 mg of crystalline **8** in 23 ml of isoosmotic phosphate buffer (pH 7.1) was left at 37° for 10 days, acidified with citric acid, and extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate, and concentrated, and the residue was chromatographed on 50 g of SilicAR CC-4 using ethyl acetate–benzene (1:1) to give 67 mg of **20**: mp 33.5–35°; ir ($CHCl_3$) 1742 (C=O), 1713 cm^{-1} (CO_2H); nmr ($CDCl_3$, 100 MHz) τ 5.92 (m, 1, $W_{1/2}$ = 7 Hz, H-11), 6.69 (m, 1, $W_{1/2}$ = 21, H-15).

Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 70.97; H, 10.21.

Cyclic Ether 21. A.—Oily **10** (161 mg) was left standing for 2 weeks and then chromatographed on 50 g of SilicAR CC-4 using ethyl acetate–benzene (1:1) to give 17 mg of **21**: ir ($CHCl_3$) 1736 (C=O), 1710 cm^{-1} (CO_2H); nmr ($CDCl_3$, 100 MHz) τ 5.67 (m, 1, $W_{1/2}$ = 13 Hz, H-11), 6.23 (m, 1, $W_{1/2}$ = 20 Hz, H-15).

B.—Oily natural dihydro-PGE$_1$ (**7**) was refrigerated for 60 days and then chromatographed on CC-4 giving **21**, which was indistinguishable by nmr, ir, and tlc (benzene–ethyl acetate–acetic acid, 25:25:1, on silica gel) from **21** obtained *via* **10**.

Cyclic Ethers 20 and 21.—Crude **15**, obtained as a by-product of **7a**, **8**, **9**, and **10**, was combined (550 mg) and chromatographed on 55 g of silver nitrate (5%) impregnated SilicAR CC-4 using 20% ethyl acetate in benzene. The eluate was concentrated and rechromatographed on 50 g of plain SilicAR CC-4 using ethyl acetate–benzene (1:1) to give 250 mg of an approximately 1:1 mixture of **20** and **21**. The nmr spectrum ($CDCl_3$, 100 MHz)

(19) The optically active forms are crystalline. See ref 2.

indicated that no other cyclic ether stereoisomeric to **20** and **21** was formed in significant quantity.

Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.93; H, 10.13. Found: C, 71.01; H, 10.25.

Registry No.—**4**, 32925-93-2; **4** dioxime, 34388-66-4; **5**, 32925-94-3; **5** oxime, 34388-96-0; **6**, 32946-04-6; **6** oxime, 34388-98-2; **7a**, 28896-13-1; **8**, 34389-00-9; **9**, 34389-01-0; **10**, 34389-02-1; **18a**, 34407-51-7; **18b**, 34407-52-8; **19**, 33803-58-6; **20**, 34389-03-2; **21**, 34389-04-3.

Acknowledgment.—The authors wish to express their gratitude to Drs. J. H. Sanner and L. F. Rozek for biological evaluation of the synthetic dihydro-PGE_1's which provided unequivocal evidence for the stereochemical assignments. The authors gratefully acknowledge the generous gift of natural PGE_2 by Dr. P. S. Cammarata and Mr. F. Fago. The authors are indebted to Dr. J. W. Ahlberg and staff for their spectral and elemental analyses, Mr. R. T. Nicholson and staff for their competent execution of column chromatography, Special Synthesis group under the direction of Dr. W. M. Hoehn for some starting materials, Messrs. M. G. Scaros and E. Saugstad for hydrogenation, and Mr. M. H. Stealey for his skillful technical assistance. We thank Dr. F. B. Colton for discussion on this work and revision of the manuscript.

Notes

Leguminosae Alkaloids. VIII. Development of an Improved Synthesis of Anagyrine as a Potential Route to Other Lupin Alkaloids[1]

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The newer lupin alkaloids multiflorine (**1**)[2] and nuttalline (**2**)[3] are related to the longer known plant base anagyrine (**3**)[4] by the common stereochemistry of the C/D ring fusion and by similar oxidation states of ring A. A total synthesis of anagyrine was developed by van Tamelen and Baran,[6] which, with suitable modification, appeared as an attractive potential route for synthesis of **1** and **2**. We report now on work which has provided substantial material improvements in the van Tamelen–Baran anagyrine synthesis, enhancing its potential role as a more general sequence.

Our modification of the van Tamelen–Baran synthesis consists of a more direct and more economical means of reaching the intermediate, *r*-(1*R*,3*S*,10*S*)-1-hydroxymethyl-3-(2-pyridyl)quinolizidine[7] (**4**). This key compound is converted to anagyrine *via* quaternization of the bromide **5**, followed by oxidation of the resulting quaternary salt **6**.

The present reaction sequence leading to **4** may be conveniently compared with the earlier one, since both start from α-methylpyridine. van Tamelen and Baran[6] reached **4** with a reaction sequence that required five isolation stages and gave **4** in an overall yield of 2.4%. In addition, that synthesis required the use of α-tripiperideine, a reagent obtained in only moderate yield and with some difficulty from piperidine.[8] The present synthesis is much more advantageous. The amino alcohol **4** is obtained in 23% overall yield from α-methylpyridine with only four isolation stages. The ancillary preparation of α-tripiperideine is not required.

In 1936, Clemo, Morgan, and Raper[9] found that treatment of ethyl (2-pyridyl)acetate (**7**, R = ethyl) with ethyl orthoformate in boiling acetic anhydride gave the quinolizone **8** quite efficiently. While utilization of **8**

(1) Work done at the University of South Carolina.

(2) S. I. Goldberg and R. F. Moates, *J. Org. Chem.*, **32**, 1832 (1967).

(3) S. I. Goldberg and V. M. Balthis, *J. Chem. Soc. D*, 660 (1969).

(4) Naturally occurring anagyrine is levorotatory. Its absolute configuration[5] is actually the mirror image of that shown in structure **3**. (−)-Multiflorine and (+)-nuttalline possess the absolute configurations shown in **1** and **2**, respectively.

(5) S. Okuda, H. Kataoka, and K. Tsuda, *Chem. Pharm. Bull.*, **13**, 487, 491 (1965).

(6) E. E. van Tamelen and J. S. Baran, *J. Amer. Chem. Soc.*, **80**, 4659 (1958).

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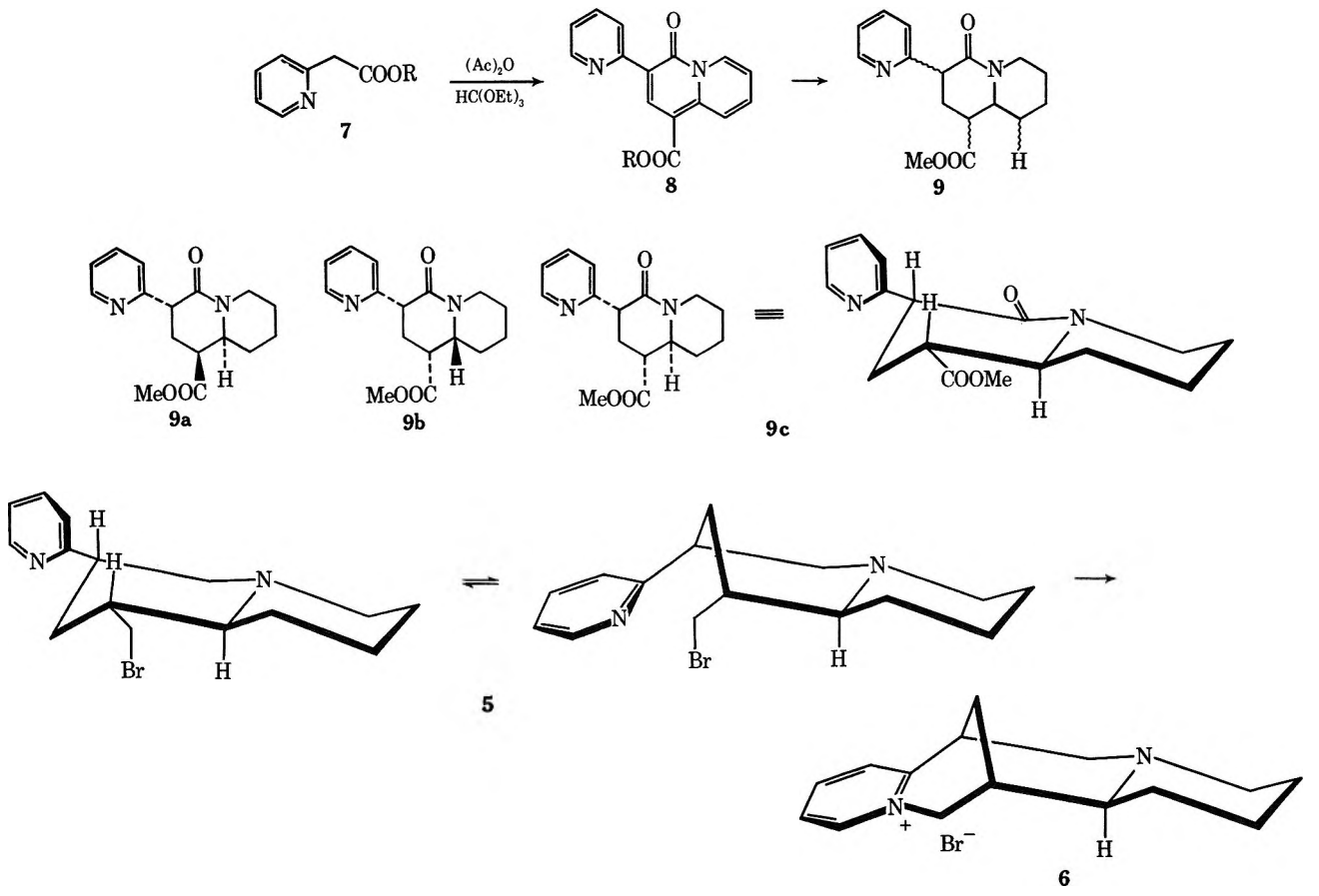
(8) C. Schöpf, A. Komzak, F. Braun, and E. Jacobi, *Justus Liebigs Ann. Chem.*, **559**, 1 (1948).

(9) G. R. Clemo, W. M. Morgan, and R. Raper, *J. Chem. Soc.*, 1025 (1936).



as a precursor of anagyrine is fairly obvious, the recently developed partial hydrogenation procedure of Liu, *et al.*,[10] was needed to make it possible. We have found that the prescribed[8] distillation for isolation of **8** (R = ethyl) is avoided when the compound is prepared as the methyl ester (from **7**, R = methyl[11]), for the latter crystallizes directly out of the dark oily reaction mixture. The methyl ester **8** is efficiently hydrogenated to its octahydro derivative **9**. This compound possesses three chiral centers, so that the hydrogenation product could exist as a mixture of four diastereomers. However, if the hydrogenation proceeded in a stepwise, syn manner, as is frequently the case,[12] only two of the diastereomers (**9a** and **9b**) would result. This was apparently the case, as evidenced by the presence of only two signals at δ 3.63 and 3.67 owing to the methoxyl protons in the nmr spectrum determined from **9**. However, neither **9a** nor **9b** is expected to be the most favored diastereomer of the set. That form is presumably **9c**, the only one that could exist in the trans-fused, chair–chair, all-equatorial form. Indeed, treatment of the mixture **9** with sodium methoxide gave a single isomer in high yield.[13] Retention of the all-cis configuration of **9c** is in fact required for **5** in order to account for the conversion of **5** to **6**. This point has already been discussed by van Tamelen and Baran.[6]

The final step in the present sequence was the routine reduction (lithium aluminum hydride) of **9c** to the desired amino alcohol **4**, followed by conversion of the latter (original van Tamelen and Baran procedure[6]) to anagyrine (**3**).

Experimental Section

General.—Temperatures were uncorrected. The Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., performed the combustion analyses. Infrared (ir) spectra were obtained with a Perkin-Elmer Model 357 grating spectrometer. Nuclear magnetic resonance (nmr) spectra were determined in chloroform-*d* solutions, containing 1–4% (v/v) tetramethylsilane (TMS) internal standard, with a Varian A-60 spectrometer. Chemical shifts were noted under the δ convention in parts per million (ppm) relative to TMS (0 ppm). A Perkin-Elmer Hitachi Model RMU-6 mass spectrometer was used for mass spectra.

1-Carbomethoxy-3-(2-pyridyl)-4-quinolizone (8).—A mixture of methyl (2-pyridyl)acetate (30.2 g, 0.200 mol), triethyl orthoformate (31.6 g, 0.214 mol), and acetic anhydride (38 ml) was heated under reflux for 8 hr. Most of the excess acetic anhydride was removed by distillation at ambient pressure. During distillation of the remaining volatile material at steam bath temperature and reduced pressure (water aspirator) a bright yellow solid formed in the undistilled material. This material was washed twice with small portions of acetone to give 1-carbomethoxy-3-(2-pyridyl)-4-quinolizone (**8**): yield 22.0 g (78.5%); mp 165–168°; ir ($CHCl_3$) 1665, 1640, 1590, 1500 (quinolizone and pyridine), 2960, 2840, 1710, 1240, and 1140 cm^{-1} (carbomethoxy); nmr ($CDCl_3$) δ 9.3, 8.6, 7.7, 7.2 (3 H, 2 H, 2 H, 2 H, multiplets,

(10) H. J. Liu, Z. Valenta, J. S. Wilson, and T. T. J. Yu, *Can. J. Chem.*, **47**, 509 (1969).

(11) R. B. Woodward and E. C. Kornfeld, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 413.

(12) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 16.

(13) While enolization processes are obvious, equilibration of **9b** and **9c** could conceivably take place *via* a pathway involving a β elimination–addition similar to that invoked[6] for another case.[14] β elimination within the enolate formed from **9b** would give a ten-membered ring possessing a negatively charged nitrogen (N-5) which would add to one of two disatereotcpic faces of a trans double bond (C-1, C-10) to provide enolate corresponding to **9c**. This notion was tested during the present work by carrying out the equilibration in the presence of (+)-1-methoxy-(2*S*)-methylbutane.[15] The absence of optical activity in the product (**9c**), however, did not allow any conclusions to be drawn.

(14) F. Galinovsky, G. Bianchetti, and O. Vogl, *Monatsh. Chem.*, **84**, 1221 (1953).

(15) S. I. Goldberg and W. S. Bailey, *J. Amer. Chem. Soc.*, **91**, 5685 (1969); *cf. J. Org. Chem.*, **36**, 716 (1971).

quinolizone and pyridine protons), and 3.9 (3 H, singlet methyl protons). The compound obtained in this way was sufficiently pure for use in the next step of the synthesis. A sample was purified for analysis by sublimation at 150° (0.05 mm) as bright yellow, needle-shaped crystals, mp 171–173°.

Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; mol wt, 280. Found: C, 68.54; H, 4.31; mol wt, 280 (mass spectrum).

r-(1*R*,3*R*,10*S*)-1-Carbomethoxy-3-(2-pyridyl)-4-quinolizidinone[7] (9c).—A stirred (magnetic) solution of 1-carbomethoxy-3-(2-pyridyl)-4-quinolizone (8) (25.7 g, 0.0918 mol) in absolute methanol (400 ml), containing a suspension of 10% palladium on charcoal catalyst (9.2 g), was hydrogenated at ambient temperature and pressure. After a volume of hydrogen corresponding to 4 equiv was absorbed (3 days), the solid catalyst was separated from the reaction mixture by filtration of the latter through a Celite bed. Ordinarily the volume of the filtrate was reduced (evaporation) to 150 ml, and the resulting solution was used in the isomer equilibration step (below).

In one instance, however, the filtrate was evaporated to dryness, and the residue was dissolved in the minimum volume of methanol and placed onto a column of alumina (150 g, Woelm, nonalkaline, Activity Grade III) that was previously packed (flow method, *n*-hexane). Development of the column gave one major, diffuse, slightly yellow band, which was eluted with ether. Removal of the ether gave a mass of yellow-colored semisolid material (*ca.* 85% of the original weight) that was examined by means of its nmr spectrum. In addition to the changes expected from hydrogenation of the quinolizone ring in **8**, the presence of only two different signals owing to the methoxyl protons (δ 3.63 and 3.67) was consistent with a mixture of stereoisomeric forms of **9**.

The mixture was converted (equilibrated) to essentially one isomer by dissolving sodium (2.1 g, 0.091 g-atom) in absolute methanol (*ca.* 30 ml), adding the resulting solution to the concentrated methanol filtrate (above), and heating the resulting solution during 2 hr under reflux. After the mixture was cooled and neutralized with acetic acid, the whole was evaporated to leave an oily semisolid. This was chromatographed on alumina (Woelm, nonalkaline, Activity Grade III) as described above. Evaporation of the ether eluant gave *r*-(1*R*,3*R*,10*S*)-1-carbomethoxy-3-(2-pyridyl)-4-quinolizidinone (**9c**): yield 23 g (86%); pale yellow needles; mp 133–136°; ir ($CHCl_3$) 3000, 1600, 1575 (pyridyl), 1635 (lactam carbonyl), 2950, 2865, 1740, 1260, and 1170 cm^{-1} (carbomethoxy); nmr ($CDCl_3$) δ 8.45, 7.55, 7.12 (multiplets, 1 H, 1 H, 2 H, pyridyl protons), 3.65 (singlet, 3 H, methoxyl protons and quinolizidinone protons), 4.78 (broad doublet, 1 H), 3.7 (partially obscured multiplet, 1 H), 2.5 (broad envelope, 4 H), and 1.7 (broad envelope, 7 H).

Recrystallization of the compound from an acetone and hexane mixture gave colorless needles, mp 143–145°.

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; mol wt, 288. Found: C, 66.50; H, 7.03; mol wt, 288 (mass spectrum).

r-(1*R*,3*S*,10*S*)-1-Hydroxymethyl-3-(2-pyridyl)quinolizidine (4).[7]—A solution of 9c (2.88 g, 0.0100 mol) in tetrahydrofuran (THF) (50 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (1.5 g, 0.039 mol) in THF (50 ml). After the addition was complete, the reaction mixture was boiled gently (reflux) for 2 hr before it was cooled and hydrolyzed by careful successive additions of water (1.5 ml), 15% aqueous sodium hydroxide solution (1.5 ml), and finally water (4.5 ml). The coagulated alumina was separated by filtration and washed with THF. The combined washings and filtrate was evaporated to give the amino alcohol 4 as a very viscous yellow oil[6]: yield 2.2 g (89%); ir ($CHCl_3$) 3630, 3300 (free and bonded hydroxyl), 2863, 2920, 2778 (*trans*-quinolizidine), 1600, 1575, 1480, and 1440 cm^{-1} (pyridyl); nmr ($CDCl_3$) δ 8.42, 7.50, 7.08 (doublet of triplets, 1 H, apparent pentet, 1 H, triplet of doublets, 2 H, all pyridyl protons), 3.75, 2.90, 1.70 (broad doublet, 5 H, broad triplet, 3 H, broad envelope, 11 H, quinolizidine and hydroxymethyl protons).

Conversion of *r*-(1*R*,3*S*,10*S*)-1-Hydroxymethyl-3-(2-pyridyl)-quinolizidine (4) to (±)-Anagyrine (3).—The following account is a modification of the original procedure of van Tamelen and Baran.[6]

The amino alcohol 4 (2.2 g, 0.0089 mol), as obtained from the previous step, was dissolved in 48% aqueous hydrobromic acid (60 ml) and heated under reflux for 22 hr. All solvent was evaporated from the acidic reaction mixture under reduced pressure (*ca.* 35 mm). The residue was dissolved in water (20 ml) before the whole was cooled in an ice bath and transferred to a separatory funnel (benzene washes). The cold solution of hydrobromide salt was made strongly basic by the addition of cold, 3 *N* sodium hydroxide. The liberated bromo amine was quickly extracted into cold benzene (50 ml). After the combined benzene extracts were dried (anhydrous sodium sulfate), they were boiled under gentle reflux for 2 hr. Recrystallization (acetone) of the collected crystalline material deposited from the benzene solution gave the crude tetracyclic quaternary salt 6, yield 492 mg (18%), mp 209–214° (lit.[6] mp 209–215°).

To a portion of this material (6) (356 mg, 1.15 mmol) dissolved in water (2 ml) was added an aqueous solution (4 ml) of sodium hydroxide (600 mg, 15 mmol) and potassium ferricyanide (800 mg, 2.43 mmol), and the whole was heated on a steam bath during 24 hr after an additional portion of water (2 ml) was used to clarify the cloudy reaction mixture. The cooled solution was exhaustively extracted with benzene (15 × 5 ml), and the combined extracts were dried (anhydrous sodium sulfate), filtered, and evaporated to a residue which was introduced into a modified Späth bulb and molecularly distilled [150° (0.05 mm), air bath] to give (±)-anagyrine (**3**): yield 129 mg (46.0%); pale yellow glass. This material was identical with authentic (−)-anagyrine generated from its hydrobromide salt,[16] as shown by chromatographic behavior [tlc, R_f 0.29 (acetone)] and by superimposability of infrared spectra.

Registry No.—**3**, 34389-11-2; **4**, 34389-12-3; **8** (R = CH_2), 34407-56-2; **9c**, 34407-57-3.

(16) L. Light and Co. Ltd., Colnbrook, England.

The Isolation, Structure, Synthesis, and Absolute Configuration of the Cactus Alkaloid Gigantine[1,2]

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Received September 1, 1971

The predominant feature of the desert landscape of southern Arizona and western Sonora, Mexico, is the giant sahuaro cactus, *Carnegiea gigantea*.[3] The presence of alkaloids in this cactus was discovered over 40 years ago with the isolation[4] and the determination[5] of structure of carnegine (1).

As part of our survey of cactus alkaloids[6,7] the basic fraction of *C. gigantea* was reexamined by gas chromatography[8] and found to contain at least two major and two minor alkaloids. The most abundant alkaloid (70% of the basic fraction) was an optically inactive oil which was characterized as carnegine (1) by comparison of its properties and those of its derivatives with a synthetic sample.[5] The other major alkaloid (25–30% of the basic fraction in the whole plant or about 50% in the growing tip) was obtained as an optically active crystalline solid whose properties differed from those of the

(1) Taken from the Texas Christian University Ph.D. Dissertations of (a) J. L. Massingill, 1968 [*Diss. Abstr.*, **29**, 2814B (1969)] and (b) S. D. Brown, 1969 [*ibid.*, **30**, 3547B (1970)].

(2) Preliminary communication: S. D. Brown and M. G. Reinecke, 24th Southwest Regional Meeting of the American Chemical Society, Austin, Texas, Dec 1968, Abstracts, p 95.

(3) N. L. Brittor and J. N. Rose, "The Cactaceae," Vol. II, The Carnegie Institute of Washington, Washington, D. C., 1920, p 164.

(4) G. Heyl, *Arch. Pharm.*, **266**, 668 (1928).

(5) E. Späth, *Chem. Ber.*, **62**, 1021 (1929).

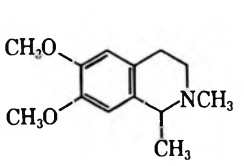
(6) S. D. Brown, J. L. Massingill, Jr., and J. E. Hodgkins, *Phytochemistry*, **7**, 2031 (1968).

(7) S. D. Brown, J. E. Hodgkins, and M. G. Reinecke, unpublished work.

(8) J. L. Massingill, Jr., and J. E. Hodgkins, *Anal. Chem.*, **37**, 952 (1965).

known cactus alkaloids.[9-11] This new alkaloid was named gigantine.[12] The minor alkaloids probably are phenethylamines[13,14] and salsolidine (2).[14] The report[14] that the latter is a major alkaloid of *C. gigantea* could not be verified with any of the plant samples at our disposal.

Analytical and spectral data[12] suggested that gigantine is a hydroxycarnegine. The originally proposed[12] structure **3** was rendered untenable by the observation that gigantine was not identical with either the cis or trans isomers of synthetic **3**.[15] The reexamination initiated by this discovery led to the conclusion[6] that gigantine must be a positional isomer of the phenolic isoquinoline alkaloid pellotine (**4**)[16] which, in contrast to gigantine, is always isolated as the racemate. This last fact is probably due to the remarkably facile racemization of optically active pellotine[17] compared to gigantine, which is stable to racemization under much more severe treatment (see Experimental Section).



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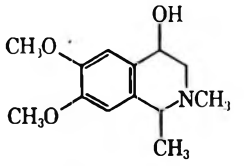

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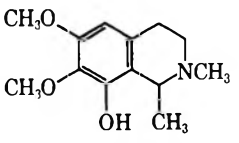

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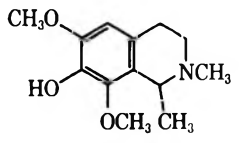

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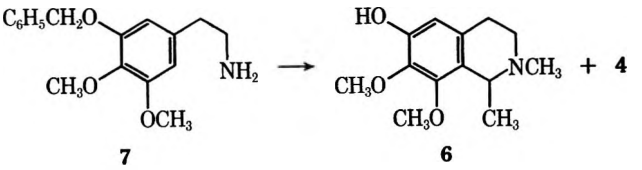
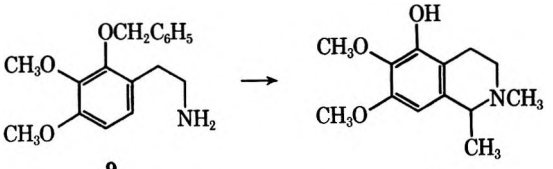
By analogy to the known cactus alkaloids[9-11] the oxygen substituents of gigantine should appear at positions 6, 7, and 8. This restriction generates two possible structures (**5** and **6**) in addition to pellotine (**4**). The former[18] was eliminated because its nmr spectrum[19] differed from that of gigantine. The physical and spectral properties of **6**, synthesized from the acetamide of the known[20] phenethylamine **7** by a Bischler–Napieralski cyclization followed by methylation and reduction, also differed from gigantine. Of the nine remaining possible isomers all but **8** were eliminated by the observation that the Gibbs' test[21] for phenols with a free para position is positive for gigantine.

This assignment was confirmed by the total synthesis of **8** from the known[22] phenethylamine **9** by the identical method used above for **6**. Since our initial



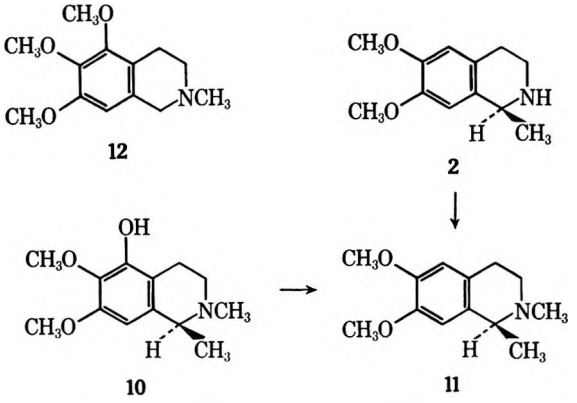
7 **6**

disclosures of this work[1,2] two preliminary communications over similar total syntheses of (±)-gigantine[23,24] and its (±)-methyl ether[25] have appeared. The melting point reported for (±)-gigantine in one of these papers[24] is the same as that of natural gigantine and differs from ours by 30°. The reason for this discrepancy is unknown.



9 **8**

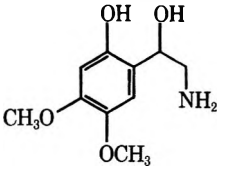
Gigantine was shown to have the *S* configuration (**10**) by converting it, *via* reductive cleavage of its diethylphosphate ester,[26] to (*S*)-carnegine (**11**) which has been related to (*S*)-salsolidine (**2**).[27]



12 **2**

10 **11**

Gigantine possesses the rare[28] 5,6,7-trioxygenated pattern previously found in only one other simple isoquinoline alkaloid, tehaunine (**12**) from the cactus *Pachycereus tehauntepecanus*.[29] The presence of the 5-hydroxy group suggests a possible relationship between gigantine and the hypothetical[30] endogenous psychotogen of schizophrenia (**13**). Preliminary tests[12] indicate that gigantine does have hallucinogenic properties, and more detailed studies are in progress.[31]



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Experimental Section

Melting points were taken on a Koefler hot stage apparatus and are corrected. Nmr spectra were recorded on a Varian A-60A spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal reference. The uv spectrum was measured on a Cary 15 spectrophotometer and the infared spectra were taken on a Perkin-Elmer Model 237 spectrophotometer. Optical rotations were measured with a Rudolph Model 76 polarimeter. The mass spectrum was recorded on a modified[32] CEC-21-103A instrument at 70 eV. Analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark, and M-H-W Laboratories, Garden City, Mich.

Isolation of Carnegine (1) and Gigantine (10).—A section of a branch from a sample of *Carnegia gigantea*[3] collected[6] in Maricopa County, Ariz., was diced (3–4 cm^3), dried (50°), and powdered in a Waring blender, and 783 g of it was extracted for 2 days from EtOH containing 0.5% HOAc in a modified Soxhlet extractor. The extracts were condensed at reduced pressure and diluted with 5% HCl, the remainder of the EtOH was removed, and the resulting alcohol-free solution was made up to a volume of *ca.* 600 ml with 5% HCl. The filtered solution was extracted with ether until fresh extracts were colorless, basified with K_2CO_3, and continuously extracted with $CHCl_3$ in a liquid–liquid extractor. The $CHCl_3$ extract was dried (Na_2SO_4) and concentrated at reduced pressure to give 10.2 g (1.3%) of crude bases which were cleanly separated into two fractions by chromatography on 300 g of Alcoa F-20 alumina. Elution with 1:1 hexane–benzene yielded 6.8 g of carnegine (1) as an optically inactive oil whose infrared and nmr spectra [δ 3.88 (s, 6, OCH_3), 2.90 (s, 3, NCH_3), 4.49 (q, J = 7 Hz, 1, $CHCH_3$), 1.28 (d, J = 7 Hz, 3, $CHCH_3$), 6.68 (s, 2, ArH), 3.5–3.8 (m, 4, CH_2)] were identical with those of a synthetic sample:[5] **1 HCl**, mp 209–211° (lit.[5] mp 210–211°); **1 picrate**, mp 211–213° (lit.[5] mp 212–213°); **1 MeI**, mp 209–211° (lit.[5] mp 210–211°); mass spectrum *m/e* (rel intensity) 221 (3), 207 (12), 206 (100), 190 (10), 178 (4), 162 (5), 148 (4), 103 (6), 91 (6), 77 (6), 58 (17).

Elution of the column with 1:1 benzene–ether yielded 2.4 g of crystalline gigantine (**10**), which after recrystallization from ether melted at 151–152°; $[\alpha]^{25}D$ +27° (*c* 1.99, $CHCl_3$); ir ($CHCl_3$) 3530 cm^{-1} (OH); nmr δ 1.37 (d, J = 6 Hz, 3, $CHCH_3$), 2.45 (s, 3, NCH_3), 2.90 (m, 4, CH_2CH_2N), 3.53 (q, J = 6 Hz, 1, $CHCH_3$), 3.82, (s, 3, OCH_3), 3.84 (s, 3, OCH_3), 6.18 (s, 1, ArH), 6.60 (broad s, 1, OH, shifts with concentration changes); mass spectrum *m/e* (rel intensity) 237 (4), 222 (100), 206 (22), 194 (25), 179 (25), 161 (10), 111 (5), 91 (12), 77 (15), 58 (60); uv max (95% EtOH) 205 mμ (log ϵ 4.8).

Anal. Calcd for $C_{13}H_{19}NO_3$ (**10**): C, 65.83; H, 8.02; N, 5.91. Found: C, 65.68; H, 8.12; N, 6.00.

A hydrochloride, mp 221.5–222.5° from absolute EtOH, was prepared.

Anal. Calcd for $C_{13}H_{20}NO_3Cl$ (**10 HCl**): C, 57.03; H, 7.37; N, 5.12. Found: C, 56.91; H, 7.46; N, 4.89.

Gigantine gave a positive $FeCl_3$ test in methanol but not in $CHCl_3$.[33] It was recovered in 50–90% optical purity after treatment with (i) 2% KOH in EtOH, 5 hr, reflux; (ii) 2 *M* aqueous KOH, 48 hr, reflux; (iii) 2% KO-*t*-Bu in DMSO, 24 hr, 70°.

1,3-Dimethyl-6-hydroxy-7,8-dimethoxyisoquincline (6).—A stirred solution of 6 g (0.02 mol) of 3-benzyloxy-4,5-dimethoxyphenylethylamine (**7**)[20] in 5% HCl and 10 ml of Ac_2O was basified with solid $NaHCO_3$ and then allowed to react for 30 min. The precipitated crude amide, mp 93–94°, was dried by dissolving it in 150 ml of dry benzene and removing half the solvent by distillation. To the resulting solution was added 4.7 ml of $POCl_3$ and the mixture was heated to 80° for 2 hr on a water bath. Removal of the volatiles on a rotary evaporator left a residue which was taken up in 10% H_2SO_4. The acid solution was washed with benzene, cooled, and basified with NaOH, and the basic solution was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed (H_2O), dried (Na_2SO_4), and evaporated to leave 4.3 g (70%) of a golden oil.

A 3.1-g portion of this oil was dissolved in 100 ml of MeOH and heated to reflux with 4 g of MeI for 1.5 hr. After concentrating the solution to 50 ml, 2 g of $NaBH_4$ was added, the mixture was stirred for 10 min, the volume was concentrated to 20 ml, 150 ml of 1 *M* NaOH was added, and the resulting mixture was extracted with $CHCl_3$. Evaporation of the washed (H_2O) and dried (Na_2SO_4) $CHCl_3$ extracts yielded 2.83 g of a mixture of the benzyloxy derivatives of 4 and 6 which could not be satisfactorily separated by chromatography on Al_2O_3 and was therefore dissolved in 100 ml of HOAc and hydrogenated at 30 psi in a Parr apparatus in the presence of 2 g of 5% Pd/C. Removal of the catalyst and evaporation of the solvent left 1.4 g of a mixture of 4 and 6 which was separated by chromatography on Alcoa F-20 Al_2O_3. Benzene eluted pellotine (**4**), mp 111–112° (lit.[17] mp 111–112°), whose infared spectrum was identical with that of an authentic sample.[19] Benzene–Et_2O (3:2) eluted **6**: mp 131.5–132.5°; nmr δ 1.25 (d, J = 6.2 Hz, 3, C-Me), 2.41 (s, 3, N-Me), 2.5–3.0 (m, 4, CH_2), 3.78 (s, 3, OMe), 3.80 (s, 3, OMe), 3.84 (q, J = 6.2 Hz, 1, CH), 6.24 (s, 1, ArH), 6.62 (broad s, 1, OH).

Anal. Calcd for $C_{13}H_{19}NO_3$ (**6**): C, 65.80; H, 8.07; N, 5.90. Found: C, 65.92; H, 8.29; N, 5.90.

1,2-Dimethyl-6,7-dimethoxy-5-hydroxytetrahydroiscquinoline [(±)-Gigantine] (8).—A mixture of 6 g of β-(2-benzyloxy-3,4-dimethoxyphenyl)ethylamine (**9**)[22] and 50 ml of Ac_2O was allowed to react overnight at room temperature, at which time the excess Ac_2O was removed on a rotary evaporator. A benzene solution of the residue was extracted with three portions of 5% HCl and one portion of saturated NaCl and dried over Na_2SO_4, and the solvent was removed at reduced pressure to give 9 acetamide as a vpc-pure oil: nmr (CCl_4) δ 1.75 (s, 3, Ac), 2.70–3.25 (m, 4, CH_2CH_2), 3.68 (s, 3, OMe), 3.73 (s, 3, OMe), 4.95 (s, 2, OCH_2), 6.43 (d, J = 9 Hz, 1, ArH), 6.70 (d, J = 9 Hz, 1, ArH), 7.20 (m, 5, C_6H_5 and NH); ir 1650 cm^{-1}.

A solution of the above amide in 50 ml of dry benzene and 3 ml of freshly distilled $POCl_3$ was heated to reflux for 3 hr and then allowed to stand at room temperature overnight. The reaction mixture was extracted with two 100-ml portions of 1 *N* NaOH, 100 ml of H_2O, and 100 ml of saturated NaCl and dried over $CaSO_4$, and the solvent was evaporated at reduced pressure to give **5-benzyloxy-6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline** as a vpc-pure oil: nmr (CCl_4) δ 2.23 (s, 3, 1-Me), 2.48–3.40 (m, 4, CH_2CH_2), 3.77 (s, 3, OMe), 3.81 (s, 3, OMe), 4.93 (s, 2, OCH_2), 6.70 (s, 1, ArH), 7.25 (m, 6, C_6H_5 and NH); ir 1625 cm^{-1}.

Reaction with methyl iodide gave 4.4 g (46% from 9) of **5-benzyloxy-6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline methiodide** as a yellow solid, which after two recrystallizations from 2-butanone had melting point 164–166°.

Anal. Calcd for $C_{20}H_{24}NO_3I$: C, 52.98; H, 5.30; N, 3.09. Found: C, 53.09; H, 5.16; N, 2.98.

To a solution of 3.8 g of the above methiodide in 50 ml of MeOH was added, in portions, 2.5 g of $NaBH_4$. After the exothermic reaction subsided, the solvent was removed at reduced pressure and the residue was dissolved in 100 ml of ether. The ether solution was extracted with three 50-ml portions of 3% NaOH, one of H_2O, and one of saturated NaCl, dried over Na_2SO_4, and evaporated at reduced pressure to give 2.3 g (85%) of oily **5-benzyloxy-6,7-dimethoxy-1,2-dimethyltetrahydroisoquinoline**: nmr (CCl_4) δ 1.30 (d, J = 6 Hz, 3, 1-Me), 2.32 (s, 3, N-Me), 2.60 (m, 4, CH_2CH_2), 3.42 (q, J = 6 Hz, 1, $CHCH_3$), 3.75 (s, 3, OMe), 3.80 (s, 3, OMe), 4.96 (s, 2, OCH_2), 6.30 (s, 1, ArH), 7.24 (m, 5, C_6H_5). A picrate, mp 168–169° dec, was prepared.

Anal. Calcd for $C_{26}H_{28}N_4O_{10}$: C, 56.12; H, 5.04; N, 10.07. Found: C, 56.31; H, 4.94; N, 9.86.

A mixture of 1.08 g of the above isoquinoline in 20 ml of HOAc was hydrogenated in the presence of 0.5 g of 5% Pd/C for 2 hr at 30 psi and room temperature. After filtration and removal of the solvent at reduced pressure, the resultant residue was dissolved in 50 ml of benzene and extracted with three 50-ml portions of 1 *N* NaOH. The combined basic extracts were adjusted to pH 9–10 with concentrated HCl and Na_2CO_3 and then extracted with three 50-ml portions of $CHCl_3$. Drying (saturated NaCl and $CaSO_4$) and evaporation of the $CHCl_3$ at reduced pressure gave 0.4 g (53%) of crude (±)-gigantine (**8**). Chromatography on Woelm activity IV Al_2O_3 followed by recrystallization from ether gave material of mp 121–123° whose nmr ($DCCl_3$) and ir ($DCCl_3$ or CS_2) spectra were identical with those of natural (+)-gigantine.

Conversion of Gigantine (10) to (*S*)-Carnegine (11).[26]—A solution of 1.03 g (0.004 mol) of gigantine and 0.64 g (0.005 mol) of $HOP(OEt)_2$[34] in 14 ml of CCl_4 was treated with 0.47 g of freshly

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distilled triethylamine and stirred at room temperature for 48 hr. The reaction mixture was diluted with 30 ml of $CHCl_3$ and extracted with 3% NaOH (3 × 20 ml) to remove 0.475 g of unreacted gigantine. The $CHCl_3$ layer was washed with saturated NaCl solution and dried over $CaSO_4$, the solvent was evaporated, and residual water was removed by azeotropic distillation with 50 ml of dry benzene.

The crude phosphate ester (1.353 g, 84%) was dissolved in 5 ml of dry, peroxide-free THF in a flask equipped with a Dry Ice condenser and a $CaCl_2$ drying tube. About 10 ml of dry NH_3 was passed through a NaOH drying tower and condensed into the reaction flask. The reaction mixture was cooled in an acetone–Dry Ice bath while 0.172 g (0.008 g-atom) of sodium metal was added in small pieces. The solution was allowed to warm up until the ammonia began to reflux in order to prevent the phosphate ester from crystallizing. When the blue color of the dissolved sodium vanished (30 min), 5 ml of absolute ethanol was added and the ammonia was allowed to evaporate. The residue was dissolved in $CHCl_3$ (100 ml), and the solution was extracted with water (3 × 50 ml), dried by shaking with a saturated salt solution (2 × 50 ml), and filtered through $CaSO_4$. Distillation of the solvent at reduced pressure left (*S*)-carnegine [(−)-*N*-methylsalsolidine] (11) as an oil which was converted to 0.475 g (43% from 10) of an hydrochloride, whose infrared spectrum (KBr) and that of the hydrochloride of natural, racemic carnegine (1) were identical, as were the nmr spectra ($DCCl_3$) of the free bases (11 and 1); a picrate, mp 229–232° (lit.[27] mp 233–234°), was also prepared. A distilled (0.03 mm) sample of the free base 11 regenerated from this picrate by passage through an Al_2O_3 column with $CHCl_3$–CH_3OH had the following rotations: $[M]^{25}D$ −110° (*c* 1.78, benzene), −51.5° (*c* 1.70 absolute EtOH), and +16.5° (*c* 1.22, 1 *N* HCl) [lit.[27] $[M]^{22}D$ −115 °(*c* ~4.5, benzene), −55° (*c* 4.45, absolute EtOH), and +17° (*c* ~4.5, 1 *N* HCl)].

Registry No.—**1**, 490-53-9; **6**, 34407-54-0; **9** acetamide, 30666-18-3; **10**, 34408-15-6; **10** HCl, 34408-16-7; 5-benzyloxy-6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline, 30666-19-4, 34402-63-6 (methiodide); 5-benzyloxy-6,7-dimethoxy-1,2-dimethyltetrahydroisoquinoline, 34389-05-4, 34402-64-7 (picrate).

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Convenient Synthesis of Frontalin—1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octane

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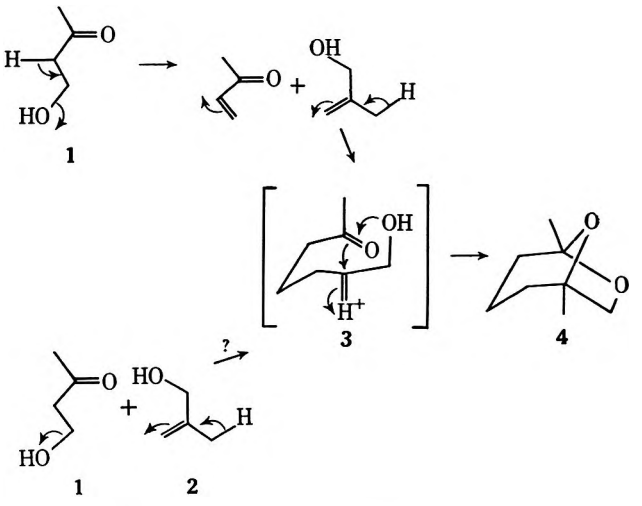
Frontalin is an aggregating pheromone of the southern pine beetle and other related bark beetles.[1] Kinzer, *et al.*,[2] reported the synthesis of the attractant without experimental details, and in unspecified yield,[3] by heating methyl vinyl ketone (MVK) and methallyl alcohol. We wish to report a simple, one-step synthesis of frontalin by heating a mixture of formaldehyde (as formalin, paraformaldehyde, or trioxane), excess of acetone, and methallyl alcohol, *without any catalyst*, in a stainless steel autoclave or sealed glass tube at 250–275° for 1 hr. Up to 35–40% of frontalin (based on methallyl alcohol consumed) has been isolated. The yield of frontalin was markedly increased (see Experimental Section) with toluene as solvent, albeit with a loss in efficiency due to loss of methallyl alcohol.

Although the yields have not been optimized, this process offers great advantage over the use of MVK or other synthetic routes for the large-scale production of frontalin.

Heating methallyl alcohol with 4-hydroxy-2-butanone, the first reaction product between formaldehyde and acetone, also yields frontalin. From glc analysis of the samples taken at shorter reaction times, MVK and its dimer have been detected (in one instance MVK was also isolated), but they disappear with time. It is, therefore, apparent that the reaction leading to the formation of frontalin proceeds *via* the intermediary of MVK formed *in situ*. This could then react with methallyl alcohol in Diels–Alder fashion[2] or by an "ene-type reaction" as shown below. A direct reaction between methallyl alcohol and 4-hydroxy-2-butanone, although less likely, cannot be ruled out.



Some of the physical properties of frontalin are recorded in the Experimental Section.

Experimental Section

Synthesis of Frontalin Using Acetone and Paraformaldehyde without Solvent.—A suspension of 480.0 g (16.0 mol) of paraformaldehyde, 1152.0 g (16.0 mol) of methallyl alcohol, and 6720.0 g (96.0 mol) of acetone was heated in a 5-gallon autoclave for 1 hr at 250°. Distillation yielded 6070.0 g of acetone, 31.0 g of methyl vinyl ketone, 770.0 g of methallyl alcohol, 267.0 g of frontalin (~98% pure), bp 60–62° (30 mm), 450.0 g of high-boiling fraction, bp 142–162° (0.8–0.9 mm), and 322.0 g of residue. Pure frontalin had bp 155° (760 mm), 91° (100 mm), $n^{20}D$ 1.4386, sp gr (20°) 0.9889. Its nmr spectrum was identical with that of the material obtained by Kinzer's method. The yield of frontalin based on reacted methallyl alcohol was 35.4%.

(1) J. P. Vité and G. P. Pitman, *J. Econ. Entomol.*, **63**, 1132 (1970), and references cited therein.

(2) G. W. Kinzer, A. F. Feintiman, Jr., T. F. Page, Jr., R. L. Foltz, J. P. Vité, and G. P. Pitman, *Nature (London)*, **221**, 477 (1969).

(3) B. P. Mundy, R. D. Otzenberger, and A. R. DeBernardis, *J. Org. Chem.*, **36**, 2390 (1971), recently reported the synthesis *via* a Diels–Alder reaction of MVK and methyl methacrylate, followed by reduction to the alcohol and cyclization, in overall yields of less than 10%.

Synthesis of Frontalin with Toluene as Solvent.—The same mixture as above was diluted with 2845.0 g (32.0 mol) of toluene and heated for 1.25 hr at 250°. Distillation yielded 6018.0 g of acetone, 356.0 g of methallyl alcohol, 2785.0 g of toluene, 376.0 g of frontalin, 270.0 g of high-boiling fraction, and 376.0 g of residue. The yield of frontalin based on reacted methallyl alcohol was 24.0%.

Synthesis of Frontalin Using 4-Hydroxy-2-butanone.—A mixture of 7.2 g (0.1 mol) of methallyl alcohol, 8.8 g (0.1 mol) of 4-hydroxy-2-butanone, and 46.0 g (0.5 mol) of toluene was heated in a sealed glass tube for 1 hr at 250°. The glc analysis (excluding the toluene peak) indicated the presence of 30.5% frontalin, 52.0% unreacted methallyl alcohol, and 12.4% higher boiling by-products.

Registry No.—Frontalin, 28401-39-0.

A Highly Stereoselective Synthesis of *meso*-*N*,*N*′-Dicarbethoxy-2,4-diaminopentane and *meso*-2,4-Diaminopentane

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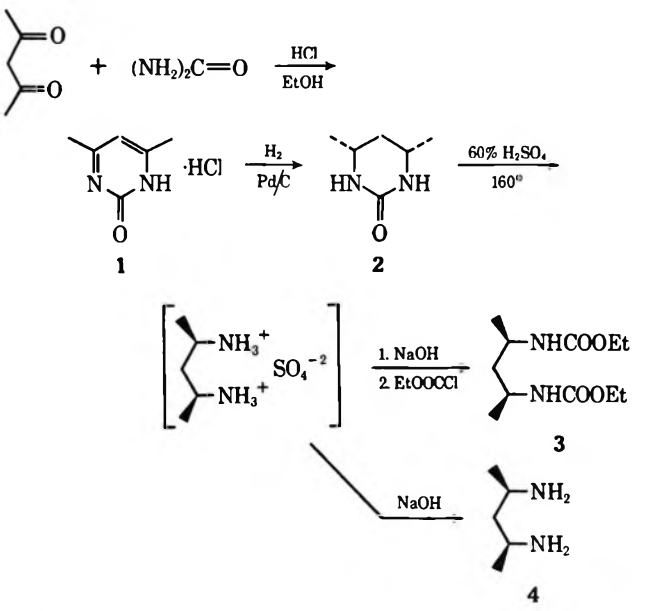
In the course of another study we required *meso*-2,4-diaminopentane. This note reports a unique, highly stereoselective synthesis of this material and its more conveniently isolated *N*,*N*′-dicarbethoxy derivative, which was also needed for further synthetic operations.

2,4-Diaminopentane has been prepared by reduction of 2,4-pentanedione dioxime by various methods,[1] the best of which was sodium in ethanol.[1] This procedure, which is inefficient and unwieldy, results in an 80% yield of product (as the dihydrochloride), only 30% of which is the meso diastereomer.[1] In addition, the meso and *dl* compounds must be separated, which is a tedious and yield-reducing process.[1] Our attempts to obtain a more favorable meso/*dl* ratio using other reducing agents did not meet with success. For example, aluminum hydride (an excellent reducing agent for oximes[2]) afforded a good yield of the diamine but the mixture contained only *ca.* 50% (by nmr) of the meso stereoisomer.

In order to obtain more conveniently the desired meso isomer, we devised a method in which the stereochemistry could be more easily controlled. The approach (outlined in Scheme I) involved establishing the proper atom arrangement within a readily formed pyrimidine ring (**1**) followed by catalytic hydrogenation[3] to the saturated cyclic urea **2** containing the correctly oriented *cis*-methyl groups. Hydrolysis then provided the desired meso diamine. The procedure takes advantage of the situation that any equilibration of **2** during hydrogenation should greatly favor the cis diequatorial disposition of the methyl groups and thus reinforce the predominance of the wanted stereoisomer.

The reaction of acetylacetone with urea in refluxing

SCHEME I



acidic 95% ethanol[4] furnished a good yield (70–75%) of 2-hydroxy-4,6-dimethylpyrimidine hydrochloride (**1**). The 2-one tautomeric structure is suggested for **1** on the basis of ir and uv spectra. An aqueous solution of **1** was hydrogenated[5] using palladium on carbon[6] and the crude cyclic urea was obtained. Recrystallization gave diastereomerically pure **2**, which *required* sublimation in order to remove the solvent (mostly water). The cis cyclic urea **2** was hydrolyzed[7] in 60% sulfuric acid and the resulting diammonium salt was converted to the dicarbamate **3** in moderate yield (50–57%), or to the free diamine **4** in fair yield (25–30%).

The assignment of the cis configuration for the cyclic urea was made on the basis of nmr comparison with *cis*- and *trans*-2-phenyl-4,6-dimethyl-2-bora-1,3-dioxacyclohexane[8] and was consistent with a noninterconverting ring with diequatorial methyl groups. The nmr spectrum of the dicarbethoxy compound **3** is consistent with the presence of the vertical mirror plane contained in the meso isomer.

Experimental Section

Melting points and boiling points are uncorrected. Microanalyses were performed by Alfred Bernhardt Microanalytisches Laboratorium, West Germany. Infrared spectra were taken on a Perkin-Elmer Model 457 spectrophotometer. Nmr spectra were obtained on a Varian A-60 or HA-100 spectrometer using tetramethylsilane as an internal reference. Ultraviolet spectra were recorded on a Perkin-Elmer Model 402 spectrophotometer.

2-Hydroxy-4,6-dimethylpyrimidine Hydrochloride (**1**).—To acetylacetone (24.0 g, 0.24 mol) and urea (12.0 g, 0.20 mol) in 250 ml of 95% ethanol was added 50 ml of concentrated hydrochloric acid. The mixture was stirred under reflux for 2 hr, cooled in ice, and filtered. The colorless crystals were rinsed with ice-cold absolute ethanol and then with dry ether, and dried *in vacuo* to afford 20–22 g (70–75%) of colorless **1**, mp 260° dec

(1) C. J. Dippel, *Recl. Trav. Chim. Pays-Bas*, **50**, 525 (1931), and references cited therein.

(2) N. M. Yoon and H. C. Brown, *J. Amer. Chem. Soc.*, **90**, 2927 (1968).

(3) Catalytic hydrogenation was anticipated to provide a predominance of the cis isomer. See (a) O. V. Bragin and A. L. Liberman, *Russ. Chem. Rev.*, **39** (12), 1017 (1970); (b) E. A. Mistryukov, E. L. Ilkova, and M. A. Ryashentseva, *Tetrahedron Lett.*, 1691 (1971).

(4) R. R. Hunt, J. F. W. McOmie, and E. R. Sayer, *J. Chem. Soc.*, 525 (1959); also see W. J. Hale, *J. Amer. Chem. Soc.*, **36**, 104 (1914).

(5) V. H. Smith and B. E. Christensen, *J. Org. Chem.*, **20**, 829 (1955).

(6) Use of activated Raney nickel as a catalyst under similar conditions resulted in complete recovery of the starting material (**1**) which was contaminated with Ni(II): J. J. Fox and D. Van Pragg, *J. Amer. Chem. Soc.*, **82**, 486 (1960).

(7) G. S. Skinner, R. H. Hall, and P. V. Susi, *ibid.*, **79**, 3786 (1957).

(8) We thank Dr. F. A. Davis and I. Turchi for nmr spectra of the boron heterocycles (to be published in *J. Org. Chem.*), which were chosen as models for comparison because of the expected geometric similarity of these rings to the corresponding cyclic ureas.

(sublimes). An additional 1–2 g of less pure product may be obtained from the filtrate: ir (KBr) ν_{max} 3420 (broad, w), 3030 (w–m), 1743 (s), 1625 cm^{-1} (s); nmr (D_2O) δ 2.63 (s, 6, methyls), 6.85 (s, 1, ring H); uv (H_2O) λ_{max} (log ϵ) 213 nm (3.97), 293.5 (3.79); uv (H_2O, pH > 7) λ_{max} (log ϵ) 226 nm (3.78), 289.5 (3.72), compare with 2-hydroxypyridine, uv (H_2O) $\lambda_{max}^{pH>7}$ (log ϵ) 230 nm (4.00), 295 (3.80),[9] which has a large contribution made to its structure by the 2-one tautomer.

Anal. Calcd for $C_6H_9ClN_2O$: C, 44.87; H, 5.65; Cl, 22.08. Found: C, 44.91; H, 5.61; Cl, 21.86.

***cis*-2-Oxo-4,6-dimethyl-1,3-diazacyclohexane (2).**—A mixture of the pyrimidine hydrochloride **1** (12.28 g, 0.076 mol) and 1.0 g of 10% palladium on carbon in 80 ml of distilled water containing a few drops of concentrated hydrochloric acid was hydrogenated (3–4 atm) in a Parr apparatus at room temperature until uptake of hydrogen had ceased (*ca.* 4 hr). The mixture was filtered as soon as possible and the filtrate was concentrated to dryness at reduced pressure to leave a colorless, clear, viscous oil which crystallized exothermically when kept under high vacuum. The crystalline mass was broken up and dried *in vacuo* overnight. The crude product (12.7 g) was recrystallized from a 1:1 mixture of ethyl acetate and tetrahydrofuran (THF) and dried *in vacuo*. The colorless, crystalline product (10.7 g), mp 110–118°, contained included solvent (10–15% solvent by weight) and was a single stereoisomer (nmr). Doubly sublimed material was clear, sparkling needles: mp 250–252° dec (strong sublimation); ir (KBr) ν_{max} 3220 (NH, s), 3075 (NH, m), 1670 cm^{-1} (C=O), s); nmr (acetone-d_6–D_2O) δ 1.32 (d, 6, methyls, J = 6.3 Hz), 1.37 (d of t, 1, axial H, J_{ab} = 13.4 Hz, J_{ax} = 11.0 Hz), 2.21 (d of t, 1, equatorial H, J_{bx} = 3.8 Hz), 3.80 (m, 2, methine), NH protons were absent due to deuterium exchange.

Anal. Calcd for $C_6H_{12}N_2O$: C, 56.22; H, 9.44. Found: C, 56.08; H, 9.25.

***meso*-*N*,*N*′-Dicarbethoxy-2,4-diaminopentane (3).**—The cyclic urea solvent-inclusion complex [29.4 g, 0.2 mol (*ca.* 25.6 g of pure urea)] was heated to reflux in 200 ml of 40% aqueous sulfuric acid (w/w). After reflux was attained (150° oil bath), five 22.0-ml portions of concentrated sulfuric acid (96–98%) were cautiously added at 30-min intervals through the top of the condenser. The mixture (*ca.* 60% in H_2SO_4) was heated at 160° for 4 days with stirring. It was cooled, diluted with 200 ml of 2-propanol, and poured into a mixture of *ca.* 3000 ml of THF and *ca.* 500 ml of dry ether.[10] The supernatant liquid was decanted and saved and the dense oil was rinsed with 200-ml portions of THF until it became a highly viscous, immobile deposit (usually two to five washings). The washings were combined with the supernatant solution and 200–300 ml of dry ether was added to force out more of the oil. Again the solvent was decanted and the oil was rinsed with THF (smaller portions). The crude diammonium salt was thus obtained and was not purified further. The cloudy oil was dissolved in 75 ml of distilled water and neutralized with *ca.* 9.0 g of sodium hydroxide (pH 8–9) with cooling and stirring. Ether (75 ml) was added, and to the stirred mixture kept at 10–15° was then added dropwise 36.0 g of ethyl chloroformate, followed by dropwise addition of 90 ml of 15% aqueous sodium hydroxide. The mixture was stirred for 1 hr at room temperature and diluted with 150 ml of ether, and the layers were separated. The aqueous phase was extracted with two 75-ml portions of ether and the combined ethereal extracts were washed with 25 ml of distilled water and dried ($MgSO_4$). Stripping of the solvent furnished 26–28 g (*ca.* 55%) of colorless dicarbamate, mp 94–95.5°. Recrystallization from hexane–ethyl acetate (prisms, mp 94–95.5°) followed by sublimation provided an analytical sample, mp 95–96°. Noteworthy is the fact that the dicarbamate, even before recrystallization, contained no detectable amount (<5%) of *dl* compound (nmr; also note melting point constancy), reinforcing the claim that the cyclic urea was stereochemically homogeneous: ir (KBr) ν_{max} 3325 (NH), 1682 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.17 (d, 6, methyls, J = 6.7 Hz), 1.22 (t, 6, ethoxy methyls, J = 7.0 Hz), 1.57 [1.43 (b), 1.70 (a)] (t of q_{ab}, J = 13.6 Hz, $J_{ax} \cong J_{ay}$ = 7.0–7.2 Hz, $J_{bx} \cong J_{by}$ = 6.5–6.8 Hz), 3.72 [d of d of d of q, methine, J (NH–CH) = 7.2–7.5 Hz], 4.12 (q, 4, ethoxy methylenes, J = 7.0 Hz), 4.80 (broad d, 2, NH, J = 7.2–7.5 Hz). The pattern for the methenyl and methinyl protons, excluding J (NH–CH) and J (CH_3–CH), represented an abxy system in which the chemical shifts of x and y were accidentally coincident. The *dl* dicarbamate prepared from predominantly *dl* diamine dihydrochloride[1] gave an nmr spectrum similar to that of **3**. The methylene resonance at 1.53 ppm, however, could be used to distinguish it from the meso isomer: nmr ($CDCl_3$) δ 1.17, 1.23, 1.53, 3.72, 4.12, 4.82.

Anal. Calcd for $C_{11}H_{22}N_2O_4$: C, 53.64; H, 9.00. Found: C, 53.54; H, 8.87.

***meso*-2,4-Diaminopentane (4).**—The diammonium salt, obtained as described above, was made strongly alkaline with *ca.* 25% aqueous sodium hydroxide (enough to dissolve most of the precipitated salts) and the resulting mixture was extracted with five equal volume portions of ether. The combined ethereal extracts were dried (Na_2SO_4, then $CaSO_4$) and carefully concentrated. The concentrate was dried over crushed KOH pellets overnight and carefully distilled at *ca.* 70 mm through a Vigreux column. After removal of a forerun, essentially pure[11] **4** distilled, bp 78–81° (70 mm) [lit.[1] bp 60–61° (22 mm)], $n^{22}D$ 1.4388. The yield of diamine from 4.52 g of **2** was 0.9–1.0 g (25–30%). The *N*,*N*′-dibenzoyl derivative of **4** recrystallized from dilute ethanol had mp 194.5–195.5° (lit.[1] mp 193–194°). A sample of the diamine purified by preparative glc had the following properties: ir (thin film) ν_{max} 3360 (NH), 3285 (NH, d), 2965, 2930, 1600, 1457, 1376, 1142, 1060, 905, 870, 818 cm^{-1}; nmr ($CDCl_3$) δ 1.09 (d, 6, methyls, J = 6.5 Hz), 1.35 (t, 2, methylene, J = 6.8 Hz), 1.39 (s, 4, NH), 3.05 [hextet (d of d of q), 2, methine]. The nmr spectrum of chiefly *dl* diamine[1] was similar to that of **4**, but clearly distinguishable by the fact that the methine protons resonated at 3.00 ppm: nmr ($CDCl_3$) δ 1.08, 1.32, 1.52, 3.00.

Registry No.—**1**, 34289-60-6; **2**, 34289-61-7; **3**, 34289-62-8; **4**, 29745-96-8.

Acknowledgment.—We thank Mrs. Carol Folk at the University of Pennsylvania for 100-MHz proton nmr spectra.

(9) See R. M. Silverstein and G. C. Bassler, "Spectrophotometric Identification of Organic Compounds," Wiley, New York, N. Y., 1968, p. 168.

(10) (a) The object at this point in the preparation is to separate the salt as a viscous, dense oil. The exact amount of solvent in the mixture may be variable; thus it is recommended that only 150 ml of 2-propanol be used initially. If the dense phase is too voluminous, then more 2-propanol may be added. The oily deposit should not be very voluminous and should show signs of increased viscosity. (b) This *work-up* is a variation of a general one[7] in which acetone was employed. Use of acetone in our case resulted in only 24–30% yield of dicarbamate **3**. We found that this was due to the formation of the *gem*-diamine, 2,2,4,6-tetramethyl-1,3-diazacyclohexane (by rapid condensation of acetone with the disalt), which was isolated pure by preparative glc (after treating the mixture of diammonium salts with aqueous alkali and extracting with ether): ir (thin film) ν_{max} 3370 (broad NH), 3275 cm^{-1} (NH); nmr ($CDCl_3$) δ 0.95 (broad s, 2, NH), 1.05 (d, 6, methyls, J = 6.3 Hz), 1.31 and 1.35 (pair of s, 6, *gem*-methyls), 1.78 (d of t, methylene, possibly one-half of an ab pattern centered at 1.34 ppm with δ_{ab} = 26 ± 2 Hz, J_{ax} = 12 ± 2, J_{bx} = 2.7, and J_{ab} = 13 Hz), 3.00 [m (d of d of q), 2, methines, 11 lines were observed of the hypothetical 13-line pattern which would be expected if the above postulated parameters were valid with J_{ax} = 12 Hz]. Reaction of this compound with 2,4-dinitrophenylhydrazine reagent gave acetone 2,4-DNP which was identical with the authentic material. *Anal.* Calcd for $C_8H_{18}N_2$: C, 67.55; H, 12.76. Found: C, 67.68; H, 12.58.

(11) No contaminants other than water (*ca.* 3%) were present in the final product. The diamine is very hygroscopic and sensitive to carbon dioxide. A more lengthy purification, which supplies an anhydrous product, is provided in ref 1.

Photochemistry of 2-Phenyloxazolo[4,5-*c*]pyridine. Photoalkylation by Diethyl Ether

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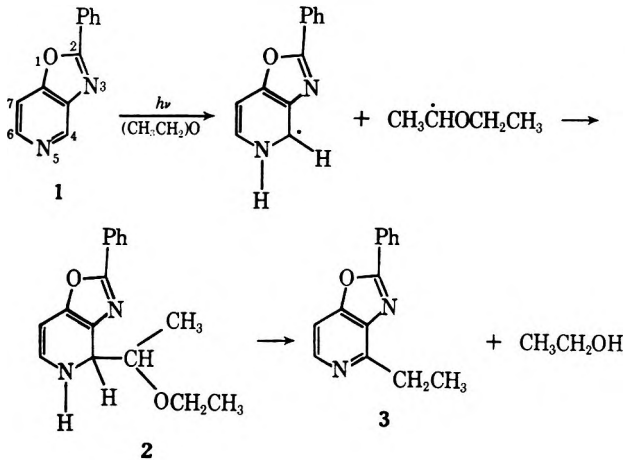
Photoalkylation of various aromatic nitrogen heterocycles has been observed in a variety of alcoholic sol-

vents.[1-7] In general these photoalkylations occur most readily with condensed ring systems such as quinoline. Alkylation by ethers is much rarer and generally involves complete incorporation of the ether moiety.[8] However, from the present work and previous work by a number of different investigators[9,10] it is becoming increasingly apparent that participation of the solvent (generally *via* formation of solvent-derived radicals) is a fairly general phenomenon.

We now report a novel example of C-ethylation of a nitrogen heterocycle by the solvent diethyl ether. Irradiation of a dilute solution of 2-phenyloxazolo[4,5-*c*]-pyridine (1) in ethanol-free diethyl ether and work-up of the resultant complex mixture by preparative layer chromatography resulted in isolation of the alkylated product **3** in reasonable yield. We suggest that this product arises as shown in Scheme I.

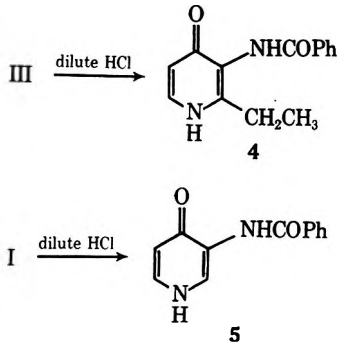
SCHEME I



The gross structure of **3** was deduced readily from the analytical and spectral data and the exact location of the ethyl substituent on the pyridine nucleus was assigned by careful comparison of the nmr spectrum of **3** with that of **1**; the spectrum of **3** showed the absence of a signal due to H_4 which was easily discernible in the spectrum of **1**.

Additional conformation of the assigned structure **3** was obtained by hydrolytic opening of the oxazole ring of **3** to give the substituted pyridone **4** which was compared with the pyridone **5** resulting from similar treatment of **1**.

Control experiments verified that the source of the ethyl substituent in **3** was not trace amounts of ethanol present in the ether used for the photolysis. The ether used for the irradiation contained less than 0.001% ethanol (vpc) and ethanol production was observed



(vpc) as the irradiation progressed (the final concentration of ethanol was ~0.002%).

One of the fractions from the preparative layer chromatography of the resultant photolysate, which could not be obtained in a pure state, has been assigned the structure **2** primarily on the basis of the observed spectral properties of this nonhomogeneous fraction. Formation of this product as the primary product of the irradiation is quite consistent with the work of Stermitz[4] on the photoalkylation of nitrogen heterocycles by alcohols. In the present case, however, the ether moiety is incorporated entirely, and subsequently a molecule of ethanol is eliminated; the net result is introduction of an ethyl group from diethyl ether onto the heterocyclic ring with the concomitant production of ethanol. The intermediate **2** probably arises by initial abstraction of the labile hydrogen atom of diethyl ether and resultant radical coupling as shown in Scheme I. Even though we feel that we have sufficient evidence to invoke the dihydropyridine **2** as the precursor of the alkylated product **3**, we do not have any evidence which permits us to characterize this transformation as either thermal or photochemical.

The present work suggests caution in using diethyl ether as solvent for irradiations of nitrogen heterocycles even though we do not know how general this photoalkylation process might be. It is not impossible that this procedure might be a general method for ether cleavage under very mild conditions.

Experimental Section[11]

Irradiation of 2-Phenyloxazolo[4,5-*c*]pyridine (1).—A solution of 2-phenyloxazolo[4,5-*c*]pyridine[12] (1.00 g, 5.10 mmol) in 400 ml of ethanol-free ether (see below) was irradiated for 41 hr using a medium-pressure Hanovia 450-W lamp contained in a water-cooled quartz immersion well containing a Corex filter sleeve. Within 5 min of the start of the irradiation a colorless precipitate formed on the immersion well and the solution emitted a blue fluorescence. As the reaction progressed it was necessary to intermittently clean the immersion probe of insoluble material. The progress of the reaction was monitored by thin layer chromatography (tlc).

Upon completion of the photolysis (as evidenced by tlc), the insoluble material (300 mg) was removed by filtration and the filtrate was evaporated to leave a residual yellow oil. This complex mixture was separated by preparative layer chromatography (plc) using 20 × 100 cm silica gel plates (six developments with

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(9) P. L. Kumler and R. A. Dybas, *J. Org. Chem.*, **35**, 125 (1970).
(10) T. R. Evans in "Energy Transfer and Organic Photochemistry," P. A. Leermakers and A. Weissberger, Eds., Wiley–Interscience, New York, N. Y., 1969, pp 311–320.

(11) Melting points were obtained on a Thomas-Hoover apparatus and are reported uncorrected. Ir spectra were measured using a Beckman IR-20-A; uv spectra were measured with a Beckman DB recording spectrophotometer. Nmr spectra were taken on a Varian Associates A-60 spectrometer; spectra were recorded in deuteriochloroform solution (unless noted otherwise) and chemical shifts are reported in τ (parts per million) relative to tetramethylsilane as internal standard. Vpc used a Varian-Aerograph Model 700 chromatograph.
(12) J. Fraser and E. Tittensor, *J. Chem. Soc.*, 1781 (1956).

2% methanol in methylene chloride) and various fractions were removed from the plate and extracted with chloroform in a Soxhlet extractor. One of these fractions gave pale yellow crystals of 4-ethyl-2-phenyloxazolo[4,5-c]pyridine (**3**, 192 mg, 17%). Recrystallization from hexane gave colorless crystals: mp 89–90°; ir (KBr) 2980–2850 cm^{-1} (aliphatic CH); uv max (95% EtOH) 282 nm (ϵ 3000); nmr ($CDCl_3$) τ 1.50 (d, J = 8 Hz, 1 H, H_6), 1.6–1.9 (m, 2 H, ortho H's of phenyl), 2.3–2.8 (m, 4 H, meta and para H's of phenyl and H_7), 6.75 (q, 2 H, CH_2), 8.53 (t, 3 H, CH_3); the nmr spectrum lacks the characteristic singlet at τ 0.87 due to H_4 in the starting material.[13]

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.73; H, 5.68; N, 11.84.

Another fraction from the plc separation yielded 79 mg of a brown nonhomogeneous oil (at least three spots by tlc) which we believe contains the dihydropyridine derivative **2**: ir (film) 3300 (broad, OH and NH), 2980–2850 cm^{-1} (aliphatic CH); nmr ($CDCl_3$) τ 6.47 (q, 2 H, CH_2CH_3), 8.47 (d, 3 H, CH_3CH), 8.77 (t, 3 H, CH_3CH_3) (although quite complex the above features could be discerned).

3-Benzamido-4-pyridone (5).—A sample of the oxazolopyridine **1** (110 mg, 0.56 mmol) was dissolved in 10 ml of dilute hydrochloric acid and allowed to stand at room temperature for 72 hr. At this stage, colorless needles had formed and they were removed by filtration, washed with water, and air dried. These crystals were shown to be the hydrochloride salt of the pyridinol tautomer of **5** (140 mg, 93%): mp 219–222°; ir (KBr) 3300 (broad, OH), 2800–2300 (broad, NH^+), 1635 cm^{-1} (amide C=O).

Anal. Calcd for $C_{12}H_{13}N_2O_3Cl$ (monohydrate of hydrochloride salt): C, 53.64; H, 4.88; N, 10.42. Found: C, 53.53; H, 4.80; N, 10.49.

The product from above was dissolved in 20 ml of water containing 1 ml of dilute sodium hydroxide, stirred for 10 min, and then acidified with glacial acetic acid; the resulting colorless solid was filtered, washed with water, and air dried. Elution of this material through a short column of alumina with 2% methanol in chloroform (to remove contaminating sodium acetate) resulted in formation of 3-benzamido-4-pyridone (**5**) which was recrystallized from acetone–hexane to give colorless needles: mp 255–256°; ir (KBr) 3360 (NH), 1670 (pyridone C=O), 1635 cm^{-1} (amide C=O); uv max (95% EtOH) 292 nm (sh, ϵ 7340), 275 (8560), 225 (10,700).

Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.20; H, 4.78; N, 12.92.

2-Ethyl-3-benzamido-4-pyridone (4).—A sample of the oxazolopyridine **3** (54 mg, 0.24 mmol) was dissolved in 20 ml of 3 *N* hydrochloric acid and allowed to stand at room temperature for 48 hr. To this solution was added 3 g of alumina and the resultant mixture was evaporated to dryness at reduced pressure. The resultant powder was packed on the top of an 8-in. alumina column and the column was eluted with 2% methanol in chloroform. Evaporation of the eluate and recrystallization from ethanol–hexane gave the pyridone **4** as colorless needles (28 mg, 48%): mp 148–149°, 178–180° (resolidifies above 148° and then melts at 178–180°); ir (KBr) 3340 (NH), 1660 (pyridone C=O), 1624 cm^{-1} (amide C=O); uv max (95% EtOH) 260 nm (ϵ 11,800), 226 (sh, 14,000); high resolution mass spectrum,[14] calcd mol wt 242.1055, found 242.1054.

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.72; H, 5.71; N, 11.74.

Detection of Ethanol.—The irradiation of **1** was monitored directly by vpc by withdrawing aliquots from the reaction mixture and analyzing on a 30% FFAP column (3/8 in., 20 ft, on 50–60 Chromosorb W) at 105°. With a helium flow rate of ~100 ml/min the approximate retention times for various components were the following: air, 3 min; ether, 4 min; ethanol, 21 min. By analyzing standard solutions of ethanol in ether (1.0, 0.1, 0.01, and 0.001% v/v) the lower limits of detectability were determined; it was shown that 0.001% ethanol could easily be detected. At the start of the irradiation the ethanol concentration in the ether used as solvent was less than 0.001%. As the photolysis progressed the buildup of ethanol could easily be observed and at completion of the irradiation (41 hr) the ethanol concentration was 0.002%.

(13) The nmr spectrum of **1** shows the following features: τ 0.87 (slightly broadened singlet, 1 H, H_4), 1.42 (d, J = 5.5 Hz, 1 H, H_5), 1.6–1.9 (m, 2 H, ortho H's of phenyl), 2.3–2.8 (m, 4 H, meta and para H's of phenyl and H_7).

(14) We thank Dr. Ted R. Evans, Eastman Kodak Laboratories, for this measurement.

Registry No.—**1**, 34297-84-2; **3**, 34282-21-8; **4**, 34282-22-9; **5**, 34282-23-0; **5** HCl, 34282-24-1; diethyl ether, 60-29-7.

The Catalytic Oxidation of Vicinal Diols to α Diketones[1]

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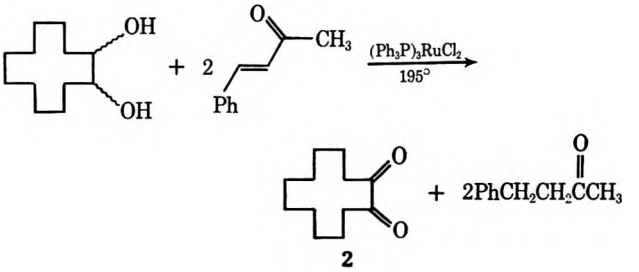
We wish to describe a convenient method for the oxidation of certain vicinal diols to α diketones, based on the ruthenium-catalyzed transfer–hydrogenation reaction reported by Sasson and Blum.[3] α diketones are of value as precursors of acetylenes and dioximes. However, despite interest in substances containing the α-diketone moiety, practical synthetic entries into this class of compounds are restricted to the oxidation of acyloins[4] and α-halo ketones[5] using metal salts or dimethyl sulfoxide, oxidation of ketones with selenium dioxide,[6] and oxidation of olefins with potassium permanganate.[7] Although in principle vicinal diols would appear to be attractive as precursors of α diketones, in practice the direct oxidation of vicinal diols produces α diketones only in erratic yields.[8]

The procedure described here involves the transition metal catalyzed transfer of hydrogen from the diol to a suitable olefinic hydrogen acceptor. Exploration of several metallic catalysts and hydrogen acceptors (Table I) suggests that the combination described by Sasson and Blum, tris(triphenylphosphine)ruthenium dichloride and benzalacetone, is the most effective, although the reaction appears less sensitive to the hydrogen acceptor than to the catalyst. At low conversion of 1,2-cyclododecanediol (**1**) to 1,2-cyclododecanedione (**2**), an appreciable quantity of α-hydroxycyclododecanone (**3**) can be detected in the reaction mixture; **3** is itself smoothly oxidized to **2** under the reaction conditions. Thus, we presume that the overall con-



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(2) A. D. Little Fellow, 1969–1970; A. P. Sloan Graduate Trainee, 1971–1972.

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TABLE I
OXIDATION OF VICINAL DIOLS TO α DIKETONES[a]

Diol	Diketone	Catalyst	Hydrogen acceptor	Time, hr	Yield, %
cis-1	2	$(Ph_3P)_3RuCl_2$	Benzalacetone	6	53
		$(Ph_3P)_3RhCl$			20
		$(PhCN)_2PdCl_2$			14
		$(Ph_3P)_2IrCOCl$			7
		Pd/C			4
		$(Ph_3P)_3RuCl_2$	Chalcone		48
			Mesityl Oxide		34
			1-Docosene		20
cis-1			Benzalacetone	10	78 (50)[b]
trans-1				10	100
2,3-Norbornanediol	2,3-Norbornanedione			1	74
trans-1,2-Cyclohexanediol	1,2-Cyclohexanedione			1	85
2,3-Butanediol	2,3-Butanedione			4	70 (40)[b]
1,2-Diphenyl-1,2-dihydroxyethane	Benzil			2	63
9,10-Dihydroxystearic acid	9,10-Diketostearic acid			4	22
α-Hydroxycyclododecanone	2			10	84

[a] Unless noted otherwise, reactions were carried out using the following starting concentrations: [diol], 0.2 *M*; [hydrogen acceptor], 1.0 *M*; [catalyst], 0.0025 *M*. Tetrahydrofuran was used as solvent; the reaction temperature was 195°. Yields were obtained by glpc. [b] Isolated yield; 1,2-bis(2-methoxyethoxy)ethane was used as solvent.

version of **1** to **2** proceeds in an unexceptional two-stage oxidation through intermediate **3**.

The advantage of this procedure for the preparation of α diketones lies in its simplicity and in its avoidance of the reactive oxidants and strong Lewis acids employed in certain of the other syntheses of these compounds; its principal disadvantage is the high temperature at which the reaction is carried out. However, perhaps because the reactions are carried out under neutral conditions, it has proved possible to obtain good yields of certain α diketones (in particular 2,3-butanedione and 1,2-cyclohexanedione) that cannot be obtained in satisfactory yields by the most convenient of these alternative procedures.[7]

Experimental Section[9]

General Methods.—Unless otherwise specified, all reagents were obtained commercially and were used without further purification. Tetrahydrofuran was dried by distillation from sodium benzophenone ketyl under a nitrogen atmosphere. The 1,2-bis(2-methoxyethoxy)ethane used was purified by distillation from calcium hydride under a nitrogen atmosphere. The following commercial catalysts (sources) were used: $(Ph_3P)_3RuCl_2$ and $(Ph_3P)_2IrCOCl$ (Strem Chemical Co); $(Ph_3P)_3RhCl$ (Alpha Inorganics); Pd/C (Engelhard).

General Procedure for Small-Scale Reactions.—Procedures similar to that described for the conversion of *cis*-1,2-cyclododecanediol to 1,2-cyclododecanedione were followed for all of the small scale oxidations described in Table I. A mixture of 16 mg (0.08 mmol) of *cis*-1,2-cyclododecanediol, 35 mg (0.24 mmol) of benzalacetone, 1 mg (0.001 mmol) of tris(triphenylphosphine)-ruthenium dichloride, and 0.4 ml of tetrahydrofuran was sealed under a nitrogen atmosphere in a 4-in., 5-mm Pyrex tube. The tube was placed in an oil bath, maintained at 195° for 10 hr, withdrawn, and cooled. An internal standard was then added to the reaction mixture, and the mixture was analyzed by glpc using a UC-W98 on Chromosorb W column.

Oxidation of *cis*-1,2-Cyclododecanediol.—To a mixture of 10 g (0.05 mol) of *cis*-1,2-cyclododecanediol, 14.6 g (0.1 mol) of benzalacetone, and 0.2 g (0.0002 mol) of tris(triphenylphosphine)-ruthenium dichloride was added 55 ml of freshly distilled 1,2-bis(2-methoxyethoxy)ethane, and the resulting solution was heated under nitrogen at 195°. The course of the reaction was monitored by glpc (the end of the reaction was indicated by the disappearance of benzalacetone from the reaction mixture). After 10 hr, the reaction mixture was cooled, poured into 300 ml of water, and extracted with 100 ml of ether. The ether solution was dried and concentrated, and the residue was distilled through a 10-cm vacuum-jacketed stainless steel spinning-band column to yield 5 g (50%) of 1,2-cyclododecanedione having bp 98–100° (1.5 mm) [lit.[10] bp 100° (1.5 mm)] and an ir and a mass spectrum indistinguishable from those of an authentic sample.[11,12]

(9) Boiling points are uncorrected. Ir spectra were taken in sodium chloride cells using a Perkin-Elmer Model 237-B spectrophotometer. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6D mass spectrometer. Product mixtures were analyzed by glpc on an F & M Model 810 flame ionization instrument.

Registry No.—*cis*-1, 4422-05-3; 2, 3008-41-1.

Acknowledgment.—We are grateful to our colleagues Rudy Lauer and Tom Flood for gifts of α-hydroxycyclododecanone and *trans*-1,2-cyclododecanediol and to Larry Trzupek and Brian Andresen for recording mass spectra.

(10) C. W. Cumper G. B. Leton, and A. I. Vogel, *J. Chem. Soc.*, 2067 (1965).

(11) An authentic sample of 1,2-cyclododecanedione was prepared by the procedure described by Sharpless, *et. al.*[7]

(12) S. Cenini, A. Fusi, and G. Capparella [*Inorg. Nucl. Chem. Lett.*, 127 (1972)] have reported the rapid reaction of $(Ph_3P)_3RuCl_2$ with molecular oxygen. Thus, these oxidations should be carried out with careful exclusion of oxygen.

A Convenient Synthesis of 1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine

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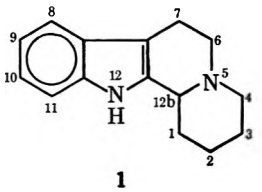
The indole alkaloid 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**) was first synthesized 20 years ago[2] and in 1966 it was found to occur in nature,

(1) The author wishes to thank the National Institutes of Health for a Public Health Service Research Career Development Award (1KO4-GM23756-01) from the National Institute of General Medical Sciences and the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Science Foundation, and the Eli Lilly Co. for providing generous financial support of this work.

(2) J. Keufer, *Ann. Pharm. Fr.*, **8**, 816 (1950); *Chem. Abstr.*, **45**, 10246c (1951).

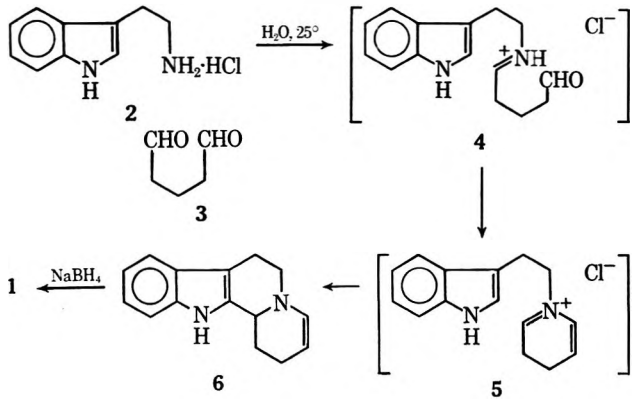


1

being isolated[3] from *Dracontomelum mangiferum*. This alkaloid is of biogenetic interest since it lacks the typical C_9–C_{10} unit found in more than 800 indole alkaloids.[4] Other syntheses of **1** have subsequently appeared[5-12] as well as a determination[13,14] of its absolute configuration.

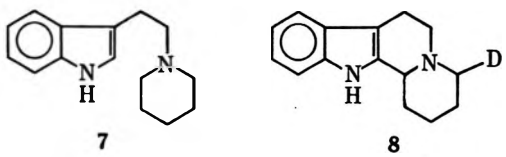
We now wish to describe a simple one-pot synthesis of **1**. Thus, an aqueous solution of tryptamine hydrochloride (**2**) and glutaraldehyde (**3**) was allowed to stand at room temperature for 7–10 days. The solution was diluted with ethanol and treated with excess sodium borohydride. Work-up of the mixture and column chromatography of the reaction product gave pure **1** in 52–55% yield, identical with authentic material.[5,9,12] A yield of 69% of **1** was obtained when a mixture of **2** and **3** was allowed to stand at 4° for 3 months in water. Lower yields of **1** were obtained when the reaction was run at 80–90° and/or when reaction periods were shorter than several days. The synthesis of **1** and a proposed reaction sequence are summarized in Scheme I.

SCHEME I



Presumably, **2** and **3** initially react to form iminium aldehyde **4** which, after deprotonation, cyclizes to dihydropyridinium ion **5**. Finally, **5** undergoes ring closure to **6** (or the corresponding iminium ion) which is reduced to **1** upon sodium borohydride treatment. This route is favored over one involving cyclization of **4** to the indole ring, giving a tetrahydro-β-carboline, because of the isolation of **7** under certain conditions (*vide infra*). There may, however, be a dependence of mechanism on pH not uncovered by the present work.

If the reaction is run in the presence of sodium cyanoborohydride[15] (at pH 6.5 or 8) of if sodium borohydride is added after a much shorter reaction period between **2** and **3**, *N*-[2-(3-indolyl)ethyl]piperidine (**7**)

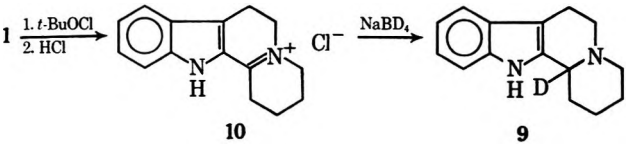


7 8

is the major or exclusive product, isolated pure, after column chromatography, in yields up to 86%. This material was identical with authentic material[9] and represents a very convenient and efficient synthesis of this compound. Presumably, in this case either **4** or **5** is reduced before cyclization to **6** can occur.

Evidence for the structure of intermediate **6** was obtained by subjecting the reaction mixture to sodium borodeuteride. Work-up gave **8** and not **9**, which was independently synthesized from **1** as shown in Scheme II. The structures of **8** and **9** are supported by infrared[16] and mass spectroscopy[17] (see Experimental Section). The mass spectrum of **8** shows an M − 1 peak, while **9** shows an M − 2 peak, corresponding to **10**.[17]

SCHEME II



10 9

Enamine **6** could also be isolated from the reaction mixture and subjected to $NaBH_4$ or $NaBD_4$ in separate reactions to give **1** and **8**, respectively.

Experimental Section

Melting points were determined in open capillaries with a Mel-Temp Laboratory Devices apparatus and are uncorrected. Infrared spectra were measured with Perkin-Elmer 137 or 337 instruments. Woelm alumina was used for column chromatography and silica gel G (Merck) was used for thin layer chromatography (tlc). The tlc solvent system generally used was EtOAc–Et_3N (~95:5) and plates were developed with a spray of 3% $Ce(SO_4)_2$–10% H_2SO_4 followed by a brief heat treatment at 110°. Organic solutions were dried with anhydrous granular K_2CO_3 and concentrated *in vacuo* with a Buchler rotary evaporator. Mass spectra were determined by Mr. Herbert A. Kirst at Harvard University.

1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (1).—To a stirred ice-cold solution of 0.50 g (0.0025 mol) of tryptamine hydrochloride (**2**) (Eastern Chemical Co.) in 500 ml of distilled H_2O was added over 10 min 1.5 g (0.0038 mol) of a 25% aqueous solution of glutaraldehyde (**3**) (Aldrich Chemical Co.). The solution was stirred at 0–5° for 1 hr and then allowed

(3) S. R. Johns, J. A. Lamberton, and J. L. Occolowitz, *Chem. Commun.*, 421 (1966); *Aust. J. Chem.*, **19**, 1951 (1966).
(4) A. I. Scott, *Accounts Chem. Res.*, **3**, 151 (1970).
(5) L. H. Groves and G. A. Swan, *J. Chem. Soc.*, 650 (1952).
(6) W. A. Reckhow and D. S. Tarbell, *J. Amer. Chem. Soc.*, **74**, 4960 (1952).
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(9) E. Wenkert and B. Wickberg, *ibid.*, **84**, 4914 (1962).
(10) J. Gootjes and W. Th. Nauta, *Recl. Trav. Chim. Pays-Bas*, **84**, 1183, 1427 (1965).
(11) E. Ochiai and M. Takahashi, *Chem. Pharm. Bull.*, **13**, 618 (1965).
(12) L. J. Dolby and G. W. Gribble, *J. Org. Chem.*, **32**, 1391 (1967).
(13) S. Yamada and T. Kunieda, *Chem. Pharm. Bull.*, **15**, 499 (1967).
(14) J. Pospisek, Z. Koblicova, and J. Trojanek, *Chem. Ind. (London)*, 25 (1969).
(15) The author is indebted to Professor Richard F. Borch (University of Minnesota) for this suggestion. See also R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Amer. Chem. Soc.*, **93**, 2897 (1971).
(16) For the C–D stretching region in the infrared spectrum of compounds similar to **8** and **9**, see G. W. Gribble, *J. Org. Chem.*, **35**, 1944 (1970). See also J. Skolik, P. J. Krueger, and M. Wiewiorowski, *Tetrahedron*, **24**, 5439 (1968).
(17) For the mass spectrum of **1**, see L. D. Antonaccio, N. A. Pereira, B. Gilbert, H. Vorbrueggen, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *J. Amer. Chem. Soc.*, **84**, 2161 (1962).

to stand under nitrogen at room temperature for 10 days. The yellow solution was cooled in an ice bath, diluted with 200 ml of 95% aqueous EtOH, and treated with 8 g of $NaBH_4$ (pellets) in portions over 3 min. The mixture was stirred at 0–5° for 1 hr and then at room temperature for 8 hr. The mixture was made strongly basic with 6 *N* NaOH and extracted with CH_2Cl_2. The organic extract was washed with aqueous NaCl, dried, and concentrated to give a yellow foam. Chromatography over 15 g of activity III basic alumina gave, with benzene elution in four 30-ml fractions, a total of 0.32 g (55%) of **1** as a white solid, mp 151–152°. Recrystallization from ether gave tiny colorless crystals, mp 153–154° (lit.[9] mp 152–153°). This material was identical (infrared, tlc) with authentic **1**.[5,9,12]

N-[2-(3-Indolyl)ethyl]piperidine (7).—To a stirred ice-cold solution of 0.50 g (0.0025 mol) of **2**, 15 ml of a KH_2PO_4–$NaHPO_4$ concentrated 6.50 pH buffer solution (Radiometer, Copenhagen), 0.20 g (0.0032 mol) of $NaCNBH_3$ (Alfa Chemical Co.) in 500 ml of distilled H_2O was added dropwise over a few min 1.5 g (0.0038 mol) of a 25% aqueous solution of **3**. The solution (pH 6–7) was stirred at 0–5° for 1 hr and then allowed to stand at room temperature for 12 days. The mixture was made strongly basic with 6 *N* NaOH and extracted with CH_2Cl_2. The organic extract was washed with water, dried, and concentrated to give 0.55 g of a white crystalline mass. Chromatography over activity III basic alumina gave, with benzene elution in 12 30-ml fractions, 0.50 g (86%) of **7** as a white solid, mp 149–151°. Recrystallization from ether gave colorless prisms, mp 151–152° (lit.[9,18] mp 151–152°). This material was identical (infrared, tlc) with authentic **7**.[9,18]

Isolation of 1,2,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinolizine (6) and Conversion to 4-*d*-1,2,3,4,6,7,12,12b-Octahydroindolo-[2,3-*a*]quinolizine (8).—The reaction mixture from 0.50 g of **2** and 1.2 g of a 25% aqueous solution of **3** after 4 days at 25° was cooled to 5°, made strongly basic with 6 *N* NaOH, and extracted with CH_2Cl_2. Concentration of the organic extract *in vacuo* gave **6** as an amber syrup. Tlc showed a single yellow-green spot of about the same R_f as **1** but with a distinctly different color pattern. No **1**, **2**, or **7** could be detected.

A mixture of 0.11 g of crude **6**, 0.30 g of $NaBH_4$, and 20 ml of 79% aqueous EtOH was stirred at 5° for 1 hr and then at 25° for 10 hr. Extraction with CH_2Cl_2 followed by the usual work-up and column chromatography (see entry for **1**) gave 0.027 g (24%) of pure **1**, identical (tlc, infrared, melting point) with authentic material.

A mixture of 0.125 g of crude **6**, 0.125 g of $NaBD_4$, and 20 ml of 70% aqueous EtOH was stirred at 5° for 1 hr and then at 25° for 10 hr. The usual work-up and chromatography gave 0.034 g (27%) of pure **8** (tlc; same as **1**), mp 150° dec.

Pertinent spectral data for **8** are as follows: ir ($CHCl_3$) 3460 (NH), 2930, 2850, 2800 (CH), and 2040 cm^{-1} (CD); mass spectrum (70 eV) *m/e* 227, 226, 198, 170, and 169.

12b-*d*-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (9).—This was prepared from **10** which in turn was synthesized from **1** according to the standard method.[12,19] To a stirred solution of 0.88 g (0.0039 mol) of **1**, 0.5 ml of Et_3N, and 100 ml of dry CH_2Cl_2 at −5 to −20° was added 0.49 g (0.0045 mol) of *tert*-butyl hypochlorite in 13 ml of dry CCl_4 dropwise over 1 hr. The mixture was then stirred at 25° for 90 min, washed with water, dried, and concentrated *in vacuo* at 25° to give an amber syrup. This was dissolved in 30 ml of dry EtOH which had been saturated with HCl gas. The mixture was refluxed for 1 hr and then concentrated *in vacuo*. The residue (crude **10**) was treated with 0.60 g of $NaBD_4$ in the usual fashion. Work-up and column chromatography gave 0.25 g (29%) of pure **9** (tlc; same as **1**), mp 150–151° dec.

Pertinent spectral data for **9** are as follows: ir ($CHCl_3$) 3465 (NH), 2940, 2850, 2800, 2750, (CH), and 2000 cm^{-1} (CD); mass spectrum (70 eV) *m/e* 227, 226, 225, 198, 171, and 170.

Registry No.—**1**, 4802-79-3; **8**, 34388-08-4; **9**, 34388-09-5.

Acknowledgment.—The author is indebted to Professor Richard F. Borch (University of Minnesota) for a discussion involving the use of sodium cyanoborohydride and for kindly informing the author of related unpublished work, and to the referees for incisive comments.

(18) R. C. Elderfield, B. F. Fischer, and J. Lagowski, *J. Org. Chem.*, **22**, 1376 (1957).

(19) W. O. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, **10**, 1414 (1956).

A Convenient Synthetic Approach to 3- and 4-Alkyl-2,3-dihydrofurans

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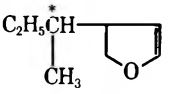
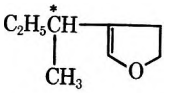
A summary survey of the possible synthetic routes leading to 2,3-dihydrofurans reported in the literature[2–7] convinced us that none could be simply applied to the preparation of optically active monoalkyl-substituted 2,3-dihydrofurans (**1a**, **2a**) containing an



1a



2a

asymmetric carbon atom directly bonded to the heterocyclic ring. Our interest in these optically active compounds and the attention received by 2,3-dihydrofurans in recent years[8–10] prompted us to develop a general procedure for the preparation of isomerically pure 2,3-dihydrofurans.

The key precursor of both series **1** and **2** is the appropriate γ-hydroxyaldehyde, readily accessible through rhodium-catalyzed hydroformylation, respectively of a 2-alkyl-allyl alcohol (Scheme I) and of a 2-alkyl-acrolein diethyl acetal[11] (followed in the second case by reduction of the free carbonyl group) (Scheme II).

The hydroformylation of allylic alcohols was long ago suggested as a promising synthetic route to γ-hydroxyaldehydes,[12] but, because of the substantial isomerization of the substrate promoted by the cobalt catalyst and simultaneous formation of several by-products,[13] no generally useful syntheses could be developed.

(1) (a) Technisch-Chemisches Laboratorium, Zürich; (b) Istituto Chimica Fisica, Pisa.

(2) (a) J. Colonge and R. Gelin, *Bull. Soc. Chim. Fr.*, 799 (1954); (b) H. Normant, *Chim. Ind. (Paris)*, **63**, 511 (1950).

(3) J. C. Anderson, D. G. Lindsay, and C. B. Reese, *Tetrahedron*, **20**, 2091 (1964).

(4) M. A. Gianturco, P. Friedel, and V. Flanagan, *Tetrahedron Lett.*, 1847 (1965).

(5) J. Huet and J. Dreux, *C. R. Acad. Sci.*, **256** (18), 4570 (1964).

(6) W. Parham and H. E. Holmquist, *J. Amer. Chem. Soc.*, **73**, 913 (1951).

(7) A. Zysman, G. Dana, and J. Wiemann, *Bull. Soc. Chim. Fr.*, 1019 (1967).

(8) (a) P. Scribe and J. Wiemann, *ibid.*, 2268 (1971); (b) J. P. Girault, P. Scribe, and G. Dana, *ibid.*, 2279 (1971).

(9) British Patent 849,192 (1959) and German Patent 1,064,957 (1958); *Chem. Abstr.*, **56**, 455 (1962).

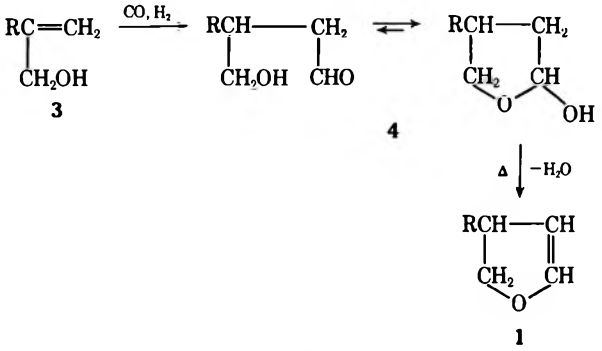
(10) M. A. Gianturco and P. Friedel, *Can. J. Chem.*, **44**, 1083 (1966).

(11) C. Botteghi and L. Lardicci, *Chim. Ind. (Milan)*, **52**, 265 (1970).

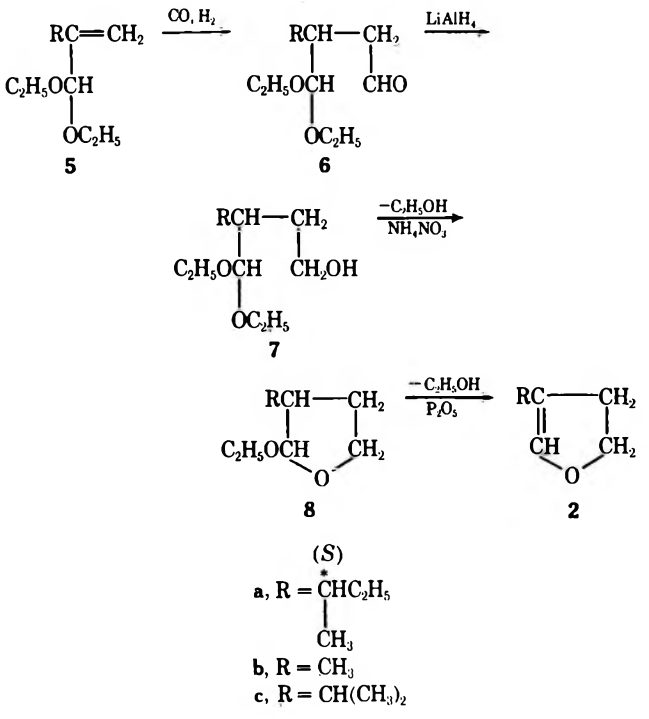
(12) P. Pino, *Gazz. Chim. Ital.*, **81**, 625 (1951).

(13) J. Falbe, "Synthesen mit Kohlenmonoxid," Springer-Verlag, West Berlin, 1967, p 46.

SCHEME I



SCHEME II



Therefore, this method has found practical use only in the case of the corresponding esters; for instance, the acetate of methallyl alcohol was used to obtain γ-acetoxy-β-methylbutyraldehyde, and hence, in two steps, 3-methyl-2,3-dihydrofuran was obtained in satisfactory yield.[6] However, using *trans*-bis(triphenylphosphine)carbonylchlororhodium(I)[14] as catalyst, we carried out the hydroformylation of **3** with exclusive formation of the desired γ-hydroxyaldehyde **4**.[15] The absence of characteristic carbonyl stretching bands in the ir spectra of **4a–c** and the absence of formyl hydrogens in their nmr spectra reveal the hemiacetalic form of the γ-hydroxyaldehydes (the hemiacetal hydrogens give their signal in the nmr spectra at δ 4.44–4.73), and rule out at the same time the formation of the possible isomers, β-hydroxyaldehydes, in the hydroformylation reaction.

Simple distillation at atmospheric pressure promotes the dehydration of **4**, and affords the 3-alkyl-2,3-dihydrofurans (**1**) exempt from isomers (the isomeric purity was established on the basis of the nmr spectra).

The cyclization of **7**, with loss of a molecule of ethanol, gave a mixture of stereoisomers **8**, the ir and nmr spectra of which showed no presence of olefinic protons.[16] The dealkoxylation of **8** was accomplished according to a known procedure,[6] upon heating in the presence of phosphoric anhydride; the resulting 4-alkyl-2,3-dihydrofurans (**2**) were isomerically pure, which was evident from their nmr spectra.

The structure of **1a–c** and **2a–c** was unequivocally confirmed by nmr analysis at 220 MHz; the spectral parameters are summarized in Table I.[17]

The nmr spectrum of **1a** shows some signals clearly split, owing to the presence of both diastereoisomers (*e.g.*, H_{2a} has a chemical shift difference of 0.01 ppm, H_{2b} 0.04 ppm, H_4 0.01 ppm). The relative peak heights of these signals give a direct measure of the diastereoisomeric composition: $(R,S)/(S,S) = 54:46$.[18]

In order to obtain an indication of the optical yield of the preparation of **1a**, a sample of this compound was dehydrogenated[10] to (+)-(*S*)-3-*sec*-butylfuran. The product obtained had $[\alpha]^{25}D$ +18.93° (*c* 8.44, mesitylene), corresponding to a minimum optical purity of 70.5%.[11]

Experimental Section

Boiling points are uncorrected. Gas chromatographic analyses were made on a Perkin-Elmer 990 gas chromatograph with FID detector using the columns specified. Infared spectra were measured on a Perkin-Elmer 221 spectrophotometer; nmr spectra at 220 MHz were obtained with a Varian spectrometer, in carbon tetrachloride solutions with tetramethylsilane as an internal standard (δ 0). Optical rotations were measured in solution in 1-dm tubes, using a Perkin-Elmer 141 polarimeter. Mass spectra were obtained with an Hitachi Perkin-Elmer RMU-6L mass spectrometer. Microanalyses were performed by the Microanalytical Laboratory, Department of Industrial and Engineering Chemistry, ETH (Zürich).

Materials.—The commercial product **3b** (Fluka A. G., Switzerland) was used without further purification. **3a** and **3c** were made according to the general procedure of Green and Hickinbottom.[19] **5a–c** were prepared from the respective α,β-unsaturated aldehydes by a known general method.[20] A common precursor of **3a**, $[\alpha]^{25}D$ +21.63° (*c* 1.655, *n*-heptane), and **5a**, $[\alpha]^{25}D$ +23.75° (*c* 2.901, *n*-heptane), was (+)-(*S*)-2-methylene-3-methylpentanal having ~95% minimum optical purity.[21]

2-Alkyl-γ-hydroxyaldehydes (4a–c).—A solution of **3** (0.4 mol) and $RhCl(CO)(PPh_3)_2$ (0.2 g) in dry benzene (80 ml) and triethyl-

(14) D. Evans, J. A. Osborn, and G. Wilkinson, *J. Chem. Soc. A*, 3133 (1968).

(15) Direct hydroformylation of allyl alcohols without appreciable isomerization was also obtained with Rh_2O_3 and tributylphosphine as catalyst: W. Rupilius, Thesis, Technische Hochschule Aachen, 1969.

(16) A gas chromatographic separation of the stereoisomers was performed and the single components were analyzed by mass spectroscopy; identical spectra for each isomer were obtained in all cases, the first significant peak corresponding to the loss of a molecule of ethanol, and the subsequent fragmentation pattern resembling that of the respective dihydrofuran **2**.

(17) Our values are in agreement with the data available in the literature: G. Dana and A. Zysman, *Bull. Soc. Chim. Fr.*, 1951 (1970), and ref 4.

(18) To determine the absolute configuration of the asymmetric carbon atom in the ring moiety of **1a**, a sample of its precursor, **4a**, was reduced with lithium aluminum hydride, and the 3-hydroxymethyl-4-methyl-1-hexanol obtained was converted into (4*S*)-3-carboxy-4-methylhexanoic acid with a known procedure: D. Pini, A. Di Corato, and L. Porri, *Chim. Ind. (Milan)*, **53**, 505 (1971). The rotatory power of the acid obtained, $[\alpha]^{25}D$ −1.63° (c 0.7, carbon tetrachloride), compared with the values of the pure diastereoisomers [D. Pini, A. Di Corato, and L. Porri, *Chim. Ind. (Milan)*, **53**, 505 (1971)] indicated the predominance of the 4*S*,3*R* isomer.

(19) M. B. Green and W. J. Hickinbottom, *J. Chem. Soc.*, 3266 (1957).

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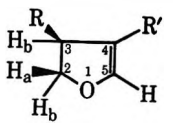
TABLE I

NMR PARAMETERS OF 3- AND 4-ALKYL-2,3-DIHYDROFURANS



R	R′	δ_{2a}	δ_{2b}	δ_3	δ_4	δ_5	J_{2a2b}	J_{2a3}	J_{2b3}	J_{34}	J_{35}	J_{45}
H	H	4.20	4.20	2.53	4.82	6.22		8 3	10.7	2.5	2.6	2.6
t-Bu	H	4.08	4.24	2.74	4.86	6.30	−9.1	7 4	9.6	2.4	2.0	2.8
(*S*)-*s*-Bu	H	3.96,[a] 3.97[b]	4.22,[a] 4.26[b]	2.86	4.86,[a] 4.87[b]	6.30	−8.7	6 9	9.8	2.3	2.2	2.5
Me	H	3.81	4.33	3.00	4.88	6.25	−8.6	6 6	9.8	2.3	1.8	2.6
H	Me	4.24	4.24	2.47		5.94	−8.8	7 0	9.6		1.7	
H	*i*-Pr	4.32	4.32	2.53		6.03	−9.0		9.8		1.7	
H	(*S*)-*s*-Bu	4.30	4.30	2.50		6.05	−9.0		9.0		2.1	

[a] *R,S* configuration. [b] *S,S* configuration.

amine (44 ml) was shaken in a high-pressure autoclave with a 1:1 mixture of carbon monoxide and hydrogen (80 atm) at a temperature of 80°. The reaction stopped when the theoretical amount of gas was absorbed. After removal of the solvents under reduced pressure (~100 mm), fractional distillation of the crude product gave **4** in 80–90% yield. Glpc of each product, using a 16 m × 0.5 mm Carbowax 20M support coated column, showed only one peak.

4a had bp 110° (0.3 mm); mass spectrum *m/e* (rel intensity) 70 (100), 41 (68), 57 (53), 55 (42), 69 (41), 56 (37), 29 (30), 42 (16.5), 83 (14.5), 43 (14).[22]

4b had bp 66° (12 mm); mass spectrum *m/e* (rel intensity) 56 (100), 41 (72), 57 (56), 72 (20), 29 (18.5), 27 (17), 43 (16), 39 (16), 58 (15.5), 55 (15).[22]

4c had bp 63° (0.1 mm); mp 35–37°; mass spectrum *m/e* (rel intensity) 70 (100), 57 (82), 41 (51), 55 (32), 83 (23), 29 (22), 43 (19.5), 42 (19), 81 (19), 69 (18).[22]

3-Alkyl-2,3-dihydrofurans (1a–c).—Each compound **4** (5 g) was placed in a distillation apparatus and heated at atmospheric pressure with an oil bath. The temperature was raised until a slow distillation of water and dihydrofuran was noticed; 160–230° were required according to the substituent (the presence of a trace of ammonium nitrate facilitates the dehydration). Heating was maintained until completion of the reaction. The distilled organic layer was dried (K_2CO_3) and redistilled over calcium hydride to afford pure **1** (70–80% yield). Glpc of each product, using a 2 m × 2.2 mm 15% polypropylene glycol column, showed only one peak.

1a had bp 90–91° (125 mm); $n^{25}D$ 1.4407; $[\alpha]^{25}D$ +21.50° (*c* 2.228, *n*-heptane); mass spectrum *m/e* (rel intensity) 69 (100), 41 (36), 68 (17), 126 (M^+, 13.5), 39 (9.5), 29 (9), 70 (7), 27 (6), 57 (5), 55 (4).

1b had bp 68°; $n^{25}D$ 1.4161 (lit.[6] bp 69–74°; $n^{25}D$ 1.4161); mass spectrum *m/e* (rel intensity) 69 (100), 41 (67), 84 (M^+, 54), 39 (39), 27 (21), 55 (20.5), 29 (17), 53 (13), 28 (10), 83 (6.5).

1c had bp 136°; $n^{25}D$ 1.4362; mass spectrum *m/e* (rel intensity) 69 (100), 41 (37), 57 (27), 68 (21), 126 (M^+, 13.5), 39 (13), 29 (12), 43 (11), 70 (10), 27 (6).

2-Alkyl-γ-hydroxyaldehyde Diethyl Acetals (7a–c).—The hydroformylation of **5** (0.4 mol) was carried out under the same conditions used for the preparation of **4**. The crude reaction mixture containing **6**[11] was added to a suspension of lithium aluminium hydride (5.0 g) in dry ether (300 ml) and stirred overnight at room temperature. The reaction mixture was worked up by the procedure described by Hill and Schearer;[23] distillation *in vacuo* afforded **7** in 80–85% yield.

7a had bp 98–99° (0.5 mm); $n^{25}D$ 1.4386–1.4390; $[\alpha]^{25}D$ −4.81° (*c* 1.061, *n*-heptane). *Anal.* Calcd for $C_{12}H_{26}O_3$: C, 66.01; H, 12.00. Found: C, 66.22; H, 12.18.

7b had bp 112–113° (14 mm); $n^{25}D$ 1.4292. *Anal.* Calcd for $C_9H_{20}O_3$: C, 61.33; H, 11.44. Found: C, 61.64; H, 11.74.

7c had bp 80–82° (0.9 mm); $n^{25}D$ 1.4400–1.4401. *Anal.* Calcd for $C_{11}H_{24}O_3$: C, 64.66; H, 11.84. Found: C, 64.60; H, 12.00.

2-Ethoxy-3-alkyl Tetrahydrofurans (8a–c).—Each compound **7** (5 g) was placed in a distillation apparatus in the presence of a trace of ammonium nitrate and heated with an oil bath at 140–150°; slow distillation of the theoretical amount of ethanol occurred; the residue, distilled *in vacuo*, afforded **8** in 80–85% yield.

8a had bp 85–95° (14 mm); **8b** had bp 52–54° (14 mm); **8c** had bp 62–68° (14 mm).

4-Alkyl-2,3-dihydrofurans (2a–c).—Each compound **8** (5 g) was placed in a distillation apparatus in the presence of a catalytic amount of phosphorus pentoxide and heated with an oil bath at 160–180°. Ethanol and dihydrofuran distilled as soon as they were formed; complete dealkoxylation was achieved in a matter of hours. Crude **2a** and **2c** were washed with water and distilled over calcium hydride to give the pure products in 75–80% yield. A pure sample of **2b** was obtained by preparative glpc on a Perkin-Elmer F 21 gas chromatograph, using a 3 m × 8 mm column packed with 20% polypropylene glycol on Chromosorb A at 80°. Glpc of each product, using a 2 m × 2.2 mm 15% polypropylene glycol column, showed only one peak.

2a had bp 145°; $n^{20}D$ 1.4450; $[\alpha]^{25}D$ +21.18° (*c* 2.762, *n*-heptane); mass spectrum *m/e* (rel intensity) 97 (100), 41 (48), 43 (31), 126 (M^-, 22), 39 (14), 55 (13), 69 (11.5), 27 (10.5), 29 (10), 111 (6).

2b had bp 63–64°; $n^{20}D$ 1.4425; mass spectrum *m/e* (rel intensity) 84 (M^+, 100), 55 (97), 83 (48), 41 (45), 39 (44), 29 (36), 27 (31), 53 (21), 56 (19), 69 (14).

2c had bp 124°; $n^{25}D$ 1.4492; mass spectrum *m/e* (rel intensity) 41 (100), 97 (93), 43 (56), 55 (42), 112 (M^+, 38), 39 (31), 27 (30.5), 67 (29), 71 (22.5), 69 (22).

Registry No.—**1a** (*R,S*), 34314-80-2; **1a** (*S,S*), 34368-07-5; **1b**, 1708-27-6; **1c**, 34314-82-4; **2a**, 34379-54-9; **2b**, 34314-83-5; **2c**, 34314-84-6; **4a**, 34379-55-0; **4b**, 34314-85-7; **4c**, 34314-86-8; **7a**, 34314-87-9; **7b**, 34314-88-0; **7c**, 34314-89-1; **8a**, 34314-90-4; **8b**, 34314-91-5; **8c**, 34314-92-6; 2,3-dihydrofuran, 1191-99-7.

(22) The molecular ion (M^+) is not recognizable, as expected for compounds of this type, but peaks at *m/e* M + 1 (<1%) are easily identifiable.

(23) R. K. Hill and W. R. Schearer, *J. Org. Chem.*, **27**, 921 (1962).

Synthesis and Reactions of γ-Alkylthio-β-butyrolactones

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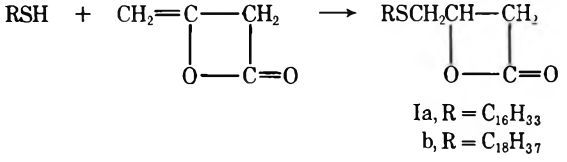
Diketene undergoes a variety of ring opening reactions to afford acetoacetate derivatives.[1] In contrast, the integrity of the β-lactone linkage may be maintained by a free-radical reaction at the olefinic linkage.

(1) D. Borrman, "Methoden der Organischen Chemie," 2nd ed, Vol. 4-II, Houben-Weyl-Müller, Ed., Georg Thieme Verlag, Stuttgart, 1968, pp 226–259.

For example, the free-radical copolymerization of diketene with ethylene or vinyl chloride has been claimed to yield products containing the unopened lactone ring.[2] Similarly, the homolytic addition of mercaptans to diketene has been reported to give γ-alkylthio-β-butyrolactones in moderate yields.[3] Prompted by interest in another area, we examined the preparation of some of these β-butyrolactone derivatives formed from linear chain mercaptans. In the course of this synthetic work we found that these β-lactone derivatives undergo a novel rearrangement and polymerization.

The reaction of *n*-hexadecyl or *n*-octadecyl mercaptan with diketene in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) gave 88–90% yields of crystalline 1:1 adducts, Ia,b. The presence of the β-lactone function in the product was indicated by a carbonyl band at 5.5 μ.[4] In the nmr spectra of the adducts the methylene protons adjacent to the carbonyl function are nonequivalent and spin coupled with the methine proton of the β-lactone ring. This latter proton is further spin coupled with the nonequivalent methylene protons adjacent to the ring connected to sulfur. This pattern is consistent with the proposed structure.



Ia, R = $C_{16}H_{33}$
b, R = $C_{18}H_{37}$

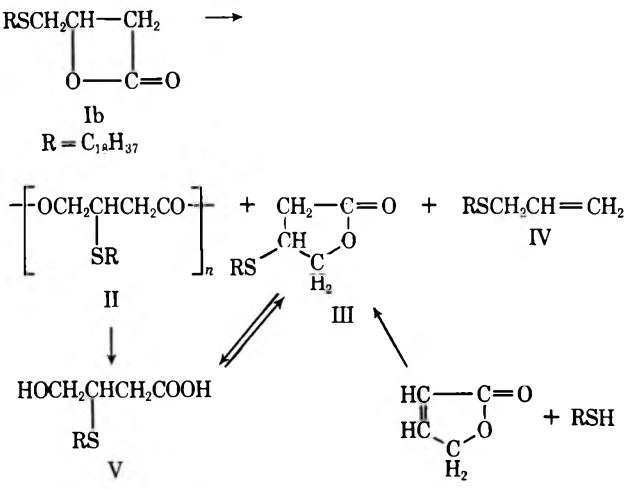
Further confirmation of the structure was obtained *via* ring opening with dimethylamine to give a 95% yield of the β-hydroxy-*N*,*N*-dimethylamide derivative.[5] In addition to AIBN, a sun lamp or normal interior lighting could also be used with equal effectiveness to catalyze the addition reaction. Hydrocarbons such as hexane or cyclohexane were the preferred solvents, since the adducts crystallized nearly quantitatively from the reaction mixture.

Heating Ib above its melting point resulted in the replacement of the β-lactone carbonyl ir absorption at 5.5 μ by new absorptions at 5.60, 5.75, and 6.1 μ. The reaction is shown in Scheme I.

Fractional crystallization gave a solid in 37% yield with the 5.75-μ absorption. This material was shown to be a polyester (II) with a molecular weight of 2160. Alkaline hydrolysis gave the monomeric γ-hydroxyl acid V. Structure V is supported by analytical and spectral data. The most structurally significant feature in the nmr spectrum of V is a doublet at δ 3.65. This is assigned to the methylene group adjacent to the hydroxyl function. The methylene group α to the carbonyl is present as an AB system at δ 2.51 and 2.75. The methine adjacent to sulfur appears as a multiplet at 3.17. These data are consistent with the rearrangement product and not with the anticipated 3-hydroxy-4-(*n*-octadecylthio)butyric acid.

Compound III was isolated in 14% yield by crystallization from the mother liquors of II. The γ-lactone

Scheme I
Rearrangement of β-Lactone Ib



assignment is based upon elemental analysis, molecular weight determination, and spectral properties. The ir spectrum contains a 5.6-μ carbonyl absorption consistent with the γ-lactone structure.[6] In the nmr spectrum of III the methylene protons adjacent to the carbonyl are nonequivalent and spin coupled with the methine hydrogen on the ring adjacent to sulfur. The spin pattern of these methylene hydrogens overlapped with the triplet associated with the methylene adjacent to sulfur on the octadecyl chain. The use of the europium shift reagent[7] clarified the pattern, moving the signals downfield into clear view. The methine hydrogen on the ring is further spin coupled with the nonequivalent methylene hydrogen adjacent to the oxygen of the lactone linkage.

Further confirmation for the structure of compound III was obtained by independent synthesis. γ-Crotonolactone[8] was treated with *n*-octadecyl mercaptan under alkaline conditions to give III. The alkaline hydrolysis of III also gave V. This was readily reconverted to III with *p*-toluenesulfonic acid in refluxing benzene. Lactonization was also observed in hot chloroform.

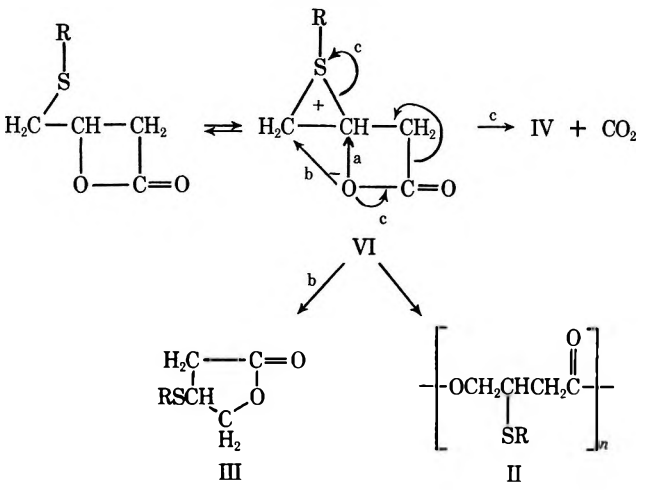
The product with the 6.1-μ absorption was purified by distillation and found to be *n*-octadecyl allyl sulfide (IV). This product is formed in 33% yield.

The rearrangement of the β-lactone has a number of unusual features. Normally, β-lactones undergo polymerization to form 3-hydroxypropionic acid polyesters.[9] In this instance the rearrangement during polymerization is due to the presence of the sulfur atom in the alkyl chain (Scheme II). The electron pair on sulfur is capable of assisting in the opening of the lactone ring[10] to give intermediate VI.

The reaction of VI along path a, *i.e.*, attack by the carboxylate anion on the secondary carbon of the episulfonium ion, would be fruitless, yielding starting material. Reaction along path b, *i.e.*, opening of the episulfonium ion on the primary carbon, yields the rearranged lactone III. The repetitive intermolecular

(2) D. D. Coffman, U. S. Patent 2,585,537 (Feb 12, 1952).
(3) C. W. Theobald, U. S. Patent 2,675,392 (April 13, 1954).
(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1966, p 188.
(5) T. L. Gresham, *et al.*, *J. Amer. Chem. Soc.*, **73**, 3168 (1951).
(6) Reference 4, p 186.
(7) J. K. M. Sanders and D. H. Williams, *J. Chem. Soc. D*, 422 (1970).
(8) C. C. Price and J. M. Judge, *Org. Syn.*, **45**, 22 (1965).
(9) H. E. Zaugg in "Organic Reactions," Vol. VIII, R. Adams, Ed., Wiley, New York, N. Y., 1954, p 327.
(10) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Company, New York, N. Y., 1959, p 572.

SCHEME II



opening of the episulfonium ion at the primary carbon yields the polyester II.

Decomposition of VI along path c yields the octadecyl allyl sulfide IV and carbon dioxide. This latter mode of reaction is very similar to a decarboxylative elimination.

The γ-lactone III was not a precursor of the polyester. Attempts to convert III to II were unsuccessful.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates DA-100-15 spectrometer. Chemical shifts are expressed in δ units parts per million downfield from tetramethylsilane. Molecular weight determinations were conducted by Mr. D. R. Stevens using a Mechrolab vapor pressure osmometer, Model 301A. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Preparation of γ-(*n*-Hexadecylthio)-β-butyrolactone (Ia).—Diketene (31.8 g, 0.378 mol) was added dropwise over a 0.25-hr period to a stirred solution of *n*-hexadecylmercaptan (107.3 g, 0.415 mol) and 0.5 g of AIBN in 210 ml of cyclohexane at ambient temperature. An exothermic reaction occurred and the internal temperature was maintained at 35–40° by external cooling. A solid separated from solution during diketene addition. After addition was complete the mixture was stirred at 20–30° for 1.5 hr. The product was removed by filtration, washed with cyclohexane, and air dried to give 105.1 g of Ia, mp 61.5–62.5°. A second crop, mp 59–60°, was obtained from the mother liquor. The total yield of Ia was 111.3 g (86%). An analytical sample was prepared by recrystallization from petroleum ether (bp 30–60°) to give material of mp 62–63°: ir ($CHCl_3$) 5.5, 8.85 μ; nmr ($CDCl_3$) δ 0.86 [t, J = 6.0 Hz, 3 H, $-(CH_2)_{15}CH_3$], 1.24 [s, 26 H, $-(CH_2)_{13}CH_3$], 1.52 [m, 2 H, $-SCH_2CH_2(CH_2)_{13}$], 2.59 (t, J = 7.0 Hz, 2 H, $-SCH_2C_{15}$), 2.80 and 3.0 (AB, two d of d, J_{AX} = 6.75, J_{BX} = 5.5, J_{AB} = 14.0 Hz, 1 H each, $-SCH_2CH-$), 3.24 and 3.56 (CD, two d of d, J_{CX} = 5.5, J_{DX} = 4.5, J_{CD} = 16.25 Hz, 1 H each, $-CH_2C(=O)-$), 4.64 (X of ABX, CDX, 11 lines, J_{AX} = 6.75, J_{BX} = J_{CX} = 5.5, J_{DX} = 4.5 Hz, 1 H, $-SCHCH_2-$).

Anal. Calcd for $C_{20}H_{38}SO_2$: C, 70.20; H, 11.11; S, 9.35. Found: C, 70.36; H, 11.04; S, 9.55.

In a similar manner Ib was prepared in 89% yield using *n*-octadecyl mercaptan. The ir and nmr spectra were identical with those of Ia with the exception of the integration of the methylene chain singlet at δ 1.24. The integral in this case indicated 30 H. The product has mp 68–69°.

Anal. Calcd for $C_{22}H_{42}SO_2$: C, 71.29; H, 11.42; S, 8.65. Found: C, 71.35; H, 11.51; S, 8.70.

Preparation of *N*,*N*-Dimethyl-3-hydroxy-4-(*n*-hexadecylthio)-butyric Acid Amide.—A solution of Ia (5.00 g, 0.0146 mol) in 100 ml of ether was added dropwise to a stirred solution of dimethylamine (4.5 g, 0.1 mol) in 150 ml of ether at −5 to 0°. After addition was complete the solution was warmed to room temperature and stirred overnight. The product crystallized during concentration of the ether to give 5.6 g (99%) of material, mp 55–57°, ir ($CHCl_3$) 2.95, 6.1 μ.

Anal. Calcd for $C_{22}H_{45}NSO_2$: C, 68.13; H, 11.70; N, 3.64; S, 8.27. Found: C, 67.91; H, 11.42; N, 3.61; S, 8.37.

Thermal Rearrangement of Ib.—A melt of Ib (29.5 g, 0.08 mol) was heated at 100° for 1 hr. An ir indicated the complete disappearance of 5.5-μ absorption and the appearance of bands at 5.6, 5.75, and 6.1 μ. The mixture was dissolved in 100 ml of boiling acetone and allowed to cool slowly to room temperature overnight. The polyester II was removed by filtration to give 11.0 g of material, mp 48–53°, ir (film) 5.75 μ, mol wt (vpo), 2160 (THF).

Anal. Calcd for $(C_{22}H_{42}O_2S)_n$: C, 71.29; H, 11.42; O, 8.63; S, 8.65. Found: C, 70.44; H, 11.36; O, 9.10; S, 8.35.

The acetone filtrate from above was evaporated to dryness and the residue was recrystallized from hexane to give 4.3 g (14%) of III, mp 52–54°. Recrystallization from ether gave an analytical sample: mp 55–56°; ir ($CHCl_3$) 5.6, 8.55 μ; nmr ($CDCl_3$) δ 0.86 [t, J = 6.0 Hz, 3 H, $-(CH_2)_{17}CH_3$], 1.24 [s, 30 H, $-(CH_2)_{15}CH_3$], 1.52 [m, 2 H, $-SCH_2CH_2(CH_2)_{15}$], 2.42 and 2.87 (AB, two d of d, J_{AX} = 7.5, J_{BX} = 8.0, J_{AB} = 18.5 Hz, 1 H each, $-CH_2C(=O)$), 2.56 [t, J = 7.0 Hz, 2 H, $-SCH_2(CH_2)_{16}-$], 3.59 (X of ABX, CDX multiplet, $-SCH<$), 4.10 and 4.54 (CD, two d of d, J_{CX} = 7.0 J_{DX} = 6.5, J_{CD} = 10.0 Hz, 1 H each, $-OCH_2CH<$). Addition of Eu(thd)$_3$ shifted resonances at δ 2.42 and 2.87 to 3.25 and 3.70, respectively; 2.56 to 2.71; and 4.10 and 4.54 to 4.64 and 5.08, respectively.

Anal. Calcd for $C_{22}H_{42}O_2S$: C, 71.29; H, 11.42; O, 8.63; S, 8.65. Found: C, 71.76; H, 11.49; O, 8.41; S, 8.62.

The hexane filtrate was evaporated to 9.1 g of an oil. Vacuum distillation gave 8.5 g (33%) of IV: bp 176–184° (0.4 mm); mol wt (vpo), 325. (calcd 326); ir (film) 6.13, 10.15, 10.9 μ; nmr ($CDCl_3$) δ 0.95 [t, J = 6.0 Hz, 3 H, $-(CH_2)_{17}CH_3$], 1.29 [s, 32 H, $-(CH_2)_{16}CH_3$], 2.52 [t, J = 7.0 Hz, 2 H, $-SCH_2(CH_2)_{16}$], 3.18 (apparent d with some traces of higher splitting, J = 7.0 Hz, 2 H, $-SCH_2CH=$), allyl pattern with peaks centered at 5.20, 5.22, and 6.02 (5.20, J = 9.5, 2.0, and 1.0 Hz), 5.22 (J = 17.5, 2.0, and 1.0 Hz), 6.02 (J = 17.5, 9.5, and 7.0 Hz, total 3 H).

Anal. Calcd for $C_{21}H_{42}S$: C, 77.21; H, 12.96. Found: C, 77.41; H, 12.86.

Preparation of V. Hydrolysis of Polyester II.—A solution of polyester II (20.0 g, 0.054 mol) and potassium hydroxide (13.2 g, 0.195 mol) in 60 ml of 50% aqueous ethanol was heated at reflux for 5 hr. The mixture was cooled and acidified to pH 2 with concentrated hydrochloric acid. The solid was filtered, washed with water, and air dried. The residue was recrystallized from chloroform to give V (6.9 g, 0.018 mol), 33%, mp 78–79°. Evaporation of the filtrate gave 8.0 g of solid, mp 43–61°. The ir spectra indicated that the material was a mixture of partially hydrolyzed polyester and lactone III: ir ($CHCl_3$) 3.2–3.9 (broad), 5.95, 7.6, and 8.2 μ; nmr ($CDCl_3$) δ 0.85 [t, J = 6.0 Hz, 3 H, $-(CH_2)_{17}CH_3$], 1.24 [s, 30 H, $-(CH_2)_{15}CH_3$], 1.52 [m, 2 H, $-SCH_2CH_2(CH_2)_{15}$], 2.51 and 2.75 (AB, two d of d, J_{AX} = 4.0, J_{BX} = 3.5, J_{AB} = 16.5 Hz, 1 H each, $CH_2C(=O)$), 2.54 [t, J = 7.0 Hz, $-SCH_2(CH_2)_{17}-$], 3.17 (m, 1 H, >CHS), 3.65 (d, J = 5.5 Hz, 2 H, $-CH_2OH$), 6.18 (b exchange H from OH and COOH, 2 H).

Anal. Calcd for $C_{22}H_{44}SO_3$: C, 67.98; H, 11.41; O, 12.35; S, 8.25. Found: C, 67.79; H, 11.50; O, 12.65; S, 8.44.

Cyclization of V to III.—A solution of V (1.0 g, 0.0026 mol) and *p*-toluenesulfonic acid (0.1 g) in 10 ml of benzene was heated at reflux for 15 hr using a water separator. The solvent was evaporated and the residue was recrystallized from petroleum ether to give III (0.9 g, 0.0026 mol), 95%, mp 53–54°. The mixture melting point with III was undepressed and the ir spectra were superimposable.

Preparation of III.—A solution of *n*-octadecyl mercaptan (3.44 g, 0.012 mol), γ-crotonolactone (0.94 g, 0.012 mol), and sodium methylate (0.054 g, 0.001 mol) in 10 ml of methanol was heated at 50° for 0.5 hr. An oily layer separated which was dissolved in chloroform and the chloroform was evaporated. The residue (3.5 g) was chromatographed over silica gel. Unreacted mercaptan was eluted with petroleum ether. Elution with 10% diethyl ether in petroleum ether gave III (0.60 g, 0.0016 mol), 13.5%, mp 54–57°. Recrystallization from ether gave material, mp 56–57°. A mixture melting point with III obtained from the rearrangement of Ib was undepressed. The ir spectra were superimposable.

Preparation of V *via* Hydrolysis of III.—A solution of III (2.0

g, 0.0074 mol) and 1.4 g of potassium hydroxide in 20 ml of 50% aqueous methanol was heated at reflux for 3.5 hr. The solution was cooled and acidified to pH 2 with concentrated hydrochloric acid. The solid material was filtered, washed with water, and dried to give 2.0 g of hydroxy acid V, mp 75–76°. A mixture melting point with the acid obtained from the hydrolysis of polyester II was not depressed and the ir spectra were superimposable.

Registry No.—Ia, 34289-54-8; Ib, 34289-55-9; polymer of Ib, 34287-66-6; II, 34268-90-1; III, 34289-56-0; IV, 34289-57-1; V, 34289-58-2; *N,N*-dimethyl-3-hydroxy-4-(*n*-hexadecylthio)butyric acid amide, 34289-59-3.

Hydrogenation of Cinnamic Acids with Iridium(I) Catalysts. Effect of Various Ligands

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Recent communications have described olefin hydrogenations using $Ir(olefin)_2L_n$ based systems as catalysts.[1-3] Green and coworkers have noted ligand and solvent effects on the rate of hydrogenation of 1,5-cyclooctadiene and 1-hexene with these systems.[2] Van der Ent *et al.*, have studied the rate of hydrogenation of 1-hexene in benzene as a function of the ligand–iridium ratio (R).[3] With L = Ph_3P the maximum rate was observed at R = 2 at which point the rate is approximately ten times the rate at R = 1. I now report that α,β-unsaturated acids can also be reduced with these iridium catalysts and note some important rate effects based on ligand type, ligand ratio, and the presence or absence of chloride ligand.

Cinnamic acid and α-methylcinnamic acid have been hydrogenated to β-phenylpropionic acid and α-methyl-β-phenylpropionic acid, respectively, with [Ir(1,5-cyclooctadiene)Cl]$_2$ and various phosphines in MeOH solvent at 100° and 75 psig of H_2. Table I records the per cent reduction after 2 hr under these conditions with a substrate–catalyst ratio of 400. It is found that cinnamic acid is reduced faster than α-methylcinnamic acid for all three phosphines (catalyst system A).

The importance of a 2:1 phosphine–iridium ratio as against a 1:1 ratio in the reduction of α-methylcinnamic acid (catalyst system A *vs.* B) manifests itself with the less basic phosphines, Ph_3P and Ph_2PEt, but entirely disappears with $PhPEt_2$. In the latter case the rates of reduction are identical for both systems. Even with Ph_2PEt the rate differences are not nearly so pronounced as with Ph_3P.[4]

Hydrogenation of α-methylcinnamic acid in the absence of chloride ligand (system C) was achieved by use of isolated [Ir(1,5-cyclooctadiene)L$_2$]BF_4 as the catalyst. In this case the reduction proceeds much more rapidly with all three phosphines than the same reduction in the presence of chloride (system A).

One further observation of note is that the rate of hydrogenation of cinnamic acid with L = Ph_3P was considerably reduced when no effort was made to eliminate the presence of atmospheric oxygen. The inhibitory effect of oxygen with this iridium catalyst is exactly the opposite of the rate-enhancing effect of oxygen in the reduction of maleic acid in DMA catalyzed by $IrX(CO)(Ph_3P)_2$ reported by James and Memon.[5] I have repeated the effect reported by these authors in the reduction of cinnamic acid with $IrCl(CO)(Ph_3P)_2$ in both DMA and MeOH.

TABLE I
PER CENT REDUCTION AT 2 HR[a]

	Cinnamic acid	α-Methylcinnamic Acid		
Catalyst[b]	A	A	B	C
Ph_3P	82	38	1.5	92
Ph_2PEt	55	19	6	39
$PhPEt_2$	64	25	25	78

[a] Reaction cessation at 2 hr was chosen arbitrarily. All catalyst systems were still alive at this point with the possible exception of system B with Ph_3P and Ph_2PEt. In these cases partial loss of catalyst by iridium plate-out was observed early in the reaction. [b] A = PR_3/Ir = 2.0 [Ir(1,5-cyclooctadiene)Cl]$_2$ and PR_3 mixed *in situ*; B = PR_3/Ir = 1.0 [Ir(1,5-cyclooctadiene)-Cl]$_2$ and PR_3 mixed *in situ*; C = Used isolated [Ir(1,5-cyclooctadiene)$(PR_3)_2$]BF_4: Prepared by previously published general procedures for analogous rhodium and iridium complexes. *Cf.* ref 1 and 2 and R. R. Schrock and J. A. Osborn, *J. Amer. Chem. Soc*, **93**, 2397 (1971).

Experimental Section

All hydrogenations were conducted in glass Fischer–Porter aerosol compatibility tubes with 20 mmol of substrate and 0.05 mmol of catalyst dissolved in 25 ml of anhydrous MeOH. For systems A and B, [Ir(1,5-cyclooctadiene)Cl]$_2$[6] and the phosphines were premixed in 5 ml of MeOH under N_2 for 15 min prior to the addition of substrate. All reaction mixtures were vigorously sparged with nitrogen prior to being pressured to 75 psig of H_2. Reaction timing commenced upon placement of a 100° oil bath under the reaction vessel and activation of a magnetic stirrer.

Analyses were performed by integrating the $CDCl_3$ nmr spectra of solvent-stripped reaction aliquots. The reported integrals for cinnamic acid are actually corrected from observed figures to allow for integral deviations observed from known values in standard mixtures. In the case of α-methylcinnamic acid and α-methyl-β-phenylpropionic acid, standard mixtures integrated correctly.

Registry No.—Cinnamic acid, 621-82-9; α-methylcinnamic acid, 1199-77-5.

(1) J. R. Shapley, R. R. Schrock, and J. A. Osborn, *J. Amer. Chem. Soc.*, **91**, 2816 (1969).
(2) M. Green, T. A. Kuc, and S. N. Taylor, *J. Chem. Soc. D*, 1553 (1970).
(3) H. van Gaal, H. G. A. M. Cuppers, and A. van der Ent, *ibid.*, 1694 (1970).
(4) Van der Ent's work on phosphine–iridium ratios (ref 3) was confined to Ph_3P and the hydrogenation of 1-hexene. It is interesting to speculate whether the rate differences would also disappear in this case with use of $PhPEt_2$ instead of Ph_3P.
(5) B. R. James and N. A. Memon, *Can. J. Chem.*, **46**, 217 (1968).
(6) Strem Chemicals, Inc.

Reduction of α-Substituted Acetoacetate Enolates with Lithium Aluminum Hydride

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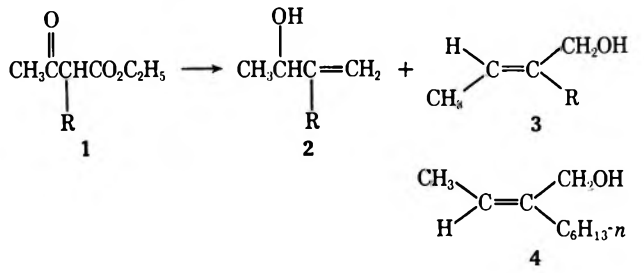
In connection with a current synthesis project we had occasion to examine the reduction of α-substituted ethyl acetoacetate enolates. A recent report concern-

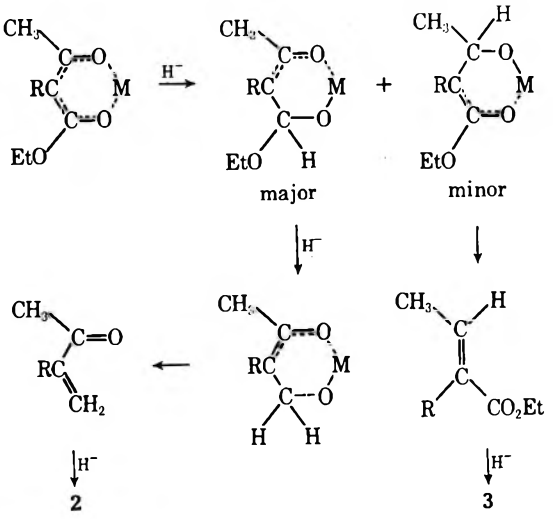


a, series R = n-C_6H_{13}
b, series R = $CH_2C_6H_5$
c, series R = C_6H_{11}

ing related β-diketone reductions prompts this brief disclosure of our findings.[1]

The keto esters **1a-c** were reduced along the lines reported in our earlier studies on malonic esters wherein sodium hydride was employed for enolate formation and ethyl formate was finally added to destroy excess lithium aluminum hydride.[2] The reductions afforded a roughly 80:20 mixture of allylic alcohols **2** and **3** for the three systems examined. This trend can be readily accommodated within the framework of previously postulated pathways for analogous reductions[1-3] as depicted in Scheme I.[4]

SCHEME I



As in the case of β-diketone enolate reductions, the elimination reaction leading to the unsaturated alcohols **3** appears to be highly stereoselective.[1] The stereochemical explanation offered for those systems would seem applicable to the present keto ester enolates as well. As a check on this stereochemical point we employed the method of Corey and Yamamoto[5] to synthesize the stereoisomer **4** of alcohol **3a**. The spectral properties of these two alcohols, while similar, showed distinct differences which left no doubt regarding their nonidentity.

From a synthetic point of view, the β-keto ester enolate reduction offers a simple, direct route to β-methylene alcohols such as **2**.

Experimental Section[6]

General Reduction Procedure.—A solution of 0.1 mol of keto ester **1** in 50 ml of tetrahydrofuran was added dropwise to 2.5 g of sodium hydride (from 5.0 g of 50% oil dispersion) in 200 ml of tetrahydrofuran and the mixture was heated at reflux for 1 hr and treated with 8.00 g of lithium aluminum hydride in portions. The mixture was heated at reflux for 4 hr and cooled, 40 ml of ethyl formate was carefully added, and the mixture was stirred at 40–50° for 1 hr. The product was isolated by through extraction with ether and distillation.

Reduction of Ethyl α-Hexylacetoacetate (1a).[7]—The above procedure afforded an 82:18 mixture of alcohols **2a** and **3a**, bp 49–50° (0.01 mm), in 71% yield. Preparative gas chromatography was used to isolate the pure isomers, which had the following properties.

2-Hexyl-1-buten-2-ol (2a) had λ_{max}^{film} 6.10 and 11.17 mμ; $\delta_{TMS}^{CCl_4}$ 4.95, 4.67 (C=CH_2), 4.0 (H-3 quartet, J = 6 Hz), 1.25 ppm (CH_3 doublet, J = 6 Hz).

Anal. Calcd for $C_{10}H_{20}O$: C, 76.78; H, 12.89. Found: C, 76.54; H, 12.95.

***Z*-2-Hexyl-2-buten-1-ol (3a)** had λ_{max}^{film} 9.43 and 9.95 mμ; $\delta_{TMS}^{CCl_4}$ 5.42 (H-3 quartet, J = 6 Hz), 1.60 (CH_3 doublet, J = 6 Hz), 3.31 ppm (CH_2O–).

Anal. Calcd for $C_{10}H_{20}O$: C, 76.78; H, 12.89. Found: C, 76.71; H, 12.87.

Reduction of Ethyl α-Benzylacetoacetate (1b).[8]—The above procedure afforded an 80:20 mixture of alcohols **2b** and **3b**, bp 55–56° (0.01 mm), in 44% yield. Preparative gas chromatography was used to isolate the pure isomers, which had the following properties.

2-Benzyl-1-buten-3-ol (2b) had λ_{max}^{film} 6.10 and 11.11 mμ; $\delta_{TMS}^{CCl_4}$ 5.00, 4.58 (C=CH_2), 4.10 (H-3 quartet, J = 6 Hz), 3.26 (benzyl CH_2), 1.20 ppm (CH_3 doublet, J = 6 Hz).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.45; H, 8.70. Found: C, 81.31; H, 8.88.

2-Benzyl-2-buten-1-ol (3b) had λ_{max}^{film} 6.28 and 11.83 mμ; $\delta_{TMS}^{CCl_4}$ 5.58 (H-3 quartet, J = 6 Hz), 1.66 ppm (CH_3 doublet, J = 6 Hz).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.45; H, 8.70. Found: C, 81.33; H, 8.98.

Reduction of Ethyl α-Cyclohexylacetoacetate (1c).[9]—The above procedure afforded an 85:15 mixture of alcohols **2c** and **3c**, bp 47–48° (0.01 mm), in 53% yield. Preparative gas chromatography was used to isolate the pure isomers, which had the following properties.

2-Cyclohexyl-1-buten-3-ol (2c) had λ_{max}^{film} 6.06, 11.11, 11.28 mμ; $\delta_{TMS}^{CCl_4}$ 5.06, 4.84 (C=CH_2), 4.13 (H-3 quartet, J = 6.5 Hz), 1.20 ppm (CH_3 doublet, J = 6.5 Hz).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.88; H, 11.76. Found: C, 77.67; H, 11.50.

2-Cyclohexyl-2-buten-1-ol (3c) had λ_{max}^{film} 11.24 mμ; $\delta_{TMS}^{CCl_4}$ 5.38 (H-3 quartet, J = 6.5 Hz), 3.90 (–CH_2O–), 1.61 ppm (CH_3 doublet, J = 6.5 Hz).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.88; H, 11.76. Found: C, 77.77; H, 11.71.

***E*-2-Hexyl-2-buten-1-ol (4).**—The procedure of Corey and Yamamoto was employed,[5] affording the title compound: bp 80° (bath temperature) (0.05 mm); λ_{max}^{film} 6.88 and 9.90 mμ; $\delta_{TMS}^{CCl_4}$ 5.27 (H-3 quartet, J = 6.2 Hz), 1.60 ppm (CH_3 doublet, J = 6.2 Hz).

Anal. Calcd for $C_{10}H_{20}O$: C, 76.78; H, 12.89. Found: C, 76.75; H, 12.82.

(1) J. W. Frankenfeld and W. E. Tyler, III, *J. Org. Chem.*, **36**, 2110 (1971).

(2) J. A. Marshall, N. H. Andersen, and A. R. Hochstetler, *ibid.*, **32**, 113 (1967).

(3) A. S. Dreiding and J. A. Hartman, *J. Amer. Chem. Soc.*, **75**, 939 (1953).

(4) Our proposed pathway for the reduction of malonic enolater (ref 2) was not intended to replace or discredit the scheme of Dreiding and Hartman (ref 3) as implied by Frankenfeld and Tyler (ref 1). We merely wished to extend the Dreiding and Hartman proposal in somewhat greater detail so as to include the formation of saturated alcohol by-products.

(5) E. J. Corey and H. Yamamoto, *J. Amer. Chem. Soc.*, **92**, 226 (1970).

(6) Reactions were conducted under a nitrogen atmosphere using the apparatus described by W. S. Johnson and W. P. Schneider, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 132. Reaction products were isolated by addition of water and extraction with the specified solvent. The combined extracts were washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was removed from the filtered solutions on a rotary evaporator.

(7) V. H. Wallingford, M. A. Thorpe, and A. H. Homeyer, *J. Amer. Chem. Soc.*, **64**, 580 (1942).

(8) H. R. Snyder, C. W. Smith, and J. M. Stewart, *ibid.*, **66**, 200 (1944).

(9) J. T. Adams, B. Abramovitch, and C. R. Hauser, *ibid.*, **65**, 552 (1943).

Registry No.—**2a**, 34220-09-2; **2b**, 34220-10-5; **2c**, 34220-11-6; **3a**, 34226-07-8; **3b**, 34220-12-7; **3c**, 34220-13-8; **4**, 34226-08-9; lithium aluminum hydride, 16853-85-3.

Acknowledgment.—We are grateful to the National Science Foundation for support of this work.

Preparation of Nitriles from 1,2,5-Oxadiazoles by Reduction with Triphenyl Phosphite[1,2]

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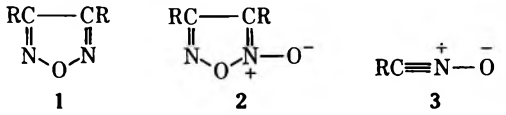
The 1,2,5-oxadiazoles **1** can be made[3a,b] by dehydration of 1,2-dioximes and by deoxygenation[4] of 1,2,5-oxadiazole 2-oxides **2**. The latter are obtained[3] from 1,2-dioximes by oxidation and from nitrile oxides **3** by dimerization.[5]



1 **2** **3**

The present note reports our results on the conversion of 1,2,5-oxadiazoles (and their 2-oxides) to nitriles. We heated a number of the oxadiazoles with triphenyl phosphite (chosen for cost and convenient boiling point) and were pleased to find that nitriles were produced in preparatively useful amounts. Since the 1,2,5-oxadiazole 2-oxides are reduced to the 1,2,5-oxadiazoles under much milder conditions[4] than ours, we believe that the reactions we report here are all conversions of 1,2,5-oxadiazoles to nitriles.

After the completion of our study a note without experimental details appeared[6] describing the cleavage and reduction to dicyano compounds of the 1,2,5-oxadiazole 2-oxides prepared from acenaphthylenequinone dioxime and camphorquinone dioxime. These workers used trimethyl phosphite and attributed the easy reduction to ring strain because the oxadiazole ring is fused to another 5-ring in each of their examples. We find their argument convincing as a reason for the ease of the reaction in the cases they report, but our findings indicate that under more strenuous conditions this reductive cleavage is general.

The ultimate utility of this sequence in preparative chemistry remains to be worked out. We note, however, that the overall conversion of a ketone with an adjacent CH_2 group to two cyano groups may be a useful alternative to other cleavage schemes.

Our results are too fragmentary to support any speculations about the effects of substituents on yield. Much of the difference in yields reported here can be accounted for by higher losses in isolation and purification of very volatile or very soluble nitriles. The yields are collected in Table I and a typical experiment is described in the Experimental Section.

TABLE I

R in 1 or 2	Ref	RCN, %	Notes
Phenyl **1**	*a*	79	*f*
Phenyl **2**	*b*	87.4	*f*
4-Methoxyphenyl **2**	*c*	31.4	*g, h*
2-Furyl **2**	*d*	22.3	*g*
Ethyl **2**	*e*	65.2	*g*
Methyl **2**	*e*	38.7	*g*

[a] K. Auwers and V. Meyer, *Ber.*, **22**, 714 (1889). [b] J. H. Boyer and U. Toggweiler, *J. Amer. Chem. Soc.*, **79**, 895 (1957). [c] G. Ponzio, *Gazz. Chim. Ital.*, **36**, 596 (1906). [d] H. Rheinboldt, *Justus Liebigs Ann. Chem.*, **451**, 167 (1926). [e] T. Mukaiyama and T. Hoshino, *J. Amer. Chem. Soc.*, **82**, 5339 (1960). [f] Reaction mixture was yellow-orange. [g] Reaction mixture was black. [h] Nitrile mp 57–58° (EtOH) [lit. mp 59°: W. Reinder and W. E. Ringer, *Recl. Trav. Chim. Pays-Bas*, **18**, 328 (1899)].

Experimental Section

It is advisable to use triphenyl phosphite that has been washed with alkali and then water and has been thoroughly dried.

Benzonitrile from 3,4-Diphenyl-1,2,5-oxadiazole 2-Oxide.—To 26.0 g (0.084 mol) of triphenyl phosphite preheated to 270° in a flask equipped with a stirrer, a thermometer in the liquid, and a reflux condenser was added a mixture of 10.00 g (0.042 mol) of 3,4-diphenyl-1,2,5-oxadiazole 2-oxide and 26.0 g of triphenyl phosphite. The reaction mixture, which heated up spontaneously and turned light yellow-orange, was kept under reflux by external heating for 15 min longer and was then fractionated in vacuum to give 7.57 g (87.4%) of benzonitrile identical (infrared) with an authentic sample.

Registry No.—Benzonitrile, 100-47-0; 3,4-diphenyl-1,2,5-oxadiazole-2-oxide, 5585-14-8; triphenyl phosphite, 101-02-0.

Nonequivalency of *exo*-*N*-Methylene Protons of Some 2-Oxazolidones

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A previous publication[1] reported the preparation of 2-oxazolidones in excellent yields using a hydrocarbon-soluble catalyst composed of lithium bromide and tributylphosphine oxide. The cycloaddition reaction of methoxymethyl isocyanate with phenyl glycidyl ether in benzene gave *N*-methoxymethylene-5-phenoxymethylene-2-oxazolidone (**1**), mp 69.5–70.5°.

Nmr analysis of this compound in *o*-dichlorobenzene and deuteriochloroform indicated that the *exo*-*N*-methylene protons were nonequivalent. We would like to report some additional nmr studies which further

(1) Taken from the Ph.D. Dissertation of Stanley M. Katzman, University of Missouri—Kansas City, January 1967.

(2) Support by the National Science Foundation under Grant No. G10031 is gratefully acknowledged.

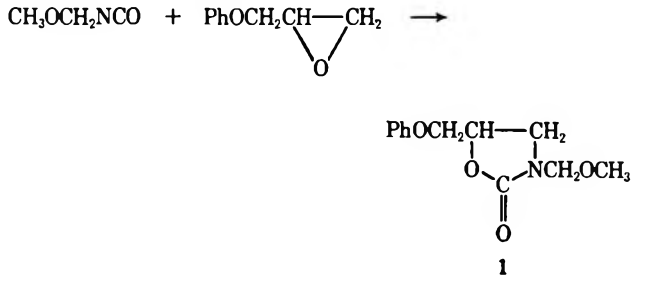
(3) (a) J. Doeuvre in "Traité de Chimie Organique," Vol. 21, V. Grignard, G. Dupont, and R. Locquin, Ed., Masson et Cie, Paris, 1953. (b) L. C. Behr in "Heterocyclic Compounds," Vol. 17, A. Weissberger and R. H. Wiley, Ed., Wiley-Interscience, New York, N. Y., 1962. (c) J. V. R. Kaufman and J. P. Picard, *Chem. Rev.*, **59**, 429 (1959).

(4) (a) T. Mukaiyama, H. Nambu, and M. Okamoto, *J. Org. Chem.*, **27**, 3651 (1962); (b) Ch. Grundmann, *Chem. Ber.*, **97**, 575 (1964); (c) A. S. Bailey and J. M. Evans, *Chem. Ind. (London)*, 1424 (1964).

(5) Ch. Grundmann and P. Grünanger, "The Nitrile Oxides," Springer Verlag, West Berlin and Heidelberg, 1971.

(6) Altaf-Ur-Rahman and A. J. Boulton, *Chem. Commun.*, 73 (1968).

(1) J. E. Herweh and W. J. Kauffman, *Tetrahedron Lett.*, 809 (1971).



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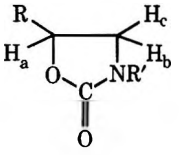
elucidate the factors affecting the nonequivalency of the *exo-N*-methylene protons.

A number of 2-oxazolidones have been prepared and their nmr spectral characteristics are tabulated in Table I. The compounds investigated were designed



to determine the effect of the asymmetric center and the methoxy group on the nonequivalency of the *exo-N*-methylene protons.

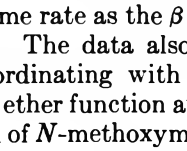
Nmr analysis of *N*-methoxymethylene-2-oxazolidone (**4**) in *o*-dichlorobenzene to −10° and deuteriochloroform to −30°, with and without europium shift reagents (see Experimental Section), indicated that the *exo-N*-methylene protons were equivalent.

Low-temperature analysis of *N*-butyl-5-phenoxymethylene-2-oxazolidone (**2**) in *o*-dichlorobenzene to −10° and deuteriochloroform to −30°, with and without spin decoupling of the adjacent butyl methylenes, indicated nonequivalency of the *exo-N*-methylene protons. However, in no case did the nonequivalency become large enough to cause sharp splitting of the nmr signals. In order to more clearly demonstrate this nonequivalency, the effect of a europium shift reagent on the *exo-N*-methylene protons was examined. The addition of $Eu(fod)_3$ to **2** (10%, $CDCl_3$) in calculated small amounts resulted in resolution of the *N*-butyl group and simultaneously the *exo-N*-methylene protons became nonequivalent. Enough shift reagent was added to shift the signals and enable spin decoupling to be accomplished. The results are shown in Table II.

Spin decoupling the $H_{e\beta}$ butyl methylene protons produced an AB quartet for the H_d *exo-N*-methylene protons and verfiied their assignment. The data (Table II) show that the *exo-N*-methylene protons shift much faster than the adjacent ring methylene protons, which shift at about the same rate as the β methylene protons of the butyl group. The data also indicate that the shift reagent is coordinating with the 2-oxazolidone function and not the ether function at ring position 5.

Nmr investigation of *N*-methoxymethylene-5-phenyl-2-oxazolidone (**3**), wherein the phenyl moiety is attached directly to the asymmetric carbon, indicated again that the *exo-N*-methylene protons were nonequivalent in *o*-dichlorobenzene, even at room temperature. However, the nonequivalency of the *exo-N*-methylene protons were not manifested at room temperature in deuteriochloroform as the solvent. In the case of compound **3** the magnitude of the nonequivalency at room temperature was not so great as in the

TABLE I
NMR SPECTRAL DATA[a]

Compd	R	R′	Chemical shifts, δ ppm (TMS = 0) H_a	H_b	H_c	$H_{dd'}$	H_e	$H_{ff'}$
1[b]	$PhOCH_2$	CH_3OCH_2	4.80 (m)	3.77 (t, J_{ba} = J_{bc} = 8.50 Hz)	3.62 (dd, J_{cb} = 8.50, J_{ca} = 6.50	4.15, 5.23 (q, $J_{dd'}$ = 10.75 Hz)[c]	3.35 (s)	4.49, 3.73 (dq, J_{fa} = $J_{f'a}$ = 4.00, $J_{ff'}$ = 10.50 Hz)
2[b]	$PhOCH_2$	$CH_3(CH_2)_2CH_2$	5.05 (m)	3.86 (t, J_{ba} = J_{bc} = 8.50 Hz)	3.70 (dd, J_{ca} = 6.50 Hz)	3.42 (t, J_{de} = 7.00 Hz)	1.50 (m)	4.07, 4.53 (dq, J_{fa} = $J_{f'a}$ = 4.00, $J_{ff'}$ = 10.50 Hz)
3[b]	Ph	CH_3OCH_2	5.50 (dd, J_{ab} = 9.00, J_{ac} = 7.50 Hz)	3.99 (t, J_{ba} = J_{bc} = 9.00 Hz)	3.32 (dd, J_{cb} = 9.00, J_{ca} = 7.50 Hz)	4.41, 4.89 (q, $J_{dd'}$ = 10.75 Hz)[d]	3.30 (s)	
4	H_i	CH_3OCH_2	4.55 (m)	3.68 (m)	3.68 (m)	4.64 (s)	3.28 (s)	4.55 (m)
5[c]	$PhOCH_2$		5.05 (m)	4.27 (t, J_{ba} = J_{bc} = 9.00 Hz)	3.98 (dd, J_{ca} = 6.25 Hz)	7.92 (d, J_{de} = 8.25 Hz)	7.50 (d)	4.15 (m, obscured)

[a] The nmr spectra were determined in *o*-dichlorobenzene (20–30%) at 25°, except compound **5** which was determined in DMSO-d_6. A comparison with spectra in deuteriochloroform indicated very little change in chemical shifts. [b] The phenyl absorptions for compound **1** occurred at δ 7.40–6.90 (m); compound **2**, 7.80–7.20 (m); compound **3**, 7.32 (s). [c] The H_D protons were also nonequivalent in $CDCl_3$ at room temperature.[1] [d] The H_D protons were equivalent in $CDCl_3$ at room temperature. [e] The ortho, meta, and para protons of the phenoxy group appear as multiplets at δ 7.25, 6.72, and 6.95, respectively. The meta absorptions were unusually shifted upfield in comparison with other 5-phenoxy-2-oxazolidones. The assignments were made by comparison with spectra of other compounds and integration of peak areas. Decoupling experiments on the H_{de} protons of **5** determined the location of the H_e protons. At 100° the meta protons were observed to shift downfield 0.1 ppm and remained constant at 150°. The ortho and para protons were unaffected by temperature changes.

TABLE II
SHIFTS AND GRADIENTS OBSERVED FOR COMPOUND 2[a]

	Shift[b]	Gradient[c]
H_a	0.7	2.6
H_b, H_c [d]	1.0	3.5
H_d	1.9	7.0
$H_{d'}$	1.6	5.8
$H_{e\beta}$	0.95	3.5
$H_{e\gamma}$	0.56	2.0
H_f	0.32	1.2
H_g	0.28	1.1

[a] A 10% solution of 2 in $CDCl_3$ with 0.27 molar equiv of Eu(fod)$_3$ per mol of substrate. [b] Expressed in parts per million downfield from the position of resonance in the absence of Eu(fod)$_3$. [c] Expressed in parts per million per mol of Eu(fod)$_3$ per mol of substrate. [d] Data undiscernible due to complexity, but both shifted approximately as described.

N-methoxymethylene-5-phenoxymethylene-2-oxazolidone (**1**). However, in both compounds the nonequivalency of the *exo*-*N*-methylene protons disappeared at the same temperature, namely at 100–120°. The temperature required for equivalency of these *exo*-*N*-methylene protons is quite high and is higher than that observed for the phenoxymethylene protons which are adjacent to the asymmetric center. In all the compounds containing the 5-phenoxymethylene protons, the methylene protons became equivalent on heating to 80° in *o*-dichlorobenzene. From considerations of Dreiding models, it can be seen that for free rotation to occur, the methoxy oxygen must eclipse the carbonyl group in position 2 and the lone pair of electrons on nitrogen. It has been reported[2] that acyclic urethanes possess the same dipolar resonance interactions as observed in amides and an energy of activation on the same order of magnitude. No such dipolar resonance has been reported in cyclic urethanes (2-oxazolidones) because of the inability to use nmr techniques as in the acyclic systems. However, this possibility cannot be discounted. Any dipolar resonance structures would increase the magnitude of the eclipsed polar interaction with the methoxyl oxygen and decrease the eclipsed interaction with the lone pair.

The temperature effect on the spectra indicates that the conformer interconversions are fast on the nmr time scale, and that the nonequivalency must be due to unequal conformer populations. The influence of the asymmetric center on the various conformers gives rise to the magnitude of the nonequivalency of the *exo*-*N*-methylene protons. The nonequivalency of these protons in the *N*-methoxymethylene-2-oxazolidones is greater than in the *N*-butyl-2-oxazolidones owing to a larger inequality in conformer population. This is caused by a greater difference in conformation energies owing to the electronic interactions of the methoxy group.

An interesting observation is that the nonequivalency of the *exo*-*N*-methylene protons is greater for **1** than for **3**. Consideration of Dreiding models indicates that in **1** the phenoxymethylene group can be oriented so that the *exo*-*N*-methylene protons are affected more strongly by the phenyl moiety.

An indication that this could be the case can be seen in the nmr spectrum of *N*-*p*-tolylsulfonyl-5-phenoxymethylene-2-oxazolidone (**5**). In this compound we observed that the meta protons on the phenoxy ring were *unusually* shifted upfield (see Table I).[3]

This upfield shift indicates a possible interaction with the *N*-sulfonyl group. The meta protons were observed to shift as a function of temperature. Nmr data indicate that the meta protons reach a constant chemical-shift value at approximately the same temperature that the phenoxymethylene protons become equivalent. At this point free rotation about the carbon–carbon bond, to which the phenoxy group is attached, occurs and any conformation preference of the phenoxy group is overcome.

In summary, we have demonstrated that the nonequivalency of the *exo*-*N*-methylene protons in *N*-methoxymethylene-2-oxazolidones is caused by unequal conformer populations, possibly owing to electronic interactions of the methoxy group. The temperature effect on the spectra indicate that the *exo*-*N*-methylene nonequivalency is not due to chirality (intrinsic nonequivalence). The equivalency of *exo*-*N*-methylene protons in compound **4** is probably accidental[4] and can best be rationalized by stating that the environment of the different conformers is not sufficiently different to allow for observation of nonequivalency. Furthermore, indications are that the nonequivalency is greater for **1** than for **3** because of increased interaction of the phenyl ring with the N substituent.

Experimental Section

General.—Phenyl glycidyl ether, *n*-butyl isocyanate, and chloromethyl methyl ether were distilled prior to use. 2-Oxazolidone was purchased from Aldrich Chemical Co. *N*-Butyl-5-phenoxymethylene-2-oxazolidone (**2**) was prepared as previously reported.[5] Solvents used as reaction media were dried by appropriate means. Melting points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared absorption spectra were obtained on a Perkin-Elmer Model 337 spectrophotometer. The nmr spectra were determined on a Japan Electron Optics Lab 4H-100 spectrometer using TMS as an internal standard and solvents as indicated. The chemical shift work was accomplished with Eu(fod)$_3$ in $CDCl_3$ at 25°.

5-Phenyl-2-oxazolidone (**6**).—Compound **6** was prepared (70.5%) according to the procedure of Poos[6] and coworkers. The crude product **6**, melting at 88–91° (lit. mp 88.5–89.5°), was used without further purification.

5-Phenoxymethylene-2-oxazolidone (**7**).—The procedure of Oda and Hata[7] was used with some modification, the latter being that a mixture of urea (120 g 2.0 mol) and phenyl glycidyl ether (171.7 g, 1.28 mol) was heated to 150°. At *ca.* 150° a relatively violent exothermic reaction occurred and the temperature rose to 215° with frothing. The reaction mixture was left to cool and then extracted with 1600 ml of hot chloroform. Enough pentane was added to produce turbidity. The resulting mixture was cooled to ice-bath temperature and the precipitate was filtered. One recrystallization of the dried filter cake from ethyl acetate gave 5-phenoxymethylene-2-oxazolidone, mp 121.5–123° (lit.[7] mp 124°).

N-**Methoxymethyl-2-oxazolidone** (**4**).—A solution of 2-oxazolidone (8.71 g, 0.1 mol) in 150 ml of monoglyme was added

(2) W. E. Stewart and T. H. Siddall, *Chem. Rev.*, **70**, 550 (1970).

(3) J. E. Herweh and W. J. Kauffman, *J. Heterocycl. Chem.* **8**, 983 (1971).

(4) We would like to acknowledge the reviewer's comments concerning this interpretation.

(5) J. E. Herweh, T. A. Foglia, and D. Swern, *J. Org. Chem.*, **33**, 4029 (1968).

(6) G. Poos, J. Carson, J. Rosenau, A. Roszkowski, N. Kelley, and J. McGowin, *J. Med. Chem.*, **6**, 266 (1963).

(7) R. Oda and M. Hata, *Nippon Kaguku Zasski*, **82**, 1426 (1962); *Chem. Abstr.*, **58**, 3337 (1963).

fairly rapidly to a stirred suspension of NaH (4.35 g of a 57% dispersion in mineral oil) in 80 ml of monoglyme at room temperature. After completing the addition, the reaction mixture containing a grayish-white solid was heated at 50° for 1 hr and then cooled to room temperature. A solution of chloromethyl methyl ether (8.86 g, 0.11 mol) in 20 ml of monoglyme was added dropwise with stirring to the reaction mixture and, upon completing the addition, the reaction mixture was heated at 50° for 2.5 hr.

After cooling to room temperature, the reaction mixture was filtered and the filter cake was washed with monoglyme. The monoglyme was evaporated off using a rotary evaporator. The liquid residue was subjected to vacuum distillation and yielded 9.7 g (80.5%) of *N*-methoxymethyl-2-oxazolidone (4), bp 80–81° (0.07 mm). Another distillation yielded an analytical sample.

Anal. Calcd. for $C_5H_9NO_3$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.92; H, 7.08; N, 10.77.

***N*-Methoxymethyl-5-phenyl-2-oxazolidone (3).**—The experimental procedure is similar to that described previously. A solution of 5-phenyl-2-oxazolidone (8.1 g, 0.05 mol) in 100 ml of monoglyme was added to a stirred suspension of NaH (2.18 g of 57% dispersion in mineral oil) in 75 ml of monoglyme at room temperature. After addition, the reaction mixture was heated at 50° for 1 hr and then cooled to room temperature. A solution of chloromethyl methyl ether (4.43 g, 0.055 mol) in 25 ml of monoglyme was added dropwise with stirring to the reaction mixture. Upon completing the addition, the reaction mixture was heated at 50° for 1 hr. After cooling to room temperature, the reaction mixture was filtered, the filter cake was washed with monoglyme, and the monoglyme was evaporated off using a rotary evaporator, yielding 8.5 g (82%) of crude **3** melting at 38–39°. One recrystallization from benzene–cyclohexane gave an analytical sample, mp 41–42°.

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; H, 6.76. Found: C, 64.04; H, 6.25; N, 6.67.

***N*-Methoxymethylene-5-phenoxymethylene-2-oxazolidone (1).**

A. From 5-Phenoxymethylene-2-oxazolidone and Chloromethyl Methyl Ether.—The experimental procedure was the same as that described above. A solution of 5-phenoxymethylene-2-oxazolidone (9.6 g, 0.05 mol) in 150 ml of monoglyme was added to a stirred suspension of NaH (2.18 g of 57% dispersion in mineral oil) in 75 ml of monoglyme at room temperature. After addition, the reaction mixture was heated at 50° for 1 hr and then cooled to room temperature. A solution of chloromethyl methyl ether (4.43 g, 0.055 mol) in 25 ml of monoglyme was added dropwise to the stirred reaction mixture. After the addition was complete, the reaction mixture was heated at 50° for 1 hr, cooled to room temperature, and filtered, and the monoglyme filtrate was evaporated on a rotary evaporator. There was obtained 10.2 g (86% yield) of crude **1** with mp 55–61°. Recrystallization from CCl_4–pentane raised the mp to 64–67°.

B. From Phenyl Glycidyl Ether and Methoxymethyl Isocyanate.—We have previously reported[1] the preparation of **1** from reaction of phenyl glycidyl ether and methoxymethyl isocyanate using a hydrocarbon-soluble tributylphosphine oxide–lithium bromide adduct. The material isolated had mp 69.5–70.5°.

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90; mol wt, 237. Found: C, 60.57; H, 6.41; N, 6.06; mol wt, 253.

Spectral data and mixture melting point indicated that this material was the same as that prepared from 5-phenoxymethylene-2-oxazolidone and chloromethyl methyl ether.

***N*-*p*-Toluenesulfonyl-5-phenoxymethylene-2-oxazolidone (5).**—A solution of 5-phenoxymethylene-2-oxazolidone (0.6 g, 0.05 mol) in 100 ml of monoglyme was added as described above to a stirred mixture of NaH (2.18 g, 57% in mineral oil) in 50 ml of monoglyme at room temperature. After addition, the reaction was heated at 40° for 0.5 hr and then cooled to room temperature. A solution of *p*-tolylsulfonyl chloride (9.5 g, 0.05 mol) in 50 ml of monoglyme was added dropwise to the stirred reaction mixture. After addition, the reaction mixture was heated at 50–55° for 2.5 hr.

After cooling to room temperature, the reaction mixture was filtered, the filter cake was washed with monoglyme, and the monoglyme was evaporated using a rotary evaporator. There was obtained 11.5 g (66%) of crude **5**. Recrystallization from benzene yielded an analytical sample, mp 156.5–157.5°.

Anal. Calcd for $C_{17}H_{17}NO_5S$: C, 58.77; H, 4.93; N, 4.03; S, 9.23; mol wt, 347. Found: C, 58.76; H, 4.94; N, 4.01; S, 9.19; mol wt, 350.

This material was also prepared in 83.7% yield by using the solubilized lithium bromide–tributylphosphine oxide catalyst with phenyl glycidyl ether and *p*-toluenesulfonyl isocyanate.[3]

Registry No.—**1**, 34277-53-7; **2**, 17539-83-2; **3**, 34277-55-9; **4**, 34277-56-0; **5**, 34277-57-1.

Organophosphorus Enamines. VI. Use of Enamine Thiophosphonates in the Synthesis of Diethyl β-Ketothiophosphonates

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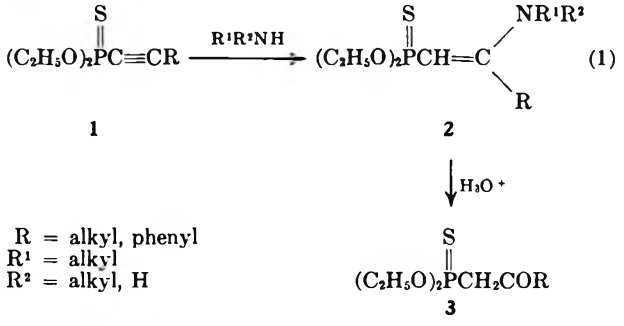
Received November 5, 1971

Recently we reported a general preparation of dialkyl alkynyl-1-thiophosphonates (**1**).[1] We also found that the addition of amines to the alkynyl-1-thiophosphonates **1** is rather facile giving enamine thiophosphonates **2** in excellent yields.[2] We now wish to report that enamine thiophosphonates **2** can be very conveniently hydrolyzed with aqueous oxalic acid to afford diethyl β-ketothiophosphonates **3** in good to excellent yields (eq 1).



Diethyl β-ketothiophosphonates (**3**) represent a new class of phosphorus(V) esters which have not been described in the literature to date. Our method affords a very simple and high-yield preparation of these compounds **3**. The success of this method is based upon the fact that the enamine moiety in **2** is much more readily hydrolyzed as compared to the ester function. Also, it is interesting to note that the rate of addition of amine to the triple bond in **1** is much faster than the rate of displacement of the ethoxy groups.

The compounds **3** prepared by this method are listed in Table I together with their boiling points and yields.

Because of their similarity to the Emmons reagents, compounds **3** should be useful in the synthesis of α,β-unsaturated ketones[3] and cyclopropyl ketones.[4] Compounds **3** also seem to be potentially important ligands; work in that direction is in progress.

The ir spectra ($CHCl_3$) of all the compounds **3a–e** show strong absorption in the region of 5.80–5.87 μ (C=O). In the nmr spectra of **3a–e**, the *P*-methylene protons exhibit a doublet (J_{PH} = 20 Hz) in the region of δ 3.21–3.34. The methylene protons from the *O*-

(1) M. S. Chattha and A. M. Aguiar, *J. Org. Chem.*, **36**, 2720 (1971).
(2) M. S. Chattha and A. M. Aguiar, *ibid.*, **36**, 2892 (1971).
(3) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).
(4) H. Normant and G. Sturts, *C. R. Acad. Sci.*, **256**, 1800 (1963).

TABLE I

DIETHYL β-KETOTHIOPHOSPHONATES 3[a]

Series	R	Bp, °C (mm)	Yield,[b] %
a	CH_3	70–71 (0.12)	85
b	n-C_3H_7	101 (0.50)	92
c	n-C_4H_9	96–97 (0.10)	93
d	n-C_6H_{13}	140 (0.76)	87
e	$C_6H_5CH_2CH_2$	157–158 (0.10)	71

[a] Satisfactory analytical values (±0.4% for C, H, P, S) were obtained for all compounds. [b] This is the per cent yield of the distilled material based on the starting alkynyl-1-thiophosphonates 1.

ethyl groups display two quartets (J_{PH} = 7.5, J_{PH} = 10.5 Hz) at δ ~4.15. However, at 100 MHz, further resolution into four quartets occurs. This splitting pattern is apparently due to the magnetic nonequivalence of these methylene protons.

Experimental Section

The nmr spectra were determined on a Varian A-60 spectrometer using deuteriochloroform as solvent and tetramethylsilane as an internal standard. The chemical analyses were performed by Geller Microanalytical Laboratories, Saddle River, N.J.

Preparation of Diethyl β-Ketothiophosphonates 3a–e. General Procedure.—The diethyl alkynyl-1-thiophosphonates 1 (0.025 mol) were refluxed with a 10–12 molar excess of n-butylamine. The reflux was continued for 2–3 days until the ir spectra of a test portion of the reaction mixture showed complete disappearance of the absorption band in the region of 4.52–4.56 μ (C≡C).[2] The excess amine was evaporated *in vacuo* at aspirator pressure. The resulting adduct was dissolved in ether (100 ml) and 100 ml of 1% aqueous solution of oxalic acid was added. The two-layer reaction mixture was stirred for 4–5 hr at room temperature and then transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted twice with 25-ml portions of ether. The combined ether extracts were dried ($MgSO_4$) and filtered, and ether was distilled off. The resulting oil was short path distilled under reduced pressure.

Registry No.—**3a**, 1067-72-7; **3b**, 34281-17-9; **3c**, 34297-64-8; **3d**, 34281-18-0; **3e**, 34281-19-1.

Acknowledgment.—We wish to acknowledge the National Institutes of Health for support of this work under Grant GM-16828 and the National Science Foundation under Grant GP-10739. We also wish to thank Dr. Joseph D. Wander for the 100-MHz spectra.

Preparation of *N*,*N*-Diethylcyanoynamine and Its Reactions with Phenyl Isocyanate and Phenylsulfene

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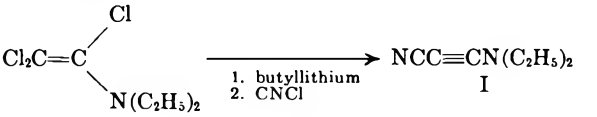
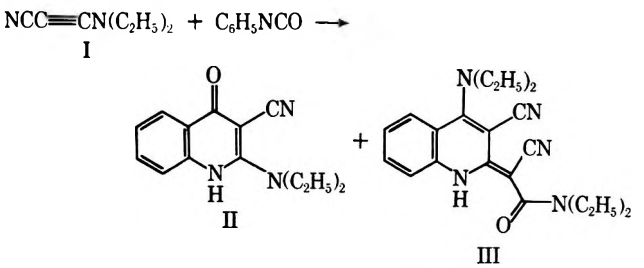
Received October 1, 1971

In a previous investigation of ynamine chemistry[1] we had prepared *N*,*N*-diethylcarbomethoxyethynylamine by a reaction of methyl chlorocarbonate with the lithium salt of *N*,*N*-diethylethynylamine. Similarly, the cyanoynamine I could be prepared in 63% yield from *N*,*N*-diethyltrichlorovinylamine, n-butyllithium, and cyanogen chloride.[2,3]



While our earlier study had shown that phenyl isocyanate adds to ynamines with methyl, phenyl, and carbomethoxy substituents to give 4-amino-2-quinolones and 2-amino-4-quinolones, we have now found that the cyanoynamine I reacts with phenyl isocyanate to produce a 2-amino-4-quinolone II and a 2:1 adduct of ynamine and phenyl isocyanate as the major product. Spectroscopic evidence indicated a conjugated dinitrile diethylamide with four aromatic protons and one NH proton [ir 3420, 2205, 2180, 1612 cm^{-1}; nmr δ 1.29 (t, 12 H), 3.6 and 3.8 (q, 8 H), 7.6 (m, 4 H), 15.0 (s, 1 H); m/e 363 (parent), 100 (100%, diethyl amide)]. A 4-amino-2-quinolone methine or a 2-amino-4-quinolone methine structure was thus possible for the 2:1 adduct. The first alternative, III, could be established by single-crystal X-ray analysis.[4]



The formation of the new product does not seem to be due to reaction of an initially formed 4-amino-2-quinolone with a second equivalent of ynamine, since attempts to add the cyanoynamine I to 3-phenyl or 3-carbomethoxy-4-amino-2-quinolones led only to recovered starting materials. Furthermore, very slow addition of the cyanoynamine to 2 equiv of phenyl isocyanate again gave only the initially observed products and unreacted phenyl isocyanate, but no 4-amino-2-quinolone.

These results demonstrate a third reaction pathway for the addition of phenyl isocyanate to an ynamine. In addition to the initially observed six-center reaction (path a, stepwise or concerted) leading directly to 4-amino-2-quinolones and the β-lactam formation (path b) as intermediate to 2-amino-4-quinolones, one now encounters addition of the ynamine to the carbonyl double bond of phenyl isocyanate (path c), followed by ring opening and addition of a second equivalent of ynamine to the keteneimine.[5,6] An alternative scheme, where the four-membered intermediate of path b is

(1) M. E. Kuehne and P. J. Sheeran, *J. Org. Chem.*, **33**, 4407 (1968).

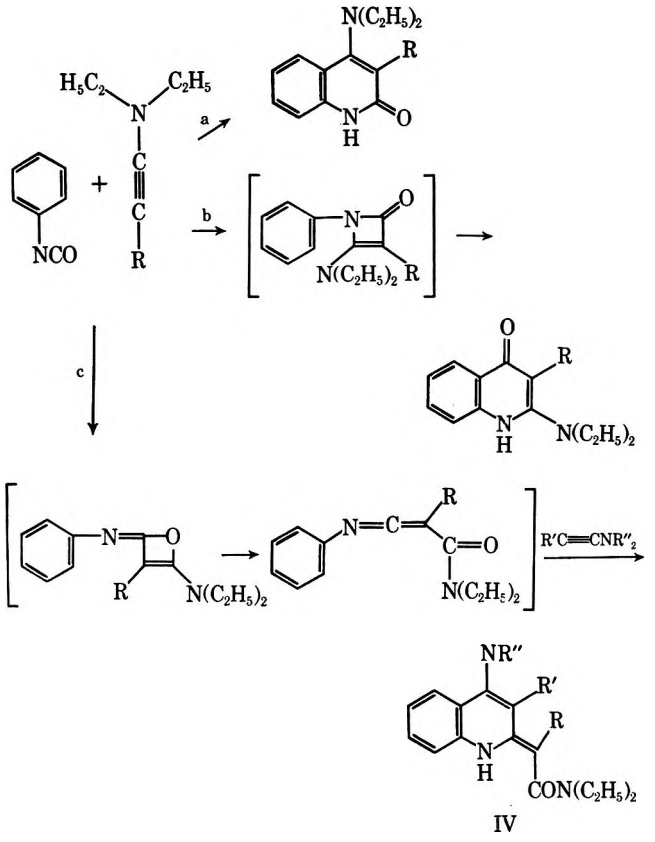
(2) The principle of this reaction was first described by J. Ficini and C. Barbara, *Bull. Soc. Chim. Fr.*, 2787 (1965).

(3) An alternative route to cyanoynamines from chlorocyanoacetylene and secondary amines has since been described: T. Sasaki and A. Kojina, *J. Chem. Soc. C*, 476 (1970).

(4) We thank Drs. J. A. Lerbscher and J. Trotter of the University of British Columbia, Vancouver, Canada, for the results of this study which will be published separately.

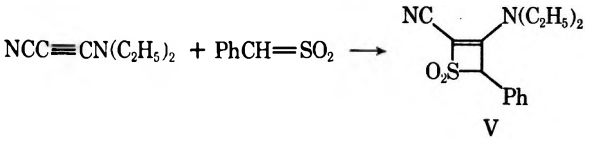
(5) Reactions of *N*-phenylketeneimines with ynamines have been found to produce 2-alkyl-4-aminoquinolines: L. Ghosez and P. de Perez, *Angew. Chem., Int. Ed. Engl.*, **10**, 184 (1971).

(6) Alkyl isocyanates and diethylamino-1-propyne gave keteneimines: J. U. Piper, M. B. Allard, and V. Lee, Abstracts, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, ORGN 103.



converted to all three product types, could not yet be ruled out rigorously.

The cyanoynamine I reacted with phenylsulfene to give a four-membered cyclic sulfone V in analogy to other ynamines reported[1] previously.



Experimental Section

Preparation of *N*,*N*-Diethylcyanoethynylamine (I).—A solution of 36.5 ml of 1.6 *M* *n*-butyllithium in hexane (58.5 mmol) diluted with 10 ml of dry ether was slowly added to 5.8 g (28.6 mmol) of *N*,*N*-diethyl-1,2,2-trichlorovinylamine at −20°. After stirring at room temperature for 45 min the mixture was cooled again to −20° and 1.75 g (28.6 mmol) of cyanogen chloride in 5 ml of dry ether was added slowly. The mixture was stirred for 45 min at room temperature and centrifuged. Evaporation of the supernatant and two ether washes of the precipitated lithium chloride gave a thick liquid which was distilled. The ynamine was collected in Dry Ice, bp 45–55° (0.04 mm). After two distillations 2.10 g (63%) of the ynamine was collected: bp 47° (0.05 mm); ν_{max}^{neat} 2945, 2210, 2135, 1432 cm^{-1}; nmr ($CDCl_3$ with TMS) δ 1.24 (t, 3 H), 3.13 (q, 2 H); uv λ_{max}^{hexane} 221, 232, 242 (ε 5.85 × 10^5), 254 mμ.

Anal. Calcd for $C_7H_{10}N_2$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.59; H, 8.27; N, 22.75.

Reaction of *N*,*N*-Diethylcyanoethynylamine with Phenylsulfene.—Benzylsulfonyl chloride, 0.932 g (4.91 mmol), suspended in 5 ml of benzene was added to a solution of 0.6 g (4.91 mmol) of the cyanoynamine and 0.6 g (5.95 mmol) of triethylamine in 15 ml of dry benzene. The solution was stirred for 18 hr and the precipitated triethylamine hydrochloride was filtered. The collected filtrate was vacuum evaporated to a thick oil which crystallized from ethyl acetate. Recrystallization from isopropyl alcohol gave 0.132 g (9.8%) of the 1:1 adduct V, mp 194–195°. Reactions in tetrahydrafuran and dichloromethane at −30° for 1 hr and subsequently at 0° for 48 hr did not give improved yields of the adduct, nor could other products be identified.

Spectral data follow: ν_{max}^{KBr} 2190, 1600, 1580, 1512, 1308, 1160, 1120 cm^{-1}; nmr (DMSO-d_6 with TMS) δ 1.12 (t, 6 H), 3.53 (q, 4 H), 4.61 (s, 1 H), 7.50 (s, 5 H); uv λ_{max}^{EtOH} 223, 283, 344 mμ.

Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.86; H, 5.84; N, 10.14; S, 11.58. Found: C, 60.93; H, 5.68; N, 10.10; S, 11.69.

Reaction of *N*,*N*-Diethylcyanoethynylamine with Phenyl Isocyanate.—A solution of 0.840 g (7.85 mmol) of phenyl isocyanate in 5 ml of dry acetonitrile or benzene was added to 0.862 g (7.12 mmol) of the ynamine I at room temperature. The solution was stirred for 60 hr under nitrogen, and the precipitated 2-amino-4-quinolone was filtered and washed with ethanol, yielding 60 mg (7.1%) of white needles: mp 297–298° dec; ν_{max}^{KBr} 2940, 2200, 1627, 1613, 1580, 1333 cm^{-1}; nmr (HMPA) sharp NH singlet at δ 8.75; uv $\lambda_{max}^{Ethanol}$ 243, 260, 308 mμ.

Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.68; H, 6.27; N, 17.42. Found: C, 69.83; H, 6.36; N, 17.16.

Changing solvent from acetonitrile to benzene did not affect this reaction and no 4-amino-2-quinolone could be obtained even when a dilute solution of ynamine (0.5 g in 10 ml) was added to a twofold excess of phenyl isocyanate in benzene or acetonitrile over a period of 7 hr. Evaporation of the filtrate and chromatography on a column of Woelm silica gel (activity I) in methylene chloride and ethanol (0.5%) gave a yellow solid, 0.592 g (46%), which was recrystallized from ethyl acetate to mp 135–136° and distilled at block temperature 170° (0.001 mm). This product is the 2:1 adduct IV by the following data: ν_{max}^{KBr} 3420, 2950, 2910, 2205, 2180, 1612, 1600, 1562, 1552 cm^{-1}; nmr ($CDCl_3$ with TMS) δ 1.29 (t, 12 H), 3.6 (q), 3.8 (q) (total 8 H), 7.6 (m, 4 H), 15.0 (s, 1 H); uv ν_{max}^{EtOH} 230, 243, 264, 333 mμ; the 333-mμ absorption shifted to 353 mμ in base and returned to 333 mμ upon acidification; major mass spectrum peaks *m*/*e* (rel intensity) 363 (10), 348 (10), 334 (10), 266 (10), 239 (10), 100 (100), 72 (40), 44 (10), 29 (20).

Anal. Calcd for $C_{21}H_{25}N_5O$: C, 69.38; H, 6.93; N, 19.27. Found: C, 69.21; H, 7.04; N, 19.49.

A reaction in tetrahydrofuran at −30° for 1 hr and 0° for 48 hr gave a 17% yield of the 2:1 adduct. No other products or intermediates could be identified. Attempted reactions of 4-*N*,*N*-diethylamino-3-phenyl-2-quinolone with *N*,*N*-diethylcyanoethynylamine.

Addition of the cyanoynamine I to the 3-phenyl- (or 3-carbethoxy-) 4-amino-2-quinolone in either hexamethylphosphotriamide or acetonitrile for 36 hr yielded only starting materials by tlc and ir.

Registry No.—I, 26391-04-8; IV, 34281-05-5; V, 34281-06-6; phenyl isocyanate, 1122-85-6; phenylsulfene, 17346-42-8; 2-amino-4-quinolone, 34281-08-8.

Acknowledgment.—This work was supported by a National Institutes of Health Research grant, R01 CA 12010-09.

A Facile Method for N-Acylation of Ring Activated Phenylhydroxylamines

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Received March 30, 1971

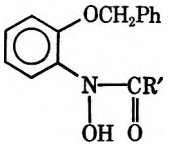
During a study of methods for the preparation of structural analogs of 2,4-dihydroxy-1,4-benzoxazin-3-one,[2] it was found that the acylation of *o*-methoxy-

(1) Taken in part from the dissertation presented by M. D. Corbett, Nov 1970, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

(2) E. E. Smissman and M. D. Corbett, *J. Org. Chem.*, **37**, 1704 (1972).

TABLE I

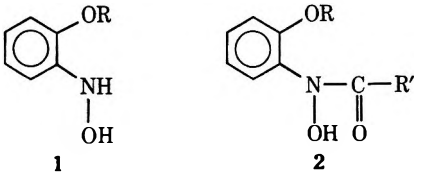
HYDROXAMIC ACIDS (2b) OBTAINED BY THE ACYLATION OF o-BENZYLOXYPHENYLHYDROXYLAMINE (1b)



Acyl halide	Registry no.	R′	Yield,[a] %	Mp, °C (crystn solvent)	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
$Cl_2CH(C{=}O)Cl$	34287-98-4	$CHCl_2$	66	124–126 (C_6H_6)	55.25	4.02	4.29	55.62	3.76	4.30
$Cl_2CH(C{=}O)Cl$	34287-99-5	CH_2Cl	82	99–101 (Et_2O)	61.76	4.84	4.80	62.06	4.92	4.74
$BrCH(C{=}O)Cl$	34288-00-1	CH_2Br	87	96–98 (Me_2CO–Et_2O)	53.59	4.20	4.17	53.84	4.21	4.26
$CH_3CHBr(C{=}O)Cl$	34288-01-2	$CHBrCH_3$	79	125–127 (Et_2O)	54.87	4.60	4.00	54.91	4.88	4.05
$Ph(CHBr(C{=}O)Cl$	34288-02-3	PhCHBr	67	115–117 (Me_2CO–Et_2O)	61.19	4.40	3.40	61.43	4.51	3.38
$EtOC{=}O(C{=}O)Cl$	34288-03-4	O=COEt	69	Oil						

[a] Yields are for purified products, except for 6.

methoxy- and o-benzyloxyphenylhydroxylamines (1a,b) proceeded in very low yields with the formation of large amounts of tarry materials. This was assumed to be due to the occurrence of the Bamberger rearrangement[3] which explains the sensitivity of phenylhydroxylamines to acidic reagents. The acylation of 1a and 1b



1 2

a, R = OCH_2OCH_3
b, R = $OCH_2C_6H_5$

with dichloroacetyl chloride under anhydrous conditions gave the corresponding hydroxamic acids 2 in yields of less than 10%. The addition of organic bases or sodium bicarbonate to neutralize the hydrochloric acid which is liberated failed to increase the yield. The use of dicyclohexylcarbodiimide and free organic acids[4] increased the yield of some hydroxamic acid products to about 30% but was found to be inapplicable for organic acids substituted on the α carbon with strongly electron-withdrawing groups. Even under relatively neutral conditions the Bamberger and related rearrangements[5,6] proceed with ring-activated phenylhydroxylamines.

The acylation of phenylhydroxylamine with long-chain aliphatic acid chlorides was reported[7] to give high yields of the desired hydroxamic acids when an aqueous solution of sodium bicarbonate was suspended in an ether solution of the reactants. This method was successfully extended to the acylation of the activated hydroxylamines 1 with highly reactive acid chlorides. Table I lists the products and yields obtained utilizing this process with o-benzyloxyphenylhydroxylamine. The spectra of all compounds are consistent with the assigned structures.

(3) H. J. Shine, "Aromatic Rearrangements," Monograph 6 of "Reaction Mechanisms in Organic Chemistry," C. Eaborn and N. B. Chapman, Ed., Elsevier, New York, N. Y., 1967.

(4) M. T. W. Hearn and A. D. Ward, *Aust. J. Chem.*, **22**, 1731 (1969).

(5) R. T. Coutts and N. J. Pound, *Can. J. Chem.*, **48**, 1859 (1970).

(6) G. T. Tisue, M. Grassmann, and W. Lwowski, *Tetrahedron*, **24**, 999 (1968).

(7) V. K. Gupta and S. G. Tandon, *J. Indian. Chem. Soc.*, **46**, 831 (1969).

Experimental Section[8]

o-(Benzyloxy)nitrobenzene.—To potassium o-nitrophenoxide (35.4 g, 0.20 mol) dissolved in 300 ml of DMF was added benzyl bromide (34.2 g, 0.20 mol) in 15 min. The mixture was stirred for 40 min, combined with 200 ml of C_6H_6 and 200 ml of H_2O, and shaken. The aqueous layer was extracted with 200 ml of C_6H_6 after adding 300 ml of H_2O. The combined C_6H_6 fractions were washed with 200 ml of 5% NaOH, 200 ml of H_2O, and 100 ml of saturated NaCl. The C_6H_6 solution was dried (Na_2SO_4) and the solvent was removed *in vacuo* to give an orange oil, which was distilled at 127–129° (0.05 mm) to give 29.8 g (65%) of a pale yellow liquid; spectral data are consistent with the assigned structure.

o-(Benzyloxy)phenylhydroxylamine (1b).—o-(Benzyloxy)nitrobenzene (55.2 g, 0.24 mol) and NH_4Cl (24.0 g, 0.44 mol) in 600 ml of 60% EtOH were stirred vigorously while Zn dust (24.0 g, 0.37 g-atom) was added in small portions in the course of 20 min. The mixture was stirred for an additional 15 min, after which 200 ml of H_2O was added and the suspension was filtered. The filter cake was washed with 200 ml of C_6H_6, and the filtrates were combined and shaken. The aqueous portion was diluted with 200 ml of H_2O and extracted with 200 ml of C_6H_6. The combined C_6H_6 fractions were washed with 100 ml of H_2O and 50 ml of saturated NaCl and dried (Na_2SO_4), and the solvent was reduced in volume *in vacuo* to about 300 ml. This solution was treated with petroleum ether (bp 60–80°) until the cloud point was attained. The opaque solution was stirred until a flocculent white solid formed. An additional 200 ml of petroleum ether (bp 60–68°) was added and the mixture was cooled in an ice bath. The solid was collected by filtration and washed with 200 ml of petroleum ether (bp 60–68°). The solid was dried at room temperature to give 26.0 g (50%) of white solid, mp 73–76°; a dark red color developed with alkaline 2,3,5-triphenyltetrazolium chloride;[9] spectral data are consistent with the assigned structures. Compound 1b could be stored for several days at 5° with little decomposition.

Acylation of o-(Benzyloxy)phenylhydroxylamine (1b).—Equimolar quantities of 1b and the acid chloride must be used to minimize the formation of side products. The purified products can be obtained by crystallization (Table I). A typical procedure follows.

***N*-[o-(Benzyloxy)phenyl]-2,2-dichloroacetohydroxamic Acid.**—o-(Benzyloxy)phenylhydroxylamine (6.5 g, 0.03 mol) dissolved in 100 ml of Et_2O was placed in a 300-ml flask with $NaHCO_3$ (2.8 g, 0.034 mol) in 12 ml of H_2O. The mixture was cooled to −5° by means of an ice–salt bath and stirred vigorously while dichloroacetyl chloride (4.5 g, 0.03 mol) in 20 ml of anhydrous Et_2O was added dropwise in the course of 30 min. The pale yellow suspension was stirred and cooled for an additional 15 min, after which it was combined with 50 ml of Et_2O and washed twice with 50 ml of H_2O. The ethereal solution was combined

(8) Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Ir data were recorded on a Beckman IR-10 spectrophotometer and nmr data on Varian Associates A-60, A-60A, and HA-100 spectrometers (TMS). Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M 185 C, H, N Analyzer, University of Kansas.

(9) G. A. Snow, *J. Chem. Soc.*, 258 (1954).

with 30 ml of C_6H_6 and dried (Na_2SO_4). Removal of the solvent produced a solid which was recrystallized twice (C_6H_6) to give 6.5 g (66%) of white crystals, mp 124.0–126°, violet color with $FeCl_3$ in EtOH; spectral data are consistent with the structure assigned.

Anal. Calcd for $C_{15}H_{13}NO_3Cl_2$: C, 55.24; H, 4.02; N, 4.29. Found: C, 55.62; H, 3.76; N, 4.30.

Registry No.—**1b**, 34288-04-5; *o*-(benzyloxy)nitrobenzene, 4560-41-2.

Acknowledgment.—The authors gratefully acknowledge the support of this project by the National Institutes of Health, Grant GM-01341.

Synthesis of 3-Chloroquinolines from Indoles and Thermally Generated Dichlorocarbenes

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The reported conversion of pyrrole to 2- and 3-chloropyridines on reaction with thermally generated dichlorocarbene[1] suggested that the reaction could be utilized in an analogous synthesis of chloroquinolines. Recently, Baker, *et al.*,[2] found that improved conversions of pyrrole to the 2- and 3-chloropyridine mixture (86% yields from a 550° pyrolysis) could be obtained with the use of a preheater (at 250°) and stated that the reaction could be extended to other five-membered ring heterocycles, methylpyrrole, and indole, although details for these latter conversions were not given.

We report here the results of experiments using thermally generated dichlorocarbene in the synthesis of 3-chloroquinoline, 3-chloroquinaldine, 3-chlorolepidine, and 3-chloro-2,4-dimethylquinoline from the appropriately substituted indole (see Table I). Syntheses of substituted chloroquinolines by a modified Reimer–Tieman procedure have been reported[3] with yields generally around 10%. The advantages of the thermal method reported here are improved yields, fewer side-reaction products, and facile isolation by column chromatography.

The effects of variations in reaction parameters on the yields of chloroquinolines were investigated briefly. In the formation of 2-chloroquinoline from indole an increase in the pyrolysis temperature resulted in a slight increase in the yield of the 2-chloroquinoline coproduct. Faster nitrogen carrier gas flow rates (from 100 to 200 ml/min) produced larger yields of 2-chloroquinoline (from indole) and smaller yields of 3-chloroquinaldine (from 2-methylindole). Decreases in the chloroform–indole ratio lowered the yield of the chloroquinoline products (a decrease of 10 and 17% in the indole and 2-methylindole experiments, respectively).

Other dichlorocarbene precursors such as carbon tetrachloride, ethyl trichloroacetate, and sodium trichloroacetate produced lower yields (1–20% of chloroquinoline product).

Experimental Section

Melting points were taken on a Fisher-Johns melting point apparatus and are corrected. Infared spectra were measured on a Beckman IR-8 spectrophotometer, ultraviolet spectra were measured on a Perkin-Elmer Model 202 spectrophotometer, and nmr spectra were measured on a Varian T-60 spectrometer.

Glpc analyses and preparative scale separations were made on an F & M Model 810 gas chromatograph using an 8 ft × 0.375 in. 25% SE-30 column heated to 100° for 7 min and then programmed at 2°/min to 250°. In the glpc analyses naphthalene was used as an internal standard.

The pyrolyses were carried out at 550° in the appratus previously described.[4] In the present experiments the pyrolysis zone (*ca.* 20 cm long) consisted of the unpacked Vycor tube positioned in the furnace such that the temperature throughout the zone was 550°. The region in the pyrolysis tube 15 cm above the pyrolysis zone served as a "preheater" and contained 20 ml of Berl saddles. The temperature of the "preheater" zone was 250°.

In a typical pyrolysis, the solution of the indole (0.01 mol) in the chloroform (0.05 mol) was introduced at a constant rate of 4 ml/hr into the preheater zone using a syringe and syringe drive. Nitrogen at a flow rate of 100 ml/min was used to sweep the volatilized mixture into the hot zone and the pyrolyzate was condensed in traps cooled in a Dry Ice–chloroform slurry. Upon completion of the pyrolysis the reaction tube was washed with 100 ml of methanol and the washings were added to the pyrolysate.

The residue obtained after evaporation of the methanol was treated with 10% NaOH (50 ml) and the resulting mixture was

TABLE I

MAJOR QUINOLINE PRODUCTS FROM REACTION OF DICHLOROCARBENE WITH THE SUBSTITUTED INDOLES

Reactant	Quinoline	Yield, % Gc	Yield, % Isolated	Mp, °C	λ_{max}, nm	δ_{TMS}, ppm
Indole[a]	3-Cl[b,c]	38.7		120 (10 mm)[d]		
Indole[a,e]	3-Cl[c]		35.6			
2-Me indole	3-Cl-2-Me	48.5	39.5	69–70[f]	218, 235, 238, 278, 309, 323	2.77 (s, 3), 7.1–8.0 (m, 5)
3-Me indole	3-Cl-4-Me	48.6	42.4	55–55.5[g]	230, 280, 308, 323	2.60 (s, 3), 7.1–8.1 (m, 5), 8.62 (s, 1)
2,3-DiMe indole	3-Cl-2,4-diMe	39.3	26.2	74–74.5[h]	231, 236, 275, 308, 322	2.41 (s, 3), 2.63 (s, 3), 7.0–8.0 (m, 4)

[a] Nitrogen flow rate was 200 ml/min. [b] Gc analysis showed that 2–5% 2-chloroquinoline[c] was present in crude products. [c] Uv, ir, nmr, and mass spectra were identical with those obtained from authentic samples. [d] Boiling point. [e] Fivefold scale up of reactants. [f] Lit. mp 71–72°, ref 3b. [g] Lit. mp 54–55°, ref 3b. [h] Lit. mp 75°: G. Plancher and O. Carrasco, *Atti Accad. Naz. Lincei*, **13**, 632 (1904).

(1) H. L. Rice and T. E. Londergan, *J. Amer. Chem. Soc.*, **77**, 4678 (1955).

(2) F. S. Baker, R. E. Busby, M. Iqbal, J. Parrick, and C. J. G. Shaw, *Chem. Ind. (London)*, 1344 (1969).

(3) (a) H. Wynberg, *Chem. Rev.*, **60**, 169 (1960); (b) G. Magnanini, *Chem. Ber.*, **20**, 2608 (1887); (c) C. W. Rees and C. E. Smithen, *J. Chem. Soc.*, 928 (1964).

(4) J. M. Patterson, A. Tsamasfyros, and W. T. Smith, Jr., *J. Heterocycl. Chem.*, **5**, 727 (1968).

extracted with three 100-ml portions of ether. After drying, the components of the ether solution were analyzed by glpc. Isolation of products could be accomplished by glpc or by liquid chromatography using acid-washed alumina. In the glpc separations, typical retention times observed for indole, 3-chloroquinoline, and 2-chloroquinoline were 39.7, 47.2, and 50.0 min, respectively. The following retention times were typical of the substituted indole experiments: 2-methylindole, 38.2; 3-chloro-2-methylquinoline, 44.2; 3-methylindole, 42.1; 3-chloro-4-methylquinoline, 51.7; 2,3-dimethylindole, 48.2; and 3-chloro-2,4-dimethylquinoline, 56.8 min. In the liquid chromatography separations, the pyrolyzate residue obtained by evaporating the ether extract was dissolved in Skellysolve B and added to the alumina column. The small quantities of unreacted indoles were eluted with Skellysolve B and the chloroquinoline products were eluted with 5% ether–Skellysolve B (3-chloroquinoline being eluted before the 2-chloroquinoline). After recrystallization from Skellysolve A, the physical properties (uv, nmr spectra, and melting point) were compared with literature values and/or authentic samples (see Table I).

Registry No.—3-Chloroquinoline, 612-59-9.

Acknowledgment.—This study was carried out under Contract No. 12-14-100-9575(73) with the Agricultural Research Service, U. S. Department of Agriculture, administered by the Southeastern Marketing and Nutrition Research Division, RRC, Athens, Ga. 30604.

Mechanism of the Reaction of Iminophosphoranes with Carbonyl Compounds. A Change in Rate-Determining Step[1]

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Received November 9, 1971

In an earlier study of the reaction of *N*-phenyliminotriphenylphosphoranes (I) with benzaldehydes (II) we demonstrated that, in general, the reaction was first order in both imine and aldehyde and that $k_2 > k_1$ for the mechanism[3]

$$\underset{\text{I}}{XC_6H_4N{=}P(C_6H_4R)_3} + \underset{\text{II}}{YC_6H_4CHO} \xrightarrow{k_1} \left[\begin{array}{l} -N-P^{+} \\ \quad | \quad - \\ -C-O \\ \quad | \end{array}\right] \xrightarrow{k_2} XC_6H_4N{=}CHC_6H_4Y + (RC_6H_4)_3P{\rightarrow}O$$

The evidence for this conclusion, briefly, was the ρ value of +2.1 for variation of the aldehyde substituent Y, faster reaction in more polar solvents, a second-order reaction with a low energy of activation (8.46 kcal/mol), and a large negative entropy of activation (−42.0 eu at 40.5°).

Recently, Aksnes and Froyen[4] have confirmed our conclusions in the course of their studying the reaction of phosphine oxides with isocyanates to form carbodiimides, the second step of which appears to involve the reaction of an iminophosphorane with isocyanate. Specifically, they reported that gradual replacement of the *P*-phenyl groups in *N*-phenyliminotriphenylphosphorane (I, X = R = H) with ethyl groups led to a steady increase in k_{obsd} of the second step, presumably due to an increase in k_1 as a result of the increasing nucleophilic character of the nitrogen atom when *P*-phenyl is replaced by *P*-ethyl (*i.e.*, less $p\pi$–$d\pi$ overlap in the latter case due to the less electronegative ethyl group replacing the phenyl group[5]). The fact that the presence of a phosphorus atom with less positive character resulted in a higher k_{obsd} clearly indicates that betaine decomposition to products, involving the attack of an oxyanion on phosphorus, cannot have been the slow step. In other words, betaine formation was the rate-determining step and $k_2 > k_1$.

In our earlier work[3] we had reported that a Hammett plot of the reaction of *N*-phenyliminotri(substituted phenyl)phosphoranes (I, X = H, R = substituents) with *p*-nitrobenzaldehyde afforded a ρ value of −0.70, indicating that electron-withdrawing groups on phosphorus slowed the reaction and confirming that $k_2 > k_1$ (otherwise, oxyanion attack on phosphorus should have been facilitated with k_2 increased and reflected in an increase in k_{obsd}). It was speculated, however, that k_1 and k_2 must be similar in magnitude due to the small ρ value and the predicted opposite effect of any substituent on the two steps, betaine formation and betaine decomposition.

Confirmation of the similarity of k_1 and k_2 was obtained by studying the effect of the *N*-phenyl substituents on the reaction of I with *p*-nitrobenzaldehyde. A Hammett plot for this reaction afforded a curve which was "concave down." For the electron-donating substituents the ρ value was +0.95 and for the electron-withdrawing substituents the ρ value was −2.4. Since "concave down" Hammett plots generally are characteristic not of a change in the mechanism of a reaction, but rather of a change in the rate-determining step,[6] it was suggested that, at least for the reaction of the imines with the one aldehyde, *p*-nitrobenzaldehyde, k_1 and k_2 were similar in magnitude and their relative magnitudes changed position as the substituent X in the imines I was changed. Because of the considerable concern in ylide chemistry about the relative rates of betaine formation and betaine decomposition in the reactions of ylides and related substances, including imines (for example, effects on stereochemical control possibilities), it was deemed worthwhile to demonstrate that this apparent change in rate-determining step was a general phenomenon and not restricted just to the specific imines and aldehydes used in our earlier work.

In Table I are reported the rates of reaction of a series of *N*-phenyl-substituted imines (I, R = H, X = substituents) with a series of four substituted benzaldehydes (II). Included are the data for the reactions of the imines (I) with *p*-nitrobenzaldehyde and the aldehydes (II) with *N*-phenyliminotriphenylphosphorane (I, X = R = H) as reported in our original work.[3] A plot of log k/k_0 *vs.* σ of the substituents X for the reac-

(1) Paper XXI in our series "The Chemistry of Ylides." For paper XX, see *J. Org. Chem.*, **35**, 2678 (1970).

(2) Department of Biological Chemistry, Harvard University Medical School, Boston, Mass. 02115. Deceased Dec 1971.

(3) A. W. Johnson and S. C. K. Wong, *Can. J. Chem.*, **44**, 2793 (1966).

(4) G. Aksnes and P. Froyen, *Acta Chem. Scan.*, **23**, 2697 (1969).

(5) A. W. Johnson, "Colloques Internationaux du Chimie Organique du Phosphore," Paris, 1970, pp 229–234.

(6) J. O. Schreck, *J. Chem. Educ.*, **48**, 103 (1971).

TABLE I

RATES OF REACTION OF *N*-(X-PHENYL)IMINOTRIPHENYLPHOSPHORANES WITH SUBSTITUTED BENZALDEHYDES[a]

$(C_6H_5)_3P{=}NC_6H_4X + YC_6H_4CHO$

Registry no.	Y	X = *p*-CH_3O (14796-89-5)[a]	X = *p*-CH_3 (2327-67-5)[a]	X = H (2325-27-1)[a]	X = *p*-Br (14987-96-3)[a]	X = *m*-Cl (14796-87-3)[a]	X = *m*-NO_2 (14796-86-2)[a]
528-75-6	2,4-$(NO_2)_2$	27.6[b]	29.6[b]	29.9[b]	9.0[b]	5.4[b]	1.03[b]
555-16-8	*p*-NO_2	19.3	23.3	34.6	24.0	16.7	2.03
105-07-7	*p*-CN			27.9			
587-04-2	*m*-Cl			8.82			
100-52-7	H	0.83	0.96	1.37	1.10	0.67	0.23
104-87-0	*p*-CH_3			0.66			
123-11-5	*p*-CH_3O	0.13	0.14	0.17	0.18	0.10	Too slow

[a] Registry number. [b] Rate constants are $\times 10^2$ l./mol sec at 40.5° in absolute ethanol solution.

tion of the *N*-phenyl-substituted imines with each of the four benzaldehydes results in four similar "concave down" curves. Accordingly, it may be concluded that the change in rate-determining step in the reaction of *N*-phenyliminotriphenylphosphoranes with aldehydes is a general phenomenon.

The delicate balance in the rates of betaine formation and betaine decomposition in the imine–carbonyl reaction is a unique observation in the field of ylide chemistry. In the imine, electron-donating substituents are expected to increase the nucleophilicity of the nitrogen atom, but at the same time increase the electron density on the phosphorus atom, thereby decreasing its susceptibility to oxyanion attack (*i.e.*, increase k_1 and decrease k_2, respectively). Electron-withdrawing substituents are expected to decrease the nucleophilicity of the nitrogen atom but also decrease the electron density on the phosphorus atom, thereby increasing its susceptibility to oxyanion attack (*i.e.*, decrease k_1 and increase k_2, respectively). Thus, any imine substituent is expected to exert opposing effects on the two rate constants. The introduction of even a methyl group on the *N*-phenyl ring seems sufficient to increase k_1 to the point that betaine decomposition (oxyanion attack on phosphorus) becomes rate-determining. The difference in the effect exerted by an electron-donating substituent seems to indicate a far more effective transmission of electronic effect through a phenyl group to nitrogen than to phosphorus.

Coincidentally, the use of 2,4-dinitrobenzaldehyde has permitted the observation of a steric effect in the imine–carbonyl reaction heretofore not observed. Although such a carbonyl group should be more electrophilic than that of *p*-nitrobenzaldehyde, in the reactions with those imines *not* carrying electron-donating groups k_{obsd} is lower for the dinitrobenzaldehyde. These observations are consistent with betaine formation being the slow step of the reaction in the former cases, and therefore the steric hindrance being reflected in k_{obsd}, but with betaine decomposition being the slow step in the latter case, and the steric effect apparently not being reflected in k_{obsd}. Steric hindrance seems to be a significant factor only in betaine formation and seems to be detectable only in those reactions in which betaine formation is the rate-determining step.

Experimental Section

The iminophosphoranes (I) were prepared as described in our earlier report.[3] The benzaldehydes were commercial samples which were purified by crystallization or distillation. The rates of the reactions of the imines with the benzaldehydes were determined at 40.5° in absolute ethanol solution according to the procedure described in our previous work.

1,2-Diazacyclooctanes

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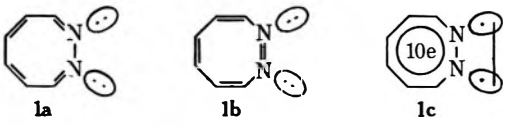
Received November 4, 1971

In light of the recent success of Trost and Cory[1] in uncovering an elegant route to 1,2-diazacyclooctatetraene (1), we have terminated our own studies in this



1a **1b** **1c**

area which were directed toward a synthesis of **1** *via* a classical halogenation–dehydrohalogenation sequence through the bis-protected diazacyclooctene **3**. Our interest in **1** derived from the conjecture that this compound might exist as the "aromatic" 10-π system **1c**.[2] Gund[3] has recently reported simple MO calculations on the classic structures **1a** and **1b** and has obtained delocalization energies similar to those calculated for cyclooctatetraene, whereas the "promoted" form **1c** leads to delocalization energies which are substantially higher. On the other hand, Trost's spectral results suggest nothing unusual about **1** but rather correlate well with structure **1a**.

Treatment of *cis*-1,6-dibromo-3-hexene (2) with *tert*-butyl hydrazodiformate and sodium hydride in dimethylformamide under relatively high dilution conditions gave **3** in 72% yield. A similar technique was used to obtain the saturated analog **7** (70%). Overberger and Stoddard[4] synthesized similarly the diethyl analog of **7**, although in only 22% yield.

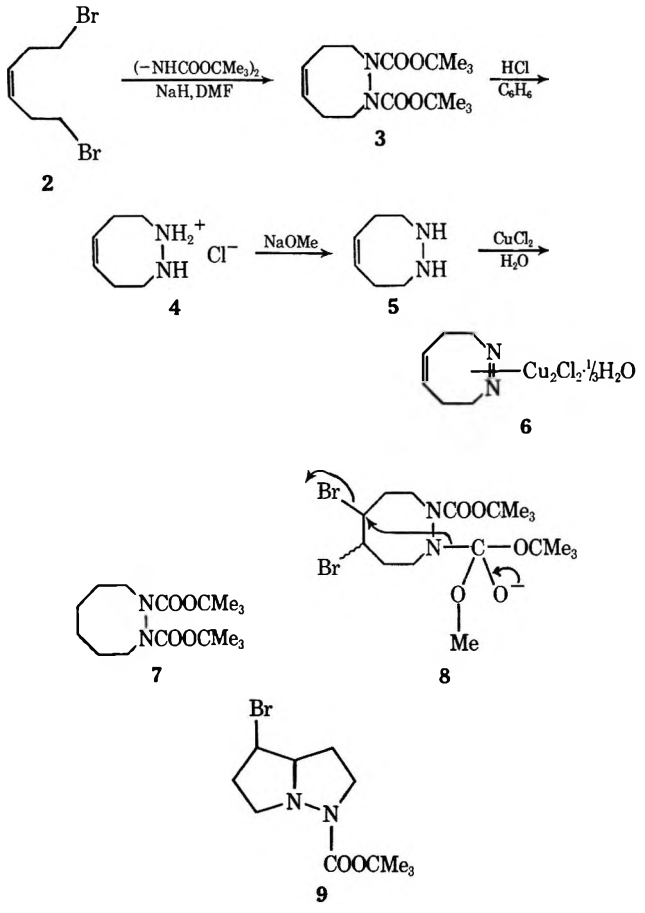
Preliminary attempts to introduce further unsaturation into **3** were carried out by bromination followed by treatment with various bases. Thus addition of bromine to a solution of **3** in ether followed by addition of potassium *tert*-butoxide led to debromination with recovery of **3** rather than dehydrobromination. The less bulky sodium methoxide apparently attacked one

(1) B. M. Trost and R. M. Cory, *J. Amer. Chem. Soc.*, **93**, 5572, 5573 (1971).

(2) For a consideration of a classical 10-π system which might also be obtainable *via* **3** see N. L. Allinger and G. A. Youngdale, *J. Org. Chem.*, **25**, 1509 (1960).

(3) P. H. Gund, Ph.D. Thesis, University of Massachusetts, Amherst, Mass., 1967.

(4) C. G. Overberger and J. W. Stoddard, *J. Amer. Chem. Soc.*, **92**, 4922 (1970).



of the carbo-*tert*-butoxy groups since in this case a compound tentatively identified as **9**, possibly derived from intermediate **8**, was the only product which could be isolated.[5,6]

Deblocking of **3** by the usual technique[7] gave the hydrazine hydrochloride **4** which was characterized by oxidation to the corresponding azo compound, isolated as the cuprous chloride complex.[8]

Experimental Section[9]

1,2-Dicarbo-*tert*-butoxy-1,2-diazacyclooct-5-ene.—To a 12-l. flask equipped with a mechanical stirrer and a nitrogen inlet tube there was added 6 l. of dry DMF followed by 50 g of *tert*-butyl hydrazodiformate.[10] After careful addition of 9 g of sodium hydride (60% in mineral oil) the mixture was stirred for 2 hr at room temperature and 52.2 g of *cis*-1,6-dibromo-3-hexene[11] in 50 ml of dry DMF was added in one portion. The mixture was stirred at room temperature for 24 hr, a second 9 g of NaH was cautiously added, and the stirring was continued for 72 hr at room temperature and 12 hr at 90°.

The volume was reduced to 1 l. at the water aspirator, 500 ml of water added, and the solution was extracted with seven 400-ml portions of ligroin (bp 61–70°). The combined extracts were washed with 500 ml of DMF–H_2O (1:1) and twice with 500-ml portions of H_2O. Removal of the solvent from the dried ($MgSO_4$) solution gave 56.6 g (83%) of crude oily hydrazide which was purified by column chromatography.[12] To a Florisil-packed column (15 × 200 cm) there was introduced 25 g of the above oil. Elution with ligroin (bp 35–60°)–acetone (9:1) gave after solvent removal a material which, if not crystalline, was stored in contact with 20 ml of ligroin (bp 61–70°) at −15° for 48 hr to aid in crystallization. Filtration followed by sublimation gave clear colorless crystals, mp 69.3–70°. The combined yield was 47.9 g (72%): ir ($CHCl_3$) 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.45 (s, 18 H, CH_3), 2.2 (br q, 4 H, CH_2), 3.08 (m, 2 H, CH_2), 3.9 (m, 2 H, CH_2), 5.78 (*t*, 2 H, =CH).

Anal. Calcd. for $C_{16}H_{28}N_2O_4$: C, 61.51; H, 9.03; N, 8.96; mol wt, 312.4. Found: C, 61.66; H, 9.01; N, 9.12; mol wt, *m/e* 312 ± 1 (mass spectrum).

1,2-Dicarbo-*tert*-butoxy-1,2-diazacyclooctane.—Treatment of 40 g of 1,6-dibromohexane with 30 g of *tert*-butyl hydrazodiformate[10] by the same technique as described above gave after column chromatography 40 g (70%) of an oil which was shown by glpc to be >95% pure. To obtain an analytical sample preparative glpc on a 10-ft column (25% SE-30 on 60/80 Chromasorb W) at 180° gave a solid which after sublimation gave clear colorless crystals: mp 47–49°; ir ($CHCl_3$) 1705 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.45 (s, 18 H, CH_3), 1.5 (m, 8 H, CH_2), 3.4 (m, 4 H, CH_2). The same compound was obtained in 65% yield from the 1,6-ditosylate and by catalytic reduction of **3** over palladium/carbon in a Parr apparatus.

Anal. Calcd. for $C_{16}H_{30}N_2O_4$: C, 61.08; H, 9.61; N, 8.90. Found: C, 61.30; H, 9.62; N, 9.18.

Treatment of 5,6-Dibromo-1,2-dicarbo-*tert*-butoxy-1,2-diazacyclooctane with Sodium Methoxide.—To a solution of 10 g of **3** in 100 ml of CH_3OH at 0° was added 5.2 g of Br_2. The solution was stirred at 0° for 0.5 hr and allowed to come to room temperature and 3.5 g of $NaOCH_3$ was added. After 2 hr, the solution was concentrated to one-third its volume and 50 ml of H_2O was added, and the mixture was extracted with two 30-ml portions of CH_2Cl_2. The oil obtained from the combined extracts was chromatographed on a 10 × 150 cm Florisil-packed column by elution with ligroin (bp 35–60°)–ethyl acetate (8:1). Concentration of appropriate fractions (tlc) gave a small amount of solid: mp 51–52°; ir ($CHCl_3$) 1698 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.48 (s, 9 H, CH_3), 2.0–4.0 (m, 9 H), 4.52 (m, 1 H).

Anal. Calcd for $C_{11}H_{19}N_2O_2Br$: C, 45.37; H, 6.57; N, 9.62; Br, 27.44. Found: C, 45.65; H, 6.56; N, 9.60; Br, 27.40.

1,2-Diazacyclooct-5-ene Hydrochloride.—Passage of gaseous HCl through a solution of 17.6 g of **3** in 200 ml of dry benzene at 0° gave 10 g (97%) of a salt, mp 89–91°, shown to be the dihydrochloride by nmr analysis. Sublimation at 20° (0.1 mm) gave the monohydrochloride: mp 120–122°; nmr (D_2O) δ 2.52 (m, 4 H, CH_2), 3.15 (m, 4 H, CH_2), 4.68 (s, 3 H, HOD), 6.0 (t, 2 H, =CH).

Anal. Calcd. for $C_6H_{13}N_2Cl$: C, 48.84; H, 8.81; N, 18.84. Found: C, 48.50; H, 8.80; N, 18.83.

1,2-Diazacyclooctane Hydrochloride.—Treatment of **7** with HCl by the method described above gave the dihydrochloride, mp 105–107°. Sublimation at 50° (0.1 mm) gave the monohydrochloride: mp 121–123°; nmr (D_2O) δ 1.68 (br s, 8 H, CH_2), 3.17 (m, 4 H, CH_2), 5.2 (s, 3 H, HOD).

Anal. Calcd. for $C_6H_{15}N_2Cl$: C, 47.83; H, 10.04; N, 18.09. Found: C, 48.10; H, 10.00; N, 18.32.

Liberation of the free base by means of trimethylamine gave a yellow oil, bp 89° (20 mm) [lit.[4] bp 71–74° (15 mm)], shown by spectral comparison to be the same as that independently obtained by Overberger and Stoddard[4] from the corresponding diethyl ester.

1,2-Diazacycloocta-1,5-diene–Cuprous Chloride Complex.—Sodium methoxide was added to a solution of 4.3 g of 1,2-diazacyclooct-5-ene dihydrochloride in 25 ml of H_2O until it was neutral to universal indicator paper. There was then added a solution of 6.7 g of $CuCl_2$ in 50 ml of H_2O. The dark red-brown precipitate was quickly filtered to give 1.1 g. (13.2%) of a complex: mp 191–197° dec; ir (KBr) 3350 (OH), 2910 (CH), 1430 cm^{-1} (N=N).

Anal. Calcd. for $C_6H_{10}N_2Cu_2Cl_2 \cdot {}^1/_3H_2O$: C, 22.94; H, 3.42; N, 8.91; Cl, 22.57; O, 1.70; Cu, 40.4. Found: C, 23.55; H, 3.46; N, 8.76; Cl, 22.70; O, 1.89; Cu, 39.6.

(5) Structure **9** is preferred over the alternate bicyclo[4.2.0] system on the basis of other transannular reactions in eight-ring systems.[6]

(6) A. C. Cope, H-H. Lee and H. E. Petree, *J. Amer. Chem. Soc.*, **80**, 2849 (1958); A. C. Cope, and P. E. Peterson, *ibid.*, **81**, 1643 (1959).

(7) L. A. Carpino, *ibid.*, **85**, 2144 (1963).

(8) For recent examples of the isolation of azo compounds as their cuprous chloride complexes, see E. L. Allred, J. C. Hinshaw, and A. L. Johnson, *ibid.*, **91**, 3382 (1969).

(9) Melting and boiling points are uncorrected. Infrared spectra were obtained on Beckman IR-10 and Perkin-Elmer 247B instruments and nmr spectra on a Varian A-60 unit. Preparative glpc was carried out on a Varian Aerograph 700 chromatograph. Elemental analyses were carried out by Charles Meade and associates, University of Massachusetts Microanalytical Laboratory.

(10) L. A. Carpino, *J. Amer. Chem. Soc.*, **79**, 4427 (1957).

(11) R. Lukes and V. Dudek, *Chem. Listy*, **52**, 1926 (1958).

(12) The same column could be reused at least five times by rinsing it after each separation with 2 l. of acetone followed by 2 l. of ligroin (bp 35–60°)–acetone (9:1).

The same compound was obtained by treatment of the dihydrochloride with trimethylamine, followed by oxidation of the free base with activated manganese dioxide[13] in dimethyl ether. This gave a crude sample of 1,2-diazacycloocta-1,5-diene which was distilled from a water bath at 10° to a receiver held at −78°. Without further purification of the free azo compound, treatment with a saturated solution of Cu_2Cl_2 in 10% HCl gave the same complex described above, identified by infrared spectral comparison.

Registry No.—**3**, 34201-71-3; **5** hydrochloride, 34201-72-4; **5** dihydrochloride, 34201-73-5; **6**, 11089-64-8; **7**, 34201-74-6; **9**, 34201-75-7; 1,2-diazacyclooctane monohydrochloride, 34201-76-8; 1,2-diazacyclooctane dihydrochloride, 34201-77-9.

Acknowledgment.—Thanks are due to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

(13) L. A. Carpino, *J. Org. Chem.*, **35**, 3971 (1970).

A Study of the Cyclization of 2′-Formamido-4′,5′-dimethoxypropiophenone with Ammonia

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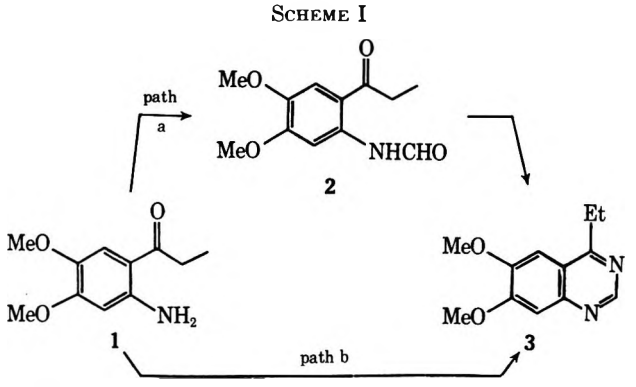
The compound [2-^{14}C]-6,7-dimethoxy-4-ethylquinazoline was required for metabolism studies. Scheme I shows the general approach considered for its

SCHEME I



synthesis. Previously, 6,7-dimethoxy-4-ethylquinazoline[1] (**3**) was prepared in these laboratories by formylation of 2′-amino-4′,5′-dimethoxypropiophenone[2] (**1**) with excess mixed formic–acetic anhydride, followed by heating the resulting 2′-formamido-4′,5′-dimethoxypropiophenone (**2**) in fused ammonium formate saturated with ammonia (path a),[3] or by heating **1** with formamide and formic acid (path b).[4] Compound **3** labeled at the 2 position could be made *via* path a if methods for the efficient incorporation of a [^{14}C]formyl group could be found. Certainly, the methods used previously for the conversions **1** to **2** or **1** to **3** would not be suitable because of the excesses of formic acid or formic acid derivatives used in each case. The synthesis of [^{14}C]formyl-**2** was easily accomplished by reaction of **1** with 1 equiv each of [^{14}C]formic acid and dicyclohexylcarbodiimide (DCC).

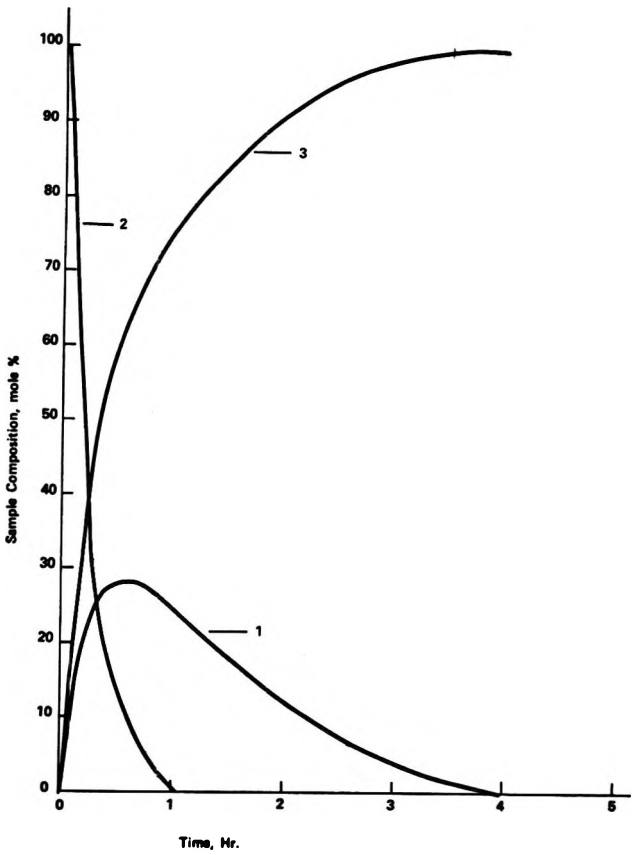


Figure 1.—The reaction of **2** with ammonia in ammonium formate at 125°. Mole per cent composition of the reaction mixture *vs.* time.

The question remaining concerned the fate of the label in **2**. Would it be lost in the conversion of **2** to **3**? The course of this reaction was studied by adding **2** with stirring to fused ammonium formate saturated with ammonia at 125° and withdrawing aliquots periodically. The samples were analyzed by glc, and the results are presented in Figure 1, in which the mole per cent composition of the sample is plotted against reaction time. Figure 1 indicates that **2** may proceed to **3** irreversibly, and/or it may equilibrate with **1**. Complete conversion to **3** is assured by the fact that it is formed essentially irreversibly. This experiment showed that ring closure of labeled **2** under these conditions would lose the label to the reaction medium.

As an alternate to the ring closure in fused ammonium formate, the reaction of **2** in ethanol saturated with ammonia in a sealed tube was investigated. The results of reactions at various temperatures and for various times are presented in Table I. It should be noted that here again the starting formanilide **2** equilibrates with the amine **1**, but the formic acid is captive and does not equilibrate with solvent.

In the actual synthesis of the labeled compound, using 23.5 mCi of [^{14}C]formic acid, in the DCC formylation procedure, 2′-formamido[^{14}C]-4′,5′-dimethoxypropiophenone was obtained, after recrystallization from methanol, in 82.8% yield. This material was

(1) The U. S. Adopted Name for this material is Quazodine.
(2) D. E. Ames and A. C. Lovesey, *J. Chem. Soc.*, 6306 (1965).
(3) J. L. Minielli and H. C. Scarborough, U. S. Patent 3,248,292 (1966).
(4) S. Palazzo, *Boll. Sedute Accad. Gioenia Sci. Natur. Catania*, **71**, 75 (1959); *Chem. Abstr.*, **55**, 12412 (1961).

TABLE I
REACTION OF 2 WITH AMMONIA IN ETHANOL

Time	Temp, °C	Sample composition, % 1	2	3	Unidentified
2 weeks	25	7.2	11.1	81.9	0
4 hr	100	5.2	29.9	65.0	0
4 hr	150	11.8	14.3	73.9	0
8 hr	150	6.8	0	84.4	8.8
12 hr	150	7.7	0	89.6	2.7

then cyclized to [2-^{14}C]-6,7-dimethoxy-4-ethylquinazoline by heating the formamido compound in a sealed tube with ethanol and ammonia at 150° for 12 hr. The residue from the reaction was recrystallized from acetone to give (in two crops) the product in 63% yield. The two crops were combined with unlabeled material by recrystallization. The total ^{14}C content was 6.41 mCi, which, allowing for the material recovery, amounts to 56.4% incorporation of the [^{14}C]formic acid.

Experimental Section

6,7-Dimethoxy-4-ethylquinazoline (3). Ammonium Formate Method.—A 100-ml three-necked flask equipped with a magnetic stirrer, gas inlet tube, thermometer, and condenser was charged with 25.2 g (0.4 mol) of ammonium formate. The ammonium formate was heated to 125° with stirring. Then 2.37 g (0.01 mol) of **2** (*vide infra*) was added; the addition of ammonia gas below the surface at a moderate rate was started immediately. Periodically, 0.1-ml samples were withdrawn, diluted with 5 ml of water, adjusted to pH 9 with NH_4OH, and extracted with $CHCl_3$ (5 ml). The extracts were analyzed by glc;[5] the results are presented in Figure 1. After 6 hr of reaction, the mixture was poured into water, made basic with NH_4OH, and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow solid. The solid was recrystallized from acetone–hexane to give 1.5 g (69%) of white product, mp 149–150.5°.

6,7-Dimethoxy-4-ethylquinazoline (3). Ammonia in Ethanol Method.—A solution of 0.5 g (2.11 mmol) of **2** in 75 ml of absolute EtOH was saturated with ammonia at 0° in a steel cylinder of 100-ml capacity. The bomb was sealed and heated to temperature and held there for a specified time. After the reaction period the cylinder was cooled and opened, and the solution was analyzed by glc without further treatment.[5] The results of several runs are presented in Table I. The solution was then evaporated to dryness, and the residue was recrystallized from acetone–hexane to give white crystalline material.

2′-Formamido[^{14}C]-4′,5′-dimethoxypropiophenone.—A 100-ml three-necked flask equipped with a mechanical stirrer, thermometer, and addition funnel was charged with 2.30 g (11.0 mmol) of **2** and 0.515 g of 97% formic acid (11.0 mmol of anhydrous HCO_2H). Then 23.5 mCi of [^{14}C]formic acid (specific activity 60 mCi/mmol) was transferred to the flask with 30 ml of CH_2Cl_2. A solution of 2.44 g (11.83 mmol) of dicyclohexylcarbodiimide in 30 ml of CH_2Cl_2 was added over 5 min, during which time the temperature was maintained at 20–25° with an ice bath. The mixture was stirred at room temperature for 1 hr, and then the dicyclohexylurea was filtered, rinsed with CH_2Cl_2, and air dried to give 2.5 g (100% of theory) of white material. The combined filtrates were evaporated *in vacuo*, and the residue was recrystallized from 15 ml of MeOH. The material was filtered, rinsed with MeOH, and air dried to give 2.16 g (82.8%) of slightly yellow material, mp 125–130°. The material was carried directly to the next step.

[2-^{14}C]-6,7-Dimethoxy-4-ethylquinazoline.—A cylindrical stainless steel pressure vessel of 100-ml capacity was charged with 2.16 g (9.12 mmol) of 2′-formamido[^{14}C]-4′,5′-dimethoxypropiophenone and 75 ml of absolute EtOH. The mixture was cooled and saturated with NH_3. The vessel was sealed and heated at 150° for 12 hr; it was then cooled and opened. The content was evaporated *in vacuo* to dryness. The residue was taken up in 75 ml of hot acetone, treated with Darco G-60 charcoal, and concentrated *in vacuo* to 25 ml. The solution was cooled, and the precipitate was filtered, rinsed with cold acetone (2 × 3 ml), and air dried to give 0.96 g of material. The combined filtrates were treated with charcoal and evaporated *in vacuo*. The residue was recrystallized from 5 ml of acetone to give 0.26 g of product. The two crops (total 1.22 g, 63%) were combined with 1.225 g of **3**, and the whole was dissolved in 30 ml of acetone. The solution was concentrated to 20 ml and cooled. The solid was filtered and air dried to give 2.275 g of off-white solid (92.9% recovery), mp 149–150°, specific activity 2.82 μCi/mg.[6] The thin layer radiochromatogram showed one spot.[7]

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.83. Found: C, 65.83; H, 6.46; N, 12.86.

Registry No.—**2**, 34314-99-3; **3**, 4015-32-1; 2′-formamido[^{14}C]-4′,5′-dimethoxypropiophenone, 34314-79-9; [2-^{14}C]-6,7-dimethoxy-4-ethylquinazoline, 34315-01-0.

Acknowledgments.—I am indebted to Dr. J. A. LaBudde and his group for the tlc and activity count, and to Mr. C. Combs and his group for the elemental analysis.

(5) The glc analyses were made using 1.2 m × 6 mm dual glass columns packed with 3.8 wt % UC W-98 on 80/100 mesh Diatoport S; the oven temperature was programmed from 150 to 250° at 10°/min. The flow rates in ml/min were He, 40; H_2, 20; and air, 300; and the detector was a dual flame-ionization model. The retention times (in min) were **4**, 4.55; **5**, 5.90; and **6**, 5.30; respectively. All the components were assumed to have the same response; and, consequently, the area per cent is taken as mole per cent composition of the sample.

(6) The radioactivity of the samples was determined in a Packard Tri-Carb liquid scintillation counter in a counting solution of 2.5-diphenyloxazole (7 g/l.) and naphthalene (100 g/l. in *p*-dioxane).

(7) The tlc was run by spotting the sample from chloroform on Eastman No. 6060 silica gel tlc sheet and eluting with 50:50 Skelly F/acetone. The eluted strips were scanned with a Varian Aerograph Berthold radioscanner which showed a single radioactive peak.

Stereoselective Synthesis of Racemic Grandisol

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Grandisol (**1a**) is one of the four components of the boll weevil sex pheromone and has been previously synthesized nonselectively[1] and stereoselectively.[2] We now report another stereoselective synthesis which provides gram quantities of pure **1a**.

Since ethylene undergoes 2 + 2 cycloaddition in the required cis manner to negatively substituted cyclohexenones[3] which are photochemically activated, we attempted the addition of ethylene to 5,6-dihydro-4-methyl-2*H*-pyran-2-one[4] (**2**).

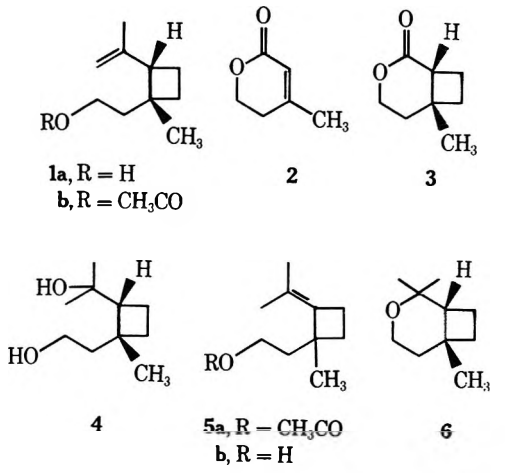
Indeed, when **2** was irradiated in benzene saturated and continuously swept with ethylene, the bicyclic lactone, 6-methyl-3-oxabicyclo[4.2.0]octan-2-one (**3**), was the major product. The reaction proceeds *via* a

(1) (a) J. H. Tumlinson, D. D. Hardee, R. C. Gueldner, A. C. Thompson, P. A. Hedin, and J. P. Minyard, *Science*, **166**, 1010 (1969); (b) J. H. Tumlinson, R. C. Gueldner, D. D. Hardee, A. C. Thompson, P. A. Hedin, and J. P. Minyard, *J. Org. Chem.*, **36**, 2616 (1971).

(2) R. L. Zurflüh, L. L. Dunham, V. L. Spain, and J. B. Siddall, *J. Amer. Chem. Soc.*, **92**, 425 (1970).

(3) W. C. Agosta and W. W. Lowrance, Jr., *Tetrahedron Lett.*, 3053 (1969). We are grateful to W. C. Agosta for providing a preprint.

(4) (a) A. L. Remizov and G. A. Tsetkova, *Chem. Abstr.*, **65**, 614*a* (1966); (b) Cornforth, *et al.*, *Tetrahedron*, **5**, 311 (1959).



triplet state of **2** with a triplet energy (E_t) of 69–74 kcal since it is photosensitized by acetophenone (E_t = 74[5]) but not by benzophenone (E_t = 69[5]).

The addition of the lactone **3** to excess methyllithium (to minimize epimerization, catalyzed by lithium alkoxide, of the intermediate methyl ketone resulting from the addition of 1 equiv of methyllithium) at 0° resulted in the formation of the cis diol[1b] **4**, mp 87–87.5°. The minor amount of the trans diol[1b] (12–15%) also formed did not crystallize and was easily removed from the cis diol by recrystallization. Selective removal of the tertiary hydroxyl group of **4** in refluxing acetic anhydride yielded two isomeric acetates, **1b** and **5a**, in a 2:1 ratio (90% yield).

Other methods of dehydration of the diol (neutral and acidic alumina in refluxing toluene, pyridine–$POCl_3$) produced the ether[2] **6** predominantly and gave a less favorable ratio of **1a**:**5b** than the acetic anhydride method. Preliminary esterification of the primary hydroxyl group in pyridine–acetic anhydride prevented the formation of the ether but gave a 45:55 and a 50:50 ratio of **1b**:**5a** using pyridine–$POCl_3$ and dimethyl sulfoxide (160°), respectively.

Thermal decomposition of isomer **1b** occurred to the extent of about 50% when the mixture of isomeric acetates **1b** and **5a** was distilled. Prior reduction of the acetates with lithium aluminum hydride and then distillation to separate the corresponding isomeric alcohols **1a** and **5b** prevented decomposition during distillation. The ir and pmr spectra of synthetic **1a** are identical with those of the natural product. In laboratory bioassays, synthetic **1a** elicited the same response as the natural material.

Experimental Section

Melting points were determined in an oil bath and are uncorrected. Infrared spectra were run in CCl_4 solution on a Beckman IR-5A spectrophotometer. Infrared peaks are reported as wavenumbers. The uv spectrum was recorded on a Beckman DK-2A spectrophotometer. All proton magnetic resonance spectra were run in CCl_4 on a Varian A-60 spectrometer. Chemical shifts are reported as δ (parts per million) relative to tetramethylsilane as an internal standard at 60 MHz. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

5,6-Dihydro-4-methyl-2*H*-pyran-2-one (2).—Mevalonic acid lactone was prepared and dehydrated to **2** by the method of Remizov and Tsetkova.[4a] Using the method of Cornforth, *et al.*,[4b] to prepare mevalonic acid lactone, Engel and Byerley, Midwest Research Institute, Kansas City, Mo., prepared lactone **2** in 80% overall yield from 4 acetoxy-2-butanone. The pmr spectrum of **2** showed resonances at δ 1.92 (broad s, 3, olefinic CH_3), 2.32 (broad t, 2, J = 6 Hz, CH_2), 4.22 (t, 2, J = 6 Hz, CH_2O), 5.57 (m, 1, C=CH); ir 1720 cm^{-1} (C=O); uv 210 nm (ε 10,000).

6-Methyl-3-oxabicyclo[4.2.0]octan-2-one (3).—In a typical run a 3.8% solution of **2** with acetophenone (1.4%) in benzene saturated and continuously swept with ethylene was irradiated with a 450-W medium-pressure mercury-vapor lamp without filter. The reaction time varied from 12 to 48 hr for 90% consumption of **2** (by glpc analysis[6a]) according to the distillation cut of **2** being used. At the end of the irradiation period the benzene was removed by distillation and the residue was extracted with pentane to isolate **2**, acetophenone, and mainly the bicyclic lactone **3**. After distillation of several combined runs, **3** was isolated in 56% yield. Glpc analysis[6b] indicated 5–12% of another component with a retention time very close to that of **3**. The pmr spectrum of **3** showed resonances at δ 1.25 (s, 3, CH_3), 1.55–2.90 (complex multiplets), 4.10–4.50 (complex multiplet, 2, CH_2O), and most importantly no olefinic H; ir spectrum 2950, 1730 (C=O), 1385 (CH_3), 1265, 1075 cm^{-1}. An analytical sample was prepared by preparative glpc.[6c]

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.60; H, 8.53.

***cis*-α-(2-Methyl-2-β-hydroxyethylcyclobutyl)-α-methylethanol (4).**—Under nitrogen 27.7 g (0.198 mol) of **3** was added during 1 hr, with stirring to an ice-cooled flask containing 410 ml (0.82 mol) of a 2 *M* methyllithium solution in ether. The mixture was stirred for another 1.75 hr and the excess methyllithium was decomposed with a saturated aqueous solution of ammonium chloride. After removal of the ether layer, the aqueous layer was further extracted with chloroform. The combined ether–chloroform fractions were concentrated *in vacuo*, and benzene was added and removed three times by distillaton to dry the diol product. A residue remained which weighed 34.3 g (theory 34.02 g) and when recrystallized from 50 ml of cyclohexane weighed 23.4 g and melted at 87–88.5°. A second recrystallization from cyclohexane did not change the melting point but yielded an odorless product, 22 g (65%), identical with the diol **4** prepared by the earlier method.[1b]

***cis*-2-Isopropenyl-1-methylcyclobutaneethanol Acetate (1b).**—A mixture of 29.0 g (0.168 mol) of diol **4** and 100 ml of acetic anhydride was refluxed and stirred for 4 hr. The excess anhydride was removed at 40 mm and the mixture of acetates remaining was quickly distilled, bp 89–94° (10 mm). The mixed acetates **1b** (67%) and **5a** (33%) were separated by distillation in an annular spinning band still. **5a** had bp 89.4° (9.2 mm); pmr spectrum δ 1.11 (s, 3, CH_3), 1.36 (broad s, 3, olefinic CH_3), 1.45 (m, 2, CH_2), 1.54–1.78 (m, 4, two CH_2, cyclobutane ring), 1.82 (s, 3, $OCOCH_3$), 2.31 (broad t, 2, J = 7 Hz, OCH_2CH_2), 3.92 (t, 2, J = 7 Hz, OCH_2); ir 1725 (C=O), 1383 (tertiary CH_3), 1358 cm^{-1} (olefinic CH_3). **1b** had bp 90.5° (8.0 mm); pmr spectrum δ 1.17 (s, 3, CH_3), 1.64 (s, 3, vinyl CH_3), 1.3–2.2 (broad m, 6, three CH_2), 1.92 (s, 3, $OCOCH_3$), 2.53 (broad t, 1, J = 8 Hz, methinyl H), 3.96 (t, 2, J = 7.5 Hz, OCH_2), 4.57 and 4.76 (broad s, 2, $C=CH_2$), ir 1730 (C=O), 1635 ($C=CH_2$), 1360 (olefinic CH_3), 887 cm^{-1} ($C=CH_2$). Under the conditions of the distillation [pot temperature 125° (8.0–9.5 mm), 55 hr], about 50% of isomer **1b** underwent thermal degradation. The yield of pure **5a** was 8.6 g (26%) and of **1b** was 9.2 g (28%).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: for **1b**: C, 73.17; H, 10.13. Found for **5a**: C, 73.32; H, 10.38.

***cis*-2-Isopropenyl-1-methylcyclobutaneethanol (1a) and 2-Isopropylidene-1-methylcyclobutaneethanol (5b).**—Lithium aluminum hydride (3 g) was refluxed for 0.5 hr in 120 ml of dry ether. The mixture was cooled to 0° and the mixed acetates **1b** and **5a**, 9.2 g (0.047 mol) in 40 ml of dry ether, were added dropwise. The mixture was refluxed for 1 hr and cooled to 0°, and the excess hydride was decomposed with aqueous 10% sodium hydroxide. The white solids were removed by filtration, and the ether was dried over sodium sulfate and removed by distillation.

(5) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, New York, N. Y., 1965.

(6) Gas chromatographic columns used were as follows: (a) 6 ft × 0.125 in. 20% Apiezon L on silanized 60/80 mesh Chromosorb W; (b) 12 ft × 0.125 in. 15% XE-60 on Gas-Chrom Q (60/80 mesh); (c) 15 ft × 0.25 in. 20% Apeizon L on silanized Gas-Chrom P (60/80 mesh). Mention of a commercial or proprietary product in this paper does not constitute an endorsement of this product by the USDA.

The undesired isomer **5b** was carefully removed by distillation on an annular spinning band still: bp 68° (1.0 mm); pmr spectrum δ 1.19 (s, 3, CH_3), 1.45 (broad s, 3, vinyl CH_3), 1.56 (m, 3, vinyl CH_3), 1.72–2.19 (m, 4, two CH_2), 2.42 (broad t, 2, J = 6 Hz, $HOCH_2CH_2$), 3.57 (t, 2, J = 7.5 Hz, $HOCH_2CH_2$), 3.77 (s, 1, $HOCH_2CH_2$); ir spectrum 3300 (broad OH), 1350 cm^{-1} (sharp, olefinic CH_3). The desired isomer **1a** boiled at 73° (1.0 mm) and had spectra identical with those of the natural material.

Registry No.—**1a**, 28117-21-7; **1b**, 34502-18-6; **3**, 33194-47-7; **4**, 34566-68-2; **5a**, 34502-20-0; **5b**, 34502-21-1.

Diphenylacetylene from the Decomposition of 2,2-Diphenyl-1-tosylazoethylene[1]

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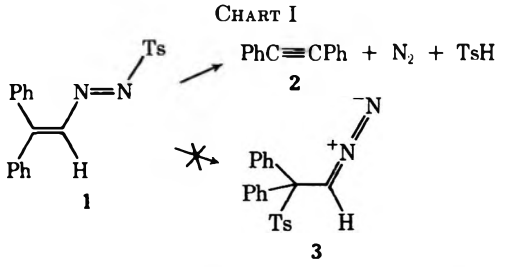
During the last few years we have investigated the chemistry of azoalkenes. In some reactions (1:4 additions,[2a] isomerizations[2b]) the S–N bond of tosylazoalkenes is retained, whereas in other cases (cycloadditions,[3] reactions with alcohols[4]) this bond is cleaved.

Earlier we reported the thermal degradation, at 90° in benzene and at 25° in chloroform, of aryl-substituted tosylazoalkenes having a vinylic proton on the carbon β to the azo group.[5] One degradation path apparently involves the formation of a vinylic carbonium ion which loses a proton from the adjacent carbon forming a triple bond as well as another principal path in which the tosylazoalkene rearranges to the corresponding α-tosyldiazo derivative which then undergoes acid-catalyzed decomposition.[5]

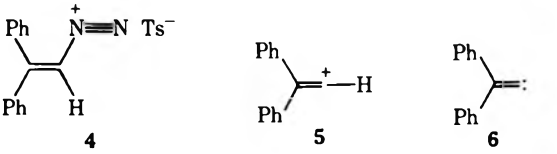
In order to extend our earlier studies, we have examined the thermal decomposition of 2,2-diphenyl-1-tosylazoethylene (**1**) which does not possess a proton on the vinylic carbon adjacent to the azo group.

In benzene at 90° and in chloroform[6] at 25°, **1** gives diphenylacetylene (**2**) as the main product (85–90%), nitrogen, and *p*-toluenesulfinic acid, without formation of 2-tosyl-2,2-diphenyl-1-diazoethane (**3**) or the decomposition products expected from **3** (Chart I).

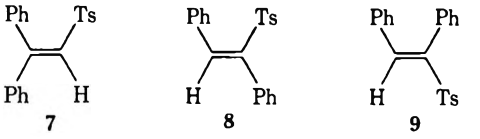
CHART I



Although the detailed mechanism for the decomposition of **1** has not been established, it seems likely that the azoalkene gives rise to the diazonium ion pair **4** which may rearrange to **2** either in a concerted manner or through the formation of a vinylic carbonium ion[7–12] **5** or a divalent intermediate[9,13,14] **6**.



However, all attempts to trap intermediates such as **5** and **6** were unsuccessful. For example, compounds **7–9** (expected by-products from the carbonium ion **5**) were not detected in the reaction mixture.



Introduction of cyclohexene did not afford any carbenoid adducts. Thus if **5** or **6** are intermediates they are too short lived to undergo any intermolecular reactions.

Experimental Section

Melting points are uncorrected. Spectra were recorded on Beckman IR-5A, Unicam SP-800, and Minimar Jeolco spectrometers. Nmr spectra were recorded using TMS as internal standard. Microanalyses were performed using C, H, N Analyzer Model 185 of Hewlett-Packard Co. Diphenylacetaldehyde and tosylhydrazine are commercial materials. Analytical-grade solvents were purified by standard methods and distilled through a Vigreux column before use.

2,2-Diphenyl-1-tosylazoethylene (**1**).—Diphenylacetaldehyde (5.0 g, 2.5 × 10^{-2} mol) was dissolved in 200 ml of diethyl ether, and 4.0 g (2.5 × 10^{-2} mol) of bromide was added dropwise. The ethereal solution obtained was shaken with an aqueous solution of sodium carbonate and then washed several times with water. The ethereal solution was dried (Na_2SO_4), and the ether was evaporated. Part (2.0 g, 7.2 × 10^{-3} mol) of the crude 2-bromo-2,2-diphenylacetaldehyde was dissolved in 200 ml of ether, and 1.3 g (7.2 × 10^{-3} mol) of tosylhydrazine was added with magnetic stirring. When the solution turned red it was shaken with a saturated aqueous solution of sodium carbonate and then washed several times with water, dried (Na_2SO_4), filtered, and concentrated under reduced pressure at room temperature until precipitation of a yellow-orange product occurred. The crystals of **1** were collected, washed with *n*-hexane, and dried (yield 65%): mp 82° dec; uv max (Et_2O) 348 mμ (ε 20,400); ir (KBr) 3000 (vw), 1580 (m), 1550 (w), 1480 (w), 1440 (m), 1415 (s), 1335 (vs), 1290 (w), 1250 (w), 1210 (vw), 1185 (m), 1160 (vs), 1120 (vs), 1080 (vs), 1025 (w), 1015 (w), 985 (m), 928 (w), 878 (m), 830 (s), 810 (s); nmr (C_6D_6) δ 7.60 (s, 1, vinylic proton), 1.85 (s, 3, methyl of tosyl group).

Anal. Calcd for $C_{21}H_{18}N_2O_2S$: C, 69.61; H, 4.97; N, 7.73. Found: C, 69.57; H, 5.00; N, 7.75.

Decomposition of 2,2-Diphenyl-1-tosylazoethylene (**1**). **Route**

(1) Work was effected with financial support of the Italian Research Council (C. N. R.).

(2) (a) L. Caglioti, A. Dondoni, and G. Rosini, *Chim. Ind. (Milan)*, **50**, 122 (1968); (b) L. Caglioti, A. Dondoni, G. Rosini, and G. Mossa, *J. Chem. Soc. B*, 1404 (1968).

(3) W. Barbieri, L. Bernardi, P. Masi, L. Caglioti, and G. Rosini, *Tetrahedron Lett.*, 1343 (1970); W. Barbieri, L. Bernardi, P. Masi, A. Vigevani, L. Caglioti, and G. Rosini, *Tetrahedron*, in press.

(4) L. Caglioti and G. Rosini, *Chem. Ind. (London)*, 1093 (1969).

(5) G. Rosini and R. Ranza, *J. Org. Chem.*, **36**, 1915 (1971).

(6) Methanol-free chloroform was used.

(7) M. S. Newman, and A. E. Weinberg, *J. Amer. Chem. Soc.*, **78**, 4654 (1956).

(8) M. S. Newman and A. Kutner, *ibid.*, **73**, 4199 (1951).

(9) D. Y. Curtin, J. A. Kampmeir, and B. R. O'Connor, *ibid.*, **87**, 863 (1965).

(10) D. Y. Curtin, J. A. Kampmeir, and M. L. Farmer, *ibid.*, **87**, 873 (1965).

(11) W. M. Jones and F. W. Miller, *ibid.*, **89**, 1960 (1967).

(12) A. C. Day and M. C. Whiting, *J. Chem. Soc. B*, 991 (1967).

(13) See J. Hine, "Divalent Carbon," Ronald Press, New York, N. Y., 1964.

(14) M. S. Newman and A. O. M. Okorodudu, *J. Amer. Chem. Soc.*, **90**, 4189 (1968).

A.—1 (3.0 g, 8.2×10^{-3} mol) dissolved in 100 ml of dried benzene in a sealed tube was heated in an oil bath at 90°. After a few minutes the color of the benzene solution disappeared with evolution of nitrogen. The colorless solution was cooled and concentrated under reduced pressure, and then a chromatographic separation was performed on a silica gel column using benzene as eluent. Diphenylacetylene was obtained in 85–90% yield, mp 59–60° (lit.[15] mp 60–61°); spectroscopic data are in agreement with those recorded on a sample independently prepared.[15]

Anal. Calcd for $C_{14}H_{10}$: C, 94.34; H, 5.66. Found: C, 94.25; H, 5.68.

Route B.—1 (3.0 g, 8.2×10^{-3} mol) was dissolved in 100 ml of chloroform and the solution was allowed to stand at 25° until the color disappeared (3–4 days); by evaporation of solvent under reduced pressure and chromatographic separation on a silica gel column using benzene as eluent, diphenylacetylene in 85–90% yield was obtained.

Registry No.—1, 34220-14-9; 2, 501-65-5.

Acknowledgment.—We wish to thank Professor Luciano Caglioti for his interest in this work and Mr. R. Bonoli, who carried out some of the experiments.

(15) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath, Boston, Mass., 1955, p 181.

The Effects of Group IVA Organometallics on the Reaction of Ethoxycarbonylnitrene with Cyclohexene[1a]

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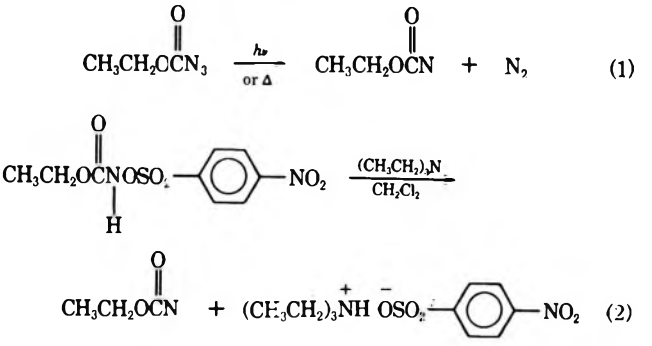
It has recently been reported that C–H bonds involving the carbon atom directly linked to a group IV metal (silicon and tin) are inert to dichlorocarbene generated by the thermal decomposition of phenyl(bromodichloromethyl)mercury. However, secondary or tertiary β C–H bonds underwent insertion readily.[2] Furthermore, the activating effect of a metal β to a C–H bond is in the order Sn > Ge > Si.[3]

We wish to report that tetramethyltin (α C–H bonds), as well as trimethylisobutyltin (β C–H bond), is inert to insertion by ethoxycarbonylnitrene generated under a variety of reaction conditions.

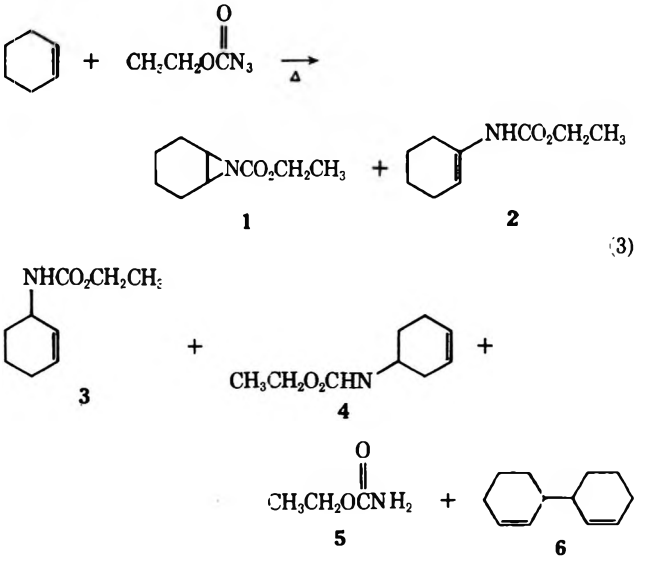
Ethoxycarbonylnitrene can be generated by the thermal or photolytic decomposition of ethoxycarbonyl azide[4] (eq 1) or by base-induced α elimination from *N*-*p*-nitrobenzenesulfonyloxyurethane (eq 2)[5] and gives addition and insertion reactions similar to carbenes.[6]

However, we have found that thermal decomposition of ethoxycarbonyl azide in pure tetramethyltin or solutions of tetramethyltin in carbon tetrachloride or methylene chloride as inert solvents gave only recovered organotin starting compound, a few per cent yield of urethane, $CH_3CH_2OC(=O)NH_2$, from hydrogen abstraction by the nitrene, and small amounts of viscous, polymeric orange-red oils as products. A polymeric gum was also observed when pivaloylnitrene was generated in unreactive solvents such as methylene chloride.[7]



The α elimination reaction (eq 2) with 33 mol % tetramethyltin in methylene chloride gave a 97% yield of triethylammonium *p*-nitrobenzenesulfonate and, upon work-up, yielded only recovered tetramethyltin and a small amount of urethane. Since a tertiary, β C–H bond is the most reactive toward dichlorocarbene for tetraalkyltin, -germanium, or -silicon compounds, trimethylisobutyltin was prepared and allowed to react in acetonitrile solution with thermally generated ethoxycarbonylnitrene. However, gas chromatography after concentration of the reaction mixture showed peaks only for solvent, starting organotin compound, and urethane.

Since insertion into C–H bonds is attributed to the carbonylnitrene principally in the singlet electronic state,[8] the effect of organometallic group IVA compounds on the singlet–triplet character of this nitrene was evaluated. The major products obtained upon thermal decomposition of ethoxycarbonylazide in cyclohexene are given in eq 3.[4] The insertion products



(2, 3, and 4) are mainly due to reaction of cyclohexene with singlet nitrene, products 5 and 6 are from triplet nitrene, and product 1 is from either singlet or triplet.[8]

(1) (a) This work was supported by a grant from the Research Corporation and by grants from the California State College, Fullerton Foundation; (b) undergraduate research assistant.

(2) D. Seyferth, *et al.*, *J. Amer. Chem. Soc.*, **92**, 4405 (1970).

(3) D. Seyferth, *et al.*, *J. Organometal. Chem.*, **29**, 371 (1971).

(4) W. Lwowski and T. W. Mattingly, Jr., *J. Amer. Chem. Soc.*, **87**, 1947 (1965).

(5) W. Lwowski and T. J. Maricich, *ibid.*, **87**, 3630 (1965).

(6) W. Lwowski, *Angew. Chem., Int. Ed. Engl.* **6**, 897 (1967).

(7) S. Linke, G. T. Tisue, and W. Lwowski, *J. Amer. Chem. Soc.*, **89**, 6308 (1967).

(8) W. Lwowski editor, "Nitrenes," Interscience Publishers, New York, N. Y., 1970, pp 200–207.

TABLE I

THERMAL DECOMPOSITION OF ETHYL AZIDOFORMATE IN CYCLOHEXENE

Reaction[a]	Solvent	Concentration, Vol %	Concentration, Mol %	Relative ratios of products[b] 1	2, 3, 4	5	6
1[c]	None	0	0	3.5	3.0	1.00	0.68
2	None	0	0	6.8	12.0	1.00	Trace
3[d]	None	0	0	8.6	8.9	1.00	0.68
4[d]	None	0	0	8.6	8.2	1.00	0.58
				(18.6)	(17.7)	(2.16)	(1.25)
5[e]	None	0	0	11.7	23.6	1.00	0.17
				(20.2)	(40.8)	(1.73)	(0.29)
6	CH_2Br_2	50.0	59.5	6.8	6.3	1.00	3.5
7	CH_2Br_2	70.7	78.2	18.7	7.21	1.00	0.30
				(63.2)	(24.4)	(3.38)	(1.00)
8	CH_2Br_2	90.0	92.8	15.8	3.6	1.00	0.42
9[d]	CH_2Br_2	90.0	92.8	19.3	4.4	1.00	0.95
10[f]	CH_2Cl_2	90.0	93.4	9.2	2.3	1.00	Trace
11	$(CH_3)_4Sn$	10.0	9.7	7.5	10.1	1.00	0.68
12	$(CH_3)_4Sn$	90.0	86.9	2.6	0.18	1.00	0.15
13[f]	$(CH_3)_4Si$	90.0	87.0	17.0	1.19	1.00	0.75

[a] Reaction mixture bubbled with N_2 and then refluxed under N_2 atmosphere, except where noted, for 72 hr at 80°. [b] Absolute yields (%) in parentheses. [c] Oxygen present, air atmosphere. [d] Duplicate run used to establish the limits of reproducibility of the system. [e] Carefully degassed, reaction under N_2. [f] Degassed, evacuated sealed-tube reaction.

The reaction was studied under a variety of conditions with the results outlined in Table I.

Discussion

The transition from the initially formed singlet nitrene to a lower energy triplet state due to collisional deactivation by inert solvent has been observed for ethoxycarbonylnitrene[9] and cyanonitrene.[10] In addition, a "heavy-atom" effect[11] was noted for cyanonitrene[10] but not for ethoxycarbonylnitrene.[9] Using the product ratios from cyclohexene to judge the singlet–triplet character of the carbonylnitrene, we find that the presence of oxygen greatly increases the triplet character of the reaction as reported earlier by Lwowski.[4] Reaction 5 gives relative ratios and absolute yields very similar to those reported by Lwowski[4] and shows the dramatic increase in singlet character obtained when the system has been thoroughly degassed of oxygen. Changing the concentration of cyclohexene from 100 to 50 to 30 to 10 mol % by dilution with methylene bromide (reactions 4, 6–8) gives an overall reduction in singlet character as expected from collisional deactivation of the nitrene.[12] This dilution effect is also evident from reactions 11 and 12. In general, the absolute yields of addition and insertion products decrease with increasing triplet character of the nitrene[4,7,10] probably owing to radical side reactions. Reaction 5 in Table I was the only instance of those which we studied in which the reaction mixture was colorless after the reaction was completed; the others were either orange solutions or, in cases where triplet character was very high, orange-red oils or gums were produced. We have no explanation at this time for the unusually high yields observed in reaction 7.

The most significant entries in Table I are reactions 12 and 13 which show a decrease in singlet character greater than can be rationalized on the basis of collisional deactivation when tetramethyltin or -silicon is used as an inert solvent. Since 12 gave much less singlet products than 13, it is tempting to invoke a heavy-atom effect to explain the results. However, methylene bromide gave more singlet product than a comparable concentration of tetramethyltin even though bromine has a higher spin-orbit coupling constant than tin,[11] there are two bromines per molecule, and the bromine atoms are less shielded than the tin atom. Furthermore, methylene chloride (reaction 10) gave less singlet products than methylene bromide (reaction 9) even though the former reaction mixture was degassed and the latter was not.

We would propose that the observed inertness to nitrene insertion of the C–H bonds of the group IV organometallic compounds studies is attributable to greatly enhanced triplet character of the carbonylnitrene partly due to collisional deactivation and partly due to an effect of the metal which we cannot explain at this time but which does not seem to be a heavy-atom effect. The inertness of even a tertiary β C–H bond, as in trimethylisobutyltin, is not unexpected given the general higher selectivity and lower reactivity of nitrenes compared to those of carbenes.

Experimental Section

Reagents.—Ethoxycarbonylazide, bp 40–41° (30 mm), was prepared from potassium azide and ethyl chloroformate.[4] Cyclohexene, bp 83°, was distilled through a 2-ft glass helices packed column and stored under nitrogen over potassium hydroxide pellets. *N*-*p*-Nitrobenzenesulfonyloxyurethane was prepared by the method previously described,[5] mp 115–116°. Tetramethylsilane, J. T. Baker, bp 26–27°, was used without purification. Tetramethyltin, bp 76–77°, and trimethylisobutyltin, bp 70° (60 mm), were prepared by the usual Grignard procedure.[13]

Product Composition.—Cyclohexene–nitrene reaction mixtures were concentrated by distillation and the relative ratios and, in a few select cases, absolute yields were determined by vpc analysis (Aerograph A-700) in which peak areas were obtained by the "cut

(9) J. S. McConaghy, Jr., and W. Lwowski, *J. Amer. Chem. Soc.*, **89**, 4450 (1967).

(10) A. G. Anastassiou, *ibid.*, **89**, 3184 (1967).

(11) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, New York, N. Y., 1965, p 29.

(12) Since collisional deactivation and the heavy-atom effect are molecular phenomena, reporting concentrations as volume per cent[10] seems inappropriate. However, the mole per cent concentrations are not significantly different for these solvents to affect the basic arguments.

(13) J. G. A. Luijten and G. J. M. Van Der Kerk, "Investigations in the Field of Organotin Chemistry," Tin Research Institute, Middlesex, England, 1955.

and weigh" technique. A 5 ft × 0.25 in. 15% XF-1150 on 60/80 Chromosorb W column gave overall satisfactory separation of the major products except for the insertion products (**2**, **3**, and **4**) which gave a broad, long-retention peak. However, a 5 ft × 0.25 in. 10% QF-1 on 60/80 Chromosorb W was needed to achieve good separation of **5** from **6**.

Products **5** and **6** were identified by comparison of retention times with those of and coinjection with authentic samples. Products **1**, **2**, **3**, and **4** were identified by collection from the gas chromatograph and comparison of nmr and ir spectra with published data.[4] To obtain calibration factors to correct for differences in detector sensitivity, it was assumed that products **1**, **2**, **3**, and **4** (isomers) have the same sensitivity. The relative ratios given are therefore corrected for the differences in detector sensitivity for **6** and **5** and **1**, **2**, **3**, and **4**.

Registry No.—Ethoxycarbonylnitrene, 2655-26-7; cyclohexene, 110-83-8; $(Me)_3Sn$, 594-27-4; $(Me)_4Si$, 75-76-3; ethyl azidoformate, 817-87-8.

Radiation and Ultraviolet Induced Addition of Alcohols to Ethyl Crotonate

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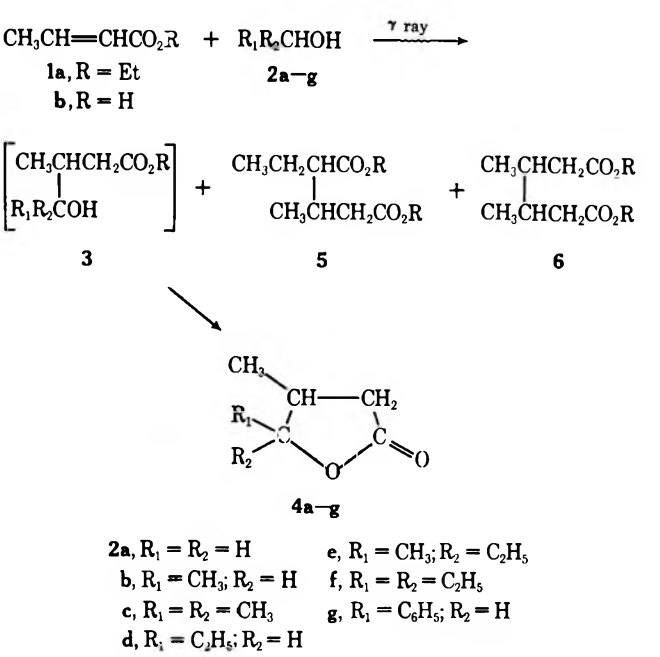
Radical addition reactions of alcohols to double bonds have been reported to be carried out using radical initiators,[2a-c] ultraviolet light,[2a,d-g] and radiation techniques.[3]

Although the radiation-induced addition of alcohol to ordinary olefins has been described to give both telomeric products and 1:1 adduct,[3a] the reaction with a relatively stable substrate such as halogeno olefin is known to produce mainly 1:1 adduct[3b-e] in good yield. The photochemical addition of alcohols to α,β-unsaturated acid derivatives in the presence of a sensitizer was reported to yield γ-butyrolactones by Schenck[2d] and Pfau,[2e-g] but the analogous radiation-induced reaction has not been known. Consequently, as a part of our studies on organic synthesis by means of radiation-induced reactions, γ-ray and ultraviolet-induced addition reactions to α,β-unsaturated acids and esters,[4] which seem to be considerably stable to γ radiation,[4b] were studied.

Irradiation of ethyl crotonate (**1a**) or crotonic acid (**1b**) in an excess of alcohol with ^{60}Co γ rays gave the corresponding 3-methyl-4-alkyl substituted γ-butyrolactones (**4**), small amounts of telomeric products of crotonate (**5**, **6**) and polymeric products.



2a, $R_1 = R_2 = H$ **e**, $R_1 = CH_3$; $R_2 = C_2H_5$
b, $R_1 = CH_3$; $R_2 = H$ **f**, $R_1 = R_2 = C_2H_5$
c, $R_1 = R_2 = CH_3$ **g**, $R_1 = C_6H_5$; $R_2 = H$
d, $R_1 = C_2H_5$; $R_2 = H$

The yield of lactones and conversion of ethyl crotonate in the radiation-induced addition reactions are summarized in Table I. The formation of γ-butyrolactone (**4**) seems to proceed through a radical chain mechanism initiated by an α-hydroxyalkyl radical. This is supported by the fact that the reaction was retarded by the addition of a radical scavenger.

TABLE I
RADIATION-INDUCED ADDITION OF ALCOHOL TO ETHYL CROTONATE[a]

Alcohol	Conversion[b,c] of **1a**, %	Yield,[b,c] % 4	5	6
Methanol	68	1	Trace	Trace
Ethanol	96	16[d]	1	0.5
2-Propanol	97	54	4	2
1-Propanol	94	9[e]	3	2
2-Butanol	95	18[f]	3	1
3-Pentanol	95	10	2	3
Benzyl alcohol	45	23[g]	0	0

[a] Irradiation time, 72 hr; dose rate, 0.9–1.0 × 10^6 r/hr; molar ratio of alcohol to ethyl crotonate, 15. [b] Based on ethyl crotonate employed. [c] By glpc analysis. [d] Trans:cis, 4:5. [e] Trans:cis, 2:3. [f] Trans and cis isomers were not separated in glpc analysis. [g] Trans:cis, 2:1.

It is of interest that a considerable amount of cis lactone was obtained from the reaction of crotonate with ethanol, 1-propanol, and benzyl alcohol. 2-Butanol also produced trans- and cis lactones, but their relative ratio could not be determined by glpc analysis. The formation of two isomeric lactones may well be the result of alternate approaches of the hydroxyalkyl radical to the double bond of ethyl crotonate. For example, if the hydroxyalkyl radical attacks the carbon–carbon double bond as shown in A, and the resulting intermediate radical abstracts hydrogen from alcohol, the cis isomer would be obtained. The attack of hydroxyalkyl radical as depicted in B would give rise to the trans isomer. Although the predominance of cis isomer in ethanol and 1-propanol, and trans isomer in benzyl alcohol, has not been adequately explained, it may well be due to the relative degree of steric interaction in pathways A and B. Similar isomeric ratios

(1) Deceased.

(2) (a) W. H. Urry, F. W. Stacey, E. S. Huyser, and O. O. Juveland, *J. Amer. Chem. Soc.*, **76**, 450 (1954); (b) J. P. LaZerte and R. J. Koshar, *ibid.*, **77**, 910 (1955); (c) E. V. Kirkland, *Ind. Eng. Chem.*, **52**, 397 (1960); (d) G. O. Schenck, G. Koltzenburg, and H. Grossmann, *Angew. Chem.*, **69**, 177 (1957); (e) R. Dulou, M. Vilkas, and M. Pfau, *C. R. Acad. Sci.*, **249**, 429 (1959); (f) M. Pfau, R. Dulou, and M. Vilkas, *ibid.*, **251**, 2188 (1960); (g) M. Pfau, *ibid.*, **254**, 2017 (1962).

(3) (a) H. Hirota and M. Hatada, *Bull. Chem. Soc. Jap.*, **34**, 1644 (1961); (b) H. Muramatsu, *J. Org. Chem.*, **27**, 2325 (1962); (c) H. Muramatsu, K. Inukai, and T. Ueda, *ibid.*, **30**, 2546 (1965); (d) H. Muramatsu, S. Moriguchi, and K. Inukai, *ibid.*, **31**, 1306 (1966); (e) H. Muramatsu, K. Inukai, and T. Ueda, *Bull. Chem. Soc. Jap.*, **40**, 903 (1967).

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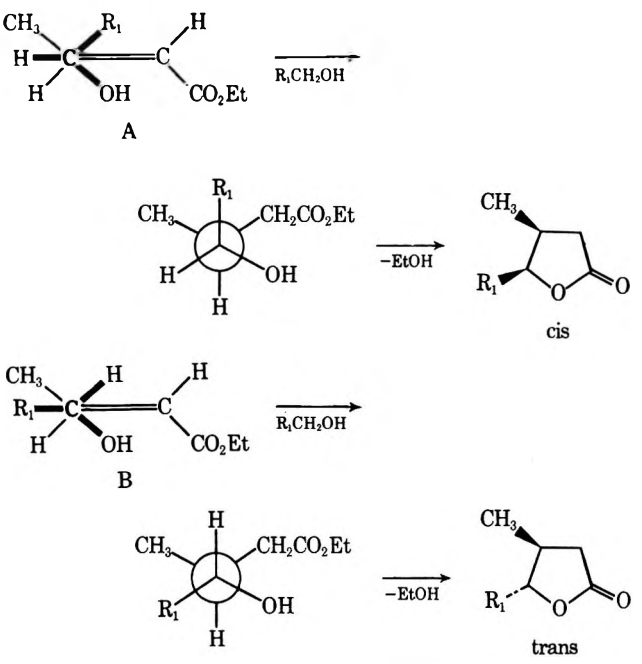

were also reported by Fukunishi, *et al.*,[5] in a radical-initiated addition of alcohols to maleic acid esters. Precise studies on these problems are currently under investigation in our laboratory.

Photochemical addition of alcohols to *trans*-ethyl crotonate (**1a**) in the presence of benzophenone as sensitizer produced γ-butyrolactones (**4**), *cis*-ethyl crotonate (**7**), ethyl 3-butenoate (**8**), polymer, and other products. Compounds **7** and **8** are known photochemical isomerization products of *trans*-ethyl crotonate.[6] Conversions of ethyl crotonate and yields of **4**, **7**, and **8** from irradiation in a quartz tube are listed in Table II. It was previously shown by us that photochemical

Table II

Photochemical Addition of Alcohol to Ethyl Crotonate in a Quartz Tube[a]

Alcohol	Conversion[b,c] of 1a, %	Yield,[b,c] % 4	7	8
Methanol	59	1	18	3
Ethanol	86	4[d]	10	16
2-Propanol	90	12	14	11
1-Propanol	88	4[e]	14	13

[a] A reaction mixture of ethyl crotonate (10 mmol), alcohol (40 mmol), and benzophenone (1.2 mmol) was externally irradiated in a quartz tube for 50 hr with a 500-W high-pressure mercury vapor lamp. [b] Based on ethyl crotonate employed. [c] By glpc analysis. [d] Trans:cis, 4:5. [e] Trans:cis, 4:5.

isomerization to β,γ isomer is not observed when an alcoholic solution of ethyl crotonate is irradiated with Pyrex-filtered light (>300 mμ).[6d] Thus, in order to avoid side reactions, reaction mixtures sealed in Pyrex tubes were irradiated with a high-pressure mercury vapor lamp (Table III).

The isomeric ratio of *trans*- and *cis*-γ-butyrolactones obtained from the photochemical reaction with ethanol and 1-propanol was almost identical with that from the radiation-induced addition reaction, even though cis–trans isomerization of ethyl crotonate was observed in the photochemical addition reaction. This might be explained by the fact that, since trans olefins are more reactive to a radical than cis isomers,[7] *trans*-ethyl crotonate would be attacked predominantly by the hydroxyalkyl radical, even if photochemical cis–trans isomerization should occur.

Table III

Photochemical Addition of Alcohol to Ethyl Crotonate in a Pyrex Tube[a]

	Conversion[b,c] of 1a, %	Yield,[b,c] % 4	7
Methanol	24	1	20
Ethanol	56	1[d]	11
2-Propanol	83	12	5
1-Propanol	75	5[e]	7
2-Butanol	98	22[f]	Trace
3-Pentanol	78	9	
Benzyl alcohol	23	6[f]	12

[a] A reaction mixture of ethyl crotonate (1.5 mmol), alcohol (60 mmol), and benzophenone (0.18 mmol) was externally irradiated in a Pyrex tube for 72 hr with a 500-W high-pressure mercury vapor lamp. [b] Based on ethyl crotonate employed. [c] By glpc analysis. [d] Trans:cis, 4:5. [e] Trans:cis, 4:5. [f] Trans:cis, not determined.

Experimental Section

Gas–liquid chromatographic analyses were carried out with a Yanagimoto Model GCG-550 and a Hitachi KGL-2A utilizing a capillary column. For preparative glpc a Wilkens Autoprep 700 was used. Infrared spectra were obtained with a Hitachi EPI-G22 and nuclear magnetic resonance spectra were measured with a Nihon Denshi 3H-60 (tetramethylsilane as the internal standard). Mass spectra were obtained with a Hitachi RMU-6E. Quantitative glpc analyses were carried out using an internal standard. All melting points and boiling points were uncorrected.

All reagents were distilled or recrystallized before use. 3-pentanol was prepared from ethylmagnesium bromide and propionaldehyde and dried over calcium oxide. Benzyl alcohol was purified by distillation. Ethyl crotonate was prepared by esterification of crotonic acid.

General Procedure for Radiation-Induced Addition.—A mixture of crotonic acid or ethyl crotonate and excess alcohol was repeatedly evacuated to *ca.* 1 mm in Dry Ice–trichloroethylene. The sample, sealed in a Pyrex tube, was irradiated with γ rays in a ^{60}Co cavity source at room temperature. The dose rate was approximately $0.9–1.0 \times 10^6$ r/hr. The irradiated sample was opened and analyzed by glpc. For quantitative analysis of the lactones, FFAP 15% column coated on Diasolid L was used at 160–230°, with 4-*tert*-butyltoluene and diethyl phthalate as the internal standard, and for ethyl crotonate, a capillary column of SE-30 (45 m) at 100° was used with cumene as the internal standard.

Neither evacuation of the tube to 10^{-5} mm nor filling it with nitrogen gave large differences when compared with the above procedure.

General Procedure for Photochemical Addition.—A reaction mixture in a quartz or Pyrex tube was cooled in water and externally irradiated with a 500-W high-pressure mercury vapor lamp. Nitrogen gas was allowed to pass through the mixture during the irradiation. The irradiated sample was analyzed by glpc as mentioned above. Glpc analysis of ethyl crotonate isomers was carried out with a capillary column (squarane, 45 m).

Analysis of Products.—The products were separated by preparative glpc (SE-30 or FFAP) and identified from the spectral data (ir, nmr, and mass spectrum).

cis-**3,4-Dimethyl-γ-butyrolactone** (*cis*-**4b**) had bp 95–97° (12 mm); $n^{25}D$ 1.4302 [lit.[8] bp 80–80.5° (5 mm), $n^{20}D$ 1.4287];

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(6) (a) M. J. Jorgenson, *Chem. Commun.*, 137 (1965); (b) P. J. Kropp, and H. J. Krauss, *J. Org. Chem.*, **32**, 3222 (1967); (c) R. R. Rando and W. von E. Doering, *ibid.*, **33**, 1671 (1968); (d) M. Itoh, M. Tokuda, K. Seguchi, K. Taniguchi, and A. Suzuki, *Kogyo Kagaku Zasshi*, **72**, 219 (1969).

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ir (CCl_4) 1790 cm^{-1}. *Anal.* Calcd for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found: C, 62.85; H, 8.75.

trans-**3,4-Dimethyl-γ-butyrolactone** (*trans*-**4b**) had bp 101–103° (12 mm); $n^{25}D$ 1.4350 [lit.[8] bp 86–86.5° (5 mm), $n^{22}D$ 1.4333]; ir (CCl_4) 1785 cm^{-1}. *Anal.* Calcd for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found: C, 62.93; H, 8.72.

3,4,4-Trimethyl-γ-butyrolactone (**4c**) had bp 97° (15 mm); $n^{20}D$ 1.4373 [lit. bp 216–217° (744 mm),[9] 219° (760 mm),[2f] $n^{17}D$ 1.4402]; ir (CCl_4) 1780 cm^{-1}. *Anal.* Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.32; H, 9.48.

cis-**3-Methyl-4-ethyl-γ-butyrolactone** (*cis*-**4d**) had bp 102–105° (11.5 mm); $n^{25}D$ 1.4375; ir (CCl_4) 1780 cm^{-1}; nmr (CCl_4) τ 8.96 (t, 3), 8.86 (d, 3), 6.13 (m, 1), 7.3–8.6 (m, 3); mass spectrum M^+ 128. *Anal.* Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.31; H, 9.58.

trans-**3-Methyl-4-ethyl-γ-butyrolactone** (*trans*-**4d**) had bp 102–105° (11.5 mm); $n^{25}D$ 1.4403; ir (CCl_4) 1775 cm^{-1}; nmr (CCl_4) τ 8.97 (t, 3), 9.00 (d, 3), 5.8 (m, 1), 7.3–8.7 (m, 3). *Anal.* Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.35; H, 9.52.

trans- **and** *cis*-**3,4-Dimethyl-4-ethyl-γ-butyrolactone** (**4e**) had bp 110–112° (15 mm); $n^{25}D$ 1.4435; ir (CCl_4) 1760–1780 cm^{-1} (broad); nmr (CCl_4) τ 8.65 [s, 3, $-OC(CH_3)$ of cis isomer], 8.78 [s, 3, $-OC(CH_3)$ of trans isomer], 8.99 (t, 3), 8.91 (d, 3), 7.66 (m, 2), 8.45 (q, 2), 7.3–8.1 (m, 1). *Anal.* Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.40; H, 9.99.

3-Methyl-4,4-diethyl-γ-butyrolactone (**4f**) had bp 80–84° (2 mm); $n^{20}D$ 1.4512; ir (CCl_4) 1770 cm^{-1}; mass spectrum M^+ 156. *Anal.* Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.92; H, 10.41.

trans- **and** *cis*-**3-Methyl-4-phenyl-γ-butyrolactone** (**4g**) had bp 128–130° (2.5 mm); $n^{25}D$ 1.5290; ir (CCl_4) 1788 cm^{-1}; nmr (CCl_4) τ 9.35 [d, 3, J = 7 Hz, $-CH(CH_3)$ of cis isomer], 8.85 [d, 3, J = 6 Hz, $-CH(CH_3)$ of trans isomer], 7.58 (m, 2), 7.1–8.2 (m, 1), 5.17 [d, 1, J = 8 Hz, $-CH(C_6H_5)O$ of trans isomer], 6.51 [d, 1, J = 6 Hz, $-CH(C_6H_5)O$ of cis isomer], 2.8 (s, 5); mass spectrum M^+ 176. *Anal.* Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 75.12; H, 6.86.

3-Methyl-γ-butyrolactone (**4a**).—The infrared spectrum of the condensed crude product revealed $\nu_{C=O}$ of γ-butyrolactone at 1780 cm^{-1}, although it could not be isolated because the quantity was so small [lit.[10] 1780 cm^{-1} ($\nu_{C=O}$ of **4a**)].

Diethyl 2-ethyl-3-methyl glutarate (**5**) had bp 105–107° (2 mm); $n^{25}D$ 1.4302; ir (CCl_4) 1735 cm^{-1}; nmr (CCl_4) τ 8.75 (t, 6), 9.07 (t, 3), 9.07 (d, 3), 5.93 (q, 4), 7.9 (m, 6); mass spectrum M^+ 230. *Anal.* Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.83; H, 9.53.

Diethyl 3,4-dimethyladipate (**6**) had bp 103–105° (2 mm), $n^{25}D$ 1.4353 [lit.[11] bp 103° (1.5 mm), $n^{25}D$ 1.4324]. *Anal.* Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.88; H, 9.47.

Registry No.—**1a**, 10544-63-5; *cis*-**4b**, 10150-95-5; *trans*-**4b**, 10150-96-6; **4c**, 2981-96-6; *cis*-**4d**, 34405-50-0; *trans*-**4d**, 34405-51-1; *cis*-**4e**, 34405-52-2; *trans*-**4e**, 34405-53-3; **4f**, 34405-54-4; *cis*-**4g**, 26620-41-7; *trans*-**4g**, 26704-17-6; **5**, 34405-57-7; **6**, 10348-54-6; **7**, 6776-19-8; **8**, 1617-18-1.

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Reductive Synthesis of α,α-Dimethylphenethylamine

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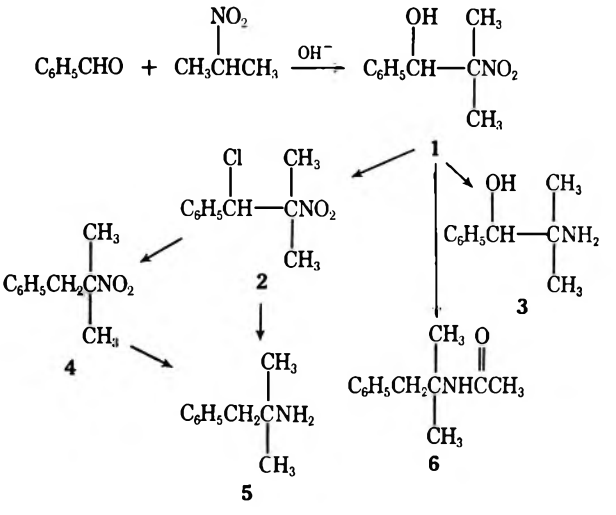
The pharmacological properties of the derivatives of α,α-dimethylphenethylamine (phenthermine) (**5**) have created considerable interest in the large-scale preparation of these compounds. The usual synthesis involves a Ritter reaction[1,2] between hydrogen cyanide and α,α-dimethylphenethyl alcohol or β,β-dimethylstyrene, to form the *N*-formyl derivative of **5**, and the hydrolysis of this intermediate. This reaction sequence is admirably suited for small-scale work, but, due to the hazards inherent in the use of hydrogen cyanide and in carrying out the Grignard reactions which lead to the alcohol or the styrene, it is not ideal for large-scale preparations. In view of these objections, a synthesis on the basis of a catalytic reduction, similar to those used for the derivatives of the less substituted phenethylamine[3] and α-methylphenethylamine (amphetamine),[4] would appear to be desirable.

The basic starting material for our work was α-(1-methyl-1-nitroethyl)benzyl alcohol (**1**), which can be prepared easily by the condensation of 2-nitropropane and benzaldehyde.[5] Palladium was used in all cases as hydrogenation catalyst, due to its well documented inactivity toward aromatic rings and its high effectiveness for the hydrogenolysis of benzyl groups and the reduction of aliphatic nitro groups.[6a] The variation of other reaction parameters resulted in rather selective reductions (Scheme I), which prompts us to report these in the present communication.

SCHEME I



The hydrogenation of the nitro alcohol **1** in ethanolic acetic acid over 10% palladium on charcoal yielded only the amino alcohol **3**,[7] as had already been reported by Zenitz, *et al.*[5] This is not an abnormal result, since the stabilization of a benzylic alcohol by a vicinal amino group is a well-known fact,[6b] which had already led Rosenmund and Kung[4] to the development of the tech-

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(4) K. W. Rosenmund and E. Kung, *Ber.*, **75**, 1850 (1942).
(5) B. L. Zenitz, E. B. Macks, and M. L. Moore, *J. Amer. Chem. Soc.*, **70**, 955 (1948).
(6) (a) P. N. Rylander, "Catalytic Hydrogenation Over Platinum Metals," Academic Press, New York, N. Y., 1967, p 320; (b) 152.
(7) The nature of all the products, except **4**,[9] can be deduced unequivocally from the elemental analysis data and the nmr and ir spectra given in the Experimental Section.

nique by which nitro alcohols are reduced to amphetamines in a mixture of acetic and sulfuric acid. However, even these conditions were not satisfactory for the reduction of **1**, since up to 50° only 3 of the required 4 equiv of hydrogen were absorbed. Only at 75° was the last equivalent of hydrogen taken up, but at that temperature the product had undergone a secondary reaction, resulting in the formation of the *N*-acetyl derivative **6** of the expected amine **5**.

The lack of success in the direct reduction of **1** to **5** led us to attempt the reduction of the chloro nitro compound **2** which, aside from being prepared easily and quantitatively from **1**, should also have been much more reactive toward benzylic hydrogenolysis. The attempt to carry out the published reduction of **2** over palladium on calcium carbonate[8] failed to show any uptake of hydrogen. On the other hand, hydrogenation took place in ethanolic acetic acid over 10% palladium on charcoal, although the reaction stopped, after the hydrogenolysis of the benzylic chlorine had taken place, yielding the nitro compound **4**.[9] The cause for this stopping of the reaction was apparently a poisoning of the catalyst by the hydrogen chloride which had been generated, since we had also been unsuccessful in our attempts to reduce the nitro group of **1** in ethanolic acetic acid and over 10% palladium on charcoal, when 1 equiv of hydrogen chloride had been added to the reaction mixture. In agreement with this poisoning hypothesis, **4** was reduced to **5** when fresh catalyst was used, and **2** was reduced directly to **5** when at least 1 equiv of sodium acetate was present in the reaction mixture, *e.g.*, when the hydrogen chloride was instantaneously inactivated by formation of its sodium salt.

Experimental Section

Melting points were determined in capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 21 infrared spectrophotometer from methylene chloride solutions. Nmr spectra were recorded on a Varian Associates A-60 spectrometer with TMS as internal standard.

α-(1-Methyl-1-nitroethyl)benzyl Alcohol (1).—To a solution of 16.8 g (0.72 g-atom) of sodium in 1.3 l. of methanol was added 340.8 g (3.83 mol) of 2-nitropropane and 12.8 g (1.20 mol) of benzaldehyde, and the mixture was stirred for 24 hr at room temperature. On acidification with 720 ml of 1 *N* sulfuric acid the mixture was evaporated *in vacuo*, and the residue was taken up in 120 ml of water and extracted three times with 100 ml of ether. The combined ether extracts were washed with 10% aqueous sodium chloride, dried with anhydrous sodium sulfate, and evaporated *in vacuo*, and the residue was recrystallized in cyclohexane to yield 115 g (0.59 mol, 49%) of **1**: mp 67–68° (lit.[5] mp 64–66°); ir 1550 and 1350 cm^{-1} (NO_2); nmr ($CDCl_3$) 83.5 (s) and 91.5 (s) (CH_3), 313.0 (s, CH), 167.0 (s, OH), 438 cps (s, C_6H_5).

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.65; H, 6.88; N, 7.06.

α-(1-Methyl-1-aminoethyl)benzyl Alcohol (3).—A mixture of 19.6 g (0.1 mol) of **1**, 250 ml of ethanol, 48 ml of glacial acetic acid, and 4 g of 10% palladium on charcoal[11] (50% water wet) was hydrogenated at 50° and 50 psi pressure until the hydrogen uptake ceased, resulting in the absorption of *ca.* 0.3 g-atom of hydrogen in 3 hr. After filtration, the solvent was distilled *in vacuo*, and the residue was taken up in 130 ml of 25% aqueous sodium hydroxide and extracted repeatedly with a total of 2.8 l. of ether. The ether solution was dried with anhydrous sodium sulfate and evaporated *in vacuo*, and the residue was recrystallized in ethyl acetate to yield 11.9 g (0.072 mol, 72%) of **3**: mp 96° (lit.[5] mp 99–101°); nmr ($CDCl_3$) 55.0 (s) and 65.5 (s) (CH_3), 258.5 (s, CH_3), 141.0 (OH and NH_2), 436.0 cps (s, C_6H_5).

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.64; H, 9.13; N, 8.46. Found: C 72.43; H, 9.40; N, 8.35.

***N*-(α,α-Dimethylphenethyl)acetamide (6).**—A mixture of 9.8 g (0.05 mol) of **1**, 50 ml of glacial acetic acid, 3.4 ml of 95% sulfuric acid, and 2.0 g of palladium black catalyst[11] was hydrogenated at 50° and 50 psi until the hydrogen uptake ceased, resulting in the absorption of *ca.* 0.15 g-atom of hydrogen in 5.5 hr (no further absorption took place in the next 15 hr). On raising the temperature to 75° another *ca.* 0.05 g-atom of hydrogen was absorbed in 9 hr. After filtration, 5 g of sodium acetate was added to the solution, the acetic acid was distilled *in vacuo*, and the residue was taken up in 100 ml of aqueous 25% sodium hydroxide and extracted twice with 100 ml of ether. Drying the combined extracts with anhydrous sodium sulfate and distillation of the solvent *in vacuo* yielded 3.8 g (0.02 mol, 40%) of **6**: mp 89–90° (lit.[12] mp 91.5–92.5°); nmr ($CDCl_3$) 78.0 (s, CH_3), 111.5 (s, CH_3CO), 318 (NH), 182.0 (s, CH_2), 431.3 cps (C_6H_5).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.40; H, 8.96; N, 7.32. Found: C, 75.77; H, 9.11; N, 7.04.

α-(1-Methyl-1-nitroethyl)benzyl Chloride (2).—A mixture of 20 g (0.1 mol) of **1** and 100 g (0.84 mol) of thionyl chloride was boiled for 2 hr under reflux and evaporated *in vacuo*. The residue was taken up in 50 ml of methylene chloride, and the solution was washed with 75 ml of water, twice with 50 ml of 5% aqueous sodium bicarbonate (to pH 8), and 50 ml of water, dried with anhydrous sodium sulfate, and evaporated *in vacuo* to yield 21.2 g (0.1 mol, 100%) of **2**, which could be crystallized from isopropyl alcohol: mp 38–39°; ir 1549 and 1349 cm^{-1} (NO_2); nmr ($CDCl_3$) 88.0 (s) and 103.5 (s) (CH_3), 333 (s, CH), 440 cps (s, C_6H_5).

Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.17; H, 5.66; N, 6.56. Found: C, 55.98; H, 5.70; N, 6.59.

(2-Methyl-2-nitropropyl)benzene (4).—A mixture of 10.7 g (0.05 mol) of **2**, 125 ml of ethanol, 24 ml of glacial acetic acid, and 2.0 g of 10% palladium on charcoal (50% water wet)[11] was hydrogenated at 40–50° and 50 psi until the hydrogen uptake ceased, resulting in the absorption of *ca.* 0.1 g-atom of hydrogen in *ca.* 1 hr. After filtration, the solvent was distilled *in vacuo*, the residue was taken up in 20 ml of water and extracted twice with 100 ml ether, and the combined ether extracts were washed with aqueous sodium carbonate and with water, dried with anhydrous sodium sulfate, and evaporated *in vacuo* to yield 5.5 g (0.029 mol, 58%) of **4** as an oil: ir 1540 and 1350 cm^{-1} (NO_2); no band above 3100 cm^{-1}; nmr ($CDCl_3$) 93 (s, CH_3), 190 (s, CH_2), 432 cps (C_6H_5).

α,α-Dimethylphenethylamine (5). A.—A mixture of 5.0 g (0.027 mol) of **4**, 63 ml of ethanol, 12 ml of glacial acetic acid, and 1.0 g of 10% palladium on charcoal (50% water wet)[11] was hydrogenated at 40° and 50 psi until the hydrogen uptake ceased, resulting in the absorption of *ca.* 0.085 g-atom of hydrogen in *ca.* 3 hr. After filtration, the solvent was distilled *in vacuo*, and the residue was taken up in 30 ml of 25% aqueous sodium hydroxide and extracted three times with 300 ml of ether. The combined extracts were dried with anhydrous sodium sulfate and evaporated *in vacuo* to yield 4.1 g (0.027 mol, 100%) of **5** as an oil: hydrochloride mp 200° (lit.[8] mp 195–196°); ir identical with that of an authentic sample (Aldrich); nmr ($CDCl_3$) 66.0 (s, CH_3), 157.5 (s, CH_2), 75 (NH_2), 432 cps (s, C_6H_5).

Anal. Calcd for $C_{10}H_{16}ClN$ (hydrochloride): C, 64.60; H, 8.14; N, 7.56. Found: C, 63.58; H, 8.87; N, 7.27.

B.—A mixture of 10.7 g (0.05 mol) of **2**, 125 ml of ethanol, 24 ml of glacial acetic acid, 4.6 g (0.055 mol) of sodium acetate, and 2.0 g of 10% palladium on charcoal (50% water wet)[11] was hydrogenated at 54° and 50 psi until the hydrogen uptake ceased, resulting in the absorption of *ca.* 0.2 mol of hydrogen (90% of this uptake in 11 hr, work-up was started after 3 days under hydrogen). With the same work-up just described, the yield was 2.9 g (0.02 mol, 39%) of **5**.

Registry No.—**1**, 33687-74-0; **2**, 34405-41-9; **3**,

(8) R. S. Shelton and M. G. Van Campen, U. S. Patent 2,408,345 (1942).

(9) Compound **4** was identified by nmr (a two-proton CH_2 signal and a single signal for the two enantiotopic methyl groups) and ir (typical NO_2 bands at 1540 and 1350 cm^{-1} [10] and no bands in the NH stretching region).

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 298.

(11) Engelhard Industries, Inc., Newark, N. J.

(12) K-H. Boltze and H. Mühlenbein, German Patent 1,144,713 (1960).

34405-42-0; **4**, 34405-43-1; **5**, 122-09-8; **5** HCl, 1197-21-3; **6**, 5531-33-9.

Acknowledgment.—We wish to acknowledge the support of Dr. J. B. Ziegler and helpful discussions with Mr. L. Dorfman, whose staff we thank for microanalyses and spectra.

The Conformation of 1,4-Dihydro-1-naphthoic Acid. II. The Nuclear Magnetic Resonance Spectrum of the Heptadeuterio Analog

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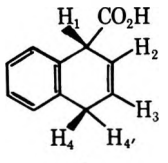
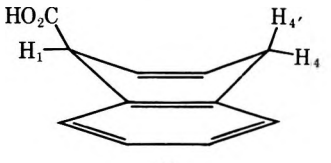
Received October 19, 1971

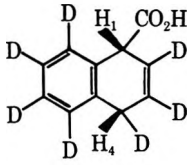
We previously reported[1] that the pmr spectrum of 1,4-dihydro-1-naphthoic acid (**1**) argued for a puckered conformation of the dihydro ring with the carboxylate group in the pseudoaxial position (see **2**) and that all nmr parameters of **1** could be determined from this study except the homoallylic coupling constants J_{14} and $J_{14'}$. We now wish to report the determination of these homoallylic parameters from the pmr spectrum of the heptadeuterio analog **3** and to present a more complete analysis of the conformation of **1**.



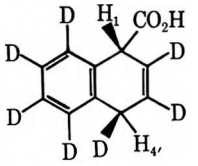
1



2



3a (cis)



3b (trans)

The heptadeuterio compound **3** was synthesized in a three-step sequence from perdeuterionaphthalene (see Experimental Section). The deuterium-decoupled pmr spectrum of **3** demonstrated an approximate 50:50 mixture of the *cis*- and *trans*-dihydro epimers (**3a** and **3b**) from the approximately equal areas corresponding to H_4 and $H_{4'}$. The H_4 and $H_{4'}$ signals were split into doublets, directly giving $J_{14} = J_{cis} = 3.84$ Hz and $J_{14'} = J_{trans} = 4.36$ Hz.[2] Since for the proposed conformation of **1** it is to be expected[3] that $J_{14} > J_{14'}$ these newly determined parameters are consistent with our previous contention that the carboxylate group was pseudoaxial.[1]

This completion of the determination of the pmr parameters for **1** allows a fuller analysis of the conformation of **1**. The similar values of J_{14} and $J_{14'}$ strongly suggest the dihydro ring is nearly flat.[4] Furthermore, a closer inspection of the previously determined parameters[1] of **1** also indicates the dihydro ring is not strongly puckered. First, if the dihydro ring of **1** were a true boat, the dihedral angle involving H_3 and $H_{4'}$ would be near 90° and $J_{34'}$ should be much less than the observed value of 2.4± Hz.[6] Second, the allylic coupling constants allow the calculation[5] that the dihedral angle involving H_2 and H_4 is much larger than 0°.[7] Third, the absolute value of $J_{44'}$[1] is suspiciously large for a highly puckered system,[8] and is much more consistent with a nearly planar ring. Thus, it appears that the conformation of **1** is a "flattened boat" in which the dihydro ring is only slightly puckered and that the pmr data for **1** lead to conclusions consistent with work for other 1,4-cyclohexadienes, in which it has been proposed that this system is planar or only slightly puckered.[9]

Experimental Section

Nmr spectra were recorded on a JEOL PS-100 spectrometer, using tetramethylsilane as the internal standard and deuteriochloroform as the solvent. Deuterium-decoupling was done with a JEOL deuterium radiofrequency oscillator JNM-RH-D, in conjunction with a JEOL heteronuclear decoupler JNM-SD-HC. Melting points were determined by a Thomas-Hoover melting point apparatus. All deuterated compounds were analyzed by pmr and were found to have a minimum isotopic purity of 98%.

Naphthalene-d_8 (minimum isotopic purity of 98%) was purchased from Diaprep, Inc., Atlanta, Ga.

1-Bromonaphthalene-d_7 was synthesized from naphthalene-d_8 in the fully developed bromination procedure[10] to give a 62% yield (9.78 g), bp 95–112° (0.5 mm) [lit.[10] bp 132–135° (12 mm), 1-bromonaphthalene].

1-Naphthoic acid-d_7 was synthesized from the bromo precursor by the usual Grignard procedure[11] to give an 88% yield (7.37 g), mp (H_2O) 155–159° (lit.[12] mp 159–160°, 1-naphthoic acid).

2,3,4,5,6,7,8-Heptadeuterio-1,4-dihydro-1-naphthoic acid (**3**) was prepared by the Birch reduction of the perdeuterionaphthoic precursor in the previous manner[1] to give a 73% yield (1.79 g), mp (hexane) 86–88° (lit.[13] mp 86°, 1).

Registry No.—**1**, 5111-73-9; **3a**, 34405-19-1; **3b**, 34405-20-4.

Acknowledgment.—Acknowledgment is made to the Robert A. Welch Foundation (Grant No. B-325) and to North Texas State University for a Faculty Research Grant for support of this work. In addition, appreciation is extended to Dr. S. Sternhell and M. Barfield for stimulating discussions and suggestions for analysis of the data.

(1) J. L. Marshall and T. K. Folsom, *J. Org. Chem.*, **36**, 2011 (1971).

(2) The methine signal (H_1) was also split into a doublet with J_{obsd} = 4.1 Hz, but resolution was not sufficient to distinguish the two J values.

(3) M. Karplus, *J. Chem. Phys.*, **33**, 1842 (1960); M. Barfield, *ibid.*, **48**, 4463 (1968).

(4) The Barfield INDO treatment[5] predicts that, for a flat dihydro ring, $J_{14'}/J_{14}$ = 1.12 and that this ratio increases with increased puckering to 3.3 for a true boat (S. Sternhell, private communication). The determined ratio is actually 1.14.

(5) M. Barfield, *J. Amer. Chem. Soc.*, **93**, 1066 (1971).

(6) K. L. Williamson and W. S. Johnson, *ibid.*, **83**, 4623 (1961); M. Karplus, *J. Chem. Phys.* **30**, 11 (1959); S. Sternhell, *Quart. Rev., Chem. Soc.*, **23**, 236 (1969); A. A. Bothner-By, S. Castellano, S. J. Ebersole, and H. Gunther, *J. Amer. Chem. Soc.*, **88**, 2466 (1966).

(7) It can be predicted[5] from the pmr data[1] of 1,4-dihydro-1-naphthoic acid that the dihedral angle involving H_2 and H_4 is ~52° and that involving H_2 and H_4 is ~68°.

(8) M. Barfield and D. M. Grant, *J. Amer. Chem. Soc.*, **85**, 1899 (1963).

(9) H. Oberhammer and S. H. Bauer, *ibid*, **91**, 10 (1969); M. J. Bennett, J. T. Purdham, S. Takada, and S. Masamune, *ibid.*, **93**, 4063 (1971); R. J. Jandacek and S. H. Simonsen, *ibid*, **91**, 6663 (1969).

(10) H. T. Clarke and M. R. Brethen, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1932, p 121.

(11) J. L. Marshall, K. C. Erickson, and T. K. Folsom, *J. Org. Chem.*, **35**, 2038 (1970).

(12) A. A. Morton, J. B. Davidson, T. R. P. Gibb, Jr., E. L. Little, E. F. Clarke, and A. G. Green, *J. Amer. Chem. Soc.*, **64**, 2250 (1942).

(13) K. Von Auwers and K. Moller, *J. Prakt. Chem.*, **109**, 144 (1925).

Novel Addition of an Alcohol to an Enol Ether. Isomerization of 1,4,5,6-Tetrahydro-3-methoxybenzyl Alcohol to 1-Methoxy-7-oxabicyclo[3.2.1]octane

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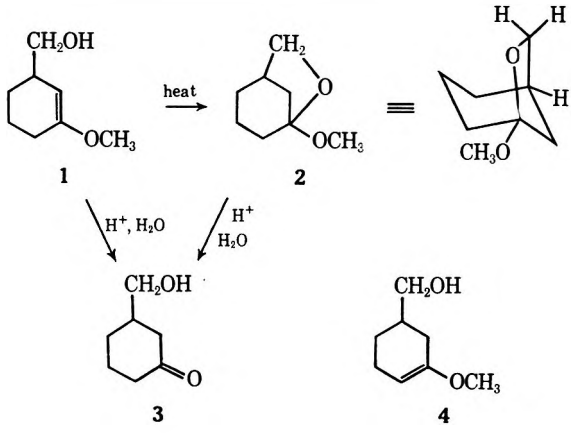
The acid[1-3] or base[1,2] catalyzed addition of alcohols to enol ethers is well known. The closely related formation of α-halo ketals by the reaction of enol ethers with a source of positive halogen in alcohol solvent apparently involves initial addition of the positive halogen followed by the alcohol.[1] We have encountered a facile, and possibly uncatalyzed, internal addition of an alcohol group to an enol ether forming the isomeric ketal.

When 1,4,5,6-tetrahydro-3-methoxybenzyl alcohol (**1**) was injected into a 5-ft 10% Carbowax 20M on Aeropak-30 glc column (150°) or a 10-ft Reoplex 400 on Chromosorb W column (170°), the eluent was previously unreported 1-methoxy-7-oxabicylo[3.2.1]octane (**2**). Experiments in lowering the column temperature of the Carbowax 20M column indicate that the isomerization occurs above 100°. Vacuum distillation of **1** through a spinning band column with condensate vapor reaching a temperature of 74–82° did not cause isomerization. However, an attempted simple distillation of **1** with the temperature of the condensing vapor reaching 150–300° also caused conversion of **1** to **2**.



While the reaction appears to be uncatalyzed, we have not rigorously excluded the possibility that trace amounts of acids may be present in the glc columns or introduced during work-up and may catalyze the reaction.

That the hydroxymethyl group in the pseudoaxial position has its oxygen in the proximity of the methoxy-substituted vinyl carbon undoubtedly contributes to the ease of this reaction. Other reactions leading to similar bicyclic ring systems have been reported, such as the acid-catalyzed formation of 1,6-anhydrohexoses from aldohexoses,[4] the base-catalyzed conversion of veracevine to cevine *via* cevaginin,[5] and the methoxide ion catalyzed formation of methyl 3,6-anhydro-β-D-glucopyranose from methyl 3-*O*-tosyl-β-D-glucopyranoside.[6] However, such ring systems do have some strain.[7]

1 was prepared by one-step reduction of *m*-methoxybenzamide with 8 or more equiv of sodium in liquid ammonia plus ethanol as proton source. The product was assigned structure **1** rather than the alternate possibility, 1,2,5,6-tetrahydro-3-methoxybenzyl alcohol (**4**), on the basis that the observed nmr signal for the single vinyl hydrogen (δ 4.53, $CDCl_3$) was split into a doublet rather than a triplet and on the basis of the expected course of the reduction in which the *m*-methoxybenzamide ring is probably reduced first to the 1,4,5,6-tetrahydro-3-methoxybenzamide (analogous to the reduction of *m*-methoxybenzoic acid[8]) followed by reduction of the amide group to the alcohol *via* the aldehyde.[9,10]

2 showed absence of OH and C=C absorption in the ir as well as absence of vinyl hydrogen in the nmr that **1** had exhibited. Thus **2** was assigned the structure shown on basis of ir and nmr spectra and the fact that 3-hydroxymethylcyclohexanone (**3**) formed upon acid hydrolysis. **3** also formed by acid hydrolysis of **1**. The mixture melting point of 2,4-dinitrophenylhydrazone samples of **3** from each gave no depression.

Experimental Section[11]

1,4,5,6-Tetrahydro-3-methoxybenzyl Alcohol (1).—To a stirred, refluxing (−33°) mixture of 1400 ml of NH_3, 270 ml of absolute ethanol, and 40.0 g (0.264 mol) of *m*-methoxybenzamide was added (5–10 min) 48.6 g (2.11 g-atoms) of sodium in small pieces. After the deep blue color disappeared, 200 g of NH_4Cl was added and the NH_3 was allowed to evaporate. The solid residue was dissolved in water and the organic material was removed by CH_2Cl_2 extractions, which were dried ($MgSO_4$). Evaporation of solvent yielded 31.4 g of liquid, which was distilled through an Annular Teflon spinning band column (0.5 mm) yielding fractions totaling 14.2 g (0.10 mol) (38%) of **1**, bp 74–82° (corrected) [lit.[12] bp 102–104° (2.75 mm)], $n^{25}D$ 1.4883–1.4890, and polymeric material: ir (neat) 2.95 (–OH), 5.99 μ (enol C=C); nmr (DMSO-d_6) δ 1.05–2.6 (m, 7, ring CH_2 and CH), 3.23 (t, 2, J = 5–6 Hz, CH_2OH), 3.42 (s, 3, OCH_3), 4.40 (t, 1, J = 5–6 Hz, primary –OH), 4.58 (d, J = 2–3 Hz, CH=C); nmr ($CDCl_3$) δ 2.55 (s, broad, 1, –OH), 3.45 (d, 2, J = 5–6 Hz, CH_2OH, with downfield half of doublet coinciding with the $-OCH_3$ absorption at δ 3.59, s), 4.53 (d, 1, CH=C).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.6; H, 9.92; O, 22.5. Found: C, 67.5; H, 9.72; O, 22.7.

1-Methoxy-7-oxabicyclo[3.2.1]octane (2).—Injection of 15 μl of **1** onto a 5-ft 10% Carbowax 20M on 80/100 mesh Aeropak-30 column (Aerograph Model A-90-P, column 150°, injector 205°,

(1) S. Patai, "The Chemistry of the Ether Linkage," Interscience, New York, N. Y., 1967, p 322.

(2) M. F. Shostakowskii, A. V. Bogdanova, and G. I. Plotnikova, *Russ. Chem. Rev.*, **33**, 66 (1964).

(3) M. L. Wolfrom, S. S. Bhattacharjee, and R. M. De Lederkremer, *Carbohyd. Res.*, **11**, 148 (1969).

(4) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 415–417.

(5) D. H. R. Barton, O. Jeger, V. Prelog, and R. B. Woodward, *Experientia*, **10**, 81 (1954).

(6) P. de Mayo, "Molecular Rearrangements," Interscience, New York, N. Y., 1964, p 758.

(7) Reference 4, pp 381, 405.

(8) M. E. Keuhne and B. F. Lambert, *J. Amer. Chem. Soc.*, **81**, 4278 (1959).

(9) A. J. Birch, J. Cymerman-Craig, and M. Slaytor, *J. Aust. Chem. Soc.*, **8**, 512 (1955).

(10) A. J. Birch, *J. Roy. Inst. Chem.*, **81**, 100 (1957).

(11) Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Boiling points are uncorrected unless otherwise stated. Analyses were by Bernhardt Mikroanalytisches Laboratorium, Elbach uber Engelskirken, West Germany. Ir spectra were obtained on a Perkin-Elmer 137B. Nmr spectra were obtained with a Varian A-60 with tetramethylsilane as internal standard. The ammonia for reduction solvent was distilled from its metal cylinder and condensed in the reduction flask but not dried before use. The sodium was freshly cut free of oxide and hydroxide just before use.

(12) O. L. Chapman and P. Fitton, *J. Amer. Chem. Soc.*, **85**, 41 (1963).

detector 200°, collector 190°, helium at 40 psi, and flow rate of 200 ml/min) yielded a small unidentified peak (2% of eluate) at 15 sec and a peak at 6 min which was 2. Repeated injections and collections yielded sufficient material for characterization (although only about 50% of injected material was accounted for): n^{25}D 1.4641; ir (neat) no absorption at 6.0 (no enol C=C), no absorption at 2.95 (no -OH), 9.18 μ; nmr ($CDCl_3$) δ 4.02 (double doublet, 1, A of ABX pattern, J_{AB} = 7–8 Hz, cis J_{AX} = 4 Hz, $-OCH_AH_BCH_X<$), 3.78 (d, 1, B of ABX pattern, J_{AB} = 7–8 Hz, trans J_{BX} = 0), 3.32 (s, 3, $-OCH_3$), 1.2–2.6 (m, 9, cyclohexane ring CH_2 and CH).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.6; H, 9.92; O, 22.5. Found: C, 67.4; H, 9.76; O, 22.7.

The conversion of **1** into **2** was also observed on a 10-ft Reoplex 400 on Chromosorb W column (injector 200°, column 170°, detector 250°). Distillate from an unsuccessful simple distillation of crude reduction product in which vapor temperature reached 150–300° was combined with additional crude reduction product and separated on a spinning band column, yielding pure samples of **2**, bp 40° (0.3 mm), and impure **1**, bp 78–86° (0.3 mm), and polymer.

Lowering the column temperature of the Carbowax 30M column below 100° resulted in **1** not being converted into **2**.

3-Hydroxymethylcyclohexanone (3).—Hydrolysis of 0.68 g (0.0048 mol) of **1** with 25% H_2SO_4 yielded 0.47 g (0.0037 mol) of **3** (77% yield): n^{25}D 1.4806; nmr ($CDCl_3$) showed absence of both vinyl hydrogen and $-OCH_3$, δ 3.6 ("filled in." d, 2, J = 4 Hz, $-CH_2OH$), 2.7–0.9 (m, 10, ring and -OH hydrogens); ir (neat) 2.88 (-OH), 5.84 μ (C=O).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.6; H, 9.44; O, 25.0. Found: C, 65.2; H, 9.62; O, 24.8.

3 was converted to its 2,4-dinitrophenylhydrazone,[13] mp 120–122° (inserted at 26°), 119–120° (inserted at 70°) (other derivatives[14]).

Anal. Calcd for $C_{13}H_{16}N_4O_5$: C, 50.6; H, 5.23; N, 18.18; O, 26.0. Found: C, 50.5; H, 5.53; N, 17.96; O, 26.1.

Sample of **3** made from acid hydrolysis of **2** had the same ir and nmr spectra and yielded 2,4-dinitrophenylhydrazone which gave no mixture melting point depression.

Registry No.—**1**, 34407-89-1; **2**, 34407-90-4; **3**, 32916-58-8; **3** DNP, 34407-91-5.

Acknowledgment.—The authors are indebted to the Research Corp. for a Frederick Gardner Cottrell grant in the preliminary stages of the investigation and to Dr. G. E. Pollard and the Shell Development Co., Modesto, Calif., for the nmr spectra.

(13) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1965, p 254.

(14) G. Stork and J. Ficine, *J. Amer. Chem. Soc.*, **83**, 4678 (1961).

The Alkaline Hydrolysis of Aryl α-Disulfones[1]

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In alkaline solution aryl α-disulfones **1** undergo rapid hydrolysis to $ArSO_3^-$ and $ArSO_2^-$ (eq 1). Several years ago Allen and Conway[2] reported some kinetic data on this reaction in ethanol whose accuracy was later called into serious question by Kice and Kasperek.[3] The latter authors measured the rate of hydrolysis, k_h, of several **1** in various Et_3N–Et_3NH^+ buffers in 60% glyme at constant ionic strength. They found that under such conditions k_h was given by eq 2, where the first term is due to eq 1 and the second to general base catalysis of the hydrolysis of **1** by Et_3N. Their results showed that k_{OH} was apparently much more dependent on aryl group substituents (ρ = +3.7) than reported by Allen and Conway[2] (ρ = +0.3). However, the lack of values of K_w and $K_a^{Et_3NH^+}$ for 60% glyme prevented Kice and Kasperek from determining the absolute magnitude of k_{OH} for any of their α-disulfones under their reaction conditions.

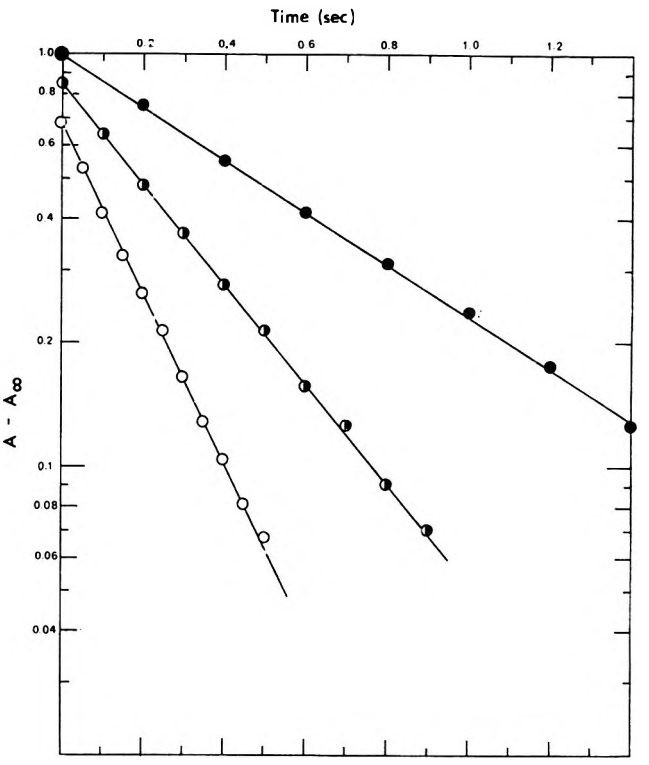
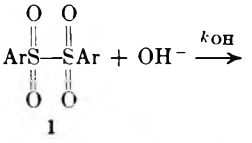


Figure 1.—Plot of log ($A - A_\infty$) *vs.* time for the alkaline hydrolysis aryl α-disulfones at 25°: ●, $PhSO_2SO_2Ph$, 3.7 × 10^{-5} *M*, $[OH]^-$, 0.02 *M*, 60% dioxane as solvent; ◑, $PhSO_2SO_2Ph$, 2.6 × 10^{-5} *M*, $[OH^-]$, 0.01 *M*, ethanol as solvent; ○, *p*-chlorophenyl α-disulfone, 1.6 × 10^{-5} *M*, $[OH^-]$, 0.01 *M*, 60% dioxane as solvent.



$$ArSO_2^- + ArSO_3H \xrightarrow[\text{fast}]{OH^-} ArSO_2^- + ArSO_3^- \quad (1)$$

$$k_h = k_{OH}\left[\frac{K_w}{K_a^{Et_3NH^+}}\right]\frac{(Et_3N)}{(Et_3NH^+)} + k_{Et_3N}(Et_3N) \quad (2)$$

In the present work, by using a stopped-flow spectrophotometer to follow the very rapid disappearance of **1**, we have been able to measure k_{OH} at 25° for several aryl α-disulfones directly in solutions 0.01 or 0.02 *M* in NaOH in either 60% dioxane (v/v) or ethanol as solvent. Figure 1 shows plots of the data for representative runs. One can see that under the conditions used, where hydroxide ion is present in huge stoichiometric excess over **1**, excellent first-order kinetics are obtained. Table I summarizes the kinetic data for the various runs. In it k_1 is the experimental first-order rate constant for a run as obtained from the slope of a plot such as shown in Figure 1. Hence $k_{OH} = k_1/(OH^-)$.

Several aspects of the results merit discussion. First,

(1) This research was supported by the National Science Foundation, Grant GP-25799.

(2) P. Allen, Jr., and P. J. Conway, *Can. J. Chem.*, **47**, 873 (1969).

(3) J. L. Kice and G. J. Kasperek, *J. Amer. Chem. Soc.*, **92**, 3393 (1970).

TABLE I
RATES OF ALKALINE HYDROLYSIS OF ARYL α-DISULFONES[a]

Solvent	$ArSO_2SO_2Ar$, Ar	Registry no.	$[ArSO_2SO_2Ar]_0$, M	$[OH^-]$, M	k_1, sec^{-1}	$k_{OH} = k_1/[OH^-]$, $M^{-1}\ sec^{-1}$
60% Dioxane	p-$CH_3C_6H_4$	10409-07-1	2.0×10^{-5}	0.010	0.17	17
	C_6H_5	10409-06-0	3.7×10^{-5}	0.010	0.75	75
				0.020	1.47	74
	p-ClC_6H_4	22040-25-1	1.6×10^{-5}	0.010	4.7	470
Ethanol[b]	p-$CH_3C_6H_4$		2.1×10^{-5}	0.010	0.76	76
	C_6H_5		2.6×10^{-5}	0.010	2.8	280

[a] All runs at 25.0°. [b] Actual solvent composition is 94% ethanol–4% dioxane–2% water; see Experimental Section.

it is obvious from the results in both 60% dioxane and ethanol that, contrary to the claim of Allen and Conway,[2] k_{OH} is very strongly dependent on the nature of the substituents in the aromatic rings of **1**. For the data in 60% dioxane a plot of log k_{OH} *vs.* σ is an excellent straight line with a slope, ρ, of +3.6, or essentially the same as that found by Kice and Kasperek[3] in 60% glyme. Clearly then the alkaline hydrolysis of aryl α-disulfones, in common with a number of other nucleophilic substitution reaction of **1**,[3,4] shows a large positive ρ value.

Second, comparison of the k_{OH} values for the *p*-tolyl and phenyl α-disulfones in ethanol in Table I with those reported by Allen and Conway[2] shows that in each case the true values are much larger than the ones they reported. Where Allen and Conway[2] list k_{OH} for phenyl α-disulfone in ethanol as 7.1 M^{-1} sec^{-1}, we find the actual value to be about 40 times larger than this, or 280 M^{-1} sec^{-1}. Similarly, the actual k_{OH} for the *p*-tolyl α-disulfone in ethanol, 76 M^{-1} sec^{-1}, is over ten times larger than their reported value of 6.5 M^{-1} sec^{-1}. The fact that the data in Table I are for 25° while theirs were obtained at 23° could hardly be responsible for any significant part of these differences, since the activation energy for the alkaline hydrolysis is almost certainly not very large. Thus the present results appear to confirm what Kice and Kasperek[3] had strongly suspected, namely, that the kinetic data of Allen and Conway[2] are almost certainly in error. Although one cannot be absolutely sure, we suspect that the explanation given in footnote 14 of ref 3 probably accounts for their low rates and apparent lack of dependence of rate on substituent.

The third point worth noting is what the k_{OH} values in Table I for 60% dioxane indicate regarding the reactivity of hydroxide ion as compared with the reactivity of various other nucleophiles toward **1** in this same solvent. From previous work[4] values of k_{Nu} are available for the reaction of a wide variety of nucleophiles with aryl α-disulfones in 60% dioxane at 21.3° (eq 3).

$$Nu^- + ArS(=O)_2SAr \xrightarrow{k_{Nu}} ArSNu(=O)_2 + ArSO_2^- \qquad (3)$$

Using this data[4] and that in Table I one calculates that OH^- is about 3×10^4 more reactive than acetate ion toward **1**. This compares with values for (k_{Nu}/k_{OAc}) of 330 for N_3^-, 59 for F^-, and 10 for NO_2^-.[4] From the various data one can also calculate that OH^- is only about five times more reactive toward **1** as a nucleophile than is a simple *n*-alkylamine like *n*-butylamine.

Kice and Kasperek[3] had previously attempted to make estimates of k_{OH} in 60% glyme by using their measured values of $k_{OH}(K_w/K_a^{Et_3NH^+})$ and what were thought to be reasonable estimates of K_w and $K_a^{Et_3NH^+}$. The values of k_{OH} actually found in 60% dioxane in the present work are uniformly smaller by about a factor of ten than their earlier estimates, indicating that their assumed values of K_w and $K_a^{Et_3NH^+}$ for 60% glyme were apparently considerably poorer ones than they had thought.

Rogne[5] has recently obtained data on the reactivity of a series of nucleophiles toward aryl sulfonyl chlorides (eq 4) in aqueous solution. He noted that a plot of log

$$Nu^- + ArSO_2Cl \xrightarrow{k_4} ArSO_2Nu + Cl^- \qquad (4)$$

k_4 *vs.* log k_{Nu} for eq 3 for those nucleophiles for which data were available for both systems was linear with a slope of about 0.7. Based on this and Rogne's measured value of k_4 for OH^-, one would calculate a value of k_{OH} for $PhSO_2SO_2Ph$ in 60% dioxane of about 50, which is reasonably close to the measured value of 75, particularly when one recalls that the actual value of k_{OH} at 21.3° would be somewhat lower than the values in Table I, which are for 25°.

Experimental Section

Preparation and Purification of Materials.—The preparation and purification of the α-disulfones and the method of purifying the dioxane used have already been described.[4] Absolute ethanol was subjected to careful fractional distillation before use.

Procedure for Kinetic Runs.—For the runs in 60% dioxane the sodium hydroxide solutions were prepared by taking either 1 or 2 ml of standard 1.000 *N* NaOH and diluting it to 50 ml with sufficient dioxane and water so that the final solution contained 60% dioxane (v/v). A stock solution of the α-disulfone in anhydrous dioxane was prepared by dissolving a carefully weighed amount of the disulfone in 25 ml of dioxane. Two milliliters of this stock solution were then pipetted into a 50-ml volumetric flask and made up to volume with sufficient dioxane and water so that the final solution contained 60% dioxane. This solution and the solution of NaOH in 60% dioxane were placed in the two separate reservoir syringes of a Durrum–Gibson stopped-flow spectrophotometer which was thermostatted at 25°, and the disappearance of **1** was followed by monitoring the change in optical density with time at an appropriate wavelength in the ultraviolet. The wavelengths used were 244 mμ for the phenyl compound, 258 mμ for the *p*-tolyl, and 263 mμ for the *p*-chlorophenyl α-disulfone.

For the runs in ethanol the sodium hydroxide solution was prepared by taking 1.00 ml of 1.000 *N* NaOH, adding 2 ml of anhydrous dioxane, and diluting to 50 ml with absolute ethanol. The solution of the α-disulfone was prepared by making a stock solution of **1** in anhydrous dioxane, pipetting 2.0 ml of this solution into a volumetric flask, adding some ethanol, then 1.0 ml of water, and finally diluting to 50 ml with ethanol. The procedure for following the kinetics was then the same as for the runs in 60% dioxane.

(4) J. L. Kice, G. J. Kasperek, and D. Patterson, *ibid.*, **91**, 5516 (1969).

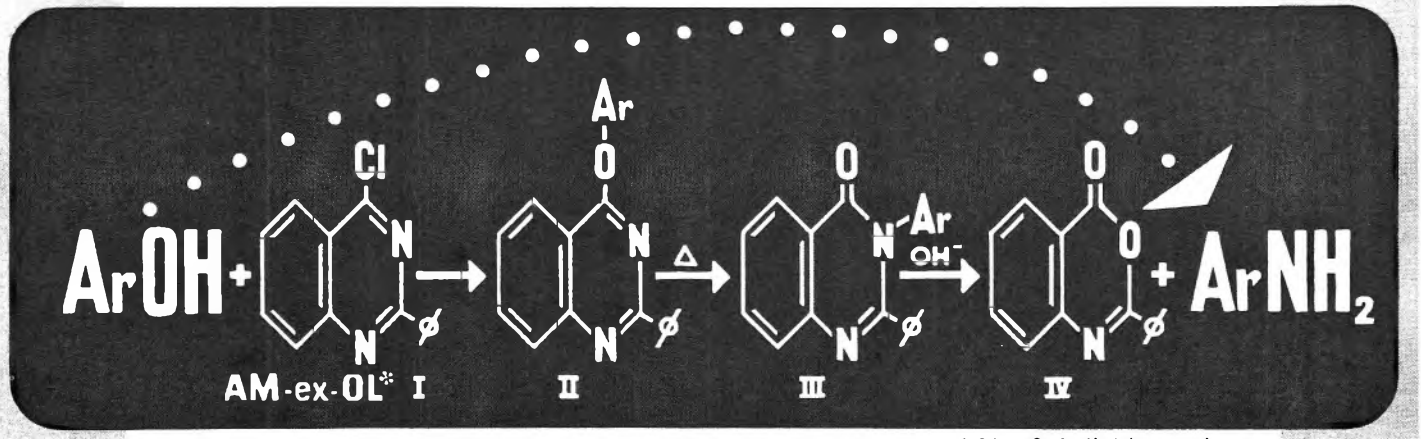
(5) O. Rogne, *J. Chem. Soc. B*, 1056 (1970).

What Every Chemist Has Often Wanted To Do -- But Couldn't:

CONVERT PHENOLS TO ANILINES

While anilines are usually easily converted to phenols via diazonium salts, the reverse has been very difficult.

Now, however, there is a quite general procedure[1] which involves reacting AM-ex-OL* (4-chloro-2-phenylquinazoline) I with the phenol to yield the 4-aryloxy-2-phenylquinazoline II, which rearranges neat or in mineral oil at 275-325° to the 3-aryl-2-phenyl-4(3H)-quinazolinone III which is easily hydrolyzed by alkali to the aniline and 2-phenyl-4H-3,1-benzoxazin-4-one IV.



Overall yields are generally good; e.g. aniline from phenol 71%, 2,4-dichloroaniline and 2,3,6-trimethylaniline from the corresponding phenols 64 and 70% respectively. Even two steroidal phenols have been converted[2] to the amines in 67 and 58% yields.

In a typical procedure, 10 g. of phenol was added to a suspension of 5 g. of sodium hydride dispersed in mineral oil in 35 ml. of diglyme. (Sodium hydride is of course not needed if the sodium phenoxide is available. Alternatively, II can be obtained in almost quantitative yield by reacting AM-ex-OL* with the phenol and anhydrous potassium carbonate in acetone.[3]) When hydrogen evolution ceased, 24 g. of Am-ex-OL* was added. The mixture was heated to 110° for 10 minutes, cooled and poured onto ice, to yield 29.8 g. of 4-phenoxy-2-phenylquinazoline II, m.p. 112-116°.

Heating this quinazoline under nitrogen at 325° for 130 minutes yielded 2, 3-diphenyl-4(3H)-quinazolinone III almost quantitatively. III need not be isolated. Thus, heating 16.3 g. of II in 30 ml. mineral oil under nitrogen for 4 hours at 325°, and then heating this mixture with a solution of 32 g. of KOH in 160 ml. ethylene glycol under nitrogen at 130° overnight, yielded on treatment with water, extraction with ether and treatment with HCl gas, 5.2 g. (76%) of aniline hydrochloride. The completion of the thermal rearrangement is best determined by IR or UV (II absorbs strongly at 259 mμ; III does not).

(1) a. R. A. Scherrer, Abstracts of Papers, 145th national meeting of the American Chemical Society, New York, N.Y., Sept. 1963, p. 33Q.
b. R. A. Scherrer and H. R. Beatty, J. Org. Chem., (vol. 37 no. 11, p. 1681, 1972) this issue.

(2) a. D. F. Morrow and M. E. Butler, J. Org. Chem. **29**, 1893 (1964).
b. D. F. Morrow and R. M. Hofer, J. Med. Chem., **9**, 249 (1966).

(3) R. B. Conrow and S. Bernstein, Steroids, **11**, 151 (1968).

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