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Ketenes. XIII. Reactions of Ketenes with Heterocumulenes[1a]

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Ketenes underwent cycloaddition reactions with several different heterocumulenes. Dialkylketenes and isocyanates gave malonimides, and diisocyanates gave bis(malonimides). Acyl isocyanates and ketenes generally underwent a 4 + 2 cycloaddition to give oxazinediones. Carbodiimides and ketenes gave azetidinones via a 2 + 2 cycloaddition. Carbon dioxide and carbon disulfide, when catalyzed by triphenylphosphine, gave 2 + 2 + 2 cycloaddition products containing 2 equiv of dialkylketenes. A ketenimine and a dialkylketene gave as the major component a 2 + 2 + 2 cycloaddition product involving two ketenimine molecules and one dialkylketene molecule.

Ketenes belong to a class of compounds known as heterocumulenes.[2] The reactions of ketenes with themselves to form dimers or trimers are well documented. In this paper we report our work on reactions of ketenes with other heterocumulenes.

Isocyanates.—Staudinger reported that diphenylketene reacted with phenyl isocyanate at 220° via a 1:1 cycloaddition to give the malonimide 1 in low

$$(C_6H_5)_2C{=}C{=}O \ + \ C_6H_5NCO \ \longrightarrow$$

1
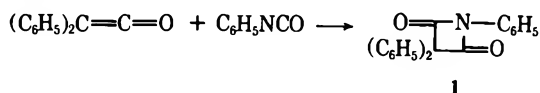
yield.[3] Similar reactions of diphenylketene with methyl and cyclohexyl isocyanates have been reported.[4] The adduct of pentamethyleneketene, generated *in situ* from the acid chloride, with phenyl isocyanate also has been reported.[5]

The reaction of monomeric dialkylketenes with isocyanates to give malonimides has not been reported. We found that, when butylethylketene was heated with phenyl isocyanate, 2-butyl-2-ethyl-*N*-phenylmalonimide (2b) was formed in 70% yield. Dimethylketene, in spite of its reactive nature, gave low yields of malonimides because the ketene dimerized rapidly. At 25°, dimethylketene and phenyl isocyanate afforded 2,2-dimethyl-*N*-phenylmalonimide (2a) in 10% yield; at 60°, the yield of 2a was 30%.

$$C_6H_5NCO \ + \ R_1R_2C{=}C{=}O \ \longrightarrow$$

2a, $R_1 = R_2 = CH_3$
b, $R_1 = C_2H_5$; $R_2 = C_4H_9$
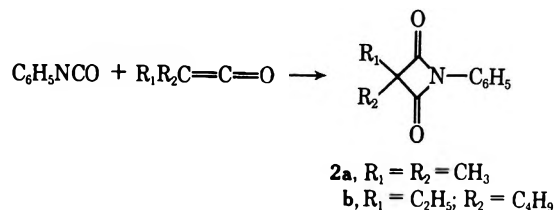
The only bis(malonimide) described in the literature was prepared by a ring-closure method.[4] We readily prepared several of these bifunctional compounds by heating diethylketene or butylethylketene with diisocyanates at 180°. The aromatic diisocyanates gave much better yields than the aliphatic analogs; with diethylketene, *p*-phenylene diisocyanate gave the bis(malonimide) 3a in 92% yield, but hexamethylene diiso-

$$OCN{-}R{-}NCO \ + \ R_1R_2C{=}C{=}O \ \longrightarrow$$

3a, $R_1 = p\text{-}C_6H_4$; $R_1 = R_2 = C_2H_5$
b, $R = (CH_2)_6$; $R_1 = R_2 = C_2H_5$
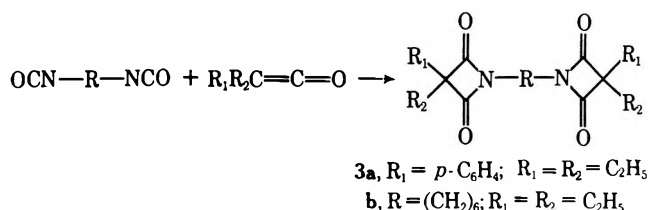
cyanate gave the bis(malonimide) 3b in 30% yield. The malonimides prepared in this work are listed in Table I.

Mundlos and Graf[6] observed that *p*-toluenesulfonyl isocyanate reacted with ketene at −10° in methylene chloride solution to give *N*-(*p*-tolylsulfonyl)malonimide (4a) (yield of crude 4a, 42%; purified, 12.5%) plus a large amount of polymeric material. We observed that, if the reaction was run in a dipolar aprotic solvent (such as acetonitrile) at 30–40°, the yield of crude 4a

(1) (a) Paper XII in this series: J. C. Martin, P. G. Gott, and H. U. Hostettler, *J. Org. Chem.*, **32**, 1654 (1967). (b) Ciba A.-G., 4000 Basel 7, Switzerland.

(2) H. Ulrich, "Cycloaddition Reactions of Heterocumulenes," Academic Press, New York, N. Y., 1967.

(3) H. Staudinger and R. Endle, *Justus Liebigs Ann. Chem.*, **401**, 263 (1913).

(4) A. Ebnöther, E. Jucker, E. Rissi, J. Rutschmann, E. Schreier, R. Steiner, R. Süss, and A. Vogel, *Helv. Chim. Acta*, **42**, 918 (1959).

(5) A. C. Poshkus and J. E. Herweh, *J. Org. Chem.*, **30**, 2466 (1965).

(6) E. Mundlos and R. Graf, *Justus Liebigs Ann. Chem.*, **677**, 108 (1964).

TABLE I

MALONIMIDES FROM KETENES AND ISOCYANATES[a]

R	R^1	R^2	Yield, %	Mp or bp (mm), °C	Registry no.
		Monomalonimides (n = 1)			
C_6H_5	CH_3	CH_3	30	36	
				71–74 $(0.01)^b$	
C_6H_5	C_2H_5	C_4H_9	70	86–88	29682-92-6
				100–105 $(0.05)^b$	
		Bis(malonimides) (n = 2)			
p-$(CH_2C_6H_4CH_2)$	C_2H_5	C_2H_5	75	130	29682-93-7
p-$(CH_2C_6H_4CH_2)$	C_2H_5	C_4H_9	50	110	29682-94-8
p-C_6H_4	C_2H_5	C_4H_9	78	75	29682-95-9
p-C_6H_4	C_2H_5	C_2H_5	92	130	
-$(CH_2)_6$-	C_2H_5	C_2H_5	20	81–82	29682-96-0
-$(CH_2)_6$-	C_2H_5	C_4H_9	10	68	29682-97-1
2,4-Tolyl	C_2H_5	C_2H_5	85	89–91	29682-98-2
2,4-Tolyl	C_2H_5	C_4H_9	80	210–220^b	29682-99-3
2,4-Tolyl	C_6H_5	C_6H_5	30	178–179	29683-00-9
p-$(C_6H_4CH_2C_6H_4)$	C_2H_5	C_2H_5	80	104–105	29683-01-0
p-$(C_6H_4CH_2C_6H_4)$	C_2H_5	C_4H_9	65	42	29683-02-1

[a] Satisfactory analytical data ($=0.3\%$ for C, H, and N) were reported for all compounds: Ed. [b] Boiling point.

was quantitative; the yield of purified 4a was 54%. Dimethylketene in this reaction gave 2,2-dimethyl-N-(p-tolylsulfonyl)malonimide (4b) in 94% yield.

4a, R = H
b, R = CH$_3$
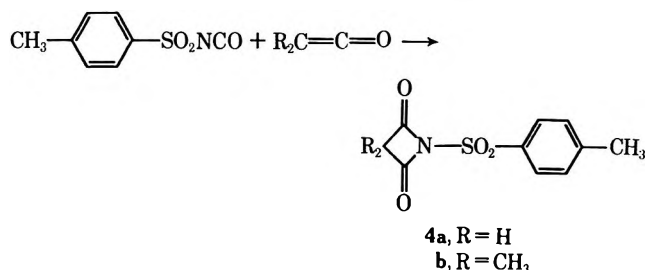
Acyl isocyanates and dimethylketene did not react to give the expected cycloaddition to a malonimide, but a product involving a 1,4 cycloaddition to the acyl isocyanate. Dimethylketene reacted with trichloroacetyl isocyanate to give 5,5-dimethyl-2-trichloromethyl-4H-1,3-oxazine-4,6(5H)-dione (5a) in 77% yield, and with benzoyl isocyanate to give 5,5-dimethyl-2-phenyl-4H-1,3-oxazine-4,6(5H)-dione (5b) in 25% yield. 5b was

5a, R = CCl$_3$
b, R = C$_6$H$_5$
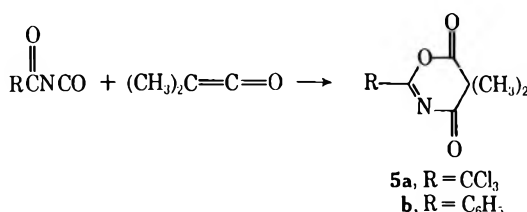
identical with the reaction product from benzamide and dimethylmalonyl chloride reported previously.[7]

Ketene reacted with benzoyl isocyanate to give the adduct 6, presumably formed *via* a 4 + 2 cycloaddition followed by enolization. In cold ether, 6 was formed

in 62% yield, but in benzene at 30–40° the acetylated product 7 (51%) was obtained. When preformed 6 was treated with ketene in benzene, 7 was formed.
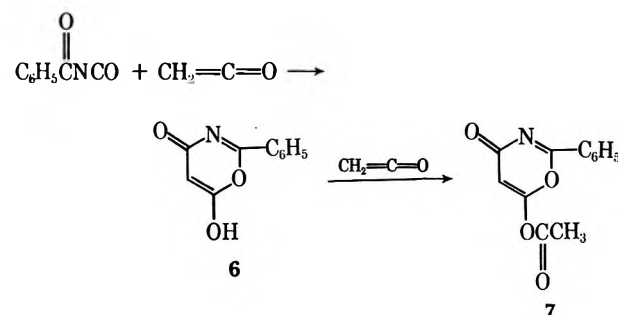
Ethanolysis of 6 gave 8 in 90% yield. The acidic hydrolysis of 6 gave 9 in 87% yield. 9 decarboxylated on warming to give 10 in 77% yield.
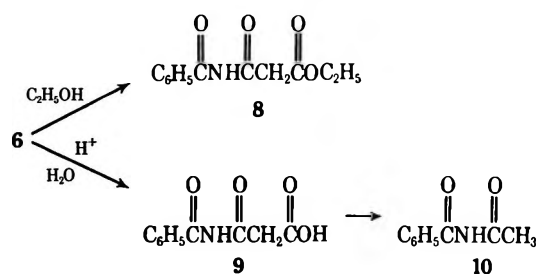
Carbodiimides.—During the course of our work, Hull[8] and Brady, *et al.*,[9] reported the reactions of several ketenes with carbodiimides. We found that diphenylketene in acetonitrile reacted readily with dicyclohexylcarbodiimide to give the 1:1 adduct, 1-cyclohexyl-4-(cy-

(7) J. C. Martin, K. C. Brannock, and R. H. Meen, *J. Org. Chem.*, **31**, 2966 (1966).

(8) R. Hull, *J. Chem. Soc.*, 1154 (1967).

(9) W. T. Brady, E. D. Dorsey, and F. H. Parry, III, *J. Org. Chem.*, **34**, 2846 (1969).

clohexylimino)-3,3-diphenyl-2-azetidinone (11). The structure of 11 was established by spectral means and by hydrolysis to the malonimide 12. No 2:1 was ob-

$$(C_6H_5)_2C=C=O + C_6H_{11}N=C=NC_6H_{11} \longrightarrow$$
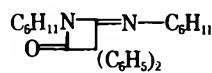
11
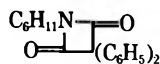
12

tained, even when excess diphenylketene in polar solvents was used.

Carbon Dioxide.—Carbon dioxide does not react with ketenes in the absence of a catalyst; however, Staudinger, et al.,[10] found that, with trimethylamine as catalyst, dimethylketene and carbon dioxide reacted to give a mixture of several products. One of these products was a compound (mp 78°) which Staudinger identified as 2,2,4,4-tetramethyl-3-oxoglutaric anhydride. Bestian and Günther later made the same compound by a different route and correctly identified it as cyclic 2-isopropylidene-5,5-dimethyl-*m*-dioxane-4,6-dione (13).[11]

$$2(CH_3)_2C=C=O + CO_2 \xrightarrow{R_3N} (CH_3)_2C=\overset{O}{\underset{O}{\bigcirc}}(CH_3)_2$$
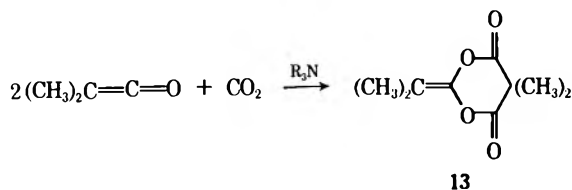
13

Our work showed that triphenylphosphine as catalyst gave 13 directly from dimethylketene and carbon dioxide in yields (68%) substantially better than those obtained with trimethylamine as catalyst. When dimethylketene and carbon dioxide were mixed in ether containing tributylphosphine, a rapid reaction gave a copious amount of a white solid. This product was unstable, and, on attempted work-up, it decomposed with evolution of dimethylketene. Triethyl phosphite as catalyst in the dimethylketene–carbon dioxide reaction gave only the lactone dimer of dimethylketene.[12]

Carbon Disulfide.—Carbon disulfide is like carbon dioxide in that it does not react with ketenes alone. Staudinger, et al.,[13] observed a reaction between dimethylketene and carbon disulfide when trimethylamine was added as catalyst; the polymeric product contained dimethylketene and carbon disulfide combined in a molar ratio of 5:2.

With triphenylphosphine as catalyst, dimethylketene and carbon disulfide gave a 2:1 adduct, 2-isopropylidene-5,5-dimethyl-4-thio-1,3-oxathiane-4,6-dione (14a) in 70% yield. The structure of 14a was established

(10) H. Staudinger, F. Felix, and H. Harder, *Helv. Chim. Acta*, **8**, 306 (1925).

(11) H. Bestian and D. Günther, *Angew. Chem., Int. Ed. Engl.*, **2**, 612 (1963).

(12) E. U. Elam. *J. Org. Chem.*, **32**, 215 (1967), reported the same reaction in the absence of carbon dioxide.

(13) H. Staudinger, F. Felix, and E. Geiger, *Helv. Chim. Acta*, **8**, 314 (1925).

$$2\overset{R}{\underset{R_1}{>}}C=C=O + CS_2 \longrightarrow$$

14a, R = R$_1$ = CH$_3$
   b, R = C$_2$H$_5$; R$_1$ = C$_4$H$_9$
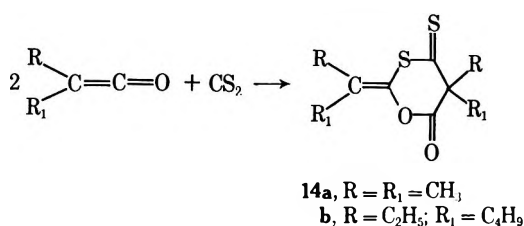
by its uv, ir, and nmr spectra, by its reactions and derivatives, and by analogy with the dimethylketene–CO$_2$ reaction.

With triethyl phosphite as catalyst, 14a was obtained in 54% yield. Other potential catalysts were tested: resinous products were obtained with sodium methoxide or tributylphosphine, and no reaction occurred with *p*-toluenesulfonic acid, boron trifluoride, or *N,N*-dimethylaniline.

The reaction of butylethylketene with carbon disulfide was catalyzed by tributylphosphine, but not by triphenylphosphine. The dark red product had an infrared spectrum similar to that of 14a, and presumably had the homologous structure 14b. It decomposed on attempted molecular distillation.

The adduct 14a decomposed vigorously with liberation of carbon dioxide at temperatures above 120°. If the decomposition was done neat, only a dark, resinous material resulted, but, when 14a was decomposed in refluxing toluene, 5-isopropyl-3-methyl-2-thiophenethiol (15) was obtained in 40% yield. No dimethylthioketene was found. The possible mechanism shown in Scheme I is suggested for the formation of 15.

14a reacted readily with amines to give eventually 2 mol of the corresponding thioisobutyramide and carbon dioxide. The reaction proceeded stepwise to give first 1 mol of thioisobutyramide and 1 mol of the thiomalonamic acid. Subsequent decarboxylation of the thiomalonamic acid afforded the second mole of thioisobutyramide. This stepwise reaction was illustrated by the treatment of 14a with benzylamine to give 83% of *N*-benzyl-2,2-dimethyl-3-thiomalonamic acid (18) and 54% of *N*-(benzylthio)isobutyramide (17a). Piperidine reacted with 14a to give 1-thioisobutyrylpiperidine (17b).
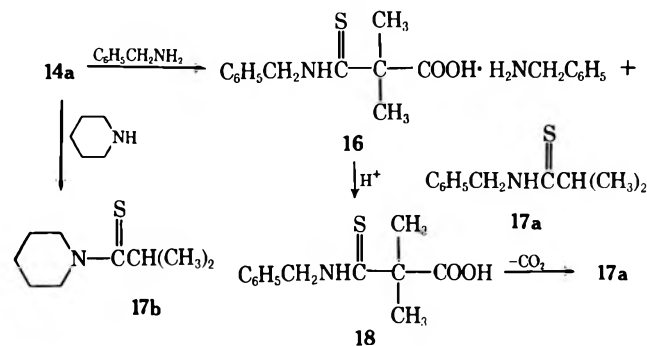
When 14a and other selected reagents were combined, the products either decomposed on attempted distillation or the reaction mixtures were intractable. Reagents that reacted with 14a, but behaved as described, were *N,N*-dimethylisobutenylamine, 4,4'-vinylidenedimorpholine, sodium methoxide in methanol, tetramethyllallene, dimethyl acetylenedicarboxylate, hexachlorocyclopentadiene, and isobutyl alcohol.

SCHEME I

14a $\xrightarrow{-CO_2}$ ...

15
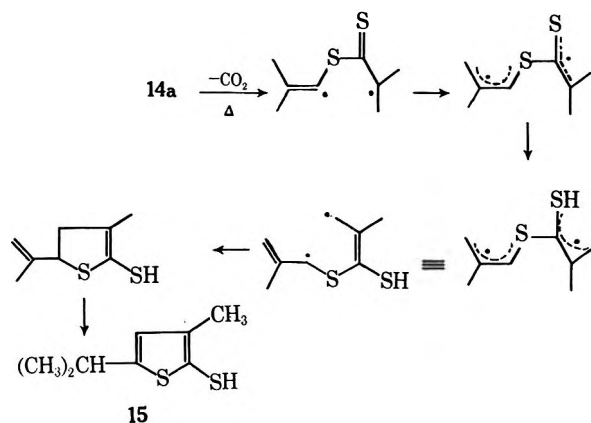
When **14a** was exposed to sunlight or ultraviolet light, it dimerized to the tricyclic derivative **19**.

14a $\xrightarrow{h\nu}$

19

Carbonyl sulfide and dimethylketene reacted in the presence of triphenylphosphine to give a high yield of a material presumed to be the 2:1 adduct analogous to **13** and **14a**. The product was unstable and could not be purified satisfactorily. The crude material reacted with piperidine to give approximately equal amounts of 1-isobutyrylpiperidine and 1-thioisobutyrylpiperidine (**17b**).

Ketenimines.—The reactions of ketenimines and ketenes have not been previously reported. When dimethylketene and N-(2-ethylbutenylidene)methylamine were combined in acetonitrile, two products were formed: 4-(1-ethylpropylidene)dihydro-2,6-diisopropylidene-5-methyl-4H-1,3,5-dioxazine (**20**) in 32% yield and tetrahydro-2,4-diisopropylidene-3,5,5-trimethyl-6H-1,3-oxazin-6-one (**21**) in 14% yield. The formation of **20** was unusual because it represented the first time that dimethylketene formed a 2:1 adduct in which *both* ketene molecules were incorporated through the carbonyl group. In the usual 2:1 adduct with C=N compounds, one molecule of dimethylketene is combined through the olefinic group, and the other through the carbonyl group.[14] Besides the usual spectral evidence, the quantitative hydrolysis under mild conditions confirmed the structure of **20**; stirring with water for several hours at room temperature produced a mixture of **22** and **23**. Complete hydrolysis of **21** to **24** required refluxing in water for several hours. (See Scheme II.)

Experimental Section

Materials.—Ketene was generated by pyrolysis of diketene,[15] and dimethylketene by pyrolysis of isobutyric anhydride or tetramethyl-1,3-cyclobutanedione. Diethylketene was prepared from diethylmalonic acid by the technique of Bestian and Günter,[11] but without isolation of an intermediate cyclic acylal. Diphenylketene was prepared from diphenylacetyl chloride.

p-Toluenesulfonyl isocyanate was obtained from the Upjohn

(14) J. C. Martin, V. A. Hoyle, Jr., and K. C. Brannock, *Tetrahedron Lett.*, 3589 (1965).

(15) S. Andreades and H. D. Carlson, *Org. Syn.*, **45**, 50 (1965).

Co. Trichloroacetyl and benzoyl isocyanates were prepared according to the methods of Speziale and Smith.[16]

Malonimides. A. General Procedure.—**2b** was prepared by heating butylethylketene with excess phenyl isocyanate (1:3 molar ratio) for 5 hr at 180° in a bomb tube. Bis(malonimides) were synthesized under the same conditions, but excess ketene was added to the diisocyanate (3:1 molar ratio). **2a** was prepared from dimethylketene and phenyl isocyanate at a much lower temperature. Properties of the malonimides are summarized in Table I. Infrared spectra of all malonimides showed strong, sharp absorptions at 5.71-5.75 μ.

B. 2,2-Dimethyl-N-phenylmalonimide (2a).—Dimethylketene (28.1 g, 0.43 mol) was added in portions to a refluxing solution of 80 g (0.67 mol) of phenyl isocyanate in 250 ml of acetonitrile. Reflux was continued for 3 hr, and the resulting solution was then distilled through a 4-in. Vigreux column to give 24.4 g (30%) of **2a**: bp 70° (0.2 mm); nmr (CDCl₃) δ 1.40 (s, 6) and 7.40 (m, 5).

C. N,N'-p-Phenylenebis(2,2-diethylmalonimide) (3a).—A solution of 3.92 g (0.04 mol) of diethylketene and 2.13 g (0.013 mol) of p-phenylene diisocyanate in 18 ml of toluene was heated for 5 hr in a sealed glass tube at 180°. The reaction mixture was evaporated to dryness, taken up in an ether-petroleum ether mixture, filtered, and evaporated to give 2 g of crude brown product. Treatment with carbon and recrystallization from methanol gave colorless crystals of **3a** (0.6 g): mp 131-132°; ir (CCl₄) 5.72 μ.

In another run, a solution of 8 g (0.05 mol) of p-phenylene diisocyanate and 14.7 g (0.15 mol) of diethylketene in 100 ml of toluene was inadvertently heated for 16 hr in a sealed glass tube at 180°. The reaction mixture was evaporated to dryness, and the crystalline residue was washed with cyclohexane. The yield of crude **3a** was 16.3 g (91%). Recrystallization from ethanol gave a product melting sharply at 130°.

N-(p-Tolylsulfonyl)malonimide (4a).—Ketene was passed into a solution of 50 g (0.254 mol) of p-toluenesulfonyl isocyanate in 150 ml of acetonitrile to a weight increase of 11 g. The reaction mixture was cooled intermittently in ice, and the reaction temperature ranged from 28 to 40°. After being stirred for 30 min, the mixture was filtered to give 46 g of crude **4a**. Evaporation of the filtrate gave an additional 15 g of crude product. The yield of combined products, mp 125-130°, was quantitative. Recrystallization from ethyl acetate yielded 33 g (54%) of **4a**: mp 144-147° dec (lit.[6] mp 125°); ir (Nujol) 5.65 μ; nmr (CH₃-NO₂) δ 2.48 (s, 3), 3.80 (s, 2), and 7.70 (typical aromatic AA', BB' pattern, 4).

2,2-Dimethyl-N-(p-tolylsulfonyl)malonimide (4b).—Dimethylketene (14 g, 0.2 mol) was added to a stirred solution of 39.4 g (0.2 mol) of p-toluenesulfonyl isocyanate in 200 ml of benzene under an atmosphere of nitrogen. The reaction was exothermic, and the temperature was kept at 10-20° by cooling with ice. The mixture was stirred for 2 hr, and the solvent was then removed under reduced pressure. The residue immediately crystallized to give 50 g (94%) of crude **4b**. A sample was recrystallized from benzene-hexane: mp 108-110°; ir (KBr) 5.60 μ; nmr (CH₂Cl₂) δ 1.32 (s, 6), 2.46 (s, 3), and 7.70 (typical aromatic AA', BB' pattern, 4).

Anal. Calcd for C₁₂H₁₃NO₄S: C, 54.0; H, 4.9; N, 5.2. Found: C, 54.0; H, 5.1; N, 5.1.

5,5-Dimethyl-2-trichloromethyl-4H-1,3-oxazine-4,6(5H)-dione (5a).—Dimethylketene (2.1 g, 0.03 mol) was added to a stirred solution of 5.7 g (0.03 mol) of trichloroacetyl isocyanate in 30 ml of benzene. The exothermic reaction was kept at 25-40° by a cooling bath. The solid that formed was removed by filtration and dried to give 6.0 g (77%) of **5a**. A sample was recrystallized from benzene-hexane: mp 152-155°; ir (KBr) 5.50, 5.73, and 6.12 μ; nmr (C₂H₂Cl₄) 1.60 (s).

Anal. Calcd for C₇H₆Cl₃NO₃: C, 32.5; H, 2.3; N, 5.4. Found: C, 32.8; H, 2.4; N, 5.2.

5,5-Dimethyl-2-phenyl-4H-1,3-oxazine-4,6(5H)-dione (5b).—Dimethylketene (11.9 g, 0.17 mol) was added to a stirred solution of 14.7 g (0.1 mol) of benzoyl isocyanate in 150 ml of benzene. The temperature of the exothermic reaction was held at 25-39° by an ice bath. Distillation of the solvent through a short Vigreux column yielded some crude solid material along with unchanged benzoyl isocyanate. The solid was recrystallized from benzene-hexane mixture to give 5.5 g (25%) of **5b**: mp 133-135°

(16) A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **27**, 3742 (1962).

SCHEME II

$(CH_3)_2CHCNCOCCH(CH_3)_2$ with O and $C(C_2H_5)_2$ groups, CH_3, O

22

$(C_2H_5)_2C$—O—$C(CH_3)_2$ ring with CH_3N, O, $C(CH_3)_2$

20

$(CH_3)_2C$=C=O + $(C_2H_5)_2C$=C=NCH$_3$

$(CH_3)_2CHCOC$—N—C—$CH(C_2H_5)_2$ with O, $C(CH_3)_2$, CH_2, O

23

O=C ring with $(CH_3)_2$, NCH_3, =$C(CH_3)_2$, $C(C_2H_5)_2$

21

$(CH_3)_2CHC$—N—C—$C(CH_3)_2COOH$ with O, $C(C_2H_5)_2$, CH_3

24
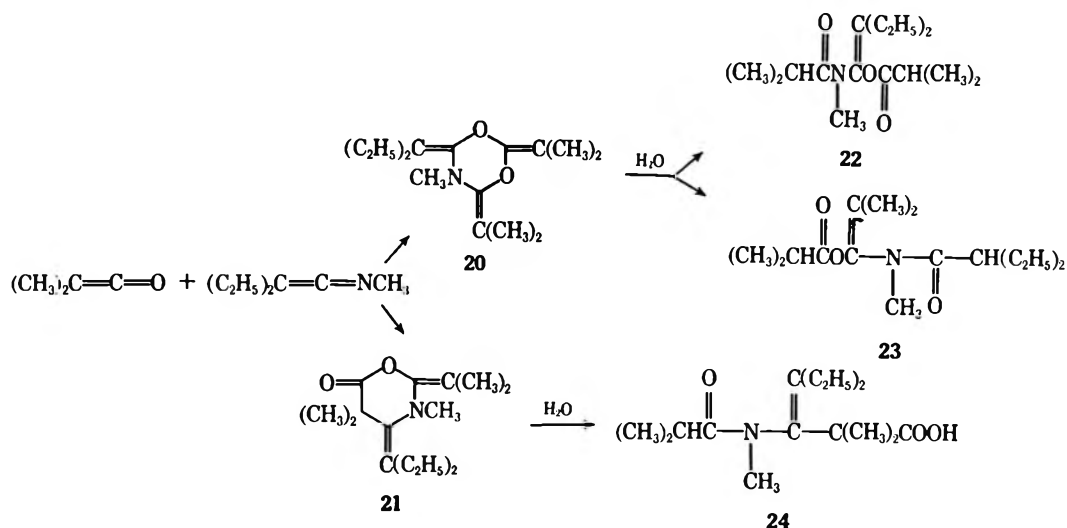
(lit.[7] 132–135°). The infrared spectrum of **5b** was identical with that of **5b** prepared by the literature method.[7]

6-Methyl-3-benzoyl-2H-1,3-oxazine-2,4(3H)-dione (7).—Ketene was bubbled into a stirred solution of 14.7 g (0.1 mol) of benzoyl isocyanate in 50 ml of benzene, under a nitrogen atmosphere, until a weight increase of 5 g was obtained. The reaction temperature was controlled at 30–40° by an ice bath. The solid that precipitated was removed by filtration and recrystallized from hexane to give 7.0 g (51%) of **7**: mp 86–88.5°; ir (KBr) 5.68 and 5.71 μ; nmr (CH$_2$Cl$_2$) δ 2.50 (s, 3), 6.40 (s, 1), and two multiplets at 8.04 and 8.73 (5, aromatic protons).

Anal. Calcd for $C_{12}H_9NO_4$: C, 62.3; H, 3.9; N, 6.1. Found: C, 62.6; H, 4.0; N, 6.3.

Five grams of **7** was obtained as insoluble material from the hexane recrystallization.

6-Hydroxy-2-phenyl-4H-1,3-oxazin-4-one (6).—Ketene (5.7 g, 0.135 mol) was passed into a solution of 20 g (0.135 mol) of benzoyl isocyanate in 100 ml of ether at 5 to 10°. A white solid separated rapidly. The reaction mixture was stirred for 15 hr at room temperature and then filtered to give 15.8 g (62%) of **6**, mp 175–178° dec. A sample was recrystallized from tetrahydrofuran: mp 176–178° (dec); ir (Nujol) 3.60–4.5, 6.05, and 6 18 μ; nmr (CD$_3$SOCD$_3$) δ 3.78 (s, 1), 7.72 (m, 5), and 12.9 (s, 1).

Anal. Calcd for $C_{10}H_7NO_3$: C, 63.5; H, 3.7; N, 7.4. Found: C, 63.3; H, 4.3; N, 7.3.

Ethyl N-Benzoylmalonamate (8).—A solution of 5.0 g of **6** in 30 ml of ethyl alcohol was refluxed for 1 hr. The solvent was removed *in vacuo*, and the solid residue was recrystallized from a mixture of benzene and hexane to give 5.5 g (90%) of **8**: mp 114.5–115.5°; ir (KBr) 5.78, 5.86, and 5.95 μ; nmr (CH$_2$Cl$_2$) δ 1.32 (t, 3), 4.12 (s, 3), 4.45 (q, 2), 8.30 (m, 5), and 10.1 (s, 1).

Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.3; H, 5.6; N, 6.0. Found: C, 61.5; H, 5.8; N, 6.0.

N-Benzoylmalonamic Acid (9).—A mixture of 3.0 g (0.016 mol) of **6** and 75 ml of 5% hydrochloric acid was stirred for 20 hr at room temperature. Filtration of the mixture gave 2.4 g (73%) of **9**. A sample was recrystallized from acetonitrile: mp 139–140° dec ir (Nujol) 3.8–4.2, 5.86, 6.00, and 6.12 μ; nmr (deuteriopyridine) δ 3.95 (s, 2), 7.58 (m, 5), 11.6 (s, 1), and 13.0 (s, 1).

Anal. Calcd for $C_{10}H_9NO_4$: C, 58.0; H, 4.4; N, 6.8. Found: C, 58.3; H, 4.4; N, 6.7.

N-Acetylbenzamide (10).—**9** (1 g, 0.0048 mol) was heated in a small test tube at 150° for 5 min. A gas evolved, and the oily residue crystallized on cooling. Recrystallization from benzene–cyclohexane gave 0.6 g (77%) of **10**: mp 114–115° (lit. 116–118°[17] and 117°[18]); ir (KBr) 3.03, 5.71, and 5.91 μ.

Anal. Calcd for $C_9H_9NO_2$: C, 66.3; H, 5.6; N, 8.6. Found: C, 66.3; H, 5.7; N, 8.7.

1-Cyclohexyl-4-(cyclohexylimino)-3,3-diphenyl-2-azetidinone (11).—A mixture of 42.5 g (0.22 mol) of diphenylketene, 44.5 g (0.216 mol) of dicyclohexylcarbodiimide, and 300 ml of acetonitrile was prepared. An exothermic reaction started and the temperature rose to 45°. The white solid that precipitated was removed by filtration after 3 hr. This solid was recrystallized from ethyl acetate to give 75.4 g (84%) of **11**: mp 160.5–162° (lit.[9] 158–159°); ir (KBr) 5.53 and 5.94 μ; nmr (CDCl$_3$) δ 1.55 (m, 20), 3.55 (m, 2), and 7.30 (s, 10).

Anal. Calcd for $C_{27}H_{32}N_2O$: C, 81.0; H, 8.1; N, 7.0. Found: C, 80.7; H, 8.1; N, 7.1.

N-Cyclohexyldiphenylmalonimide (12) by Hydrolysis of 11.—A mixture of 30 g (0.075 mol) of **11** and 150 ml of 10% HCl was refluxed with stirring for 3 hr. The mixture was cooled, taken up in ether, washed with water, and dried (MgSO$_4$). Distillation through a 3-in. Vigreux column gave 18.2 g (76%) of **12**, bp 210–215° (1.5 mm). This material solidified on cooling and was recrystallized from methyl alcohol to give **11**: mp 81–82°; ir (KBr) 5.75 μ; nmr (CDCl$_3$) δ 1.56 (m, 10), 3.62 (m, 1), and 7.34 (m, 10).

Anal. Calcd for $C_{21}H_{21}NO_2$: C, 79.0; H, 6.6; N, 4.4. Found: C, 78.7; H, 6.4; N, 4.7.

2-Isopropylidene-5,5-dimethyl-m-dioxane-4,6-dione (13).—A solution of 2 g of triphenylphosphine in 275 ml of ether was chilled to −60° and saturated with CO$_2$. To this stirred solution was added 70 g (1.0 mol) of dimethylketene. A white solid precipitated rapidly, and a slow stream of carbon dioxide was passed through the solution while it warmed to room temperature. The solvent was removed *in vacuo* to give 92 g (100%) of crude product. Recrystallization from hexane gave 57 g (62%) of **13**, mp 75–77°. A sample was recrystallized from petroleum ether: mp 77–79° (lit. 78°[10] and 80°[11]); nmr (CHCl$_3$) δ 1.50 (s, 6) and 1.74 (s, 6).

Anal. Calcd for $C_9H_{12}O_4$: C, 58.6; H, 6.6. Found: C, 58.7; H, 6.6.

2-Isopropylidene-5,5-dimethyl-4-thio-1,3-oxathiane-4,6-dione (14a).—Dimethylketene (127.5 g, 1.85 mol) was added to a stirred solution of 2 g of triphenylphosphine in 500 g (6.6 mol) of carbon disulfide under a nitrogen atmosphere. The temperature of the exothermic reaction was kept at 25–37° by an ice bath. After 2 hr the reaction solution was transferred to a large evaporating dish, and the excess carbon disulfide was allowed to evaporate at room temperature. The resulting crystalline residue was recrystallized from hexane to give 138 g (70%) of 14a: mp 75–78°; ir (KBr) 5.75 and 6.10 μ; nmr (CHCl$_3$) δ 1.62 (s, 6), 1.85 (s, 3), and 1.93 (s, 3); uv max (hexane) 244 mμ (ε 6630) and 344 (10,775).

Anal. Calcd for $C_9H_{12}O_2S_2$: C, 50.0; H, 5.6; S, 29.6. Found: C, 50.2; H, 5.5; S, 29.1.

5-Isopropyl-3-methyl-2-thiophenethiol (15) by Thermolysis of 14a.—A solution of 15.0 g (0.069 mol) of 14a in toluene was refluxed for 4 hr. Carbon dioxide evolved during this period. The toluene was removed *in vacuo* and the residue was distilled to give crude 15, bp 52–78° (0.2–0.5 mm). A glpc assay indicated that this fraction contained 4.8 g (40% yield) of 15. A

(17) S. D. Work, D. R. Bryant, and C. R. Hauser, *J. Amer. Chem. Soc.,* **86,** 872 (1964).

(18) J. B. Polya and T. M. Spotswood, *Rec. Trav. Chim. Pays-Bas,* **67,** 927 (1948).

sample was purified by glpc; $n^{20}D$ 1.5588; nmr (CCl₄) δ 1.23 (d, 6), 3.27 (septet, 1), 1.90 (s, 3), 2.47 (s, 1), and 6.38 (s, 1).

Anal. Calcd for C₈H₁₂S₂: C, 55.8; H, 7.0; S, 37.2. Found: C, 56.3; H, 6.8; S, 37.1.

N-Benzylthioisobutyramide (17a) and N-Benzyl-2,2-dimethyl-3-thiomalonamic Acid (18) from Benzylamine and 14a.—A solution of 17.2 g (0.16 mol) of benzylamine in 25 ml of toluene was added with stirring and ice cooling to a solution of 10.8 g (0.05 mol) of 14a in 150 ml of toluene. The addition was controlled so that the temperature of the exothermic reaction did not rise above 30°. Filtration gave 14.2 g (83%) of the benzylamine salt 16, mp 130–131°. Recrystallization from warm ethanol gave 11.1 g (65%) of 16 as white needles: mp 134–135° dec; nmr (acetone) δ 1.50 (s, 6), 4.11 (s, 2), 4.86 (d, 2), and 5.85 (s, 4).

Anal. Calcd for C₁₂H₁₅NO₂S·C₇H₉N: C, 66.3; H, 7.0; N, 8.1; S, 9.3. Found: C, 66.0; H, 7.0; N, 7.8; S, 9.6.

The solution that remained after isolation of the benzylamine salt was distilled through a short Vigreux column to give 66 g (60%) of 17a: bp 141–147° (0.7 mm), 87% purity by glpc. A sample was purified by glpc: nmr (CCl₄) δ 1.18 (d, 6), 2.82 (septet, 1), 4.70 (d, 2), 7.22 (s, 5), and 8.67 (s, 1).

Anal. Calcd for C₁₁H₁₅NS: C, 68.3; H, 7.8; N, 7.3; S, 16.6. Found: C, 68.8; H, 7.9; N, 7.4; S, 16.4.

Trituration of the benzylamine salt 16 with 10% HCl gave 18: mp 100–102° dec; nmr (Cl₂CHCHCl₂) δ 1.60 (s, 6), 4.82 (d, 2), 7.33 (s, 5), 8.25 (broad s, 1), and 10.8 (s, 1).

Anal. Calcd for C₁₂H₁₅NO₂S: C, 60.7; H, 6.4; N, 5.9; S, 13.5. Found: C, 61.0; H, 6.5; N, 6.3; S, 13.5.

1-Thioisobutyrylpiperidine (17b) from Piperidine and 14a.—Piperidine (5.1 g, 0.06 mol) was added slowly to 6.48 g (0.03 mol) of 14a. CO₂ evolved and the mixture was cooled intermittently to keep the temperature at 50–60°. After the exothermic reaction was over, the reaction solution was warmed for 1 hr on the steam bath and then distilled through a 4-in. Vigreux column to give 5.8 g (57%) of 17b: bp 100–102° (0.8 mm); nmr (CDCl₃) δ 1.22 (d, 6), 3.20 (septet, 1), and 1.73, 3.20, 3.80, 4.30 (multiplets, 10).

Anal. Calcd for C₉H₁₇NS: C, 63.1; H, 10.0; S, 18.7. Found: C, 62.9; H, 10.0; S, 18.8.

2,10-Diisopropylidene-5,5,13,13-tetramethyl-3,11-dioxa-1,7,-9,14-tetrathiadispiro[5.1.5.1]tetradecane-4,12-dione (19) by Dimerization of 14a.—14a (3.5 g, 0.016 mol) was placed in a petri dish and covered with a watch glass. The sample was irradiated with a Hanovia high-pressure mercury-vapor lamp for 24 hr. The solid changed from orange to white during irradiation. The material was washed with hexane and recrystallized from benzene to give 2.0 g of 19: mp 213°; ir (KBr) 5.73 and 6.10 μ; nmr (CDCl₃) δ 1.75 (s, 12) and 1.82 (s, 12).

Anal. Calcd for C₁₈H₂₄O₄S₄: C, 50.0; H, 5.6; S, 29.6; mol wt, 432. Found: C, 50.3; H, 5.5; S, 29.8; mol wt (ebullioscopic in benzene), 446.

N-(2-Ethylbutenylidene)methylamine.—This compound was prepared by dehydrohalogenation of N-(1-chloro-2-ethylbutylidene)methylamine according to the method of Stevens and French.[19] It had the following properties: bp 55–57° (50 mm); ir (neat) 4.95 μ; nmr (neat) δ 1.00 (t, 6), 1.93 (q, 4), and 3.07 (s, 3).

Anal. Calcd for C₇H₁₃N: C, 75.6; H, 11.8; N, 12.6. Found: C, 75.4; H, 11.8; N, 12.6.

4-(1-Ethylpropylidene)dihydro-2,6-diisopropylidene-5-methyl-4H-1,3,5-dioxazine (20) and Tetrahydro-2,4-diisopropylidene-3,5,5-trimethyl-6H-1,3-oxazin-6-one (21).—Dimethylketene (64 g, 0.91 mol) was added rapidly to a stirred solution of 44.4 g

(0.4 mol) of N-(2-ethylbutenylidene)methylamine in 200 ml of acetonitrile under a nitrogen atmosphere. The reaction was slightly exothermic, and the temperature was held at 20–30° by periodic use of an ice bath. The reaction solution was stirred for 12 hr at room temperature and then distilled through a 6-in. Vigreux column to give 61 g of a mixture boiling from 85 to 148° (8 mm). Glpc indicated this mixture to be mostly 20 and 21.

The mixture was fractionated through a 24-in. spinning band column to give 24 cuts. Cuts 5–19, bp 78–79° (0.7 mm), weighed 31.7 g and consisted mainly of 20: ir (neat) 5.88, 5.92, 8.35, and 8.60 μ; nmr (CDCl₃) δ 1.00 (t, 6), 1.60 (s, 6), 1.63 (s, 6), 2.08 (q, 4), and 2.84 (s, 3).

Anal. Calcd for C₁₅H₂₅NO₂: C, 71.7; H, 10.0; N, 5.6. Found: C, 71.1; H, 9.7; N, 5.4.

Cuts 20–24, bp 90–94° (0.7 mm), weighed 8.8 g and consisted mainly of 21: ir (neat) 5.53 (w), 5.70, 5.85, 6.03, 8.80, and 9.43 μ; nmr (CCl₄) δ 1.00 (t, 6), 1.49 (s, 6), 1.64 (s, 3), 1.72 (s, 3), 2.18 (q, 2), 2.35 (q, 2), and 2.59 (s, 3).

Anal. Calcd for C₁₅H₂₅NO₂: C, 71.7; H, 10.0; N, 5.6. Found: C, 71.6; H, 10.3; N, 5.6.

1-(N,2-Dimethylpropionamido)-2-ethyl-1-butenyl Isobutyrate (22) and 1-(2-Ethyl-N-methylbutyramido)-2-methylpropenyl Isobutyrate (23) by Hydrolysis of 20.—A mixture of 2.1 g of 21 and 5 ml of water was refluxed with stirring for 1 hr. The organic layer afforded quantitative yields of 22 and 23. These two components were separated by glpc.

22: ir (neat) 5.70, 6.00, 8.92, and 9.30 μ; nmr (CDCl₃) δ 1.00 (t, 6), 1.08 (d, 6), 1.20 (d, 6), 1.95 (q, 2), 2.04 (q, 2), 2.50 (septet, 1), 2.72 (septet, 1), and 3.02 (s, 3).

Anal. Calcd for C₁₅H₂₇NO₃: C, 66.9; H, 10.1; N, 5.2. Found: C, 67.1; H, 10.3; N, 4.9.

23: ir (neat) 5.71, 6.01, 8.95, and 9.32 μ; nmr (CDCl₃) 0.83 (t, 6), 1.17 and 1.21 (2 doublets, 6), 1.45 (broadened quartet, 4), 1.60 (s, 3), 1.68 (s, 3), 2.50 [m, 2 (CH₃)₂CH and (C₂H₅)₂CH], and 3.04 (s, 3).

Anal. Calcd for C₁₅H₂₇NO₃: C, 66.9; H, 10.1; N, 5.2. Found: C, 66.3; H, 10.2; N, 4.9.

4-Ethyl-2,2-dimethyl-3-(N-methylisobutyramido)-3-hexenoic Acid (24) by Hydrolysis of 21.—One gram of 21 was refluxed with 5 ml of water for 12 hr. The organic layer was extracted, dried (MgSO₄), and evaporated to give 0.8 g of 24 as a viscous oil that crystallized on standing. A sample was recrystallized from cyclohexane: mp 87–88°; ir (KBr) 3.85 (broad), 5.79, and 6.30 μ; nmr (CDCl₃) δ 0.92 (t, 3), 1.02 (t, 3), 1.22 (s, 3), 1.46 (s, 3), 1.22 (d, 6, *J* = 7.0 Hz), 2.00 (q, 2), 2.16 (q, 2), 2.92 (septet, 1), 3.20 (s, 3), and 12.80 (s, 1).

Anal. Calcd for C₁₅H₂₇NO₃: C, 66.9; H, 10.1; N, 5.2. Found: C, 66.9; H, 10.0; N, 5.2.

(19) C. L. Stevens and J. C. French, *J. Amer. Chem. Soc.*, **76**, 4398 (1954).

Ketenes. XIV. Adducts of Dimethylketene with C=N Compounds[1]

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The structures of the 2:1 adducts of dimethylketene with azomethines and N heterocycles were incorrectly assigned in the early literature. These materials are oxazinone derivatives rather than piperidinediones. For some C=N compounds, bulky substituents on the nitrogen of the azomethine and use of solvents of low polarity favor β-lactam formation at the expense of oxazinone.

In his pioneering work on ketenes, Staudinger described in detail the preparation and properties of adducts of ketenes with various azomethine compounds and N heterocycles.[2-6] The 1:1 adducts were β-lactams **1**; the 2:1 adducts, the so-called "ketene bases," were formulated as piperidinediones **2**. Despite the suspiciously facile hydrolysis of these latter compounds and the puzzling appearance of hydrolytically stable isomers,[2] the piperidinedione structure went unchallenged for over 50 years.[7] Preliminary studies in these laboratories,[8] and simultaneous work by Taylor and coworkers,[9] showed that most "ketene bases" are, in fact, dihydrooxazinones **3**.
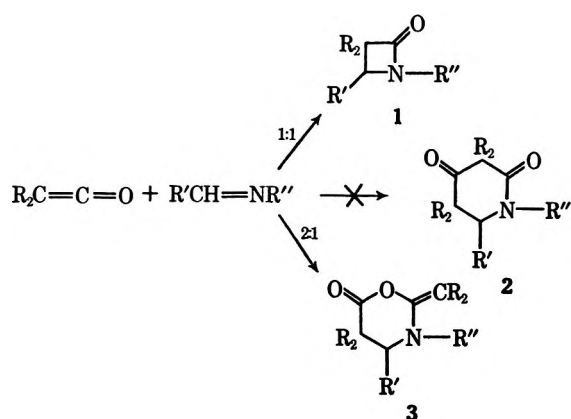
The present paper is a detailed account of the structural assignments of the adducts from C=N compounds and ketenes, reactions of these adducts, and variations of reactivity with structure of C=N compounds. Rigorous structural assignments were made for the dimethylketene adducts with N-benzylideneethylamine and quinoline. These C=N compounds represent widely different types and both adducts are well known in the literature.[2-6]

Dimethylketene and N-benzylideneethylamine reacted in benzene (and more rapidly in acetonitrile) to give 3-ethyldihydro-2-isopropylidene-5,5-dimethyl-4-phenyl-2H-1,3-oxazin-6(5H)-one (**4**) in high yield.

This product was sensitive to moisture and hydrolyzed overnight in moist air to 3-(N-ethyl-2-methylpropionamido)-2,2-dimethyl-3-phenylpropionic acid (**5a**). Refluxing **4** in 10% aqueous sodium carbonate solution effected the same hydrolysis to **5a** (97% yield) in 30 min. When **4** was heated with a small amount of sodium methoxide in refluxing cyclohexane, a facile and virtually quantitative rearrangement to the piperidinedione **6** occurred. **6** was resistant to hydrolysis; it was recovered unchanged after prolonged refluxing in 10% sodium carbonate solution.[10]

$$C_6H_5CH=NC_2H_5 + (CH_3)_2C=C=O \longrightarrow$$
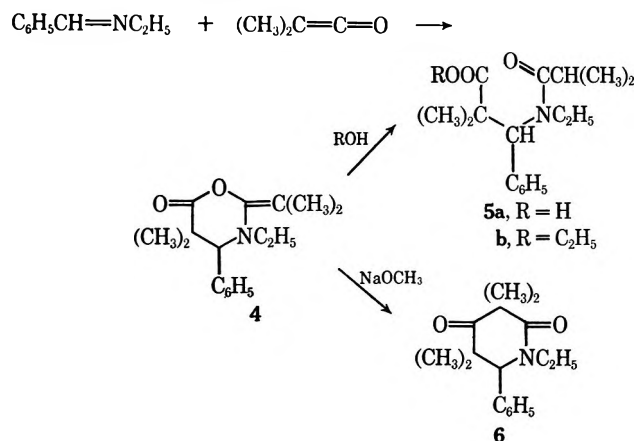
The rearrangement of the oxazinone **4** to the piperidinedione **6** is equivalent to that of the derivative **7** from dimethylmalonyl chloride and N-methylisobutyramide to the piperidinetrione **8**.[11] The pair of isomers **4** and **6** provided models for characterization of other derivatives by infrared and nmr spectra.
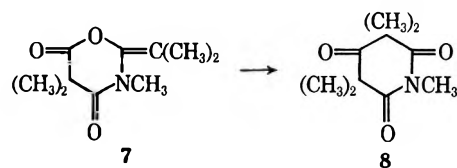
Hydride reductions of the oxazinones produced derivatives of the piperidinediones, presumably by the base-catalyzed rearrangement cited above. Treatment of **4** with sodium borohydride in tert-butyl alcohol gave the hydroxypiperidone **9** as a mixture of isomers. Oxidation of **9** with dichromate in sulfuric acid produced the piperidinedione **6**. The action of lithium aluminum

(1) Paper XIII in this series: J. C. Martin, R. D. Burpitt, P. G. Gott, M. Harris, and R. H. Meen, *J. Org. Chem.*, **36**, 2205 (1971).

(2) H. Staudinger, H. W. Klever, and P. Kober, *Justus Liebigs Ann. Chem.*, **374**, 1 (1910).

(3) H. Staudinger and H. W. Klever, *Ber.*, **39**, 968 (1906).

(4) H. Staudinger, *ibid.*, **40**, 1145 (1907).

(5) H. Staudinger, *ibid.*, **39**, 3062 (1906).

(6) H. Staudinger and H. W. Klever, *ibid.*, **40**, 1149 (1907).

(7) S. A. Ballard, D. S. Melstrom, and C. W. Smith in "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949, p 992.

(8) J. C. Martin, V. A. Hoyle, Jr., and K. C. Brannock, *Tetrahedron Lett.*, 3589 (1965).

(9) (a) R. N. Pratt, S. A. Proctor, and G. A. Taylor, *Chem. Commun.*, 574 (1965); (b) R. N. Pratt, G. A. Taylor, and S. A. Proctor, *J. Chem. Soc. C*, 1569 (1967).

(10) In the reaction of N-benzylidenemethylamine with dimethylketene, Staudinger[2] found an isomeric 2:1 adduct, mp 115°, in a 3% yield. The piperidinedione made by isomerization of the initially formed dihydrooxazinone melts at 115°, and we conclude that Staudinger's small amount of isomeric material was actually the piperidinedione.

(11) J. C. Martin, K. C. Brannock, and R. H. Meen, *J. Org. Chem.*, **31**, 2966 (1966).
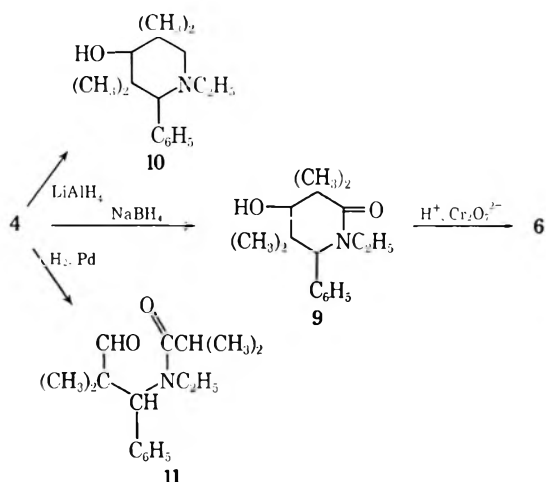
hydride on **4** gave the piperidinol **10**. A corresponding rearrangement occurred in the reduction of the 2:1 adduct of dimethylketene and *N-N*-dialkylisobutenylamines.[12] The catalytic hydrogenation of **4** over palladium did not effect saturation of the isopropylidene groups, but gave instead the unusual hydrogenolysis to the acyclic aldehyde **11**.

Dimethylketene and quinoline reacted rapidly in acetonitrile to afford the 2:1 adduct **12** in 92% yield. Rearrangement of this product, catalyzed by sodium methoxide, produced the piperidinedione **13** in 76%
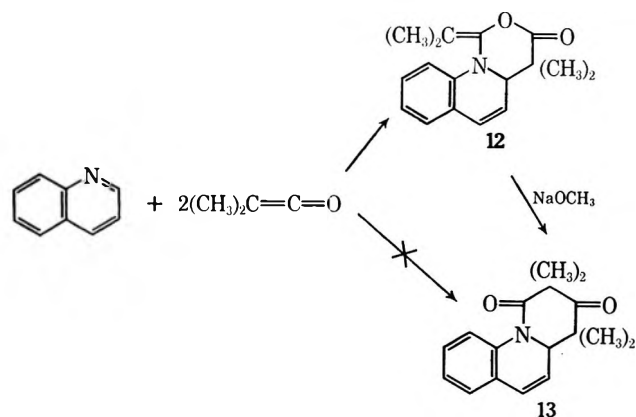
yield. Structural assignments for these compounds were made by methods cited for the benzylideneethylamine derivatives. Catalytic hydrogenation of **12** over palladium did not affect the oxazinone structure but only saturated the endocyclic double bond to give the corresponding tetrahydroquinoline **14**.
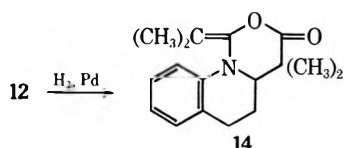
With few exceptions, 1:1 cycloadditions of ketenes and azomethines have been limited to fully aromatic Schiff bases, *i.e.*, anils of aromatic aldehydes or ketones; studies of the reaction have been concerned with substituent effects. Huisgen, *et al.*,[13] described the reaction of diphenylketene and benzylidenemethylamine

(12) J. C. Martin, P. G. Gott, and H. U. Hostettler, *J. Org. Chem.*, **32**, 1654 (1967).

(13) R. Huisgen, B. A. Davis, and M. Morikawa, *Angew. Chem.*, **80**, 802 (1968).

and reported that a change in the order of addition greatly changed the relative amounts of 1:1 and 2:1 adducts formed. In the addition of dimethylketene to a series of *N*-benzylidenealkylamines, we noted two significant factors which affected the mode of cycloaddition; β-lactam formation was favored, at the expense of 2:1 cycloaddition, by the presence of bulky *N*-alkyl groups and by the use of nonpolar solvents. The magnitudes of these effects are shown in Table I.
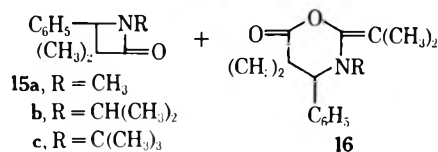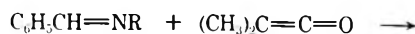
TABLE I

YIELDS OF PRODUCTS FROM $C_6H_5CH=NR$ AND DIMETHYLKETENE

R	In hexane solvent		In acetonitrile solvent	
	15, %	**16**, %	**15**, %	**16**, %
a, Methyl	40	60	0	100
b, Isopropyl	88	12	15	85
c, *tert*-Butyl	95	5	24	76

The effects observed here are compatible with a mechanism involving a dipolar intermediate, generated by combination of the electrophilic center of dimethylketene with the nitrogen atom to give the zwitterions A and B. In polar solvents the zwitterion is stabilized,
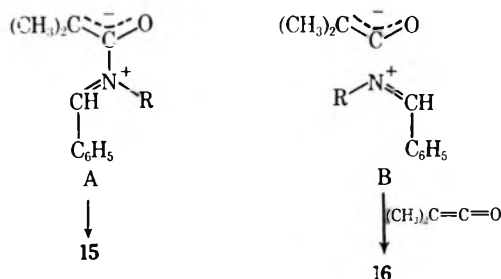
and another molecule of dimethylketene reacts with the dipolarophile B to afford the 2:1 adduct **16**. The presence of a bulky R group would sterically favor the less hindered rotamer A, which is the favored conformation for collapse to the β-lactam **15**. There is an alternative explanation that the reaction is proceeding by a combination of mechanisms, concerted and stepwise polar, and that the polar solvents favor the dipole mechanism at the expense of the concerted pathway.

Imines derived from aliphatic aldehydes also reacted with dimethylketene to give dihydrooxazinones. The general reaction was also extended to include butylethylketene. A list of dihydrooxazinones prepared is presented in Table II. In Table III, other piperidinediones prepared by rearrangement of dihydrooxazinones are listed.

Several C=N heterocycles reacted with dimethylketene to give the dihydrooxazinones listed in Table IV. Benzoxazole and benzothiazole gave the oxazinone type of closure rather than the piperidinedione closure reported for these compounds with diphenylketene.[14] Benzoxazole gave a low yield in this reaction, but 2-

(14) R. D. Kimbrough, Jr., *J. Org. Chem.*, **29**, 1242 (1964).

TABLE II
DIHYDROOXAZINONES FROM KETENES AND ACYCLIC C=N COMPOUNDS[a]
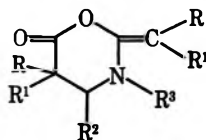
R	R[1]	R[2]	R[3]	Yield, %	Mp or bp (mm), °C	Registry no.
CH₃	CH₃	C₆H₅	CH₃	80	126–129	29668-71-1
CH₃	CH₃	C₆H₅	(CH₃)₃C	35	100–103	29668-72-2
CH₃	CH₃	(CH₃)₂CH	C₃H₇	80	102 (1)	29668-73-3
CH₃	CH₃	C₂H₅	C₃H₇	59	82 (0.1)	29668-74-4
CH₃	CH₃	(CH₃)₂CH	C₂H₅	71	92–97 (0.5)	29668-75-5
CH₃	CH₃	–(CH₂)₅–[b]	C₃H₇	86	124–125 (0.1)	29668-76-6
CH₃	CH₃	H	(CH₃)₃C	75	96–97	29668-77-7
C₂H₅	C₄H₉	C₆H₅	CH₃	90	130–170 (0.1)	29668-78-8

[a] Satisfactory analytical values (±0.35% for C and H) were reported for all compounds in the table: Ed.   [b] Spiro structure.

TABLE III
PIPERIDINEDIONES FROM DIHYDROOXAZINONES[a]
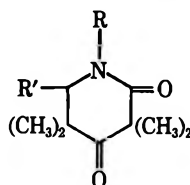
R	R′	Yield, %	Mp, °C	Formula	Registry no.
CH₃	C₆H₅	89	115	C₁₆H₂₁NO₂	29668-79-9
C₃H₇	(CH₃)₂CH	89	95–97	C₁₅H₂₇NO₂	29668-80-2

[a] Satisfactory analytical values (±0.35% for C and H) were reported for all compounds in the table: Ed.

methylbenzoxazole gave an exothermic reaction and a high yield of product. Isoquinoline and dimethylketene gave the oxazinone **17**.
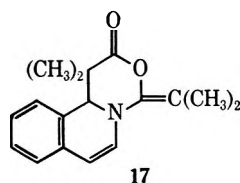
17

Yields and physical constants of β-lactams prepared in this study are given in Table V.

When N-methylene-*tert*-butylamine and dimethylketene reacted under the usual conditions and with no catalyst present, the oxazinone **18** was formed, but,
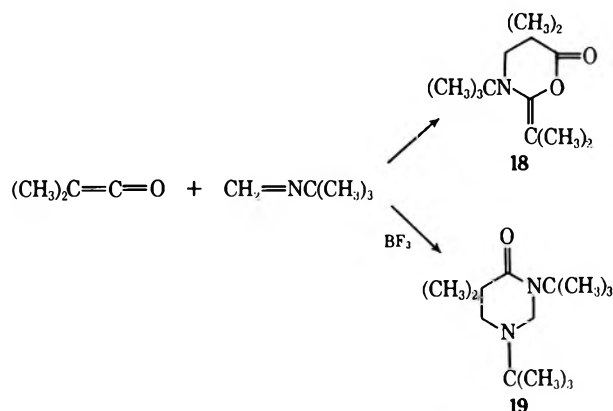
when a catalytic amount of boron trifluoride was present, the adduct **19** from 2 mol of azomethine and 1 mol of ketene was obtained. There is precedent for this in

the work of Clemens and Emmons, who found that ketene and N-methylene-*tert*-butylamine gave a structure analogous to **19**.[15] However, the reaction of dimethylketene with benzylideneethylamine in the presence of boron trifluoride gave only the usual oxazinone adduct.

Holley and Holley[16] reported that an imino thioether and dimethylketene gave a β-lactam. We found that a compound of a similar type, an imino ether, gave a 2:1 adduct **20**, which lost methanol on distillation to give the oxazinone **21**.

20   **21**
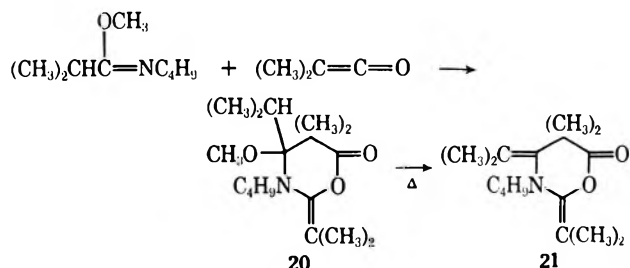
The reaction of dimethylketene with C=N compounds seems to be general for a wide variety of C=N linkages. The products were shown to be dihydrooxazinones, not the piperidinediones previously reported.[2-6] Heterocyclic C=N compounds always gave 2:1 adducts of the dihydrooxazinone type, while azomethines afforded 2:1 and 1:1 adducts in varying ratios depending upon structure of the azomethine and polarity of the reaction solvent.

(15) D. H. Clemens and W. D. Emmons, *J. Org. Chem.*, **26**, 949 (1961).
(16) A. D. Holley and R. W. Holley, *J. Amer. Chem. Soc.*, **73**, 3172 (1951).

<div align="center">

TABLE IV

DIHYDROOXAZINONES FROM DIMETHYLKETENE AND HETEROCYCLIC C=N COMPOUNDS[a]

</div>

C=N compound	Yield, %	Mp, °C	Formula	Registry no.
6-Methoxyquinoline	72	85–86.5	$C_{18}H_{21}NO_3$	29668-81-3
Isoquinoline	60	107–110	$C_{17}H_{19}NO_2$	29784-72-3
Benzoxazole	25	103–104	$C_{15}H_{17}NO_3$	29668-82-4
Benzothiazole	90	83.5–85	$C_{15}H_{17}NO_2S$	29668-83-5
2-Methylbenzothiazole	93	100.5–101.5	$C_{16}H_{19}NO_2S$	29668-84-6

[a] Satisfactory analytical values (±0.35% for C and H) were reported for all compounds in the table: Ed.

<div align="center">

TABLE V

β-LACTAMS FROM DIMETHYLKETENE AND C=N COMPOUNDS[a]

</div>

$$C_6H_5\!-\!\!\!\underset{(CH_3)_2}{\overset{}{\boxed{}}}\!\!\!\begin{array}{c} N\!-\!R \\ =O \end{array}$$
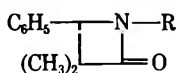
R	Yield, %	Mp or bp (mm), °C	Formula	Registry no.
CH₃	24	117–121 (4.6)	$C_{12}H_{15}NO$	29668-85-7
C₂H₅	88	101–103 (1)	$C_{13}H_{17}NO$	29668-86-8
(CH₃)₃C	81	85.5–87	$C_{16}H_{21}NO$	29668-87-9

[a] Satisfactory analytical values (±0.35% for C and H) were reported for all compounds in the table: Ed.

Experimental Section

3-Ethyldihydro-2-isopropylidene-5,5-dimethyl-4-phenyl-2H-1,3-oxazin-6(5H)-one (4).—Dimethylketene (21.0 g, 0.3 mol) was added to a solution of 20.0 g (0.15 mol) of benzylideneethylamine in 100 ml of acetonitrile at −20° over a period of 10 min. The characteristic yellow color of dimethylketene was discharged rapidly and the temperature rose to −10°. The mixture was allowed to warm to room temperature, and the acetonitrile was then removed *in vacuo*. The residual white solid was washed with several portions of pentane and dried in a vacuum desiccator to obtain 34.0 g (83%) of 4: mp 101.5–104°; ir (CCl₄) 5.72 and 5.92 μ; nmr (CCl₄) δ 0.98 (t, 3), 1.04 (s, 3), 1.07 (s, 3), 1.78 (s, 3), 1.85 (s, 3), 2.80 (m, 2), 4.07 (s, 1), and 7.43 (s, 5).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.7; H, 8.5; N, 5.1. Found: C, 74.9; H, 8.2; N, 5.1.

1-Ethyl-3,3,5,5-tetramethyl-6-phenyl-2,4-piperidinedione (6). —A mixture of 50.0 g of 4, 1.5 g of sodium methoxide, and 200 ml of cyclohexane was refluxed for 2 hr. The mixture was filtered to remove a small amount of solid and then washed with two 100-ml portions of water. The organic layer was concentrated and cooled. The white solid that precipitated was filtered and dried to give 46.0 g (92%) of 6, mp 86–90°. A sample for analysis was recrystallized from an ethyl alcohol–water mixture: mp 89.5–91°; ir (cyclohexane) 5.87 and 6.10 μ; nmr (CCl₄) δ 0.83 (s, 3), 1.08 (t, 3), 1.43 (s, 6), 1.50 (s, 3), 2.78 (m, 1), 3.81 (m, 1, NCH₂), 4.25 (s, 1), and 7.14 (m, 5).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.7; H, 8.5; N, 5.1. Found: C, 74.7; H, 8.7; N, 5.1.

3-(N-Ethyl-2-methylpropionamido)-2,2-dimethyl-3-phenylpropionic Acid (5a).—A mixture of 7.0 g (0.025 mol) of 4, 2.5 g of sodium carbonate, and 23 ml of water was refluxed for 3 hr. The resulting solution was acidified with dilute HCl, and the solid that formed was removed by filtration, washed with water, and dried to give 7.1 g (97%) of 5a, mp 118–120°. A sample for analysis was recrystallized from aqueous methanol: mp 120–121° (lit[7] 114–114.5°); ir (KBr) 5.82 and 6.22 μ; nmr (CCl₄) δ 0.50 (t, 3), 1.10 and 1.19 (two sets of doublets, 6), 1.31 (s, 3), 1.36 (s, 3), 2.82 (septet, 1), 3.45 (q, 2), 6.15 (s, 1), 7.50 (broad peak, 5), and 9.1 (s, 1).

Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.1; H, 8.6; N, 4.8. Found: C, 70.4; H, 8.5; N, 5.0.

Ethyl 3-(N-Ethyl-2-methylpropionamido)-2,2-dimethyl-3-phenylpropionate (5b).—The quantity of 4 that resulted from mixing 100 g (0.75 mol) of benzylideneethylamine and 135 g (1.5 mol) of dimethylketene in 200 ml of acetonitrile was treated with 259 ml of ethyl alcohol and stirred for 8 hr at room temperature. Distillation of this solution through a 6-in. packed column gave 221 g (93%) of 5b, bp 128–130° (0.4 mm). This material solidified on standing. A sample for analysis was recrystallized from cyclohexane: mp 44–45°; ir (KBr) 5.84 and 6.12 μ; nmr (CCl₄) δ 0.51 (t, 3), 1.16 (t, 3), 1.08 (s, 3), 1.20 (s, 3), 1.40 (s, 3), 2.86 (septet, 1), 3.45 (q, 2), 4.15 (q, 2), 6.30 (s, 1), and 7.25–7.75 (m, 5).

Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.4; H, 9.2; N, 4.4. Found: C, 71.7; H, 9.5; N, 4.3.

1-Ethyl-4-hydroxy-3,3,5,5-tetramethyl-6-phenyl-2-piperidinone (9).—A solution of 50.0 g (0.18 mol) of 4 in 150 ml of *tert*-butyl alcohol was heated to 40°, and 3.7 g of sodium borohydride was then added. The temperature was kept at 65° for 20 hr, and then 15 ml of acetic acid was added. The mixture was added to 500 ml of water and 30 ml of 10% HCl. The alcohol was removed on a steam bath, and the remaining organic layer was extracted with ether. Evaporation of the ether layer gave 42 g of syrup. Washing with ether and water gave 11 g (22%) of 9, mp 188–189°, as a mixture of isomers: ir (KBr) 2.93, 6.22, and 9.40 μ.

Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.1; H, 9.1; N, 5.1. Found: C, 74.4; H, 8.8; N, 5.0.

1-Ethyl-3,3,5,5-tetramethyl-2-phenyl-4-piperidinol (10).—4 (25 g) was added slowly to a slurry of 6 g of lithium aluminum hydride in 300 ml of ether. The mixture was refluxed for 2 hr after the addition. Ethyl acetate (25 ml) was added to destroy the excess hydride, followed by 6 ml of water, 4.5 ml of 20% sodium hydroxide solution, and 21 ml of water. The mixture was filtered to remove the solid, and the filtrate was then distilled to give 17.5 g (73%) of 10, bp 115° (0.5 mm), which partly solidified on standing.

Anal. Calcd for $C_{17}H_{27}NO$: C, 78.1; H, 10.4; N, 5.4. Found: C, 78.3; H, 10.5; N, 5.7.

N-Ethyl-N-(2-formyl-2-methyl-1-phenylpropyl)-2-methylpropionamide (11).—A solution of 27.0 g (0.1 mol) of 4 in 200 ml of ethyl acetate was hydrogenated in a magnetically stirred pressure bottle over 2 g of 5% palladium on powdered carbon at 25° (40 psi). A reaction time of 9 hr was required for the absorption of 0.1 mol of hydrogen. The catalyst was removed by filtration, and the solvent was then removed *in vacuo* to give 27.0 g (99%) of practically pure 11, which, after two washings with pentane, melted at 84–85°: ir (KBr) 5.86 and 6.09 μ; nmr (CCl₄) δ 0.82 (t, 3), 1.05 (s, 6), 1.15 (d, 6), 2.75 (septet, 1), 3.35 (q, 2), 4.92 (s, 1), 6.41 (m, 5), and 9.68 (s, 1, CHO).

Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.2; H, 9.1; N, 5.1. Found: C, 73.7; H, 9.2; N, 4.8.

4,4a-Dihydro-1-isopropylidene-4,4-dimethyl-1H-1,3-oxazino-[3,4-a]quinolin-3-one (12).—Dimethylketene (28.9 g, 0.4 mol) was added to a stirred solution of 26.0 g (0.2 mol) of quinoline in 100 ml of acetonitrile at −35°. The reaction was rapid and exothermic, and the temperature rose to 10°. The mixture was stirred for 2 hr at room temperature and then distilled through a 6-in. Vigreux column to give 50.0 g (92%) of 12, bp 143–147° (0.1–0.2 mm). This material solidified on standing. A sample for analysis was recrystallized from an ethyl alcohol–water mixture: mp 82–83.5° (lit[2] mp 81–82°); ir (CCl₄) 5.75 and 5.92 μ; nmr (CCl₄) δ 1.18 (s, 6), 1.49 (s, 3), 1.83 (s, 3), 4.27 (d, 1), 5.55 (pair of doublets, 1), and 6.30 to 7.10 (m, 5).

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.8; H, 7.1; N, 5.2. Found: C, 75.9; H, 7.2; N, 4.9.

4,4a-Dihydro-2,2,4,4-tetramethyl-1H-benzo[c]quinolizine-1,3-(2H)-dione (13).—A solution of 5.0 g of 12 and 0.1 g of sodium methoxide in 50 ml of cyclohexane was heated at 65° for 2 hr. The infrared spectrum of the solution indicated that the starting material was gone and a new compound had been formed. The solution was concentrated *in vacuo*, and the solid that precipitated was removed by filtration and dried to give 3.8 g (76%) of 13, mp 84–86°. A sample for analysis was recrystallized from methanol: mp 87–88°; ir (cyclohexane) 5.92 and 6.00 μ; nmr (CH$_2$-Cl$_2$) δ 1.13 (s, 3), 1.28 (s, 3), 1.32 (s, 3), 1.38 (s, 3), 4.38 (t, 1, J = 2.4 Hz, 4a proton), 5.82 (pair of doublets, 1, J = 9.8 and 2.4 Hz, 5 proton), 6.55 (pair of doublets, 1, J = 9.8 and 2.4 Hz, 6 proton), 7.07 (m, 1), and 7.73 (m, 3).

4,4a,5,6-Tetrahydro-1-isopropylidene-4,4-dimethyl-1H-1,3-oxazino[3,4-a]quinolin-3-one (14).—A solution of 10 g (0.037 mol) of 12 in 75 ml of cyclohexane was hydrogenated over 2 g of 75% palladium on carbon at 25° (40 psi) in a magnetically stirred pressure bottle until 0.037 mol of hydrogen had been absorbed. The reaction mixture was filtered to remove the catalyst and the filtrate concentrated *in vacuo*. The residual oil crystallized and was recrystallized from hexane to give 7.5 g (74%) of 14, mp 97–98°. A sample for analysis was recrystallized from methanol: mp 97–98°; ir (CCl$_4$) 5.70 and 5.91 μ; nmr (CCl$_4$) δ 1.21 (s, 3), 1.30 (s, 3), 1.40 (s, 3), 1.83 (s, 3), 2.02 (m, 2, methylene group at 5 position), 2.75 (m, 2, methylene group at 6 position), 3.40 (m, 1, 4a proton), 6.80 (m, 4).

Anal. Calcd for C$_{17}$H$_{21}$NO$_2$: C, 75.3; H, 7.8; N, 5.2. Found: C, 75.6; H, 7.7; N, 5.4.

Data for Table I.—Dimethylketene (0.1 mol) was added rapidly to 0.1 mol of an N-benzylidenealkylamine in 100 ml of either hexane or acetonitrile, and the reaction mixture was kept at 68–70° for 18 hr. The mixture was assayed by glpc (5% silicone fluid FS-1265 QF-1 on Chromosorb P). The only products formed were 15 and 16, and the values reported in the table are percentages of the total area of 15 and 16.

1-Isopropyl-3,3-dimethyl-4-phenyl-2-azetidinone (15b).—Dimethylketene (41.3 g, 0.59 mol) was added rapidly to a refluxing solution of 73.6 g (0.5 mol) of N-benzylideneisopropylamine in 500 ml of refluxing hexane. Refluxing was continued for 6 hr. Examination of the reaction solution by glpc (5% silicone fluid FS-1265 QF-1 on Chromosorb P) showed 88% 15b and 12% 16b. Distillation through a 6-in. packed column gave 89.0 g (82%) of 15b: bp 114° (2 mm); ir (KBr) 5.70 μ; nmr (CCl$_4$) δ 0.70 (s, 3), 1.09 and 1.31 (pair of doublets, 6, isopropyl methyls), 1.29 (s, 3), 3.57 (septet, 1), 4.29 (s, 1), and 7.22 (s, 5).

Anal. Calcd for C$_{14}$H$_{19}$NO: C, 77.4; H, 8.8; N, 6.4. Found: C, 77.4; H, 9.1; N, 6.2.

3-Isopropyl-2-isopropylidene-5,5-dimethyl-4-phenyl-2H-1,3-oxazin-6(5H)-one (16b).—Dimethylketene (30.8 g, 0.44 mol) was added to a stirred solution of 29.4 g (0.2 mol) of N-benzylideneisopropylamine in 100 ml of acetonitrile. The reaction was quite exothermic, and the temperature was kept at 30–60° by a water bath. The yellow color of the dimethylketene was discharged in about 10 min. Examination of the reaction solution by glpc (5% silicone fluid FS-1265 QF-1 on Chromosorb P) showed 15% 15b and 85% 16b. The solid that precipitated on cooling was removed by filtration and dried to give 43 g (76%) of 16b, mp 108–110°. Recrystallization from hexane gave 38.0 g: mp 111–113°; ir (CCl$_4$) 5.72 and 5.91 μ; nmr (CCl$_4$) δ 0.87, 1.11 (pair of doublets, 6, isopropyl methyls), 0.99 (s, 3), 1.17 (s, 3), 1.78

(s, 3), 1.92 (s, 3), 3.25 (septet, 1), 4.00 (s, 1), and 7.42 (m, 5).

Anal. Calcd for C$_{18}$H$_{25}$NO$_2$: C, 75.2; H, 8.8; N, 4.9. Found: C, 74.9; H, 8.8; N, 4.8.

4,4a-Dihydro-1-isopropylidene-4,4,4a-trimethyl-1H,3H-[1,3]oxazino[4,3-b]benzoxazol-3-one.—Dimethylketene (16.1 g, 0.23 mol) was added to a stirred solution of 13.3 g (0.1 mol) of 2-methylbenzoxazole in 75 ml of acetonitrile. The solution was stirred for 15 hr at room temperature, and the solvent was then removed *in vacuo*. The white, crystalline residue weighed 27.3 g, and, after recrystallization from hexane, gave 19.5 (72%) of 4,4a-dihydro-1-isopropylidene-4,4,4a-trimethyl-1H,3H-[1,3]-oxazino[4,3-b]benzoxazol-3-one: mp 103–104°; ir (KBr) 5.65 and 5.85 μ; nmr (CDCl$_3$) δ 1.37 (s, 3), 1.42 (s, 3), 1.50 (s, 3), 1.75 (s, 3), 1.92 (s, 3), and 6.75 (m, 4).

Anal. Calcd for C$_{16}$H$_{19}$NO$_3$: C, 70.3; H, 7.0; N, 5.1. Found: C, 70.3; H, 6.9; N, 4.8.

1,3-Di-tert-butyltetrahydro-5,5-dimethyl-4(1H)-pyrimidinone (19).—Dimethylketene (9.1 g, 0.13 mol) was added rapidly to a stirred solution of 23 g (0.27 mol) of N-methylene-*tert*-butylamine and 1 ml of boron trifluoride etherate in 100 ml of ethyl acetate. An exothermic reaction took place, and some cooling was necessary to keep the temperature under 35°. The solvent was removed *in vacuo* to give 27 g of residue that slowly crystallized. Glpc indicated that this residue contained 63% 19. This quantity represented a yield of 56%. Distillation through a 4-in. packed column gave 10.3 g (32%) of 19, bp 96–100° (1.2 mm), that was pure by glpc. A sample recrystallized from hexane melted at 60–61°: ir (KBr) 6.13 μ; nmr (CHCl$_3$) δ 1.01 (s, 6), 1.10 (s, 9), 1.37 (s, 9), 2.38 (s, 2), and 3.96 (s, 2, –NCH$_2$N–).

Anal. Calcd for C$_{14}$H$_{28}$N$_2$O: C, 70.0; H, 11.7; N, 11.7. Found: C, 70.2; H, 11.8; N, 11.8.

3-Butyl-4-isopropyl-2-isopropylidene-4-methoxy-5,5-dimethyl-2H-1,3-oxazin-6(5H)-one (20) and 3-Butyl-2,4-bis(isopropylidene)-5,5-dimethyl-2H-1,3-oxazin-6(5H)-one (21).—Dimethylketene (12.5 g, 0.18 mol) was added rapidly to a stirred solution of 14 g (0.089 mol) of N-(1-methoxy-2-methylpropylidene)butylamine in 75 ml of acetonitrile. The reaction solution was stirred for 15 hr at room temperature. The solvent was then removed *in vacuo* to give 24.5 g of crude 20 as an oily residue: ir (neat) 5.70, 5.91, and 9.28 μ; nmr (CCl$_4$) δ 0.90 (m, 3), 1.02, 1.15 (pair of doublets, 6, isopropyl methyls), 1.27 (s, 6), 1.35 (m, 4), 1.65 (s, 3), 1.69 (s, 3), 2.22 (septet, 1), 3.00 (m, 2), and 3.05 (s, 3). Distillation of crude 20 through a 3-in. Vigreux column gave methanol as a forecut and 15.1 g (57%) of 21: bp 110–121° (0.15–0.25 mm); ir (neat) 5.65 and 5.82 μ; nmr (CCl$_4$) δ 0.90 (t, 3), 1.28 (m, 4), 1.49 (s, 6), 1.67 (s, 3), 1.73 (s, 3), 1.79 (s, 3), 1.84 (s, 3), and 2.68 (m, 2).

Anal. Calcd for C$_{16}$H$_{27}$NO$_2$: C, 72.5; H, 10.2; N, 5.3. Found: C, 72.2; H, 10.1; N, 5.2.

Ketenes. XV. Synthesis and Reactions of 3,3-Dimethyl-1-oxaspiro[3.5]nona-5,8-diene-2,7-dione[1]

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3,3-Dimethyl-1-oxaspiro[3.5]nona-5,8-diene-2,7-dione (2) was formed from 1 equiv of dimethylketene and 1 equiv of p-benzoquinone in ether solvents at 0 to 25°. The chemistry of this spiro lactone was investigated and compared with that of an analogous compound 1 made from diphenylketene and p-benzoquinone. The spiro lactone 2 was found to undergo an acid-catalyzed rearrangement, thermal and photochemical loss of carbon dioxide, and addition reactions such as halogenation, hydrogenation, and Diels–Alder addition.

Staudinger and coworkers reported that 1 equiv of p-benzoquinone reacted with 1 equiv of diphenylketene at room temperature to give the mono-β-lactone 1.[2]

1, R = C$_6$H$_5$
2, R = CH$_3$

We found that dimethylketene and p-benzoquinone reacted at room temperature in an analogous manner to give 3,3-dimethyl-1-oxaspiro[3.5]nona-5,8-diene-2,7-dione (2). The purpose of our work was to study the reactions of the parent compound 2.

The reaction between dimethylketene and p-benzoquinone appears to be general for monoalkyl- and dialkyl-substituted p-benzoquinones as shown by the formation of 3 (see Table I); however, tetramethyl-p-benzoquinone did not react.

3

The spiro systems 3 are rich in reactive sites held in a fairly rigid array; therefore, it was of interest to investigate the interaction and reactivity of these sites. Furthermore, the fully substituted β-lactone rings of 1 and 2 might be sterically prevented from reacting as simple β-lactones. It was also desirable to ascertain any differences in reactivity due to variations of steric and electronic properties as a result of dialkyl *vs.* diaryl substitution on the β-lactone ring.

Staudinger found that a second equivalent of diphenylketene reacted with 1, and by decarboxylation 3,6-bis(diphenylmethylene)-1,4-cyclohexadiene (4) was formed in low yields.[2] When a second equivalent of di-

methylketene was added to 2, only polymeric material was obtained.

4

Both β-lactones 1 and 2 liberated CO$_2$ under uv irradiation and upon thermolysis. β-Lactone 1 gave 4-(diphenylmethylene)-2,5-cyclohexadien-1-one (5), and 2 gave p-isopropenylphenol (6) presumably *via* a transient quinonemethide.[3]

5

6

Staudinger reported that 1 reacted with phenylhydrazine in dichloromethane at 0° to give the phenylhydrazone derivative.[2] We found that in a protic solvent, ethyl alcohol, either 1 or 2 reacted with phenylhydrazine to give the azo compounds 7 and 8, respectively. Al-

7, R = C$_6$H$_5$
8, R = CH$_3$

though both β-lactones, 1 and 2, lost carbon dioxide, it was reported by Staudinger that 1 reacted with glacial acetic acid to give the lactone 9;[2] however, our interpretations of nmr and ir spectra indicate that the correct structure of the product is 10. This assignment is supported by Staudinger's own observation that the reaction product was insoluble in sodium carbonate but soluble in sodium hydroxide and was decomposed by hot alkali into benzilic acid and hydroquinone.

(1) Paper XIV in this series: J. C. Martin, K. C. Brannock, R. D. Burpitt, P. G. Gott, and V. A. Hoyle, Jr., *J. Org. Chem.*, **36**, 2211 (1971).

(2) (a) H. Staudinger, *Justus Liebigs Ann. Chem.*, **356**, 51 (1907); (b) H. Staudinger, *Ber.*, **41**, 1355, 1493 (1908); (c) H. Staudinger and S. Bereza, *Ann Chem.*, **380**, 243 (1911).

(3) This transient quinonemethide can be detected by irradiation of 2 at liquid nitrogen temperature. In the uv spectrum, a 320-mμ band (ε 18,000) can be seen at this temperature.

TABLE I
β-LACTONES PREPARED FROM DIMETHYLKETENE AND *p*-BENZOQUINONES[a]

R₁	R₂	R₃	Mp, °C	Yield, %	H₁	H₂	H₃	H₄	CH₃	Registry No.
							—Nmr (CDCl₃), δ—			
H	H	H	107–109	64	6.49, d	7.26, d	6.49, d	7.26, d	1.48, s, 6	
tert-C₄H₉	H	H	98–99			6.88, m	6.20, d	6.88, m	1.36, s, 3	29818-32-4
									1.40, s, 3	
—C₄H₄—		H	110–113	70			6.52, d	7.33, d	0.92, s, 3	29818-33-5
									1.38, s, 3	
CH₃	H	CH₃	135–137	84		6.82, m	6.10, m		1.28, s, 3	29818-34-6
									1.33, s, 3	

[a] Satisfactory analytical values (±0.35% for C and H) were reported for all compounds in the table: Ed.

Pure β-lactone **2** did not react with glacial acetic acid; however, when a catalytic amount of concentrated H_2SO_4 was added, the γ-lactone **11** was formed in 95% yield. In the infrared spectrum of **11** a shift of the
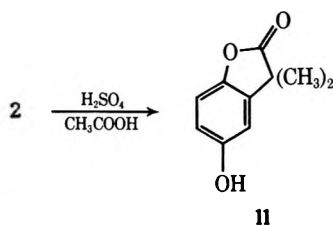
5.66-μ band toward 5.5 μ with increasing dilution in carbon tetrachloride was observed; this shift indicated intermolecular H bonding. The spectral data for this rearrangement product are in agreement with structure **11** or the isomer with the oxygens in a meta relationship. Structure **11** is the correct one because base-promoted opening of the lactone ring gave a substituted hydroquinone which was oxidized to the *p*-benzoquinone derivative **12**. The γ-lactone **11** can be produced directly
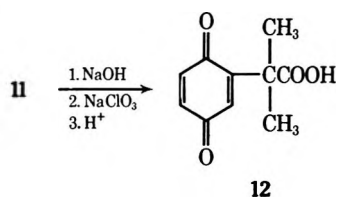
from dimethylketene and *p*-benzoquinone when the solution of **2** is acidified before isolation of the adduct.

We obtained a compound, **13**, analogous to **11** by refluxing **1** in benzene with a trace of *p*-toluenesulfonic

acid (*p*-TSA). This rearrangement was reported by Staudinger who also synthesized the product **13** from
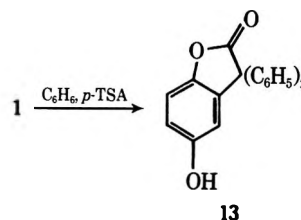
hydroquinone, benzilic acid, and tin(IV) chloride in benzene. Staudinger stated that the rearrangement occurred in refluxing benzene in the presence of light; however, in our work only decarboxylation occurred in benzene (no catalyst) at reflux, under irradiation at room temperature, or under irradiation at reflux.

Staudinger reported that methanol reacted with **1** under acid catalysis to give an adduct analogous to **9** which was decomposed by hot alkali into methoxydiphenylacetic acid and hydroquinone.[2] The ir and nmr spectra indicated that the actual structure was **14**, a compound analogous to **10**.
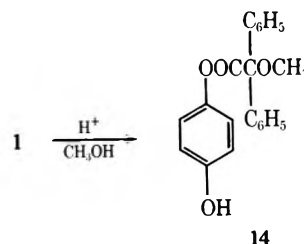
The acid-catalyzed addition of methanol to **2** proceeded in a different fashion to give **15**. The elemental
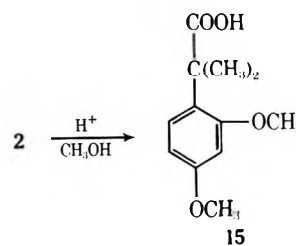
analysis and spectral data were consistent with this assignment. Again, both **15** and one of its isomers, **16**,
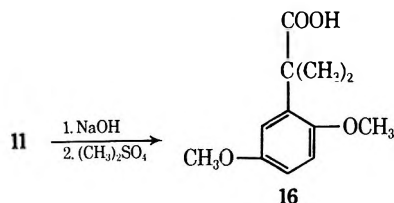
fit the spectral data. Compound **16**, synthesized from **11** with dimethyl sulfate, was easily distinguishable from **15** by ir and nmr spectroscopy.

Although both β-lactones, **1** and **2**, lost carbon dioxide upon heating and uv irradiation, and gave similar adducts with phenylhydrazine, the different electronic properties of the two systems fostered divergent reaction pathways under the other reaction conditions studied. The reactions of **1** and **2** in acetic acid and in methanol indicated that the active sites of the β-lactone rings of both systems are sterically hindered. Therefore, the initial attack must occur on the six-membered ring.[4] The possible pathways for these reactions appear in Schemes I and II. For compound **1** (Scheme

SCHEME I
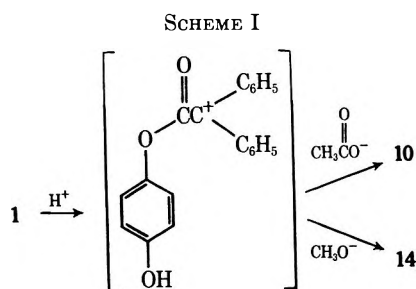
I), the two phenyl groups sufficiently stabilize the positive charge α to the carbonyl to allow the β-lactone ring to open. The cation is then trapped by either an acetate or a methoxide ion to form **10** or **14**, respectively. In benzene, a solvent of low nucleophilicity and low dielectric constant, compound **1** rearranges to relieve ring strain, and the potential cationic center is trapped intramolecularly to give **13**.

For compound **2**, the two methyl groups do not stabilize the cationic center sufficiently to allow ring opening by a pathway analogous to that for **1**. Instead, as shown in Scheme II, a rearrangement occurred in acetic acid with a mineral acid catalyst to give the more stable γ-lactone **11**. Methanol is more nucleophilic than acetic acid, and, in the presence of acid catalyst, it trapped the protonated β-lactone to give **15**.

The remainder of this paper is devoted to the reactions of β-lactone **2**. The halogenation of **2** and the reactions of these halogenated products are summarized in Scheme III. One equivalent of bromine added rapidly to **2** at room temperature to give the dibromide **17**. The second equivalent of bromine added at a much slower rate to give the tetrabromide **18**. These structural assignments are based primarily upon ir and nmr spectral data. The ir spectrum of **17** showed a β-lactone ring (5.48 μ) and an enone (5.90 μ). The nmr spectrum of **17** showed nonequivalent methyl groups as

(4) The normal reaction pathways for simple β-lactones are reviewed by H. E. Zaugg, *Org. React.*, **8**, 305 (1954).

SCHEME II
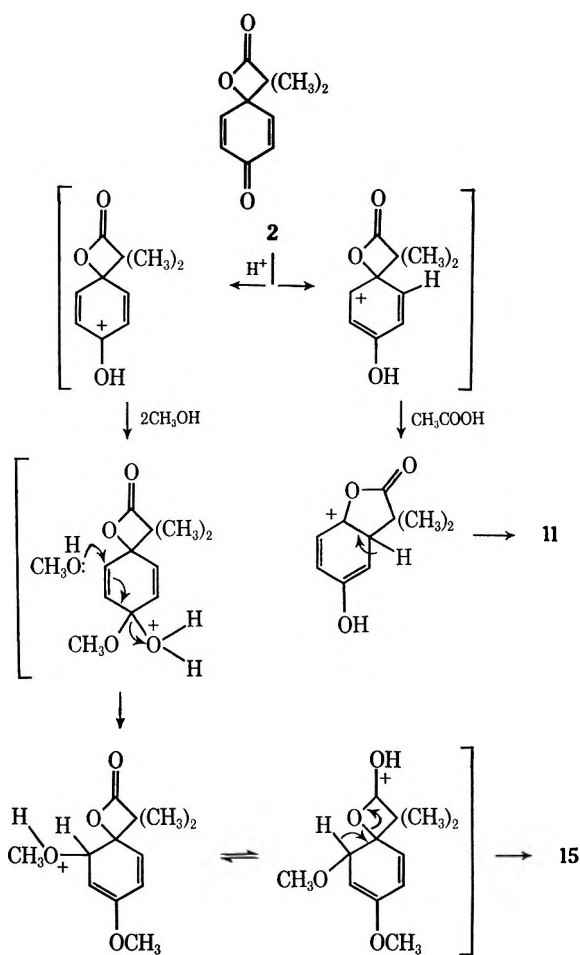
singlets at δ 1.72 and 1.42. The two vinyl protons appeared as a doublet of doublets at δ 6.68 (1 H) and a doublet of doublets at δ 6.23 (1 H).[5] The higher field signal is due to the vinyl proton adjacent to the carbonyl group since compound **3**, where $R_1 = tert-C_4H_9$ and $R_{2,3} = H$, has two hydrogen atoms at the lower field position and only one at the higher field position. The protons on the carbons bearing bromine also appeared as doublets at δ 5.06 and 4.70. The δ 4.70 methylidyne proton is coupled to the vinyl proton α to the carbonyl by a coupling constant of 1.5 Hz, indicating that the higher field methylidyne proton is also α to the carbonyl. The β-vinyl proton is coupled to the β-methylidyne proton by a coupling constant of 2.5 Hz. The coupling constant between the two protons on the carbons bearing bromine is 2.5 Hz, indicating that the bromines are either equatorial-axial or axial-axial.[6,7] Since bromination generally proceeds in a trans manner, the bromines are assigned to axial-axial positions. The methyl groups of **18** are also nonequivalent; they appear as two singlets. One pair of adjacent ring protons is

(5) Similar field positions were reported for 4,4-disubstituted-2,5-cyclohexadienones. For a discussion see W. Regel and W. von Philipsborn, *Helv. Chim. Acta*, **52**, 1354 (1969).

(6) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, pp 193, 390.

(7) One reviewer felt that only cis and trans terminology (not axial or equatorial) was relevant in cyclohexenones; however, examination of molecular models suggests that axial and equatorial terms are relevant with the cyclohexenone preferring a monoplaner (half-chair) conformation: E. Toromanoff in "Topics in Stereochemistry," Vol. 2, N. L. Allinger and E. L. Eliel, Ed., Interscience Publishers, New York, N. Y., 1967, p 157.

coupled by 3.0 Hz and the other by 11.0 Hz. This coupling suggests that one bromine pair is axial–axial and the other is equatorial–equatorial. In an attempt to obtain additional information about this halogenation reaction, β-lactone 2 was chlorinated to give 19 which was brominated to give 20; however, the chemical shifts of the protons on the carbons bearing halogen were not sufficiently sensitive to halogen type to determine if the chlorines were equatorial or if the entering bromines were equatorial.[8]

SCHEME III
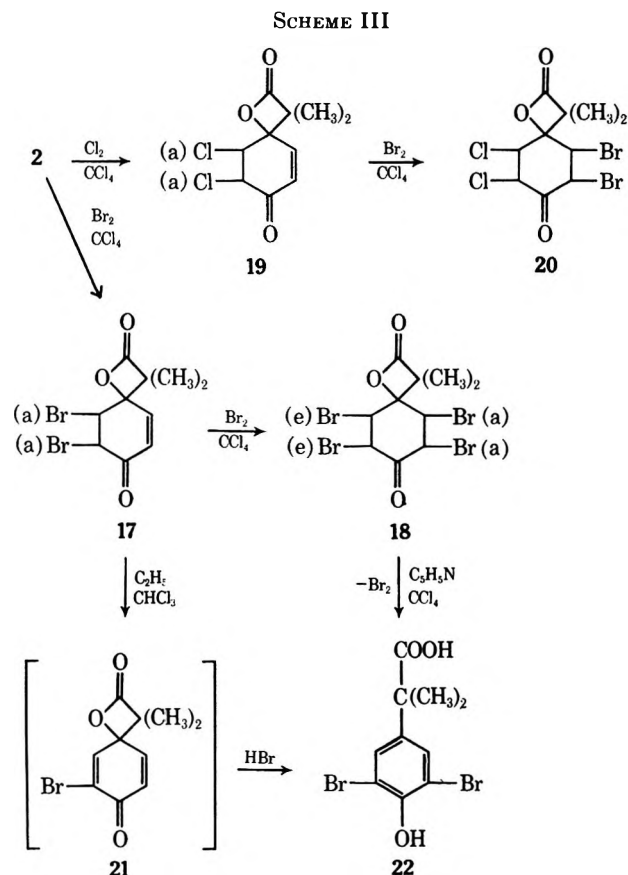
When a few drops of pyridine was added to an nmr tube containing 17 in chloroform-*d*, an elimination–addition reaction took place that could be monitored by nmr. Compound 17 rapidly lost HBr to give 21. Hydrogen bromide then added to 21 (conjugate addition to the β-lactone ring) to give 3,5-dibromo-4-hydroxy-α-methylhydratropic acid (22). This reaction was also run on a preparative scale to give a 75% isolated yield of 22. This compound also resulted from the rearrangement of 18 in the presence of pyridine. The observation of the readdition of HBr to 21 suggested that under similar conditions HBr might add to the parent β-lactone, 2. It was found by ir and nmr that HBr did indeed add to 2 to give 23. The halogen compounds had low thermal stabilities which made mass spectral and elemental analyses difficult.

Even though 2 decarboxylated rapidly at temperatures around 100° and slowly at room temperature, 2 underwent a Diels–Alder addition with cyclopentadiene
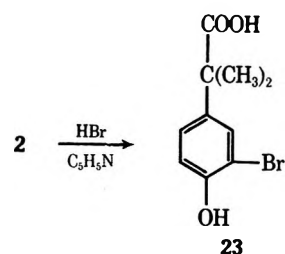
at 40° followed by the loss of CO_2 to give the bicyclic adduct 24. The six-membered ring appeared to be
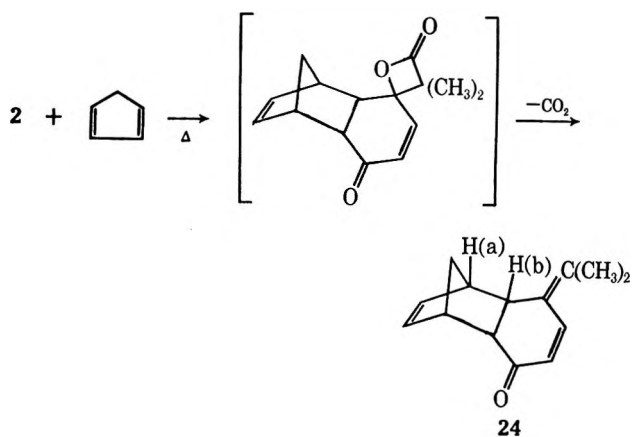
exclusively endo to the norbornene system since the coupling constant between protons a and b (4.0 Hz) was of the correct magnitude for the endo configuration.[9]

When 2 was hydrogenated over a palladium/carbon catalyst, the ring-opened product 25 was obtained.
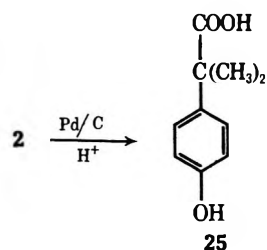
This reaction can be viewed formally as a 1,6 addition of hydrogen.

In conclusion, the differences in the reactivities of β-lactones 1 and 2 can be explained by the greater stability of a positive charge on the tertiary carbon atom α to the carbonyl group for compound 1 (benzylic cation) compared with the stability of the corresponding cation of the dimethyl compound 2. It was found that the enone system of 2 could react independently of the β-lactone ring but that reactions of the β-lactone ring always involved the enone system with the concomitant energy gain of aromatization.

Experimental Section

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(8) One reviewer suggested that the *gem*-dimethyl part of the β-lactone will be preferentially equatorial (over the acyloxy group) once the tetrahalo compound is formed; thus, the stereochemistry of the initial two halogens relative to the β-lactone will determine which halogens are axial or equatorial in the final product.

(9) P. Laszlo and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1171 (1964)

3,3-Dimethyl-1-oxaspiro[3.5]nona-5,8-diene-2,7-dione (2).[10]—Dimethylketene (12.0 ml, 0.14 mol) was added to a stirred solution of 15.0 g (0.14 mol) of *p*-benzoquinone in 100 ml of tetrahydrofuran at 0° under an atmosphere of nitrogen. After 2 hr, the solution was allowed to warm to room temperature. A Dry Ice–acetone condenser prevented the loss of dimethylketene. After 15 hr, the solvent was removed by a rotary evaporator at room temperature and reduced pressure to give a yellow residue. The residue was repeatedly slurried with cold ether–petroleum ether (4:1) and filtered until 13.0 g (52%) of 2 remained as a pure white powder: mp 109° dec; ir (KBr) 5.45, 5.98, and 6.15 μ; nmr (CDCl$_3$) δ 6.68 (d, 2, J = 10 Hz), 6.30 (d, 2, J = 10 Hz), and 1.40 (s, 6); uv max (95% C$_2$H$_5$OH) 238 mμ (ϵ 12,254).

Anal. Calcd for C$_{10}$H$_{10}$O$_3$: C, 67.41; H, 5.66. Found: C, 67.73; H, 5.77.

Substituted β-Lactones 3.—The procedures employed in the syntheses of these compounds (Table I) were essentially identical with the procedure for the preparation of 2.

Decarboxylation of 1 to Give 4-(Diphenylmethylene)-2,5-cyclohexadien-1-one (5).—A stirred solution of 1.0 g of 1 in 250 ml of benzene was flushed with helium for 30 min prior to and during an 11-hr irradiation (450-W Hanovia lamp, Pyrex filter). Irradiation occurred through a double-walled quartz immersion well which was cooled by flowing chilled water between the walls to avoid localized heating of the reaction mixture. A thermometer immersed in the benzene solution detected no temperature increase with irradiation. The solution became intensely yellow as the starting material was converted to 5 (ir verification). The solvent was removed at room temperature and reduced pressure to give a quantitative yield of 5, mp 153–158°. A small sample was recrystallized from benzene–ether to give orange needles: mp 167.5–169.0° (lit.[11] 168°); ir (KBr) 3.30, 6.20, and 6.69 μ; nmr (CDCl$_3$) δ 7.5–7.0 (complex, 12 H) and 6.35 (d, 2, J = 10.0 Hz).

A solution of 1.0 g of 1 in 150 ml of benzene was refluxed for 8 hr. The solution became intensely yellow. The benzene was removed at room temperature and reduced pressure to give a quantitative yield of 5.

An additional decarboxylation in refluxing benzene under uv light gave only 5.

Decarboxylation of 2 to Give *p*-Isopropenylphenol (6).—A 400-mg portion of 2 was pyrolyzed through a Vycor tube at 500° under an atmosphere of nitrogen. The effluent was trapped in a liquid nitrogen cooled collection vessel. A 50% yield (150 mg) of 6 was isolated: mp 82–85° (lit.[12] 83–84°); ir (Nujol) 3.05 and 11.25 μ; nmr (CDCl$_3$) δ 7.33 (d, 2, J = 8.5 Hz), 6.75 (d, 2, J = 8.5 Hz), 5.25 (broad s, 1), 5.10 (broad s, 1, OH), 4.96 (m, 1, J = 1.5 Hz), and 2.12 (m, 3, J = 1.0 Hz).

When 2 was irradiated under conditions similar to those employed in the photolysis of 1, high yields of 6 were obtained.

2-Methyl-2-{*p*-[(*p*-nitrophenyl)azo]phenyl}propionic Acid.—One gram (5.62 mmol) of 2 was added to a solution of 0.861 g (5.62 mmol) of (*p*-nitrophenyl)hydrazine in 40 g of anhydrous ethyl alcohol. The solution was stirred at room temperature for 16 hr and filtered to remove a small amount of insoluble material. The orange filtrate was concentrated *in vacuo*, and the solid that formed was removed by filtration and recrystallized from methanol–chloroform to give 1.3 g (74%) of 2-methyl-2-{*p*-[(*p*-nitrophenyl)azo]phenyl}propionic acid: mp 195–199° dec; ir (KBr) 2.96 (broad), 3.30, 3.42, 5.92, 6.61, and 7.50 μ; nmr (CDCl$_3$) δ 10.9 (broad s, 1), 9.37–7.53 (m, 8), and 1.73 (s, 6); uv max (CH$_2$Cl$_2$) 344 mμ (ϵ 26,538); visible max (CH$_2$Cl$_2$) 443 mμ (ϵ 1122); mass spectrum (70 ev) *m/e* 313 (molecular ion).

Anal. Calcd for C$_{16}$H$_{15}$N$_3$O$_4$: C, 61.34; H, 4.83; N, 13.14. Found: C, 61.42; H, 5.00; N, 13.66.

By a similar procedure, the reaction of phenylhydrazine with 1 and 2 gave diphenyl[*p*-(phenylazo)phenyl]acetic acid (7) and 2-methyl-2-[*p*-(phenylazo)phenyl]propionic acid (8), respectively.

7, 82% yield: mp 199.5–200.5° dec; ir (KBr) 2.97, 3.33, 3.88, 5.93, and 6.3 μ; nmr (CDCl$_3$) δ 9.88 (broad s, 1) and 8.0–7.1

(m, 19); uv max (CH$_2$Cl$_2$) 327 mμ (ϵ 22,290); visible max (CH$_2$Cl$_2$) 440 mμ (ϵ 948).

Anal. Calcd for C$_{26}$H$_{20}$N$_2$O$_2$: C, 79.57; H, 5.14; N, 7.14. Found: C, 78.19; H, 5.18; N, 6.95.

Esterification of 7 with diazomethane gave the corresponding methyl ester in quantitative yield: mp 164–166°; ir (KBr) 3.28, 3.39, 5.77, and 6.24 μ; nmr (CDCl$_3$) δ 8.00–7.13 (m, with strong line at 7.22, 19) and 3.75 (s, 3); uv max (CH$_2$Cl$_2$) 327 mμ (ϵ 21,001); visible max (CH$_2$Cl$_2$) 441 mμ (ϵ 894); mass spectrum (70 ev) *m/e* 406 (molecular ion).

Anal. Calcd for C$_{27}$H$_{22}$N$_2$O$_2$: C, 79.78; H, 5.46; N, 6.89. Found: C, 79.65; H, 5.54; N, 6.78.

8, 60% yield: mp 150.5–152.5°; ir (KBr) 2.75–3.7 (broad), 3.8, 5.9, and 6.25 μ; nmr (CDCl$_3$) δ 10.25 (broad s, 1), 8.01–7.34 (m, 9), and 1.63 (s, 6); uv max (CH$_2$Cl$_2$) 324 mμ (ϵ 20,973); visible max (CH$_2$Cl$_2$) 440 mμ (ϵ 859).

Anal. Calcd for C$_{16}$H$_{16}$N$_2$O$_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.82; H, 6.17; N, 10.66.

Reaction of 3,3-Diphenyl-1-oxaspiro[3.5]nona-5,8-diene-2,7-dione (1) with Acetic Acid to Give *p*-Hydroxyphenyl Acetoxydiphenylacetate (10).—A slurry of 3.0 g (9.2 mmol) of 1[2] and 10 ml of glacial acetic acid was stirred for 3 days at room temperature. The slurry was filtered to give 2.9 g (84%) of 10: mp 158–163° (lit.[2] 163°). A small sample was recrystallized from acetic acid and washed with ether and hexane: mp 165.5–167.5°; ir (KBr) 2.93 (broad), 5.65, and 5.85 μ; nmr (CDCl$_3$) δ 10.3 (broad s, 1), 7.85–7.55 (complex, 5), 7.40–7.00 (complex, 5), 6.82 (s, 4), and 2.05 (s, 3).

Anal. Calcd for C$_{22}$H$_{18}$O$_5$: C, 72.92; H, 5.01. Found: C, 72.69; H, 5.08.

Catalyzed Rearrangement of 2 to 3,3-Dimethyl-5-hydroxy-2-(3*H*)-benzofuranone (11).—To a stirred slurry of 1.0 g (5.6 mmol) of 2 in 10 ml of glacial acetic acid was added 8 drops of concentrated H$_2$SO$_4$ (pH of slurry $\sim$1). The slurry was stirred for 16 hr at room temperature. The solvent was removed by rotary evaporation at room temperature and reduced pressure. The residue was taken up in ether, washed with a saturated aqueous solution of NaHCO$_3$, and dried (MgSO$_4$). Evaporation of the ether gave 0.95 g (95%) of 11 as a white powder, mp 138–143°. After sublimation at 120° (0.1 mm) the melting point was 149–152°; ir (KBr) 2.95, 5.66, and 6.20 μ (the 5.66 μ bond shifts to lower λ on dilution in CCl$_4$); nmr (CDCl$_3$) δ 6.9–6.7 (complex, 3), 6.35 (broad s, 1), and 1.50 (s, 6).

Anal. Calcd for C$_{10}$H$_{10}$O$_3$: C, 67.40; H, 5.60. Found: C, 67.39; H, 5.94.

Oxidation of 11 to α,α'-Dimethyl-3,6-dioxocyclohexadiene-1-acetic Acid (12).—A 1.0-g (5.6 mmol) portion of 11 was added to a stirred solution of 0.5 g (12.5 mmol) of NaOH in 3 ml of water. The reaction was exothermic and gave a dark red solution. All of 11 went into solution within a few minutes. After the basic solution of 11 cooled to room temperature, an oxidant, made by dissolving 0.34 g (3.1 mmol) of sodium chlorate in 30 ml of 2% aqueous H$_2$SO$_4$ and adding *ca.* 100 mg of vanadium oxide,[13] was added with stirring. The resulting solution was basic, and concentrated H$_2$SO$_4$ was added dropwise until the solution became acidic. The solution was dark green. Within 4 hr, a large quantity of yellow solid had precipitated. The reaction mixture was stirred an additional 15 hr. The slurry was filtered and the residue was washed with water and a small amount of ether. The pale yellow residue (0.5 g, 46%) was then sublimed at 135° (0.3 mm) to give 12 as a pale yellow powder: mp (sealed capillary) 180–181° dec; ir (KBr) 5.85, 6.02, and 6.25 μ; nmr [(CD$_3$)$_2$SO] δ 8.3 (broad s, 1), 6.79 (d, 1, J = 1.5 Hz), 6.78 (s, 1), 6.60 (d, 1, J = 1.5 Hz), and 1.36 (s, 6); uv max (95% C$_2$H$_5$OH) 244 mμ (ϵ 14,200) and 290 (1300).

Anal. Calcd for C$_{10}$H$_{10}$O$_4$: C, 61.85; H, 5.19. Found: C, 61.91; H, 5.17.

Acid-Catalyzed Rearrangement of 1 in Benzene to Give 3,3-Diphenyl-5-hydroxy-2(3*H*)-benzofuranone (13).—A solution of 1.0 g of 1 and 100 mg of *p*-toluenesulfonic acid hydrate in 150 ml of benzene was maintained at reflux for 24 hr. The ir spectrum indicated that all the starting material had been consumed. The solvent was removed by rotary evaporation at room temperature and reduced pressure to give a viscous, dark oil. A red oil was removed from this residue in a sublimation apparatus at 140° (0.1 mm), and 0.85 g (85%) of 13 was left as a tan powder:

(10) Caution! A 100-g portion of 2 which had been stored for 3 days at room temperature in a loosely capped glass jar decomposed violently. We recommend that large-scale preparation of 2 be avoided and that the neat material be stored in small quantities (10 g or less), preferably under refrigeration.

(11) A. Baeyer and V. Villiger, *Ber.*, **36**, 2792 (1903).

(12) B. B. Corson, W. J. Heintzelman, L. H. Schwartzman, H. E. Tiefenthal, R. J. Lokken, J. E. Nickels, G. R. Atwood, and F. J. Pavlik, *J. Org. Chem.*, **23**, 544 (1958).

(13) "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 553.

mp 192–195° (lit.[2] 196°); ir (KBr) 2.95 and 5.68 μ; nmr (CDCl₃) δ 7.45 (s, 10) and 6.85–6.55 (complex, 4).

Acid-Catalyzed Rearrangement of 1 in Methanol to Give *p*-Hydroxyphenyl Methoxydiphenylacetate (14).—To a stirred slurry of 2.0 g (6.2 mmol) of 1 in 20 ml of methanol was added 6 drops of concentrated H₂SO₄. The resulting solution was stirred 15 hr. The acid was neutralized with a saturated NaHCO₃ solution, and the solvent was removed at room temperature and reduced pressure by rotary evaporation. The oil obtained was dissolved in ether and washed with water. The ether layer was separated, dried (MgSO₄), and evaporated to give 1.9 g (86%) of a pale yellow solid, mp 117–120°. A small sample was recrystallized from ether acetate–cyclohexane to give 14 as a white solid: mp 121–123° (lit.[2] 122–123°); ir (KBr) 3.00, 5.67, and 5.78 μ; nmr (CDCl₃) δ 8.3 (broad s, 1), 7.70–7.20 (complex, 10), 6.78 (s, 4), and 3.22 (s, 3).

Anal. Calcd for C₂₁H₁₈O₄: C, 75.43; H, 5.43. Found: C, 75.34; H, 5.54.

Acid-Catalyzed Rearrangement of 2 in Methanol to Give 2,4-Dimethoxy-α-methylhydratropic Acid (15).—To a stirred solution of 2.0 g (11.2 mmol) of 2 in 20 ml of methanol was added 4 drops of concentrated H₂SO₄. The solution was stirred at room temperature for 16 hr. Work-up similar to that for 14 gave 1.2 g (48%) of 15, mp 94–104°. A small sample was recrystallized from ethyl acetate–petroleum ether to give tan crystals: mp 107.5–109°; ir (KBr) 3.4 (broad) and 5.98 μ; nmr (CDCl₃) δ 10.7 (broad s, 1), 7.10 (d, 1, J = 9.0 Hz), 6.40 (m, 2, J = 2.0 Hz), 3.72 (s, 3), 3.69 (s, 3), and 1.50 (s, 6).

Anal. Calcd for C₁₂H₁₆O₄: C, 64.27; H, 7.19. Found: C, 64.09; H, 7.06.

2,5-Dimethoxy-α-methylhydratropic Acid (16).—A 3.0-g (17 mmol) portion of 7 was dissolved in a NaOH solution (4.5 g of NaOH in 30 ml of H₂O). The solution was cooled in an ice bath and 3 ml of dimethyl sulfate was added. After 1 hr, a second 3-ml portion was added. After 10 min, the solution was heated on a steam bath for 2 hr. A solution of 7.0 g of NaOH in 6 ml of water was added, and the mixture was refluxed for 1.5 hr. The solution was cooled, acidified with 10% aqueous HCl, and extracted with three portions of ether. The ether layers were combined, and the ether was evaporated. The residue was dissolved in warm, aqueous NaHCO₃, washed with ether, and acidified with 10% aqueous HCl. A solid separated which was collected by filtration and washed with cold pentane to give 2.3 g (61%) of 16, mp 108–111°. A small sample was sublimed at 100° (0.1 mm): mp 110–113°; ir (KBr) 3.4 (broad) and 5.88 μ; nmr (CDCl₃) δ 11.1 (broad s, 1), 6.75 (complex, 3), 3.70 (s, 3), 3.65 (s, 3), and 1.50 (s, 6).

Anal. Calcd for C₁₂H₁₆O₄: C, 64.27; H, 7.19. Found: C, 64.06; H, 7.23.

8,9-Dibromo-3,3-dimethyl-1-oxaspiro[3.5]non-5-ene-2,7-dione (17) from Reaction of 2 with Bromine.—Bromine (3.2 g, 20 mmol) was added in small portions with stirring to a slurry of 3.6 g (20 mmol) of 2 in 50 ml of CCl₄. Near the end of the addition the bromine color began to linger, and the slurry was red after all the bromine had been added. The slurry was filtered and the residue washed with petroleum ether to give 5.9 g (87%) of 17: mp 111.5–112° dec; ir (KBr) 5.45 and 5.90 μ; nmr (CDCl₃) δ 6.68 (d of d, 1, J = 11.0 and 2.5 Hz), 6.23 (d of d, 1, J = 11.0 and 1.5 Hz), 5.06 (t, 1, J = 2.5 Hz), 4.70 (d of d, 1, J = 2.5 and 1.5 Hz), 1.72 (s, 3), and 1.42 (s, 3).

Anal. Calcd for C₁₀H₁₀Br₂O₃: C, 35.53; H, 2.98; Br, 47.31. Found: C, 35.29; H, 3.05; Br, 47.38.

5,6,8,9-Tetrabromo-3,3-dimethyl-1-oxaspiro[3.5]nonane-2,7-dione (18) from Reaction of 17 with Bromine.—Bromine (1.43 g, 9 mmol) was added with stirring to a slurry of 2.8 g (8.3 mmol) of freshly prepared 17 in 25 ml of CCl₄. Stirring was continued at room temperature for 20 hr. The red slurry was filtered, and the resulting solid was washed with ether–petroleum ether to give 3.1 g (75%) of 18 as a pale yellow powder: mp 129.5–131° dec; ir (Nujol) 5.45 and 5.73 μ; nmr (CDCl₃) δ 5.65 (d, 1, J = 11.0 Hz), 5.05 (d, 1, J = 11.0 Hz), 4.92 (d, 1, J = 3.0 Hz), 4.80 (d, 1, J = 3.0 Hz), 1.75 (s, 3), and 1.65 (s, 3); mass spectrum (70 eV) m/e 293 (B), no molecular ion.

Anal. Calcd for C₁₀H₁₀Br₄O₃: C, 24.13; H, 2.02. Found: C, 24.29; H, 2.13.

An additional 0.9 g of solid (approximately 1:1 mixture of 17 and 18) was recovered by evaporation of the filtrate. Compound 17 was unstable at room temperature and slowly decomposed with evolution of Br₂ and HBr.

8,9-Dichloro-3,3-dimethyl-1-oxaspiro[3.5]non-5-ene-2,7-dione (19) from Reaction of 2 with Chlorine.—A slurry of 2.0 g (11.2 mmol) of 2 in 25 ml of CCl₄ was stirred under an atmosphere of chlorine for 1.5 hr. After 15 min a yellow-green solution formed, followed by re-formation of a slurry. The solid was filtered to give 2.15 g (77%) of 19: mp 123–125°; ir (KBr) 5.45 and 5.88 μ; nmr (CDCl₃) δ 6.78 (d of d, 1, J = 11.0 and 2.5 Hz), 6.26 (d of d, 1, J = 11.0 and 1.5 Hz), 4.96 (d of d, 1, J = 2.5 and 4.0 Hz), 4.46 (d of d, 1, J = 1.5 and 4.0 Hz), and 1.70 (s, 3).

Anal. Calcd for C₁₀H₁₀Cl₂O₃: C, 48.3; H, 4.04. Found: C, 48.87; H, 4.12.

5,6-Dibromo-8,9-dichloro-3,3-dimethyl-1-oxaspiro[3.5]nonane-2,7-dione (20) from Reaction of 19 with Bromine.—Bromine (1.43 g, 9 mmol) was added to a stirred slurry of 1.60 g (0.4 mmol) of 19 in 20 ml of CCl₄. The slurry was stirred for 16 hr at room temperature, filtered, and washed with ether–petroleum ether (1:1) to give 2.45 g (93%) of 20 as a white solid: mp 151–155° dec; ir (KBr) 5.46 and 5.72 μ; nmr (CDCl₃) δ 5.49 (d, 1, J = 11.0 Hz), 4.96 (d, 1, J = 11.0 Hz), 4.85 (d, 1, J = 2.5 Hz), 4.77 (d, 1, J = 2.5 Hz), 1.75 (s, 3), and 1.58 (s, 3).

Anal. Calcd for C₁₀H₁₀Br₂Cl₂O₃: C, 29.4; H, 2.47. Found: C, 29.9; H, 2.56.

3,5-Dibromo-4-hydroxy-α-methylhydratropic Acid (22) by Base-Catalyzed Rearrangement of 17.—A solution of 0.5 g of 17 and 100 μl of pyridine in 24 ml of chloroform was heated at reflux for 15 min. The solvent was removed at reduced pressure. The residue was taken up in ether and extracted with a saturated aqueous NaHCO₃ solution. The organic layer gave 0.1 g of 17. The aqueous layer was acidified with concentrated HCl and extracted with ether. The ether layer was dried (MgSO₄) and evaporated to give 0.3 g (80% yield at 75% conversion) of 22: mp 166–176°; ir (Nujol) 3.00, 3.5 (broad), and 5.97 μ; nmr (CDCl₃) δ 9.6 (broad s, 2), 7.56 (s, 2), and 1.59 (s, 6). High-resolution mass spectrum. Calcd for C₁₀H₁₀Br₂O₃: 335.8998. Found: 335.9002.

This rearrangement was also run and monitored in an nmr tube. Compound 17 lost HBr before the first scan could be completed to give 6-bromo-3,3-dimethyl-1-oxaspiro[3.5]nona-5,8-diene-2,7-dione (21): nmr (CDCl₃) δ 7.55 (d, 1, J = 3.0 Hz), 7.20 (d of d, 1, J = 3.0 and 10.0 Hz), 6.45 (d, 1, J = 10.0 Hz), 1.46 (s, 3), and 1.42 (s, 3). Compound 21 reacted rapidly with HBr to give 22.

3-Bromo-4-hydroxy-α-methylhydratropic Acid (23) from Reaction of 2 with HBr.—Gaseous HBr was bubbled through a stirred solution of 1.0 g of 2 in 25 ml of chloroform. After the HBr addition was started, 250 μl of pyridine was added and the solution was refluxed for 5 min. The solvent was removed at room temperature and reduced pressure. The residue contained starting material and an acid identified by ir. The residue was dissolved in saturated aqueous NaHCO₃, washed with ether, acidified with 10% aqueous HCl, and extracted with ether. The ether solution was dried (MgSO₄), and the ether was removed at room temperature and reduced pressure to give 0.8 g (55%) of 23: mp 108–109°; ir (KBr) 3.5 (broad), 3.02, and 5.85 μ; nmr (CDCl₃) δ 7.75 (broad s, 2), 7.50–6.65 (complex, 3), and 1.51 (s, 6). High-resolution mass spectrum. Calcd for C₁₀H₁₁BrO₃: 257.9904. Found: 257.9908.

***endo*-1,4,4a,8a-Tetrahydro-8-isopropylidene-1,4-methanonaphthalen-5-one (24).**—Cyclopentadiene (9.0 g, 0.135 mol) was added to a stirred slurry of 24.0 g (0.135 mol) of 2 in 125 ml of benzene. The slurry was maintained at 40° for 48 hr. A total of 12 ml of solution was withdrawn during the 48-hr period in order to monitor the reaction. The solvent was removed at room temperature and reduced pressure to give 23.0 g (75%) of 24, mp 70–75°. Small amounts of the product were purified by recrystallization from petroleum ether and by sublimation at 75° (0.1 mm): mp 74–75°; ir (Nujol) 6.10 and 6.24 μ; nmr (CDCl₃) δ 7.25 (d, 1, J = 10.0 Hz), 5.92 (t, 2, J = 1.5 Hz), 5.57 (d, 1, J = 10.0 Hz), 3.50–3.15 (complex, 3), 2.96 (d of d, 1, J = 4.0 and 9.5 Hz), 2.03 (s, 3), 1.92 (s, 3), and 1.35 (finely split s, 2); uv max (95% C₂H₅OH) 319 (ϵ 14,234) and 225 (7032); mass spectrum (70 eV) m/e 134 (B), no molecular ion.

Anal. Calcd for C₁₄H₁₆O: C, 83.96; H, 8.05. Found: C, 84.14; H, 8.15.

4-Hydroxy-α-methylhydratropic Acid (25).—A solution of 10 g (0.056 mol) of 2 in 100 ml of ethyl acetate was hydrogenated at room temperature over 1.0 g of 5% palladium-on-carbon catalyst at 2.7 atm of hydrogen. The catalyst was removed by filtration and the solvent by evaporation. The residue was slurried in hexane and filtered to give 8.1 g (80%) of 25, mp 149.5–

152.0°. Recrystallization from benzene–ethyl acetate gave 6.0 g of 25 as a white solid: mp 154–155°; ir (KBr) 3.00, 3.4 (broad), and 6.00 μ; nmr [(CD$_3$)$_2$CO] δ 9.0 (broad s, 2), 7.30 (d, 2, J = 9.0 Hz), 6.75 (d, 2, J = 9.0 Hz), and 1.55 (s, 6).

Anal. Calcd for C$_{10}$H$_{12}$O$_3$: C, 66.65; H, 6.71; mol wt, 180.2. Found: C, 66.28; H, 6.69; mol wt, 178 (ebullioscopic in acetone).

Registry No.—2, 29818-35-7; 7, 29818-36-8; 7 methyl ester, 29818-37-9; 8, 29818-38-0; 10, 29818-39-1; 11, 26172-13-4; 12, 29818-40-4; 14, 29843-54-7;

Ketenes. XVI. The Reactions of Dimethylketene with α-Dicarbonyl and Related Compounds[1]

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Reaction of dimethylketene with benzil and its mono-*p*-tolylimine gave 4,4-dimethyl-1,5-diphenyl-2,6-dioxabicyclo[3.1.0]hexan-3-one (8) and 4,4-dimethyl-1,5-diphenyl-2-*p*-tolyl-6-oxa-2-azabicyclo[3.1.0]hexan-3-one (18), respectively. These adducts underwent hydrolysis to afford derivatives of 3-phenylhydracrylic acid. Treatment of 8 with boron trifluoride gave 3,3-dimethyl-5,5-diphenyl-2,4(3H,5H)-furandione (12). Dimethylketene reacted with α-dianils to give pyrazinones.

The reactions of ketenes with isolated carbonyl groups to give β-lactones is well known, but their reactions with α-dicarbonyl groups have received little attention. This paper describes the reactions of dimethylketene with α-diketones, α-ketoanils, and α-dianils.

In 1947 Schönberg and Mustafa obtained the cycloadduct 2 from diphenylketene and phenanthrenequinone (1) in the presence of sunlight.[2] We also obtained 2
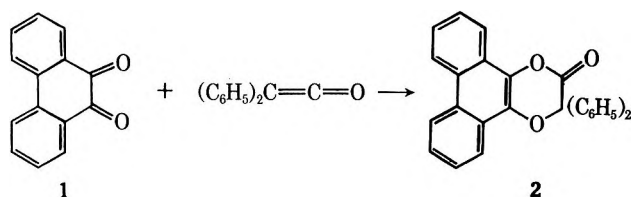
and found that the addition did not require ultraviolet light but proceeded smoothly using a Lewis acid catalyst. Dimethylketene and 1 in the presence of zinc chloride did not react in an analogous fashion but gave the mono β-lactone 3. Structure 3 was assigned on the
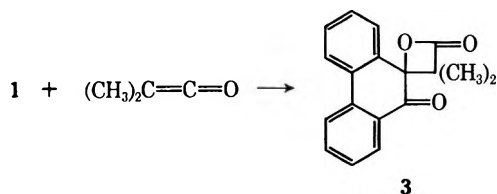
basis of its infrared spectrum which showed bands at 5.49 μ (β-lactone carbonyl) and 5.9 μ (ketone carbonyl).

Ried and Radt reported that diphenylketene (5a) underwent a 1,4 cycloaddition reaction with the halo-

genated *o*-quinones 4a and 4b to give 6a and 6b.[3-5] Dimethylketene (5b) reacted similarly to give 6c.[6]
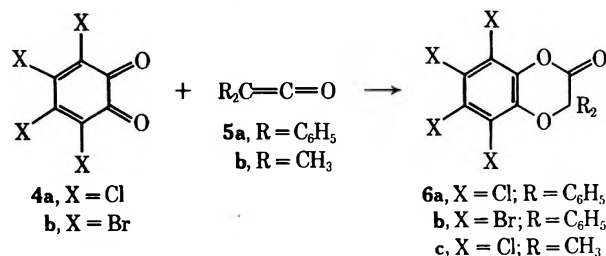
Several other examples of the 1,4 addition of ketenes[2,6,7] and ketenimines[5] to *o*-quinones have been reported. Hagemeyer reported that ketene combined with 2,3-butanedione to give 3-methyl-3-buten-2-one and 2,3-dimethyl-1,3-butadiene, presumably *via* β-lactone intermediates, but no evidence supporting these structures was presented.[8]

We found that dimethylketene did not react with benzil in the absence of a Lewis acid catalyst. In the presence of zinc chloride reaction occurred, not to give the expected 1:4 cycloadduct 7, but the bicyclic com-
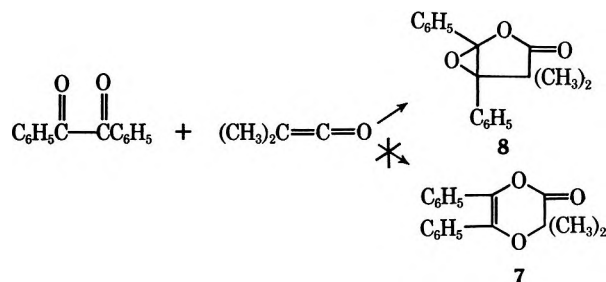
(1) Paper XV in this series: J. L. Chitwood, P. G. Gott, J. J. Krutak, Sr., and J. C. Martin, *J. Org. Chem.*, **36**, 2216 (1971).

(2) A. Schönberg and A. Mustafa, *J. Chem. Soc.*, 997 (1947).

(3) W. Ried and W. Radt, *Angew. Chem., Int. Ed. Engl.*, **2**, 397 (1963).

(4) W. Ried and W. Radt, *Justus Liebigs Ann. Chem.*, **676**, 110 (1964).

(5) W. Ried and W. Radt, *ibid.*, **688**, 170 (1965).

(6) L. Horner, E. Spietschka, and A. Gross, *ibid.*, **573**, 17 (1951).

(7) J. L. E. Erickson and J. M. Dechary, *J. Amer. Chem. Soc.*, **74**, 2644 (1952).

(8) H. J. Hagemeyer, *Ind. Eng. Chem.*, **41**, 765 (1949).

pound **8** in 84% yield. Structure **8** was assigned on the basis of spectral and chemical evidence. In the nmr spectrum the methyl groups of **8** appeared as two singlets at δ 1.20 and 1.47 which did not coalesce on heating in the nmr probe. The methyl groups of **7** would have been expected to appear as a singlet. The uv spectrum of **8** showed reasonable agreement with that reported for *cis-α,α'*-epoxybibenzyl[9] but not for stilbene itself.

When heated with methanol in the presence of a catalytic amount of sodium methoxide, **8** gave benzil and

$$8 \ + \ CH_3OH \ \xrightarrow{\ ^-OCH_3\ } $$

$$C_6H_5C{\overset{O}{\overset{\|}{-}}}CC_6H_5 \ + \ (CH_3)_2CHCOCH_3$$
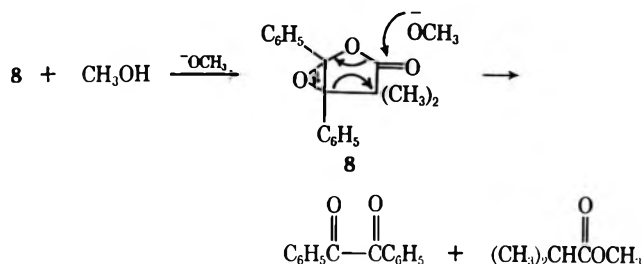
methyl isobutyrate. The same products could have arisen from structure **7**; however, aqueous base and acid hydrolysis gave products **9** and **10**, respectively,
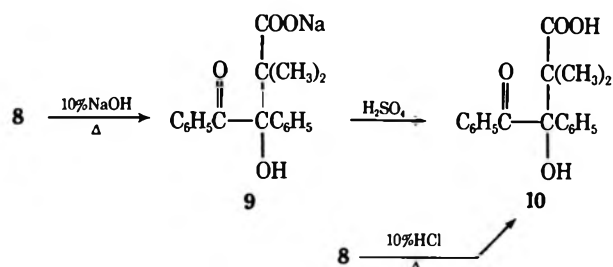
which can only arise from **8**. The sodium salt **9** was extremely insoluble in water, and hot 50% sulfuric acid was necessary to liberate the free acid **10**. Hydrolysis of **8** with 10% lithium hydroxide followed by treatment with hydrochloric acid at room temperature gave a 95% yield of **10**. On thermolysis in the absence of a catalyst, **8** evolved CO$_2$ and gave 3-methyl-2-phenylcrotonophenone (**11**) as the main product, together with small amounts of 3,3-dimethyl-5,5-diphenyl-2,4(3H,5H)-furandione (**12**) and benzil.
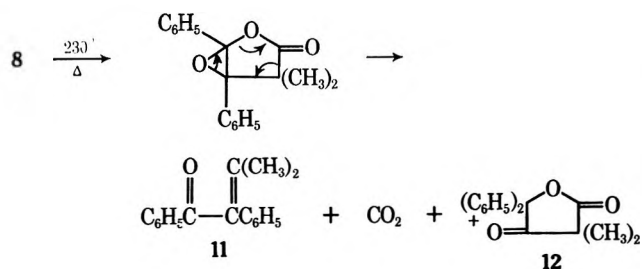
Thermolysis of **8** in the presence of zinc chloride gave 3,3-dimethyl-2-phenyl-1-indanone (**13**) which probably arose from ring closure of **11**.
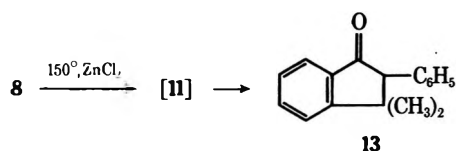
When the reaction of benzil with dimethylketene was carried out in the presence of boron trifluoride instead of zinc chloride, **12** was obtained in 70% yield; however, **8** is probably an intermediate since it is also rearranged to **12** by boron trifluoride.

Hydrogenation of **8** over Raney nickel gave **14** in modest yield.
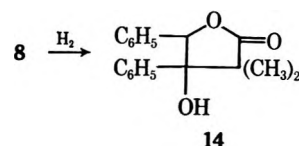
Ketene and diphenylketene did not react with benzil in the presence of zinc chloride. Dimethylketene reacted with 2,3-butanedione in the presence of either zinc chloride or boron trifluoride to give intractable mixtures.

The reaction of the dianils **15a** and **15b** with dimethylketene gave pyrazinones **16a** and **16b**, respectively. No
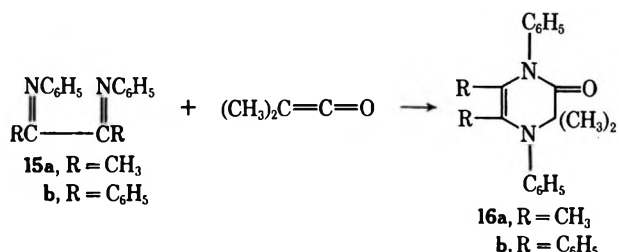
catalyst was necessary. Pfleger and Jäger[10] reported similar results from the 1,4 cycloaddition of phenylketene and diphenylketene to the dianil **15a**.

The α-ketoanil, 2-phenyl-2-(*p*-tolylimino)acetophenone (**17**), reacted with dimethylketene to give 4,4-dimethyl-1,5-diphenyl-2-*p*-tolyl-6-oxa-2-azabicyclo[3.1.0]-hexan-3-one (**18**) in 87% yield. The structure assign-

ment for **18** was based on spectral evidence and on the fact that hydrolysis with 10% hydrochloric acid gave **19**, which was also obtained by treatment of **8** with *p*-toluidine.
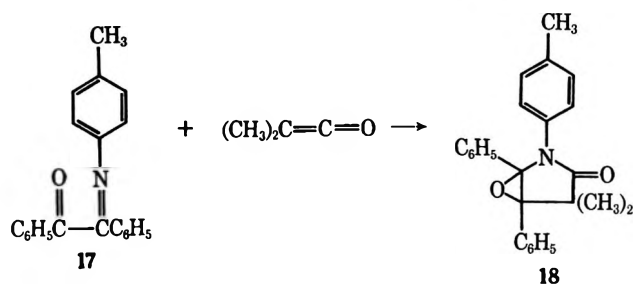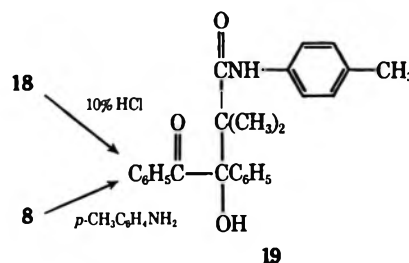
The reaction of ketenes with α-dicarbonyl compounds is obviously not general but varies with the ketene, the structure and reactivity of the α-dicarbonyl compound, and the catalyst used.

(9) L. A. Strait, D. Jambotkar, R. Ketcham, and M. Hrenoff, *J. Org. Chem.*, **31**, 3976 (1966).

(10) R. Pfleger and A. Jäger, *Chem. Ber.*, **90**, 2460 (1957).

Experimental Section

3,3-Diphenylphenanthro[9,10-b]-p-dioxin-2-one (2).[2]—Phenanthrenequinone (5.2 g, 0.025 mol) was added to a solution of 4.8 g (0.025 mol) of diphenylketene in 100 ml of tetrahydrofuran containing 0.5 g of zinc chloride. The solution was stirred overnight and filtered to remove 2.3 g of 2. The filtrate, when concentrated, gave an additional 4.8 g of 2 (total yield: 7.1 g, 71%): mp 233–235° (lit.[2] mp 227–230°); ir (KBr) 5.61 μ; uv max (CH$_2$Cl$_2$) 255 mμ (ϵ 40,737) and 225 (27,158).

3,3-Dimethylspiro[oxetane-2,9'(10'H)-phenanthrene]-4,10'-dione (3).—Dimethylketene (2.9 g, 0.034 mol) was added to a solution of 5.2 g (0.025 mol) of phenanthrenequinone in 200 ml of tetrahydrofuran containing 0.5 g of zinc chloride. The mixture was stirred overnight at room temperature and yielded 8 g of viscous oil when the solvent was removed *in vacuo*. A 3-g sample of this crude product was purified by column chromatography; a 500 × 25 mm column packed with 120 g of Grace silica gel, grade 12, 28–200 mesh was used. The elution solvent was an 85:15 petroleum ether–ethyl acetate solution. Twelve 125-ml fractions were collected; fractions 4–12 were combined and yielded 2 g of solid when the solvent was removed *in vacuo*. Recrystallization of this solid from cyclohexane gave 1.62 g (62%) of 3: mp 108–109°; ir (KBr) 5.49 and 5.9 μ; nmr (CDCl$_3$) δ 0.92 (s, 3), 1.20 (s, 3), and 7.2–8.1 (m, 8); uv max (CH$_3$OH) 244 mμ (ϵ 53,388) and 204 (41,914).

Anal. Calcd for C$_{18}$H$_{14}$O$_3$: C, 77.68; H, 5.07. Found: C, 77.35; H, 5.15.

4,4-Dimethyl-1,5-diphenyl-2,6-dioxabicyclo[3.1.0]hexan-3-one (8).—Dimethylketene (53 g, 0.76 mol) was added in 10-ml portions to a slurry of 105 g (0.5 mol) of benzil in 300 ml of ether containing 1 g of zinc chloride. The reaction was slightly exothermic and the temperature rose to a maximum of 30.5°. The solution was stirred overnight and washed with a 10% K$_2$CO$_3$ solution, and the ether was removed *in vacuo*. The residue, when recrystallized from acetonitrile, gave 118 g (84%) of 8: mp 91–92°; ir (KBr) 5.59 μ; ir (Nujol) 5.61 μ; nmr (CDCl$_3$) δ 1.20 (s, 3), 1.47 (s, 3), and 7.23 (m, 10); uv max (CH$_3$OH) 208 mμ (ϵ 22,774) and 256 (651).

Anal. Calcd for C$_{18}$H$_{16}$O$_3$: C, 77.12; H, 5.75. Found: C, 76.96; H, 5.72.

Treatment of 8 with Methanolic Sodium Methoxide.—8 (5 g, 0.018 mol) was combined with 15 ml of methanol containing 0.1 g of sodium methoxide, and the solution was refluxed for 2.5 hr. Glpc showed the presence of methyl isobutyrate. The methanol and methyl isobutyrate were removed by distillation, and the residue, when treated with petroleum ether, yielded 3 g (80%) of benzil.

Sodium 3-Benzoyl-2,2-dimethyl-3-phenylhydracrylate (9).—8 (14 g, 0.05 mol) was combined with a solution of 150 ml of aqueous 10% NaOH, and the mixture was refluxed for 22 hr. The solution was cooled and the product filtered and dried to give 13.5 g (85%) of 9: mp (as a DTA endotherm) 258°; ir (KBr) 6.0 and 6.4 μ; nmr (CD$_3$SOCD$_3$) δ 0.97 (s, 3), 1.20 (s, 3), 7.64 (m, 2), 7.3 (m, 3), and 9.8 (s, 1). An analytical sample was recrystallized from dimethylformamide. Heating 4.75 g of 9 with 75 ml of concentrated HCl gave 4.4 g of recovered 9. It was necessary to heat the salt with 50% H$_2$SO$_4$ in order to obtain the free acid 10.

3-Benzoyl-2,2-dimethyl-3-phenylhydracrylic Acid (10).—8 (14 g, 0.05 mol) was combined with 200 ml of aqueous 10% HCl, and the slurry was stirred and refluxed for 2.5 hr. The mixture was cooled and filtered, and the white solid was washed with water and dried to give 14.7 g (99%) of 10: mp 209.5–210.5°; ir (KBr) 5.96 and 6.03 μ; nmr (CDCl$_3$, CD$_3$SOCD$_3$) δ 1.21 (s, 3), 1.26 (s, 3), 6.3 (s, 1), 7.64 (m, 2), 7.3 (m, 3), and 11.4 (s, 1); uv max (CH$_3$OH) 252 mμ (ϵ 7336). Recrystallization from ethyl acetate gave an analytical sample with mp 210–211°.

Anal. Calcd for C$_{18}$H$_{18}$O$_4$: C, 72.47; H, 6.08. Found: C, 72.55; H, 6.14.

10 was also prepared from 8 and aqueous lithium hydroxide as follows. 8 (14 g, 0.05 mol) was combined with 200 ml of 10% lithium hydroxide solution, and the slurry was stirred and refluxed for 20.5 hr. The resulting lithium salt was collected by filtration and stirred overnight with 100 ml of concentrated HCl. The solid was removed by filtration, washed with water, and dried; the yield of 10 was 14.2 g (95%).

3-Methyl-2-phenylcrotonophenone (11) by Thermolysis of 8.—8 (14 g, 0.05 mol) was placed in a flask and heated in an oil bath at *ca.* 230° for 2.3 hr. Carbon dioxide, detected by ir, was

evolved during the early part of the heating period. The residual oil weighed 12.1 g: ir (neat) 5.58, 5.7, and 6.03 μ. Samples collected by preparative glpc showed the oil to be a mixture of *ca.* 75% 11, 15% 12, and 10% benzil.

11: ir (neat) 6.03 μ; nmr (CDCl$_3$) δ 1.75 (s, 3), 1.83 (s, 3), 7.9 (m, 2), and 7.3 (m, 8).

Anal. Calcd for C$_{17}$H$_{16}$O: C, 86.41; H, 6.82. Found: C, 85.91; H, 6.79.

12: mp 78–80°; ir (neat) 5.58 and 5.7 μ; nmr (CDCl$_3$) δ 1.42 (s, 6), and 7.35 (m, 10).

Anal. Calcd for C$_{18}$H$_{16}$O$_3$: C, 77.12; H, 5.75. Found: C, 76.92; H, 5.81.

3,3-Dimethyl-5,5-diphenyl-2,4(3H,5H)-furandione (12).—Dimethylketene (7.7 g, 0.11 mol) was added in three portions to a solution of 21 g (0.1 mol) of benzil in 150 ml of ether containing 3 ml of boron trifluoride etherate. The mixture was allowed to stand overnight, and removal of the ether *in vacuo* left an oil that crystallized. The crude product, after recrystallization from a mixture of cyclohexane and petroleum ether, gave 19.6 g (70%) of 12. Glpc showed it to be contaminated with *ca.* 10% 11.

The rearrangement of 8 to 12 was carried out by treatment of 2.8 g (0.01 mol) of 8 in 10 ml of CHCl$_3$ with 5 drops of boron trifluoride etherate. Removal of the solvent *in vacuo* left 2.8 g of crude 12 contaminated with benzil and 11, as shown by glpc.

3,3-Dimethyl-2-phenyl-1-indanone (13) by Thermolysis of 8 in the Presence of Zinc Chloride.—8 (14 g, 0.05 mol) was placed in a flask along with 0.2 g of ZnCl$_2$ and the flask immersed in an oil bath at 150°. Vigorous evolution of gas began immediately and ceased in less than 5 min. The bath temperature was raised to 225° and kept there for 1 hr. The resulting oil crystallized on cooling. Recrystallization from benzene gave 6.2 g (53%) of 13.

An analytical sample was recrystallized from CHCl$_3$: mp 157–158°; ir (KBr) 5.86 μ; nmr (CDCl$_3$) δ 0.87 (s, 3), 1.53 (s, 3), 3.70 (s, 1), and 6.8–7.8 (m, 9).

Anal. Calcd for C$_{17}$H$_{16}$O: C, 86.41; H, 6.82. Found: C, 86.39; H, 6.89.

Dihydro-4-hydroxy-3,3-dimethyl-4,5-diphenyl-2(3H)-furanone (14).—8 (14 g, 0.05 mol) was hydrogenated in 200 ml of cyclohexane at 100°, 1500 psi of H$_2$, over 2 g of Raney nickel for 2 hr. Removal of the catalyst by filtration and removal, *in vacuo*, of the solvent from the filtrate left 14.8 g of a mixture of 14 and 8. Recrystallization from ethanol gave 4.7 g (42%) of 14. Concentration of the filtrate gave 3.5 g of 8. An analytical sample of 14 was obtained by recrystallization from benzene: mp 210–212°; ir (KBr) 5.75 μ; nmr (CDCl$_3$, CD$_3$SOCD$_3$) δ 0.86 (s, 3), 1.50 (s, 3), 5.75 (s, 1), 5.90 (s, 1), and 6.8–7.4 (m, 10).

Anal. Calcd for C$_{18}$H$_{18}$O$_3$: C, 76.57; H, 6.43. Found: C, 76.20; H, 6.51.

3,4-Dihydro-3,3,5,6-tetramethyl-1,4-diphenyl-2(1H)-pyrazinone (16a).—Dimethylketene (9.8 g, 0.14 mol) was added in six portions to a solution of 23.6 g (0.1 mol) of N,N'-(dimethylethanediylidene)dianiline (15a)[10] in 300 ml of ether. The product began to separate during the addition. The solution was stirred overnight and the ether evaporated to give 29 g (95%) of 16a. An analytical sample was recrystallized from cyclohexane: mp 160–161°; ir (KBr) 5.71 and 5.99 μ; nmr (CDCl$_3$) δ 1.38 (s, 3), 1.42 (s, 3), 1.82 (s, 6), and 6.5–7.6 (m, 10); uv max (CH$_3$OH) 203 mμ (ϵ 38,872) and 250 (16,201).

Anal. Calcd for C$_{20}$H$_{22}$N$_2$O: C, 78.40; H, 7.25; N, 9.14. Found: C, 78.51; H, 7.30; N, 9.09.

3,4-Dihydro-3,3-dimethyl-1,4,5,6-tetraphenyl-2(1H)-pyrazinone (16b).—Dimethylketene (7.0 g, 0.1 mol) was added to a solution of 18 g (0.05 mol) of N,N'-(diphenylethanediylidene)dianiline (15b)[11] in 100 ml of tetrahydrofuran. The solution, stirred overnight and filtered, yielded 7.3 g of 16b. Evaporation of the filtrate solvent gave an additional 10.3 g of 16b (total yield: 17.6 g, 82%). An analytical sample was recrystallized from acetonitrile: mp 198–199°; ir (KBr) 5.69 and 6.09 μ; nmr (CDCl$_3$) δ 0.92 (s, 3), 1.73 (s, 3), and 6.4–7.7 (m, 20); uv max (CH$_3$OH) 203 mμ (ϵ 50,724).

Anal. Calcd for C$_{30}$H$_{26}$N$_2$O: C, 83.69; H, 6.09; N, 6.51. Found: C, 83.68; H, 6.20; N, 6.51.

2-Phenyl-2-(p-tolylimino)acetophenone (17).—Benzil (84 g, 0.4 mol) and 51 g of p-toluidine were combined and heated at 170–220° for 2.5 hr with slow removal of water. The resulting

(11) J. S. Walia, J. Singh, M. S. Chattha, and M. Satyanarayana, *Tetrahedron Lett.*, 195 (1969).

oil was cooled and added to ethanol, and the crystals were collected by filtration. The yield of 17 was 72 g (60%): mp 113–114°; ir (KBr) 6.0 and 6.18 μ; nmr (CDCl₃) δ 2.27 (s, 3) and 6.4–8.0 (m, 14).

Anal. Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.13; H, 5.84; N, 4.59.

4,4-Dimethyl-1,5-diphenyl-2-p-tolyl-6-oxa-2-azabicyclo[3.1.0]-hexan-3-one (18).—Dimethylketene (7.7 g, 0.11 mol) was added in two portions to a solution of 30 g (0.1 mol) of 17 in 250 ml of ether. The temperature rose to 34°, and product began to separate after about 0.5 hr. The mixture, stirred overnight and filtered, gave 26 g (71%) of 18: mp 183–184°; ir (KBr) 5.75 μ; nmr (CDCl₃) δ 1.21 (s, 3), 1.43 (s, 3), 2.05 (s, 3), and 6.8–7.5 (m, 14).

Anal. Calcd for $C_{25}H_{23}NO_{2}$: C, 81.27; H, 6.27; N, 3.79. Found: C, 81.26; H, 6.41; N, 3.51.

3-Benzoyl-2,2-dimethyl-3-phenyl-p-hydracrylotoluidide (19).—18 (5 g, 0.014 mol) was combined with 75 ml of aqueous 10% HCl and the mixture refluxed with stirring for 4 hr. An ir spectrum of the crude material showed a band at 5.73 μ (starting material). The solid was dried, ground in a mortar, and re-

fluxed for an additional 2 hr in 75 ml of aqueous 10% HCl. Filtration of the cooled solution gave 4.6 g (88%) of crude 19. An analytical sample was recrystallized from xylene: mp 216–217°; ir (Nujol) 6.0 μ; nmr (CDCl₃, CD₃SOCD₃) δ 1.02 (s, 3), 1.60 (s, 3), 2.24 (s, 3), 5.17 (s, 1), 7.45 (m, 2), and 6.6–7.3 (m, 12).

Anal. Calcd for $C_{25}H_{25}NO_{3}$: C, 77.49; H, 6.50; N, 3.61. Found: C, 77.49; H, 6.58; N, 3.30.

19 was also obtained by treatment of 8 with p-toluidine. 8 (14 g, 0.05 mol) and 5.35 g (0.05 mol) of p-toluidine were combined and heated at 100° for 1 hr. The ir spectrum showed a new band at 6.0 μ. An additional 0.05 mol of p-toluidine was added and the mixture heated at 150° for 2 hr. The oil was cooled and treated with cyclohexane to give 5.9 g (31%) of 19.

Registry No.—3, 29689-76-7; 8, 29689-77-8; 9, 29689-78-9; 10, 29689-79-0; 11, 29689-80-3; 12, 29689-81-4; 13, 29689-82-5; 14, 29689-83-6; 16a, 29689-84-7; 16b, 29689-85-8; 17, 29689-86-9; 18, 29784-79-0; 19, 29784-80-3; dimethylketene, 598-26-5.

Some Reactions of Tetramethylallene

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Tetramethyllallene (TMA) reacted with sulfonyl isocyanate *via* a 2 + 2 cycloaddition to give the azetidinone 1. Trichloroacetyl isocyanate and TMA reacted *via* a 4 + 2 cycloaddition to give 2, which rearranged readily to the acyclic product 3. TMA reacted thermally with acrylonitrile to give a mixture of the cyclobutane 4 and the acyclic diene 5. Dimethyl acetylenedicarboxylate and TMA reacted to afford a mixture of the isomeric trienes 9 and 10.

The purpose of this paper is to report some of the reactions of tetramethylallene (TMA) with activated isocyanates, electron-deficient olefins, and acetylenes.

TMA undergoes facile cycloaddition reactions with heterocumulenes. The reactions of TMA with dimethylketene and diphenylketene have been reported.[1] Moriconi and Kelly[2,3] have reported the cycloaddition of chlorosulfonyl isocyanate to TMA and other allenes. In agreement with Moriconi's work, we found that activated isocyanates react readily with TMA. p-Tolylsulfonyl isocyanate and TMA, when warmed in benzene, gave 3-isopropylidene-4,4-dimethyl-1-(p-tolylsulfonyl)-2-azetidinone (1) in 67% yield.
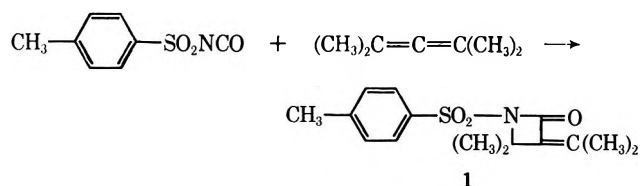
Interestingly, replacement of the p-tolylsulfonyl moiety by a trichloroacetyl group results in facile formation of 2, a 1,4 cycloadduct of a type not available from sulfonyl isocyanates. The reaction between trichloroacetyl isocyanate and TMA in carbon tetrachloride at ambient temperature was followed by nmr. The complete conversion to 2 required about 18 hr and was evidenced by the disappearance of the TMA singlet and

the appearance of three singlets characteristic of the methyl groups of 2.
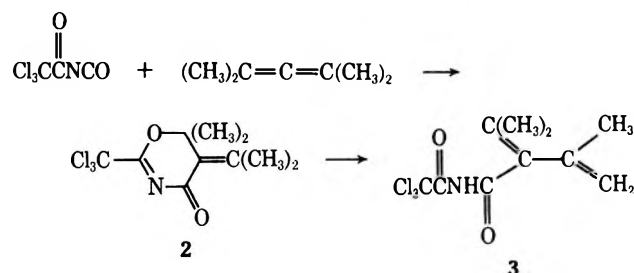
After 9 days at room temperature, 2 had completely rearranged to 3, as evidenced by the disappearance of the spectrum of 2 and the appearance of a new spectrum characteristic of 3. A preparative run gave 3 in 82% yield.

The thermal reaction of TMA with electron-deficient olefins was reported to yield six-membered-ring products, resulting from a preliminary isomerization of the allene to 2,4-dimethyl-1,3-pentadiene (7) followed by a Diels–Alder reaction.[4] Instead, we found that the reaction of TMA and acrylonitrile at 150° gave a 73% conversion to a 3:2 mixture of 3-isopropylidene-2,2-dimethylcyclobutanecarbonitrile (4) and 4-isopropenyl-5-methyl-4-hexenenitrile (5). None of the reported product (6) was found, but, when TMA was deliberately isomerized to the conjugated diene 7 and then heated with acrylonitrile, the cyclohexene 6 was the exclusive product.

(1) J. C. Martin, P. G. Gott, V. W. Goodlett, and R. H. Hasek, *J. Org. Chem.*, **30**, 4175 (1965).

(2) E. J. Moriconi and J. F. Kelly, *J. Amer. Chem. Soc.*, **88**, 3657 (1966).

(3) E. J. Moriconi and J. F. Kelly, *J. Org. Chem.*, **33**, 3036 (1968).

(4) D. R. Taylor and D. B. Wright, *Chem. Commun.*, 434 (1968).
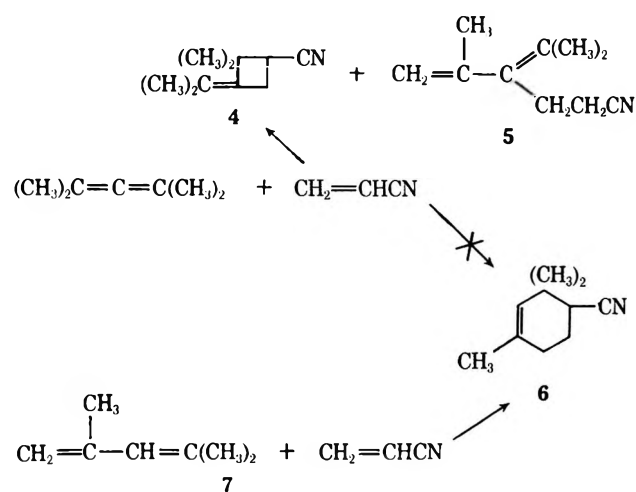
The identities of **4** and **5** were assigned on the basis of their nmr and ir spectra. Compound **5** showed no maximum in its ultraviolet spectrum. Precedent for this absence is found in the work of Criege and Noll,[5] who observed that certain isomers of polymethylated 1,3-butadienes had no uv maximum.

The addition of TMA to dimethyl acetylenedicarboxylate occurred readily in a variety of solvents at temperatures of 80–110°.[6] In each solvent, most of the volatile material obtained consisted of two 1:1 adducts, dimethyl (1-isopropylidene-2-methylallyl)fumarate (**8**) and dimethyl (1-isopropylidene-2-methylallyl)maleate (**9**).[7] The combined yields of **8** and **9** varied between 25 and 50% (see Table I). In addition to **8** and **9**,

TABLE I

REACTION CONDITIONS AND PRODUCT COMPOSITIONS FOR
THE ADDITION OF TMA TO DIMETHYL ACETYLENEDICARBOXYLATE

Solvent	Temp, °C	Reaction time, hr	Yield of 1:1 adduct isolated, %	9/8 ratio
No solvent	100–120	4	35	65/35
Toluene	110	7	47	85/15
Benzene	80	42	35	73/27
Benzene	25	25 days	Not isolated	47/53
Tetramethyl-allene[a]	100	3	45	75/25
Cumene	110	5	35	70/30
Acetonitrile	82	24	57	35/65
Carbon tetrachloride	77	46	58	38/62

[a] 1 M in dimethyl acetylenedicarboxylate.

these reactions yielded red, high-boiling residues whose spectral data indicated them to be 1:2 adducts from TMA and dimethyl acetylenedicarboxylate. The ratios of **8** and **9** were solvent dependent, varying from 85:15 in toluene to 35:65 in acetonitrile (see Table I); however, the reaction rate was relatively independent of solvent polarity.

Structural assignments for **8** and **9** were made on the basis of spectral data and hydrogenation results. The individual isomer assignments of **8** and **9** were based

(5) R. Criege and K. Noll, *Justus Liebigs Ann. Chem.*, **627**, 3 (1959).

(6) Kiefer and Okamura reported recently that TMA and dimethyl fumarate or maleate gave exclusively the diene-type product analogous to **5**: E. F. Kiefer and M. Y. Okamura, *J. Amer. Chem. Soc.*, **90**, 4187 (1968).

(7) Varying amounts of two other components were detected. Generally their combined areas represented 15% or less of the volatile material. They were not identified.

upon a comparison of the chemical shift values of the vinyl hydrogen adjacent to the carboxylate group with those of dimethyl fumarate and dimethyl maleate.
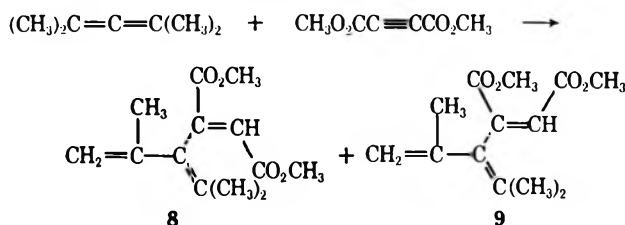
The hydrogenation of a mixture of **8** and **9** to dimethyl (1-isopropyl-2-methylpropyl)succinate (**11**) proved to be difficult, requiring 5% palladium on carbon at 150° and 100 atm. There was very little hydrogen uptake with 5% palladium on carbon at 2.7 atm and room temperature. Hydrogenation over Raney nickel at 150° and 100 atm gave a mixture of dimethyl (1-isopropyl-2-methylpropenyl)succinate (**10**) and **11**. This mixture was resistant to further hydrogenation. Pure
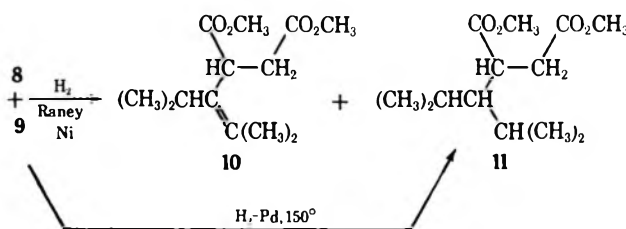
8 gave mostly **11** (85%) upon hydrogenation over Raney nickel, and pure **9** gave approximately equal amounts of **10** and **11**. It is apparent from these results that the tetrasubstituted double bond is hydrogenated over Raney nickel only when the double bond between the carboxylates is in place, perhaps by a 1,4 addition of hydrogen.

Experimental Section

3-Isopropylidene-4,4-dimethyl-1-(p-tolylsulfonyl)-2-azetidinone (1).—A solution of 19.7 g (0.1 mol) of p-tolylsulfonyl isocyanate and 9.6 g (0.1 mol) of TMA[8] in 30 ml of benzene was heated for 12 hr on a steam bath. The solvent was evaporated at room temperature to give 29.1 g of crystalline residue. Recrystallization from ethyl alcohol yielded 19.6 g (67%) of **1**: mp 131–133°; ir (KBr) 5.70 and 5.90 μ; nmr (CH$_2$Cl$_2$) δ 1.59 (s, 6), 1.74 (s, 3), 1.99 (s, 3), 2.39 (s, 3), and 7.60 (typical aromatic AA', BB' pattern, 4).

Anal. Calcd for C$_{15}$H$_{19}$NO$_3$S: C, 61.4; H, 6.5; N, 4.8; S, 10.9. Found: C, 61.6; H, 6.5; N, 4.7; S, 10.9.

2-Isopropenyl-3-methyl-N-(trichloroacetyl)crotonamide (3).—A solution of 3.0 g (0.03 mol) of TMA and 5.7 g (0.03 mol) of trichloroacetyl isocyanate in 10 ml of benzene was stirred under an atmosphere of nitrogen without any noticeable evolution of heat. After standing at room temperature under nitrogen for 9 days, the mixture contained no isocyanate as evidenced by its infrared spectrum. Removal of the solvent *in vacuo* left a low-melting, solid residue. This solid was recrystallized twice from pentane and once from hexane to give 7.0 g (82%) of **3**: mp 61–62°; ir (KBr) 5.63, 5.90, and 6.20 μ; nmr (CCl$_4$) δ 1.91 (s, 3), 2.06 (s, 3), 1.92 (s, 3, C=CCH$_3$ shows fine splitting but is overlapped by peak at 1.91), 5.14 (s, 1), 5.43 (s, 1), and 9.63 (s, 1).

Anal. Calcd for C$_{10}$H$_{12}$Cl$_3$NO$_2$: C, 42.2; H, 4.3; N, 4.9; Cl, 37.4. Found: C, 42.0; H, 4.4; N, 4.7; Cl, 37.4.

A slight excess of trichloroacetyl isocyanate was added to TMA and carbon tetrachloride in an nmr tube. The mixture was

(8) J. C. Martin (to Eastman Kodak Co.), U. S. Patent 3,131,234 (1964).

scanned periodically for several days. After 18 hr the methyl peak at δ 1.60 (TMA) had disappeared, and peaks at δ 1.79 (s, 6), 2.04 (s, 3), and 2.06 (s, 3) characteristic of 5,6-dihydro-5-isopropylidene-6,6-dimethyl-2-(trichloromethyl)-4H-1,3-oxazin-4-one (2) appeared. The infrared spectrum of the solution at this time showed maxima at 5.68, 5.87, and 6.16 μ, which are characteristic of 2. After the solution had stood 2 days at room temperature, the nmr spectrum indicated the start of the decay of 2 to 3. This process was substantially complete after 9 days.

3-Isopropylidene-2,2-dimethylcyclobutanecarbonitrile (4) and 4-Isopropenyl-5-methyl-4-hexenenitrile (5).—A mixture of 50 g (0.5 mole) of TMA, 52 g (1.0 mol) of acrylonitrile, 0.5 g phenothiazine, and 3 g of potassium carbonate was heated in a stainless steel rocking autoclave at 150° for 24 hr. The reaction mixture was filtered, and the filtrate was distilled through a 6-in. Vigreux column to give 52.5 g (73%) of material, bp 69–72° (4 mm). Glpc (Carbowax on Chromosorb at 140°) showed two closely associated peaks (4 and 5) in the area ratio of 3 to 2. Analytical samples were isolated by glpc to give 4 and 5.

4: ir (neat) 4.45 μ (no absorption near 6.0 μ); nmr (CCl$_4$) δ 1.28 (s, 3), 1.35 (s, 3), 1.45 (t, 3, J = 1.0 Hz), 1.56 (t, 3, J = 1.4 Hz), and 2.70 (m, 3).

Anal. Calcd for C$_{10}$H$_{15}$N: C, 80.5; H, 10.1; N, 9.4. Found: C, 80.2; H, 10.4; N, 9.2.

5: ir (neat) 6.13 and 11.1 μ; nmr (CCl$_4$) δ 1.51 (q, 3), 1.68 (s, 6), 2.28 (m, 4), 4.55 and 4.59 (2 quartets, H^{1}H^{2}C=C(CH$_3$^{3})–, $J_{1,2}$ = 2.4 Hz and $J_{1,3}$ = 1.0 Hz), and 4.90 and 4.92 (2 quartets, H^{1}H^{2}C=C(CH$_3$^{3})–, $J_{1,2}$ = 2.4 Hz, $J_{2,3}$ = 1.4 Hz, 1).

Anal. Calcd for C$_{10}$H$_{15}$N: C, 80.5; H, 10.1; N, 9.4. Found: C, 80.5; H, 10.1; N, 9.3.

2,2,4-Trimethyl-3-cyclohexene-1-carbonitrile (6).—A mixture of 40.0 g (0.416 mol) of 2,4-dimethyl-1,3-pentadiene (7),[9] 44 g (0.832 mol) of acrylonitrile, and 0.5 g of phenothiazine was heated in an autoclave at 150° for 12 hr. Distillation through an 8-in. packed column gave 19.1 g (31%) of 6: bp 48° (12 mm); nmr (CCl$_4$) δ 1.13 (s, 6), 1.64 (s, 3), 1.98 (m, 4), 2.44 (m, 1), and 5.07 (finely split singlet, 1).

Dimethyl (1-Isopropylidene-2-methylallyl)fumarate (8) and Dimethyl (1-Isopropylidene-2-methylallyl)maleate (9).—The general procedure used for running the addition reaction of TMA and dimethyl acetylenedicarboxylate follows. Details are given in Table I.

A solution containing 16.0 g (0.16 mol) of TMA and 21.3 g (0.15 mol) of dimethyl acetylenedicarboxylate in 300 ml of solvent was maintained at a constant temperature, usually the reflux temperature.[11] The disappearance of dimethyl acetylenedicarboxylate was monitored by glpc (5% QF-1 silicone on Chromosorb P), and the reaction was allowed to proceed to completion. The solvent and excess TMA were removed at reduced pressure.

The dark red residue was distilled through a 10-in. Vigreux column to give a 35–58% yield of volatile material, bp 85–90° (0.6 mm). The volatile material contained compounds 8 and 9 and varying amounts of two minor components which were not identified. Analytical samples of compounds 8 and 9 were obtained by preparative glpc (QF-1).

8: ir (neat) 3.25, 5.79, and 11.15 μ; nmr (CCl$_4$) δ 1.58 (s, 3), 1.80 (complex, 6), 3.65 (s, 3), 3.72 (s, 3), 4.80 (m, 1), 4.95 (m, 1), and 6.72 (s, 1); mass spectrum (70 eV) m/e base peak 119, molecular ion 238.

Anal. Calcd for C$_{13}$H$_{18}$O$_4$: C, 65.53; H, 7.61. Found: C, 65.61; H, 7.42.

9: ir (neat) 3.25, 5.80, and 11.15 μ; nmr (CCl$_4$) δ 1.8 (complex, 9), 3.68 (s, 3), 3.72 (s, 3), 4.70 (m, 1), 5.05 (m, 1), and 5.80 (s, 1); mass spectrum (70 eV) m/e base peak 119, molecular ion 238.

Anal. Calcd for C$_{13}$H$_{18}$O$_4$: C, 65.53; H, 7.61. Found: C, 65.76; H, 7.53.

The nmr spectra (CCl$_4$) of the residues showed approximately equal area patterns centered at δ 3.7 and δ 1.7. In the nmr spectra of the residues from the reaction in cumene, however, these two patterns were accompanied by a third absorption centered at δ 7.3 with relative areas of 4 (δ 7.3):3 (δ 3.7):12 (δ 1.7). The ir (neat) of the residue showed intense bands at 5.80 and 8.00 (broad) μ.

Hydrogenation of Adducts 8 and 9.—A 22.1-g (0.093-mol) portion of 8 and 9 (ratio of 8 to 9 = 36:64) was dissolved in 200 ml of reagent grade cyclohexane and hydrogenated over 0.5 g of palladium on carbon at 2.7 atm for 8 hr. There was little hydrogen uptake during this time and little change in the glpc trace. The catalyst was removed by filtration, and hydrogenation was attempted with 5.0 g of Raney nickel (alcohol washed) at 150° and 100 atm for 3 hr. The catalyst was removed by filtration and the solvent by rotary evaporation at reduced pressure. Two major components were obtained, each with a different glpc retention time (QF-1) from either 8 or 9. Distillation gave 15.7 g of a mixture of dimethyl (1-isopropyl-2-methylpropenyl)succinate (10) and dimethyl (1-isopropyl-2-methylpropyl)-succinate (11), bp 86.5–88.0° (0.7 mm), in the ratio of 59 to 41. Pure samples were separated by glpc.

10: ir (neat) 5.75 μ; nmr (CDCl$_3$) δ 0.8–1.4 (complex, 6), 1.53 (s, 3), 1.66 (s, 3), 2.0–3.9 (complex, 4), 3.60 (s, 3), and 3.65 (s, 3); mass spectrum (70 eV) m/e base peak 169, molecular ion 242. High-resolution mass spectrum (single peak by glpc). Calcd for C$_{13}$H$_{22}$O$_4$: 242.1518. Found: 242.1520.

11: ir (neat) 5.78 μ; nmr (CDCl$_3$) δ 0.9 (complex, 12), 1.4–3.1 (complex, 6), and 3.62 (s, 6); mass spectrum (70 eV) m/e base peak 114, no molecular ion.

Anal. Calcd for C$_{13}$H$_{24}$O$_4$: C, 63.91; H, 9.90. Found: C, 64.02; H, 9.76.

A sample of the mixture of 10 and 11 was hydrogenated again over Raney nickel at 150° and 100 atm for 6 hr. The ratio of 10 to 11 remained constant. A cyclohexane solution of 8 and 9 from a Raney nickel hydrogenation was hydrogenated over 5% palladium on carbon at 150° and 100 atm for 6 hr. The product was shown to be 11 by glpc retention time and comparison of ir spectra.

Hydrogenation of Adduct 8.—A 2.0-g portion of pure 8 was obtained by preparative glpc. This sample was dissolved in 200 ml of cyclohexane and hydrogenated over Raney nickel at 150° and 100 atm for 3 hr. Analysis by glpc showed 15% 10 and 85% 11.

Hydrogenation of Adduct 9.—A 1.5-g portion of pure 9 was obtained by preparative glpc. The sample was dissolved in 200 ml of cyclohexane and hydrogenated over Raney nickel at 150° and 100 atm for 3 hr. Analysis by glpc showed approximately equal amounts of 10 and 11.

Registry No.—1, 29689-67-6; 3, 29689-68-7; 5, 29689-69-8; 6, 19788-20-6; 8, 29689-71-2; 9, 29689-72-3; 10, 29689-73-4; 11, 29689-74-5; TMA, 1000-87-9.

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(9) Prepared according to ref 4.

(10) To avoid the isomerization of TMA to 2,4-dimethyl-1,3-pentadiene, either the glassware was washed with ammonium hydroxide solution or a pellet of sodium hydroxide was added to the reaction mixture.

Reactions of Trichloroacetyl Isocyanate with Unsaturated Ethers

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The reaction of trichloroacetyl isocyanate with unsaturated ethers gave 1:1 adducts. In most of these reactions the adducts, 3-alkoxy-N-(trichloroacetyl)acrylamides (4 and 5), were linear; however, both four- and six-membered cyclic intermediates, 3-alkoxy-1-(trichloroacetyl)-2-azetidinones (2) and 6-alkoxy-5,6-dihydro-2-(trichloromethyl)-$4H$-1,3-oxazin-4-ones (3), were observed by infrared and nmr spectroscopy. The initially formed mixture of intermediates 2 and 3 went smoothly to linear product. The four-membered-ring intermediate 2 opened to the linear product *via* 3. The cyclic intermediates appear to be formed stereospecifically, and the observed rate enhancement with increasing solvent polarity suggests polar transition states for the formation of both cyclic intermediates and linear products.

The reaction of unsaturated ethers with ketenes has been shown to yield four-membered-ring 1:1 adducts.[1] The highly reactive arylsulfonyl isocyanates were reported by Effenberger and Gleiter to react with unsaturated ethers to give 1:1 adducts, either cyclic or linear depending upon reaction conditions and structure of the ethers.[2a] These authors indicated that acyl isocyanates do not react with unsaturated ethers. Our studies show that trichloroacetyl isocyanate does react with unsaturated ethers to give 1:1 adducts 4,[3] by way of cyclic intermediates 2 and 3.[4]
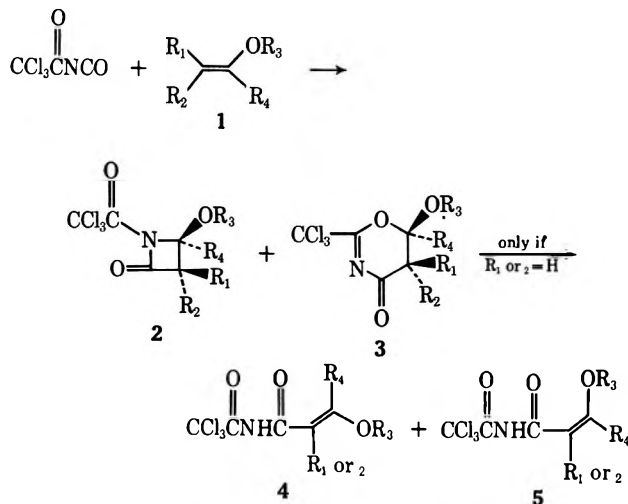
a, $R_{1,2,4}$ = H; R_3 = C_2H_5
b, $R_{2,4}$ = H; $R_{1 \text{ and } 3}$ = $(CH_2)_3$
c, $R_{1,2}$ = CH$_3$; R_4 = H; R_3 = C_2H_5
d, R_1 = CH$_3$; $R_{2,4}$ = H; R_3 = C_2H_5
e, R_2 = CH$_3$; $R_{1,4}$ = H; R_3 = C_2H_5
f, $R_{1,2,3}$ = CH$_3$; R_4 = OCH$_3$
g, $R_{1,2}$ = H; R_3 = C_2H_5; R_4 = OC$_2H_5$

We found that the behavior of acyl isocyanates with unsaturated ethers parallels that of arylsulfonyl isocyanates; therefore, our work confirms that of Effenberger.[2b]

(1) R. H. Hasek, P. G. Gott, and J. C. Martin, *J. Org. Chem.*, **29**, 1239 (1964), and references contained therein.

(2) (a) F. Effenberger and R. Gleiter, *Chem. Ber.*, **97**, 1576 (1964); (b) F. Effenberger and G. Kiefer, *Angew. Chem., Int. Ed. Engl.*, **6**, 95 (1967).

(3) As this paper was being prepared, Speziale and coworkers [L. R. Smith, A. J. Speziale, and J. E. Fedder, *J. Org. Chem.*, **34**, 633 (1969)] reported that chloroacetyl isocyanate and dihydropyran gave a linear 1:1 adduct in low yield. They did not detect any cyclic intermediates. Effenberger and Gleiter[2a] had previously reported that benzoyl isocyanate and unsaturated ethers did not react.

(4) Cyclic products analogous to 2 and 3 were recently reported for the addition of α,β-dialkoxy-substituted olefins and acyl isocyanates: R. Lattrell, *Justus Liebigs Ann. Chem.*, **722**, 142 (1969).

and extends it to isocyanates activated by certain acyl groups.

Infrared and nmr spectroscopy were employed to monitor the course of the reaction and to assign structures to the cyclic intermediates. Preparative runs readily gave the linear products in good yield.

Ethyl vinyl ether (1a) and trichloroacetyl isocyanate reacted vigorously. If the temperature was allowed to rise to *ca.* 50°, a 77% yield of 3-ethoxy-N-(trichloroacetyl)acrylamide (4a) resulted; however, when these same reagents were combined at room temperature in deuteriochloroform, the reaction gave complete conversion to 6-ethoxy-5,6-dihydro-2-(trichloromethyl)-$4H$-1,3-oxazin-4-one (3a). No four-membered-ring intermediate 2a was detected, even when the reaction was run at −45°. That the structure of the intermediate was 3a and not the 1,2 cycloadduct 2a was established from its infrared spectrum. In carbon tetrachloride solution, 3a exhibited maxima at 5.75 (C=N) and 6.21 μ (C=O). If the compound were 2a, it would be expected to show a maximum at shorter wavelength for the strained-ring carbonyl, since Effenberger and Gleiter[2a] found that the carbonyl in analogous sulfonyl compounds absorbed at about 5.54–5.59 μ. Ethyl vinyl ether also reacted with benzoyl isocyanate to form the linear product N-(3-ethoxyacryloyl)benzamide. No effort was made to detect intermediate products.

Benzoyl isocyanate did not react with 3,4-dihydro-$2H$-pyran (1b) in refluxing benzene, but trichloroacetyl isocyanate reacted at room temperature to give a 74% yield of 3,4-dihydro-N-(trichloroacetyl)-$2H$-pyran-5-carboxamide (4b). When the reaction was run in carbon tetrachloride at room temperature and monitored by nmr, the starting materials rapidly formed approximately equal amounts of 2b and 3b. The four-membered cyclic intermediate decayed into 3b, so that at one point during the reaction 3b was the sole species present. Then 3b slowly opened to give 4b.

Trichloroacetyl isocyanate and ethyl 2-methylpropenyl ether (1c) gave 80–87% yields of a mixture of 2c and 3c in carbon tetrachloride or acetonitrile. Initially, about 60% of the mixture was 2c, but 3c rapidly became predominant in acetonitrile solution. The linear product was not formed, since neither R_1 nor R_2 was hydrogen.

Both *cis-* and *trans-*ethyl propenyl ether (1d and 1e) reacted with trichloroacetyl isocyanate in carbon tetrachloride to form four- and six-membered-ring intermediates. The cis isomer 1d gave the intermediates assigned as 2d and 3d, whereas the trans isomer 1e gave

two different intermediates **2e** and **3e**. For each reaction, the six-membered-ring intermediate was the major species formed, and the four-membered-ring intermediate decayed slowly into the six-membered-ring intermediate. Furthermore, the trans intermediate **2e** rearranged to **3e**, and **3e** rearranged into the cis intermediates **2d** and **3d**. After 2–5 days, two linear products **4d** and **5d** began to form. The ratio of **4d:5d** (7:3) remained fairly constant until all cyclic intermediates were consumed; however, after an additional week at room temperature the ratio had reversed.

The vinyl thioether, 2-(vinylthio)ethyl acetate, reacted like vinyl ethers **1a–d** with trichloroacetyl isocyanate; it gave a linear 1:1 adduct **6**.

$$CH_2{=}CHSCH_2CH_2O\overset{\overset{\displaystyle O}{\|}}{C}CH_3 + CCl_3\overset{\overset{\displaystyle O}{\|}}{C}NCO \longrightarrow$$

$$CCl_3\overset{\overset{\displaystyle O}{\|}}{C}NH\overset{\overset{\displaystyle O}{\|}}{C}CH{=}CHSCH_2CH_2O\overset{\overset{\displaystyle O}{\|}}{C}CH_3$$

6
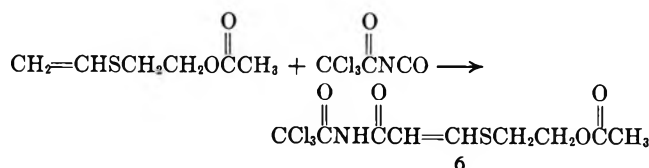
Scarpati and coworkers reported that phenyl isocyanate reacted with disubstituted ketene acetals to form four-membered-ring 1:1 cycloadducts, with monosubstituted ketene acetals to form linear 1:1 adducts, and with unsubstituted ketene acetals to form six-membered-ring 2:1 cycloadducts.[5] In general, we found that the reactions of trichloroacetyl isocyanate with ketene acetals did not parallel those of phenyl isocyanate. Trichloroacetyl isocyanate and dimethylketene dimethyl acetal (**1f**) gave a 1:1 adduct in quantitative yield tentatively assigned as the six-membered-ring compound **3f**. Since the adduct was hydrolyzed rapidly by moisture in the air, isolation was difficult. Unsubstituted ketene acetal (**1g**) and trichloroacetyl isocyanate gave the linear 1:1 adduct, 3,3-diethoxy-*N*-(trichloroacetyl)acrylamide (**4g**). No cyclic intermediates were observed by nmr, even at −45° in deuteriochloroform.

The reaction of ethyl ethynyl ether with trichloroacetyl isocyanate gave 6-ethoxy-2-(trichloromethyl)-4*H*-1,3-oxazin-4-one (**7a**) in quantitative yield and with benzoyl isocyanate gave 6-ethoxy-2-phenyl-4*H*-1,3-oxazin-4-one (**7b**) in 85% yield. The structure of the 1,4

$$R{-}\overset{\overset{\displaystyle O}{\|}}{C}NCO + HC{\equiv}COC_2H_5 \longrightarrow$$

7a, R = CCl₃
b, R = C₆H₅
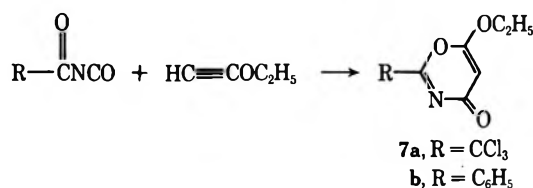
cycloaddition product **7** was assigned from nmr and ir spectra and from hydrolysis and hydrogenation. The hydrolysis of **7a** in acetonitrile containing moist formic acid gave ethyl *N*-(trichloroacetyl)malonamate (**8a**) in quantitative yield. The hydrolysis of **7b** under the same conditions or with dilute aqueous hydrochloric acid gave ethyl *N*-benzoylmalonamate (**8b**). Hydrogenation of **7b** over palladium on carbon gave ethyl *N*-benzylmalonamate (**9**) in 83% yield.

(5) (a) R. Scarpati, *Rend. Accad. Sci. Fis. Mat. (Soc. Naz. Sci. Napoli)*, [4] **26**, 7 (1958); *Chem. Abstr.*, **55**, 11423 (1961). (b) R. Scarpati, G. Del Re, and T. Maone, *Rend. Accad. Sci. Fis. Mat. (Soc. Naz. Sci. Napoli)*, [4] **26**, 26 (1959); *Chem. Abstr.*, **55**, 11423 (1961). (c) R. Scarpati and R. A. Nicolaus, *Rend. Accad. Sci. Fis. Mat. (Soc. Naz. Sci. Napoli)*, [4] **29**, 154 (1962).

$$7 \xrightarrow{H_2O^+} R{-}\overset{\overset{\displaystyle O}{\|}}{C}NH\overset{\overset{\displaystyle O}{\|}}{C}CH_2C\overset{\overset{\displaystyle O}{\|}}{}OC_2H_5$$

8a, R = CCl₃
b, R = C₆H₅

$$7b \xrightarrow[Pd]{H_2} C_6H_5CH_2NH\overset{\overset{\displaystyle O}{\|}}{C}CH_2\overset{\overset{\displaystyle O}{\|}}{C}OC_2H_5$$

9
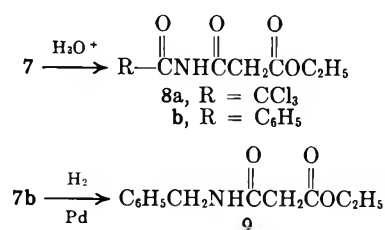
The reaction of 1-buten-3-ynyl methyl ether with trichloroacetyl isocyanate resulted in a cycloaddition involving only the acetylenic bond to give 6-(2-methoxyvinyl)-2-(trichloromethyl)-4*H*-1,3-oxazin-4-one (**10**).

$$CCl_3\overset{\overset{\displaystyle O}{\|}}{C}NCO + HC{\equiv}CCH{=}CHOCH_3 \longrightarrow$$

10
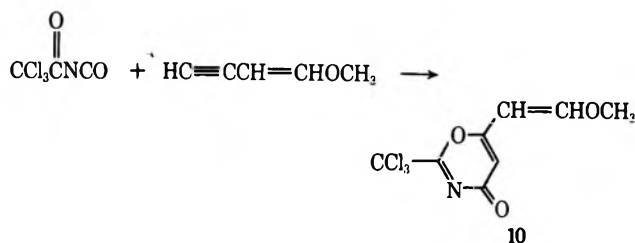
Table I presents the initial ratios of the intermediates and the approximate reaction half-lives for the formation of cyclic intermediates and linear products. Both

TABLE I

INITIAL RATIOS OF INTERMEDIATES AND REACTION HALF-LIVES[a] AT 30° FOR TRICHLOROACETYL ISOCYANATE AND UNSATURATED ETHERS

Ether	Initial ratio of 2/3	$T_{1/2}$ for disappearance of ether in CCl₄,[b] min	$T_{1/2}$ of 2 → 3 in CH₃CN, hr	$T_{1/2}$ of 3 → 4[c] in CCl₄, days
1a	0/1	5		1
1b	1/1	90	<0.5[d]	2
1c	3/2	120	18[e]	
1d	1/4	1	...[f]	6[g]
1e	1/4	10	...[f]	6[g]
1g	Linear adduct only	...[h]		
Ethyl ethynyl ether	0/1	<0.5		

[a] For all systems, [acyl isocyanate] was *ca.* 0.8 *M*; [ether] was *ca.* 0.5 *M*. [b] In CH₃CN, ether was always consumed in 30 sec or less. Rate was *ca.* 350 times faster in CH₃CN. [c] In all systems but dihydropyran, all **2** went to **3** before any linear product was detected; therefore, $T_{1/2}$ was taken as the time from complete disappearance of **1** until half of **4** was formed. [d] $T_{1/2}$ (CCl₄) = *ca.* 5 hr. [e] The rearrangement of **2** to **3** in CCl₄ was too slow for convenient measurement. [f] This system was relatively stable to the **2** to **3** conversion. The conversion of trans products to cis products had a $T_{1/2}$ of *ca.* 5 days in CCl₄. [g] $T_{1/2}$ of *ca.* 1 day in CH₃CN. [h] Too fast to measure.

acetonitrile and carbon tetrachloride were used as solvents in order to obtain convenient reaction rates and to ascertain the effects of solvent polarity. The reaction pathway and the initial ratios of intermediates were virtually the same for both solvent systems. The rate of disappearance of unsaturated ether was about 350 times faster in acetonitrile than in carbon tetrachloride.

The increase in reaction rate with increasing solvent polarity indicates that a polar species is involved in the

formation of these cyclic intermediates[6,7] and in the conversion of 2 to 3. A probable reaction pathway is illustrated below where $k_1 \geq k_2 > k_3$, $k_{-2} > k_{-3}$, both k_2 and $k_3 > k_{-2}$ and k_{-3}, and all the above k's $> k_4$.
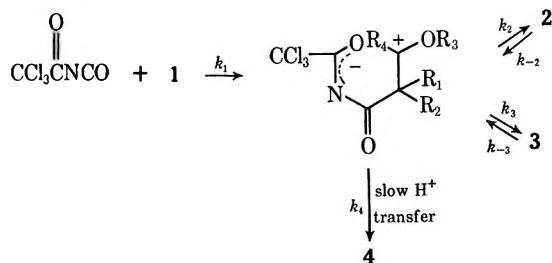
The initial ratio of four-membered-ring intermediate 2 to six-membered-ring intermediate 3 is probably determined largely by the initial conformation of the zwitterion, with orientation A leading to 2 and B to 3.
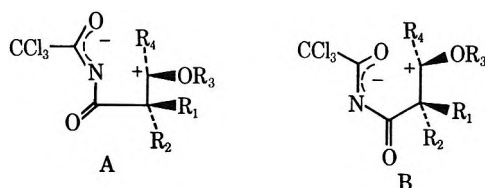
The cycloaddition reactions appear to be stereospecific, since only one isomer of each cyclic intermediate was detected, and, more critically, *trans*-ethyl propenyl ether (1e) gave two distinct, cyclic intermediates, one six-membered and one four-membered, which changed to the two different cyclic intermediates obtained from *cis*-ethyl propenyl ether (1d). Cis addition to the unsaturated ethers is assumed, but there is no unequivocal proof. One might have anticipated that the cyclic products from *trans*-ethyl propenyl ether (1e) would be more stable than those from the cis isomer; however, sulfonyl isocyanates are reported to react with *cis*- and *trans*-methyl propenyl ethers to give compounds analogous to 2d and 2e *via* stereospecific *cis* additions where the product corresponding to 2d is only 0.27 kcal/mol less stable than the one analogous to 2e.[7]

The ethyl propenyl ethers gave two isomeric, linear products 4d and 5d, the relative amount of 4d decreasing with time. The thermodynamic preference for 5d may be due to this isomer's ability to H bond between the N–H and ethoxy oxygen.

In summary, although the relative magnitudes of k_1–k_4 vary somewhat from one unsaturated ether system to another, the trend of the rates appears to be the same. The rate enhancement with increasing solvent polarity suggests polar transition states, but the subtle features controlling the magnitude of the rates are not apparent at this time. The cyclic intermediates appear to be formed stereospecifically.

Experimental Section

Trichloroacetyl isocyanate,[3,9] benzoyl isocyanate,[8] and ketene diethyl acetal[10] were prepared according to literature methods.

2-(Vinylthio)ethyl acetate was prepared by acetylation of the alcohol, which was obtained from Rohm and Haas Co. Ethyl ethynyl ether was obtained from Pfister Chemical Works, and 1-buten-3-ynyl methyl ether was obtained from Chemische Werke Hüls.

3-Ethoxy-*N*-(trichloroacetyl)acrylamide (4a).—Trichloroacetyl isocyanate (9.4 g, 0.05 mol) was added to a stirred solution of 4.0 g (0.056 mol) of ethyl vinyl ether in 25 ml of benzene under a nitrogen atmosphere. The temperature of the mixture was controlled under 50° by an ice bath. The solid that precipitated on standing was removed by filtration. Recrystallization from hexane yielded 10 g (77%) of 4a: mp 80–82°; ir (Nujol) 5.77, 5.98, and 6.30 μ; nmr (CCl₄) δ 1.43 (t, 3), 4.12 (q, 2), 6.58 (d, 1), 7.95 (c, 1), and 9.67 (s, 1).

Anal. Calcd for $C_7H_8Cl_3NO_3$: C, 32.3; H, 3.1; N, 5.4; Cl, 40.8. Found: C, 32.3; H, 3.3; N, 5.2; Cl, 41.4.

Monitoring Intermediate Formation by Nmr and Ir.—The standard procedure used for detecting cyclic intermediates was as follows. An nmr tube containing ca. 150 μl of unsaturated ether in ca. 1 ml of CCl₄ with tetramethylsilane as an internal standard was scanned; ca. 300 μl of trichloroacetyl isocyanate was added at ambient temperature; and the spectrum again was scanned. Repeated scans were made at appropriate intervals, and the ir spectrum of the solution was recorded when sufficient change was observed in the nuclear magnetic resonance. The procedure was then repeated with CH₃CN as solvent. For 1a and 1g in CDCl₃, the isocyanate was added to the solution at −45°; however, no additional intermediates were detected at this lower temperature. The pertinent spectral data are given in Table II.

N-(3-Ethoxyacryloyl)benzamide.—A solution of 20 g (0.136 mol) of benzoyl isocyanate and 10 g (0.138 mol) of ethyl vinyl ether in 75 ml of benzene was refluxed under an atmosphere of nitrogen for 8 hr. The white crystals which deposited on cooling were removed by filtration to give 17 g (57%) of crude product. Recrystallization from ethyl alcohol gave 13 g of *N*-(3-ethoxyacryloyl)benzamide: mp 136–138°; ir (KBr) 5.89, 6.05, and 6.32 μ; nmr (CH₂Cl₂) δ 1.37 (t, 3), 4.10 (q, 2), 6.78 (d, 1), 7.80 (m, aromatic protons and C=CHO, 6), and 9.40 (s, 1).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.8; H, 5.9; N, 6.4. Found: C, 65.9; H, 5.8; N, 6.4.

3,4-Dihydro-*N*-(trichloroacetyl)-2*H*-pyran-5-carboxamide (4b). —Trichloroacetyl isocyanate (5.7 g, 0.03 mol) was added to a stirred solution of 2.6 g (0.031 mol) of dihydropyran in 10 ml of benzene. When the reaction had been stirred at room temperature for several hours, 30 ml of hexane was added, and the resulting crystals of 4b were removed by filtration. After the crystals had been washed with ether and dried, the yield was 6.0 g (74%) of 4b, mp 135–138°. A sample, after recrystallization from ethyl acetate, melted at 136.5–138°: ir (KBr) 5.73, 6.00, and 6.19 μ; nmr (CDCl₃) δ 2.00 (m, 2), 2.41 (t, 2), 4.21 (t, 2), 7.75 (s, 1), and 8.85 (broad singlet, 1).

Anal. Calcd for $C_8H_8Cl_3NO_3$: C, 35.3; H, 3.0; N, 5.1; Cl, 39.0. Found: C, 34.9; H, 3.1; N, 5.1; Cl, 39.0.

4-Ethoxy-3,3-dimethyl-1-(trichloroacetyl)-2-azetidinone (2c) and 6-Ethoxy-5,6-dihydro-5,5-dimethyl-2-(trichloromethyl)-4*H*-1,3-oxazin-4-one (3c).—Two runs were made using different solvents, CCl₄ and CH₃CN. Trichloroacetyl isocyanate (1.0 g, 0.01 mol) was added with stirring to 1.75 g (0.01 mol) of ethyl 2-methylpropenyl ether (1c) in 5 ml of solvent. After the mixture had been stirred 30 min at room temperature, the ir spectra indicated that the reaction in CH₃CN was complete and that the reaction in CCl₄ was about one-half complete. The CCl₄ mixture was stirred for an additional 3.5 hr. The solvents were removed by rotary evaporation to give a mixture of 2c and 3c in the ratio of 3:2. The yield of the mixture was 2.3 g (80%) from CCl₄ and 2.5 g (87%) from CH₃CN. These neat mixtures after standing for several days changed to a ratio of 2:3. The elemental analysis was done on the latter mixture.

Anal. Calcd for $C_9H_{12}Cl_3NO_3$: C, 37.5; H, 4.2; Cl, 36.9; N, 4.9. Found: C, 37.3; H, 4.2; Cl, 37.0; N, 4.8.

2-{[3-Oxo-3-(trichloroacetamido)propenyl]thio}ethyl Acetate (6).—Trichloroacetyl isocyanate (5.7 g, 0.03 mol) was added to a stirred solution of 4.5 g (0.03 mol) of 2-(vinylthio)ethyl ace-

(6) A similar zwitterion was postulated by Lattrell in ref 4.

(7) In addition to postulating a similar interconversion *via* a zwitterion for arylsulfonyl isocyanate cycloadditions, Effenberger proposed a synchronous $\pi 2_s + \pi 2_a$ cycloaddition [F. Effenberger, *Angew. Chem., Int. Ed. Engl.*, **8**, 295 (1969)]; see ref 2 also.

(8) (a) A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **27**, 3742 (1962); (b) *ibid.*, **28**, 1805 (1963).

(9) Speziale and Smith reported a boiling point of 80–85° (20 mm); on repeated preparations we observed that the material distilled at 58° (30 mm).

(10) "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 506.

<div style="text-align:center">

TABLE II

SPECTRAL DATA FOR UNSATURATED ETHERS AND
CYCLIC INTERMEDIATES

</div>

1a Nmr (CCl₄) δ 1.28 (t, 3, J = 7.0 Hz), 3.68 (q, 2, J = 7.0 Hz), 3.86 (d of d, 1, J = 7.0 and 2.0 Hz), 4.03 (d of d, 1, J = 14.0 and 2.0 Hz), and 6.32 (d of d, 1, J = 7.0 and 14.0 Hz)

3a Nmr (CCl₄) δ 1.28 (t, 3, J = 7.0 Hz), 2.70 (d of d, 1, J = 2.5 and 15.5 Hz), 3.08 (d of d, 1, J = 4.0 and 15.5 Hz), 3.90 (m, 2, J = 7.0 Hz), and 5.92 (d of d, 1, J = 4.0 and 2.5 Hz); ir (neat) 5.66 and 6.15 μ

1b Nmr (CCl₄) δ 1.80–2.10 (complex, 4), 3.85 (t of d, 2, J = 5.0 and 1.5 Hz), 4.50 (complex, 1), and 6.20 (d of t, 1, J = 6.5 and 1.5 Hz)

2b Nmr (CCl₄) δ 1.50–2.15 (complex, 4), 3.55 (complex, 1), 3.70–4.05 (complex, 2), and 5.79 (d, 1, J = 5.5 Hz); ir (CCl₄) 5.48 and 5.90 μ

3b Nmr (CCl₄) δ 1.50–2.15 (complex, 4), 3.92 (m, 1, J = 2.5 Hz), 3.70–4.05 (complex, 2), and 5.92 (d, 1, J = 3.5 Hz); ir (CCl₄) 5.73 and 6.20 μ

1c Nmr (CCl₄) δ 1.20 (t, 3, J = 7.0 Hz), 1.52 (t, 6, J = 1.0 Hz), 3.61 (q, 2, J = 4.0 Hz), and 5.66 (m, 1, J = 1.5 Hz)

2c Nmr (CCl₄) δ 1.15–1.40 (complex, 9), 3.50–4.25 (complex, 2), and 5.21 (s, 1); ir (neat) 5.50 and 5.83 μ

3c Nmr (CCl₄) δ 1.15–1.40 (complex, 9), 3.50–4.25 (complex, 2), and 6.03 (s, 1); ir (neat) 5.75 and 6.20 μ

1d Nmr (CCl₄) δ 1.22 (t, 3, J = 6.5 Hz), 1.50 (d of d, 3, J = 7.0 and 1.5 Hz), 3.70 (q, 2, J = 7.0 Hz), 4.23 (d of d, 1, J = 13.0 and 6.5 Hz), and 5.80 (d of m, 1, J = 6.5 and 1.5 Hz)

2d Nmr (CCl₄) δ 1.20 (d, 3, J = 7.0 Hz), 1.25 (t, 3, J = 7.0 Hz), 2.90 (d of d, 1, J = 7.0 and 5.5 Hz), 3.95 (q, 2, J = 7.0 Hz), and 5.52 (d, 1, J = 5.5 Hz); ir (CCl₄) 5.52 and 5.80 μ

3d Nmr (CCl₄) δ 1.20 (d, 3, H = 7.0 Hz), 1.25 (t, 3, J = 7.0 Hz), 3.03 (d of d, 1, J = 7.0 and 4.0 Hz), 3.90 (q, 2, J = 7.0 Hz), and 5.75 (d, 1, J = 4.0 Hz); ir (CCl₄) 5.70 and 6.15 μ

1e Nmr (CCl₄) δ 1.21 (t, 3, J = 7.0 Hz), 1.50 (d of d, 3, J = 6.5 and 1.5 Hz), 3.60 (q, 2, J = 7.0 Hz), 4.59 (d of q, 1, J = 12.5 and 6.5 Hz), and 6.10 (d, 1, J = 12.0 and 1.5 Hz)

2e Nmr (CCl₄) δ 1.20 (d, 3, J = 7.0 Hz), 1.28 (t, 3, J = 7.0 Hz), 3.1 (complex, 1), 3.85 (q, 2, J = 7.0 and 5.0 Hz), and 5.11 (d, 1, J = 2.0 Hz); ir (CCl₄) 5.50 and 5.80 μ

3e Nmr (CCl₄) δ 1.20 (d, 3, J = 7.0 Hz), 1.25 (t, 3, J = 7.0 Hz), 3.05 (d of d, 1, J = 7.0 and 5.0 Hz), 3.90 (q, 2, J = 7.0 Hz), and 5.46 (d, 1, J = 5.0 Hz); ir (CCl₄) 5.70 and 6.15 μ

1g Nmr (CCl₄) δ 1.26 (t, 3, J = 7.0 Hz), 2.94 (s, 1), and 3.73 (q, 2, J = 7.0 Hz)

tate in 30 ml of benzene under an atmosphere of nitrogen. The reaction was not noticeably exothermic. After the reaction mixture had been stirred for 10 hr at room temperature, the solvent was removed *in vacuo* to give 6 g (60%) of crude 6, mp 110–113°. Two recrystallizations from ethyl acetate afforded 3.0 g of 6: mp 114.5–116.5°; ir (KBr) 5.75 and 6.03 μ; nmr (CH₂Cl₂) δ 2.06 (s, 3), 3.08 (t, 2), 4.31 (t, 2), 7.06 (d, 1), 7.59 (d, 1), and 9.08 (broad singlet, 1).

Anal. Calcd for C₉H₁₀Cl₃NO₄S: C, 32.3; H, 3.0; N, 4.2; Cl, 31.8; S, 9.6. Found: C, 32.6; H, 3.1; N, 3.9; Cl, 32.3; S, 9.6.

6,6-Dimethoxy-5,5-dimethyl-2-(trichloromethyl)-4H-1,3-oxazin-4-one (3f).—Trichloroacetyl isocyanate (5.7 g, 0.03 mol) was added to a stirred solution of 3.6 g (0.031 mol) of dimethyl-ketene dimethyl acetal (1f) in 25 ml of benzene under an atmosphere of nitrogen. The reaction temperature gradually climbed to 40° before receding. The solvent was removed *in vacuo* and the residue crystallized to give 3f in a quantitative yield. The product was extremely hygroscopic. A small sam-

ple, recrystallized twice from hexane, melted at 53–54°: nmr (CCl₄) δ 1.50 (s, 6), 3.37 (s, 3), and 3.75 (s, 3).

3,3-Diethoxy-N-(trichloroacetyl)acrylamide (4g).—Trichloroacetyl isocyanate (5.7 g, 0.03 mol) was added to a stirred solution of 3.6 g (0.03 mol) of ketene diethyl acetal (1g) in 25 ml of benzene under a nitrogen atmosphere. The temperature of the mixture was controlled under 50° by an ice bath. A solid which precipitated was removed by filtration, recrystallized from ethyl acetate, and washed with ether to give 3.7 g (40%) of 4g: mp 140–143°; ir (KBr) 5.72, 6.00, and 6.26 μ; nmr (CHCl₃) δ 1.44 (t, 6), 4.16 (q, 2), 4.45 (q, 2), 4.80 (s, 1), and 10.1 (broad singlet, 1).

Anal. Calcd for C₉H₁₂Cl₃NO₄: C, 35.5; H, 4.0; N, 4.6; Cl, 34.9. Found: C, 35.9; H, 4.0; N, 4.4; Cl, 34.9.

6-Ethoxy-2-(trichloromethyl)-4H-1,3-oxazin-4-one (7a).—A 5.0-g (0.027 mol) portion of trichloroacetyl isocyanate was added with stirring and cooling to 2.1 g (0.030 mol) of ethyl ethynyl ether in 15 ml of carbon tetrachloride under nitrogen. After 30 min at room temperature, the solvent was removed by rotary evaporation at reduced pressure to give 7.0 g (100%) of 7a: mp 61–64°; ir (Nujol) 6.05 and 6.24 μ; nmr (CCl₄) δ 1.53 (t, 3, J = 7.0 Hz), 4.38 (q, 2, J = 7.0 Hz), and 5.50 (s, 1).

Anal. Calcd for C₇H₆Cl₃NO₃: C, 32.4; H, 2.3; N, 5.2. Found: C, 31.9; H, 2.7; N, 5.1.

6-Ethoxy-2-phenyl-4H-1,3-oxazin-4-one (7b).—Benzoyl isocyanate (20 g, 0.136 mol) was added to a stirred solution of 10 g (0.143 mol) of ethyl ethynyl ether (1a) in 100 ml of benzene under a nitrogen atmosphere. The temperature of the mixture was controlled between 30 and 40° with an ice bath. As the solution cooled, a finely divided solid precipitated. This solid was removed by filtration, washed thoroughly with hexane, and dried in a vacuum oven to give 25 g (85%) of 7b, mp 132–135°. Recrystallization from a mixture of benzene and hexane yielded 22 g of 7b: mp 133.5–135° dec; ir (KBr) 6.11, 6.31, and 6.40 μ; nmr (acetone) δ 0.65 (t, 3), 3.80 (q, 2), 4.75 (s, 1), and 7.20 (m, 5).

Anal. Calcd for C₁₂H₁₁NO₃: C, 66.4; H, 5.1; N, 6.4. Found: C, 66.4; H, 5.1; N, 6.3.

Ethyl N-(Trichloroacetyl)malonamate (8a) by Hydrolysis of 7a.—A sample of 7a was placed in a nmr tube containing acetonitrile. When an excess of moist formic acid was added, the disappearance of 7a and the appearance of 8a were observed by nmr. The reaction required about 2 hr at room temperature. Although the product was not isolated, its ir and nmr spectra were recorded: ir (Nujol) 3.15, 5.65, 5.78, and 5.83 μ; nmr (CH₃CN, HCOOH) δ 1.30 (t, 3, J = 7.0 Hz), 3.80 (s, 2), and 4.40 (q, 2, J = 7.0 Hz) (NH obscured by formic acid).

Ethyl N-Benzoylmalonamate (8b) by Hydrolysis of 7b.—A suspension of 5 g of 7b in 80 ml of water containing 10 ml of 10% HCl was stirred for 15 min at room temperature. The solid was removed by filtration, washed with water, and dried in an oven at 80° to give 5.7 g of crude 8b, melting at 102–110°. Recrystallization from a mixture of benzene and hexane yielded 5.4 g of 8b, mp 114.5–115.5° (lit.[11] mp 114.5–115.5°).

Anal. Calcd for C₁₂H₁₃NO₄: C, 61.3; H, 5.6; N, 6.0. Found: C, 61.5; H, 5.8; N, 6.0.

Ethyl N-Benzylmalonamate (9) by Hydrogenation of 8b.—A solution of 5 g of 8b in 200 ml of ethyl acetate was hydrogenated at room temperature and 40 psi over 3 g of 5% palladium on carbon. After hydrogen absorption ceased, the catalyst was removed by filtration and the filtrate evaporated to yield 4.2 g of 9: mp 46–49°; ir (KBr) 5.81 and 6.08 μ; nmr (CCl₄) δ 1.10 (t, 3), 3.08 (s, 2), 3.95 (q, 2), 4.19 (d, 2), 7.12 (s, 5), and 8.06 (broad singlet, 1).

Anal. Calcd for C₁₂H₁₅NO₃: C, 65.1; H, 6.8; N, 6.3. Found: C, 65.4; H, 6.7; N, 6.4.

6-(2-Methoxyvinyl)-2-(trichloromethyl)-4H-1,3-oxazin-4-one (10).—A solution of 2.6 g (0.032 mol) of 1-buten-3-ynyl methyl ether and 5.7 g (0.03 mol) of trichloroacetyl isocyanate in 25 ml of benzene was stirred for several days at room temperature under nitrogen. The crystals that precipitated were filtered and dried to give 6.0 g of 10. A sample for analysis was recrystallized twice from ethyl acetate and dried in a vacuum desiccator to give a product with mp 126–127.5°; ir (KBr) 5.95, 6.08, and 6.20 μ; nmr (CH₃CN) δ 3.80 (s, 3), 5.69 (d, 1), 5.94 (s, 1), and 7.57 (d, 1).

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Synthesis of 3-Alkoxyoxetanes

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3-Alkoxyoxetanes are prepared by chlorination of allyl alcohol in the presence of an excess of an aliphatic alcohol (including allyl alcohol) followed by ring closure with hot aqueous NaOH. The product distribution during chlorination is consistent with a carbonium ion mechanism, yielding 2,3-dichloropropanol and the isomers 2-alkoxy-3-chloropropanol and 3-alkoxy-2-chloropropanol in the ratio of about 65:35. Side reactions include oxidation and ether formation by reaction of the three main chlorination products with the intermediate carbonium ion. The yield of the three major chlorination products is 65–80%. Yields of alkoxyoxetane based on 2-alkoxy-3-chloropropanol are in the range of 55–75%. A series of alkoxyoxetanes, $\overline{OCH_2CH(OR)CH_2}$, were prepared where R = methyl, ethyl, allyl, *n*-butyl, cyclohexyl, and *n*-dodecyl. These were treated with anhydrous HCl to form the pure precursor 2-alkoxy-3-chloropropanol.

The halogenation of olefins in reactive (nucleophilic) solvents has been studied extensively. The reaction proceeds *via* a carbonium ion mechanism involving intermediate halonium ions. In alcoholic media, the main products are ethers and dihalides.[2-4]

We have studied the chlorination of allyl alcohol since the dichloropropanol and 1,2- and 1,3-chlorohydrin ethers produced offer a route to alkoxyoxetanes as well as epichlorohydrin and alkyl glycidyl ethers.

The present work deals with the synthesis of a series of 3-alkoxyoxetanes[5] and their reaction with anhydrous hydrogen chloride to produce pure 2-alkoxy-3-chloropropanols.

Discussion

Chlorination of allyl alcohol in the absence of water leads mainly to chlorohydrin ethers, dichloropropanol, and oxidation products. Dichloropropanol formation
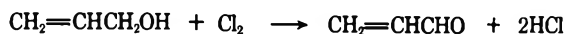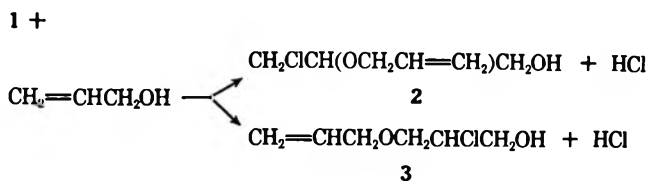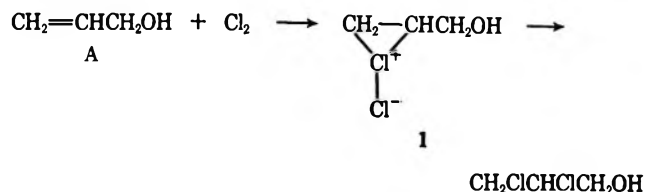
is initially competitive with ether formation; the respective rates of formation remain approximately the same over the first 20% reaction. At higher conversion, it is expected that dichloropropanol formation would increase relative to ether formation due to the increased HCl concentration ($1 + Cl^- \rightarrow CH_2ClCHClCH_2OH$). The isomeric allyloxychloropropanols (2 and 3) are formed in the ratio of about 65:35.

The initial oxidation product is probably acrolein but it rapidly undergoes further reaction producing an acetal containing a labile chlorine. Acrolein can add HCl and form acetals of β-chloropropionaldehyde.[6] Chlorination followed by acetal formation would give $CH_2ClCHClCH(OR)_2$, $CH_2=CHCH_2OCH_2CHClCH(OR)_2$, and $CH_2ClCH(OCH_2CH=CH_2)CH(OR)_2$.

The conversion of allyl alcohol was kept low (about 20%) to minimize formation of polyethers resulting from chlorination of the allyloxychloropropanols. A

$$CH_2=CHCH_2OH + Cl_2 \longrightarrow CH_2\!-\!CHCH_2OH \longrightarrow$$
$$A \qquad\qquad\qquad \underset{Cl^-}{\overset{Cl^+}{\diagdown\!\diagup}}$$
$$1$$

$$CH_2ClCHClCH_2OH$$

$$1 +$$
$$CH_2=CHCH_2OH \overset{\text{—}}{\underset{\text{—}}{\big<}} \begin{array}{l} CH_2ClCH(OCH_2CH=CH_2)CH_2OH + HCl \\ \qquad\qquad\qquad 2 \\ CH_2=CHCH_2OCH_2CHClCH_2OH + HCl \\ \qquad\qquad\qquad 3 \end{array}$$

$$CH_2=CHCH_2OH + Cl_2 \longrightarrow CH_2=CHCHO + 2HCl$$

$$2 \overset{Cl_2}{\underset{A}{\big<}} \begin{array}{l} CH_2ClCH(CH_2OH)OCH_2CHClCH_2Cl \\ \qquad\qquad\qquad 4 \\ CH_2ClCH(CH_2OH)OCH_2CH(CH_2Cl)OCH_2CH=CH_2 \\ \qquad\qquad\qquad 5 \\ CH_2ClCH(CH_2OH)OCH_2CHClCH_2OCH_2CH=CH_2 \\ \qquad\qquad\qquad 6 \end{array}$$
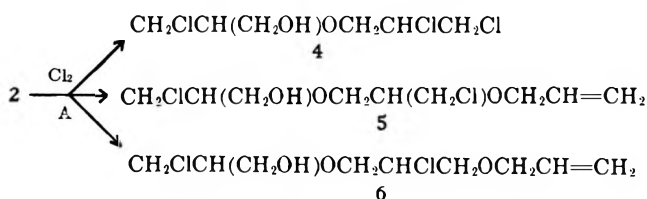
similar reaction can be written for the linear ether 3. The same products can be formed by reaction of the intermediate carbonium ion 1 with 2,3-dichloropropanol and with 2 and 3.

Hennion[7] reported the preparation of 2-allyloxy-3-chloropropanol (but not the linear isomer) in 36% yield by reaction of *tert*-butyl hypochlorite with allyl alcohol but did not study its reaction with base. Later work has shown that reaction of *tert*-BuOCl with allyl alcohol

(1) To whom correspondence should be addressed.

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TABLE I

PREPARATION OF 3-ALKOXYOXETANES

Allyl alcohol, mol	Chlorine, mol	Solvent, mol	2,3-Dichloro-propanol, mol	Alkoxychloro-propanol,[a] mol	Dehydrochlorination			
					Time, hr	Conversion,[b] %	Alkoxy-oxetane, mol	% yield[c]
5.0	5.05	CH₃OH, 74	0.85	3.34	2	98	1.18	55
5.0	5.05	C₂H₅OH, 51	1.17	2.46	4	98	1.16	74
0.5	0.5	HOC₂H₄OH, 2.5	d	0.17	6	100	e	
250[f]	45.6		12.0	12.0	10.5	86	4.1	63
2.0	2.1	n-C₄H₉OH, 4.7	0.6	0.9	14	98	0.40	70
2.0	1.01	n-C₁₂H₂₅OH, 2.5	0.45	0.40	20	13	0.019	56
2.0	2.04	C₆H₁₁OH, 10.7	0.62	0.68	25	82	0.23	60

[a] Sum of 2-alkoxy-3-chloropropanol and 3-alkoxy-2-chloropropanol which are formed in a ratio of about 65:35. [b] Based on chromatographic analysis. [c] Based on 2-alkoxy-3-chloropropanol. [d] Not determined. [e] No oxetane formed; isolated 10.5 g, 0.89 mol of 2-hydroxymethyl-1,4-dioxane. [f] Conversion of allyl alcohol was 22%.

TABLE II

PHYSICAL PROPERTIES OF 3-ALKOXYOXETANES[a]

R	Registry no.	Bp, °C (mm)	d²⁴	n²⁵D	MR Calcd	MR Found
Methyl	1872-45-3	43 (50)	0.9801	1.4068	22.2	22.1
Ethyl	6777-01-1	42 (25)	0.9578	1.4098	26.8	26.4
Allyl	6777-00-0	64 (25)	0.9788	1.4372	31.0	30.6
n-Butyl	6776-84-7	90 (50)	0.9231	1.4215	36.1	35.7
Cyclohexyl	6777-02-2	93 (9)	1.000	1.4640	43.1	43.1
n-Dodecyl	6776-85-8	92 (0.03)	0.875	1.4420	73.3	73.2

[a] Satisfactory analyses (±0.3% in C and H) were reported for all compounds in the table: Ed.

in the presence of $BF_3 \cdot Et_2O$ as catalyst yields both isomers of allyloxychloropropanol.[8]

Other alkoxychloropropanols were prepared using an excess of aliphatic alcohol and incremental addition of allyl alcohol to minimize competitive reaction of allyl alcohol and the main chlorination products with the carbonium ion 1. In methanol the latter reaction gives the following products: 4, $CH_2ClCH[OCH_2CH(OCH_3)-CH_2Cl]CH_2OH$, and $CH_2ClCH(OCH_2CHClCH_2OCH_3)-CH_2OH$. Three additional isomeric products are also possible. The yield of the three main chlorination products was between 65 and 80%. The data are summarized in Table I.

The preparation of methoxy-[9] and n-butoxychloropropanols[10] by chlorination of allyl alcohol in methanol and in 1-butanol has been reported.

The susceptibility of the solvent to chlorination must be considered. For example, chlorination of allyl alcohol in excess phenol resulted in formation of p-chlorophenol (no phenoxychloropropanols were detected). When dichlorophenol was used, only dichloropropanol and allyloxychloropropanols were observed. 2-Phenoxy-3-chloropropanol and 3-phenoxyoxetane have been synthesized from $CH_2OHCH(OPh)CH_2OSO_2C_6H_4Br$.[11]

Treating crude reaction mixtures (after removal of solvent) with aqueous NaOH at room temperature produced epichlorohydrin and alkyl glyceryl ethers. The epoxides were formed in high yield and could be readily removed by distillation of the organic layer. When the dehydrochlorination is conducted without prior removal of the excess alcohol solvent, 1,3-dialkyl glyceryl ethers are obtained in good yield. In the presence of excess

allyl alcohol, an 84% yield of 1,3-diallyloxy-2-propanol was obtained. Zunino[12] prepared a series of 1,3-dialkyl glyceryl ethers by reacting epichlorohydrin with alcohols (methyl, ethyl, n-propyl, allyl, and isoamyl) in the presence of KOH. Fairborne[13] prepared glycerol diethers in 70% yields by reaction of dichloropropanol with alcohols in the presence of base.

Instead of dehydrochlorinating the crude chlorohydrins batchwise with caustic, distillation from lime slurry was used. This technique gave good yields of epichlorohydrin and allyl glycidyl ether. The oxetane precursor steam distils unreacted in this procedure.

Dehydrochlorination of 1,3-chlorohydrins to oxetanes requires more vigorous thermal conditions than the corresponding formation of epoxides from 1,2-chlorohydrins. Higher 1,3-chlorohydrins required longer reac-

tion times due primarily to their low solubility in aqueous base. Oxetane yields based on chlorohydrin were in the 55–75% range (see Table I). Physical properties of the 3-alkoxyoxetanes prepared are tabulated in Table II. Ethoxy-, allyloxy-, n-butoxy-, cyclohexoxy-,

(8) H. L. Plant, unpublished data.

(9) J. A. Flint and G. T. Merrall, British Patent 988,116 (1965).

(10) K. B. Cofer and R. W. Fourie, U. S. Patent 3,093,689 (1963).

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(13) A. Fairborne, G. P. Gibson, and D. W. Stephens, *Chem. Ind. (London)*, **49**, 1021 (1930).

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TABLE III

PHYSICAL PROPERTIES OF 2-ALKOXY-3-CHLOROPROPANOLS[a]

$ClCH_2CH(OR)CH_2OH$

</div>

R	Registry no.	Bp, °C (mm)	d^{25}	$n^{25}D$	MR Calcd	MR Found
Methyl	2858-55-1	96 (25)	1.156	1.4472	28.7	28.8
Ethyl	6798-40-9	101 (25)	1.098	1.4440	33.3	33.5
Allyl	10433-29-1	98 (11)	1.121	1.4650	37.4	37.1
n-Butyl	6776-89-2	99 (2)	1.043	1.4460	42.6	42.6
Cyclohexyl	6776-87-0	67 (0.03)	1.112	1.4780	49.5	49.0
n-Dodecyl	29903-08-5	115 (0.03)	0.947	1.4545	79.5	79.7

[a] Satisfactory analyses (±0.3% in C and H) were reported for all compounds in the table: Ed.

and n-dodecoxyoxetanes have not been previously reported. 3-Methoxyoxetane has been prepared in 65% yield by a similar route.[14]

Possible side reactions in the dehydrochlorination of 1,3-chlorohydrins are ether formation (intermolecular Williamson reaction), olefin formation (by HCl elimination), and oxyalkylation. Intermolecular ether
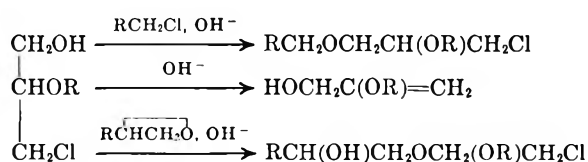
formation is an important side reaction in the dehydrochlorination of bis(2-chloroethyl) acetals to divinyl acetals with alcoholic alkali.[15] Olefin formation in preparation of oxetanes from 1,3-chlorohydrins is a common competing reaction.[16] The oxyalkylation reaction would occur during formation and destruction of epichlorohydrin and alkyl glycidyl ethers. Glycol or ether formation from the oxetane product would not be significant since oxetanes are stable to base at moderate temperatures. Searles[17] has shown that oxetane reacts on prolonged heating at elevated temperatures (175°) with alcohols in the presence of alkoxides to form monoalkyl ethers of trimethylene glycol.

No oxetane was obtained from 2(2'-hydroxyethyl)-3-chloropropanol; dioxane ring formation occurred ex-

clusively. The linear isomer $HOCH_2CH_2OCH_2CHCl-CH_2OH$[18] is also capable of forming methyloldioxane. The same product was obtained by dehydrochlorination of $CH_2ClCHOHCH_2OCH_2CH_2OH$ as well as $CH_2ClCHOHCH_2OCH_2CH_2Cl$.[19]
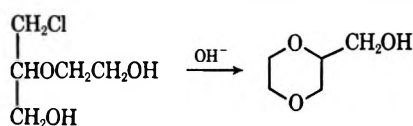
Although 3-alkoxyoxetanes are stable at moderate temperatures (100–110°) to base and chloride ion (unlike epoxides), they react readily with anhydrous HCl (like epoxides) to form the precursor 2-alkoxy-3-chloropropanol. Yields are in the vicinity of 85–90% (see Table III). Reaction with concentrated HCl gives mainly chlorohydrin and some 1,3-diol while dilute aqueous HCl (or H_2SO_4)[20] favors 1,3-diol formation.
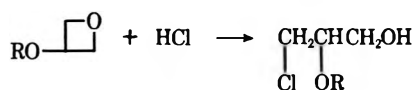
The epoxide precursors $ROCH_2CHClCH_2OH$, which were formed in yields as high as 24%, are formed in only minor amounts by the reaction of alkyl glycidyl ethers with anhydrous HCl.

Experimental Section

Materials.—Allyl alcohol was from Olin Corp., assaying 97–98% by bromate–bromide analysis. Other chemicals were commercially available reagent grade.

Analyses.—Product distributions were determined by gas–liquid chromatography (glc). Quantitative analyses were obtained using standards of approximately the same concentration as the sample. Normally a 5-ft silicone SF-96 (20% on 80–100 firebrick) column was employed, operating isothermally from 125 to 200° with a He flow of 40 cc/min at 20 psig. The dodecyl compounds were analyzed using a 1-ft silicone SE-30 (15% on 80–100 Chromosorb) column programming from 100 to 350°. The ratio of the isomeric alkoxychloropropanols was determined using a 3-ft Igepal (5% on Fluoropak) column programming from 100 to 200°. The ratio of 2-alkoxy-3-chloropropanol/3-alkoxy-2-chloropropanol was about 65:35. Allyl alcohol was analyzed using a 3-ft polyethylene glycol 400 (15% on 80–100 mesh Chromosorb) column operating at 70°.

Infrared spectra of liquid samples between salt plates were recorded with a Perkin-Elmer Infracord. Absorption bands reported by Searles[21] were used in interpreting the spectra of the oxetanes. The ring C–O–C is characterized by a strong broad band in the region of 10.2–10.3 μ.

[1]H nmr spectra were obtained with a Varian A-60 spectrometer using tetramethylsilane as internal standard.

The pyridinium chloride method[22] was used to assay alkoxyoxetanes via the oxetane ring. Redistilled products analyzed above 99%.

Attempts to assay alkoxyoxetanes with aqueous $Na_2S_2O_3$ were unsuccessful due to the very slow and incomplete reaction even at reflux temperature. For methoxyoxetane, the initial rate constant was $k^{100} = \sim 2 \times 10^{-4}$ min^{-1}. In contrast, simple epoxides such as ethylene and propylene oxides exhibit rate constants at 64° of 0.67 and 0.36 min^{-1}, respectively.[23]

Searles[24] reports a value of $k^{35} = 0.013$ min^{-1} for oxetane (at pH 8). We observed no base release at 35° and found a measurable reaction rate only at reflux temperature. The initial rate constant was similar to that found for methoxyoxetane; $k^{100} = \sim 2 \times 10^{-4}$ min^{-1}.

Apparatus.—Chlorinations were conducted in a three-neck round-bottom flask fitted with stirrer, thermometer, and chlorine sparger. In the case of methanol and ethanol, the end point (presence of excess Cl_2) was determined potentiometrically (Beckman pH meter) using calomel as reference and platinum as indicating electrodes. This technique was not adaptable to the higher alcohols. Reaction temperature was usually maintained between 30 and 40° by external cooling.

(14) J. A. Flint and G. T. Merrall, British Patent 988,117 (1965).

(15) J. A. Wojtowicz, unpublished data.

(16) N. C. Gaylord, et al., J. Amer. Chem. Soc., **76**, 59 (1954).

(17) S. Searles and C. F. Butler, ibid., **76**, 56 (1954).

(18) M. S. Kharasch and W. Nudenberg, J. Org. Chem., **8**, 189 (1943).

(19) French Patent, 1,084,038 (1955).

(20) J. A. Flint and G. T. Merral, British Patent 991,232 (1965).

(21) G. M. Barrow and S. Searles, J. Amer. Chem. Soc., **75**, 1175 (1953).

(22) R. T. Keen, Anal. Chem., **29**, 1041 (1957).

(23) W. C. J. Ross, J. Chem. Soc., London, 2257 (1950).

(24) S. Searles, J. Amer. Chem. Soc., **73**, 4515 (1951).

Dehydrochlorinations were carried out using an excess of aqueous NaOH at reflux (100–110°) in a three-neck, round-bottom flask equipped with stirrer, thermometer, condenser, and addition funnel.

Reaction of anhydrous HCl with alkoxyoxetanes was run in a three-neck, round-bottom flask fitted with stirrer, thermometer, and sparger. Reaction temperature was maintained between 20 and 30° by external cooling.

Yields.—Yields of chlorination products are based on allyl alcohol while yields of oxetanes are based on 3-chloro-2-alkoxypropanol.

3-Allyloxyoxetane.—Chlorine (3.242 kg, 45.6 mol) was introduced at about 4 g/min into allyl alcohol (145 kg, 250 mol). The following products were identified: 2,3-dichloropropanol (12.0 mol, 21% yield), 3-allyloxy-2-chloropropanol (4.2 mol, 15% yield), 2-allyloxy-3-chloropropanol (7.6 mol, 28% yield), and a chloro acetal (5.3 mol). The latter (determind by the oxime method) released an equimolar amount of HCl on hydrolysis which indicates that its structure is either $CH_2ClCH_2CH(OR)_2$ or $CH_2ClCHClCH(OR)_2$. The conversion of allyl alcohol was 22%. The unreacted allyl alcohol was removed by distillation leaving a crude product of 4.643 kg. Aqueous NaOH (1550 g in 2775 cc of H_2O) was added to the crude product over a 0.5-hr period maintaining the temperature below 30°. The well-stirred mixture was then heated to 100–110° and maintained for 10.5 hr (conversion of 2-allyloxy-3-chloropropanol was 86%). As the temperature was raised (from room temperature), the formation and disappearance of epichlorohydrin and allyl glycidyl ether was observed. Sufficient water to dissolve the salt was added. After separating layers, the aqueous layer was extracted three times with 500-cc portions of CCl_4. The CCl_4 was removed by distillation and the residue combined with the main organic layer. Distillation through a 12-in. glass helices packed column gave 435 g (59% yield) of 3-allyloxyoxetane: bp 64° (25 mm); d^{25} 0.9788; $n^{25}D$ 1.4372; ir 1.633 and 2.113 (terminal CH_2), 6.07 (C=C), 8.9 (COC), 10.2 (oxetane ring), and 10.7 μ (CH out of plane bending); nmr (CDCl_3) multiplet at 3.9 ppm (intensity 2) assigned to CH_2O of the allyloxy group, multiplet at 5.2 ppm (intensity 2) and 5.9 ppm (intensity 1) assigned to CH_2 and CH of the vinyl group, and a multiplet at 4.6 ppm (intensity 5) assigned to CH and CH_2 of the oxetane ring. Mass spectral analysis gave no parent peak but the cracking pattern was consistent with the proposed structure. Observed molecular weight (cryoscopic) was 114. Assay by pyridinium chloride or bromination (bromate–bromide reagent) indicated a purity of >98%.

Anal. Calcd for $C_6H_{10}O_2$: C, 63.1; H, 8.8. Found: C, 63.2; H, 8.8.

The solubility of allyloxyoxetane in water is about 15% and is similar to that of allyl glycidyl ether.

3-Methoxyoxetane.—Chlorine (359 g, 5.05 mol) and allyl alcohol (265 g, 4.57 mol) were introduced at about 30 mmol/min into a solution of allyl alcohol (25 g, 0.43 mol) in methanol (2.336 kg, 74 mol). The excess methanol was removed by distillation leaving a residue of 622 g consisting of 2-chloro-3-methoxypropanol (1.17 mol, 23% yield), 2-methoxy-3-chloropropanol (2.17 mol, 43% yield), and 2,3-dichloropropanol (0.85 mol, 17% yield). The crude product was added to 2 l. of 10% NaOH solution and stirred for 2 hr at 25° and then at 105° for 2 hr (conversion of 2-methoxy-3-chloropropanol was 98%). The mixture was extracted twice with 2-l. portions of methyl ethyl ketone. After stripping off of the solvent, the product was vacuum distilled through a 24-in. Berl saddles packed column providing 93 g (50% yield) 3-methoxyoxetane, bp 43° (53 mm). A redistilled sample analyzed 99.9% and had the following physical properties: bp 110.5°; d^{25} 0.9801; $n^{25}D$ 1.4068; ir 7.25 (CH_3), 8.85 (C–O–C), and 10.25 μ (oxetane ring). The nmr spectrum in benzene showed three absorptions in the ratio 3:1:4; singlet at δ 2.85 (OCH_3), triplet of triplets at δ 3.93 (OCH), and a doublet at δ 4.42 (OCH_2). A first-order spectrum was not obtained.

Anal. Calcd for $C_4H_8O_2$: C, 54.5; H, 9.1. Found: C, 54.6; H, 9.1.

Experimental and physical data on the preparation of other alkoxyoxetanes are shown in Tables I and II.

2-Allyloxy-3-chloropropanol.—Anhydrous HCl (15.3 g, 0.42 mol) was introduced slowly into 3-allyloxyoxetane (49 g, 0.43 mol) over a 1-hr period. Analysis (glc) indicated a yield of about 90%. Vacuum distillation through a 12-in. glass helices packed column gave 38 g of a heart cut: bp 98–100° (11–11.5 mm); d^{25} 1.121; $n^{25}D$ 1.4650; assay for unsaturation by bromate–

bromide reagent showed a purity of 98%; ir 2.9 (COH), 6.07 (C=C), 9.0 (COC), 10.7 (CH out-of-plane bending), and 13.4 μ (CCl).

Anal. Calcd for $C_6H_{11}O_2Cl$: C, 47.8; H, 7.3; Cl, 23.5. Found: C, 47.5; H, 7.3; Cl, 23.7.

Data on the preparation of other 2-alkoxy-3-chloropropanols are given in Table III.

Hydroxyethylchloropropanol.—Chlorine (106 g, 1.5 mol) and allyl alcohol (87 g, 1.5 mol) were added at about 14 mmol/min to ethylene glycol (393.5 g, 6.35 mol). The excess glycol was distilled out under vacuum (25 mm) through a 12-in. glass helices packed column. The residue (134 g) was further distilled yielding 77 g of isomeric hydroxyethylchloropropanols: bp 140–145° (5 mm); d^{25} 1.235; $n^{25}D$ 1.4697; ir 3.0 (COH), 8.9 (COC), and 13.4 μ (CCl).

Anal. Calcd for $C_5H_{11}O_3Cl$: C, 38.9; H, 7.1; Cl, 23.0. Found: C, 38.5; H, 7.1; Cl, 22.6.

2-Hydroxymethyl-1,4-dioxane.—Chlorine (35 g, 0.5 mol) and allyl alcohol (29 g, 0.5 mol) were added at 14 mmol/min to ethylene glycol (155 g, 2.5 mol). Excess glycol was removed under vacuum (30 mm). The residue (50 g containing 0.17 mol of hydroxyethylchloropropanol) was stirred at reflux with excess NaOH for 6 hr. The reaction mixture was extracted three times with 150-cc portions of methyl ethyl ketone. The solvent was removed by distillation at atmospheric pressure, and the residue vacuum distilled yielding 10.5 g of distillate: bp 100–105° (18 mm); d^{20} 1.159; $n^{25}D$ 1.4555. The product was identified as 2-hydroxymethyl-1,4-dioxane by ir and mass spectral analysis.

Anal. Calcd for $C_5H_{10}O_3$: C, 50.8; H, 8.5. Found: C, 50.8; H, 8.4.

1,3-Diallyloxy-2-propanol.—Chlorinated allyl alcohol solution (405 g) containing dichloropropanol (0.142 mol) and allyloxychloropropanols (0.136 mol) was vigorously stirred at reflux (~90°) with excess 30% aqueous NaOH for 6 hr. Water was added to dissolve salt, the layers were separated, and the aqueous phase was extracted three times with 50-cc portions of CCl_4. The stripped extract was combined with the main organic layer. Chromatographic analysis showed the presence of some unreacted 2-allyloxy-3-chloropropanol (0.014 mol) and 3-allyloxyoxetane (0.043 mol, 59% yield) as well as 1,3-diallyloxy-2-propanol (0.160 mol, 84% yield). The ir of chromatographically trapped product was identical with the ir of that from reaction of epichlorohydrin with excess allyl alcohol in the presence of KOH.

Epichlorohydrin and Allyl Glycidyl Ether.—Steam was passed into a lime slurry [10 g Ca(OH)_2 in 200 g H_2O] in a 500-cc, three-neck flask fitted with stirrer, thermometer, addition funnel, and take-off condenser. A crude chlorohydrin mixture (20 g), stripped of excess allyl alcohol, containing dichloropropanol (52 mmol), 3-allyloxy-2-chloropropanol (18 mmol), and 2-allyloxy-3-chloropropanol (34 mmol) was added dropwise over a 30-min period. The distillate was saturated with salt and extracted with methyl ethyl ketone. Oxirane analysis (thiosulfate method) of the extract indicated the presence of 58.5 mmol of epoxide. Chromatographic analysis showed epichlorohydrin (44 mmol, 85% yield), allyl glycidyl ether (13 mmol, 72% yield), and unreacted 2-allyloxy-3-chloropropanol (32 mmol, 94% recovery).

Reactivity of Alkoxyoxetanes.—A 3% solution of allyloxyoxetane exhibited no decomposition when refluxed for several hours in 1 *N* NaOH, 1 *N* NaOH saturated with NaCl, or in saturated aqueous NaCl.

Refluxing methoxyoxetane in 0.1 *N* HCl resulted in 21% conversion to chlorohydrin and the balance to 1,3-glycol. In 1 *N* HCl the conversion to chlorohydrin was 59%. In concentrated HCl (11 *N*) cyclohexoxyoxetane was converted in about 90% yield to chlorohydrin.

Methoxyoxetane (1.07 mmol) in 25 cc of H_2O containing 5 g of $Na_2S_2O_3 \cdot 5H_2O$ was refluxed and the liberated base titrated periodically with 0.1 *N* HCl. After 67.3 hr the extent of reaction was 45.3%. The initial rate constant was $k^{100} = \sim 2 \times 10^{-4}$ min⁻¹. With oxetane, an identical initial rate was obtained.

3-Methoxy-2-chloropropanol.—The reaction mixture from chlorination of allyl alcohol in excess methanol was neutralized with NaHCO_3 and stripped of solvent. 3-Methoxy-2-chloropropanol was isolated from the residue by chromatographic trapping using a 5-ft column (15% Igepal on 90–100 Anakrom ABS) at 135°. The product had $n^{20}D$ 1.4494.

Anal. Calcd for $C_4H_9O_2Cl$: C, 38.6; H, 7.3; Cl, 28.5. Found: C, 38.5; H, 7.3; Cl, 28.4.

Chloromethoxypropoxychloropropanols.—The reaction mixture from chlorination of allyl alcohol (1.0 mol) in methanol (10 mol) containing Na_2CO_3 (0.5 mol) was filtered and stripped of solvent. The residue was vacuum distilled through a 12-in. glass helices packed column giving 96 g of a mixture of chloromethoxypropanols and dichloropropanol [bp 65° (5 mm)–45° (0.5 mm)]. The pot residue was extracted with ether to eliminate salt. After stripping, it was refluxed in acidified 1:1 $MeOH–H_2O$ to hydrolyze acetals. The mixture was stripped of solvent and the residue vacuum distilled giving an additional 5 g of chlorohydrins and 8 g of a higher boiling fraction (140–145° at 0.5 mm). Chromatographic analysis (220°, 5-ft 15% CW20M/Anakrom ABS) showed two peaks in the ratio 9:1 at retention times of 8 and 12.5 min. The first (major) peak was trapped and identified (ir, mass spectrum, and nmr) as an isomeric mixture of chloromethoxypropoxychloropropanol. The four possible isomers are: $CH_2ClCH[OCH_2CH(OCH_3)CH_2Cl]CH_2OH$, $CH_2ClCH(OCH_2CHClCH_2OCH_3)CH_2OH$, $CH_2ClCH(OCH_3)CH_2OCH_2CHClCH_2OH$, and $CH_3OCH_2CHClCH_2OCH_2CHClCH_2OH$. Mass spectral analysis showed a molecular ion at mass 216 and indicated a compound containing two chlorine atoms. The cracking pattern was consistent with the proposed structures. Nmr (60 MHz) showed a complex region (3.50–4.30 ppm) assigned to the methylene and methine protons, two singlets for methoxy at 3.48 and 3.43 ppm, and a broad absorption due to hydroxyl at 2.88 ppm. At 90 MHz the methoxy protons were resolved into six singlets (3.478, 3.474, 3.467, and 3.417, 3.408, 3.404 ppm). Since each positional isomer contains two asymmetric centers a total of eight singlets is possible. Assigning the higher field group to primary methoxy and the lower field group to secondary methoxy gives values of 73% primary and 27% secondary.

Dichloropropoxychloropropanols.—Peak number two from the higher boiling fraction in the isolation of chloromethoxypropoxychloropropanols was trapped and identified (ir, mass spectrum, and nmr) as an isomeric mixture of $CH_2ClCH(OCH_2CHClCH_2Cl)$-$CH_2OH$ and $CH_2ClCHClCH_2OCH_2CHClCH_2OH$.

Cyclopropylthiophenes. Syntheses, Reactions, and Ultraviolet Spectra

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Synthetic routes to 2- and 3-cyclopropylthiophenes are described. Electrophilic deuteration, bromination, formylation, and iodination occur exclusively at the 5 position of 2-cyclopropylthiophene and at the 2 position of 3-cyclopropylthiophene. Nitration is less selective, proceeding at the 3 and 5 positions of 2-cyclopropylthiophene (40 and 60%, respectively) and at the 2 and 5 positions of 3-cyclopropylthiophene (88 and 12%, respectively). The cyclopropyl ring does not open during electrophilic substitution. Upon irradiation in benzene the iodo substituents of 2-cyclopropyl-5-iodothiophene and 3-cyclopropyl-2-iodothiophene are replaced by phenyl. The effect of cyclopropyl on the uv spectra approximates that of phenyl contrasting strongly the behavior of simple cyclopropyl-substituted aryl systems where only modest bathochromic shifts are found. The larger effect in thiophenes is attributed to a relatively larger decrease in electron density upon excitation at the carbon to which cyclopropyl is attached thereby making a greater demand upon the conjugative abilities of cyclopropyl. Comparisons with literature data are made.

Discussions of the effect of a cyclopropyl group on an aromatic ring have generally concentrated on the degree and type of conjugative interaction existing between the two bonded rings. Strong *ground-state* conjugative interaction in cyclopropyl aromatics may occur[2] providing that significant electronic demands are made on the cyclopropyl group[3] and providing that a conformation can be attained allowing maximum overlap between

the Walsh[4] orbitals for cyclopropyl and the aryl π system. The latter condition is best satisfied with the bisected conformation illustrated for cyclopropylbenzene.

Evidence for conjugative interaction in the excited state is less clear-cut. A modest bathochromic shift of 5 mμ (740 cm⁻¹) of the 0–0 band of cyclopropylbenzene over that for isopropyl benzene is indeed found,[5,6] but, as judged from bathochromic shifts, the degree of interaction seems not to be a sensitive function of cyclopropane geometry.[7] The reasonable suggestion has been made recently that significant conjugative interaction (and thereby geometrical influence) in the excited state (as in the ground state) will only occur if the aromatic moiety has "sufficient electron-attracting power to make . . . . . . demand on the conjugative ability of the cyclo-

(1) To whom inquiries should be addressed.

(2) For leading references, see (a) R. C. Hahn, T. F. Corbin, and H. Shechter, *J. Amer. Chem. Soc.*, **90**, 3404 (1968); (b) H. C. Brown and J. D. Cleveland, *ibid.*, **88**, 2051 (1966); T. Sharpe and J. C. Martin, *ibid.*, **88**, 1815 (1966). For examples of cyclopropylinteraction in aliphatic systems, see (d) R. C. Bingham, W. F. Sliwinsky, and P. v. R. Schleyer, *ibid.*, **92**, 3471 (1970); (e) C. D. Poulter, E. C. Friedrich, and S. Winstein, *ibid.*, **92**, 4274 (1970).

(3) R. Fuchs, C. A. Kaplan, J. J. Bloomfield, and L. F. Hatch, *J. Org. Chem.*, **27**, 733 (1962); R. Fuchs and J. J. Bloomfield, *ibid.*, **28**, 910 (1963).

(4) A. D. Walsh, *Trans. Faraday Soc.*, **45**, 179 (1949).

(5) W. W. Robertson, J. F. Music, and F. A. Matson, *J. Amer. Chem. Soc.*, **72**, 5260(1950).

(6) A molecular orbital model for interaction has been proposed: H. H. Jaffé, *Z. Elektrochem.*, **59**, 823 (1955).

(7) A. L. Goodman and R. H. Eastman, *J. Amer. Chem. Soc.*, **86**, 908 (1964); see also J. C. Bourmanne, G. Leroy, and J. Weiler, *Tetrahedron*, **26**, 2281 (1970).

propyl group."[8] In support of this contention, the magnitudes of the relative bathochromic shifts in para-nitro-substituted arylcyclopropanes are larger than those of the nonnitrated compounds and, in addition, the magnitude becomes a spectroscopically detectable function of cyclopropane geometry.

This concept provides a viable qualitative tool with which to rationalize substituent effects on the spectra of arylcyclopropanes but gives only limited help in estimating the effects of an intrinsic change of the aryl system itself. Consider the replacement of phenyl by thienyl. The thiophene system is unquestionably aromatic as evidenced by reactions,[9] nmr spectral data,[10] [13]C nmr coupling constants,[11] and resonance energy.[12] However, it is inductively more strongly electron-withdrawing than phenyl (2-thienylcarboxylic acid has a pK_a of 3.53 in water, benzoic acid has pK_a of 4.17).[13] Resonance interaction with a positive center seems to be significantly greater than for phenyl.[14] The appreciable dipole moment, 0.54 D,[15] and greater reactivity in electrophilic substitution with selective activation of positions adjacent to the sulfur atom[16] further accent the difference with phenyl.[17] On the other hand, the effectiveness of transmission of inductive (and presumably also resonance) effects from the 2 to the 5 position is nearly the same as in benzene.[16] Using the guideline of "increased electron-attracting ability" we might predict an increase in the auxochromic effect of cyclopropyl as a substituent on thiophene, but no intelligent guess as to the magnitude can be made. In an effort to probe further into this problem we have synthesized a number of cyclopropylthiophenes and have studied their ultraviolet spectra.

Results

A facile synthesis of 2-cyclopropylthiophene (**4**) is achieved from the sodium amide induced cyclization of the requisite quaternary ammonium iodide (**1**) (eq 1). This procedure was developed by Bumgartner[18] for the synthesis of cyclopropylbenzene and has also been used for the synthesis of 4-cyclopropylpyridine.[19] Its application to the synthesis of **4** has been described briefly in Russian literature.[20,21] This approach, although a trifle lengthy, gives good yields and may be scaled up readily. No difficulties were experienced in adaptation to the synthesis of 2-cyclopropyl-5-phenylthiophene (**5**) and 2,5-dicyclopropylthiophene (**6**).

(8) R. C. Hahn, P. H. Howard, S.-M. Kong, G. A. Lorenzo, and N. L. Miller, *J. Amer. Chem. Soc.*, **91**, 3558 (1969).

(9) S. Gronowitz, *Advan. Heterocycl. Chem.*, **1**, 1, (1963).

(10) H. A. P. de Jongh and H. Wynberg, *Tetrahedron*, **21**, 515 (1965).

(11) T. F. Page, Jr., J. T. Alger, and D. M. Grant, *J. Amer. Chem. Soc.*, **87**, 5333 (1965).

(12) See, *e.g.*, M. J. S. Dewar and N. Trinajstić, *ibid.*, **92**, 1453 (1970).

(13) A. R. Butler, *J. Chem. Soc. B*, 867 (1970).

(14) E. A. Braude and J. S. Fawcett, *J. Chem. Soc.*, 4158 (1952).

(15) Taken from V. Schomaker and L. Pauling, *J. Amer. Chem. Soc.*, **61**, 1769 (1939).

(16) See for recent quantitative studies of this phenomenon (a) A. R. Butler and J. B. Hendry, *J. Chem. Soc. B*, 848 (1970); (b) A. R. Butler and J. B. Hendry, *ibid.*, 852 (1970); (c) G. Marino, *Tetrahedron*, **21**, 843 (1965).

(17) A popular molecular orbital picture for thiophene is that given by H. C. Longuet-Higgens, *Trans. Faraday Soc.*, **45**, 173 (1949).

(18) C. L. Bumgartner, *J. Amer. Chem. Soc.*, **83**, 4423 (1961).

(19) A. P. Gray and H. Kraus, *J. Org. Chem.*, **31**, 399 (1966).

(20) E. G. Treshchova, D. Ekkhardt, and Yu. K. Yur'ev, *Zh. Fiz. Khim.*, **38**, 295 (1964); *Chem. Abstr.*, **60**, 14027d (1964); and earlier references.

(21) The synthesis of carboalkoxy substituted cyclopropylthiophenes by addition of diazo esters to vinylthiophenes has been described: A. Burger, D. G. Markess, W. R. Nes, and W. L. Yost, *J. Amer. Chem. Soc.*, **71**, 3307 (1949).

4, R = H
5, R = C₆H₅
6, R = cyclopropyl

1, R = H
2, R = C₆H₅
3, R = cyclopropyl
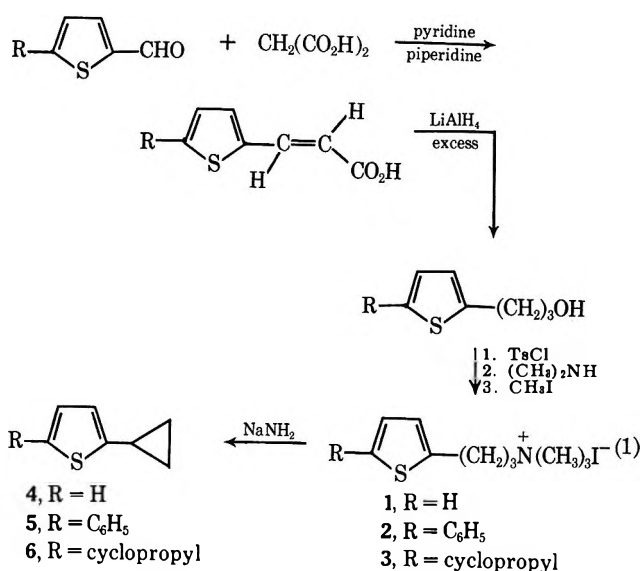
An alternative route had to be sought for 3-cyclopropylthiophene (**9**) since sodium amide induced ring closure of the quaternary ammonium iodide (**7**) gave chiefly the E2 elimination product, 3-(3-thienyl)-1-propene (**8**) (eq 2).[22] This demonstrates well (but unhap-

pily) the difference in acidity of α-methylene groups in 2- compared with 3-thenyl derivatives. A successful synthesis of **9** was obtained by appropriate modification (eq 3) of a well-known route to cyclopropylbenzene.[23]
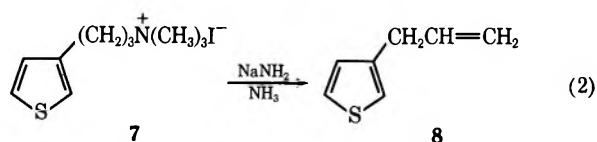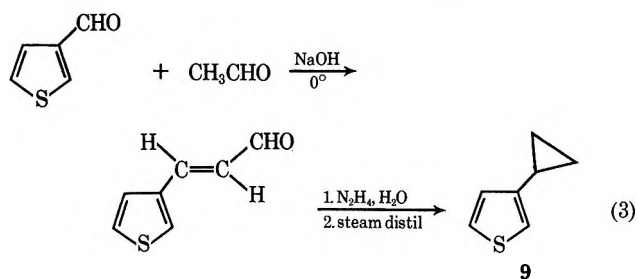
Yields are not exceptional (overall 30%), but nevertheless this procedure is sufficiently simple as to justify recommendation.

The reactions carried out on **4** are presented in Scheme I. Electrophilic bromination,[24] deuteration,[24] formylation, and iodination[25] proceed exclusively in the 5 position as is expected for 2-substituted thiophenes.[26] Electrophilic nitration is, however, less selective giving both 3- and 5-substituted products paralleling the situation with 2-phenylthiophene.[27] Irradiation of 2-cyclopropyl-5-iodothiophene (**14**) in benzene gives 2-cyclo-

(22) We are grateful to Miss Karon Armstrong for this experiment.

(23) R. J. Petersen and P. S. Skell, *Org. Syn.*, **47**, 98 (1967).

(24) NBS has been shown to be an extremely effective electrophilic bromination agent for activated thiophenes: R. M. Kellogg, A. P. Schaap, E. T. Harper, and H. Wynberg, *J. Org. Chem.*, **33**, 2902 (1968). Selective deuterium exchange with alkyl- and arylthiophenes in refluxing deuterioacetic acid is also described.

(25) Assumed to involve electrophilic mercuration as the initial step.

(26) Orientational factors in thiophenes are discussed in detail in ref 9.

(27) S. Gronowitz and N. Gjøs, *Acta Chem. Scand.*, **21**, 2823 (1967).

SCHEME I

10, R_1 = CHO; R_2 = H

$$4 \xrightarrow[\text{CHCl}_3/\text{HOAc}]{\text{NBS}} 11, R_1 = Br; R_2 = H$$

$$4 \xrightarrow{\text{DOAc}} 13, R_1 = D; R_2 = H$$

$$4 \xrightarrow[\text{I}_2]{\text{HgO}} 14, R_1 = I; R_2 = H$$

$$4 \xrightarrow[\text{Ac}_2\text{O}]{\text{Cu(NO}_3)_2} \begin{array}{l} 15, R_1 = NO_2; R_2 = H \\ 16, R_1 = H; R_2 = NO_2 \end{array}$$

$$11 \xrightarrow[\text{CO}_2]{\text{Mg}} 12, R_1 = CO_2H; R_2 = H$$

$$14 \xrightarrow[\text{C}_6\text{H}_6]{h\nu} 5, R_1 = C_6H_5; R_2 = H$$
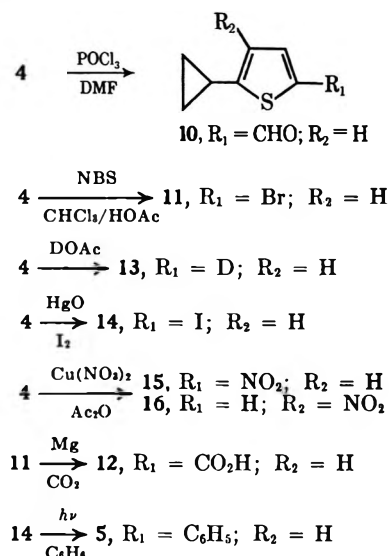
propyl-5-phenylthiophene[28] (6) [also synthesized by an alternative route (eq 1)].

With 3-cyclopropylthiophene (9) electrophilic bromination, deuteration, formylation, and iodination take place within the limits of detectability only in the 2 po-

SCHEME II

17, R_1 = CHO; R_2 = H

$$9 \xrightarrow[\text{CHCl}_3/\text{HOAc}]{\text{NBS}} 19, R_1 = Br; R_2 = H$$

$$9 \xrightarrow{\text{DOAc}} 20, R_1 = D; R_2 = H$$

$$9 \xrightarrow[\text{I}_2]{\text{HgO}} 21, R_1 = I; R_2 = H$$

$$9 \xrightarrow[\text{Ac}_2\text{O}]{\text{Cu(NO}_3)_2} \begin{array}{l} 23, R_1 = NO_2; R_2 = H \\ 24, R_1 = H; R_2 = NO_2 \end{array}$$

$$17 \xrightarrow{\text{Ag}_2\text{O}} 18, R_1 = CO_2H; R_2 = H$$

$$21 \xrightarrow[\text{C}_6\text{H}_6]{h\nu} 22, R_1 = C_6H_5; R_2 = H$$
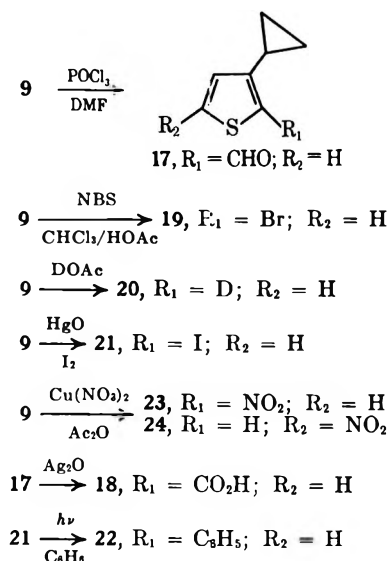
sition (Scheme II). Electrophilic nitration also occurs chiefly in the 2 position giving 2-nitro-3-cyclopropyl-thiophene (23) along with some 2-nitro-4-cyclopropyl-thiophene (24) the presence of which can be deduced from the nmr spectrum. Again the cyclopropyl ring is not opened. Irradiation of 3-cyclopropyl-2-iodothio-phene (21) in benzene gives 3-cyclopropyl-2-phenylthio-phene (22).

Discussion

Electrophilic Substitution.—In cyclopropylbenzene both bromination and acylation are known to go exclusively in the para position at $-75°$.[29] Attack

on the cyclopropyl ring is also a possibility as witnessed by ring opening during sulfonation[30] and during bromination in acetic acid–sodium acetate.[31] With cyclopropylthiophenes under mild conditions no attack on the cyclopropyl group is observed and substitutions are highly selective. For 2-cyclopropylthiophene attack at the 5 position is completely predictable. The exclusive reaction at the 2 position of 3-cyclopropylthiophene, while at first sight surprising, follows the pattern found with analogous aryl and alkylthiophenes.[24] Most likely this orientation arises from the capability of the cyclopropyl substituent to stabilize directly the positively charged intermediate formed during electrophilic substitution. Formylation of 3-cyclopropylthiophene is more selective than with 3-methylthiophene which gives a 4:1 mixture of 2- and 5-formylated products[32] or with 3-isopropylthiophene which gives a 1:1 mixture of isomers (Experimental Section); with 3-phenylthiophene a 94:6 ratio of 2- to 5-substituted products is found.[33]

Electrophilic nitration in benzenoid systems is usually less selective than most other types of electrophilic substitution[34] and the same holds in thiophenes.[9] Nitration of 2-phenylthiophene gives a 6:4 mixture of 5-nitro- and 3-nitro-2-phenylthiophenes (in addition to dinitrated products) and 3-phenylthiophene gives a 9:1 mixture of 2-nitro- and 5-nitro-3-phenylthiophenes.[27] This parallels closely the isomer distribution obtained from the cyclopropylthiophenes. There appears to be no need to invoke any special stabilization factors such as suggested for nitration of cyclopropylbenzene in which a decided preference for ortho substitution is found.[2]

Ultraviolet Spectra.—The extent of the putative conjugative interaction of a cyclopropyl group with an excited chromophore depends strongly on the system. An unambiguous example of interaction occurs with certain cyclopropyl ketones where the cyclopropyl group lowers the energy of the $\pi-\pi^*$ transition some 7–8 kcal/mol providing that the preferred bisected geometry can be attained.[35,36] This clear-cut case is contrasted by the behavior of vinylcyclopropanes where the cyclopropyl group, although behaving as a fairly strong auxochrome relative to isopropyl, surprisingly appears to have no geometric preference for conjugative interaction.[37] On the other hand, closely related cyclopropyl-acrylic esters (carboalkoxy substituted vinylcyclopropanes) exhibit bathochromic shifts relative to their isopropyl analogs as well as a clear preference for bisected geometry for maximum conjugative interaction.[38]

For the specific case of aryl-substituted cyclopropanes one finds that a cyclopropyl group in simple benzenoid aromatics causes only modest to negligible shifts compared with isopropyl. Some pertinent spectra are col-

(28) Technique of W. Wolf and N. Kharasch, *J. Org. Chem.*, **30**, 2493 (1965).

(29) Ya. Levina and P. A. Gembitskii, *Zh. Obshch. Khim.*, **31**, 3480 (1961); *Chem. Abstr.*, **57**, 701f (1962).

(30) Yu. S. Shabarov, R. Ya. Levina, and V. K. Potapov, *Zh. Obshch. Khim.*, **32**, 3184 (1962); *Chem. Abstr.*, **58**, 11241h (1963).

(31) A product of incompletely determined structure is formed.[2a]

(32) S. Gronowitz, P. Moses, A. B. Hörnfeldt, and R. Håkansson, *Ark. Kemi*, **17**, 165 (1961).

(33) S. Gronowitz, N. Gjøs, R. M. Kellogg, and H. Wynberg, *J. Org. Chem.*, **33**, 463 (1967); N. Gjøs and S. Gronowitz, *Acta Chem. Scand.*, **24**, 99 (1970).

(34) R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier, Amsterdam, 1965, pp 61–91.

(35) E. M. Kosower and M. Ito, *Proc. Chem. Soc.*, 25 (1962).

(36) See also W. G. Dauben and G. H. Berezin, *J. Amer. Chem. Soc.*, **89**, 3449 (1967).

(37) C. H. Heathcock and S. R. Poulter, *ibid.*, **90**, 3766 (1968).

(38) M. L. Jorgenson and T. Leung, *ibid.*, **90**, 3769 (1968).

lected in Table I. The long wavelength $^1B_{2u} \rightarrow {}^1A_{1g}$ transition is bathochromically shifted only 7 mμ in

TABLE I

ULTRAVIOLET SPECTRA OF SOME SELECTED
CYCLOPROPYL SUBSTITUTED AROMATIC COMPOUNDS

Compounds	λ_{max} (log ϵ)
Cyclopropylbenzene	275 (2.26)[a,b]
Isopropylbenzene	268 (2.57)[a,b]
4-Nitro-n-propylbenzene	265.5[c,d] (....)[e]
4-Nitrocyclopropylbenzene	283 (4.05)[b,f]
α-Cyclopropylnaphthalene	224.5 (4.86), 283 (3.82)[f,g]
α-Methylnaphthalene	224 (4.99), 282 (3.69)[f,g]
β-Cyclopropylnaphthalene	227.5 (4.90), 277 (3.72)[f,g]
β-Methylnaphthalene	224 (4.94), 275 (3.68)[f,g]
2-Cyclopropylpyridine	268.5 (3.60)[h,i]
2-Isopropylpyridine	261.5 (3.58), 267.8 (3.48)[h,i]
4-Cyclopropylpyridine	259 (3.38)[i,g]
4-Isopropylpyridine	255 (3.32), 261 (3.20)[i,g]

[a] Reference 5. [b] Cyclohexane. [c] Heptane. [d] W. M. Schubert and J. Robins, *J. Amer. Chem. Soc.*, 80, 559 (1958). [e] Not given. [f] Reference 8. [g] 95% EtOH. [h] Reference 39. [i] 0.1 *N* NaOH. [j] Reference 19.

cyclopropylbenzene compared with that in isopropylbenzene and in α- and β-substituted naphthalenes the long wavelength absorption is shifted only 1–2 mμ relative to alkyl.[8] For a heterocyclic system closely resembling benzene, *i.e.*, pyridine, cyclopropyl causes negligible bathochromic shifts in 2-[39] and 4-substituted[19] compounds (although protonation causes considerable enhancement of the long wavelength band of 4-cyclopropylpyridine).[19] On the other hand, the long wavelength absorption of 4-nitrocyclopropylbenzene, where the electronic demand made on cyclopropyl is greatly increased, is shifted some 2330 cm^{-1} (17.5 mμ) over that of the isopropyl derivative. Moreover, the magnitudes of the bathochromic shifts decrease steadily as the cyclopropyl group is twisted away from the preferred bisected geometry.[8]

The spectral properties of thiophene must be considered before attempting to apply the electron-withdrawing ability proportional to bathochromic shift concept[8] to cyclopropylthiophenes. Thiophene has in solution a broad, featureless absorption band located at 231 mμ (log ϵ 3.87) which in the gas phase is resolved into overlapping absorptions at 240, 233, and 220 mμ.[40] A shorter wavelength band with a maximum at 188 mμ is also seen.[41] A recent molecular orbital treatment of thiophene using a five-orbital model, *i.e.*, four carbon 2p orbitals and the sulfur 3p orbital, successfully accounts for the overlapping long wavelength $\pi-\pi^*$ absorptions.[42] Analysis of substituent effects on spectra is complicated by this band overlap which often leads to structureless absorptions. In the present discussion we shall try only to distinguish qualitative features between related sets of thiophenes sufficient to allow an evaluation of the magnitudes of the batho-

chromic shifts of the major thiophene absorption bands which are thought to reflect the extent of cyclopropyl interaction in the excited state. Since no safely interpretable trend of intensities can be distinguished, this aspect is not treated in any detail.

Pertinent spectroscopic data are listed in Table II. The isopropyl compounds listed were synthesized to provide reference compounds with roughly the same inductive contributions as a cyclopropyl group. Only absorption maxima are given; in several cases overlap of peaks leads to a featureless band undoubtedly embodying more than one transition.[43] Casual inspection would suggest an enormous bathochromic shift of 41 mμ for 2-cyclopropylthiophene (4) over 2-isopropylthiophene. Although the effect of cyclopropyl, presumably attributable chiefly to conjugative interaction, must be large, one should note that the 274-mμ band of 4 is much less intense than the 239 mμ band which suggests that, rather than a simple shift phenomenon, a new band having some degree of "intramolecular charge-transfer character," is being formed.[44]

Particularly valuable and more easily interpretable information can be gained from the 5-substituted 2-cyclopropylthiophenes. Particularly the long wavelength absorption bands as well as a second shorter wavelength band in CHO, CO$_2$H, and NO$_2$ derivatives display appreciable bathochromic shifts over the isopropyl reference compounds. Inspection of spectra indicates clear similarities between the spectra for the cyclopropyl compounds and analogous 5-substituted 2-*phenyl*thiophenes. The 2-phenylthiophenes have two well-developed bands of the same general form as observed in the cyclopropyl compounds;[43] the third band seen for 5-CHO or –CO$_2$H derivatives at 231 and 222 mμ, respectively, may be hypsochromically shifted in the cyclopropyl derivatives and therefore not observable. The phenyl derivatives have absorption maxima shifted bathochromically with respect to the cyclopropyl compounds. If cyclopropyl participation is indeed sensitive to the electron-withdrawing capacities of the aryl ring to which it is attached, maximum shifts (indicative of conjugative interaction) would be expected with 2-cyclopropyl-5-nitrothiophene (15) with a steady decrease in interaction as the electron-attracting ability of the 5 substituent is varied in the order NO$_2$ > CHO > CO$_2$H > halogen. This hypothesis can be tested. To a first approximation, the degree of inductive and resonance interaction by phenyl in 5-substituted 2-phenylthiophenes will be roughly the same in all compounds or at least more constant than in the analogous 2-cyclopropyl compounds. In Table III the relative bathochromic shifts of the longest wavelength absorption bands for 2-phenyl compared with 2-cyclopropyl compounds are compiled. The ratio of bathochromic shifts for phenyl compared with cyclopropyl increases steadily from NO$_2$ through CHO through CO$_2$H consistent with strongest cyclopropyl

(39) R. P. Mariella and K. H. Brown, *J. Org. Chem.*, **34**, 3191 (1969). Note that this is a correction of an earlier report of the synthesis of 2-cyclopropylpyridine: R. P. Mariella, L. F. A. Peterson, and R. C. Ferris, *J. Amer. Chem. Soc.*, **70**, 1494 (1948).

(40) E. Milazzo, *Gazz. Chim. Ital.*, **78**, 835 (1948).

(41) W. C. Price and A. D. Walsh, *Proc. Roy. Soc. (London)*, **A179**, 201 (1941).

(42) M. J. Bielefeld and D. D. Fitts, *J. Amer. Chem. Soc.*, **88**, 4804 (1966). For pioneering work on the electronic structure of thiophene, see ref 15 and for an original MO description ref 17 as well as A. J. H. Wachters and D. W. Davies, *Tetrahedron*, **20**, 2841 (1964).

(43) Drawings of the spectra of **4**, **15**, **9**, and **23** (in 95% EtOH) along with appropriate reference compounds will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth Street, N. W., Washington, D. C. 20036. Remit $3 for photocopy or $2 for microfilm.

(44) (a) S. Nagakura and J. Tanaka, *J. Chem. Phys.*, **22**, 236 (1954); (b) S. Nagakura, *ibid.*, **23**, 1441 (1955); (c) S. Nakakura, *J. Mol. Phys.*, **3**, 105 (1960); (c) K-K. Cheong, Y-C. Fu, R. K. Robins, and H. Eyring, *J. Phys. Chem.*, **73**, 4219 (1969), and references therein; (d) this point was stressed by a referee.

TABLE II

COMPARISON OF ULTRAVIOLET SPECTRA OF SOME THIOPHENE DERIVATIVES[a]

A   B

λ_{max} (log ϵ)

R_2	$R_1 = CH(CH_3)_2$	$R_1 = H$	$R_1 = C_6H_5$	$R_1 = C_3H_5$
		Thiophene A		
H (a[b])	233 (3.86)	215 (3.80), 231 (3.87)[c,d]	252 (3.86), 282 (4.16)	239 (3.88), 274 (3.05)
CHO (b)	265 (3.96), 296 (4.04)	260 (4.04), 286 (3.86)[c,d]	231 (3.98), 286 (3.83), 328 (4.33)	268 (3.87), 308 (4.15)
CO$_2$H (c)	254 (3.95), 277 (4.04)	246 (3.96), 260 (3.84)[c,d]	222 (4.00), 280 (sh), (4.00), 310 (4.31)	233 (2.85), 258 (3.49), 285 (3.72)
NO$_2$ (d)	290 (sh) (3.64), 329 (3.99)	270 (3.80), 296 (3.78)[c,d]	248 (3.99), 366 (4.21)[d,e]	222 (3.64), 345 (4.26)
Br (e)	242 (3.88)	236 (3.90)[c,d]	293 (4.22)	254 (3.93)[f]
I (f)	254 (4.00)		293 (4.28)	260 (4.04)[f]
C$_6$H$_5$	291 (4.19)[d,g]		230 (4.08), 324 (4.45)[f]	297 (3.98)
C$_3$H$_5$				256 (3.94), 290 (3.29)
		Thiophene B		
H (g)	235 (3.78)		227 (4.16), 258 (4.12)	232 (3.26), 243 (3.64)
CHO (h)	276 (4.05)		229 (4.10), 295 (4.08)	290 (4.08)
CO$_2$H (i)	257 (4.02)		224 (4.11), 276 (4.06)	265 (4.16)
NO$_2$ (j)	307 (3.91)		250 (3.55), 319 (3.95)[d,e]	240 (sh) (3.39), 319 (4.03)
C$_6$H$_5$	267 (3.96)[d,g]		238 (4.31), 278 (4.60)[d,g]	233 (3.89), 273 (4.08)
Br (k)	238 (3.89)		229 (4.22), 253 (4.05)	241 (3.88)[f]
I				248 (3.96)[f]

[a] Compounds cited without reference are from this work and spectra are in 95% EtOH. [b] Registry numbers: a [R$_1$ = CH(CH$_3$)$_2$], 4095-22-1; a (R$_1$ = C$_6$H$_5$), 825-55-8; b (R$_1$ = CH(CH$_3$)$_2$), 29481-40-1; b (R$_1$ = C$_6$H$_5$), 19163-21-4; c [R$_1$ = CH(CH$_3$)$_2$], 29481-42-3; c (R$_1$ = C$_6$H$_5$), 19163-24-7; d [R$_1$ = CH(CH$_3$)$_2$], 29481-18-3; d (R$_1$ = C$_6$H$_5$), 18150-93-1; e [R$_1$ = CH(CH$_3$)$_2$], 29488-23-1; e (R$_1$ = C$_6$H$_5$), 29488-24-2; f [R$_1$ = CH(CH$_3$)$_2$], 29488-25-3; f (R$_1$ = C$_6$H$_5$), 13781-37-8; g [R$_1$ = CH(CH$_3$)$_2$], 29488-27-5; g (R$_1$ = C$_6$H$_5$), 2404-87-7; h [R$_1$ = CH(CH$_3$)$_2$], 29488-29-7; h (R$_1$ = C$_6$H$_5$), 26170-85-4; i [R$_1$ = CH(CH$_3$)$_2$)], 29488-31-1; i (R$_1$ = C$_6$H$_5$), 10341-88-5; i (R$_1$ = C$_3$H$_5$), 29488-33-3; j [R$_1$ = CH(CH$_3$)$_2$], 29488-34-4; j (R$_1$ = C$_6$H$_5$), 18132-94-0; k [R$_1$ = CH(CH$_3$)$_2$], 29488-36-6; k (R$_1$ = C$_6$H$_5$), 10341-87-4. [c] S. Gronowitz, *Ark. Kemi*, **13**, 239 (1958). [d] 95% EtOH. [e] S. Gronowitz and N. Gjøs, unpublished results. [f] Identical λ_{max} (log ϵ) in C$_6$H$_{12}$; likely a long wavelength band is buried. [g] From ref 45d with methyl instead of isopropyl.

TABLE III

SHIFTS OF LONG WAVELENGTH BANDS AS A FUNCTION
OF SUBSTITUENT X OF COMPOUNDS

Shift (cm^{-1}) = $\nu_{R(C_3H_7)} - \nu_{R(R)}$		Shift of C$_6$H$_5$/	
R = C$_6$H$_5$	R = C$_3$H$_5$	shift of C$_3$H$_5$	X
3070	1410	2.18	NO$_2$
3300	1320	2.50	CHO
3850	1020	3.78	CO$_2$H
7200	1950	3.70	Br

interaction for the 5-nitro-substituted compounds but with the extent of participation relative to phenyl becoming progressively less as the electron-withdrawing ability of the 5 substituent decreases.
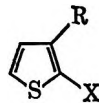
A further demonstration that the magnitude of conjugative interaction is proportional to electronic demand is obtained on comparison of the spectrum of 2,5-divinylthiophene,[45a] λ_{max} 315 mμ (log ϵ 4.70) and 328 (3.69), with that of 2,5-dicyclopropylthiophene (**6**) which absorbs at some 25-mμ shorter wavelength (Table II). Obviously, since less strong electronic demands are made on the cyclopropyl substituents in **6**, the magnitude of interaction is lessened. The extent of cyclo-

(45) (a) J. W. van Reijendam, Thesis (Groningen), 1968; (b) J. W. van Reijendam, G. J. Heeres, and M. J. Janssen, *Tetrahedron*, **26**, 1291 (1970); (c) J. W. van Reijendam and M. J. Janssen, *ibid.*, **26**, 1303 (1970); (d) H. Wynberg, H. van Driel, R. M. Kellogg, and J. Buter, *J. Amer. Chem. Soc.*, **89**, 3487 (1967); R. M. Kellogg and H. Wynberg, *Tetrahedron Lett.*, 5895 (1968).

propyl participation should not be underestimated, however, since even in **4** the fluorescence maximum is found at 335 mμ compared with 319 mμ for 2-phenyl-thiophene.[45]

Important trends are found from the spectra of the 2-substituted 3-cyclopropylthiophenes. First, these derivatives consistently absorb at shorter wavelength than the corresponding 2-cyclopropyl 5-substituted derivatives. The effect of cyclopropyl substitution in 3-cyclopropylthiophene (**9**) compared with that in the isopropyl compound is much less drastic than that observed for **4**. Second, the similarities between the 2-NO$_2$-, CHO-, CO$_2$H-, and Br-substituted derivatives and the corresponding *phenyl* derivatives are particularly striking as is seen from comparison of data in Table II.[43] The same trend of decreasing degree of interaction with decreasing electron-withdrawing ability of the 2 substituent is apparent from Table IV where the same arguments are invoked as used for the 5-substituted 2-cyclopropylthiophenes. Direct comparison of the data of Tables III and IV is unwarranted since the degree of interaction of either a cyclopropyl or *phenyl* substituent in the 3 position will necessarily be different from that in the 2 position. Finally, expected steric effects in the 2,3-substituted compounds come into play. This point is made obvious on observing the hypsochromic shifts of the long wavelength bands in the 3-isopropyl 2-substituted reference compounds compared with those of the 2-isopropyl 5-substituted compounds. The shifts are too great to be at-

TABLE IV

SHIFTS OF LONG WAVELENGTH BANDS AS A FUNCTION OF SUBSTITUENT X OF COMPOUNDS

| Shift (cm^{-1}) = $\nu_{R(C_3H_7)}$ − $\nu_{R(R)}$ | | Shift of C_6H_5/ | |
R = C$_6$H$_5$	R = C$_3$H$_5$	shift of C$_3$H$_5$	X
1230	1230	1.00	NO$_2$
2340	1750	1.34	CHO
2680	1180	2.27	CO$_2$H
2490	520	4.78	Br

tributed to different inductive contributions. Rather, twisting of the 2 substituent from coplanarity owing to steric interaction with the isopropyl group is more likely responsible for this effect. Similar steric interactions would be expected to hold for the cyclopropyl derivatives in view of the bulk similarities of isopropyl and cyclopropyl. For cyclopropyl, steric effects will likely again be reflected chiefly in deviation of the 2 substituent from coplanarity with the ring; the cyclopropyl group, although it may be crowded, still has a readily accessible bisected conformation available with the methine hydrogen directed away from the 2 substituent (conformation 25). Conformation 25 should be of lower energy than 26 or intermediate twisted conformations.
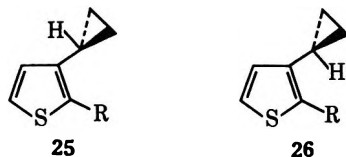
The various bromo- and iodocyclopropylthiophenes listed in Table II exhibit very slight hypsochromic shifts relative to the unsubstituted cyclopropylthiophenes contrary to the usual effect of a halogen substituent[46] and also contrary to what is usually found in simple thiophenes.[9] An economical explanation is that any bands which have been bathochromically shifted are buried as shoulders and are simply not resolved; the resolution could not be improved by changing solvents.

Obviously, a cyclopropyl group may induce large bathochromic shifts of various thiophene bands, the effect being most pronounced for 2-cyclopropylthiophenes.[47] A priori, the cause could be either destabilization of the ground state relative to the excited state or greater stabilization of the excited state relative to the ground state. Since there is no good reason to postulate ground-state destabilization, the latter must pertain. Any factors which intrinsically lower the electron density of the carbon to which cyclopropyl is attached should enhance cyclopropyl participation both in the ground and excited states. In this light the trends with 5-substituted 2-cyclopropylthiophenes and 2-substituted 3-cyclopropylthiophenes are entirely reasonable. The relatively large shifts in 2-cyclopropylthiophene (4) itself, and to a lesser extent with 3-cyclopropylthiophene (9), are more puzzling if interpreted by extension of the above rationalizations. The impor-

tant, and thus far overlooked, factor here, however, is the appreciable charge redistribution in thiophene upon excitation wherein the electron density increases on sulfur at the expense of chiefly the 2 and, to a lesser extent, the 3 position. This can be best illustrated in terms of the charge density q defined as in eq 4. Using

$$q_r = \sum_j n_j c_{jr}^2 \qquad (4)$$

the five-orbital model of Bielefeld and Fitts[42] for thiophene and taking as an example the $\varphi_4 \leftarrow \varphi_3$ transition, it is seen that particularly the charge density at the 2 and 5 carbons decreases significantly on excitation (Table V). The effect is even more pronounced if the

TABLE V

CHANGE IN CHANGE DENSITY q FOR $\varphi_4 \rightarrow \varphi_3$ TRANSITION IN THIOPHENE FOR A FIVE-ORBITAL MODEL

	Ground state^a	Excited state (φ_4 occupied)
S	1.793	1.896
C$_{2,5}$	1.064	0.861
C$_{3,4}$	1.040	1.020

^{a} From ref 42.

3d orbitals on sulfur are included in the orbital picture for thiophene (data of ref 42). This situation is, of course, exactly what is required for effective cyclopropyl participation in the excited state.

In summary, we believe that good support for the general idea of cyclopropyl participation in the excited state has been provided by the present examples. Moreover, the concept of increasing conjugative interaction with increasing electronic demand has been not only supported but also modified in the sense that any factors causing a significant electronic redistribution in the excited state will enhance cyclopropyl participation so long as the effect operates in an electron-withdrawing sense relative to cyclopropyl.

Experimental Section

Melting points were determined on a calibrated melting point block and boiling points are uncorrected. Ultraviolet (uv) spectra were recorded on a Zeiss PMQ II spectrophotometer. Infrared spectra (ir) were obtained with a Perkin-Elmer Model 125 infrared spectrophotometer. Nuclear magnetic resonance (nmr) spectra were taken on a Varian A-60 instrument using TMS as the internal standard. Fluorescence spectra were taken in cyclohexane solution at room temperature using an Aminco-Bowman spectrophotofluorometer. Analytical gas chromatography (glpc) was done on a F & M Model 810 gas chromatograph equipped with flame detectors and preparative work was done with a F & M Model 700 unit with thermal conductivity detectors. Irradiations were carried out using a Hanau TQ-81 medium pressure lamp equipped with quartz jackets. Many of the uv, ir, and nmr spectra were taken by Mrs. K. S. Rozema. Microanalyses were done by the analytical section of this laboratory under the direction of Mr. W. Hazenberg.

Syntheses of the various phenyl- and isopropylthiophenes used for comparison purposes were carried out along the lines detailed in Schemes I and II. Formylation and iodination of 3-isopropylthiophene produced ca. 50:50 mixtures of 2,3- and 2,4-substituted isomers; bromination, however, was completely-selective to the 2 position. The aldehyde derivative was therefore prepared from 2-lithio-3-isopropylthiophene prepared from the 2-bromo derivative; the carboxylic acid was obtained by oxidation of the aldehyde. All reference compounds were shown to be isomerically pure by nmr spectroscopy as well as glpc.

2-Cyclopropylthiophene (4) was prepared following the general synthesis for cyclopropylbenzene described by Bumgartner.[18]

(46) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962, pp 242–259.

(47) For favorable cases the conjugative ability of cyclopropyl has been calculated to be similar to that of phenyl and vinyl: R. Hoffmann, *Tetrahedron Lett.*, 3819 (1965).

Since some modifications have been made, important details of the procedure are given. Condensation of 2-thienylaldehyde with malonic acid in pyridine gave 3-(2-thienyl)acrylic acid.[48] This compound (28.5 g, 0.185 mol) was placed in the thimble of a Soxhlet extractor attached to a flask containing LiAlH$_4$ (11.0 g, 0.29 mol) in 1200 ml of ether.[49] The acid was completely transferred to the ether solution after 30–60-min refluxing; after refluxing 15 min more, the solution was cooled and water (or ethyl acetate) was added slowly to decompose the excess LiAlH$_4$. A solution of 300 ml of 10% H$_2$SO$_4$ was added, whereupon a clear solution resulted which was separated in a separatory funnel. The ether layer was neutralized with NaHCO$_3$ solution, washed once with water, and dried over MgSO$_4$. Distillation gave 18.7 g (0.132 mol, 71%) of 3-(2-thienyl)-1-propanol:[50] bp 88° (0.6 mm); ir (neat) 3350 cm^{-1}; nmr (CCl$_4$) δ 1.84 (quint, 2, J = ~6.5 Hz, CH$_2$), 2.86 (t, 2, J = 8.0 Hz, CH$_2$OH), 3.57 (t, 2, J = 8.0 Hz, ThCH$_2$), 3.80 (s, 1, OH), and 6.60–7.12 (m, 3, Th), no vinyl protons observable.

Anal. Calcd for C$_7$H$_{10}$OS: C, 59.12; H, 7.09; S, 22.54. Found: C, 58.91; H, 6.95; S, 22.58.

The above alcohol (17.1 g, 0.12 mol) was converted to 3-(2-thienyl)-1-propyl tosylate by treatment with *p*-toluenesulfonyl chloride in pyridine[51] to give 34.5 g (0.116 mol, 96.5%) of product, mp 63.5–64.5°.

Anal. Calcd for C$_{14}$H$_{16}$O$_3$S$_2$: C, 56.73; H, 5.44; S, 21.63. Found: C, 56.62; H, 5.43; S, 21.55.

The above tosylate (30 g, 0.107 mol) in 120 ml of benzene containing dimethylamine [25 g (0.55 mol, excess)] was sealed in a heavy-walled glass tube and heated (with shaking) at 65–70° for 3 days. The reaction mixture was washed successively with 10% NaHCO$_3$ solution and water and dried over MgSO$_4$. Distillation gave 15.0 g (0.90 mol, 84%) of 3-(2-thienyl)-*n*-propyldimethylamine: bp 104–106° (14 mm); $n^{20.5}$D 1.5090.

Anal. Calcd for C$_9$H$_{15}$NS: C, 63.86; H, 8.93; N, 8.27; S 18.94. Found: C, 63.85; H, 8.98; N, 8.27; S, 19.13.

The above amine (22 g, 0.13 mol) was treated with excess MeI in ether to give 39 g (0.125 mol, 96%) of the quaternary salt (1), mp 186–186.5°.

Anal. Calcd for C$_{10}$H$_{19}$NSI: C, 38.59; H, 5.84; N, 4.50; S, 10.30; I, 40.78. Found: C, 38.74; H, 5.91; N, 4.49; S, 10.23; I, 40.75.

A 2-l. three-necked flask containing a magnetic stirring bar was fitted with a condenser through which cold MeOH (−15°) was pumped and which was protected with a drying tube. To another neck was attached a piece of Teflon tube connected to an erlenmeyer flask containing the iodide. The apparatus was flame-dried. Ammonia (750 ml) was added followed by Na (5.0 g, 0.22 g-atom) and *ca.* 200 mg Fe(NO$_3$)$_3$ while the flask was contained in a solid CO$_2$–acetone bath. After the sodium had dissolved the above quaternary salt (39 g, 0.125 mol) was added portionwise to the solution over a period of *ca.* 20 min. A deep green color immediately developed later turning to black. After the mixture was allowed to stand for 4 hr, NH$_4$Cl (15.8 g, 0.30 mol) was added followed by 430 ml of ether. The ammonia was allowed to evaporate overnight. Water was added to the solution, the layers were separated, and the ether layer was washed once with dilute HCl solution, once with water, once with 10% NaHCO$_3$ solution, and once again with water and finally dried over MgSO$_4$. Distillation gave 13.38 g (0.108 mol, 86%) of 2-cyclopropylthiophene (4): bp 58° (10 mm); n^{20}D 1.5473; ir (neat) 1045 cm^{-1} (cyclopropyl); nmr (CCl$_4$) δ 0.5–1.20 (complex multiplet, 4, cyclopropylmethyl), 1.80–2.30 (complex multiplet, 1, *tert*-H), and 6.40–7.00 (complex multiplet, 3, thiophene).

Anal. Calcd for C$_7$H$_8$S: C, 67.69; H, 6.49; S, 25.82. Found: C, 67.45; H, 6.46; S, 25.87.

2-Bromo-5-cyclopropylthiophene (11) was obtained when 2-cyclopropylthiophene (1.000 g, 0.08 mol) was allowed to react with NBS (1.500 g, 0.008 mol) in 30 ml of a 1:1 CHCl$_3$–HOAc solution. Distillation provided 1.45 g (0.007 mol, 87.5%) of 11: bp 106° (14 mm); nmr (CCl$_4$) δ 0.6–1.1 (multiplet, 4, cyclopropylmethylene), 1.75–2.20 (multiplet, 1, *tert*-H), 6.47

(q, 1, J = 4.0 Hz, 1.0 Hz, 4 proton), 6.76 (d, 1, J = 4.0 Hz, 3 proton), no vinyl absorption was observable even at high attenuation.

Anal. Calcd for C$_7$H$_7$SBr: C, 41.40; H, 3.47; S, 15.79; Br, 39.34. Found: C, 41.86; H, 3.47; S, 15.84; Br, 39.39.

Deuterium exchange with 4 was carried out with 4 (287 mg, 1.93 mmol) in a refluxing solution of acetic anhydride (5 ml) and D$_2$O (3 ml). After 6 hr the mixture was worked up.[24] The product 13 had a nmr spectrum (CCl$_4$) identical with that of 4 except that in the aromatic region a set of doublets (J = 4.0 Hz) at δ 6.46 and δ 6.56 were seen indicating 100% exchange at the 5 position.

5-Cyclopropylthiophene-2-carboxylic acid (12) was obtained from the Grignard reagent obtained from 11 (650 mg, 3.2 mmol) with Mg (80 mg, 3.5 g-atoms) in ether. The Grignard reagent was poured on to solid CO$_2$, the resulting solution was acidified and extracted with ether, the ether layer was extracted with dilute NaOH solution, and the water layer was acidified whereupon crude acid precipitated. Recrystallization from petroleum ether (bp 40–60°) gave 240 mg (1.43 mmol, 45%) of 12: mp 113–114.5°; ir (KBr) 1630 (C=O), 1045 cm^{-1} (cyclopropyl); nmr (C$_3$D$_6$O) δ 0.6–1.2 (multiplet, 4, cyclopropylmethylene), 1.90–2.35 (multiplet, 1, *tert*-H), 5.6–6.3 [s (broad), 1, OH], 6.82 (q, 1, J = 4.0 Hz, 1.0 Hz, 4 proton), and 7.55 (d, 1, J = 4.0 Hz, 3 proton).

Anal. Calcd for C$_8$H$_8$O$_2$S: C, 57.12; H, 4.79; S, 19.06. Found: C, 57.25; H, 4.90; S, 19.07.

5-Cyclopropylthiophene-2-carboxaldehyde (10) was obtained upon slow addition of 2-cyclopropylthiophene (1.0 g, 9 mmol) to a solution of dimethylformamide (900 mg, 9 mmol) containing POCl$_3$ (1900 mg, 9 mmol) with the temperature being held at 10–20°. After addition was complete the magnetically stirred mixture was warmed gently for 1 hr and therafter poured onto ice. The solution was extracted with ether; the ether solution was neutralized with NaHCO$_3$ solution washed with water, and dried over MgSO$_4$. Distillation gave 750 mg (4.9 mmol, 56%)[52] of 10: bp 135° (18 mm); ir (CCl$_4$) 1650 (C=O) and 1040 cm^{-1} (cyclopropyl); nmr (CCl$_4$) δ 0.6–1.3 (multiplet, 4, cyclopropylmethylene), 1.8–2.3 (multiplet, 1, *tert*-H), 6.78 (q, 1, J = 4.0 Hz, ~0.5 Hz, 4 proton), 7.47 (d, 1, J = 4.0 Hz, 3 proton), and 9.67 [s, 1, C(=O)H].

Anal. Calcd for C$_8$H$_8$OS: C, 63.13; H, 5.29; S, 21.06. Found: C, 62.82; H, 5.27; S, 21.02.

2-Cyclopropyl-5-iodothiophene (14) was prepared using a previously described iodination procedure.[53] Starting from 4 (6.21 g, 50 mmol), iodine (12.8 g, 0.05 g-atom), and mercuric oxide (8.02 g, 0.04 mol) there was obtained after distillation[54] 10.91 g (43.6 mmol, 87%) of 14: bp 90° (2.5 mm); ir (neat) 1040 cm^{-1} (cyclopropyl); nmr (CCl$_4$), δ 0.5–1.1 (multiplet, 4, cyclopropylmethylene), 1.7–2.2 (multiplet, 1, *tert*-H), 6.28 (q, 1, J = 3.9 Hz, ~0.5 Hz, 3 proton), and 6.88 (d, 1, J = 3.9 Hz, 4 proton).

Anal. Calcd for C$_7$H$_7$SI: C, 33.62; H, 2.82; S, 12.82; I, 50.74. Found: C, 33.56; H, 2.69; S, 12.94; I, 50.78.

Nitration of 4 was carried out in a manner similar to that described for the phenylthiophenes.[27] 2-Cyclopropylthiophene (5.0 g, 0.04 mol) in 65 ml of acetic anhydride was added dropwise to a solution of Cu(NO$_3$)$_2$·3H$_2$O (4.88 g, 0.02 mol) in 65 ml of acetic anhydride. The solution was held at 10–12° for 2 hr whereupon the copper salts were removed by filtration and the residue was poured into ice water. Continuous extraction with ether gave a thick oil which consisted of mono- and dinitrothiophenes as determined by nmr. Distillation gave, in addition to a small amount of unreacted 4 and pot residue, 2.1 g (1.24 mmol, 30%) of a mixture consisting, as determined by nmr, of 60% 2-cyclopropyl-5-nitrothiophene (15) and 40% 2-cyclopropyl-3-nitrothiophene (16): bp 146° (11 mm); ir (neat) 1035 cm^{-1} (cyclopropyl).

Anal. Calcd for C$_7$H$_7$NO$_2$S: C, 49.69; H, 4.17; N, 8.27; S, 18.95. Found: C, 49.87; H, 4.18; N, 8.11; S, 18.91.

The individual compounds were obtained pure by preparative glpc (SE-30, 6 ft, 185°): 15, nmr (CCl$_4$) δ 0.6–1.3 (multiplet, 4,

(48) M. J. Mihailović and M. Tot, *J. Org. Chem.*, **22**, 682 (1957).

(49) R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, **69**, 2548 (1947).

(50) This procedure should be followed rigorously to obtain good yields of alcohol. Minor deviations lead to decreased yield.

(51) L. Fieser and M. F. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1968, p 1180; S. W. Pelletier, *Chem. Ind.*, 1034 (1953).

(52) Scaling up the reaction continually resulted in a lowered yield. We have not, despite repeated efforts, been able to circumvent this difficulty.

(53) W. Minnis, *Org. Syn.*, **12**, 44 (1933).

(54) This material can decompose quite violently above ~100° and care should be exercised in distilling it. We have observed that brominated or iodinated thiophenes have in general an unpredictable tendency to decompose violently even at room temperature. Extra care is therefore strongly recommended in the distillation and storage of these materials.

cyclopropylmethylene), 1.85–2.30 (multiplet, 1, *tert*-H), 6.67 (q, 1, $J = 4.0$ Hz, ~0.8 Hz, 3 proton), and 7.66 (d, 1, $J = 4.0$ Hz, 4 proton); 16, nmr (CCl_4) δ 0.7–1.45 (multiplet, 4, cyclopropylmethylene), 1.7–3.2 (multiplet, 1, *tert*-H), 6.92 [d, 1, $J = 5.5$ Hz, 4(?) proton], and 7.46 [d, 1, $J = 5.5$ Hz, 5(?) proton].

Nitration of 2-isopropylthiophene was carried out as described above to yield 50% of a fraction of bp 141–142° (23 mm) consisting of a 80:20 mixture of 2-isopropyl-5-nitro and 2-isopropyl-3-nitrothiophenes as evidenced by nmr absorptions in the aromatic region with J values of 4.0 and 5.5 Hz, respectively.

Anal. Calcd for $C_7H_9NO_2S$: C, 49.11; H, 5.30. Found: C, 49.12; H, 5.31.

Repeated attempts to obtain satisfactory N and S analyses failed; the mass spectrum, however, showed the parent peak at m/e 171.

The 2-isopropyl-5-nitrothiophene was purified by preparative glpc (DEGS, 6 ft, 170°): nmr (CCl_4) δ 1.36 (d, 6, $J = 6.5$ Hz, CH_3), 3.15 (complex multiplet, 1, methine H), 6.71 [d (slightly split), 1, $J = 4.0$ Hz, 3 H), and 7.68 (d, 1, $J = 4.0$ Hz, 4 H).

2-Cyclopropyl-5-phenylthiophene (5) was prepared in an analogous manner to that described for 4. 5-Phenylthiophene-2-carboxaldehyde[55] was obtained from 2-phenylthiophene and condensation with malonic acid yielded 3-(5-phenyl-2-thienyl)-propenoic acid in 91% yield, mp 206.5–207.5° (from ethanol).

Anal. Calcd for $C_{13}H_{10}O_2S$: C, 67.80; H, 4.33; S, 13.92. Found: C, 67.75; H, 4.37; S, 13.83.

Reduction of the acid gave 3-(5-phenyl-2-thienyl)-1-propanol in 81% yield as a crude solid which was not purified further (no alkene absorption in ir). Conversion to the tosylate proceeded in 90% yield, mp 63.5–64.5° (from 40–60° petroleum ether).

Anal. Calcd for $C_{20}H_{20}O_3S_2$: C, 64.49; H, 5.41; S, 17.21. Found: C, 64.80; H, 5.50; S, 17.23.

The above tosylate with excess dimethylamine in benzene at 65° (sealed tube) for 2 days gave dimethyl-*n*-[3-(5-phenyl-2-thienyl)]propylamine in 70% yield, bp 152° (0.7 mm).

Anal. Calcd for $C_{15}H_{19}NS$: C, 73.42; H, 7.81; S, 5.71; N, 13.07. Found: C, 73.46; H, 7.66; S, 5.51; N, 13.46.

The amine was treated with excess methyliodide in ether to give trimethyl-*n*-[3-(5-phenyl-2-thienyl)]propylammonium iodide (2) in 78% yield, mp 226.5–227°.

Anal. Calcd for $C_{16}H_{22}NSI$: C, 49.62; H, 5.72; N, 3.61; S, 8.28; I, 32.72. Found: C, 49.57; H, 5.74; N, 3.65; S, 8.22; I, 32.65.

Treatment of 2 (12 g, 0.031 mol) in 250 ml of NH_3 in which sodium (1.3 g, 0.057 g-atom) and a trace of ferric nitrate had been dissolved gave in 50% yield 5: bp 123–125° (0.75 mm); nmr (CCl_4) δ 0.6–1.0 (multiplet, 4, cyclopropylmethylene), 1.8–2.3 (multiplet, 1, *tert*-H), 6.62 (q, 1, $J = 3.8$ Hz, <0.5 Hz, 3 proton), 6.99 (d, 1, $J = 3.8$ Hz, 4 proton), and 6.9–7.6 (multiplet, 5, C_6H_5).

Anal. Calcd for $C_{13}H_{12}S$: C, 77.95; H, 6.04; S, 16.01. Found: C, 77.77; H, 6.07; S, 16.08.

2,5-Dicyclopropylthiophene (6) was prepared beginning with the condensation of 10 with malonic acid to give 3-(5-cyclopropyl-2-thienyl)propenoic acid, mp 106–108° (from ethanol), in 81% yield. This was reduced with excess $LiAlH_4$ to 3-(5-cyclopropyl-2-thienyl)-1-propanol which was converted to the tosylate without any purification. The tosylate was an oil which failed to crystallize. Treatment with excess dimethylamine in benzene for 2 days at 65° (sealed tube) gave 55% (based on tosylate) dimethyl-*n*-[3-(5-cyclopropyl-2-thienyl)]-propylamine, bp 102–106° (0.8 mm). Treatment with excess methyl iodide gave trimethyl-*n*-[3-(5-cyclopropyl-2-thienyl)]-propylammonium iodide (3) in quantitative yield, mp 88.5–90°.

Anal. Calcd for $C_{13}H_{22}NSI$: C, 44.45; H, 6.31; N, 3.98; S, 9.13; I, 36.13. Found: C, 44.04; H, 6.32; N, 3.92; S, 9.05; I, 36.45.

Treatment of 3 with sodium amide in ammonia gave in 62% yield 2,5-dicyclopropylthiophene: bp 112–114° (10 mm); nmr (CCl_4) δ 0.55–1.05 (multiplet, 8, cyclopropylmethylene), 1.7–2.15 (multiplet, 2, *tert*-H), and 6.42 (s, 2, 3,4 protons).

Anal. Calcd for $C_{10}H_{12}S$: C, 73.12; H, 7.36; S, 19.52. Found: C, 73.20; H, 7.27; S, 19.43.

3-Cyclopropylthiophene (9) was prepared by modification of a published procedure.[23] Base-catalyzed condensation of 3-thiophenealdehyde with acetaldehyde at 0° proceeded smoothly to

give 3-(3-thienyl)acrylaldehyde.[56] To a refluxing mixture of 85% hydrazine (3.9 ml) in 10 ml of 95% ethanol was added slowly the above aldehyde (3.5 g, 25 mmol). The mixture was refluxed for 1.5 hr after which time distillation was begun. When the head temperature reached 120° (bath 200°) gas evolution began, after which colorless liquid distilled over. Water was added to the distillate which was then extracted twice with ether. The ether layer was backwashed twice with water and dried over $CaCl_2$. Distillation gave 9 (800 mg, 6.35 mmol, 25%): bp 58° (10 mm); ir (neat) 1040 cm^{-1} (cyclopropyl); nmr (CCl_4) δ 0.5–1.0 (complex multiplet, 4, cyclopropylmethylene), 1.6–2.0 (complex multiplet, 1, *tert*-H), and 6.65–7.15 (complex multiplet, 3, aromatic H).

Anal. Calcd for C_7H_8S: C, 67.69; H, 6.49; S, 25.82. Found: C, 67.39; H, 6.41; S, 25.57.

3-Cyclopropyl-2-iodothiophene (21) was prepared in a manner analogous to that described for 14. From 9 (464 mg, 3.74 mmol) was obtained 750 mg (3.0 mmol, 80%) of 21 which was purified by chromatography over Al_2O_3 using benzene. Removal of the benzene left a clear oil (explosion upon distillation) which had ir (neat) 1045 cm^{-1} (cyclopropyl) and nmr (CCl_4) δ 0.4–1.1 (complex multiplet, 4, cyclopropylmethylene), 1.5–2.0 (complex multiplet, 1, *tert*-H), 6.29 (d, 1, $J = 5.5$ Hz, 4 H), and 7.22 (d, 1, $J = 5.5$ Hz, 5 H).

Anal. Calcd for C_7H_7SI: C, 33.62; H, 2.82; S, 12.82; I, 50.74. Found: C, 33.79; H, 2.80; S, 12.87; I, 50.69.

2-Bromo-3-cyclopropylthiophene (19) was obtained by bromination of 3-cyclopropylthiophene (200 mg, 1.61 mmol) with NBS in HOAc–$CHCl_3$ as described for 11. There was obtained 262 mg (1.28 mmol, 80%) 19: bp 97° (10 mm); ir (neat) 1050 cm^{-1} (cyclopropyl); nmr (CCl_4) δ 0.4–1.25 (complex multiplet, 4, cyclopropylmethylene), 1.6–2.2 (complex multiplet, 1, *tert*-H), 6.36 (d, 1, $J = 5.6$ Hz, 4 H), and 7.03 (d, 1, $J = 5.6$ Hz, 5 H).

Anal. Calcd for C_7H_7SBr: C, 41.40; H, 3.47; S, 15.79; Br, 39.34. Found: C, 41.49; H, 3.60; S, 15.90; Br, 39.34.

Deuterium exchange with 3-cyclopropylthiophene (200 mg, 1.61 mmol) was carried out at reflux temperature for 5 hr with a mixture of D_2O (2 ml) and acetic anhydride (5 ml). After workup the product (20) had nmr (CCl_4) δ 0.45–1.0 (complex multiplet, 4, cyclopropylmethylene), 1.6–2.1 (complex multiplet, 1, *tert*-H), 6.72 (d, 1, $J = 5.0$ Hz, 4 H), and 7.08 (d, 1, $J = 5.0$ Hz, 5 H). This indicates 100% exchange (by nmr) of the 2 hydrogen with undetectable exchange at other positions.

3-Cyclopropylthiophene-2-carboxaldehyde (17) was obtained in a manner analogous to that described for 10. From 9 (1.09 g, 8.79 mmol) there was obtained 1.00 g (6.58 mmol, 75%) 17: bp 132° (10 mm); ir (neat) 1050 cm^{-1} (cyclopropyl); nmr (CCl_4) δ 0.6–1.3 (complex multiplet, cyclopropylmethylene), 2.2–2.7 (complex multiplet, 1, *tert*-H), 6.59 [d, 1, $J = 5.0$ Hz, 4(?) H], 7.47 [q, 1, $J = 5.0$ Hz, ~0.5 Hz, 5(?) H], and 10.08 (d, 1, $J = 1.2$ Hz, COH).[57]

Anal. Calcd for C_8H_8OS: C, 63.13; H, 5.29; S, 21.06. Found: C, 63.11; H, 5.48; S, 21.07.

Nitration of 9 was carried out in a manner analogous to that described for 4. From 9 (1.30 g, 10.5 mmol) was obtained a crude mixture of mononitrothiophenes (1.31 g, 7.75 mmol, 74% crude yield), bp 150° (12 mm). This mixture consisted of ~12% 4-cyclopropyl-2-nitrothiophene (24) as judged from absorptions at δ 1.6–2.2 (complex multiplet, *tert*-H), 7.06 ($J = 2.0$ Hz), and 7.54 ($J = 2.0$ Hz) with the cyclopropylmethylene absorptions buried under those for 3-cyclopropyl-2-nitrothiophene (23) which constituted 88% of the mixture. Repeated attempts by glpc, tlc, and column chromatography failed to effect a separation of the nitrothiophenes. The crude mixture was recrystallized three times from absolute methanol to give 23: mp 48.5–50°; nmr (CCl_4) δ 0.6–1.4 (complex multiplet, 4, cyclopropylmethylene), 2.7–3.2 (complex multiplet, 1, *tert*-H), 6.52 (d, 1, $J = 5.8$ Hz, 4 H), and 7.32 (d, 1, $J = 5.8$ Hz, 5 H).

Anal. Calcd for $C_7H_7O_2NS$: C, 49.69; H, 4.17; N, 8.27; S, 18.95. Found: C, 49.74; H, 4.30; N, 8.10; S, 18.74.

Nitration of 3-isopropylthiophene was carried out as described above for 4. A 73% yield of a fraction of bp 140–150° (20 mm)

(55) P. Demerseman, Ng. Ph. Buu-Hoi, and R. Royer, *J. Chem. Soc.*, 4193 (1954).

(56) L. H. Klemm and K. W. Gopinath, *J. Heterocycl. Chem.*, **2**, 225 (1965).

(57) Usually the aromatic protons can be assigned from chemical shift values, *i.e.*, β protons absorb at higher field.[9] With 17 the resonance at δ 7.47 shows long-range, probably allylic coupling. This should come from the methine proton of the cyclopropyl ring but the chemical shifts are inverted from what would be expected.

was obtained which consisted of about 50% 3-isopropyl-2-nitro-thiophene and 50% 4-isopropyl-2-nitrothiophene.

Anal. Calcd for $C_7H_9NO_2S$: C, 49.11; H, 5.30; N, 8.18; S, 18.72. Found: C, 49.48; H, 5.35; N, 8.20; S, 18.59.

The isomers were separated by preparative glpc (DEGS, 6 ft, 170°): 2-nitro-3-isopropylthiophene, nmr (CCl_4) δ 1.28 (d, 6, J = 7.0 Hz, CH_3), 3.98 (complex m, 1, methine H), 7.03 (d, 1, J = 5.5 Hz, aromatic H), and 7.38 (d, 1, J = 5 Hz, aromatic H); 2-nitro-4-isopropylthiophene, nmr (CCl_4) δ 1.27 (d, 6, J = 7.5 Hz, CH_3), 2.98 (complex m, 1, methine H), 7.19 [d (slightly split), 1, J = 2.0 Hz, 5 H), and 7.76 (d, 1, J = 2.0 Hz, 3 H), and uv (95% EtOH) 289 mμ (log ε 3.76) and 327 (3.80).

3-Cyclopropyl-2-phenylthiophene (22) was prepared by irradiating with a high pressure mercury lamp 21 (500 mg, 2 mmol) in 125 ml of benzene containing 1 mol % anhydrous $Na_2S_2O_3$. After 6 hr irradiation stopped. The benzene solution was washed repeatedly with aqueous $Na_2S_2O_3$ and then dried over $MgSO_4$. After removal of the solvents the residue was chromatographed over Al_2O_3 using benzene to give chiefly 22 (50% yield from glpc) which was purified by preparative glpc (F & M 700, 150°) to give a clear liquid: ir (neat) 1035, 1055 cm^{-1} (cyclopropyl); nmr (CCl_4) δ 0.5–1.0 (complex multiplet, 4, cyclopropylmethylene), 1.7–2.2 (complex multiplet, 1, *tert*-H), 6.55 [d, 1, J = 5.5 Hz, 4(?) H], 7.04 [d, 1, J = 5.5 Hz, 5(?) H], and 7.1–7.6 (complex multiplet, 5, phenyl). Too little sample was obtained for an elemental analysis.

Attempted Synthesis of 9 from Quaternary Iodide 7.—In a manner analogous to that described for 1, condensation of 3-thiophenealdehyde with malonic acid gave 3-(3-thienyl)acrylic acid.[48] Reduction with LiAlH₄ gave 3-(3-thienyl)-1-propanol in 66% yield, bp 141–145° (12 mm). Treatment with tosyl chloride gave an oily tosylate which was not purified but allowed to react with dimethylamine to give 3(3-thienyl)-1-dimethylaminopropene in 32% yield based on alcohol: bp 104–107° (12 mm); n^{18}D 1.5130. Treatment with methyl iodide gave in 90% yield the quaternary iodide (7), mp 167–169°.

Anal. Calcd for $C_{10}H_{18}SNI$: C, 38.59; H, 5.84; S, 10.30; N, 4.50; I, 40.78. Found: C, 38.45; H, 5.71; S, 10.30; N, 4.40; I, 40.73.

Attempted cyclization in liquid ammonia with sodium amide gave, after work-up, a liquid (about 30%), bp 60° (10 mm), which,

besides some weak signals ultimately attributed to 9, showed strong absorptions at δ 6.3–6.5 indicating vinyl protons presumed to arise from 3-(3-thienyl)-1-propene (8). The reaction mixture was not investigated further.

Reactions of Phosphorus Compounds. XXVI. Preparation and Reactions of 3- and 4-Substituted 5-Benzoyl-2,2,2,5-tetraphenyloxa-2-phospholanes[1]

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Substituted (1- and 2-) vinylphosphonium salts reacted with the sodium salt of benzoin in DMSO to give 3- and 4-substituted 5-benzoyl-2,2,2,5-tetraphenyloxa-2-phospholanes, respectively. Methyl-substituted oxaphospholanes were separated into diastereoisomers while 3- and 4-phenyl-substituted oxaphospholanes were isolated as single isomers. Diastereomeric mixtures of oxaphospholanes substituted at C_3 tended to isomerize to one stable isomer while those substituted at C_4 did not isomerize. Reaction of 1- and 2-substituted vinylphosphonium salts with the sodium salt of benzoin in acetonitrile gave 2,5-dihydrofurans in all cases except 1-phenylvinyltriphenylphosphonium bromide which gave only the oxaphospholane. Pyrolysis of the oxaphospholanes gave benzil, triphenylphosphine, and an olefin.

In a previous article[2] we described the preparation and reactions of 5-benzoyl-2,2,2,5-tetraphenyloxa-2-phospholane (5) formed by attack of the benzoin enolate carbanion 1a on vinyltriphenylphosphonium bromide (2) in dimethyl sulfoxide (DMSO). In contrast, the dihydrofuran 3 was exclusively formed when acetonitrile was used as solvent (Scheme I).[2]

We now wish to report the reactions of 1 with 1- and 2-substituted vinylphosphonium salts which yield oxaphospholanes and dihydrofurans. The basis for the

stereochemical assignments of the oxaphospholanes obtained is discussed. The fusion reaction products of the oxaphospholanes are also examined.

Previous workers have had variable success in obtaining products from conjugate additions to propenyltriphenylphosphonium bromide[3] 6. When 1 was allowed to react with this salt in DMSO, a 40% yield of oxaphospholanes was realized, which was easily separated into two diastereomeric oxaphospholanes 7a,b by selective extraction with chloroform and fractional crys-

(1) E. E. Schweizer and W. S. Creasy, *J. Org. Chem.*, **36**, 2379 (1971).

(2) E. E. Schweizer, W. S. Creasy, J. G. Liehr, M. E. Jenkins, and D. L. Dalrymple, *ibid.*, **35**, 601 (1970).

(3) (a) P. Keough and M. Grayson, *ibid.*, **29**, 631 (1964); (b) D. Seyferth and J. Fogel, *J. Organometal. Chem.*, **6**, 205 (1966).

SCHEME I

$$\text{1b} + \text{CH}_2{=}\overset{+}{\text{CH}}\text{P(Ph)}_3\text{Br}^- \xrightarrow{\text{CH}_3\text{CN}} \text{3} + \text{(Ph)}_3\text{PO} \quad \text{4}$$

la ⇌ 5a ⇌ 5b
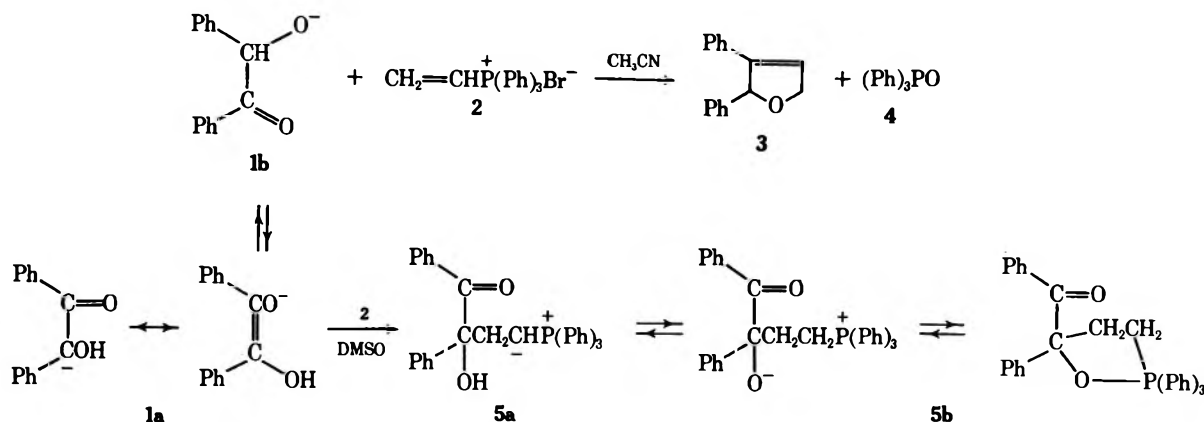
tallization. The structural identity of these two compounds was related by basic hydrolysis to identical mixtures of the same products.[4] Infrared spectra of **7a** and **7b** are identical but the methyl absorptions in the

$$\text{1} + \text{R}^1\text{CH}{=}\overset{+}{\text{CR}}^2\text{(Ph)}_3\text{Br}^- \xrightarrow{\text{DMSO}}$$

6, R¹ = CH₃; R² = H
8, R¹ = Ph; R² = H
10, R¹ = H; R² = CH₃
12, R¹ = H; R² = Ph

7a,b, R¹ = CH₃; R² = H
9, R¹ = Ph; R² = H
11a,b, R¹ = H; R² = CH₃
13, R¹ = H; R² = Ph

14, R¹ = CH₃; R² = H
15, R¹ = Ph; R² = H
16, R¹ = H; R² = CH₃
17, R¹ = H; R² = Ph

$$\text{7a} \longrightarrow \text{(Ph)}_2\text{CHOH} + \text{HO}_2\text{CCHCH}_2\overset{\text{O}}{\overset{\|}{\text{P}}}\text{(Ph)}_2 \longleftarrow \text{7b}$$
18

proton nmr are significantly different. That of **7b** appears at 0.6 ppm, considerably shielded with respect to the absorption observed in **7a** (1.1 ppm). Compound **7b** undergoes a deuterium for proton exchange at C₃ when a sample in CDCl₃ is shaken with D₂O (requiring 48 hr), a reaction similarly reported for **5**.[2] The remaining methine proton, on C₄, then appears as a doublet of quartets at δ 3.4 ppm with a vicinal P–H coupling constant of 34 Hz. This agrees very well with data reported for Hₐ in compound **5**, with the relatively large coupling constant indicating an anti relationship to phosphorus.[5] Methyl should then occupy the same position as H_B in compound **5** and is shielded, accord-

(4) A mechanism for this reaction has been proposed in ref 2.
(5) (a) J. G. Verkade, R. W. King, and C. W. Heitsch, *Inorg. Chem.*, **3**, 886 (1964); (b) J. G. Verkade and R. W. King, *ibid.*, **1**, 948 (1962).

ingly, due to proximity of the phenyl group on C₅. Although **7a** was insufficiently soluble for determination of proton nmr fine structure, it may very well be the other diastereoisomer as indicated. The predominance of **7a** is probably a reflection, then, of the pseudoaxial position of methyl on the oxaphospholane ring of **7b**.

5, R_A = H_A; R_B = H_B
7a, R_A = CH₃; R_B = H_B
7b, R_A = H_A; R_B = CH₃
9, R_A = Ph; R_B = H_B
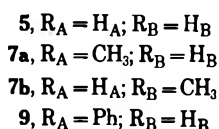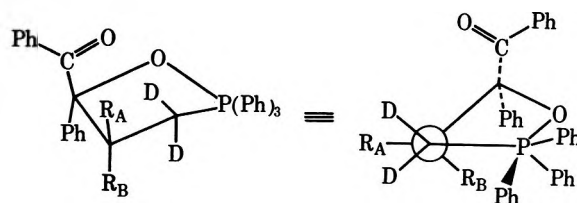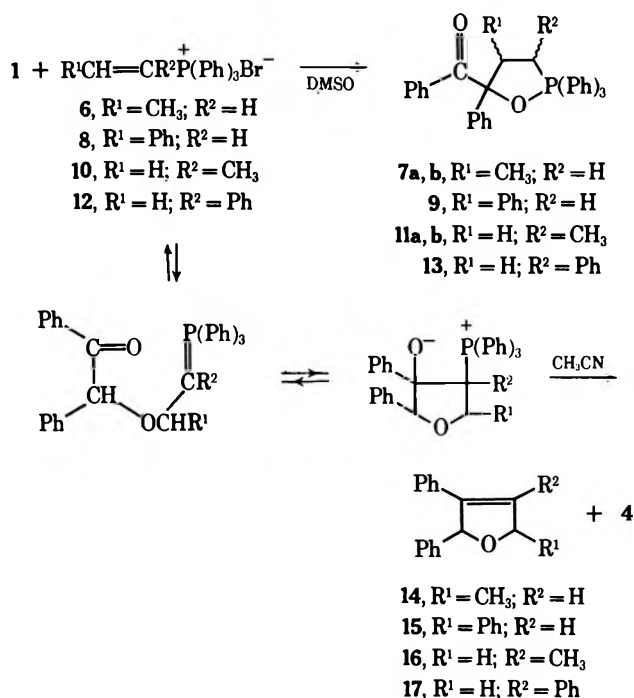
Reaction of benzoin (**1**) and 2-phenylvinyltriphenylphosphonium bromide (**8**) gave only one diastereoisomer **9**. The C₄ methine proton of **9** after deuterium exchange had δ 4.6 ppm and $J_{HCCP} = 11$ Hz, indicating a gauche relationship to phosphorus. Compound **9** then corresponds in structure to **7a**. Phenyl would be expected to have steric requirements similar to methyl with respect to protons.

Compounds **7a**, **7b**, and **9** were allowed to react with hydrobromic acid to give the corresponding hydroxyphosphonium bromides **19a**, **19b**, and **20**, respectively.

$$\text{7a, b} \xrightleftharpoons[\text{NaOH}]{\text{HBr}}$$
19a, b

There were only very small changes in position of the nmr methyl absorptions when **7a** and **7b** were converted to their salts. These salts, therefore, retain the basic geometry of the oxaphospholanes from which they are

$$\text{9} \xrightleftharpoons[\text{NaOH}]{\text{HBr}}$$
20

derived. On basification good reconversion to the parent oxaphospholanes was observed with no destruction of the stereochemistry of the ring, *i.e.*, no conversion to the opposite isomer.

Reaction of **1** and 1-methylvinyltriphenylphosphonium bromide (**10**) afforded 70% of a 1:1 mixture of two diastereomeric oxaphospholanes, **11a,b**, separated by fractional crystallization. Compound **11a** had methyl absorption at δ 1.4 ppm (d d) and compound **11b** showed an identical pattern centered at δ 1.2 ppm. Both patterns collapsed to doublets on shaking the sample with D₂O and absorptions due to methylene protons on C₄ appear as shown in Table I.

TABLE I
PROTON NMR SPECTRA OF
5-BENZOYL-3-METHYL-2,2,5-TETRAPHENYLOXA-2-PHOSPHOLANES

	11a			11b	
Proton	δ, ppm	J_{HCCP}, Hz	Proton	δ, ppm	J_{HCCP}, Hz
H_A	3.4	35	$H_{A'}$	3.3	20
H_B	2.3	9	$H_{B'}$	2.0	27

Oxaphospholane **11a** exhibits proton nmr patterns and coupling constants quite similar to **5**. However, the magnitudes of P–H coupling constants for protons of **11b** differ from other oxaphospholanes described, although there is little difference in chemical shifts between protons of **11a** and **11b**. A reasonable explanation is as follows. The methyl in **11a** is pseudoequatorial on the ring which is conformationally similar to **5**. However, to accommodate the methyl group in an equatorial position, the ring of **11b** must undergo a conformational change which then places $H_{A'}$ essentially gauche and $H_{B'}$ anti to phosphorus, resulting in larger P–H coupling to the higher field proton $H_{B'}$. Notably, the sum of P–H coupling constants in **11b** (44 Hz) is identical with that in **11a** (44 Hz).

11a, R = CH₃
13, R = Ph

11b, R = CH₃
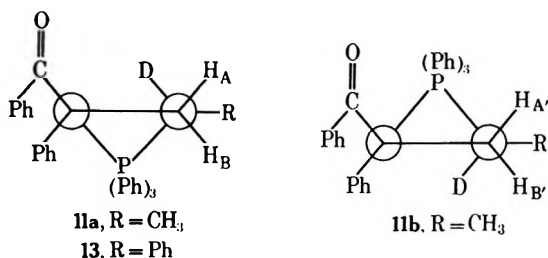
Furthermore, **11a** was found to isomerize slowly to **11b** on standing in chloroform. Conversion was 50% after 24 hr and required more than 1 week to reach the limits of nmr sensitivity. The compounds are relatively stable in the solid state but have identical melting points and mixture melting point, suggesting rapid isomerization at elevated temperatures.

The observance of interconversion further confirms earlier observations concerning the presence of the phosphonium ylide in equilibrium with the oxaphospholane,[2] although ³¹P nmr spectra consistently indicate that the latter form is predominant at 25° in chloroform.

Reaction of **11a** with hydrobromic acid yielded one pure salt **21a**, which was converted into pure **11a** by aqueous base (85% overall) with no apparent isomerization. Similar treatment of **11b** gave, however, a mixture of salts containing 21% of **21a**, which gave on

treatment with alkali a mixture consisting of 20% of **11a** and 80% of **11b** (78% overall). The impurity must arise from selective protonation since **11b** showed no tendency to isomerize to **11a**.
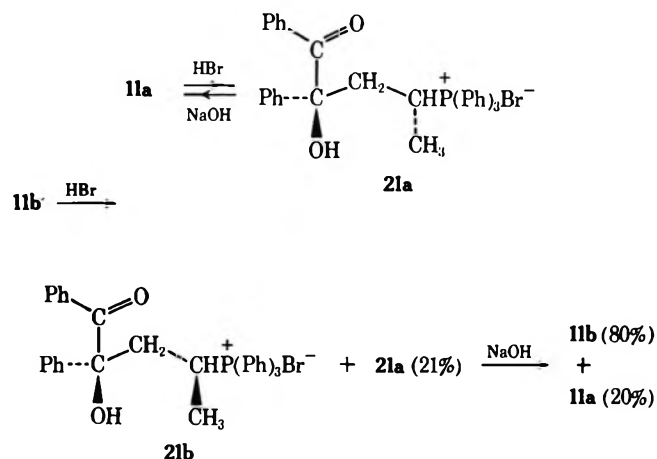
The oxaphospholane **13**, formed from reaction of **1** and 1-phenylvinyltriphenylphosphonium bromide (**12**), is isolated as a single diastereoisomer. The methylene protons on C₄ exhibit coupling constants and patterns similar to **5**, after deuterium exchange (rapid). The low-field proton (δ 4.1 ppm) had J_{HACCP} = 38 Hz and the high-field proton (δ 2.55 ppm) had J_{HBCCP} = 10 Hz. Compound **13** is, therefore, one isomer as opposed to a rapidly equilibrating mixture and corresponds in structure to **11a**.

Reaction of **13** with hydrobromic acid afforded an apparent 1:1 mixture of phosphonium salts **22a,b** which could not be separated into two components but which was converted to one pure salt, **22a**, on boiling in benzene or warming with a catalytic amount of potassium *tert*-butylate in DMSO (quantitative recovery). Basic treatment of either the mixture or pure **22a** gave pure **13** (74 and 67%, respectively), indicating that **13** is probably the more stable of the two possible isomers formed by the reaction of **1** and **12**, the other isomerizing rapidly upon formation. These results suggest the phosphonium ylide is the form of **13** which undergoes protonation and that this oxaphospholane possesses significantly more ylide character than other oxaphospholanes examined. Indeed, the ³¹P nmr absorption at +43.4 ppm is the smallest positive shift reported here, consistent with the lowest pentavalent phosphorus character. The increased acidity of benzylphosphonium salts as compared to ethyl and propyl salts[6] is undoubtedly responsible for the observed behavior of **13**.

22a, b
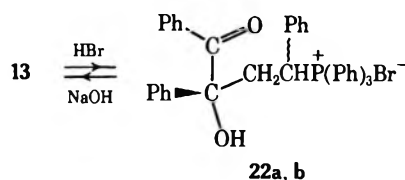
Oxaphospholanes **7a, 7b, 9, 11a, 11b,** and **13** thermally decomposed to benzil (**23**), and triphenylphosphine (**24**) on a vpc column at temperatures between 150 and 250°. In addition, styrene was detected in the decom-

(6) A. W. Johnson. "Ylid Chemistry," Academic Press, New York, N. Y., 1966.

position of **9** and **13**. The apparent mechanism involves fragmentation of the five-membered ring into two π systems and a neutral phosphine.
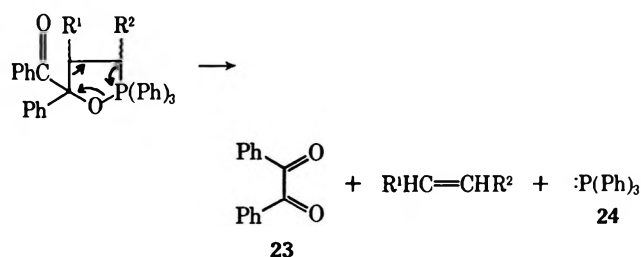
Similar results were obtained by pyrolysis of **5** in a hot tube pyrolysis apparatus.[7] The oxaphospholanes were relatively stable at temperatures of refluxing *tert*-butyl alcohol.

The vinylphosphonium salts **6**, **8**, **10**, and **12** were allowed to react with benzoin (**1**) in acetonitrile in order to prepare corresponding 4- and 5-substituted 2,3-diphenyl-2,5-dihydrofurans.[8] The results are shown in Table II.

TABLE II

PREPARATION OF 2,5-DIHYDROFURANS

Salt	Dihydrofuran (% yield)	Oxaphospholanes (%)
6	14 (30)	7a + 7b (32)
8	15 (50)	9 (8)
10	16 (28)	11a + 11b (34)
12	17 (0)	13 (76)

It is surprising that **15** was formed in highest yield since the Michael addition would be expected to encounter greatest hindrance in attack on **8**. Isolation of **13** only from reaction of **1** and **12** is probably a reflection of the decreased reactivity of the benzyl ylide (counterpart of **5a**) and greater hindrance to attack on the carbonyl, slowing intramolecular Wittig reaction and allowing effective competition for **12** by enolate **1a**. The latter observations are probably interrelated and provide valuable insight into the nature of the very complex interacting equilibria.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer Infracord 137 proton nmr spectra on a Varian A-60A analytical nmr spectrometer using tetramethylsilane as standard and ^{31}P nmr spectra on a Varian HR-60 nmr spectrometer using an 85% phosphoric acid capillary as reference. Melting points are uncorrected and were obtained with a Thomas-Hoover capillary melting point apparatus. Analysis are by M-H-W Laboratories, Garden City, Mich. Unless otherwise indicated all reactions were undertaken in anhydrous conditions under a blanket of dry nitrogen. Sodium hydride used was a 52% dispersion in mineral oil obtained from Metal Hydrides, Inc., Beverly, Mass.

5-Benzoyl-4-methyl-2,2,2,5-tetraphenyloxa-2-phospholanes (7a and 7b).—To a prereacted (1 hr at 40°) mixture of NaH, 9.6 g (0.2 mol), and dry DMSO (200 ml) was added 4.4 g of benzoin (**1**, 0.2 mol). When frothing had essentially ceased, salt **6**, 77 g (0.2 mol), was introduced dropwise as a solution in DMSO with the green color giving way near the equivalence point to a light green precipitate. The reaction was stirred 6 hr at ambient temperature and filtered, and the residue washed with small amounts of DMSO, water, methanol, and ether to

give 44.7 g of mixed oxaphospholanes **7a** and **7b**. Extraction of the mixture with chloroform followed by filtration gave a residue of **7a**, pure by nmr, and a solution containing **7b**. The latter was recovered in pure form by crystallization in two fractions from chloroform–hexane. Yields were 3.4 g of **7a** (34%), mp 206–206.5°, and 5.8 g (6%) of **7b**, mp 174-175°, mmp (between **7a** and **7b**) 174–187°.

5-Benzoyl-4-methyl-2,2,2,5-tetraphenyloxa-2-phospholane (7a): ir (Nujol) ν 1075 (s, COC), 1110 (m, CP), 1155 (m, POC), 1235 (s), 1655 cm⁻¹ (s, C=O); nmr (AsCl₃) δ 1.1 (d, 3, CH₃, J = 7 Hz), 2.8–3.5 (m, 3, H$_A$CCH₂P), 7.2–8.0 ppm (m, 25, C₆H₅) (the compound was not sufficiently soluble in any other solvent); ^{31}P nmr (AsCl₃) δ −21.3 ppm.

Anal. Calcd for C₃₅H₃₁O₂P: C, 81.69; H, 6.07; P, 6.02. Found: C, 81.41; H, 5.98; P, 5.87.

5-Benzoyl-4-methyl-2,2,2,5-tetraphenyloxa-2-phospholane (7b): ir (Nujol) ν 1070 (s, COC), 1100 (m, CP), 1130 (s, POC), 1220 (s, POC), 1655 cm⁻¹ (s, C=O); nmr (CDCl₃) δ 0.6 (d, 3, CH₃, J = 7 Hz), 2.5–3.9 (m, 3, H$_A$CCH₂P), 6.7–7.7 ppm (m, 25, C₆H₅).

After the sample was shaken with D₂O and allowed to stand 48 hr, the following spectrum was observed: δ 0.6 (d, 3, CH₃), 3.4 (doublet of quartets, 1, H$_A$CCP, J_{HAP} = 34 Hz), 6.7–7.7 ppm (m, 25 C₆H₅).

When **7b** was impure with **7a**, a methyl doublet corresponding to that described for the latter could be seen at high amplitude. [31]P nmr (AsCl₃) showed δ −21.5 ppm, (CHCl₃) δ +56.5 ppm.

Anal. Calcd for C₃₅H₃₁O₂P: C, 81.69; H, 6.07; P, 6.02. Found: C, 81.66; H, 6.06; P, 6.05.

From the DMSO reaction filtrate was isolated 5 g of impure 2,3-diphenyl-5-methyl-2,5-dihydrofuran (**14**) which oxidized on work-up, as described in a later experiment, to 1,2-diphenyl-2-pentene-1,4-dione, 4.8 g, corresponding to a 10% yield of the dihydrofuran. When allyltriphenylphosphonium bromide was substituted for **6**, identical results were obtained.

Hydrolysis of 7a and 7b in Aqueous–Ethanolic Sodium Hydroxide.—A sample of **7a**, 1.0 g (0.0002 mol), was allowed to reflux 72 hr in a mixture of 15 ml of ethanol and 15 ml of 20% aqueous sodium hydroxide. The solution was diluted with 100 ml of water and extracted with two 50-ml portions of chloroform which was dried (MgSO₄) and concentrated to give benzhydrol, 0.28 g (82%). Acidification of the aqueous solution followed by extraction with chloroform, drying (MgSO₄), and concentration afforded 2-carboxypropyldiphenylphosphine oxide (**18**): 0.43 g (77%); mp 135–137°, after recrystallization from acetonitrile–ether (lit.[9] 136°); ir (CHCl₃) ν 1120 (s, CP), 1160 (s, P=O), 1720 cm⁻¹ (s, C=O); nmr (CDCl₃) δ 1.3 (d, 3, CH₃), 2.2–3.2 (m, 3, CHCH₂), 7.2–8.0 (m, 10, C₆H₅), 10.5 ppm (s, 1, COOH)

Similar treatment of **7a**, 1.0 g, gave benzhydrol, 0.26 g (77%), and 2-carboxypropyldiphenylphosphine oxide (**18**), 0.41 g (73%).

2-Phenylvinyltriphenylphosphonium Bromide (8).[10-12]—Triphenyl phosphine (**24**), 13.1 g (0.05 mol), and anhydrous aluminum chloride, 6.7 g (0.05 mol), were fused at 150–200° for 2 hr and 2-bromostyrene, 13.8 g (0.075 mol), was added. The mixture was stirred at 180° for 4 hr and then at 120° for 2 days. The remaining aluminum chloride complex was decomposed with water and organic products were extracted with chloroform which was dried (MgSO₄), boiled with decolorizing charcoal, filtered, and concentrated. Salt **8** was recovered by precipitation in anhydrous ether and was recrystallized several times from acetone–ether. The yield, after a final recrystallization from chloroform–ether, was 12.1 g (54%), mp 263–265°.[11]

5-Benzoyl-2,2,2,4,5-pentaphenyloxa-2-phospholane (9).—To a prereacted mixture of NaH, 0.9 g (0.02 mol), and 50 ml of dry DMSO was added **1**, 6.4 g (0.03 mol). After this stirred for 15 min at ambient temperature, a solution of salt **8**, 9.0 g (0.02 mol, freshly dried at 100° for 24 hr), in 50 ml of DMSO was added slowly and the reaction mixture allowed to stir 24 hr. No precipitate formed but the green color of the sodium salt of benzoin faded slowly leaving a clear, tan solution which was diluted with 300 ml of water and extracted with two 150-ml portions of chloroform. These were combined, dried over molecular sieves, filtered, concentrated to approximately 75 ml, and dropped slowly into ether (anhydrous). The resulting precipi-

(7) Unpublished results, W. S. Creasy.

(8) E. E. Schweizer and J. G. Liehr, *J. Org. Chem.*, **33**, 583 (1968).

(9) H. Hoffman, *Chem. Ber.*, **94**, 1331 (1961).

(10) J. Chatt and F. G. Mann, *J. Chem. Soc.*, 1192 (1940).

(11) D. W. Allen and J. C. Tebby, *Tetrahedron*, **23**, 2795 (1967).

(12) S. Trippett and B. J. Walker, *J. Chem. Soc. C*, 887 (1966).

tate was collected by filtration yielding **20**, 1.6 g (12%), mp 176–179°, identified by ir and nmr (described elsewhere). Concentration of the ether filtrate, dilution with an equal volume of methanol, and cooling at 0° produced very slow crystallization of oxaphospholane **9** which was dissolved in chloroform and recrystallized by the addition of hexane and cooling. The yield of **9** was 2.7 g (24%), mp 158–159°. This appeared to be one isomer only: ir (CHCl₃) ν 1070 (s), 1085 (s, CO), 1110 (s, CP), 1150 (m), 1180 (m, POC), 1240 (s), 1675 cm⁻¹ (s, C=O); nmr (CDCl₃) δ 3.1–3.9 (m, 2, CH₂P), 4.2–4.9 (m, 1, CH), 6.6–7.8 ppm (m, 30, C₆H₅).

When this sample was shaken with D₂O and allowed to stand 48 hr, the following spectrum was observed: δ 4.6 (d, 1, HCCP, J_{HP} = 11 Hz), 6.6–7.8 ppm (m, 30, C₆H₅). ³¹P nmr (CHCl₃) showed δ +58.1 ppm.

Anal. Calcd for C₄₀H₃₃O₂P: C, 83.41; H, 5.77; P, 5.37. Found: C, 83.19; H, 5.59; P, 5.74.

The remaining solution was concentrated and the resulting oil dissolved in a small amount of chloroform, diluted with hexane until turbid, and allowed to stand. White crystals of 1,2-diphenylethyldiphenylphosphine oxide were deposited, mp 228–230° (lit.¹² 232–233°), 3.9 g (51%). This probably arises from basic hydrolysis of **8**.

Concentration of the remaining solution gave an oil which proved to be benzil (**23**) (probably *via* autoxidation of benzoin in alkaline solution) contaminated with trace amounts of benzaldehyde, styrene, and triphenylphosphine oxide, identified by nmr, vpc, and tlc. The oil weighed 2.9 g, corresponding to approximately 44% of the benzoin used.

Total recovery of phosphorus was 87%. No evidence for the other oxaphospholane isomer was observed and, if present at all, this must be formed in very small amounts.

1-Methylvinyltriphenylphosphonium Bromide (10).¹³,¹⁴—Anhydrous nickel bromide, 10.9 g (0.05 mol), and triphenylphosphine, 13.1 g (0.05 mol), were fused at 200° for 1 hr in a three-necked round-bottomed flask. Benzonitrile (100 ml) was added and water was removed by means of a Dean-Stark trap (about ¹/₃ of the solvent was removed), and the temperature reduced to 50°, at which time 2-bromopropene, 9.0 g (0.075 mol), was introduced. The mixture was allowed to stir 24 hr at 50° and then 72 hr at 200° (mantle temperature) and filtered to remove lumps of black intractible material. Benzonitrile was removed by steam distillation and the salt extracted with chloroform. Concentration followed by several precipitations in ether and several recrystallizations from ethyl acetate-ether gave **10**, 13.4 g (70%), mp 195–197° (lit.¹⁴ 196.5–197.5°). This is a modification of a previously reported method which failed to give the desired product.¹⁴

5-Benzoyl-3-methyl-2,2,2,5-tetraphenyloxa-2-phospholanes (11a and 11b).—To a prereacted mixture of NaH, 0.65 g (0.015 mol), and 50 ml of dry DMSO was added 1, 3.2 g (0.015 mol), and then (slowly) **10**, 5.8 g (0.015 mol), as a solution in 50 ml of DMSO. A light green precipitate formed slowly and was collected by filtration after 4 hr. The residue was washed with DMSO, water, and ether. Fractional crystallization of this product from a chloroform-hexane mixture afforded two similar oxaphospholanes, **11a** and **11b**, the bulk of the latter being recovered by concentration of the clear solution after addition of hexane failed to bring about further precipitation.

Although the melting points and mixture melting point of these compounds are identical, 179–181°, the nmr spectra show that they are different. Yields were 2.6 g of **11b** (34%) and 2.8 g of **11a** (36%). Integration of the nmr spectrum of the original product mixture (methyl peaks) gave relative percentages of 48 (**11b**) and 52 (**11a**).

5-Benzoyl-3-methyl-2,2,2,5-tetraphenyloxa-2-phospholanes (11b): ir (CHCl₃) ν 1065 (s, CO), 1100 (s, CP), 1200 (m), 1230 (m), 1250 (m), 1650 cm⁻¹ (s, C=O); nmr (CDCl₃) δ 1.2 (d d, 3, CH₃), 1.6–2.5 (m, 1, H_B, CCP), 2.9–3.8 (m, 2, H_A, CCHP), 6.9–8.0 ppm (m, 25, C₆H₅).

When the above sample was shaken with D₂O and allowed to stand 10 min, the following spectrum was observed: δ 1.2 (d, 3, CH₃, J_{H_3CCP} = 21 Hz), 2.0 (d d, 1, H_B′ CCP, $J_{HB'P}$ = 27, $J_{H_A'HB'}$ = 13 Hz), 3.3 (d d, 1 H_A'CCP, $J_{H_A'P}$ = 20 Hz), 6.9–8.0 ppm (m, 25, C₆H₅). This spectrum was unchanged after 24 hr. ³¹P nmr showed δ +48.5 ppm.

(13) The authors wish to thank R. Cambell for refinement of this procedure.

(14) J. G. Thompson, Doctoral Dissertation, University of Delaware, 1968.

Anal. Calcd for C₃₅H₃₁O₂P: C, 81.67; H, 6.07; P, 6.02. Found: C, 81.74; H, 5.91; P, 6.20.

5-Benzoyl-3-methyl-2,2,5-tetraphenyloxa-2-phospholanes (11a): ir (CHCl₃) was identical with that reported for **11b**; nmr (CDCl₃) δ 1.4 (d d, 4, CH₃), 2.1–2.6 (m, 1, H_BCCP), 2.7–3.9 (m, 2, H_ACCHP), 6.9–8.0 ppm (m, 25, C₆H₅).

When the above sample was shaken with D₂O and allowed to stand 10 min, the following spectrum was observed: δ 1.4 (d, 3, CH₃, J_{H_3CCP} = 21 Hz), 2.3 (d d, 1, H_BCCP, J_{HBP} = 9 Hz), 3.4 (d d, 1, H_ACCP, J_{H_AP} = 35 Hz), 6.9–8.0 ppm (m, 25, C₆H₅).

After 24 hr the sample had isomerized to a 50:50 mixture of **11a** and **11b**, as determined by the nmr integration. After 10 days the sample was essentially pure **11b**. Solubility was not sufficient for determination of a ³¹P nmr spectrum.

Anal. Calcd for C₃₅H₃₁O₂P: C, 81.69; H, 6.07; P, 6.02. Found: C, 81.72; H, 5.98; P, 5.88.

5-Benzoyl-2,2,2,3,5-pentaphenyloxa-2-phospholane (13).—To a prereacted mixture of NaH, 0.9 g (0.02 mol), and 50 ml of dry DMSO was added benzoin (1), 4.5 g (0.2 mol), and then (slowly) a solution of **12**,¹⁵ 9.0 g (0.02 mol), in 50 ml of DMSO. A light green precipitate formed slowly and was collected by filtration after 4 hr. The residue was washed with small amounts of DMSO, water, acetonitrile, and ether and fractionally crystallized from a chloroform-hexane mixture. All of these recovered fractions, as well as the material recovered from washings of the initial residue, proved to be the same compound, **13**: combined yield 8.0 g (70%); mp 169–171°; ir (CHCl₃) ν 1070 (s, CO), 1100 (m, CP), 1120 (m), 1170 (m, COP), 1230 (s), 1660 cm⁻¹ (s, C=O); nmr (CDCl₃) δ 2.2–2.8 (m, 1, H_BCCP), 3.5–4.6 (m, 2, H_ACCHP), 6.8–8.0 ppm (m, 30, C₆H₅).

When this sample was shaken with D₂O approximately 2 min, the following spectrum was observed: δ 2.5 (d d, 1, H_BCCP, J_{HBP} = 10, $J_{H_AH_B}$ = 14 Hz), 4.1 (d d, 1, H_ACCP, J_{H_AP} = 38 Hz), 6.3–8.0 ppm (m, 30, C₆H₅). ³¹P nmr (CHCl₃) showed δ +43.4 ppm.

Anal. Calcd for C₄₀H₃₃O₂P: C, 83.31; H, 5.77; P, 5.37. Found: C, 83.29; H, 5.66; P, 5.54.

Additional material recovered from washings of the initial residue was shown to be **22a**, 2.8 g (21%), mp 229–230° (described elsewhere), identified by comparison to authentic sample.

Salts of 3- and 4-Substituted Phospholanes.—The salts were made by dissolving or suspending the phospholanes in chloroform, adding excess 6 *M* HBr, and shaking vigorously for about 1 hr. The chloroform solution was then separated, washed with water, dried (MgSO₄), concentrated, dropped into a 1:1 ether-hexane mixture, filtered, and recrystallized from a chloroform-hexane mixture. Products and yields are as follows.

Phospholane **7a** gave pure salt **19a**: 98%; mp 246–248°; ir (CHCl₃) ν 1110 (s, CP), 1230 (m), 1680 (s, C=O), 3150 cm⁻¹ (s, OH); nmr (CDCl₃) δ 1.0 (d, 3, CH₃), 2.3–3.2 (m, 2, HCCHP), 4.4–5.1 (m, 1, CHP), 6.2 (s, 1, OH, disappeared on shaking sample with D₂O), 7.2–8.1 ppm (m, 25, C₆H₅).

Anal. Calcd for C₃₅H₃₂O₂PBr: C, 70.59; H, 5.42; Br, 13.42. Found: C, 70.35; H, 5.31; Br, 13.65.

Phospholane **7b** gave pure salt **19b**: 90%; mp 216–219°; ir (CHCl₃) ν 1110 (s, CP), 1235 (m), 1670 (s, C=O), 3100 cm⁻¹ (s, OH); nmr (CDCl₃) δ 0.6 (d, 3, CH₃), 2.6–3.2 (m, 1, CH), 3.3–4.0 (m, 1), and 4.0–4.8 (m, 1, CH₂P), 5.3 (s, 1, OH, disappeared on shaking sample with D₂O), 7.0–8.1 ppm (m, 25, C₆H₅).

Anal. Calcd for C₃₅H₃₂O₂PBr: C, 70.59; H, 5.42; Br, 13.42. Found: C, 70.70; H, 5.45; Br, 13.80.

Phospholane **9** gave pure salt **20**: 88%; mp 178–182°; ir (CHCl₃) ν 1110 (s, CP), 1230 (s), 1670 (s, C=O), 3100 cm⁻¹ (s, OH); nmr (CDCl₃) δ 2.0 (s, 1, OH, disappeared on shaking with D₂O), 3.4–4.9 (m, 3-HCCH₂P), 6.6–8.2 ppm (m, 30, C₆H₅).

Anal. Calcd for C₄₀H₃₄O₂PBr: C, 73.06; H, 5.21; Br, 12.15. Found: C, 72.83; H, 5.28; Br, 12.46.

Phospholane **11a** gave pure salt **21a**: 97%; mp 240–244°; ir (CHCl₃) ν 1115 (s, CP), 1240 (s), 1680 (s, C=O), 3150 cm⁻¹ (s, OH); nmr (CDCl₃) δ 0.8 (d d, 3, CH₃, J_{H_3CCP} = 21 Hz), 1.9–3.5 (m, 3, CH₂ plus OH, broad singlet disappeared and integration dropped to 2 when sample was shaken with D₂O), 5.0–5.7 (m, 1, CHP), 6.9–8.2 ppm (m, 25, C₆H₅).

Anal. Calcd for C₃₅H₃₂O₂PBr: C, 70.59; H, 5.42; Br, 13.42. Found: C, 70.42; H, 5.30; Br, 13.81.

Phospholane **11b** gave salt **21b**, 92%, containing, however,

(15) E. E. Schweizer and A. T. Wehman, *J. Chem. Soc.*, 343 (1971).

21% of salt **21a**, mp (of the mixture) 138–145°. These salts were inseparable by column chromatography, tlc, and fractional crystallization and showed no tendency to isomerize to one pure salt under the influence of base. For an 80% pure sample of **21b**, ir (CHCl₃) was identical with that described for **21a**; nmr (CDCl₃) δ 1.5 ppm (d d, CH₃, J_{H_3CCP} = 20 Hz). Other absorptions cannot be identified with certainty due to contamination with **21a**.

Anal. Calcd for C₃₅H₃₁O₂PBr (mixture of isomers): C, 70.59; H, 5.42; Br, 13.42. Found: C, 70.27; H, 5.45; Br, 13.63.

Phospholane **13** gave a 1:1 mixture of salts **22a** and **22b** 96%. The ratio was determined by nmr integration. Two spots were shown by tlc. When separation of these components was attempted with refluxing benzene in a Soxlet extractor, pure salt **22a** was recovered quantitatively, mp 234–236°. Heating the mixture at 100° in DMSO containing a trace of potassium *tert*-butylate also afforded pure **22a** after 48 hr.

For **22a**: ir (CHCl) ν 1110 (s, CP), 1230 (s), 1670 (s, C=O), 3150 cm⁻¹ (s, OH); nmr (CDCl₃) δ 2.1 (broad s, 1, OH, disappeared when sample was shaken with D₂O), 2.9–3.5 (m, 3, H₂CCHP), 6.8 (broad s, 5, C₆H₅), 7.0–8.0 ppm (m, 25, C₆H₅).

Anal. Calcd for C₄₀H₃₄O₂PBr: C, 73.06; H, 5.21; Br, 12.15. Found: C, 72.83; H, 5.28; Br, 12.46.

A 90% pure sample of salt **22b** was obtained by fractional crystallization from chloroform solution in an ether atmosphere, mp 191–193°.

For **22b**: ir (CHCl₃) was essentially the same as that described; nmr (CDCl₃) δ 2.5 (broad s, 1, OH, disappeared on shaking with D₂O), 2.8–3.5 (m, 1), and 3.6–4.2 (m, 1, CH₂), 5.2–5.8 (m, 1, CHP, appears as broad d d), 6.8–8.0 ppm (m, 33, C₆H₅, including a small peak at 6.8 corresponding to that in the spctrum of **22a**).

Anal. Calcd for C₄₀H₃₄O₂PBr (1:1 mixture of **22a** and **22b**): C, 73.06; H, 5.21; Br, 12.15. Found: C, 72.99; H, 5.04; Br, 12.50.

Conversion of Salts to Phospholanes.—The salts were dissolved in a small amount of methanol and 10 *M* NaOH was added dropwise until the solution became turbid. On standing the phospholanes crystallized and water was added at intervals until no further precipitation occurred. The crystals were recovered by filtration and washed with water and ether. Results are in Table III.

TABLE III

CONVERSION OF OXAPHOSPHOLANE SALTS TO OXAPHOSPHOLANES

Salt	Product	Yield, %
19a	**7a**	95
19b	**7b**	85
20	**9**	90
21a	**11a**	88
21b + **21a** (21%)	**11b** + **11a** (20%)	85
22a	**13**	67
22a + **22b** (50%)	**13**	74

Pyrolysis of 3- and 4-Substituted Oxaphospholanes A.— Samples of oxaphospholanes **7a**, **7b**, **9**, **11a**, **11b**, and **13** were injected into a vpc (column W-98 on Chromosorb, 200°). The only peaks recorded corresponded to benzil (**23**), triphenyl phosphine (**24**), and, in the cases of **9** and **13**, styrene. These products were collected and their identities confirmed by comparison to authentic samples.

B.—Samples of each of the above phospholanes (except **13**) were recovered unchanged from a 4-day reflux in *tert*-butyl alcohol, although very small amounts of benzil, triphenylphosphine, and, triphenylphosphine oxide could also be detected. Compund **13** was recovered in only 32% yield and significant amounts of benzil (**23**, 30%), triphenylphosphine (**24**, 17%), and triphenylphosphine oxide (**4**, 18%) were isolated. Styrene was detected by vpc but no other products were observed.

2,3-Diphenyl-5-methyl-2,5-dihydrofuran (14).—To a suspension of sodium hydride (2.1 g, 0.05 mol) in 50 ml of anhydrous ether was added benzoin (**1**), 12.8 g (0.05 mol), and then a solution of salt **6**, 19.2 g (0.05 mol), in 150 ml of dry CH₃CN. After a 48-hr reflux the mixture was filtered and the residue was washed with ether and air-dried to give 8.3 g of **7a**, plus a small amount of **7b** (32% total).

Dilution of the filtrate with 500 ml of water followed by extraction with two 100-ml portions of ether, drying (MgSO₄), concentration, and dropping into 400 ml of hexane gave a gummy precipitate and a clear yellow solution which was decanted. The gum solidified on stirring and proved to be slightly impure triphenylphosphine oxide (**4**), 7.8 g (56%). Concentration of the decantate and chromatography on silica gel afforded 3.6 g of a light yellow gum which proved to be pure **14** (30%), identified by its ir and nmr spectra. However, after repeated attempts to crystallize this product, only 1,2-diphenyl-2-pentene-1,4-dione was recovered. Recrystallization from cold CCl₄-hexane gave colorless needles, mp 119–121°, 2.6 g (68%).

2,3-Diphenyl-5-methyl-2,5-dihydrofuran (14): ir (CHCl₃) ν 1070 cm⁻¹ (s, COC); nmr (CDCl₃) δ 1.2 (d d, 3, CH₃), 4.8–5.2 (m, 1, CH), 6.2–5.8 (m, 2, ArCH + C=CH), 7.6–6.9 ppm (m, 10, C₆H₅).

Anal. Calcd for C₁₇H₁₆O: C, 86.40; H, 6.83. Found: C, 86.74; H, 6.58.

1,2-Diphenyl-2-pentene-1,4-dione: ir (CHCl₃) ν 1680 (s, C=O), 1580 (s, C=C), 1280 (m), 1190 (s), 985 cm⁻¹ (m); nmr (CDCl₃) δ 2.2 (s, 3, CH₃), 6.8 (s, 1, C=CH), 7.2–7.7 and 7.8–8.0 ppm (m, 8, and m, 2, respectively, C₆H₅).

Anal. Calcd for C₁₇H₁₄O₂: C, 81.58; H, 5.64. Found: C, 81.36; H, 5.71.

This reaction was repeated using salts **8**, **10**, and **12**.

(A) Reaction of **1** and salt **8** gave compound **9** (8%), 2,3,5-triphenylfuran [4%, mp 93–94° (lit.[16] 92–93°)], 1,2,4-triphenyl-2-butene-1,4-dione [6%, mp 129–129.5° (lit.[17] 129°)], and 2,3,5-triphenyl-2,5-dihydrofuran[18] (**15**) [50%; ir (CHCl₃) ν 1030 (m), 1060 (s, COC), 1070 (m), 1600 cm⁻¹ (m, C=C); mp 78–80° (lit.[17] 79–80°); nmr (CDCl₃) δ 5.8–6.1 (m, 1, C=CH), 6.2–6.4 (m, 2, HCOCH), 6.9–7.16 ppm (m, 15, C₆H₅)].

Anal. Calcd for C₂₂H₁₈O (**15**): C, 88.59; H, 6.00. Found: C, 88.40; H, 5.90.

(B) Reaction of **1** and salt **10** gave compound **11a** containing 36% of **11b** (34% combined) and 2,3-diphenyl-4-methyl-2,5-dihydrofuran (**16**) [28%; ir (CHCl₃) ν 1070 cm⁻¹ (s, COC); mp 72–74°; nmr (CDCl₃) δ 1.7 (broad doublet, 3, CH₃, *J* = 2 Hz), 4.7 (m, 2, CH₂), 6.0 (m, 1, CH), 6.9–7.7 ppm (m, 10, C₆H₅)].

Anal. Calcd for C₁₇H₁₆O (**16**): C, 86.40; H, 6.83. Found: C, 86.44; H, 6.79.

(C) Reaction of **1** and salt **12** gave compound **13** (76%). There was no discernible evidence for the formation of the dihydrofuran **17** or any products resulting directly from it.

(16) F. R. Japp and F. Klingemann, *Chem. Ber.*, **21**, 2932 (1888).

(17) F. R. Japp and N. H. J. Miller, *J. Chem. Soc. Trans.*, 35 (1885).

(18) L. F. Chelpanova and V. A. Kormer, *Zh. Obshch. Khim.*, **29**, 2348 (1959). However, the spectral data reported for this compound leaves some doubt as to the validity of the previous characterization.

Amino-Protecting Groups Removable by Neighboring-Group Assistance. II.[1] The o-Phenazophenoxyacetyl Moiety

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The o-phenazophenoxyacetyl moiety has been found to be an effective amino-protecting group for several amino esters. It can be introduced *via* acylation of the amino ester with an appropriate carboxylic acid. The removal of this blocking group was easily accomplished by reduction of the azo portion using potassium borohydride and palladium on carbon followed by acidification of the reaction mixture. An intramolecular rearrangement occurred which was followed by fragmentation into a benzoxazinone and the regenerated amino ester. Both the introduction and removal of this amino-protecting group were completed in higher yields than those obtained in previous procedures which employed the o-nitrophenoxyacetyl blocking group.

The rapid removal of the o-nitrophenoxyacetyl amino-protecting group by neighboring group assistance was recently reported.[2] The procedure involved the reduction of the nitro portion to the hydroxylamino stage using zinc and ammonium chloride. The blocking group was then removed as a result of the attack of the nucleophilic hydroxylamino moiety on the neighboring amide linkage. The overall yields of this procedure ranged from 45 to 78% depending on which amino acid was involved.

The mild conditions and the simplicity of this procedure led us to extend the investigation to other functional groups which are also capable of intramolecular participation. As a result, we have found that the o-phenazophenoxyacetyl moiety was superior in almost every way when compared with the o-nitro compound. Specifically, we used two phenazo blocking groups, one derived from α-methyl-α-(4,5-dimethyl-2-phenazophenoxy)propionic acid (1, herein named the DAZ group) and the other derived from α-methyl-α-(4-methyl-2-phenazophenoxy)propionic acid (2, herein named the MAZ group). Either of these compounds were easily coupled to the amino portion of several amino acid esters *via* the EEDQ procedure[2] in excellent yield (Scheme I). The protected amino esters 3 and 4 were generally obtained as highly colored oils or glasses that were homogeneous products according to their thin layer chromatograms. Characterization of these intermediates (3 and 4) was made from spectral data (uv, ir, nmr) and from subsequent chemical reactions.

The conversion of the phenazo group in 3 or 4 to a nucleophilic reduction product, 5 or 6, was accomplished using several reducing agents. Zinc dust and ammonium hydroxide and aluminum amalgam were both found to effect the desired reduction. However, the preferred reagent was potassium borohydride and palladium on carbon, which rapidly and completely reduced 3 or 4 within 45 min at 5°.

The phenylhydrazo (5) or the anilino (6) intermediates were not isolated and characterization was difficult because of their unstable nature. The method of reduction of 3 or 4 could yield either or both of these intermediates and either would be expected to be an effective nucleophile[3] in the subsequent fragmentative cyclization.

The 45-min reduction of 3 or 4 with potassium boro-hydride and palladium on carbon was immediately followed by acidification of the reaction mixture. An assisted cleavage of the amide bond resulted and two products were isolated and identified. One was the deblocked amino ester hydrochloride 7 and the other was a 3,4-dihydro-2,2-dimethyl-2H-1,4-benzoxazin-3-one, 8 or 9. The formation of 8 and 9 indicated that the reduction of the phenazo group of 3 or 4 apparently proceeded all the way to the amino stage. It is still unclear at what point the phenylhydrazo moiety in 5 fragmented: before or after the acidification step. Aniline was never isolated from the reaction mixture and did not interfere with the main object of the experiment: the deblocking of an amino ester.

The starting materials 1 and 2 were prepared by the following reaction scheme (Scheme II). The 2-phenylazo-4,5-xylenol (10) was obtained from a commercial source (however, it is no longer available). The 2-phenylazo-4-cresol (11) was prepared by a classical diazotization and coupling experiment.[4] The preparations of the phenazophenoxypropionic acids, 1 and 2, from 10 and 11 were accomplished using a procedure that has been previously employed in the preparation of a variety of α-aryloxy aliphatic carboxylic acids.[5]

Deblocking experiments were performed on five different amino esters which were each protected with the DAZ and MAZ groups. The MAZ-amino esters 4 were found to be deblocked in better yield than the DAZ-amino esters 3 in every case. Table I summarizes the results of these experiments. For comparison purposes, this table also contains the results of the reduction and subsequent deblocking of DAZ-amino esters with other reducing agents.

The yields of amino ester hydrochlorides 7 obtained by the reductive fragmentation of MAZ-amino esters (Table I) are the results of one-run experiments in most cases. The present procedure of preparing and removing amino-protecting groups has advantages other than high yields. The protected amino esters 3 and 4 are very deeply colored derivatives of the colorless amino acids or amino esters with characteristic ultraviolet and visible spectra (intermediate 1 has an ultraviolet maximum at 333 mμ). The starting materials are inexpensive and the chemical conversions involved are simple procedures which give uniformly high yields. The present method, therefore, represents a simple, rapid,

(1) Paper I: C. A. Panetta, *J. Org. Chem.*, 34, 2773 (1969).

(2) B. Belleau and G. Malek, *J. Amer. Chem. Soc.*, 90, 1651 (1968).

(3) For a report on the nucleophilic amino group in a similar reaction, see R. W. Holley and A. D. Holley, *ibid.*, 74, 3069 (1952).

(4) E. Nölting and O. Kohn, *Ber.*, 17, 351 (1884); C. Liebermann and St. V. Kostanecki, *ibid.*, 17, 876, (1884).

(5) W. G. M. Jones, J. M. Thorp, and W. S. Waring, British Patent 860,303 (Feb 1, 1961); *Chem. Abstr.*, 55, 24680b (1961).

SCHEME I

1, R¹, R² = CH₃
2, R¹ = H, R² = CH₃

EEDQ

reduction

3, R¹, R² = CH₃
4, R¹ = H; R² = CH₃

5

acid

6

7

8, R¹, R² = CH₃
9, R¹ = H; R² = CH₃

SCHEME II

10, R¹, R² = CH₃
11, R¹ = H; R² = CH₃
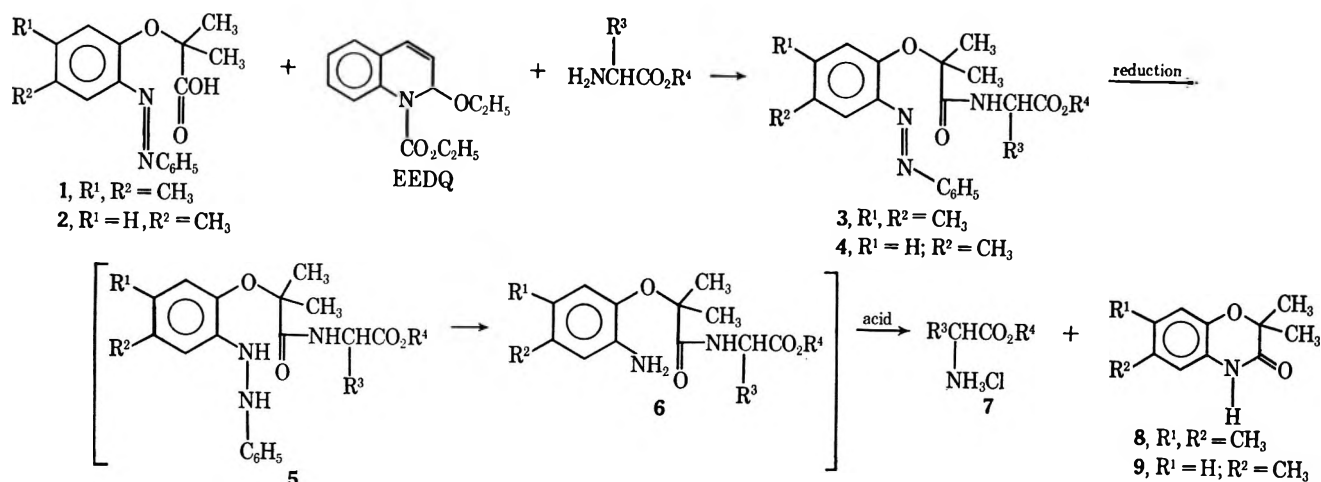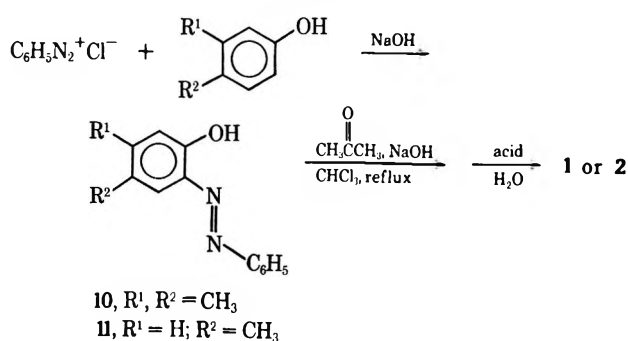
and effective procedure for the temporary protection of amino groups found in amino acids or amino esters.

Experimental Section[6]

2-Phenylazo-4-cresol (11).—This starting material was prepared using a published procedure.[4] It was obtained in quantitative yield and melted at 105–106° (lit.[4] mp 105–106°).

α-Methyl-α-(4-methyl-2-phenylazophenoxy)propionic Acid (2).—A mixture of 6.36 g (0.03 mol) of 2-phenylazo-4-cresol, 12.1 g (0.03 mol) of sodium hydroxide, and 33.9 g (0.58 mol) of acetone was heated to reflux. Chloroform, 8.4 g (0.07 mol), was added dropwise and, after the addition was complete, the resulting mixture was heated to reflux for 5–6 hr. The solvents were removed by distillation at reduced pressure and the residue was then distributed between water and chloroform at pH 2. The dried chloroform extract was concentrated to a small volume under reduced pressure and the concentrate was eluted on a silicic acid (100-mesh) column with benzene. Crystals were obtained, 4.3 g (48.1%), mp 83–84°.

Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.56; H, 5.90; N, 9.49. Found: C, 68.45; H, 6.04; N, 9.39.

General Procedure for the Preparation of MAZ-Amino Esters 4.—The following procedure was used essentially unchanged for the preparation of all of the MAZ-amino esters. The amino ester hydrochloride (3.3 mmol) was dissolved in water and extracted with chloroform at pH 9.0. The chloroform solution was dried and the solvent was removed by distillation under reduced pressure. The residual oil was dissolved in 50 ml of THF. To the resulting solution was added 1.0 g (3.3 mmol) of α-methyl-α-(4-methyl-2-phenylazophenoxy)propionic acid (2) and 0.82 g (3.3 mmol) of EEDQ.[2] The reaction mixture was stirred at ambient temperature for 5–6 hr. The solvent was removed *in vacuo* and the residue was purified by silicic acid column chro-

matography with benzene as the eluting solvent. The MAZ-amino esters were obtained as deep red or orange colored oils or glasses that were homogeneous according to thin layer chromatography on silica gel coated plates using benzene–ethyl acetate (90:10) as the eluting solvent. The ir and nmr spectra of these products were consistent with the structure given 4. The yields obtained for the various MAZ-amino esters are as follows: MAZ-glycine ethyl ester, 93.7%; MAZ-leucine ethyl ester, 91.2%; MAZ-valine methyl ester, 94.2%; MAZ-phenylalanine methyl ester, 96.9%; and MAZ-alanine ethyl ester, 82.9%.

General Procedure for the Deblocking of MAZ-Amino Ester 4.—A solution of 3.8 mmol of the MAZ-amino ester 4 in 50 ml of methyl isobutyl ketone was added dropwise to a stirred and chilled mixture of 46.5 mmol of KBH₄ and 0.17 g of 5% Pd on carbon in 50 ml of water. The mixture was stirred for 1 hr after the addition was completed. It was filtered through Celite and the pH of the filtrate was adjusted to 1.0. The organic layer was separated and dried and the methyl isobutyl ketone was removed by distillation under reduced pressure. The crystalline residue was recrystallized from EtOAc and petroleum ether (bp 30–60°) to afford pure 3,4-dihydro-2,2,6-trimethyl-2H-1,4-benzoxazin-3-one (9), mp 153–154°; homogeneous according to thin layer chromatography on silica gel coated plates using benzene–ethyl acetate (90:10) as the eluting solvent. The ir and nmr spectra were consistent with the structure of 9. The yields obtained in five different experiments are listed in Table I.

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.11; H, 6.80; N, 7.33. Found: C, 69.33; H, 7.00; N, 7.40.

The pH 1.0 aqueous layer was adjusted to pH 11–12 and extracted with ether, and the resultant ether extract was dried over anhydrous MgSO₄. The drying agent was removed by filtration and the filtrate was then treated with gaseous HCl until it was thoroughly saturated. An oily solid at first separated and then slowly crystallized. It was recrystallized from ether–ethanol to yield the pure deblocked amino ester hydrochloride 7. This was characterized by direct comparison of thin layer chromatogram R_f values and ir spectral properties with those of authentic samples. The chromatograms were run on silica gel coated plates and the eluting solvent was CH₃OH–NH₄OH (98:2). The ir spectra were run on Nujol mulls. The yields obtained in deblocking experiments on five different MAZ-amino esters are listed in Table I. Two amino ester hydrochlorides (valine and phenylalanine) required chromatography on silicic acid (100-mesh) columns (eluent, methanol) before they were obtained as homogeneous products.

α-Methyl-α-(4,5-dimethyl-2-phenylazophenoxy)propionic Acid (1).—2-Phenylazo-4,5-xylenol (10) (Aldrich Chemical Co.) was treated with NaOH, CHCl₃, and acetone in essentially the same manner as was 2-phenylazo-4-cresol (above). Chromatography on a silicic acid column was performed first with petroleum ether (bp 30–60°) as the eluting solvent, in order to remove some starting material, and then with a 1:1 mixture of petroleum ether and benzene which eluted the product. The latter was recrystallized from petroleum ether (bp 30–60°) to afford pure 1, mp 125–126°; ir and nmr spectra were consistent with the structure of 1.

Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.32; H, 6.58; N, 9.13.

(6) Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., or by Alfred Bernhardt Mikroanalytisches Laboratorium, 5251 Elbach über Engelskirchen, West Germany. Melting points were not corrected.

TABLE I

SUMMARY OF RESULTS OF DEBLOCKING EXPERIMENTS ON SEVERAL MAZ- AND DAZ-AMINO ESTERS

Protected amino ester[a]				Benzoxazinone		
Formula no.	R^3	R^4	% yield of deblocked amino ester hydrochloride 7	% yield	Formula no.	Reducing agent
4	H	C_2H_5	89.4 (glycine)	47.0	9	KBH_4
4	$(CH_3)_2CHCH_2$	C_2H_5	87.6 (leucine)	40.0	9	KBH_4
4	$(CH_3)_2CH$	CH_3	83.5 (valine)	51.0	9	KBH_4
4	CH_3	C_2H_5	89.2 (alanine)	31.0	9	KBH_4
4	$C_6H_5CH_2$	CH_3	79.8 (phenylalanine)	36.0	9	KBH_4
3	H	C_2H_5	61.8 (glycine)	35.0	8	KBH_4
3	$(CH_3)_2CHCH_2$	C_2H_6	53.0 (leucine)	75.0	8	KBH_4
3	$(CH_3)_2CH$	CH_3	72.7 (valine)	34.0	8	KBH_4
3	CH_3	C_2H_5	48.0 (alanine)	30.0	8	KBH_4
3	C_6H_5CH	CH_3	53.3 (phenylalanine)	29.0	8	KBH_4
3	H	C_2H_5	45 (glycine)	36.0	8	$Zn + NH_4OH$
3	$(CH_3)_2CHCH_2$	C_2H_5	45 (leucine)	39.0	8	$Zn + NH_4OH$
3	H	C_2H_5	44 (glycine)	42.0	8	Al(Hg)
3	$(CH_3)_2CHCH_2$	C_2H_5	33 (leucine)	37.0	8	Al(Hg)

[a] The L isomer of each amino ester (except glycine) was used.

DAZ-L-Valine Methyl Ester [3, R^3 = $(CH_3)_2CH$; R^4 = CH_3] and DAZ-L-Phenylalanine Methyl Ester (3, R^3 = $C_6H_5CH_2$; R^4 = CH_3).—These amino ester derivatives were prepared by the EEDQ method.[2] The procedure was essentially the same as the general procedure described in detail above for the preparation of MAZ-amino esters. Benzene–EtOAc (90:10) was employed as the eluting solvent for chromatography on a silicic acid column. These DAZ-amino esters were obtained as deep red or orange colored oils or glasses that were homogeneous according to thin layer chromatography (same conditions as those used with the MAZ-amino esters). The ir and nmr spectra of these products were consistent with their proposed structures (3). The DAZ-L-valine methyl ester and the DAZ-L-phenylalanine methyl ester were obtained in 98.5 and 98.7% yields, respectively.

DAZ-Glycine Ethyl Ester (3, R^1 = H; R^4 = C_2H_5), DAZ-L-Leucine Ethyl Ester [3, R^3 = $(CH_3)_2CHCH_2$; R^4 = C_2H_5], and DAZ-L-Alanine Ethyl Ester (3, R^3 = CH_3; R^4 = C_2H_5).—These amino ester derivatives were prepared by a general carbodiimide procedure which is described below. A mixture of 6.7 mmol of the amino ester hydrochloride, 60 ml of acetonitrile, 6.7 mmol of triethylamine, and 6.7 mmol of α-methyl-α-(4,5-dimethyl-2-phenylazophenoxy)propionic acid (1) was treated with 6.7 mmol of 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (Aldrich Chemical Co.) in one portion. The resultant mixture was stirred at 40–50° for a period of 12 hr. The acetonitrile was replaced with $CHCl_3$ and the $CHCl_3$ solution was washed successively with water, aqueous HCl, Na_2CO_3, and water. The dried organic solution was distilled under reduced pressure until all of the solvent was removed and the residue was chromatographed on a silicic acid (100 mesh) column. Elution with benzene–EtOAc (90:10) separated a yellow fraction which afforded the DAZ-amino ester as a homogeneous highly colored glass. The ir and nmr spectra of these products were consistent with the proposed structures (3). The yields were 60.0, 31.0, and 73.0%, respectively.

General Procedure for the Deblocking of DAZ-Amino Esters 3. —The deblocking of DAZ-amino esters with KBH_4 and 5% Pd on carbon was accomplished by essentially the same procedure as that used on the MAZ-amino esters which was described in detail above. The crystalline, cyclic by-product, 3,4-dihydro-2,2,6,7-tetramethyl-2*H*-1,4-benzoxazin-3-one (8) melted at 201–202°. Table I lists the yields of 8 obtained in five different experiments.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.31; N, 6.83. Found: C, 70.22; H, 7.26; N, 6.80.

The yields of amino ester hydrochlorides 7 obtained in deblocking experiments on five different DAZ-amino esters are listed in Table I.

Deblocking DAZ-Glycine Ethyl Ester (3, R^3 = H; R^4 = C_2H_5) and DAZ-Leucine Ethyl Ester [3, R^3 = $(CH_3)_2CHCH_2$; R^4 = C_2H_5]. A. Zn and NH$_4$OH.—The following procedure was used for both of these DAZ-amino esters. Zinc dust (46 mg-atoms) was added in one portion to a stirred solution of 3.8 mmol of DAZ-amino ester 3, 50 ml of methanol, and 5 ml of NH$_4$OH. The resultant mixture was stirred at room temperature for 4 hr and was then filtered. The filtrate was adjusted to pH 1.0 and some inorganic salts precipitated which were removed by filtration. The resulting filtrate was distilled under reduced pressure until a solid residue was obtained. This was chromatographed on a silicic acid (100-mesh) column using a mixture of benzene and EtOAc (50:50) as the eluting solvent. This procedure washed the benzoxazinone 8 from the column first. The amino ester hydrochloride 7 was then collected after the eluting solvent was changed to methanol. The yields of each of these products are listed in Table I.

B. Aluminum Amalgam.—Al(Hg) was prepared by dipping strips of Al foil (75 mmol) in a 5% aqueous solution of $HgCl_2$ and then washing the treated strips successively in EtOH and ether. The Al(Hg) was then added to a stirred solution of the DAZ-amino ester (2.5 mmol) in 40 ml of THF and 15 ml of water during a 30-min period. The amalgam dissolved and the mixture was filtered. The filtrate was concentrated under reduced pressure until all of the THF was removed. The aqueous residue was adjusted to pH 1.0 and then extracted with EtOAc. The organic layer afforded the benzoxazinone 8. The aqueous layer was adjusted to pH 7.0 and extracted with ether. The dried ether extract was saturated with HCl gas and the amino ester hydrochloride 7 precipitated. The yields of the two products are listed in Table I.

Asymmetric Synthesis. I.   Synthesis and Absolute Configuration of α-Aminoalkanesulfonates Derived from (−)-Ephedrine and Aromatic Aldehyde Bisulfites

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Equimolar amounts of aromatic aldehyde bisulfites and (−)-ephedrine in aqueous solution give equimolar amounts of each of an optically pure α-aminoalkanesulfonate and an oxazolidine. This is a stereospecific reaction. The induced asymmetric center in the α-aminoalkanesulfonate has the R configuration. In the presence of an excess of sodium bisulfite or in buffer pH 7, a diastereoisomeric mixture of the α-aminoalkanesulfonates is formed. Acetaldehyde, propionaldehyde, chloral, acetone, and other ketones also yield a mixture of diastereoisomers.

In a continuation of earlier studies[2] the reaction of aldehyde and ketone bisulfites with (−)-ephedrine (1) and (+)-pseudoephedrine was studied. Benzaldehyde bisulfite in aqueous solution reacts with an equimolar amount of (−)-ephedrine to yield an equimolar amount of an α-aminoalkanesulfonate (2) and an oxazolidine[3] (3). Initially, diastereoisomeric aminoalkanesulfonates are probably formed, one of which is unstable and gives the oxazolidine (3). Other aromatic aldehydes
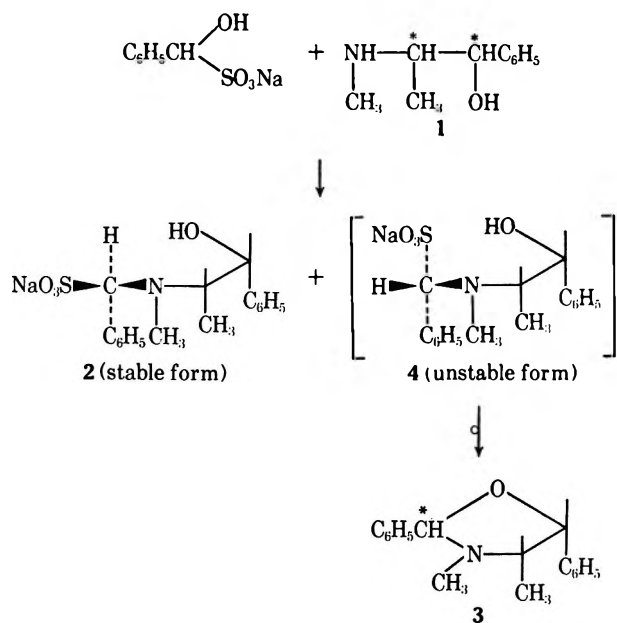
such as p-chlorobenzaldehyde, p-tolualdehyde, and piperonal undergo the same reaction.

When (−)-ephedrine is added carefully with stirring and cooling to benzaldehyde bisulfite in the presence of excess sodium bisulfite, no oxazolidine formation takes place, and an almost quantitative yield of the mixture of diastereoisomeric α-aminoalkanesulfonates is obtained. Similarly, no oxazolidine is formed with equimolar quantities of benzaldehyde, sodium bisulfite, and (−)-ephedrine in phosphate buffer pH 7. The infrared spectrum of the diastereoisomeric mixture is very similar to that of the optically pure α-aminoalkanesulfonate. Partial separation of the diastereoisomers can be accomplished by fractional crystallization from ab-

solute alcohol, but in the process some oxazolidine is always formed. Apparently one of the diastereoisomers easily cyclizes.

With potassium cyanide in methanol, sodium (−)-α-ephedrinophenylmethanesulfonate[4] (2) gives (+)-α-ephedrinophenylacetonitrile (5) which, with concentrated hydrochloric acid, gives the morpholone-2 (6). The morpholone, on hydrolysis with alkali, gives (+)-α-ephedrinophenylacetic acid (7) which, with lead tetraacetate, yields (−)-α-phenylsarcosine (8) identical with D(−)-α-phenylsarcosine of Sheehan.[5]

D(−)-α-phenylsarcosine
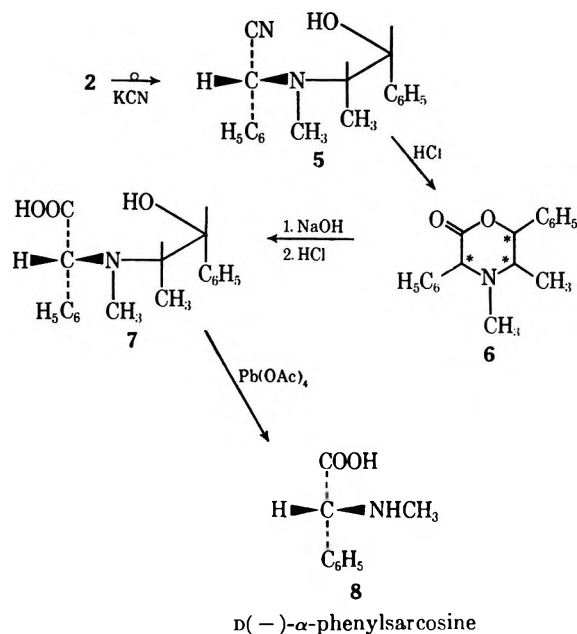
The conversion of the aminoalkanesulfonate to the aminonitrile is a base displacement reaction accompanied by an inversion. Lactone formation, hydrolysis, and the final degradation proceed without affecting the configuration of the induced asymmetric center. One can, therefore, ascribe the R configuration[6] to the induced asymmetric center in such (−)-α-ephedrinoaryl-methanesulfonic acids.

Lead tetraacetate or periodate oxidation of the optically pure α-ephedrinoalkanesulfonates gave a variety

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(2) L. Neelakantan and W. H. Hartung, *J. Org. Chem.*, **24**, 1943 (1959).

(3) L. Neelakantan, *ibid.*, **36**, 2256 (1971).

(4) The term "(−)-ephedrino" is used to denote the D$_g$(−)-erythro-N,1-dimethyl-2-hydroxy-2-phenylethylamino group.

(5) J. C. Sheehan, H. G. Zachau, and W. B. Lawson, *J. Amer. Chem. Soc.*, **80**, 3349 (1950).

(6) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

of degradation products. Lead tetraacetate oxidation of α-ephedrinophenylacetonitrile (5) gave (−)-α-methylaminophenylacetonitrile (10). However, hydrolysis to the corresponding α-phenylsarcosine (11) results in an almost complete racemization.[4,7]

$$5 \xrightarrow{\text{Pb(OAc)}_4} \underset{\substack{| \\ \text{NHCH}_3 \\ \textbf{10}}}{\text{C}_6\text{H}_5\overset{*}{\text{C}}\text{HCN}}$$

$$\downarrow \overset{\text{H}_2\text{O, }\Delta}{\underset{\text{HCl}}{}}$$

(±)-α-phenylsarcosine
11

α-Ephedrinoalkanesulfonates (type 2) undergo reactions typical of other α-aminoalkanesulfonates. With dilute alkali or hot water they form the corresponding oxazolidines. They react with aromatic amines to give α-arylaminoalkanesulfonic acids as the (−)-ephedrine salt (12). The same compound (12) is obtained from sodium α-anilinophenylmethanesulfonate (13) and ephedrine hydrochloride. Product 12 with potassium cyanide gives optically inactive α-anilinophenylacetonitrile (14). A simple amine displacement with a Walden inversion should give an optically pure compound. Complete breakdown of 2 to the starting materials and re-formation of an aminoalkanesulfonate would probably have yielded some oxazolidine. The possibility of a true amine exchange with subsequent racemization of the α-anilinoalkanesulfonate cannot be ruled out. Results from preliminary studies support this mechanism. When an aqueous

$$2 + \text{C}_6\text{H}_5\text{NH}_2 \longrightarrow \underset{\substack{| \\ \text{NHC}_6\text{H}_5}}{\text{C}_6\text{H}_5\text{CHSO}_3\text{H}}, \quad (-)\text{-ephedrine salt}$$

$$\underset{\substack{| \\ \text{NHC}_6\text{H}_5 \\ \textbf{13}}}{\text{C}_6\text{H}_5\text{CHSO}_3\text{Na}} \xrightarrow{\text{1. HCl}} \textbf{12} \xrightarrow[\text{KCN}]{} \underset{\substack{| \\ \text{NHC}_6\text{H}_5 \\ \textbf{14}}}{\text{C}_6\text{H}_5\text{CHCN}}$$

$$\underset{\substack{| \\ \text{NH}_2 \\ \textbf{15}}}{\text{C}_6\text{H}_5\text{CHSO}_3\text{Na}} \xrightarrow[\substack{\text{H}_2\text{O} \\ (-)\text{-ephedrine}}]{\text{HO}^-} \textbf{3}$$

solution of sodium α-aminophenylmethanesulfonate (15) is treated with (−)-ephedrine, oxazolidine formation is the predominant reaction. Again, it is not quite clear whether amine exchange and cyclization or complete breakdown and recombination is the mechanism. Further study is in progress.

Sodium (−)-α-ephedrinophenylmethanesulfonate reacts with potassium or ammonium thiocyanate to give (−)-ephedrine thiocyanate (16). Compound 16

$$2 \xrightarrow{\text{KSCN}} \underset{\substack{| \quad | \quad | \\ \text{CH}_3 \ \text{CH}_3 \ \text{OH} \\ \textbf{16}}}{\text{NH—CH—CHC}_6\text{H}_5} \text{HSCN} + \underset{\substack{| \\ \text{SO}_3^-}}{\text{C}_6\text{H}_5\text{CHOH}}$$

$$\downarrow \overset{\text{HCl,}}{\underset{\text{H}_2\text{O}}{}}$$

(−)-ephedrine HCl

(7) F. Ehrlich, *Biochem. Z.*, **8**, 446 (1908).

can also be prepared from ephedrine and ammonium thiocyanate.[8,9] Potassium thiocyanate and ephedrine give 16 only in the presence of sodium bisulfite or acids. Other α-ephedrinoarylalkanesulfonates undergo the same reaction.

When carbonyl compounds such as acetaldehyde, propionaldehyde, acetone, methyl ethyl ketone, chloralhydrate, cyclopentanone, 2-carbethoxycyclopentanone, and cyclohexanone reacted with (−)-ephedrine in the presence of sodium bisulfite, optically pure aminoalkanesulfonates were not obtained. Also, in those cases where oxazolidines were formed, they existed as a mixture of diastereoisomers.

(+)-Pseudoephedrine reacts with aromatic aldehyde bisulfites to give optically pure α-aminoalkanesulfonates and oxazolidines. This reaction is also stereospecific. The results will be published elsewhere.

Experimental Section

All melting points are uncorrected. Microanalyses were carried out by Messrs. Wiler and Strauss, Oxford, England, or by Scandinavian Microanalytical Laboratory, Copenhagen, Denmark.

Sodium (−)-α-Ephedrinophenylmethanesulfonate (2).—Benzaldehyde (10.6 g, 0.1 mol) was stirred with sodium bisulfite (10.4 g, 0.1 mol) in water (60 ml) for 2 hr. To the cooled aldehyde bisulfite solution was added (−)-ephedrine (16.5 g, 0.1 mol) all at once, and the mixture was stirred at room temperature for 24 hr. The mass was cooled and the solid collected by filtration and dried in air. The dry powder was stirred with ether (100 ml) for 4 hr and the solid was separated, washed with ether, and air-dried (the ether extract A and washes were saved), yield 16.5 g (45%). The product was recrystallized from alcohol: mp 119–120° (dec); [α]²⁰D −23.1° (c 1, ethanol).
Anal. Calcd for C₁₇H₂₀NO₄SNa: C, 57.13; H, 5.64; N, 3.92; S, 8.97. Found: C, 57.03; H, 5.54; N, 4.03; S, 9.21.

The ether extract A and the washes were combined and evaporated to dryness when colorless crystals were obtained which were identified as 2,5-diphenyl-3,4-dimethyl-oxazolidine (3), yield 12.5 g (49%). The oxazolidine was crystallized from alcohol: mp 73–74°; [α]²⁰D −55.0° (c 1, ethanol).
Anal. Calcd for C₁₇H₁₉NO: C, 80.06; H, 7.51; N, 5.53. Found: C, 80.20; H, 7.58; N, 5.61.

Sodium (−)-α-Ephedrino-p-chlorophenylmethanesulfonate (18).—Similarly, p-chlorobenzaldehyde (14.0 g, 0.1 mol), sodium bisulfite (10.4 g, 0.1 mol), and (−)-ephedrine (16.5 g, 0.1 mol) reacted to give 18.6 g (47%) of the aminoalkanesulfonate. The product was crystallized from alcohol: mp 123–124° dec; [α]²⁰D −21.4° (c 1, ethanol).
Anal. Calcd for C₁₇H₁₉ClNO₄SNa: C, 52.05; H, 4.85; N, 3.54; S, 8.16. Found: C, 51.86; H, 5.09; N, 3.34; S, 8.05.

2-p-Chlorophenyl-5-phenyl-3,4-dimethyloxazolidine (19), 14.5 g (50%), was also isolated, which on crystallization from alcohol has mp 86–87°; [α]²⁰D −52.0° (c 1, ethanol).
Anal. Calcd for C₁₇H₁₈ClNO: C, 70.80; H, 6.25; N, 4.86. Found: C, 71.08; H, 6.52; N, 4.64.

Sodium (−)-α-Ephedrino-p-tolylmethanesulfonate (20).—Similarly, 0.1 mol (12.0 g) of p-toluldehyde reacted to give an aminoalkanesulfonate, yield 17.1 g (45%). On recrystallization from alcohol the product has mp 118–119° dec; [α]²⁰D −21.2° (c 0.6, ethanol).
Anal. Calcd for C₁₈H₂₂NO₄SNa: 3, 57.25; H, 5.93; N, 3.77. Found: C, 56.95; H, 6.30; N, 3.75.

2-p-Tolyl-5-phenyl-3,4-dimethyloxazolidine (21), 31.1 g (49%), was also isolated which, on crystallization from alcohol, has mp 56–57°; [α]²⁰D −66.7° (c 0.5, ethanol).
Anal. Calcd for C₁₈H₂₁NO: C, 81.00; H, 7.86; N, 5.25. Found: C, 80.84; H, 7.94; N, 5.47.

Sodium (−)-α-Ephedrino-3,4-methylenedioxyphenylmethanesulfonate (22).—Piperonal (15.0 g, 0.1 mol) was similarly treated and the corresponding aminoalkanesulfonate was isolated, yield

(8) K. Koczka, *et al.*, *Acta Chim. Acad. Sci. Hung.*, **13**, 89 (1957).
(9) Japanese Patent 649 (1959); *Chem. Abstr.*, **54**, 6650 (1960).

18.5 g (45%). The product was recrystallized from alcohol: mp 121–122° dec; $[\alpha]^{20}D$ −20.0° (c 1, ethanol).

Anal. Calcd for $C_{18}H_{20}NO_6SNa$: C, 54.10; H, 5.02; N, 3.50; S, 8.00. Found: C, 54.30; H, 5.20; N, 3.48; S, 7.85.

The corresponding oxazolidine (23) was isolated in a yield of 14.8 g (50%) and on crystallization from alcohol has mp 82–83°; $[\alpha]^{20}D$ −64.3° (c 2, ethanol).

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.73; H, 6.40; N, 4.71. Found: C, 72.69; H, 6.28; N, 4.68.

Sodium α-Ephedrinophenylmethanesulfonate (Mixture of Diastereoisomers) (24).—Benzaldehyde (10.6 g, 0.1 mol) was stirred with sodium bisulfite (32.0 g, 0.3 mol) in water (160 ml). The solution was cooled and under good stirring was added (−)-ephedrine (16.5 g, 0.1 mol) in 50% alcohol (60 ml), dropwise. The pH was maintained close to 7.0 by controlling the rate of addition of ephedrine. The clear solution was allowed to stand at room temperature for 2 days and evaporated to dryness with a current of air, and the residue was extracted with absolute alcohol, concentrated, and diluted with ether. The product was collected and air-dried: yield 31.8 g (85%); mp 105–115° dec; $[\alpha]^{20}D$ −15.1° (c 1, ethanol).

Anal. Calcd for $C_{17}H_{20}NO_4SNa$: C, 57.13; H, 5.64; N, 3.92; S, 8.94. Found: C, 57.11; H, 6.00; N, 3.62; S, 8.84.

(+)-α-Ephedrinophenylacetonitrile (5).—2 (7 g) and potassium cyanide (2.1 g) in methanol (50 ml) were stirred at room temperature for 48 hr. The methanol was evaporated by a current of air, the residue treated with water, and the oily product extracted with ether and concentrated. On dilution with petroleum ether (bp 30–60°) and cooling, large, colorless crystals were obtained: mp 94–95°; yield 4.8 g (85%); $[\alpha]^{20}D$ +9.3° (c 4, methanol).

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.10; H, 7.15; N, 10.01. Found: C, 77.30; H, 7.30; N, 9.80.

(+)-3,6-Diphenyl-4,5-dimethylmorpholone-2 (6).—The aminonitrile (5) (5 g) was dissolved in benzene (25 ml), cooled, and treated with ice-cold concentrated hydrochloric acid (30 ml). The mixture was stirred at room temperature for 2 days and cooled, and the crystalline solid was separated. It was then suspended in water and carefully neutralized with sodium carbonate. The product was collected, washed with a little water, and air-dried to give a yield of 4.7 g (92%). The product crystallizes from alcohol–water: mp 93–94°; $[\alpha]^{20}D$ +200.3° (c 0.6, ethanol).

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 77.0; H, 6.80; N, 4.97. Found: C, 77.02; H, 6.84; N, 4.94.

(+)-α-Ephedrinophenylacetic Acid (7).—The morpholone 6 (5 g) was stirred with a solution of KOH (2.0 g) in water (25 ml) and methanol (10 ml) for 24 hr at room temperature. The solution was carefully neutralized with dilute hydrochloric acid, and the crystalline product was collected, washed with water, and air-dried, yield 4.8 g (90%). When recrystallized from alcohol–water, the amino acid has mp 206–208° dec; $[\alpha]^{20}D$ +198.2° (c 0.1, water).

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.25; H, 7.12; N, 4.69. Found: C, 72.28; H, 7.30; N, 4.60.

Tosyl D(−)-α-Phenylsarcosine (9).—(+)-α-Ephedrinophenylacetic acid (7) (3 g) was stirred in benzene to obtain a fine suspension. To this was added a solution of lead tetraacetate (5 g, 85–90% pure) in chloroform (10 ml); the mixture was stirred at room temperature for 4 hr. It was then treated with dilute hydrochloric acid (excess) and stirred for another hour, the lead chloride filtered off, and the aqueous layer separated. This aqueous solution was made alkaline with sodium hydroxide, tosyl chloride (2.5 g) in ether (30 ml) was added, and the mixture was stirred for 5 hr after which it was made acid to congo red. The ether layer was separated, the solvent removed, and the residue washed repeatedly with petroleum ether and recrystallized from ethyl acetate–petroleum ether, when the pure tosyl derivative is obtained, which has mp 115–117°; yield 2.2 g (70%); $[\alpha]^{20}D$ −61.1° (c 0.5, ethanol) [reported⁴ 115.5–117°; $[\alpha]^{20}D$ −63.0° (c 0.8, ethanol)].

(+)-α-Ephedrino-p-chlorophenylacetonitrile (25).—Sodium α-ephedrino-p-chlorophenylmethanesulfonate (18) reacted with potassium cyanide in methanol, as before, to yield the product, yield 90%. The aminonitrile crystallizes from benzene–petroleum ether to give colorless crystals with mp 97–98°; $[\alpha]^{20}D$ +13.1° (c 8, ethanol).

Anal. Calcd for $C_{18}H_{19}ClN_2O$: N, 8.90. Found: N, 8.79.

(+)-3-p-Chlorophenyl-6-phenyl-4,5-dimethylmorpholone-2 (26).—The aminonitrile (25) was treated with concentrated hydrochloric acid as before and the product worked up and finally re-

crystallized from alcohol: mp 153–154°; yield 90%; $[\alpha]^{20}D$ +201.2° (c 0.8, ethanol).

Anal. Calcd for $C_{18}H_{18}ClNO_2$: C, 68.50; H, 5.72; N, 4.44. Found: C, 68.62; H, 5.81; N, 4.40.

(+)-α-Ephedrino-p-chlorophenylacetic Acid (27).—The morpholone (26) was hydrolyzed with potassium hydroxide, and the product isolated and crystallized from water has mp 212–213° dec; $[\alpha]^{20}D$ +193.1° (c 0.1, water).

Anal. Calcd for $C_{18}H_{20}ClNO_3$: C, 64.89; H, 6.00; N, 4.21. Found: C, 64.73; H, 6.20; N, 4.10.

Tosyl D(−)-α-p-Chlorophenylsarcosine (28).—27 (3.2 g) was oxidized with lead tetraacetate (5.0 g) and the amino acid directly converted to the tosyl derivative as before, yield 2.2 g (68%). The pure product crystallizes from ethyl acetate–petroleum ether and has mp 120–121°; $[\alpha]^{20}D$ −58.2° (c 1, ethanol).

Anal. Calcd for $C_{16}H_{16}ClNO_4S$: C, 54.50; H, 4.54; N, 3.97. Found: C, 54.62; H, 4.60; N, 3.82.

Tosyl α-Phenylsarcosine (29).—(+)-α-Ephedrinophenylacetonitrile (5) (2.8 g) was stirred with lead tetraacetate (5.0 g) in ether for 1 hr at room temperature. The lead salts were removed and the aminonitrile was taken up in ether (the ether solution is levorotatory). The ether was removed, the oil allowed to stand with concentrated hydrochloric acid for a day, the solution diluted with water and refluxed for 6 hr, most of the excess of hydrochloric acid removed under reduced pressure, and the residue tosylated as before. The product was isolated and recrystallized from ethyl acetate–petroleum ether, mp 144–145° [reported⁴ mp (for the tosyl derivative) 145.5–146.5°]. The product obtained showed no optical rotation in alcohol solution.

α-Anilinophenylmethanesulfonic Acid (−)-Ephedrine Salt (12). Procedure A.—Compound 2 (3.5 g) in water (20 ml) was stirred with aniline (1.0 g) for 15 min. The crystalline precipitate was collected, washed with water and ether, and recrystallized from alcohol: mp 150–151° dec; $[\alpha]^{20}D$ −14.1° (c 0.5, ethanol); yield 3.2 g.

Procedure B.—α-Anilinophenylmethanesulfonate (13) (7.2 g) was added under stirring to a solution of (−)-ephedrine hydrochloride (5 g) in water (25 ml). The product was collected and crystallized from alcohol: mp 150–151° dec; yield 9.0 g; $[\alpha]^{20}D$ −13.9° (c 1, alcohol). The mixture melting point of the two products shows no depression. Their infrared spectra are identical.

Anal. Calcd for $C_{23}H_{28}N_2O_4S$: C, 64.46; H, 6.59; N, 6.54; S, 7.48. Found: C, 64.20; H, 6.61; N, 6.62; S, 7.66.

α-Anilinophenylacetonitrile (14).—Compound 12 (3.0 g) was stirred with potassium cyanide (1.0 g) in water for 1 hr. The product was isolated and recrystallized from alcohol, mp 85–86° (reported¹⁰ mp 85°). The product shows no optical rotation.

(−)-3,4-Dimethyl-2,5-diphenyloxazolidine (3). Procedure A. —2 (7 g) was dissolved in water (30 ml) and the solution made alkaline with sodium hydroxide (pH 11) and stirred at room temperature for 4 hr. The product (4.7 g, 95%) was recrystallized from alcohol: mp 73–74°; $[\alpha]^{20}D$ −55.1° (c 1, ethanol).

Procedure B.—A solution of α-aminophenylmethanesulfonate (15) (0.05 mol) in water was stirred with (−)-ephedrine (0.05 mol) for 48 hr at room temperature. The product was collected and washed with water to give a yield of 11.0 g (90%). The product was recrystallized from alcohol: mp 73–74°; $[\alpha]^{20}D$ −55.0° (c 1, ethanol).

(−)-Ephedrine Thiocyanate (16). A.—An alcohol solution of 3.7 g of 2 was treated with a warm solution of potassium thiocyanate (1.5 g) in alcohol and allowed to stand for 1 hr and the bisulfite compound filtered off. The alcohol solution was concentrated and cooled, and the product was collected. The product was recrystallized from alcohol: mp 140–141°; $[\alpha]^{20}D$ −28.9° (c 1, water).

B.—Ammonium thiocyanate was used instead of potassium thiocyanate.

C.—A solution of (−)-ephedrine and ammonium thiocyanate in water also gives the same product.

D.—A solution of (−)-ephedrine and potassium thiocyanate in water does not give the product in 3 hr; on adding sodium bisulfite to the solution the product crystallizes out [reported⁹ mp (for the product) 138–140°; $[\alpha]^{20}D$ −31.0°].

Anal. Calcd for $C_{11}H_{16}N_2OS$: C, 58.75; H, 7.22; N, 12.48. Found: C, 58.68; H, 7.23; N, 12.26.

(10) E. Knoevenagel, *Ber.*, **37**, 4087 (1904).

Asymmetric Synthesis. II. Synthesis and Absolute Configuration of Oxazolidines Derived from (−)-Ephedrine and Aromatic Aldehydes

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When D(−)-ephedrine reacts with aromatic aldehydes, oxazolidines are formed. This is a stereospecific reaction resulting in an asymmetric synthesis. The oxazolidines were cleaved by Grignard reagents to give tertiary amino alcohols which were further degraded with cyanogen bromide or lead tetraacetate or through the Hofmann elimination reaction to compounds of known absolute configuration. The oxazolidines thus prepared have the $2R{:}4S{:}5R$ configuration. These results have been confirmed by X-ray diffraction studies.

Though oxazolidines have been known for a number of years,[2,3] the structures of some of the compounds reported as oxazolidines have recently been questioned.[4] When primary β-amino alcohols are treated with carbonyl compounds, the products obtained (oxazolidines) may exist as a mobile tautomeric system with the corresponding Schiff bases. However, when a secondary
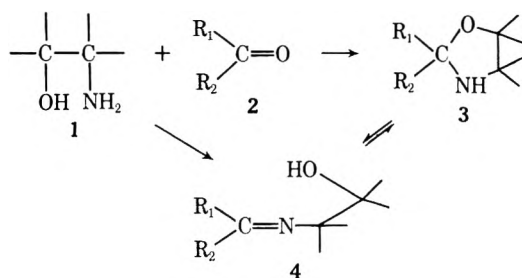
amino alcohol reacts with carbonyl compounds, true oxazolidines are formed.[5–13] Bergmann[14] in his comprehensive review has discussed their structure, syntheses, and reactions.

The present study is concerned with the reaction of (−)-ephedrine with aromatic aldehydes to form oxazolidines. When equimolar amounts of the amino al-

cohol and the carbonyl compounds are refluxed in benzene or ethanol or allowed to stand at room temperature, high yields of oxazolidines are formed. Similarly,
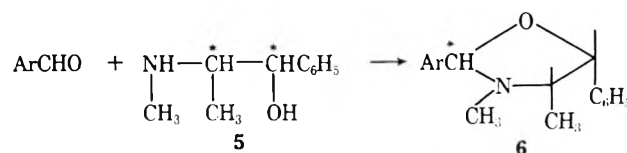
α-aminoalkanesulfonates derived from aromatic aldehydes, (−)-ephedrine, and sodium bisulfite[15] are easily converted into oxazolidines in the presnce of base.
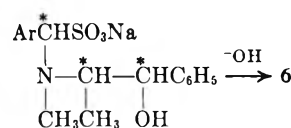
The present author contends that, when D(−)-ephedrine or L(+)-pseudoephedrine is allowed to react with aromatic aldehydes, the reaction proceeds through a totally stereospecific mechanism. Under these conditions, the oxazolidine formed is optically pure. Though predominance of one of the diastereoisomers has been encountered in many asymmetric syntheses, due to the unusual steric features present here, formation of one of the diastereoisomers is not feasible. This results in an asymmetric synthesis.

The configuration of the asymmetric carbon at position 2 of the oxazolidine ring was established by the following sequence of reactions. The oxazolidine ring was cleaved by a Grignard[16,17] reagent to give a β-amino alcohol 9. The tertiary amino alcohol was then degraded by the Hofmann elimination reaction to yield (R)-$(+)$-

(1) Division of Molecular Biophysics, Laboratory of Molecular Biology University of Alabama Medical Center, Birmingham, Ala. 35233.

(2) L. Knorr and P. Roessler, *Chem. Ber.*, **36**, 1278 (1903).

(3) L. Knorr and H. Mathes, *ibid.*, **34**, 3484 (1901).

(4) G. E. McCasland and E. C. Horswill, *J. Amer. Chem. Soc.*, **73**, 3923 (1951).

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(6) H. Haury, *Arch. Pharm.* (*Weinheim*), **297**, 447 (1964).

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(8) W. Davies, *J. Chem. Soc.*, 1580 (1932).

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(10) E. Engelhardt, F. S. Crossley, and J. M. Sprague, *J. Amer. Chem. Soc.*, **72**, 2718 (1950).

(11) A. Wickstrom and J. K. Wold, *Acta Chem. Scand.*, **15**, 686 (1961).

(12) Z. Fondi, *Acta. Chim. Acad. Sci. Hung.*, **10**, 1 (1956).

(13) E. D. Bergmann and H. Resnick, *J. Chem. Soc.*, 1662 (1956).

(14) E. D. Bergmann, *Chem. Rev.*, **63**, 309 (1953).

(15) L. Neelakantan, *J. Org. Chem.*, **36**, 2253 (1971).

(16) L. H. Goodson and H. Christopher, *J. Amer. Chem. Soc.*, **72**, 358 (1950).

(17) M. Senkus, *ibid.*, **62**, 1515 (1945).
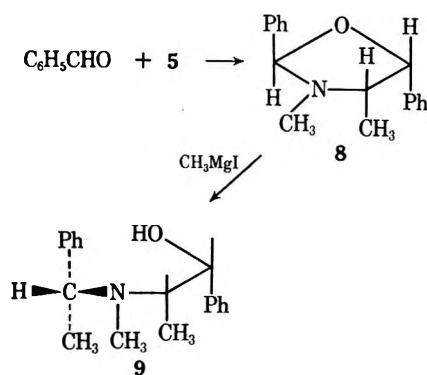
N,N-dimethyl-α-phenethylamine (12) and this was characterized[18-22] as the quaternary iodide 16.
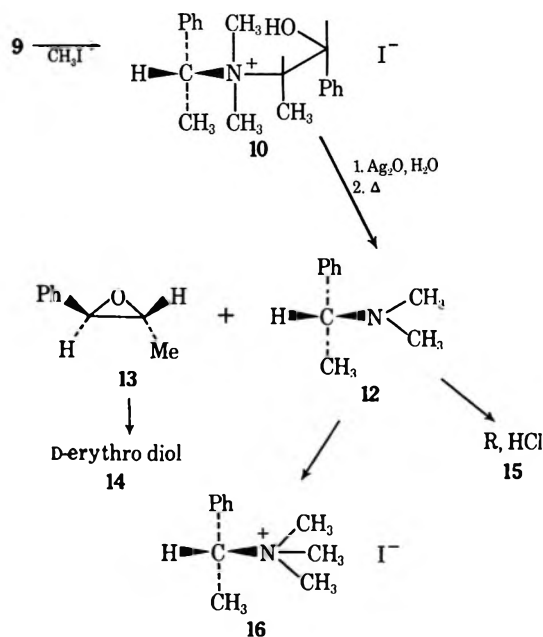
The tertiary amino alcohol 9 can be treated with cyanogen bromide to obtain L($-$)-α-phenethyl bromide (17) of known configuration.[23-25] The alkyl bromide
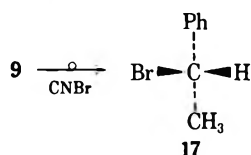
was converted to the corresponding D($+$)-α-phenethylisothiouronium bromide (18) or picrate for characterization.[26,27] The infrared spectra of the L($-$)-α-phenethyl bromide and its derivatives are identical with those of the corresponding DL compound.

A third method of assigning the configuration of the induced asymmetric center was to cleave the tertiary

amino alcohol with lead tetraacetate[28,29] to obtain D($+$)-N-methyl-α-phenethylamine (20).[30-32] The secondary amine was characterized as the hydrochloride salt or the p-nitrobenzoyl derivative 21. Their infrared spectra were identical with those of the corresponding DL compound.
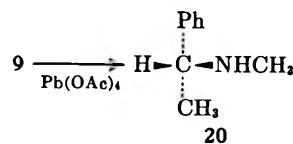
The oxazolidines derived from other aromatic aldehydes and D($-$)-ephedrine are also optically pure products, and the configurations of the asymmetric centers at position 2 of the ring were determined by identical procedures. Further, such oxazolidines were also cleaved by EtMgI, $C_6H_5CH_2MgX$, ArMgX, and other Grignard reagents to obtain tertiary amino alcohols which, on degradation, yielded optically pure amines of known configuration.

Discussion

From the foregoing it is quite evident that the reaction of aromatic aldehydes with D($-$)-ephedrine proceeds by a stereospecific mechanism. No fractional crystallization is involved, and the yields of the products are close to theoretical. These oxazolidines on degradation yield optically pure α-aryl ethylamines or α-aryl ethyl halides of known configuration. It is clear, therefore, that this is an asymmetric synthesis.

The first step in the degradation of these oxazolidines is the cleavage of the ring with Grignard reagents. The mechanism of this reaction is not fully understood. The exceptional steric features present in the oxazolidines under discussion, however, favor its reaction with Grignard reagents to proceed in a stereospecific manner. The following mechanism is proposed.
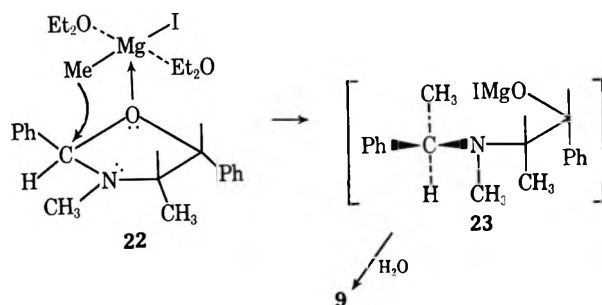
Let us consider the stereochemistry of these oxazolidines. It is obvious that the oxazolidine ring is fairly planar. Studies on boroxazolidines[33] and other oxazolidines[34,35] indicate that the conformation of ephedrine is retained in the ring structure. Molecular models show severe steric interaction between substituents in such oxazolidines when they are cis oriented. This interaction is relieved when the aryl group on C-2 lies

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on the opposite side of the plane. In support of this hypothesis are the following observations.

(a) When acetaldehyde reacts with D(−)-ephedrine, the product obtained is a mixture of diastereoisomers.

CH₃CHO + 5 ⟶ (structure **24**)

(structures **26**, **25**, **27**, **28** with reaction arrows labeled PhMgI, Hofmann, CH₃I, CNBr, Pb(OAc)₄)

26
(±) comp

25

27
(±) comp

28
(±) comp
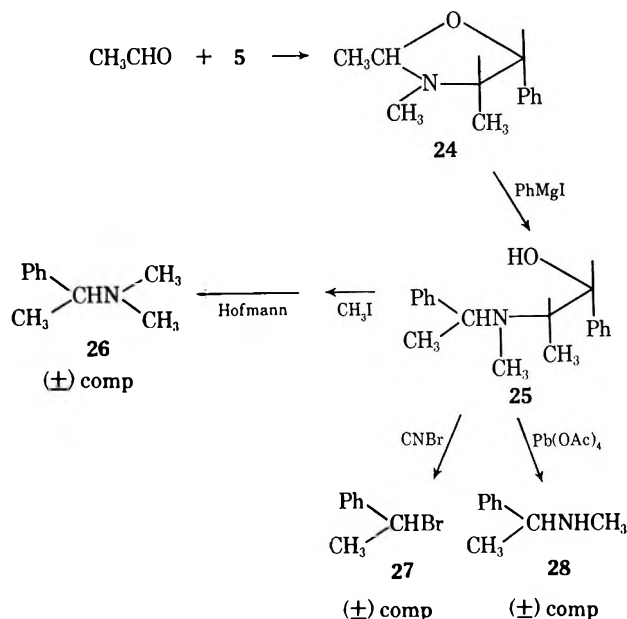
(b) When benzaldehyde reacts with (+)- or (−)-phenylephrine, the product obtained is a mixture of diastereoisomers, as indicated by the preliminary studies. The absence of the methyl of position 4 is probably responsible for the nonstereospecific nature of the ring formation.

PhCHO + (structure **29**)

(structure **30**)
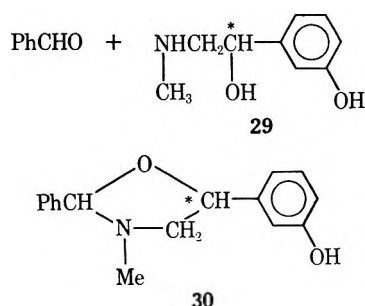
(c) Chloral and ketones as methyl ethyl ketone, acetophenone, cyclopentanone, and cyclohexanone failed to give the desired oxazolidines with D(−)-ephedrine. This again indicated the rigid steric requirements for the formation of such oxazolidines.

(d) It is noteworthy that ketones do form oxazolidines with norephedrine.[12] Hence, the steric interaction on the *N*-methyl group may be a contributing factor.

In conclusion, it can be stated that, when aromatic aldehydes are allowed to react with D(−)-ephedrine, optically pure oxazolidines are obtained. This is a stereospecific reaction and an asymmetric synthesis. In such oxazolidines the induced asymmetric center can be represented by the *R* configuration and hence named 2*R*:4*S*:5*R* oxazolidines. The results are confirmed by a three-dimensional structural analysis using the X-ray diffraction technique.[36]

Further study is in progress to find out the effects of

(a) changing the bulk of the group at position 2,
(b) changing the substitution on the nitrogen, and
(c) changing the bulk of the groups on positions 4 and 5 on the oxazolidine ring system. Aromatic aldehydes react with L(+)-pseudoephedrine to give optically pure oxazolidines; this is also a stereospecific reaction and an asymmetric synthesis. These results will be published elsewhere.

Experimental Section

All melting points are uncorrected. Microanalyses were carried out by Messrs. Wiler and Strauss, Oxford, England, or by Scandinavian Microanalytical Laboratory, Copenhagen, Denmark.

Preparation of Oxazolidines. Procedure A.—Ephedrine hydrate (alkaloid) (0.1 mol) and the aldehyde (0.1 mol) were heated under reflux in benzene (100 ml) for 1 hr. The calculated amount of water was then removed using a Dean-Stark column. The excess of benzene was distilled off under reduced pressure and the residue recrystallized from alcohol to give the pure product.

Procedure B.—The aldehyde (0.1 mol) and ephedrine alkaloid (0.1 mol) were refluxed in alcohol (100 ml) for 2 hr. Most of the alcohol was removed under reduced pressure and the residue recrystallized from alcohol.

Procedure C.—α-Ephedrinoalkanesulfonates were prepared from equimolar amounts of the aldehyde, sodium bisulfite, and ephedrine alkaloid in water at room temperature and working up the product as previously described. The pure aminoalkanesulfonates were dissolved in water and the solution made alkaline with sodium hydroxide (pH 9). After being stirred at room temperature for 1 day, the product was collected and recrystallized from alcohol. Table I lists the oxazolidines prepared.

Reaction of Oxazolidines with Grignard Reagents.—The Grignard reagent from magnesium (5 g, 0.2 g-atom), methyl iodide (28 g, 0.2 mol), and anhydrous ether (200 ml) was prepared in the usual way. To this was added 8 (13 g, 0.05 mol) in ether (150 ml) during 15 min with stirring. The solution was then heated under reflux for 8 hr and cooled, the complex decomposed with water, and the ether layer separated. The solution was dried over anhydrous sodium sulfate and the ether was removed under reduced pressure to leave the tertiary amino alcohol as a thick oil, yield 13 g (95%). The amine was converted to the quaternary iodide for characterization. The various tertiary amino alcohols prepared in this manner are listed in Table II.

Attempted Preparation of Tertiary Amino Alcohols.—When α-phenethyl bromide was treated with D(−)-ephedrine in benzene the only product isolated was ephedrine hydrobromide. Attempts to prepare the tertiary amino alcohol by hydrogenation of acetophenone and ephedrine in the presence of palladium-on-charcoal catalyst were also unsuccessful.

Hofmann Degradation of Tertiary Amino Alcohols.—*N*-(α-phenethyl)ephedrine methiodide (6.5 g, 0.016 mol) was suspended in water (50 ml). To this was added silver oxide from silver nitrate (3.4 g, 0.02 mol) and the mixture stirred for 24 hr at room temperature. The silver salts were removed by centrifugation and the aqueous solution was heated under reflux for 2 hr. The solution was cooled, acidified, and extracted with ether. (The ether extract was saved.) The aqueous acidic solution was concentrated under reduced pressure and made alkaline with sodium hydroxide, and the amine was extracted with ether. The amine was characterized as the methiodide or the hydrochloride salt. The results are listed in Table III.

The ether solution was concentrated to dispel the solvent and the residue hydrolyzed to give the diol which was benzoylated and the product characterized as D-*erythro*-1-phenyl-1,2-propanediol dibenzoate,[37] mp 95–96°, [α]²⁰D −60.45° (c 1, chloroform).

Reaction of Tertiary Amino Alcohols with Cyanogen Bromide.—A solution of the crude amino alcohol 9 (0.05 mol) in ether (30 ml) was treated with cyanogen bromide (0.15 mol) in ether (50 ml), allowed to stand at room temperature for 24 hr, heated under reflux for 4 hr, and then diluted with petroleum ether (bp 30–60°) (50 ml). The clear solution was separated from the syrupy part formed at the bottom of the flask, the solvent removed, and the residue distilled under reduced pressure. The fraction, bp 92–94° (18 mm), was collected, yield 3 g, αD −68.5°

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TABLE I
OXAZOLIDINES
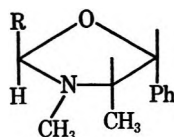
No.	R	Mp, °C	Crystals from	$[\alpha]^{20}$D, deg	Yield, %	Procedure	Mol formula	Calcd, % C	H	N	Found, % C	H	N
					98	a							
8	C_6H_5	73–74	Alcohol	−55.0	96	b	$C_{17}H_{19}NO$	80.06	7.51	5.53	80.20	7.58	5.61
				(c 1, ethanol)	91	c							
8a	p-ClC$_6$H$_4$	86–87	Alcohol	−52.0	100	a	$C_{17}H_{18}ClNO$	70.80	6.25	4.86	71.08	6.52	4.64
				(c 1, ethanol)	98	b							
					97	c							
8b	p-CH$_3$C$_6$H$_4$	56–57	Alcohol	−66.7	95	a	$C_{18}H_{21}NO$	81.00	7.86	5.25	80.84	7.94	5.47
				(c 1, ethanol)	92	b							
					85	c							
8c	3,4-Methylene-dioxy-C$_6$H$_3$	82–83	Alcohol	−64.3	98	a	$C_{18}H_{19}NO_3$	72.73	6.40	4.71	72.69	6.28	4.68
				(c 2, ethanol)	97	b							
					92	c							
8d	p-NO$_2$C$_6$H$_4$	79–80	Alcohol	−62.5	98	a	$C_{17}H_{18}N_2O_3$	68.45	6.04	9.40	68.51	6.12	9.40
				(c 0.6, ethanol)	96	b							
24	CH_3	Oil			98	a							
					50	c							
31	i-C$_5$H$_{11}$	Oil			94	a							
					60	c							

TABLE II
TERTIARY AMINO ALCOHOLS FROM OXAZOLIDINES
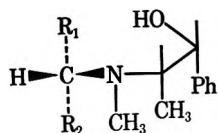
No.	R$_1$	R$_2$	Yield, %	Mp, °C (dec)	Crystals from	Methiodide $[\alpha]^{20}$D, deg (ethanol)	Mol formula	Calcd, % C	H	N	Found, % C	H	N
9	C_6H_5	CH_3	95	183–184	Ethanol	+34.5	$C_{19}H_{26}INO$	55.58	6.32	3.41	56.04	6.37	3.33
9a	C_6H_5	C_2H_5	90	168–169	Ethyl acetate	+27.1	$C_{20}H_{28}INO$	56.46	6.65	3.29	56.40	6.42	3.19
9b	p-ClC$_6$H$_4$	CH_3	90	159–160	Ethyl acetate	+34.1	$C_{19}H_{25}ClINO$	51.19	5.66	3.14	51.33	5.61	3.10
9c	C_6H_5	$C_6H_5CH_2$	92	136–137	CH$_3$OH–ethyl acetate	−12.7	$C_{25}H_{30}INO$	61.60	6.22	2.87	61.48	6.11	2.80
9d	p-ClC$_6$H$_4$	$C_6H_5CH_2$	90	142–143	Ethyl acetate	−14.5	$C_{25}H_{29}ClINO$	57.41	5.60	2.68	57.26	5.62	2.59
25	CH_3	C_6H_5	95	168–170	Ethanol	−11.7	$C_{19}H_{26}INO^a$			3.41			3.49

^{a} Mixture of diastereoisomers.

TABLE III
METHIODIDE DERIVATIVES OF TERTIARY AMINES FROM HOFMANN ELIMINATION
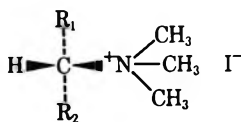
No.	R$_1$	R$_2$	Yield, %	Mp, °C	Crystals from	$[\alpha]^{20}$D, deg (methanol)	Mol formula	Calcd, % C	H	N	Found, % C	H	N
16	C_6H_5	CH_3	95	157–158 dec^a	Alcohol–ethyl acetate	+19.8	$C_{11}H_{18}IN$	45.30	6.22	4.70	45.30	6.31	4.68
16a	p-ClC$_6$H$_4$	CH_3	92	161–162 dec	Alcohol–ethyl acetate	+17.9	$C_{11}H_{17}ClIN$	40.55	5.22	4.30	40.50	5.28	4.34
16b	C_6H_5	C_2H_5	95	163–164 dec	Ethyl acetate	+18.6	$C_{12}H_{20}IN$	47.25	6.70	4.48	47.30	6.79	4.45
16c	C_6H_5	$C_6H_5CH_2$		Mixture of products									
16d	p-ClC$_6$H$_4$	$C_6H_5CH_2$		Mixture of products									
26	CH_3	C_6H_5	95	144–145^b	Alcohol–ethyl acetate	−0.5				4.70			4.66

^{a} Reported mp 157°, $[\alpha]^{20}$D +19.6°; see ref 20. ^{b} Reported mp 145–146°; see ref 21.

TABLE IV
SECOND AMINES BY LEAD TETRAACETATE OXIDATION

$$R_1$$
$$H-C-NHCH_3$$
$$R_2$$

			Yield,	Hydrochloride		
No.	R_1	R_2	%	Crystals from	Mp, °C (found)	$[\alpha]^{20}D$ (found)
20	C_6H_5	CH_3	88	EtOH-acetone	211–212[a]	+29.5
20a	C_6H_5	C_2H_5	85	EtOH-acetone	208–209[b]	+27.5
20b	p-ClC$_6$H$_4$	CH_3	90	EtOH-acetone	233–234[c]	+25.0
20c	C_6H_5	$C_6H_5CH_2$	92	EtOH-acetone	221–222[d]	−83.5
20d	p-ClC$_6$H$_4$	$C_6H_5CH_2$	90	EtOH-acetone	230–232[e]	−74.3
28	CH_3	C_6H_5	82	EtOH-acetone	177–178[f]	Nil

[a] Reported[29] mp 213°, $[\alpha]^{20}D$ +29.7°; p-nitrobenzoyl derivative, mp 75–76°, $[\alpha]^{20}D$ +180.0°. [b] *Anal.* Calcd for $C_{10}H_{16}ClN$: C, 64.69; H, 8.63; N, 7.55. Found: 64.60; H, 8.55; N, 7.62. [c] *Anal.* Calcd for $C_9H_{13}Cl_2N$: C, 52.43; H, 6.31; N, 6.80. Found: 52.55; H, 6.30; N, 6.75. [d] Reported [K. Oglu, H. Fujimura, and Y. Yamakawa, *Yakugaku Zasshi*, **80**, 283 (1960)] mp 221–222°, $[\alpha]^{20}D$ −84.5°; p-nitrobenzoyl derivative, mp 127–128°, $[\alpha]^{20}D$ +99.0°. [e] *Anal.* Calcd for $C_{15}H_{17}Cl_2N$: C, 63.82; H, 6.03; N, 4.96. Found: 63.68; H, 6.22; N, 5.07. [f] Reported[30] mp 178–179°. The compound is a DL mixture.

(neat). The infrared spectrum is identical with that of α-phenethyl bromide.

L(−)-α-phenethyl bromide (1.3 g) and thiourea (6.0 g) were refluxed in alcohol (40 ml) for 8 hr. The alcohol was removed under reduced pressure and the residue treated with dry benzene (40 ml). On being allowed to stand in the refrigerator for a day, the D(+)-α-phenethylisothiouronium bromide (18) separated, which was collected, washed with dry ether, and dried, mp 165–167°, $[\alpha]^{20}D$ +45.0° (c 2, water).

Part of the bromide 18 was treated with picric acid in alcohol to obtain the corresponding picrate which was crystallized from alcohol to give mp 167–168°, $[\alpha]^{20}D$ +28.2° (c 2, ethanol).

Anal. Calcd for $C_{15}H_{15}N_5SO_7$: C, 44.00; H, 3.68; N, 17.20. Found: C, 43.99; H, 3.63; N, 18.22.

The DL compound was made in a similar way, mp 156–157° (reported[28] mp 158–159°).

In the same way p-Cl-phenethylephedrine gave with cyanogen bromide L(−)-α-p-Cl-phenethyl bromide, bp 103–104° (15–20 mm), αD −55.0° (neat). This was converted to the corresponding isothiouronium picrate, mp 215–216°, $[\alpha]^{20}D$ +24.2° (c 1, ethanol).

Anal. Calcd for $C_{15}H_{14}N_5SO_7Cl$: C, 40.50; H, 3.16; N, 15.80. Found: C, 39.65; H, 3.28; N, 16.25.

Lead Tetraacetate Oxidation.—To a solution of 0.05 mol of the crude α-phenethylephedrine (9) in ether (100 ml) was added a solution of lead tetraacetate (0.05 mol) in ethyl acetate (50 ml). The mixture was stirred at 60° for 4 hr, cooled, treated with excess of dilute hydrochloric acid, and stirred at room temperature for 1 hr. The lead chloride was removed by filtration, the clear organic layer separated, and the aqueous phase evaporated to dryness. The residue was taken up in alcohol and diluted with acetone to yield D(+)-*N*-methyl-α-phenethylamine hydrochloride (20). The organic layer was carefully distilled to collect

first acetaldehyde which was identified as the semicarbazone. The residue was worked up in order to isolate benzaldehyde as its phenylhydrazone.

The tertiary amino alcohol 9 in the form of its hydrochloride can also be cleaved by lead tetraacetate by heating the two in ethyl acetate at 60° for 6 hr and working up the product.

The secondary amines with their physical constants are listed in Table IV.

Registry No.—5, 299-42-3; 8, 29843-09-2; 8a, 29843-16-1; 8b, 29843-18-3; 8c, 29850-76-8; 8d, 29850-77-9; 10, 29936-54-7; 10a, 29936-55-8; 10b, 29850-78-0; 10c, 29936-56-9; 10d, 29936-57-0; 16a, 29850-79-1; 16b, 29850-81-5; 18, 29850-82-6; 18 picrate, 29850-83-7; 20a HCl, 29850-84-8; 20b HCl, 29850-85-9; 20d HCl, 29850-86-0; 21, 29850-87-1; 21c, 29850-88-2; 25 methiodide, 29936-59-2; L(−)-α-p-Cl-phenethyl bromide, 29850-89-3, 29850-90-6 (isothiouronium picrate).

Crystal and Molecular Structure of
2-*p*-Bromophenyl-3,4-dimethyl-5-phenyloxazolidine

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D(−)-Ephedrine was allowed to react with *p*-bromophenylbenzaldehyde to give 2-*p*-bromophenyl-3,4-dimethyl-5-phenyloxazolidine. The oxazolidine ring has the 2R:4S:5R configuration. The crystals belong to the orthorhombic space group $P2_12_12_1$ with four molecules in a unit cell. The interatomic distances, bond angles, and a three-dimensional representation are reported.

Aromatic aldehydes react with D(−)-ephedrine to give oxazolidines. This is a stereospecific reaction and a totally induced asymmetric synthesis. Selective degradative studies showed that such oxazolidines have the 2R:4S:5R configuration.[1] In order to confirm this finding, X-ray diffraction studies were conducted on 2-*p*-bromophenyl-3,4-dimethyl-5-phenyloxazolidine, a model compound containing a heavy atom. The results show that while the oxazolidine ring is not quite planar the aromatic group on C-2 is on the opposite side of the ring from the substitutions on C-4 and C-5.

Experimental Section

p-Bromobenzaldehyde (18.5 g, 0.1 mol) and D(−)-ephedrine hydrate (17.4 g, 0.1 mol) were dissolved in absolute alcohol (150 ml), and the solution was heated under reflux for 2 hr on the steam bath. Most of the alcohol was removed under reduced pressure to leave a residue which on cooling gave the crystalline product. The crude product was collected on a filter, pressed dry, and washed with a little ice-cold absolute alcohol, yield 31.5 g (95%). A sample was recrystallized from absolute alcohol twice to give colorless crystals of the product which has a melting point of 87–88°, $[\alpha]^{20}$D −65.8° (*c* 2, absolute alcohol).

Anal. Calcd for $C_{17}H_{18}BrNO$: C, 61.49; H, 5.42; N, 4.22; Br, 24.10. Found: C, 61.23; H, 5.53; N, 4.31; Br, 24.71.

The product crystallizes from isopropyl alcohol, benzene, ether, and ethyl alcohol as flakes. However, by seeding an alcoholic solution and repeated heating and cooling, well-defined crystals were obtained which were used for the X-ray diffraction studies.

Structure Determination.—2-*p*-Bromophenyl-3,4-dimethy-5-phenyloxazolidine crystals belong to the orthorhombic space group $P2_12_12_1$ with four molecules in a unit cell with dimensions of *a* = 17.85 (2) Å, *b* = 8.04 (1) Å, and *c* = 10.97 (1) Å. The calculated density is 1.40 g/cm³, as compared with a density of 1.36 (2) g/cm³ observed by flotation in $ZnCl_2$ solution. A total of 1219 reflections above background were collected around the *c* axis of a crystal approximately 0.35 × 0.40 × 0.50 mm on a semiautomatic linear diffractometer with Mo Kα radiation and a graphite monochromator to a maximum θ of 21°. For each reflection ω was scanned at 1.0 deg/min through 1.5–2.1° with 10-sec background counts on each side. The linear absorption coefficient for this crystal is 27.9 cm⁻¹ for Mo Kα radiation.[2a] The data were corrected for Lorentz and polarization effects. Because of the somewhat irregular edges of the crystal, no correction was made for absorption.

The Harker peaks of an $E^2 − 1$ synthesis yielded the bromine positions, and subsequent Fourier maps led to positions of all the nonhydrogen atoms. The atomic scattering factors were taken from Hanson, *et al.*,[3] with dispersion corrections for Br taken from

the International Tables.[2b] Full-matrix least-squares refinement with SORFLS[4] was employed in which positional parameters for all 20 nonhydrogen atoms, anisotropic thermal parameters for the bromine atom, and isotropic thermal parameters for the other atoms were varied. A plot of $\sqrt{\Sigma_n(F_o − F_c)^2/n}$ in intervals of F_o near the end of the refinement led to the following weighting scheme

$$F_o < 12.28 \qquad \sigma = −0.040F_o + 1.56$$
$$F_o \gtrless 12.28 \qquad \sigma = 0.016F_o + 0.873$$

where $\sigma = 1/\sqrt{w}$.

Refinement was continued with each of the enantiomers of this optically active compound. The final weighted residual

$$R_w = \left[\frac{\Sigma w(|F_o| − |F_c|)^2}{\Sigma w|F_o|^2} \right]^{1/2}$$

index indicated the correct enantiomer with an R_w of 8.61% as compared with an R_w of 9.90% for the other enantiomer. A statistical test[5] based on the ratio of the two residual indices indicated that the correct enantiomer was known with a probable error of less than 0.5%.[6]

The interatomic distances and bond angles with errors as calculated by SORFFE[7] are listed in Table II[6] and three-dimensional representations drawn by the local version of ORTEP[8] are given in Figures 1a and b. The variation in the bond distances within the phenyl group indicates that the true error is at least twice that calculated by SORFFE. See p 2262.

The molecules appear to be held together in the crystal only by van der Waals interactions. Figure 1a shows the molecule as viewed along an axis almost parallel to the *a* axis. The other three molecules in the unit cell pack behind this one in about 4.4-Å intervals along the *a* axis with orientations dictated by the screw axes.

Figure 1b shows the aromatic group on C-2 to be on the opposite side of the five-membered ring from the methyl group on C-4 and the aromatic group on C-5. In Table III[6] are listed the distances of the ring and its attached atoms from the best (least-squares) plane through the five-membered ring.

Registry No.—2-*p*-Bromophenyl-3,4-dimethyl-5-phenyloxazolidine (2R:4S:5R), 29863-93-2.

(1) L. Neelakantan, *J. Org. Chem.*, **36**, 2256 (1971).

(2) "International Tables for X-ray Crystallography," Vol. 3, Kynoch Press, Birmingham, England, 1968: (a) pp 166–169; (b) Table 3.3.2C, p 216.

(3) H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Crystallogr.*, **17**, 1040 (1964).
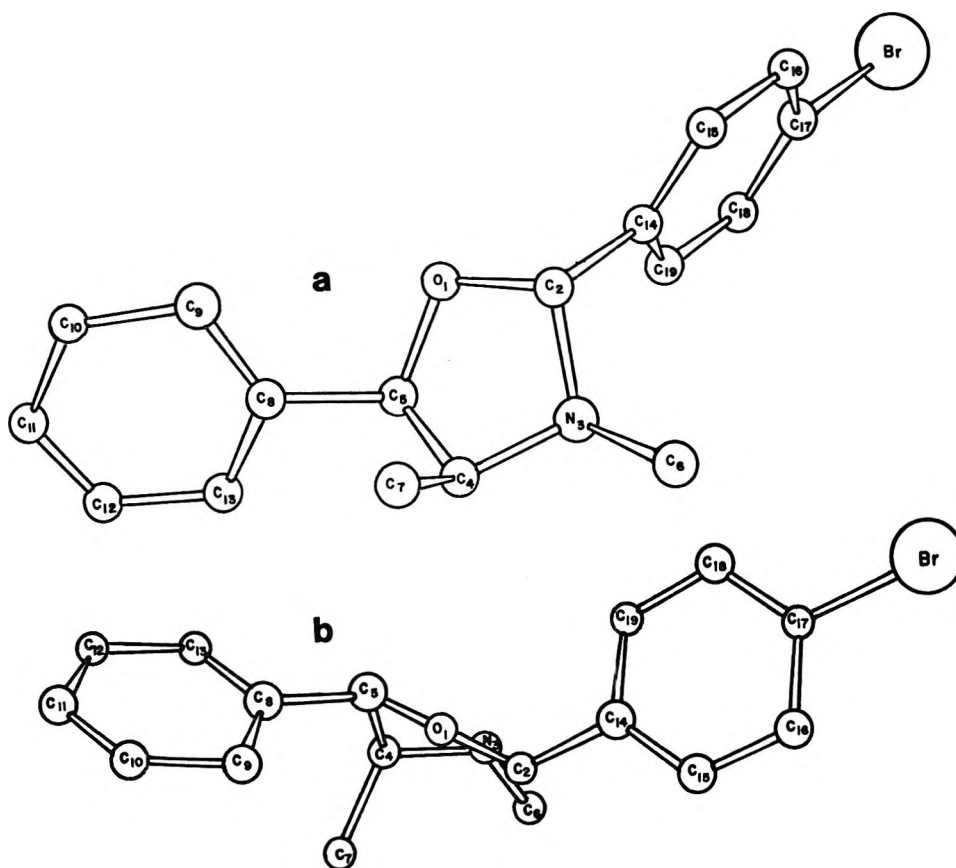
(4) Local version of ORFLS: W. R. Busing, K. O. Martin, and H. A. Levy, Report No. ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1962.

(5) W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).

(6) A listing of final positional and thermal parameters and observed and calculated structure factors will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit $3.00 for photocopy or $2.00 for microfiche.

(7) Local version of ORFFE: W. R. Busing, K. O. Martin, and H. A. Levy, Report No. ORNL-TM-306, Oak Ridge National Lboratory, Oak Ridge, Tenn., 1964.

(8) C. K. Johnson, Report No. ORNL-3794, Oak Ridge, National Laboratory, Oak Ridge, Tenn., 1965.

Figure 1.

Some Properties of Triarylimidazolyl Radicals and Their Dimers

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The electronic spectra of 2,4,5-triarylimidazolyl radicals 1 are strongly influenced by substitution on phenyl rings; spectra of dimers 2 are not. The rates of disappearance of 1 in benzene at 27° vary over 100-fold with substitution of phenyl rings. Any ortho substituent in Ar increases the rate constant relative to position isomers, a fact consistent with radical destabilization by ortho substituents through steric disruption or ring coplanarity.

Colored triarylimidazolyl free radicals 1 are formed from the thermal or photolytic dissociation of hexaarylbiimidazoles, the oxidation products of triarylimidazoles 4.[2] Two hexaarylbiimidazole isomers have been reported.[3] In solution, the more stable 2 is produced at room temperature and 3 is formed below −20°.

Interconversion of 2 and 3 involves 1. Structures were inferred from infrared data.[3] Dimer 2 is referred to by some authors as the photochromic dimer and 3 as the thermochromic dimer. The kinetics of radical recombination have been reported to be second order in radical concentration.[2c,d] Longer reaction times reveal deviation from second-order kinetics. Wilks and Willis reported 3/2 order which, after several half-lives, changed to first-order kinetics in radical disappearance.[4]

We have prepared some new hexaarylbiimidazoles, particularly a group bearing ortho substituents in the aromatic rings, and report here the effect of substitution on the rate of radical disappearance and on spectra of

(1) To whom inquiries should be addressed.

(2) (a) T. Hayashi and K. Maeda, *Bull. Soc. Chem. Jap.*, **33**, 565 (1960); (b) T. Hayashi and K. Maeda, *ibid.*, **35**, 2057 (1962); (c) T. Hayashi, K. Maeda, and M. Morinaga, *ibid.*, **37**, 1563 (1964); (d) T. Hayashi, K. Maeda, and M. Takenchi, *ibid.*, **37**, 1717 (1964); (e) T. Hayashi and K. Maeda, *ibid.*, **38**, 685 (1965); (f) T. Hayashi and K. Maeda, *J. Chem. Phys.*, **32**, 1568 (1960); (g) L. A. Cescon, Belgium Patent 509,415 (Aug 30, 1963); (h) S. M. Blinder, M. J. Peller, N. W. Lord, K. C. Aamodt, and N. S. Ivanclinkov, *J. Chem. Phys.*, **36**, 540 (1962); (i) H. Zimmerman, H. Baumgartel, and F. Bakka, *Angew. Chem.*, **73**, 808 (1961).

(3) D. M. White and J. Sonnenberg, *J. Amer. Chem. Soc.*, **88**, 3825 (1966).

(4) H. Neda, *J. Phys. Chem.*, **68**, 1304 (1964); M. A. J. Wilks and M. R. Willis, *J. Chem. Soc.*, 1526 (1968); M. A. J. Wilks and M. R. Willis, *Nature (London)*, **212**, 500 (1966).

TABLE I

SPECTRAL PROPERTIES AND RATE CONSTANTS OF THE DIMERIZATION OF SOME SUBSTITUTED TRIPHENYLIMIDAZOLYL RADICALS IN BENZENE AT 27 ± 1°

	Substituents			Biimidazoles 2 — In CH₃OH		Cm⁻¹, KBr pellets		Imidazolyl radicals 1 — λ_{max}, mμ	$10^{-3}\epsilon$, l. mol⁻¹ cm⁻¹	Dimerization at 27 ± 1° to 2 — Benzene $10^3 k/\epsilon$	$k^{b,d}$	1:1 methanol-benzene k^b	Methanol $k^{b,e}$	Toluene,^{c} k^b
No.	Ar	Ar'	Ar''	mμ	$10^{-4}\epsilon$									
a						1550 s	1497 m	550	3.28	7.7	25.2			12.4
b	4-Methoxy			263	3.09	1552 m	1506 s	610	6.90	1.5	10.3			9.4
c	2,4-Dimethoxy			262	2.99	1554 m	1501 m	620	8.13	13.7	111.0	2820		
d	2-Chloro			265	2.79	1548 s	1495 m	540	2.80	122.0	342.0	3242	7800^d	315
e	4-Chloro			267	2.74	1550 m	1498 m	570	4.49	6.8	30.5			
f	4-Bromo			265	2.89	1552 s	1498 w	560	3.90	6.0	23.4			
g	4-Nitro					1550 sh		530	1.38	6.2	8.56			
h	4-Cyano			264^a		1547 s	1500 sh	560	2.19	10.0	21.9			
i	3-Chloro			265	2.78	1550 m	1500 m	550	2.90	16.2	47.0			
j	3-Nitro			265	3.92	1550 sh		540	1.14	12.8	14.6			
k	2-Bromo			265	2.69	1549 s	1493 w	560	4.07	123.0	501.0	1304		
l	2,4,6-Trimethyl					1540 m	1490 m	590	5.10	16.7	85.2			
m	2,4-Dichloro			265	2.53	1551 s	1498 w	570	4.60	283.0	1302.0	5888		
n			2-Chloro	262^a		1552	1500	530	2.94	3.3	9.7			
o		2-Chloro	2-Chloro	261	2.15	1550 sh	1488 m	560	1.32	18.5	24.4			

^{a} In acetonitrile solvent. ^{b} In l. mol⁻¹ sec⁻¹. ^{c} From D. C. Reitz, private communication (in toluene at 26°). ^{d} Assumes that $\epsilon_{benzene} = \epsilon_{benzene-methanol}$. ^{e} $\epsilon_{methanol} = 1940$.

radicals and dimers. In the following paper, some reactions of 1 other than dimerization are covered. Subsequently, three additional papers appear which deal with the mechanism of certain oxidation reactions of 1.

Results and Discussion

All hexaarylbiimidazoles studied, including those, with ortho substituents on aromatic rings, were readily prepared in good yields.

Substitution on 2 resulted in little spectral change in the ultraviolet (6 mμ in λ_{max} and less than a factor of two in ϵ_{max}). See Table I. Spectra of 1, on the other hand, were more sensitive to structural changes (80 mμ in λ_{max} and a factor of seven in extinction coefficients). These results are consistent with the assumption that the radicals are more nearly planar than parent dimers. Absorption maxima correlated roughly with electron-releasing ability of substituents, e.g., λ_{max} p-OCH₃ > p-Br > p-NO₂.[5]

The infrared spectra of the dimers (Table I) exhibited the 1550- and 1500-cm⁻¹ bands considered diagnostic of 2.[3] All dimers also could be converted into their less stable isomers 3 by irradiating a solution below −20° as previously reported by White and Sonnenberg.[3] If the 2 position in Ar was unsubstituted, 3 could be obtained which contained very little 2, by evaporating the solvent under vacuum or by adding a nonsolvent; however, only very crude 3 was obtained with biimidazole having groups in the 2 position in Ar. A third dimer, first discovered by Reitz,[6,7] was observed for all dimers studied. It could be detected by cooling a solution of 2 to −85° and irradiating for 10–15 min. Radical color disappeared after irradiation was stopped. (Reitz reports concomitant esr signal loss.) When this solution was slowly warmed to room temperature, the following changes occurred. At about −40° radical color (and esr signal according to Reitz) reappeared. The solution once again became colorless on standing at about −35°. Further warming above −20° caused dissociation of dimer 3 to radical with final loss of color as the temperature reached about 12°. Dimer 2 was the predominant product at the end. Dimer 3 was identified in this experiment by its instability in solution at room temperature and by its uv spectrum. (The λ_{max} of 3 are about 10 mμ higher than of 2.) The structure of the third dimer was not determined. The important fact is that all dimers behaved the same way, at about the same conditions.

Dissociation constants of 2 have been reported to be higher for dimers with electron-donating substituents in the para positions of the phenyl rings.[8] We found that these groups in ortho positions resulted qualitatively in very different properties. Any ortho substituent in Ar decreased dissociation. Thus, a benzene solution of the stable dimer of 2-(2-chlorophenyl)-4,5-diphenylimidazolyl radical 2d exhibited no radical absorption spectrum below 80°, whereas the 4-chloro compound 2e was partially dissociated in solution at room temperature. Ortho substituents in Ar' and Ar'' affected the equilibrium quite modestly but appeared to

(5) A similar trend has been reported for the substituted benzyl radicals: J. E. Hodgkins and E. D. Megarity, *J. Amer. Chem. Soc.*, **87**, 5322 (1965). The similarity in the two groups of radicals still holds if one includes the following 2-(para-substituted phenyl)-4,5-diphenylimidazolyl radicals: CH₃, λ_{max} 565 mμ; C₆H₅, λ_{max} 600 mμ; and F, λ_{max} 545 mμ.

(6) D. C. Reitz, private communication.
(7) A. MacLachlan and R. Riem, *J. Org. Chem.*, **36**, 2275 (1971).
(8) H. Baumgärtel and H. Zimmermann, *Z. Naturforsch*, **18**, 406 (1963).

have the opposite effect, that is, increased dissociation. Qualitatively, meta substituents had little effect on the equilibrium of dissociation.

The wide variation in thermal stability of dimers and (where ortho groups are present in Ar) the high reactivity encountered at temperatures where dissociation was readily observable discouraged our measuring equilibria or thermal dissociation kinetics. Photodissociation was complete at the end of a 5-μsec flash with no evidence for short-lived intermediates.

Radical disappearance, however, was readily followed spectrally. Benzene solutions at 27 ± 1° were irradiated and absorbance, A, at λ_{max} was determined at measured time intervals. A graphic method was utilized to obtain rate constants. Linear plots of $1/A$ vs. t were obtained until A was about half of A_0, when deviations from a second-order plot became apparent. The slopes of the linear first half-life was taken as equal to $k/\epsilon l$ in cm sec^{-1} ($l = 1$ cm) from which the rate constants, k, were obtained. The values of k/ϵ and k are in Table I.

Our presentation of results in terms of second-order rate constants fitted to initial rates during about one half-life does not imply knowledge of the detailed mechanism of radical disappearance. We observed, as did Wilks and Willis, that 3/2 order plots are linear for longer reaction times, but that these too deviate from linearity as well as vary in slope with A_0 and with the presence of sensibly inert additives. This information convinces us that the detailed mechanism of radical disappearance will remain to be understood until all reaction components can be measured quantitatively as reaction proceeds. We are attempting to develop such techniques.

At this time we are concerned with the effect of structure on radical dimerization and assume only that a common mechanism prevails for all. The low-temperature dimerization experiment, in which all compounds behaved comparably under similar conditions, supports this assumption.

A method was devised to determine extinction coefficients of radicals. A flash photolysis unit with filters to confine irradiation to a spectral region where only biimidazoles absorbed was utilized to generate radicals 1 whose initial absorbance was recorded photographically from an oscilloscope. In the same cell another solution was then photolyzed as above. This second solution contained an identical concentration of biimidazole to the first plus leuco crystal violet dye, tris-(4-dimethylaminophenyl)methane, and toluenesulfonic acid. The absorbance of dye produced by oxidation of leuco dye by 1 was observed at an unobstructed wavelength. The extinction of the dye at this wavelength in this medium was determined experimentally. The stoichiometry of radical attack on dye was known[2g,7] and the quantum yield of this reaction under these conditions had been previously determined experimentally by Kellogg and Kooser to be unity[9] (that is, one dye molecule is formed per biimidazole dissociated or per two radicals). Calculation of initial radical concentration corresponding to dye produced allowed calculation of radical extinction coefficient in the usual fashion from observed absorbance.

(9) R. E. Kellogg and R. H. Kooser, private communication in advance of publication. These workers report that ϕ varies substantially with acid concentration and leuco dye structure but is invariant with radical structure.

Our value for ϵ of 3280 cm^{-1} for **2a** in benzene–methanol compares with Wilks and Willis value 4150 cm^{-1} in dioxane–water and 3900 in benzene–pyridine. We consider these values in agreement.

The disparity in rates required use of different experimental techniques for different solvents. Radical absorbance was followed with a spectrometer when benzene was solvent, whereas a flash photolysis unit was employed in the methanol-containing solvent runs. In the latter, a photograph was made of the oscilloscopic trace of radical transmittance vs. time.

Radical extinction coefficients were measured in 50:50 vol benzene–methanol and, in one case, in methanol as well. It proved impossible to determine extinction coefficients by this method in benzene, the preferred solvent for kinetic runs, because of reagent insolubility. Rate constants in benzene are, therefore, equal to those reported multiplied by the experimentally unattainable ratio, $\epsilon_{benzene}/\epsilon_{benzene-methanol}$. The ratio is assumed to be relatively constant for the radicals studied. The method is the best compromise which would allow all rates to be measured by a common method.

Our rate constants agree reasonably well with those of Reitz,[6] determined by epr in toluene at 26°. The rate constant for disappearance of **1a**, 25.2, compares with second-order values approximated from Hayashi's data of 3.3 at 19° and 7.4 at 23° and from Wilks and Willis' data of between 7 and 18, depending on **2a** concentration.

The solvent exerts a profound influence; dimerization is 30-fold faster in methanol than in benzene. The degree of rate enhancement by methanol is disturbingly large. Efforts to characterize photolysis products other than dimer after prolonged periods of irradiation of methanol solutions showed a variety of products in trace amounts insufficient to characterize by liquid chromatography and inseparable by other techniques. Second-order plots showed the same deviations as were found in benzene. Rate studies were attempted in other solvents in the hope of shedding some light on medium effect. Unfortunately, a combination of problems precluded measurement of extinction coefficients in most of these. The k/ϵ values of dimerization of **1a** in various solvents are listed in Table II.

TABLE II

DIMERIZATION OF
2,4,5-TRIPHENYLIMIDAZOLYL RADICAL AT 27°

Solvent	$10^4 k/\epsilon$, cm sec^{-1}
Benzene	25.2
Anisole	24.6
Benzonitrile	21.0
tert-Butylbenzene	43.2
1,2-Dimethoxybenzene	28.2
Nitrobenzene	31.8

A substituent in the ortho position of Ar but not of Ar' or Ar'' unmistakably enhances the rate of radical combination. Thus, the 2-o-chlorophenyl compound **1d** (Table I) dimerized seven and ten times as fast as its meta and para isomers **1i**, and **1e**, respectively, 30 times as fast as the isomer with an ortho chloro group in Ar' (**1n**), and an order of magnitude faster than the analog having ortho chloro groups in Ar' and Ar'' (**1o**).

Bromo-substituted radicals followed a similar trend, the ortho isomer 1k being 50-fold faster than the para isomer 1f; the methoxy compounds 1b and 1c behaved similarly. The largest rate constant of dimerization was shown by 1m.

The influence on rate by meta and para substituents was not great. Compare 1a with 1b, 1g, 1h, 1i, and 1j. Groups which are either strongly electron donating or attracting appear to retard the rate by a small factor.

From the equilibrium constants of Baumgärtel and Zimmerman[8] obtained in toluene at 25° and our rate constants for association, the rate constants of dissociation are calculated to be about 4.4×10^{-5} and 2.6×10^{-4} sec^{-1} for 2a and 2b, respectively.

The unusual aspect of these data is that the most hindered dimers, namely, those having ortho groups in Ar, form fastest. The effect is clearly steric since all groups have a similar influence. The results are consistent with two hypotheses. Ortho substituents in Ar result in (a) a different product, at least initially, or (b) a lower transition state of 2, due to destabilization of 1.

Hypothesis a implies, for example, that hexaaryl-biimidazoles without substituents in Ar would be represented by the energy diagram in Chart A, due to White and Sonnenberg,[3] whereas those with ortho substituents on Ar would be represented by that in Chart B. The similar low temperature behavior of all radicals, that is, their dimerization to the same isomers at similar temperatures, argues against this hypothesis. The products at the completion of kinetic runs did not differ observably among radicals studied. Hypothesis a, furthermore, would imply that ortho substitution in Ar somehow stabilizes that transition state which involves coupling closest to the hindrance. We can find no precedent for this in the literature.
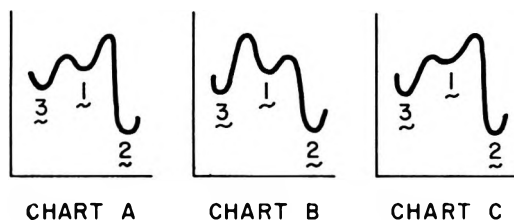
Hypothesis b allows the unsubstituted biimidazole system still to be represented by Chart A. The diagram for biimidazoles with ortho groups in Ar can be depicted by Chart C. Radical destabilization is to be expected from steric hindrance of ring coplanarity. X-Ray crystallography has shown that crystalline dimer 2k has no two rings which are coplanar.[10] Models of the radical, however, show that unsubstituted Ar can achieve coplanarity with the heterocyclic nucleus. They also show that ortho substitution in Ar does greatly interfere with rotation to achieve ring coplanarity of Ar and the imidazole nucleus. Models further reveal that Ar' and Ar'' cannot simultaneously be coplanar with the imidazole ring and strongly suggest that individually this may also be impossible. Because neither radical nor dimer gains appreciable resonance stabilization from Ar' and Ar'', kinetics and

CHART A   CHART B   CHART C

equilibria of reactions of radicals or dimers should not be greatly effected by ortho substituents on these rings.

A further test of ring coplanarity should be found in spectral data. The high sensitivity of radical spectra, both λ_{max} and ϵ, to substituents contrasts markedly with the biimidazoles (Table I). Parallel observations in the biphenyl series have been related to ring coplanarity.[11]

Experimental Section

Triarylimidazoles were prepared by the method of Davidson, Weiss, and Jelling[12] on a 0.01-mol scale. The reaction mixture was refluxed until unreacted benzil could no longer be detected by paper chromatography. If the product did not precipitate when the mixture was added to 200 ml of distilled water, the diluted mixture was neutralized in the cold with 15 *N* ammonium hydroxide. The product was recrystallized twice from an appropriate solvent. Spectra were obtained in methanol. Melting points were measured on a Thomas-Hoover apparatus. Analytical data are presented in Table III.

Hexaphenylbiimidazoles.—The two methods employed are exemplified. Method B is preferred for its wider applicability and for its suitability for preparing larger quantities. Analytical data are presented for individual compounds in Table IV. Spectroscopic data are in Table I.

Method A is essentially that reported by Hayashi and Maeda.[2a] The precipitated product was washed with water until added ferrous ion failed to give a positive ferricyanide test and dried overnight in a vacuum oven at 50° and subsequently for 8 hr at 56° (0.1 mm). Recrystallization from benzene–ethanol and redrying as before gave an 88% yield of product, mp 199–201° (recrystallization mp 200–201°).

Method B.—Solid 2-(2,4-dimethoxyphenyl)-4,5-diphenylimidazole (5.35 g) and 150 g of benzene were added to a solution of 6.0 g of sodium hydroxide and 9.9 g of potassium ferricyanide in 100 ml of water, and the resulting mixture was stirred vigorously for 16 hr. The benzene layer was separated and washed three times with 150 ml of water, dried over sodium sulfate, and concentrated to about 20 ml (preferably under vacuum for easily dissociated dimers). The product was allowed to crystallize. Purification procedure is the same as in method A, yield 91%, mp 120–121°.

Drying.—Irrespective of the method of preparation or solvent used for crystallization, the products held solvent tenaciously. Most normal drying methods proved ineffective. For most compounds, it was necessary to hold the sample at 110° (0.1 mm) for 24 hr to obtain solvent-free samples for analytical purposes. The appearance of color due to the radical during this process did not damage the samples so far as could be detected by their analytical, spectroscopic, and chemical properties. Benzene proved to be the easiest solvent to remove in most cases.

Spectral Studies.—Infrared absorption spectra were obtained with a Perkin-Elmer Model 221. Fluorescence measurements utilized a 0.75-m Jarrell-Ash spectrograph. Electronic absorption spectra were determined with a Cary Model 14M spectrophotometer. Molar extinction coefficients of radicals were determined by flash photolysis in an apparatus similar to that described by Porter.[13] Two Corning filters, 0-52 and 760, were inserted between the sample and the flash lamp, whose pulse duration at half peak width was 4 μsec. This array, in conjunction with concentration of materials employed, ensured that the dimer absorbed >95% of the radiation. The analyzing lamp was operated from a 6-V storage battery. Solutions were degassed with argon, although this procedure was shown not to be necessary.

Radical absorbance was measured at λ_{max} for each radical in the apparatus. Radical concentration was obtained by flash photolysis of a second solution (50:50 vol methanol–benzene) of biimidazole of identical concentration (2×10^{-4} *M*) but which

(10) G. Teufer, private communication in advance of publication.

(11) For leading references, see J. N. Murrell, "The Theory of the Electronic Spectra of Organic Molecules," Wiley, 1963, pp 238–246. Drawing conclusions about the relative effect on coplanarity of position isomers on the basis of magnitudes of λ_{max} and ϵ is not valid without condsideration of the magnitude and direction of the dipole due to the substituent.

(12) D. Davidson, M. Weiss, and M. Jelling, *J. Org. Chem.*, **2**, 319 (1937).

(13) G. Porter, *Proc. Roy Soc.*, London, **200**, 284 (1950).

TABLE III
PREPARATION OF TRIARYLIMIDAZOLES (4)[a]

Compd 4	Yield, %	Mp, °C	Crystn solvent	λmax (MeOH), mm	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Halogen, % Calcd	Halogen, % Found	Mol wt	Lit. Mp, °C	Ref
a	92	273–275	MeOH	298	$C_{21}H_{16}N_2$	85.1	85.0	5.4	5.4	9.5	9.4			296.36	275	b
b	83	231–232	MeOH	297	$C_{22}H_{18}N_2O$	81.0	80.7	5.6	5.6	8.6	8.8			326.38	229	c
c	90	164–165	EtOH–H$_2$O	304	$C_{23}H_{20}N_2O_2$	77.5	77.8	5.7	5.7	7.9	8.0			356.41		d
d	94	196–197	EtOH–H$_2$O	286	$C_{21}H_{15}N_2Cl$	76.2	76.4	4.6	4.6	8.5	8.3	10.7	10.5	330.8	197.3–197.8	d
e	98	263.5–264	EtOH–H$_2$O	303	$C_{21}H_{15}N_2Cl$	76.2	76.3	4.6	4.4	8.5	8.3	10.7		320.8	266–268	e
f	94	263–263.5	EtOH–H$_2$O	310	$C_{21}H_{15}N_2Br$	67.2	67.1	4.0	3.9	7.5	7.5	21.3		375.27	253–254	d
g	99	237–238	EtOH–PhI		$C_{21}H_{15}N_3O_2$	73.9	74.2	4.4	4.4	12.3	12.4			341.36	240	
h	97	272.5–273	EtOH–PhH	338	$C_{21}H_{15}N_3$	82.2	82.0	4.7	4.7	13.1	13.1			321.37		
i	90	295–296	EtOH–PhH	300	$C_{21}H_{15}N_2Cl$	76.2	76.5	4.6	4.6	8.5	8.4	10.7		320.8		
j	94	*f*	*f*	*f*	$C_{21}H_{15}N_3O_2$	73.9	73.6	4.0	4.4	12.3	12.3			338.44	*f*	g
k	97	205.5–206.5	EtOH–H$_2$O	288	$C_{21}H_{15}N_2Br$	67.2	67.1	4.0	4.0	7.5	7.4			375.27		
l	89	230–230.5	EtOH–H$_2$O	~267	$C_{24}H_{22}N_2$	85.2	84.9	6.6	6.9	8.3	8.0			338.44		
m	96	174.5–175	EtOH		$C_{21}H_{14}N_2Cl_2$	69.1	69.2	3.9	4.0	7.7	7.4	19.4		365.24	176.5–177.0	d
n	95	232.5–233.5	PhH	298[h]	$C_{21}H_{15}N_2Cl$	76.2	76.0	4.6	4.7	8.5	8.3	10.7		320.8		
o	94	245.5–246.5	PhH	290	$C_{21}H_{14}N_2Cl_2$	69.1	69.0	3.9	4.0	7.7	7.6	19.4		338.44		

[a] Satisfactory combustion analytical data (±0.4) were provided for all of the compounds of this table: Ed. [b] B. Radziszewski, *Ber.*, 10, 70 (1877). [c] A. H. Cook and D. G. Jones, *J. Chem. Soc.*, 278 (1941). [d] D. M. White and J. Sonnenberg, *J. Org. Chem.*, 29, 1926 (1964). [e] K. Skoichiro and S. Narisawa, *Asahi Garasu Kenkyu Hokoku*, 12, 55 (1962); *Chem. Abstr.*, 59, 1622 (1963). [f] Insoluble, mp >360°. [g] J. Troegger, *J. Prakt. Chem.*, 64, 532 (1901). [h] In acetonitrile. Troegger reports that it did not melt to 295°.

TABLE IV
PREPARATION OF HEXAARYLBIIMIDAZOLES II[a]

Compd 2	Yield, %	Method	Crystn solvent	Drying (24 hr), °C (mm)	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Halogen, % Calcd	Halogen, % Found	Lit. Mp, °C	Ref
a	88	A	PhH–EtOH	110 (0.1)	200–201	$C_{45}H_{30}N_4$	85.4	85.4	5.1	5.0	9.5	9.3			198–201	2a
b	85	A	PhH–EtOH	110 (0.1)	127–128	$C_{48}H_{34}N_4O_2$	81.2	81.0	5.3	5.3	8.6	8.5			146	8
c	91	B	PhH	110 (0.1)	120–121	$C_{49}H_{38}N_4O_4$	77.7	77.8	5.4	5.2	7.9	7.8			115–120	3
d	89	B	PhH–EtOH	110 (0.1)	202–203	$C_{45}H_{28}N_4Cl_2$	76.5	76.8	4.3	4.5	8.5	8.4	10.7	10.4	203–205	3
e	85	B	Ph–PH ether	56 (760)	210.5–212	$C_{45}H_{28}N_4Cl_2$	76.5	76.7	4.3	4.4	8.5	8.2	10.7	10.8		
f	82	B	Ether	110 (0.1)	210–211	$C_{45}H_{28}N_4Br_2$	67.4	67.3	3.8	3.8	7.5	7.6	21.4			
g	85	A	PhH	110 (0.1)	~162–168	$C_{45}H_{28}N_6O_4$	74.1	74.2	4.1	4.3	12.3	12.2				
h	70	B	PhH	110 (0.1)	167.5–168.5	$C_{44}H_{28}N_8$	82.5	82.5	4.4	4.4	13.1	13.0				
i	81	B	PhH	110 (0.1)	~150	$C_{45}H_{28}N_4Cl_2$	76.5	76.7	4.3	4.4	8.5	8.6	10.7	10.5	165–167	3
j	74	B	PhH	110 (0.1)	190–191	$C_{45}H_{28}N_6O_4$	74.1	73.9	4.2	4.1	12.4	12.5				
k	90	B	PhH–EtOH	110 (0.1)	195–203	$C_{45}H_{28}N_4Br_2$	67.4	67.4	3.8	3.8	7.5	7.6	21.4			
l	78	A	PhH–EtOH	110 (0.1)		$C_{48}H_{42}N_4$	85.4	85.5	6.3	6.2	8.3	8.1				
m	95	A	PhH	110 (0.1)	~190	$C_{45}H_{26}N_4Cl_4$	69.2	69.4	3.6	3.7	7.7	7.8	19.5	19.4	Glass	3
n	43	B	PhH	110 (0.1)	~210	$C_{45}H_{28}N_4Cl_2$	76.5	76.7	4.3	4.1	8.5	8.3	10.7			
o	94	A	PhH–EtOH	110 (0.1)		$C_{45}H_{26}N_4Cl_4$	69.2	69.3	3.6	3.8	7.7	7.5	19.5			

[a] Satisfactory combustion analytical data were provided for all of the compounds in this table: Ed.

was also 10^{-4} M in leuco crystal violet and 2×10^{-4} M in toluene-sulfonic acid. From the amount of crystal violet dye obtained as determined spectrally, and from the reaction stoichiometry (1 mol of dye per biimidazole dissociated) and quantum yield of unity,[9] both experimentally determined, radical concentration immediately after the flash was obtained.

Rates of Triarylimidazolyl Radical Dimerization.—A Perkin-Elmer "Spectrachord" Model 400A was set up in a dark room to record absorbance (at λ_{max} of each radical) vs. time. A solution of biimidazole in carefully purified benzene was irradiated until a steady state was established and absorbance was recorded for several half-lives and determined eventually at "$t = \infty$." From the usual second-order expression, the slope of $1/A$ plotted vs. t gave k/ϵ (cell length = 1 cm) reported in Table I. From these values k was calculated.

Extreme care was necessary to free solvents of impurities which react with radicals. Normally, three distillations of reagent grade solvent sufficed. Even with carefully purified solvents, radical dimerization was not the exclusive fate of radicals in the media studied. A small but detectable deviation from strict second-order was apparent sometime during the second half-life[4] and A_∞ was slightly greater than A measured prior to irradiation. Rate constants were taken from the first half-life.

Rates in 50:50 vol methanol–benzene were measured both in the spectrometer and in the flash photolysis apparatus used to determine extinction coefficients. An oscillographic trace of absorbance vs. time was photographed.

Some Reactions of Triarylimidazolyl Free Radicals

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Contribution No. 443 from the Research and Development Division, Organic Chemicals Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

Triarylimidazolyl free radicals 2 were found to oxidize electron-rich substances by rapid electron abstraction from tert-amines, iodide ion, and metal ions and hydrogen atom abstraction from phenols, mercaptans, primary and secondary amines, and activated C–H compounds. The rate constants for electron abstraction from tert-amines were related to σ^+ values via oxidation potentials which were determined by cyclic voltametry.

The formation of triarylimidazolyl free radicals 2 from the thermal or photolytic dissociation of hexaarylbiimidazoles 1 has been reported.[2-6] These radicals are known to dimerize to regenerate a hexaarylbiimidazole, usually one of the two favored isomers 1 or 3 (Scheme I).[3,5,7] They are also known to react with nitric oxide to give N-nitrosotriarylimidazoles[2] and to react with hydrogen peroxide to give 4-hydroperoxytriarylimidazoles.[8]

We report here further exploration of triarylimidazolyl radical chemistry. Two types of oxidations by 2 were studied: abstraction of electrons and of hydrogen atoms. Both reactions normally yield triarylimidazole 4 as the reduction product, the proton being obtained from the solvent if necessary. Results are summarized in Scheme II. Examples of representative

reactions are the subject of mechanistic studies reported in subsequent papers.[9-13]

Radicals 2 do not react with aromatic hydrocarbons, aliphatic alcohols, oxygen, or vinyl monomers at rates which compete detectably with dimerization or the oxidation reactions studied. Thus, benzene and methanol could be used as solvents under conditions employed without observing side products due to their presence. Reactions proceeded equally well with or without degassing. When radicals 2a or 2b were produced photolytically in neat monomers such as ethyl acrylate, acrylonitrile, or pentaerythritol triacrylate, no polymerization could be detected.

The reactivity of photolytically and thermally produced 2 was identical. Hence, in the reactions studied, only the ground state 2 is presumed to be involved.

Reactions 1–4 (Scheme II) involve as the first step electron abstraction by 2 which is two to three orders of magnitude faster than dimerization of 2.[9,13,14]

(1) To whom inquiries should be addressed.

(2) T. Hayashi and K. Maeda, *Bull. Soc. Chem. Jap.*, **33**, 565 (1960).

(3) T. Hayashi and K. Maeda, *ibid.*, **35**, 2057 (1962).

(4) T. Hayashi and K. Maeda, *J. Chem. Phys.*, **32**, 1568 (1960).

(5) H. Zimmermann, H. Baumgartel, and F. Bakka, *Angew. Chem.*, **73**, 808 (1961).

(6) S. M. Blinder, M. J. Peller, N. W. Lord, K. C. Aamodt, and N. S. Ivanclinkov, *J. Chem. Phys.*, **36**, 540 (1962).

(7) L. A. Cescon, Belgium Patent 509,415 (Aug 30, 1963).

(8) J. Sonnenberg and D. M. White, *J. Amer. Chem. Soc.*, **86**, 5685 (1964).

(9) A. MacLachlan and R. H. Riem, *J. Org. Chem.*, **36**, 2275 (1971).

(10) R. E. Kellogg and R. H. Kooser, personal communication.

(11) R. L. Cohen, *J. Org. Chem.*, **36**, 2280 (1971).

(12) R. L. Cohen, private communication.

(13) R. H. Riem, A. MacLachlan, G. R. Coraor, and E. J. Urban, *J. Org. Chem.*, **36**, 2272 (1971).

(14) L. A. Cescon, G. R. Coraor, R. Dessauer, E. F. Silversmith, and E. J. Urban, *J. Org. Chem.*, **36**, 2262 (1971).

SCHEME I

a, X = H; Y = H   c, X = 4-MeO; Y = H
b, X = 2-Cl; Y = H   d, X = 2-Br; Y = H
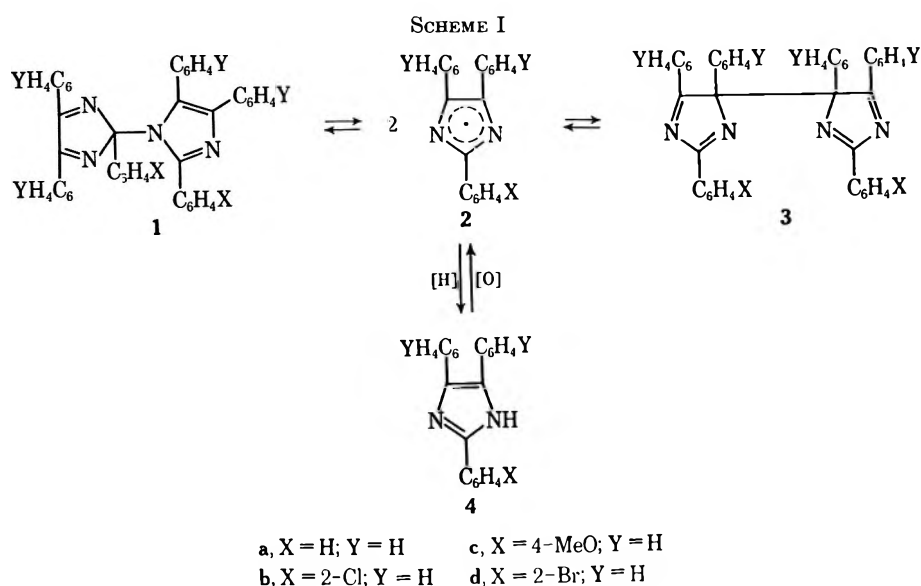
The inability of **2** to initiate vinyl polymerization is not due to an energetic deficiency since the intermediate products (radicals or radical ions) formed in reactions 1 and 4 do initiate polymerization. Thus, if a mixture of *N,N'*-dimethylaniline, a biimidazole, and a monomer such as pentaerythritol triacrylate is photolyzed, a hard polymer is formed. If the *N,N*-dimethylaniline is omitted, no polymerization occurs, no monomer double bond loss is evident from the infrared spectrum, and radical dimerization is observed at a rate normal for inert solvents.

The failure of **2** to initiate polymerization may result from steric or resonance factors; however, justification for neither is evident. However, other delocalized radicals which contain nitrogen atoms, especially when hindered, do not initiate polymerization and sometimes inhibit it.[15]

Reaction 4 involves stoichiometrically 1 mol of leuco dye salt, 1 mol of biimidazole, and 1 equiv of acid. MacLachlan and Reim[9] found the mechanism to be

$$1 \longrightarrow 2$$

$$7 + 2 \xrightarrow{k} 4 + 7\cdot^+$$

$$7\cdot^+ \rightleftharpoons 7\cdot + H^+$$

$$7\cdot + 7\cdot^+ \longrightarrow 8 + 7$$
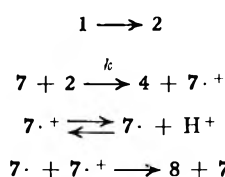
where $7\cdot^+$ and $7\cdot$ are the intermediate radical ion and radical, respectively, of the triarylmethane leuco dye **7**. With proper choice of components and conditions, this reaction can give unit quantum yield of dye even in the presence of oxygen.[10]

Cohen[11] examined the effect of substitution on the rate of disappearance of **2** in reaction 4. His selection of compounds was designed to emphasize steric variations in **2**. A plot of Cohen's rate constants *vs.* $-E_{p/2}$ values for various imidazole–imidazolyl radical redox couples (Table I) (Figure 1) is linear. The linear relationship of $E_{p/2}$ and σ^+ values is shown by Table II and Figure 2. Rate differences in reaction 4 which result from substituents X are thus strongly influenced by electron delocalization.

(15) C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957, p 163.

TABLE I

CYCLIC VOLTAMMETRIC OXIDATION–REDUCTION OF TRIARYLIMIDAZOLES IN ACETONITRILE SOLUTION

X	Y	Registry no.	$-E_p$, V vs. sce	$-E_{p/2}$, V vs. sce	Log k (step 1), reaction 4[a]
H	H	484-47-9	0.923[b]	0.808[b]	6.08
2-Cl	H	1707-67-1	0.994	0.891	7.45
2-F	H	1740-26-7	1.024	0.904	7.13
2-Br	H	1740-25-6	1.036	0.931	7.50
2-Me	H	13730-60-4	0.889	0.774	6.15
2-NO₂	H	29864-19-5	1.088	0.963	7.63
2-MeO	H	1965-19-1	0.899	0.862	6.20
H	4-MeO	7044-99-7	0.738	0.668	4.41
H	2-MeO	29864-26-4	0.898	0.718	5.40

[a] From Cohen.[11] [b] Compare with values obtained by reduction of **2a**; $-E_p = 0.976$, $-E_{p/2} = 0.816$.

Rate constants of reaction 4 with variously substituted leuco dyes have been found by Cohen[12] to correlate with σ. Delocalization effects were specifically excluded in the leuco dyes employed in that study. Reaction 1 actually is an exact model of the first step in reaction 4 with the added degree of freedom that substituents para to the dimethylamino group can be varied to include those capable of strong delocalization effects. This reaction has been studied kinetically with various para substituents, and rate constants were found to correlate with σ^+.[13]

Reactions 6–10, formally, involve hydrogen atom abstraction. The lower rate constant observed by MacLachlan, *et al.*, when O-deuterated phenols were used instead of normal phenols, was consistent with a rate-determining hydrogen atom abstraction in reaction 6.[13] Reactions 7–10 have not been studied mechanistically as yet; all are sufficiently fast to preclude observable radical dimerization. Rate constants of reactions 5 and 6 (with variously substituted phenols and hydroquinones) were found to be several orders of magnitude greater than that for radical dimerization.

Scheme II

$$\text{(1)}$$

$$M(A)Cl_n + HCl \xrightarrow{2b} M(A+1)Cl_{n+1} \quad (2)$$

$$M(A) = Fe(II), Cu(I)$$

$$KI \xrightarrow{2b} I_2 \quad (3)$$

$$\text{(4)}$$

a, R = Et; R' = Me; X = H·3HCl (**2b**)
b, R = Me; R' = H; X = SCH$_2$Ph (**2a**)
c, R = Me; R' = H; X = CO$_2$C$_2$H$_5$ (**2b**, AlCl$_3$)
d, R = Me; R' = H; X = NHNHPh (**2b**)

$$\text{(5)}$$

$$\text{(6)}$$

$$4c + 2a \longrightarrow 2c + 4a \quad (7)$$

$$\text{(8)}$$

$$\text{(9)}$$

$$RSH \xrightarrow{2a} RSSR \quad (10)$$

$$R = n\text{-Bu, Ph}$$
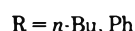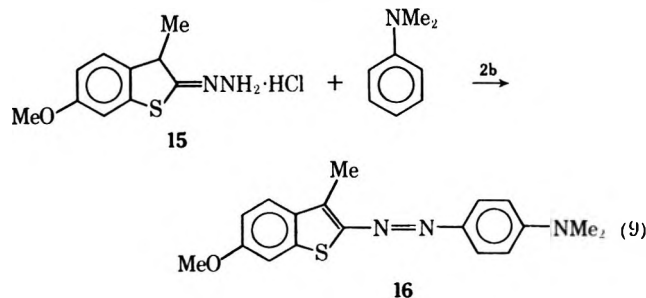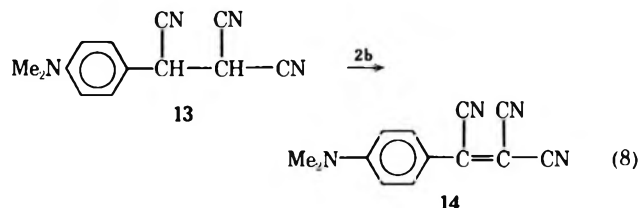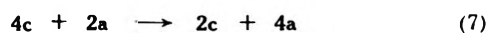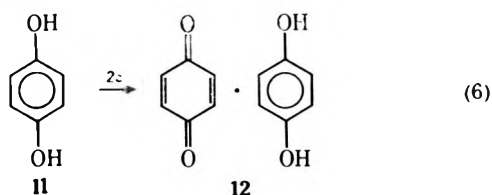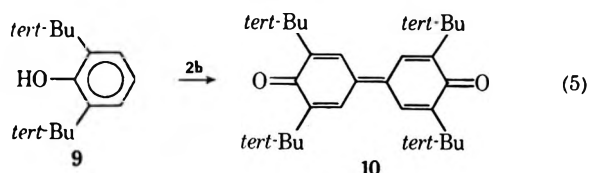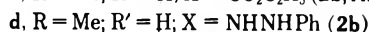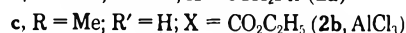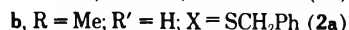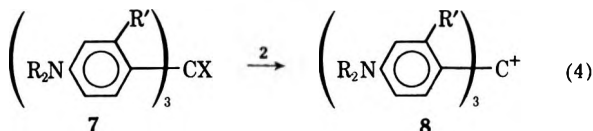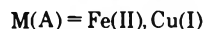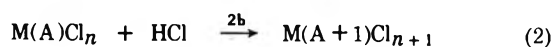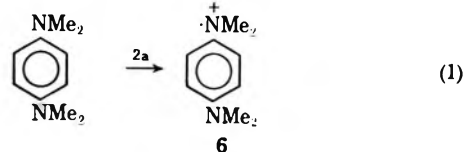
Because visible spectra of radicals **2** vary considerably, reaction 7 can serve as a convenient method for determining the relative oxidation potential of different radicals. For example, reddish purple **2a** (formed by adding to the reaction mixture its less stable dimer **3a**) rapidly oxidized the colorless imidazole **4c** to a blue radical **2c**. Colorless imidazole **4a** was the other product.
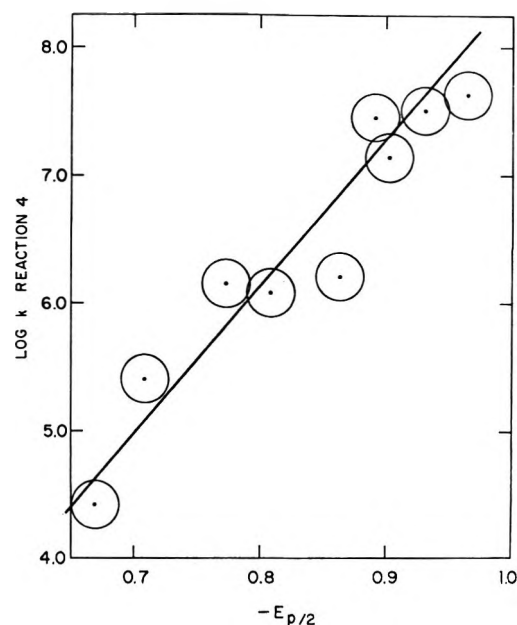
Figure 1.—Plot of rate constants of various imidazolyl free radicals in reaction with tris(4-diethylamino-2-methylphenyl)-methane trihydrochloride vs. the half-wave potential of the reversible oxidation of parent triarylimidazoles.

Table II

Oxidation Potentials of Some Triarylimidazoles in Acetonitrile Solvent

X	Registry no.	$-E_p$ V vs. sce	$-E_{p/2}$ V vs. sce	σ^a	σ^{+a}
H		0.923	0.808	0.00	0.00
4-MeO	1728-95-6	0.716	0.641	−0.27	−0.78
3-Cl	29898-73-5	0.918	0.778	0.37	0.37
4-Cl	5496-32-2	0.978	0.928	0.23	0.11
3-Br	29913-29-9	1.038	0.878	0.39	0.39
4-Br	5496-33-3	0.981	0.856	0.27	0.15
4-I	29936-60-5	0.974	0.768	0.30	0.13
3-F	29913-31-3	0.990	0.840	0.34	0.35
4-F	2284-96-0	0.931	0.836	0.06	−0.07
4-Me	5496-31-1	0.850	0.765	−0.17	−0.31
3-NO$_2$	5496-38-8	1.236	0.986	0.71	0.66
4-NO$_2$	5496-39-9	0.969	0.919	0.78	0.78
4-CN	29898-72-4	1.121	0.936	0.66	0.66
3,4-Benzo^b	13866-85-8	0.882	0.787	0.48	−0.13
4-Me$_2$N	1728-97-8	0.461	0.376	−0.83	−1.70

^{a} C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 334 (1964). ^{b} That is, "C$_6$H$_4$X" = β-naphthyl.

Redox potentials, $-E_{p/2}$, of imidazole–radical systems provide a quantitative ranking of the oxidizing ability of different radicals. Some $-E_{p/2}$ values determined by cyclic voltammetry appear in Tables I and II.

A number of additional reactions were carried out on a crude scouting basis to test the generality of this oxidation technique. Thus, irradiation of a 1:4 dimethylformamide–methanol solution of N,N-diethyl-p-phenylenediamine, thenoylacetonitrile, and **1b** gave a magenta-colored product as expected for the "oxidative coupling" product, 2-(4-diethylaminophenylimino)-3-thenylpropionitrile. Similarly, irradiation of a solu-

TABLE III
PREPARATION OF TRIARYLIMIDAZOLES

$$\underset{\underset{C_6H_4X}{\underset{\|}{N}}{\overset{C_6H_4Y \qquad C_6H_4Y}{\bigvee_{NH}}}}{}$$
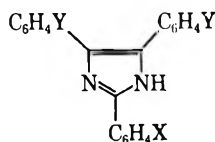
X[a]	Y	Recrystn solvent	Yield, %	Mp, °C	λ_{max},[b] mμ	Formula	Lit. Mp, °C	Ref
4-F	H	EtOH–H₂O	98	254–255	303	$C_{21}H_{15}N_2F$	243–244 dec	c
2-OMe	H	EtOH	89	207.5–208.5	308	$C_{22}H_{18}N_2O$	210–210.5	d
2-Me	H	PhH–EtOH	98	252.5–253.5	294	$C_{22}H_{18}N_2$	244–246	e
H	2-OMe	PhH–Hexane	88	175.5–176.5	303	$C_{23}H_{20}N_2O_2$		
H	4-OMe	PhH	99	197.5–198.0	298	$C_{23}H_{20}N_2O_2$		
3-Br	H	PhH–Tetra-hydrofuran	91	302–303	312	$C_{21}H_{15}N_2Br$		
4-I	H	PhH	100	267.5–268.5	315	$C_{21}H_{15}N_2I$		
3-F	H	EtOH–H₂O	98	254.5–255.0	295	$C_{21}H_{15}N_2F$		
2-F	H	EtOH–H₂O	99	254.5–255.0	295	$C_{21}H_{15}N_2F$		
4-Me	H	EtOH	91	234.5–235.5	300[f]	$C_{22}H_{18}N_2$	237–237.5	d
4-NMe₂	H	EtOH	100	258–259		$C_{23}H_{21}N_3$	259.5–260	d
3,4-Benz[g]	H	EtOH	84	277–278	h	$C_{25}H_{18}N_2$		

[a] Satisfactory combustion analytical data for C, H, and N (±0.3%) were provided for all of the compounds of this table: Ed. [b] In MeOH. [c] G. E. Philbrook, M. A. Maxwell, R. E. Taylor, and J. R. Trotter, *Photochem. Photobiol.*, 4 (6), 1175 (1965). [d] D. M. White and J. Sonnenberg, *J. Org. Chem.*, 29, 1926 (1964). [e] S. Kori and S. Narisawa, *Asaki Garasu Kenkyu Hokoku*, 12, 55 (1962). [f] In acetonitrile. [g] Thus, the imidazole is substituted in its 2 position with α,β-naphthyl. [h] 232, 271, 281, 313 mμ.
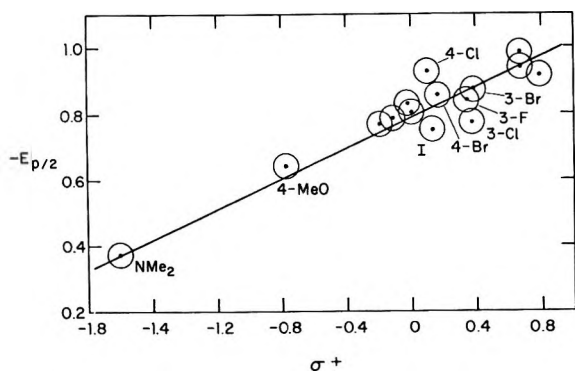
Figure 2.—Oxidation potentials of some substituted triphenylimidazoles plotted *vs.* σ⁺ values for their substituents.

tion of *N*,*N*-dimethyl-*p*-phenylenediamine, phenol, and **1b** gave a blue color typical of 4-(*N*,*N*-dimethylaminophenylimino)cyclohexadienone. Also, irradiation of a benzene solution of phenothiazine and **1d** gave the blue-green color of oxidized phenothiazine; similarly, 10-propionyl-3,7-bis(dimethylamino)phenothiazine and **1b** in acetone produce methylene blue. In each case, products were identified by comparison with known dye spectra. If the biimidazole was omitted from the above mixtures, no color developed.

It is thus obvious that radicals **2** can serve as highly selective oxidizing agents. When generated from biimidazoles photochemically, a convenient and versatile means is provided for carrying out photoinduced oxidations with high quantum yield without the problem of triplet quenching by oxygen.

It is probably true that all reactions studied involve electron abstraction or hydrogen abstraction. However, formally, a wide variety of organic oxidation reactions are represented: O–H, N–H, S–H, and C–H bond cleavage (reactions 6, 7, 8, and 10), oxidative coupling (reactions 5, 9, and 10), and electron abstraction (reactions 1–4).

Experimental Section

Reagents. Triarylimidazoles (4).—Samples of **4** (Table III) were prepared by previously described methods.[11,14]

Hexaarylbiimidazoles (2).—Samples of **2** were obtained as described.[11,14] 2-Methoxyphenyl-4,5-diphenylimidazole gave **2c** in 87% yield: λ_{max} ~270 mμ; ir 1497, 1551 cm⁻¹ (lit.[16] mp 182–185°; ir 1502, 1555 cm⁻¹).

Tris(4-dimethylaminophenyl)benzylthiomethane (7b).—A solution of 8.1 g of crystal violet in 50 ml of dry dimethylformamide was added to a mixture of 20 ml of α-toluenethiol, 50 ml of dry dimethylformamide, 50 ml of dry benzene, and 1 g of a 52% dispersion of sodium hydride in mineral oil. Removal of the solvent under vacuum left a colorless solid. Recrystallization (acetone) gave 8.4 g of white solid, mp 190°.

Anal. Calcd for $C_{32}H_{37}N_3S$: C, 77.5; H, 7.5; N, 8.5; S, 6.5. Found: C, 77.5; H, 7.5; N, 8.3; S, 6.5.

Tris(4-dimethylaminophenyl)ethoxycarbonylmethane (7c).—The method of Guyot[17] was used.

1-Tris(4-dimethylaminophenyl)methyl-2-phenylhydrazine (7d).—Tris(4-dimethylaminophenyl)methanol (8 g) was heated with 10 g of phenylhydrazine at 100–120° for 1 hr under nitrogen. Ether (50 ml) was added to the cooled mixture followed by 75 ml of ethanol. A yellow solid (7.1 g, 59%) crystallized, mp 171–172°.

Anal. Calcd for $C_{31}H_{37}N_5$: C, 77.6; H, 7.8; N, 14.6. Found: C, 77.9; H, 7.6; N, 14.4.

1,2,2-Tricyanoethyl-*N*,*N*-diethylaniline (13).—A sample supplied by Dr. B. C. McKusick was used without further purification.

Other Reagents.—Eastman White Label or Reagent Grade (from other manufacturers) were used without further purification.

Acetonitrile in 1-l. batches was dried by passage four times through a ½-ft column in diameter containing 6 in. of Linde 3 Å molecular sieves on the bottom, and the remainder filled with 13X molecular sieves. Acceptability was determined by a good blank (flat) polarogram after the solvent was made 0.5 *M* with LiClO₄. Imidazoles were dried at 110° (0.1 mm) for 8 hr over P₂O₅.

Equipment. Radiation Sources.—The sun lamp, 275-W input, was manufactured by General Electric Co. The mercury–xenon flash lamp used had 100-W input, 2400 effective candle second output, (450 μF at 475 V), and spectral output centers at

(16) D. M. White and J. Sonnenberg, *J. Amer. Chem. Soc.*, **88**, 3825 (1966).

(17) M. A. Guyot, *R. Acad. Sci.*, **144**, 1051 (1907); *ibid.*, 1122 (1907).

Figure 3.—Cyclic voltammeter: A, voltage source, 3–1.35-V mallory mercury batteries; B, 200-Ω 10-turn helipot; C, off-on switch; D, scan motor, bristol model 830-20, 60 cycles, 8-V; E, 25-Ω 10-turn helipot; F, voltmeter, 5 V, D.C. Simpson; G, platinum electrode, Beckman; H, saturated calomel electrode; J, decade box, Shallcross Mfg. Co., No. 8285; K, electrolytic cell; L, X–Y recorder, Mosley Autograf, Model 3S; P, vessel containing aqueous saturated KCl; S, agar-saturated KCl salt bridge.

420–430 mμ with detectable emission at 220 mμ. The low-pressure mercury resonance source emitted primarily at 253.7 mμ.

Cyclic Voltametry Equipment.—The equipment employed is described in Figure 3. Figure 4 provides details of cell construction.

Reactions of Triarylimidazolyl Radicals (2). 1. With N,N,N',N'-Tetramethyl-4-phenylenediamine (5).—To 0.5 g of 5 in 5 ml of water was added a solution of 0.17 g of sodium hydroxide in 6 ml of water to yield a white solid 5 which, after filtration, was stable in the dark over 4 hr. Addition of biimidazole 3a to 2 ml of benzene containing a few mg of 5 gave a yellow solution which became blue when phenol was added. If, instead, water was added, a blue, lower layer formed. The blue product was shown by match in uv and visible spectra (600 mμ) to be identical with Wurster's blue prepared by boiling 5 in xylene and adding phenol or water.[18]

2. With Metal Ions.—Equal volumes of two solutions of 1.65 g of biimidazole 1b in 300 ml of 95% ethanol and 0.31 g of freshly prepared ferrous chloride in 300 ml of 95% ethanol were mixed. The resulting solution was divided into four 5-ml portion A, B, C, and D. The FeCl₂ solution was also divided into 5-ml portions of E, F, G, and H. To each of B, D, G, and H was added 5 drops of concentrated HCl. A, B, E, and G were heated on the steam bath for 1 hr under an N₂ atmosphere, whereas C, D, F, and H were irradiated with the sun lamp for 1 hr. The initially colorless, very faintly yellow solutions of A, B, C, and D developed orange Fe(III) ion, whereas E, F, G, and H developed no Fe(III). Copper(I) chloride was treated similarly. The intense blue copper(II) ion was formed in A, B, C, and D, the portions in which radical 2b was formed. The remaining solutions were essentially unchanged.

3. With Iodide Ion.—To a solution of 100 mg of biimidazole 1b in 20 ml of methanol was added 5 ml of saturated methanolic potassium iodide. Irradiation with a sun lamp gave a yellow solution, a sample of which when added to a starch solution gave the purple color characteristic of a starch–iodine complex. Irradiation of methanolic KI alone did not give a positive starch–iodine test.

4. With Triarylmethane Derivatives. a. Tris(2-methyl-4-diethylaminophenyl)methane Trihydrochloride (7a).—A solution of 5.2 g of 7a and 6.6 g of biimidazole 1b in 350 ml of ethanol prepared in the dark was irradiated under nitrogen with a mercury resonance lamp for 8 hr. The solution changed from essentially colorless to dark blue. Solvent was stripped under

(18) V. Franzen, *Justus Liebigs Ann. Chem.*, **604**, 251 (1957).
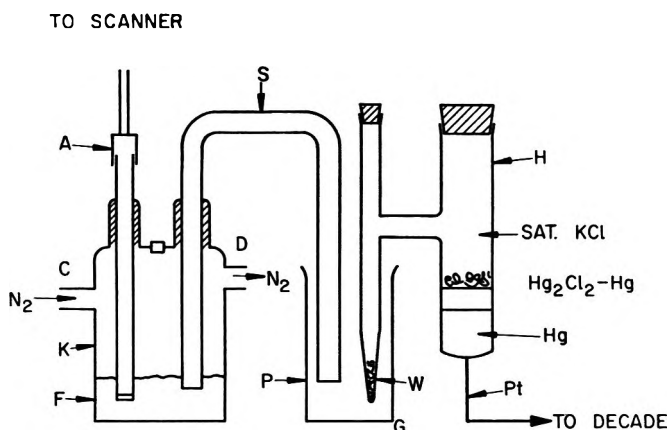
Figure 4.—Electrolysis cell–electrode system: A, flat platinum electrode, Beckman; C, nitrogen inlet; D, nitrogen outlet; K, electrolysis cell; F, supporting electrolyte and solvent (*e.g.*, 0.5 *M* LiClO₄ in acetonitrile); G, aqueous saturated KCl; H, saturated calomel electrode (aqueous); P, vessel containing saturated KCl (G); S, saturated agar–KCl salt bridge (aqueous); W, glass wool plug.

vacuum. The solid residue was extracted with petroleum ether (bp 30–60°) and then with 4 l. of benzene. The benzene extract was stripped of solvent and the blue solid was chromotographed on neutral alumina. Compound **4b** (2.4 g) was eluted with benzene and minor bands with 1:1 and subsequently 2:1 by volume chloroform–benzene. The remaining blue band was eluted with 8:1:1 by volume benzene–chloroform–ethanol. Evaporation gave 0.6 g of the dye **8a** [λ_max 610 mμ (ethanol) (ε 128,000)] which was identical with a sample of the dye prepared from its leuco form by lead dioxide oxidation.[19]

b. Tris(4-dimethylaminophenyl)benzylthiomethane (7b).—A solution of **7b** (0.15 g) and biimidazole **3a** (0.20 g) in 25 ml of acetone was irradiated with the flash lamp to give a solution of crystal violet dye **8b** as characterized by comparison to its uv and visible spectra with those of an authentic sample. Similar exposure of a solution of 0.15 g of the leuco dye in 25 ml of acetone gave no crystal violet dye **8b**.

c. Tris(4-dimethylaminophenyl)ethoxycarbonylmethane (7c).—A benzene solution of **7c** in the presence of aluminum chloride gave no color when irradiated with a flash lamp. Addition of biimidazole **1b** to a similar solution caused no change in color but, when this solution was irradiated, crystal violet dye **8b** was formed. Characterization was as above.

d. 1-Tris(4-dimethylaminophenyl)methyl-2-phenylhydrazine (7d).—A solution of 4 g of **7d** and 6.6 g of biimidazole **1b** in 15 ml of ethanol was irradiated with one flash of the flash lamp. The yellow solution immediately became intensely colored. The product was identified spectrally as crystal violet **8b**. Similar treatment of a solution lacking the biimidazole did not cause a color change.

5. With 2,6-Di-*tert*-butylphenol (9).—A solution prepared in the dark from 1.3 g of 9, 1.5 g of biimidazole **1b**, and 100 ml of benzene was irradiated 1 hr, 6 in. from a sun lamp. The colorless solution became bright yellow. Concentration on a steam bath gave a mixture of dark red and light yellow crystals. The mixture was treated with petroleum ether, and the insoluble yellow crystals of triarylimidazole **4b** were removed by filtering. Methanol was added to the filtrate to precipitate the product. Crystallization from petroleum ether–methanol gave 0.29 g of 3,3',5,5'-tetra-*tert*-butyl-4,4'-diphenoquinone (10), mp 245.0–245.5°. The uv and infrared spectra of the product were identical with those of a sample prepared according to the procedure of Hart.[20]

Similarly, to a solution of 2,6-dimethoxyphenol was added solid biimidazole **3a**. A purple solid, the diphenoquinone, precipitated. It was identical in all respects with that prepared by dichromate oxidation.[21]

6. With Hydroquinones.—A solution of biimidazole **1c** and 0.44 g of hydroquinone 11 in 65 ml of benzene was heated at re-

(19) C. C. Barker, M. H. Bride, G. Hallas, and A. Stamp, *J. Chem. Soc.*, 1285 (1961).

(20) H. Hart and F. A. Cassis, Jr., *J. Amer. Chem. Soc.*, **73**, 3179 (1951).

(21) A. W. Hofmann, *Ber.*, **11**, 335 (1878).

VOLTS vs. SCE
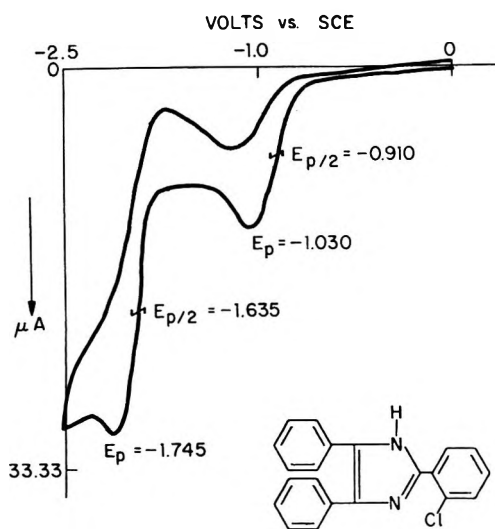
2-(2-chlorophenyl)-4,5-diphenylimidazole, 0.00130 *M*

Figure 5.—Cyclic voltammetry: temperature 25 ± 0.1°; electrode system Pt *vs*. sce; 0.5 *M* LiClO₄ in acetonitrile.

flux 3.5 hr. A precipitate, formed when the solution cooled, was crystallized from benzene to give 0.33 g of 2-(4-methoxyphenyl)-4,5-diphenylimidazole (4c), mp 230–232°, λ_{max} 297 mμ. From the remaining solid product was isolated 0.14 g of dark green quinhydrone 12, mp 169–171°.

7. **With 2-(4-Methoxyphenyl)-4,5-diphenylimidazole (4c).**—A 25-ml benzene solution of 0.05 g of biimidazole 1a and 0.05 g of 4c was irradiated with a sun lamp to give a blue solution of radical 2c, λ_{max} 610 mμ. Irradiation of a benzene solution of 4c in the absence of biimidazole 1a gave no radical which could be detected spectrally or by esr.

8. **With 1,2,2-Tricyanoethyl-*N*,*N*-dimethylaniline (13).**—A solution of 1:1 by volume acetone–benzene, containing 0.5% each of 13 and biimidazole 1b, was irradiated with the sun lamp. The known orange 4-(1,2,2-tricyanovinyl)-*N*,*N*-dimethylaniline (14) was identified spectrally.[22]

9. **With 3-Methyl-2-benzothiazole Hydrazone Hydrochloride (15). Oxidative Coupling with *N*,*N*-Dimethylaniline Hydrochloride.**—A solution prepared in the dark of 0.635 g of 15, 0.468 g of *N*,*N*-dimethylaniline hydrochloride, and 1.0 g of bi-

imidazole 1b was irradiated for 10 min with the sun lamp. The solution was diluted with 100 ml of water and extracted with three 50-ml portions of petroleum ether, which were discarded. The aqueous methanol solution was concentrated on a steam bath, cooled to room temperature, and filtered. The filtrate was saturated with sodium chloride and a blue-black crystalline solid formed. The uv and visible spectra (methanol) of this solid were identical with those of 3-methyl-2,4-(dimethylaminophenyl-azo)benzothiazolium chloride (16) prepared according to Hünig.[23]

10. **With Mercaptans. a. 1-Butanethiol.**—Under an atmosphere of dry nitrogen, a mixture of 2.7 g of butanethiol, 3.3 g of biimidazole 1b, and 20 ml of benzene was heated with stirring. The refluxing solution was irradiated (through Pyrex glass) with the sun lamp, 2 in. distant for 20 hr. The mixture was cooled and precipitate formed. This solid, mp 193.0–194.5°, was identical in infrared spectrum with authentic 2-(2-chlorophenyl)-4,5-diphenylimidazole (4b). The filtrate was shown by comparison of its ir spectrum and gas chromatographic analysis with those of authentic material to contain a high concentration of dibutyl disulfide.

b. **Thiophenol.**—A similar reaction was carried out with 0.44 g of thiophenol and 1.2 g of biimidazole 1a in 15 ml of benzene. Triphenylimidazole 4a, mp 190.0–191.5°, formed as a precipitate, and the phenyl difulfide was identified, as above, in the filtrate.

Spectral Determinations.—A Cary Model 14 spectrophotometer was used for uv and visible measurements. A Perkin-Elmer Model 221 instrument was employed for the infrared.

Cyclic Voltammetry.—The cell–electrode system was flushed with dry nitrogen and thermostated at 25 ± 0.5°. Acetonitrile (25 ml), 0.5 *M* in LiClO₄, and the sample (0.001–0.005 mol) were further flushed 5 min. The potential was scanned cyclically between 0 and +2.0 ,V *vs*. sce at a scan rate experimentally varied between 1 and 2.5 V/min. The cell was blanketed under nitrogen and shielded from light during the reaction. A representative polarogram is shown in Figure 5.

Reversibility of electrolytic triarylimidazole ⇌ biimidazole redox reaction was demonstrated by (a) observing no hysteresis in repetitive cycling and (b) obtaining the same cyclic trace from the biimidazole as from the corresponding imidazole.

(22) B. C. McKusick, R. E. Heckert, T. L. Cairns, D. D. Coffman, and F. W. Mower, *J. Amer. Chem. Soc.*, **80**, 2806 (1958).

(23) S. Hünig and K. H. Fritsch, *Justus Liebigs Ann. Chem.*, **609**, 143 (1957).

The Flash Photolysis of a Substituted Hexaarylbiimidazole and Reactions of the Imidazolyl Radical

R. H. RIEM, A. MACLACHLAN, G. R. CORAOR,* AND E. J. URBAN

Contribution No. 459 from the Organic Chemicals Department and Contribution No. 1582 from the Central Research Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

The rate of reaction of 2-(*o*-chlorophenyl)-4,5-diphenylimidazolyl radicals (L·) with additives has been studied in various solvents. Evidence based on measured rate constants, including kinetic deuterium isotope effects, prove that the rate-determining step in the reaction L· + aromatic amine is an electron exchange reaction at the amino nitrogen, while in the reaction L· + hydroquinone the rate-determining step is hydrogen abstraction.

Lophine dimer [(bis(2,4,5-triphenylimidazole)] has been known and studied for many years. It was first prepared in 1960[1] although at the time the structure was incompletely characterized. The first clearly recognized synthesis[2] was published the following year. The observed photochromism[1] of the hexaarylbiimid-

azole was subsequently shown to be due to the formation of imidazolyl radicals[3,4] upon photodissociation of the parent compound. In the present study, the kinetics and mechanism of reactions of 2-(*o*-chlorophenyl)-4,5-diphenylimidazolyl radicals (L·) with aromatic

(1) T. Hayashi and K. Maeda, *Bull. Chem. Soc. Jap.*, **33**, 565 (1960).

(2) H. Zimmermann, H. Baumgärtel, and F. Bakke, *Angew. Chem.*, **73**, 808 (1961).

(3) H. Baumgärtel and H. Zimmermann, *Z. Naturforsch.*, *B*, **18**, 406 (1963).

(4) T. Hayashi, K. Maeda, and M. Takeuchi, *Bull. Chem. Soc. Jap.*, **37**, 1717 (1964).
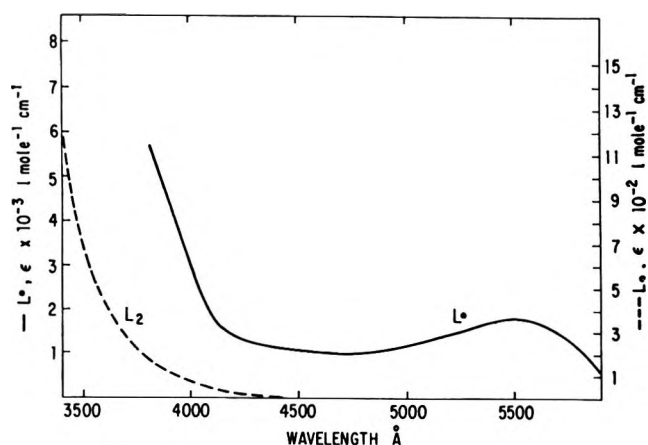
Figure 1.—Spectrum of L_2 (- - -) in CH_3OH; spectrum of $L\cdot$ (—) in EPA at $-196°$.

Figure 2.—The integrated flash intensity *vs.* the optical density of $L\cdot$, both observed at 3900 Å.

amines and with hydroquinone are studied in detail. The absence of thermal dissociation of the parent biimidazole at room temperature dictated the selection of this particular compound.[5]

Experimental Section

All compounds, except solvents, used in this study were prepared and supplied as described in ref 5. Solvents were the highest purity grades commercially available and were used directly. Linde high-purity dry (99.996%) argon was used in deoxygenating the solution in all flash-photolysis experiments. Spectra were recorded on Model 14 and Model 15 Cary spectrophotometers.

The flash-photolysis apparatus was of conventional design;[6,7] 160 *J* per flash were discharged through a PEK Laboratory XE 1-3 flash lamp placed parallel to the long axis of a 1-cm-diameter, 4-cm-long quartz cell. The flash was filtered with a combination 0-52 plus 7-60 Corning filter to provide light of 3700 ± 200 Å. The width of the flash intensity at half-peak height was 4.8 μsec. The appropriately filtered high-intensity analysis light was focused on the input slits of a Bausch and Lomb monochromator. A Dumont 6292 photomultiplier was used in conjunction with a Tektronic oscilloscope to monitor the transient absorptions.

Results and Discussions

Spectra.—The spectrum of 2,2′-bis(*o*-chlorophenyl)-4,4′,5,5′-tetraphenylbiimidazole (L_2) in CH_3OH is given in Figure 1. The spectrum of $L\cdot$ (Figure 1) was obtained by photolysis of L_2 in EPA at $-196°$. The time involved in recording the $L\cdot$ spectrum was shown to be short compared to the rate of $L\cdot$ disappearance at the temperature employed. The method used to determine the extinction coefficient of $L\cdot$ at 5480 Å is described below. This spectrum is also identical with that taken point by point at room temperature using the flash-photolysis apparatus. A plot of the integrated flash intensity *vs.* the optical density change (OD) due to $L\cdot$ formation is a straight line (Figure 2). The small intercept in Figure 2 is due to experimental inaccuracies. The decay of $L\cdot$ was measured by flash photolysis at 25° in various deoxygenated solvents. This decay, which was followed at 3900 and at 5450 Å, was found to be slow and to follow second-order kinetics. A typical second-order plot ob-
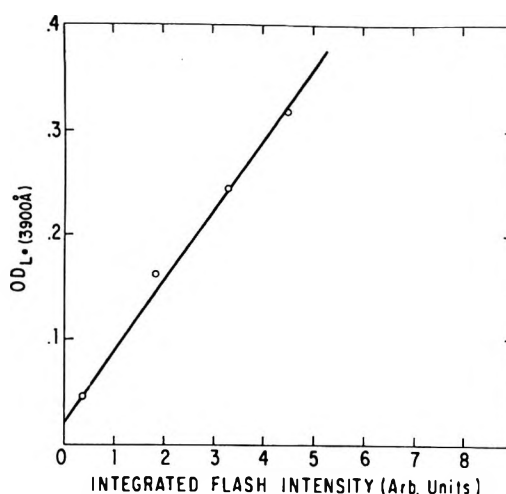
(5) L. A. Cescon, G. R. Coraor, R. Dessauer, A. S. Deutsch, H. L. Jackson, A. MacLachlan, K. Marcali, E. M. Potrafke, R. E. Reed, E. F. Silversmith, and E. J. Urban, *J. Org. Chem.*, 2267 (1971).

(6) E. J. Land and G. Porter, *Trans. Faraday Soc.*, **59**, 2027 (1963).

(7) A. MacLachlan, *J. Phys. Chem.*, **71**, 718 (1967).

tained is given in Figure 3. In view of the photochromic behavior of the hexaarylbiimidazoles, the observed decay is interpreted as

$$2L\cdot \xrightarrow{k_1} L_2 \tag{1}$$

Reactivity of $L\cdot$ with Aromatic Amine.—The flash photolysis of L_2 in the presence of various aromatic amines was investigated. Adequate amine was incorporated to yield pseudo-first-order kinetics as shown by variation of the amine concentration. The rate constants are listed in Table I.

TABLE I

FLASH PHOTOLYSIS OF L_2 (2×10^{-4} *M*) AT 25° IN CH_3OH IN THE PRESENCE OF AMINES

No.	Compd	k_t,[a] l. M^{-1} sec^{-1}	k'_t,[b] l. M^{-1} sec^{-1}
1	*N,N*-Diethylaniline		4.4×10^4
2	*N,N*-Dimethyl-*p*-toluidine		1.6×10^6
3	*N,N,N′,N′*-Tetramethyl-*p*-phenylenediamine	7.0×10^7	3.5×10^7
4	Tris(*p*-diethylaminophenyl)methane (leuco ethyl crystal violet)	1.2×10^7	4.0×10^6
5	Tris(*p*-diethylamino-*o*-methylphenyl)methane	2.5×10^7	8.3×10^6
6	Pyridine	No reaction	
7	2,6-Lutidine	No reaction	
8	*p*-Cyano-*N,N*-diethylaniline		3.74×10^2
9	*p*-Methoxy-*N,N*-diethylaniline		1.0×10^7
10	*p*-Chloro-*N,N*-diethylaniline		3.8×10^3

[a] k_t is the overall second-order rate constant for $L\cdot$ reaction with the aromatic amine. k'_t was calculated from the experimentally determined pseudo-first-order rate constant and the concentration of amine. k_t was calculated on the basis of the "amino group concentration" and is equivalent to k'_t/number of amino functions per molecule of amine. [b] k'_t is the rate constant calculated on the basis of amino group concentration.

If the point of attack of $L\cdot$ on the leuco triphenylmethane dyes no. 4 and 5 of Table I is considered to be the hydrogen atom attached to the central C atom, it is difficult to imagine how in the more sterically hindered case (no. 5) the rate constant could be double that found with compound no. 4. The gen-

TABLE II

DEUTERIUM ISOTOPE EFFECT AT 25° DEOXYGENATED SOLUTIONS[a]

No.	Compd	Solvent	Rate constant for attack of L·, l./(mol sec)	Isotope effects, k_H/k_D
1	Hydroquinone (H_2Q)	H_2O saturated benzene	2.16×10^7	5.6/1
2	Hydroquinone (D_2Q)	D_2O saturated benzene	$3.86 + 10^6$	
3	Hydroquinone (H_2Q)	$CH_3CN + 0.8\%$ H_2O	2.68×10^6	10/1
4	Hydroquinone (D_2Q)	$CH_3CN + 08\%$ D_2O	2.6×10^6	
5	Hydroquinone (H_2Q)	CH_3CN + various H_2O amounts	2.7×10^6	
6	Tris(p-diethylamino-o-methylphenyl)methane	$CH_3CN + 0.8\%$ H_2O	1.07×10^4	1/1
7	Tris(p-diethylamino-o-methylphenyl)-methane	CH_3CN–0.8% H_2O	0.99×10^4	

[a] $L_2 = 4 \times 10^{-4}$ M, hydroquinone $= 2 \times 10^{-4}$ M, tris(p-diethylamino-o-methylphenyl)methane $= 10^{-4}$ M.
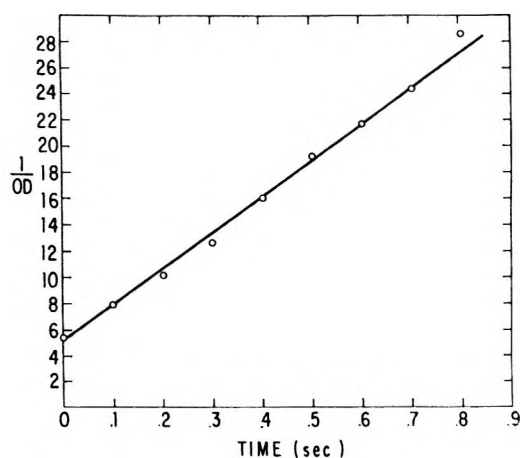
Figure 3.—Second-order plot obtained for the L· decay in CH_3OH measured at 5450 Å.
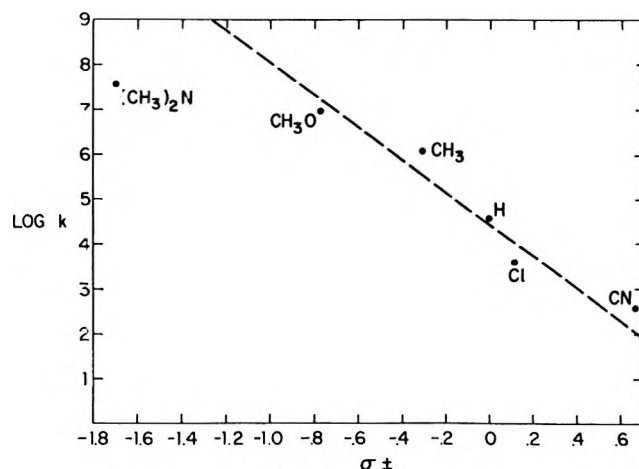
Figure 4.—Hammett plot of lophine radical reactivity with para-substituted N,N-diethylaniline. The dimethylamino substituent was done with N,N,N',N'-tetramethyl-p-phenylenediamine.

eral trend in Table I indicates that the reaction of L· with the amines listed occurs at the nitrogen atom. Substitutions which increase the electron density at this atom increase k_4. The reaction, therefore, is formulated as an electron-exchange reaction.

$$L· + >\overset{\cdot\cdot}{N}- \longrightarrow L^- + >\overset{\cdot}{\underset{+}{N}}- \qquad (2)$$
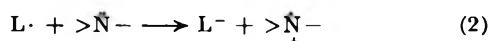
Additional evidence for the involvement of the free electron on the nitrogen can be obtained from the Hammett plot of para-substituted N,N-diethylaniline derivatives in Figure 4. A fairly good straight line is obtained with $\sigma \pm$ values, which suggests strong resonance interaction during the electron-exchange reaction. For information, the rate for p-N,N-dimethylamino is included in the plot. Nitrogen-positive radical ions of the type shown in eq 2 have been observed in the CCl_4-sensitized oxidation of leuco ethyl crystal violet.[7]

Reactivity of L· with Phenols.—Deuterium isotope effects were measured by flash photolysis in the reaction of L· with amines and hydroquinone. The hydroquinone reaction was studied to establish whether hydrogen abstraction or electron exchange is rate determining for phenol type structures, as it must be

for the aromatic amines examined. The results are listed in Table II.

The data in Table II clearly demonstrate that in the reaction

$$L· + \text{hydroquinone} \longrightarrow$$

hydrogen abstraction is the rate-determining step and support the concept of electron exchange (eq 2) in aromatic amine + L· reactions by showing the isotope effect is not related to deuteration of the L· radical. The dual mode of reactions by lophine radicals is interesting and it remains for further experimentation to establish if a phenol structure can be highly substituted enough to change the mode of reaction from hydrogen abstraction to electron exchange. The solvent effect on the magnitude of the isotope effect is also interesting. The solvating nature of the aqueous acetonitrile slows the overall reaction rate down by a factor of approximately ten and at the same time gives a much greater isotope effect. The slower reaction in acetonitrile suggests that a strong interaction between L· and substrate is involved which, if tempered by outside solvating, is rendered less efficient. The much larger isotope effect is consistent with the picture.

The Biimidazole-Sensitized Photooxidation of Leuco Triphenylmethane Dyes

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The oxidation of tris(2-methyl-4-diethylaminophenyl)methane by photogenerated 2-(o-chlorophenyl)-4,5-diphenylimidazolyl radical (L·) was studied by flash photolysis. An electron-exchange reaction involving L· occurs at an unprotonated amino nitrogen of the leuco dye and is responsible for the first oxidation step. Subsequent reactions do not involve the L· radical and depend only on the structure of the leuco dye and environmental effects. The influence of pH on both the course and rate of the dye-forming reaction is discussed.

Several investigators have studied the nature of the intermediates formed and the reactions which occur when dyes are photoreduced.[1-3] The participation of radicals and radical ions in the photoreduction of methylene blue has long been recognized.[1-3] Except for the work of Lewis[4-7] and Linschitz[8,9] and a previous publication[10] from this laboratory, little direct evidence has been reported on the nature of the intermediates formed in the oxidation of triphenylmethane leuco dyes or the kinetics of the reactions which they undergo.

The halocarbon-sensitized photooxidation of tris(4-diethylaminophenyl)methane, referred to as leuco ethyl crystal violet (LECV), was recently described and a mechanism presented.[10] Previous papers in this series[11] discussed the reactions of the 2-(o-chlorophenyl)-4,5-triphenylimidazolyl radicals (L·), formed from the corresponding dimer (L₂), with reducing agents. The present paper is a study of L· induced oxidation of triphenylmethane dyes and their trihydrochloride salts.

Experimental Section

Tris[2-methyl-4-(diethylaminophenyl)]methane (o-MLECV), LECV, and their trihydrochloride salts as well as L₂ were prepared by Cescon.[11a] The solvent CH₃OH was Matheson reagent grade. Linde argon (dry 99.99% pure) was used to deoxygenate all solutions. Spectra were recorded on Cary Model 14 and 15 instruments.

The flash photolysis apparatus was of conventional design and has been described previously.[10] The flash was filtered with a combination of 0-52 plus 7-60 Corning filters to provide light of (3700 ± 200 Å). The analysis light was appropriately filtered to preclude photolysis of solutions.

The absorption spectrum of the leuco dye radical-ion intermediate was obtained using an apparatus designed by Dr. D. C. Reitz. The methanol solution containing leuco dye and CCl₄ was placed in a rectangular quartz cell and suspended in a cold stream of nitrogen within a multiwalled dewar flask constructed to fit inside the sample compartment of a Cary Model 14 uv-visible spectrometer. Optically flat quartz windows were provided on the dewar flask for analysis. Photolysis was accomplished through a hole in the sample compartment on a direct line with the sample cell. The photolysis light was filtered with a Corning 7-39 filter to prevent photolysis of the intermediate.

Results and Conclusions

Structure of o-MLECV·3HCl and L₂ in Various Solutions.—Ultraviolet absorption spectra of the o-MLECV·3HCl + L₂ mixture in methanol revealed no complexing between initiator and leuco dye. (Unless specified otherwise, all work was performed with o-MLECV at 6.6 × 10⁻⁵ M and L₂ at 4 × 10⁻⁴ M.) The equilibrium constant K at 25° for the reaction

o-MLECV·3(H⁺Cl⁻) ⇌

o-MLECV·2(H⁺Cl⁻) + H⁺ + Cl⁻ ⇌ etc.
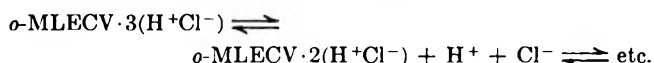
was determined in methanol, glycerol, acetonitrile, and dimethylformamide (Table I). These values were ob-

TABLE I
DEGREE OF PROTONATION AT 25°[a]

DH·3HCl ⇌ DH·2HCl + HCl ⇌ etc.
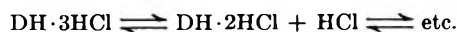
	k, mol l.⁻¹	Degree of protonation (statistical structure)
Methanol	4 × 10⁻⁵	DH·2.5HCl
Glycerol–methanol 60:40	7 × 10⁻⁵	DH·2.4HCl
Dimethylformamide		DH·0HCl
Acetonitrile	∼10⁻⁷	DH·2.9HCl

[a] DH·3HCl = 6.6 × 10⁻⁵ M and L₂ = 4 × 10⁻⁴ M.

tained by comparing the extinction coefficient at 2650 Å of o-MLECV·3HCl dissolved in the various solvents with that of the o-MLECV free base and of o-MLECV·3HCl dissolved in methanolic 0.1 M HCl (Figure 1). It is assumed that the free base extinction coefficient at

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Figure 1.—Effect of acid on the *o*-MLECV (6.65 × 10⁻⁵ *M*) spectrum in methanol.

2600 Å is equal to three times the extinction coefficient for an individual 4-diethylaminophenyl structure. The free or available amino group concentration for the salt is calculated from the optical density at 2600 Å, assuming Beers law is obeyed. These data allow a calculation of the statistical degree of protonation and, as will be shown later, have an important effect on the ease of oxidation of the leuco dye. The results may be summarized by noting that in methanol and 60% glycerol–40% methanol only the first of the three deprotonating steps is important with the trihydrochloric salts. In the two hydroxyl-containing solvents the equilibrium is such that an equimolar mixture of di- and triprotonated species is present. In acetonitrile very little dissociation occurs, while in DMF the free base is the major species, quite likely due to the basic character of this solvent.

Quantum Yield of Color Formation *vs.* Wavelength as a Function of the Absorbing Species.—Table II

TABLE II

COLOR QUANTUM YIELD (Φ_c) *vs.* IRRADIATING WAVELENTH[a]

Irradiating wavelength, Å	Φ_c[b]
2537	0.66
3130	0.49
3660	0.55

[a] *o*-MLECV·3HCl was 6.6 × 10⁻⁵ *M* in methanol; L₂ was 4 × 10⁻⁴ *M*. [b] Quantum yield was obtained by correcting for screening by *o*-MLECV·*n*HCl.

contains the experimentally determined color quantum yield (Φ_c) as a function of exciting wavelength. All the yields are identical within experimental error. No effect of L₂ concentration on Φ_c in methanol with 3660-Å irradiation was found (Table III). The Φ_c values in Tables II and III were all corrected for screening due to *o*-MLECV·*n*HCl, implying that only light absorbed by L₂ was effective in producing color. Justification for this was obtained by varying the relative concentrations of *o*-MLECV·3HCl and L₂ such that in one case most of the incident light was absorbed by L₂ and in
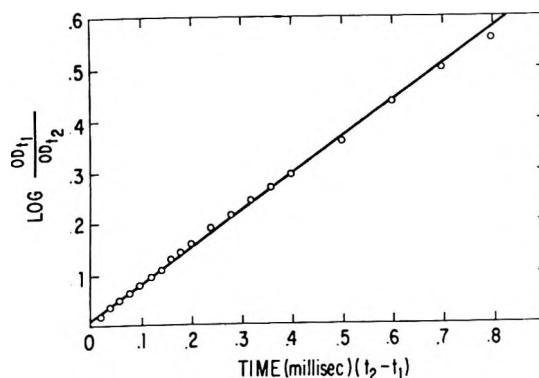
Figure 2.—*o*-Chlorolophine radical decay at 3900 Å in the presence of *o*-MLECV.

TABLE III

Φ_c *vs.* REACTANT CONCENTRATIONS IN METHANOL[a]

Concn, *M*, *o*-MLECV·3HCl	Concn, *M*, L₂	Φ_c[b]
6.6 × 10⁻⁵	8 × 10⁻⁴	0.61
6.6 × 10⁻⁵	2 × 10⁻⁴	0.50
6.6 × 10⁻⁵	4 × 10⁻⁴	0.52

[a] Photolyzing wavelength was 3660 Å. [b] Corrections for screening by *o*-MLECV·*n*HCl were always applied.

the other most of the light was absorbed by *o*-MLECV·3HCl. Color was produced only in the former case.

The extinction coefficient of *o*-MLECV cationic dye, which is necessary for Φ_c determinations, was obtained by photolyzing a deoxygenated mixture of a known concentration of *o*-MLECV·3HCl with excess L₂ to the point where no more color was formed. The value for ϵ_{6200} obtained in this manner is 11.5 × 10⁴ l./(mol cm), and in the event that some dye was photolyzed it represents a minimum value. However, under the condition of the experiment the quantum yield for dye degradation was determined as less than 0.02 compared to Φ_c = 0.55.

Flash Photolysis.—Flash photolysis of LECV–CCl₄ mixtures in methanol and ethanol yielded one observable intermediate.[10] At 4500–4900 Å (called 4600-Å species from now on) an absorption was detected which decayed in about 20 msec to produce the final color (5900 Å). The rate of color formation coincided in both kinetic order and lifetime with the 4600-Å decay. In the present system, initiator fragments should present an additional complication; therefore, the initiation was investigated separately.

L₂ Photolysis.—When L₂ is flash photolyzed in methanol, transient absorptions at 5450 and 3900 Å are detected. Both decay with approximately second-order kinetics, and correcting for differences in extinction coefficient of the lophine radical at 5450 and 3900 Å leads to the conclusion that both absorptions correspond to the same radical species. Whether L₂ is re-formed or whether different products result is not known.

***o*-MLECV Free Base plus L₂.**—Filters were adjusted to allow only photolysis of L₂. A transient was observed at 3900 Å, whose decay rate was much faster than the normal lophine radical disappearance rate and, in addition, was first order. At 4660 Å an absorption appeared at a rate and order corresponding to the 3900-Å decay (Figures 2 and 3) thus suggesting
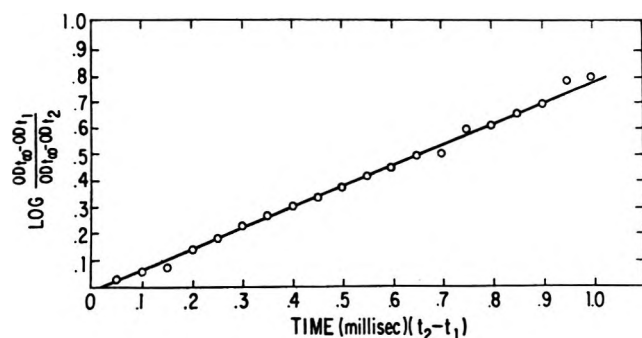
Figure 3.—"4600-Å" formation.
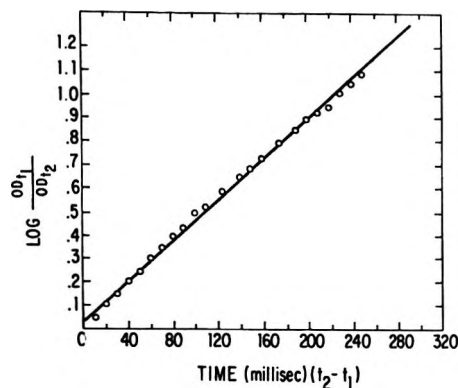
Figure 4.—Decay of "4600 Å" (first order).
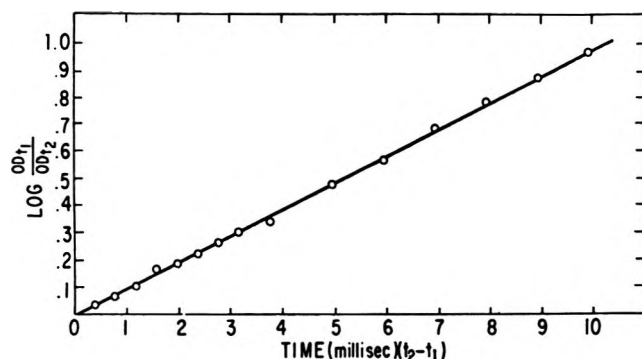
Figure 5.—Reaction of lophine radicals (3900 Å) (first order).

Figure 6.—Formation of "4600 Å" by lophine radicals (first-order kinetics).

Figure 7.—"4600-Å" decay.

that the 3900 Å reacts to produce the 4600-Å transient. That the observed 3900-Å decay was in reality only pseudo first order was shown by decreasing the o-MLECV free base concentration to a point where it was no longer in excess over the concentration of lophine radicals (L·). Under these conditions second-order kinetics was observed. The reaction

$$L\cdot + DH \longrightarrow 4600\text{-Å absorbing species}$$

is in agreement with the results. The true second-order rate constant for 3900-Å (L·) decay was obtained by dividing the observed pseudo-first-order rate constant by the concentration of "free amino groups." The significance of this latter normalization becomes apparent when the data are analyzed with acid in the system. No color is formed when the system o-MLECV free base reacts with lophine radicals. The possible reasons for this will be discussed later. The decay at 4600 Å is shown in Figure 4.

Flash Photolysis of o-MLECV·3HCl plus L₂ in Methanol.—When o-MLECV·3HCl plus L₂ is flash photolyzed, using light absorbed only by L₂, the following transient reactions are observed. (a) 3900 Å (L·) decays by pseudo-first-order kinetics in a time short compared to the disappearance rate (Figure 5). (b) 4600 Å is formed with a rate and order corresponding to the 3900-Å decay (Figure 6). (c) 6200 Å (color) is formed with a rate and order corresponding to the 4600-Å decay (Figures 7 and 8).

As mentioned earlier, when the trihydrochloride is dissolved in methanol, equilibrium between di- and triprotonated leuco base is established and it is possible to determine the number of protonated and nonprotonated amine functions available for L· reaction by ultraviolet spectroscopy. When the pseudo-first-order rate constant obtained in this system is divided by the concentration of free aromatic amine groups, the true second-order rate constant obtained is identical with that measured for the free base. This quite conclusively points to the amine function as the primary point of attack.
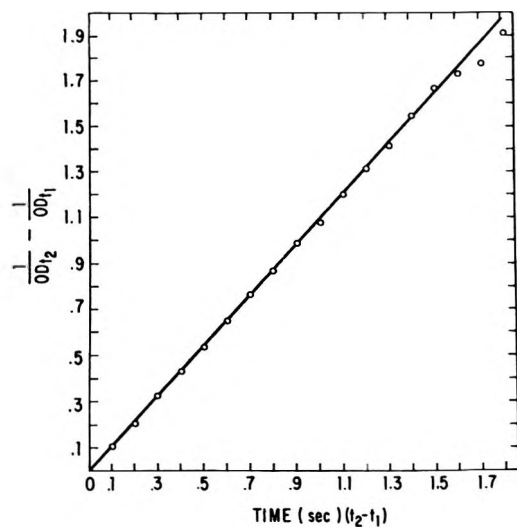
Figure 8.—Color formation.

Since the rate of attack of L· on o-MLECV depends on the number of free amine functions, the first intermediate formed would be the radical ion

$$DH(HCl)_n$$

where $n = 1$
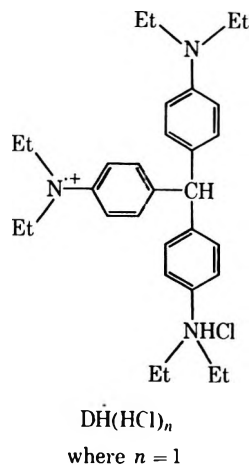
Such radical ions have analogy both in the formation of Würster-type radicals with aromatic diamines and as postulated intermediates in the Hofmann–Löffler reaction

$$R_2NH \cdot {}^+Cl \xrightarrow{h\nu} R_2N {}^+H + Cl \cdot$$
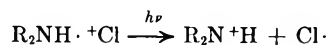
The rapid rate of L· disappearance and its kinetic order, when compared to the slow rate of disappearance of the 4600-Å transient, show the only purpose of L· is to initiate the reaction. Once the electron exchange reaction has occurred, the final dye formation rate depends only on the dye structure and any environmental effects on the 4600-Å intermediate.

Evidence for Identification of the Reaction Intermediates.—Strong evidence that the 4600-Å transient is a radical was obtained by electron spin resonance techniques. Two different means of generating the radical were used.

o-MLECV·3HCl and L_2 were dissolved in methanol and deoxygenated. This solution was circulated through the esr cavity (25°) and irradiated directly. A single line was obtained and could not be resolved. Lophine radicals cannot be responsible, since their rate of disappearance as obtained from the flash photolysis experiments renders their concentration much too
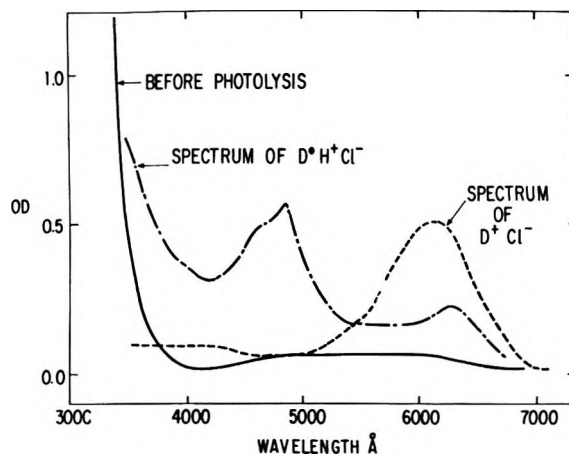
Figure 9.—Absorption spectrum of D·H$^+$Cl$^-$ in methanol at $-90°$.

low. A second method relied on the sensitized decomposition of the o-MLECV free base. Free base was dissolved in a 10% carbon tetrachloride–90% methanol solution, cooled to $-80°$, and irradiated directly in the esr cavity. Again, a single-line spectrum was obtained which could not be resolved. These spectra do not allow a structure to be assigned the radical and do not even prove that the same radical is obtained by either route but they clearly show a radical intermediate that corresponds in lifetime to the optically observed 4600-Å transient intermediate described below.

The optical absorption spectrum of the radical intermediate was also obtained. Figure 9 shows the results of photolysis of o-MLECV free base in 10% carbon tetrachloride–90% methanol at $-90°$. The radical intermediate has two peaks in the vicinity of 4800 Å and apparently one at 6300 Å. On warming the normal 6200-Å absorption of the dye cation forms. Mixing was not possible in the low-temperature cell used in this experiment, and thus extinction coefficient relationships cannot be obtained from Figure 9.

The possibility that the 4800-Å species might be simply a protonated form of the final dye was eliminated by examining the behavior of the dye spectrum as a function of added sulfuric acid. The major change is a shift to longer wavelengths (6700 Å) and then an almost complete loss of the 6700-Å absorption. No absorption at 4800–4900 Å is ever formed by protonation.

The optical spectral data make it apparent why the formation of the 4800-Å transient and the loss of the 3900 Å (lophine radical) could not be followed over their entire range. The marked spectral overlap of the two species at 3900 Å is easily seen in Figure 9.

The Role of Protons in Promoting Color Formation.—Reactions 1, 2, 3, and 4 have been discussed.

$$L\text{-}L \xrightarrow{h\nu} + L\text{-}L^* \tag{1}$$

$$L\text{-}L^* \longrightarrow L\text{-}L \tag{2}$$

$$\Phi_{\text{dissociation}} = 0.55$$

$$L\text{-}L^* \longrightarrow 2L \cdot \tag{3}$$

$$L \cdot + DHnH^+ \longrightarrow L^- + DHnH^+ \tag{4}$$
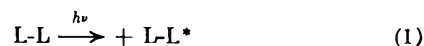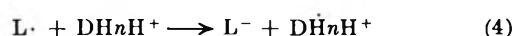
$$0 < n < 3$$

$$k = 0.83 \times 10^7 \text{ l./(mol sec) in methanol at } 25°$$

Scheme I

O-MLECV + D$^+$ $\xleftarrow{2C}$ (C)

O-MLECV + D$^+$ (A) $\xrightarrow{2A}$ degradation products

L·

L· + HCl

CCl$_4$ + hν

(B) $\xrightarrow{2B}$ D$^+$ + *O*-MLECV
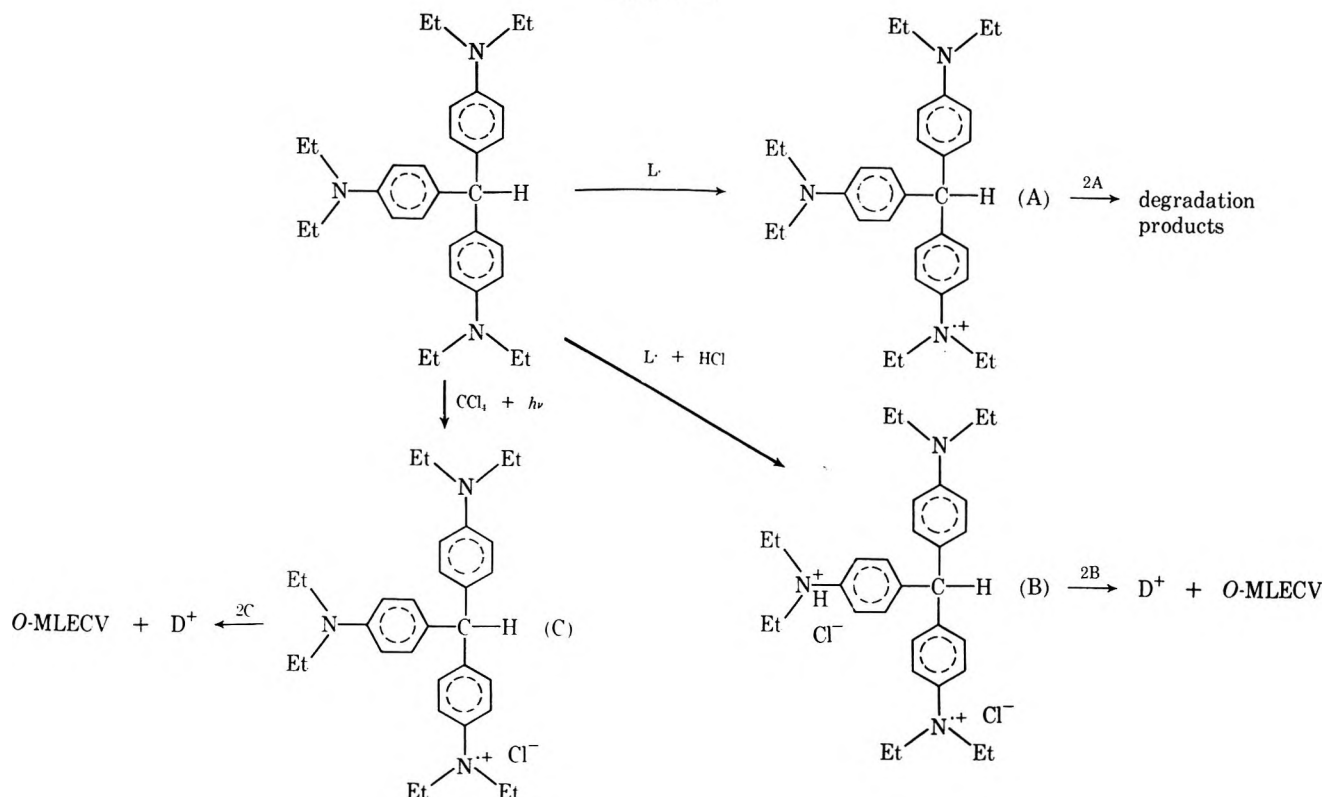
The question of the degree of protonation of the 4600-Å intermediate and its effect on the rate of color formation will now be explored.

In methanol, the *o*-MLECV·3HCl plus L$_2$ composition yields a 4600-Å transient that decays by good second-order kinetics with a lifetime of approximately 0.2 sec (Figure 6). When *o*-MLECV free base is photolyzed with carbon tetrachloride as sensitizer, the 4600-Å absorption is formed but decays with a lifetime of approximately 4 sec (first order).[12] However, when *o*-MLECV·3HCl is sensitized with CCl$_4$, the lifetime of 4600-Å decay again becomes second order with a lifetime of 0.2 sec. These three experiments illustrate the influence of [H$^+$] on the observed kinetics as well as the independence of the 4600-Å intermediate from the initiator. They also show that no long-lived complex with lophine radicals is responsible for the 4600-Å transient absorption and its decay rate.

The effect of HCl on this disproportionation is undoubtedly due to the degree of protonation of the intermediate and must be included in the mechanism. With no initial concentration of HCl, the concentration of HCl generated photochemically cannot exceed the final concentration of dye formed, and therefore the minimum degree of protonation would be present. This is the case for CCl$_4$-sensitized decomposition of the free leuco base.[12]

As hydrochloric acid is added to the system (in the form of the leuco trihydrochloride), the rate of attack of

lophine radicals on the dye is decreased, and the rate of disproportionation of the 4600-Å transient is increased. No significant change in color quantum yield occurs; thus, the change in half-life is not a concentration effect. However, when lophine radicals react with *o*-MLECV free base, no color is formed, and its 4600-Å transient disappears with the highest rate. End product analysis showed that the oxidized form of the dye is not present under these conditions. Thus, the effect of acid is twofold: (1) it increases the rate of disproportionation of the 4600-Å transient, and (2) it actually controls the chemical course of the reaction.

To understand these results we need to examine LECV oxidation by L· under neutral conditions. Photolysis of a methanolic solution of L$_2$ plus LECV gives color (D$^+$) with a quantum yield equivalent to the *o*-MLECV·3HCl yield ($\sim$0.5). The only difference in structure between the leuco bases is the presence of the three ortho methyl groups in *o*-MLECV. Thus, the most reasonable effect is a steric one that interferes with reaction at the central C–H bond. Since it has already been shown that the 4600-Å transient is a free radical and does disproportionate to form the final products, this too must be considered in the mechanism. Schematically, we can represent the experimental facts as follows.

o-MLECV + L· $\longrightarrow$ 4600 Å (basic)   (A)

o-MLECV·3HCl + L· $\longrightarrow$ 4600 Å·nH$^+$ (acidic)   (B)

o-MLECV* + CCl$_4$ $\longrightarrow$ 4600 Å (neutral)   (C)

LECV + L· $\longrightarrow$ 4600 Å (basic)   (D$_{LECV}$)

LECV* + CCl$_4$ $\longrightarrow$ 4600 A (neutral)   (E$_{LECV}$)

2A $\longrightarrow$ degradation products $t_{1/2}$ = $\sim$0.10 sec

2B $\longrightarrow$ D$^+$ $t_{1/2}$ = $\sim$0.4 sec

2C $\longrightarrow$ D$^+$ $t_{1/2}$ = $\sim$3 sec

2D$_{LECV}$ $\longrightarrow$ D$^+_{LECV}$ $t_{1/2}$ = 0.010 sec

2E$_{LECV}$ $\longrightarrow$ D$^+_{LECV}$ $t_{1/2}$ = 0.036 sec

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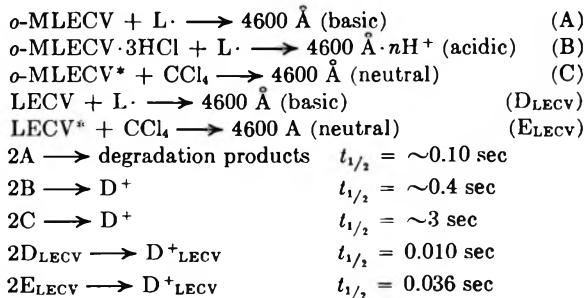
(12) For reference the scheme for CCl$_4$ photosensitized oxidation of *o*-MLECV[10] is

o-MLECV + hν $\longrightarrow$ S* (singlet state)

S* $\longrightarrow$ T (triplet state)

S* or T* + CCl$_4$ $\longrightarrow$ DH·$^+$ + CCl$_4$·$^-$

DH·$^+$ + CCl$_4$·$^-$ $\longrightarrow$ D$^+$Cl$^-$ + CHCl$_3$

DH + CCl$_4$·$^-$ $\longrightarrow$ DH·$^+$Cl$^-$ + CCl$_3^-$

DH·$^+$ $\rightleftharpoons$ D· + H$^+$

DH·$^+$ + D· $\longrightarrow$ DH + D$^+$
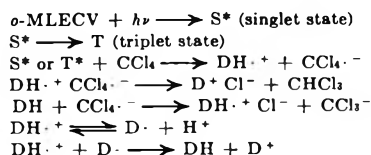
The ortho methyl group steric effect is exhibited in the reduced reactivity of all the species derived from o-MLECV vs. LECV. Under basic conditions, LECV yields the final dye. Reactivity of the ortho methyl groups of o-MLECV might explain the results if disproportionation occurred at these groups to give degradation products. However, the methyl groups are meta to the amino function and should not yield a highly resonance-stabilized benzyl radical; in fact, reactivity little greater than that of toluene might be expected. Furthermore, the effect of acid could not be explained by reaction at the methyl groups, because protonation would reduce the reactivity of the triphenylmethane carbon–hydrogen bond to the same extent as the meta methyl group, and thus no change in chemistry would be expected.

Assuming that 0.036 sec is the normal "unhindered" rate of disproportionation of unprotonated 4600-Å species, it is seen that with the ortho methyl groups present in o-MLECV the rate is significantly slower (0.10 sec). In the normal "unhindered" reaction we know oxidation at the triphenyl methane carbon–hydrogen bond occurred since color is formed. In the hindered case reaction at some other point must occur since no color will form on acidification. A reasonable suggestion is either oxidation at the N-ethyl function or ring addition products. Reaction at the α-C–H bond of the N-ethyl group yields a relatively stable amidinium compound. Further reaction with solvent leads to ethers, etc. Acid or even chloride ion might interfere with

this reaction, since they tie up the nonbonding nitrogen electrons and make the α hydrogens less reactive. In this case the color forming reaction has time to occur.

To check to see if it is possible to bring about the destructive reaction with LECV by adding base to the solution, the photooxidation with lophine was carried out in the presence of methanolic sodium methoxide. Even 0.1 M alkoxide ion in methanol is not sufficient to interfere with the color reaction with LECV. This must mean that, even if the equilibrium

$$DH \cdot^+ \rightleftharpoons D \cdot + H^+$$
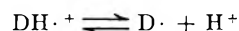
is completely to the right, the triphenylmethyl radicals will disproportionate with LECV to produce the cation. Using these same arguments for o-MLECV, it is interesting to speculate how an apparently small change in acidity can have a dramatic effect on both the rate and course of the disproportionation reaction. A tentative set of intermediates that explain these results are shown in Scheme I, p 2279.

Substituent Effects on the Reactivity of Triarylimidazolyl Free Radicals toward Tris(2-methyl-4-diethylaminophenyl)methane

ROBERT L. COHEN

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The effect of aryl substituents on the reactivity of substituted triarylimidazolyl free radicals, photolytically generated from their corresponding dimers, in an electron-exchange reaction with an aminotriphenylmethane substrate was studied by flash photolysis. The reaction rate was retarded by electron-donating substituents and enhanced by electron-withdrawing groups on the imidazolyl radical. Bulky substituents, ortho to the imidazole ring, also increased the reactivity. These results are consistent with the previously proposed mechanism for the reaction.

The preparation of 2,4,5-triphenylimidazole (lophine) was first reported in 1882.[1] In 1960, Hayashi and Maeda reported that oxidation of lophine 1 and its de-

rivatives yields dimeric products which are photo-, piezo-, and thermochromic due to the reversible formation of a colored 2,4,5-triarylimidazolyl free radical. They proposed a hydrazine-type structure 2 to account
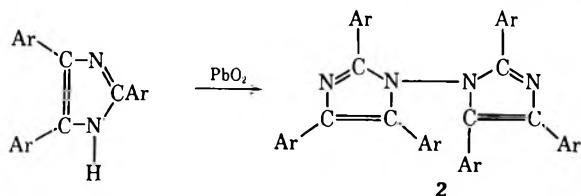
for the dimer's properties.[2] The same structure was suggested by Zimmermann and coworkers[3] who prepared a series of these compounds. On the basis of infrared spectral data, White and Sonnenberg[4] proposed that the thermally unstable dimer originally formed in the oxidation of unsubstituted lophine is the 4,4' isomer 3 which isomerizes in solution to the thermally stable 1,2' dimer 4 through the intermediacy of the free radical 5. The stable 1,2' isomer is the only dimer readily obtained on oxidation of lophines containing an

(1) (a) F. R. Japp and H. H. Robinson, *Ber.*, **15**, 1268 (1882); (b) B. Radziswewski, *ibid.*, **15**, 1493 (1882).

(2) (a) T. Hayashi and K. Maeda, *Bull. Chem. Soc. Jap.*, **33**, 565 (1960); (b) *ibid.*, **35**, 2057 (1962); (c) T. Hayashi, K. Maeda, S. Shida, and K. Nakeda, *J. Chem. Phys.*, **32**, 1568 (1960).

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(4) (a) D. M. White and J. Sonnenberg, *J. Amer. Chem. Soc.*, **88**, 3825 (1966).

ortho substituent in the 2-phenyl ring.[4,5] An X-ray crystallographic study[6] on the dimer obtained from the 2-ortho bromo substituted lophine which showed it to be the 1,2′ isomer lends further credence to this conclusion.
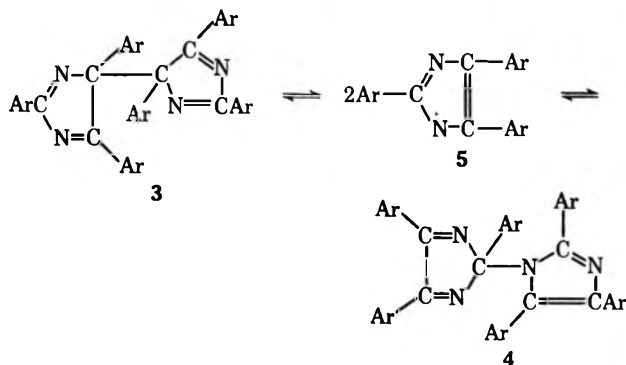
The triarylimidazolyl free radicals formed by homolytic cleavage of the respective dimers in an inert solvent will, in the absence of light, revert to a dimeric form.[5,7-9] The radicals are relatively unreactive toward molecular oxygen, vinyl monomers, aromatic hydrocarbons, and aliphatic alcohols,[10] but are converted by reducing agents such as amines and phenols to the corresponding imidazole.[3b,7,10] The effect of aryl substituents on the rate of radical dimerization has been studied.[5] In this paper, the effect of aryl substituents on the rate of the electron-exchange reaction between triarylimidazolyl radicals and an aromatic amine, tris(2-methyl-4-diethylaminophenyl)methane (6) will be discussed. This reaction has been shown to involve electron exchange at the amino nitrogen atom yielding the lophyl anion 7 and the aminium ion 8.[11]
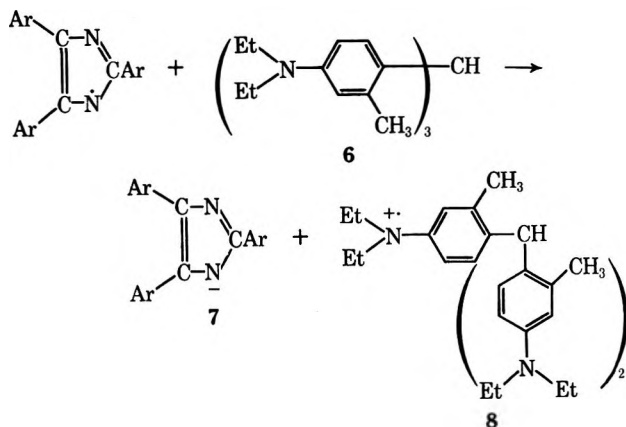
If the reaction is carried out in the presence of acid, the aminium ion reacts further to form a triarylmethane dye by a mechanistic route[11] similar to that proposed by MacLachlan for the photochemical reaction between tris(*p-N,N*-diethylaminophenyl)methane and carbon tetrachloride.[12] In the absence of acid, the condition employed in this study, no dye is formed from the tri-

(5) L. A. Cescon, G. R. Coraor, *et al., J. Org. Chem.,* **36**, 2262 (1971).

(6) G. Teufer, private communication in advance of publication.

(7) R. H. Riem, A. MacLachlan, G. R. Coraor, and E. J. Urban, *J. Org. Chem.,* **36**, 2272 (1971).

(8) (a) T. Hayashi, K. Maeda, and M. Moringa, *Bull. Chem. Soc. Jap.,* **37**, 1563 (1964); (b) T. Hayashi, K. Maeda, and M. Takeuchi, *ibid.,* **37**, 1717 (1964); (c) H. Neda, *J. Phys. Chem.,* **68**, 1304 (1964).

(9) M. A. J. Wilks and M. R. Willis, *J. Chem. Soc. B,* 1526 (1968).

(10) L. A. Cescon, G. R. Coraor, *et al., J. Org. Chem.,* **36**, 2267 (1971).

(11) A. MacLachlan and R. Reim, *ibid.,* **36**, 2275 (1971).

(12) A. MacLachlan, *J. Phys. Chem.,* **71**, 718 (1967).

Figure 1.—Reactivity of 2-ortho-substituted phenyl-4,5-diphenylimidazolyl radicals as a function of size of ortho substituent.

arylmethane, but rather the aminium ion proceeds to unidentified, noncolored products.

Results and Discussion

The triarylimidazolyl free radicals were photochemically produced from the corresponding dimers in the presence of the aminotriarylmethane and the reaction kinetics measured using flash photolysis. Imidazolyl radical decay was followed at 5480 or 3900 Å. The reaction followed first-order kinetics under the conditions employed: methanolic solutions 2×10^{-4} M in hexaarylbiimidazole and 1×10^{-3} to 2×10^{-5} M in tris(2-methyl-4-diethylaminophenyl)methane. Riem and MacLachlan[7] showed that these kinetics were actually pseudo first order when the concentration of amine is much larger than that of the photogenerated radical, as it is in this case. In a few instances, the rate and order of aminium ion appearance at 4600 Å[11] was checked against imidazolyl radical decay and good agreement was found. The true second-order rate constants for the reaction were obtained by dividing the pseudo-first-order rate constants, calculated from the observed transient half-lives, by the amine concentration. The resulting values are given in Tables I and II. The individual determinations were generally reproducible within 20%. In most cases, the rate constants for a single imidazolyl radical determined at two different amine concentrations were in good agreement. If future studies show that these second-order rate constants are responsive to imidazolyl dimer concentration, as was found by Wilks and Willis for the radical dimerization reaction,[9] then the constants presented herein would include a dimer concentration term. Since dimer concentration was held constant in this study, none of the conclusions would be changed thereby.

Substituent Effects in the 4- and 5-Phenyl Rings.—The rate constants for several series of substituted imidazolyl radicals and rate ratios using the simple 2-ortho substituted species as the standard are given in Table I. The data illustrate the effect of both electronic and steric factors on the reaction rate. Electron-donating groups on the 4- and 5-phenyl
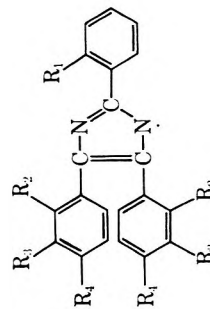
Table I

Rate of Electron Abstraction by Substituted Triarylimidazolyls

Row	R2	R3	R4	R1 = H k^a	b	$(k/k_{III})^c$	R1 = F k^a	b	(k/k_{III})	R1 = Cl k^a	b	(k/k_{III})	R1 = Br k^a	b	(k/k_{II})	R1 = NO2 k^a	b	(k/k_{II})
a	H	OCH₃	H	1.5 ± 0.2[d]	2	1.25	15.5 ± 0.5	2	1.14	32.0 ± 4.5	2	1.16	2.6 ± 0.2	3	0.08	27.5 ± 0.5	2	0.69
b	H	OCH₂CH₃	H	1.0	1	0.83				23.7 ± 0.9	3	0.86						
c	H	CH₃	H	0.5 ± 0.07	3	0.42				13	1	0.47						
d	OCH₃	H	H	0.25	1	0.21				3.4 ± 0.3	3	0.12				0.5 ± 0.1	2	0.013
e	H	H	OCH₃	0.026	1	0.022				0.27 ± 0.05	2	0.01						

^{a} Rate constant × 10^{-6} M^{-1} sec^{-1}. ^{b} Number of kinetic runs. ^{c} Rate constant for compound divided by that for corresponding 2-ortho-substituted phenyl-4,5-diphenylimidazolyls obtained from Table II. ^{d} Average deviation. $^{e\text{-}i}$ Registry no. are as follows: ^{e} 29883-67-8 (b); 29883-69-0 (c); 29883-70-3 (d); 30008-96-9 (e). ^{f} 29883-71-4 (d). ^{g} 29883-65-6 (a). ^{h} 30041-83-9 (e). ^{i} 29883-62-3 (a); 29883-66-7 (b); 29883-68-9 (c); 29969-80-0 (d); 29883-72-5 (e). ^{j} 29883-63-4 (a). ^{k} 29883-64-5 (a).

Table II

Rate or Electron Abstraction by A from Tris(2-methyl-4-diethylaminophenyl)methane

A
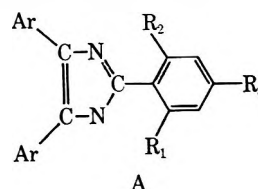
No.	Registry no.	R₁	R₂	R₃	$k \times 10^{-6}$ M^{-1} sec^{-1}	a
i	1724-47-6	H	H	H	1.2 ± 0	2
ii	29864-07-1	F	H	H	13.5 ± 0.5[b]	2
iii	29897-74-3	Cl	H	H	27.6 ± 1.8	3
iv	29898-50-8	Br	H	H	32.5 ± 1.5	2
v	29864-09-3	CH₃	H	H	1.4 ± 0.1	2
vi	29979-75-7	OCH₃	H	H	1.5 ± 0.1	3
vii	29864-10-6	OCH₂CH₃	H	H	1.1 ± 0	3
viii	29864-11-7	NO₂	H	H	40.0 ± 9.0	3
ix	29864-12-8	Cl	Cl	H	953 ± 62	3
x	29898-51-9	CH₃	CH₃	CH₃	23.5 ± 1.5	2

^{a} Number of kinetic runs. ^{b} Average deviation.

rings tend to reduce the rate of reaction with the amine, a finding consistent with the electron-exchange mechanism proposed by MacLachlan and Reim.[11]

The tenfold decrease in reactivity between the ortho and para methoxy substituted compounds shows the influence of steric factors on the reaction rate. There are two steric factors which combine to produce the rate difference observed. Forced rotation of both the 4- and 5-phenyl rings out of the imidazole ring plane because of the bulk of the ortho substituents tends to reduce conjugation with the imidazole ring. This steric inhibition of resonance acts to increase the reactivity of the ortho relative to the more stable para substituted free radicals. The forced rotation of the 4- and 5-phenyl rings also further facilitates the close approach of the aminotriarylmethane in the plane of the imidazolyl ring, thus promoting the electron-transfer reaction.

Substituent Effects in the 2-Phenyl Ring.—Substituents on the 2-phenyl ring of the imidazolyl radical also influence its reactivity by electronic and steric effects, as shown in Table II. The latter factor is particularly important because of this ring's ability to be completely coplanar with the imidazole ring when unsubstituted, and its tendency, as shown by molecular models, to twist out of plane when ortho substituted. The 4- and 5-phenyl rings cannot both be coplanar with the imidazole nucleus at the same time, even when unsubstituted.[13]

In the series of 2-ortho halogen substituted radicals, the rate of reaction with the amine increases as a linear function of the substituent's van der Waals radius (Figure 1). In view of the similarity of the polar effects exerted by the halogens from the ortho position,[14] this relationship exemplifies the steric acceleration of the electron-exchange reaction which results when the imidazole ring is exposed to close approach of the aminotriarylmethane because of forced rotation of the 2-phenyl ring. The electrical influence of the substituent on the rate is seen if one tries to extend the relationship found for the halogens to electron-supplying substit-

(13) M. A. J. Wilks and M. R. Willis, *J. Phys. Chem.*, **72**, 4717 (1968).

(14) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 590.

TABLE III
2-SUBSTITUTED ARYL-4,5-DIPHENYLIMIDAZOLES AND DIMERS[a]

2-Phenyl substituent	Registry no.	Recrystn solvent	% yield	Mp, °C	λ_{max}, mμ	Source
p-F						b
	29864-14-0	EtOH·H₂O	78	139–165		c
p-CH₃						b
	29864-15-1	PhH–PE	62	114–125		c
p-CH₃O						b
	7292-18-4	EtOH	87	169–200		c
p-EtO	5496-42-4	EtOH	97	168–169	232 310	c
	29864-18-4	EtOH·H₂O	76	138–154		c
o-NO₂	29864-19-5	Acetone–EtOH	94	233–234	292	c
	29864-20-8	PhH–PE	78	219–220[d]		c
o,o'-Cl₂	29864-21-9	EtOH	95	230–231	220	c
	29859-94-7	PE	74	210–225[f]		e

[a] For each pair of compounds, the properties of the imidazole are listed first, followed by those of the corresponding dimer. Satisfactory combustion analytical data (±0.4%) were provided for all of the compounds of this table: Ed. [b] Described in ref 9. [c] Prepared and kindly donated by Drs. L. A. Cescon and R. Dessauer. [d] Mol wt calcd 681; found 653. [e] Prepared and kindly donated by E. Urban. [f] Mol wt calcd 1458; found 1360 (tetramer).

sluggish reactivity is observed for radicals substituted with electron-supplying alkoxy groups at the ortho position of the 2-phenyl ring (IIvi, vii). The strongly electron-withdrawing nitro group, which has a smaller effective size than chlorine on the basis of rates of racemization of hindered biphenyls,[15] promotes the electron-exchange reaction at a rate even faster than bromine.

These data suggest that imidazolyl radicals substituted in both ortho positions of the 2-phenyl ring with fairly large electron-withdrawing substituents would be particularly reactive toward an electron donor. This prediction was borne out by the determination of a second-order rate constant of 9.5×10^8 M^{-1} sec^{-1} for the reaction of di ortho chloro substituted radical IIii with the aminotriarylmethane. Addition of the second ortho chloro substituent increased the reaction rate by a factor of 35 compared with the mono ortho chloro substituted radical. Species IIix showed the greatest reactivity of any of the free radicals examined and, in fact, reacted 30,000 times faster than the most sluggish radical, 2-phenyl-4,5-bis(p-methoxyphenyl)imidazolyl (IIix). In this case, both steric and electronic factors

TABLE IV
SUBSTITUTED TRIARYLIMIDAZOLES AND DIMERS[a]

Registry no.	2-Phenyl substituent	4- and 5-phenyl substituent	Recrystn solvent	% yield	Mp, °C	λ_{max}, mμ	Source
29864-22-0	H	m-CH₃O	EtOH	82	188–189	307	b
29864-23-1			PhH–PE[f]	85	105–110		b
29969-82-2	H	m-EtO	EtOH	92	180–181	223	b
29864-24-2			EtOH–H₂O	81	110–120		b
29864-25-3	H	m-CH₃	THF–EtOH	72	261–262	308	b
29969-83-3			PE	94	156–157		b
29864-26-4	H	o-CH₃O	EtOH	91	175.5–176.5	307	c
29864-27-5			PhH–PE	86	134–150		b
7044-99-7	H	p-CH₃O	PhH	99	197.5–198	298	c
30041-84-0			EtOH–H₂O	51	147–155		c
29864-29-7	o-F	m-CH₃O	EtOH	97	142.5–143.5	306	d
29864-30-0			PhH–PE	98	110–112		d
29864-31-1	o-Cl	m-CH₃O	MeOH	85	135–136.5	303	e
29864-32-2			EtOH	81	175–178.5		e
29864-33-3	o-Cl	m-EtO	EtOH	87	135.5–137.5		e
29864-34-4			EtOH	75	151–151.5		e
29864-36-6	o-Cl	m-CH₃	EtOH	79	158–159	233	b
29864-35-5			PhH–PE	99	133–135		b
30041-85-1	o-Cl	o-CH₃O	EtOH	98	118–119	312	b
29864-37-7			PhH–PE	93	135–165		b
29864-38-8	o-Cl	p-CH₃O	EtOH	92	136–137	293	b
29969-84-4			PhH–PE	90	157–158		b
29864-39-9	o-Br	o-CH₃O	EtOH	78	124–125	309	d
29864-40-2			PhH–PE	85	133–135		d
29864-41-3	o-NO₂	m-CH₃O	EtOH	69	188–190		e
29864-42-4			MeCl₂–PE	94	124–134		e
29864-43-5	o-NO₂	p-CH₃O	PhH–PE	70	169–170	290	e
29864-44-6			PhH–PE	66	165–167		e

[a] For each pair of compounds, the properties of the imidazole are listed first, followed by those of the corresponding dimer. Satisfactory combustion analytical data (±0.4%) were provided for all of the compounds of this table: Ed. [b–d] Prepared and kindly donated by [b] E. Urban; [c] Drs. L. A. Cescon and R. Dessauer; [d] Dr. W. M. Hardham. [e] Prepared by author. [f] Petroleum ether, bp 30–60°.

uents. The methyl-substituted radical (IIv) reacts only slightly faster than the unsubstituted one (IIi) even though the van der Waals radius for methyl is approximately the same as that for bromine. Similarly,

work together to produce an extremely potent radical with respect to electron abstraction.

(15) E. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 160.

As a further check on the importance of steric effects in the 2-phenyl ring, the reaction rate of 2-mesityl-4,5-diphenylimidazolyl (IIx) was measured and compared with that for 2-o-tolyl-4,5-diphenylimidazolyl (IIv). If steric considerations were important, the former compound should react faster, while, if the electronic effect of the methyl groups were the primary determinant of the rate, the latter compound would be the more reactive. The rate constant for the mesityl compound is $2.35 \times 10^7 M^{-1} sec^{-1}$, some 17 times greater than that for the ortho methyl substituted radical. This difference is probably a lower limit, since the steric effect of the ortho methyl groups in the mesityl compound is negated somewhat by the electronic effect of that radical's para methyl substituent.

It is interesting to note that, whereas ortho disubstitution in the 2-phenyl ring tends to increase the imidazolyl radical's reactivity toward electron abstraction, it decreases its dimerization rate.[16] These two phenomena have the same basic cause. The formation of the thermally stable 1,2' isomer is severely hindered in a ortho disubstituted radical with the 2-phenyl ring preferring a conformation nearly perpendicular to the imidazole ring plane. In this conformation, the ortho substituents on the 2-phenyl ring lie above and below the carbon at position two, effectively shielding it from bond formation with a second radical's imidazole nitrogen. Thus, the same steric factor which tends to make im-

idazole radicals more reactive toward electron abstraction also makes them more resistant to dimerization.

Experimental Section

(16) Unpublished data, R. L. Cohen.

(17) G. Porter, *Proc. Roy. Soc., Ser. A,* **200,** 284 (1950).

Substituent Effects on the Basicity of Pyridine. Elucidation of the Electronic Character of β-Substituted Vinyl Groups

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Pyridines substituted in the 3 and 4 positions by groups -CH=CHX, where X = NO$_2$ (only the 3-substituted compound), CN, CHO, COCH$_3$, COOC$_2$H$_5$, COC$_6$H$_5$, COC$_6$H$_4$NO$_2$, have been synthesized and their pK_a values measured. The correlation of pK_a values of substituted pyridines with the Hammett equation is discussed, with particular regard to the above substituents. Also prepared were *m*- and *p*-vinylbenzoic acids, and substituent constants for the vinyl group of 0.08 (σ_m) and -0.08 (σ_p) have been established.

Halogeno substituents are well known for their ability to direct electrophilic attack at the positions ortho and para to their point of attachment to a benzene ring, but reducing the rate of attack below that of benzene itself. This is attributed in simple terms to the opposing influence of the mutually independent inductive and resonance effects. A similar situation arises in the case of the β-nitrovinyl substituent and other substituents made up of attachment of a group of $-I$ or ($-I$, $-M$) character to the β position of the vinyl group. Thus Truce and Simms[2] found only 2% of meta nitration in β-styryltrimethylammonium picrate, while Baker and Wilson, Underwood and Kochmann, and Bordwell and Rohde obtained analogous results with β-nitrostyrene,[3] cinnamic acid,[4,5] and

β-styrenesulfonyl chloride.[5] The latter workers also demonstrated correspondence between the rate of nitration of such compounds and that of chlorobenzene. These and other workers[6,7] have consequently likened the electronic character of such substituents to that of the halogens, while at the same time remarking on the apparent high energy of the canonical form I

I
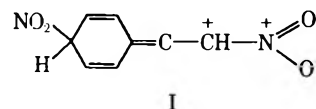
involving adjacent positive charges of the Wheland intermediate resonance hybrid for para nitration of β-nitrostyrene.

Stewart and Walker[7] have also measured the dissociation constants for the *m*- and *p*-β-nitrovinyl derivatives of benzoic acid and thus shown that the σ_m and σ_p

(1) Munton and Fison Ltd., Stowmarket, Suffolk, England.

(2) W. E. Truce and J. A. Simms, *J. Org. Chem.,* **22,** 762 (1957).

(3) J. W. Baker and I. S. Wilson, *J. Chem. Soc.,* 842 (1927).

(4) H. W. Underwood and E. L. Kochmann, *J. Amer. Chem. Soc.,* **48,** 254 (1926).

(5) F. G. Bordwell and K. Rohde, *ibid.,* **70,** 1191 (1948).

(6) L. N. Ferguson, *J. Chem. Educ.,* **32,** 42 (1955).

(7) R. Stewart and L. G. Walker, *Can. J. Chem.,* **35,** 1561 (1957).

values are closely similar to those for iodine. The implication of this interesting result is that the conjugation of the nitro group with the double bond is far weaker than expected. Thus, despite the fact that the substituent is no longer joined to a nucleus in the transition state of electrophilic substitution, and thus bears a positive charge in conjugation with it, the substituent still acts overall as of $(-I, +M)$ rather than $(-I, -M)$ character.

We were therefore prompted to extend the determination of σ values to other groups of potentially the same electronic character to see if this behavior was general. It was apparent, however, that the range of values encompassed by such groups would be small compared with the overall extent of σ values. It thus seemed necessary to carry out measurements using a reaction site which gave a good correlation with σ, but had a large ρ value. A suitable system appeared to be the pyridinium ion–pyridine equilibrium which in water has a sixfold greater sensitivity than the benzoic acid system to substituent effects.[8]

Compounds **2**, **3**, and **4** were generally prepared by base-catalyzed condensation between 2-, 3-, or 4-pyridinecarboxaldehyde and CH_3X; the majority of these compounds had been prepared previously. *p*- (**5a**) and *m*-vinylbenzoic acids (**5b**) were also prepared.

a, X = NO$_2$	**d**, X = COCH$_3$	**f**, X = COC$_6$H$_5$
b, X = CN	**e**, X = COOC$_2$H$_5$	**g**, X = COC$_6$H$_4$NO$_2$
c, X = CHO		
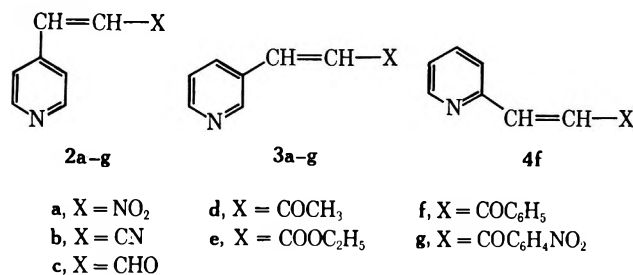
Experimental Section

Melting points were uncorrected. Infrared spectra were measured on a Perkin-Elmer 257 grating spectrometer. Nmr spectra were taken on a Perkin-Elmer R12 60-MHz spectrometer, using tetramethylsilane as a standard. Peaks were integrated and the proton assignments indicated in all cases corresponded to the areas thus measured. The choice of solvents was dictated by ease of solution and convenience, as no systematic correlation or complex interpretation was intended; the sole purpose of the nmr measurements was for authentication of the compounds. Mass spectra were taken with a Hitachi Perkin-Elmer RMU-6E spectrometer operating with an ionization energy of 70 eV.

Pyridine and 4-vinylpyridine were commercial samples. They were distilled under reduced pressure just before use.

Compounds **2b**,**d–g** and **3a–g** and the Michael addition product from **2f** were obtained by literature methods.[9,10] Yields and melting points were in agreement with previous workers. Nmr spectra of all the compounds were run, generally in CF$_3$COOH, and in all cases the proton assignments were compatible with the proposed (trans) structures.

(8) A. Fischer, W. J. Galloway, and J. Vaughan, *J. Chem. Soc.*, 3591 (1964).

(9) C. S. Marvel, L. E. Coleman, and G. P. Scott, *J. Org. Chem.*, **20**, 1785 (1955).

(10) J. Klosa, *Arch. Pharm. (Weinheim)*, **289**, 177 (1956); Z. S. Ariyan and H. Suschitzky, *J. Chem. Soc.*, 2242 (1961); A. R. Katritzky and A. M. Monro, *ibid.*, 150 (1958); A. R. Katritzky, A. M. Munro, and J. A. T. Beard, *ibid.*, 3721 (1958); P. R. Falkner and D. Harrison, *ibid.*, 2148 (1962); C. S. Marvel and J. K. Stille, *J. Org. Chem.*, **22**, 1451 (1957); M. Strell and E. Kopp, *Chem. Ber.*, **91**, 162 (1958); A. Dornow and F. Boberg, *Justus Liebigs Ann. Chem.*, **578**, 101 (1952); M. Strell and E. Kopp, *Chem. Ber.*, **91**, 2854 (1958).

4-β-Formylvinylpyridine[11] (**2c**).—4-Pyridinecarboxaldehyde (15.0 g) was dissolved in water (25 ml) containing Amberlite IR-4B (OH) ion-exchange resin (10.0 g). Acetaldehyde (8 ml) in water (20 ml) was added with stirring over 20 min. A yellow precipitate was formed which persisted until the temperature of the solution was raised to 50°. A further addition of acetaldehyde (3 ml) in water (10 ml) was made and the dark brown solution stirred at 40° for 5 hr. The solution was allowed to stand overnight at 25° and then was extracted twice with chloroform (two 100-ml portions). The solvent layer was dried (anhydrous Na$_2$SO$_4$) and the solvent removed on a rotary evaporator. The resulting brown liquid was distilled at reduced pressure giving unreacted 4-pyridinecarboxaldehyde (5.5 g). The residue was refluxed for 30 min with *n*-hexane (100 ml) and the hexane layer was decanted. On long standing, it deposited white needles of **2c** (0.07 g, 0.6%), mp 39–41°. *Anal.* Calcd for C$_8$H$_8$NO: C, 72.17; H, 5.30; N, 10.52. Found: C, 71.89; H, 5.34; N, 10.51.

The mass spectrum showed *m/e* (M$^+$) 133. The ir spectrum showed peaks at 1684 (C=O), 1632, 980 cm^{-1} (trans C=C); nmr (CCl$_4$) τ 0.49 (d, *J* = 7 Hz, CHO), 1.53 (m, 2 and 6 H), 2.77 (m, 3 and 5 H and α-vinyl H), 3.35 (two d, *J* = 17 and 7 Hz, β-vinyl H).

***m*-Vinylbenzoic Acid (5b).**—Isophthalaldehydic acid (20 g prepared by the method of Landgrebe and Rynbrandt[12a]) was dissolved in anhydrous ethanol (50 ml) saturated with dry HCl, and the solution was refluxed for 4 hr while HCl was bubbled in. The ethanol was evaporated, water added (20 ml), and the solution extracted with ether. The ethereal solution was dried (anhydrous Na$_2$SO$_4$), the ether removed, and the ethyl isophthalaldehydate distilled, bp 122–124° (6 mm) (15.4 g, 71%).

The formyl was converted to the vinyl group by the Wittig reaction. Triphenylphosphonium methyl bromide (40 g) in benzene (100 ml) was refluxed for 4 hr with sodium hydride (9.2 g of 50% in liquid paraffin), and the resulting yellow suspension was refluxed for a further 6 hr with ethyl isophthalaldehydate (10 g). The cold mixture was then poured into water (100 ml) and extracted with benzene. The benzene was removed, leaving an orange solid and a pale green oil. The oil was removed and distilled, bp 82–84° (2 mm) (1.30 g, 12%).

The ethyl *m*-vinylbenzoate (0.2 g) was refluxed for 6 hr with ethanol (0.5 ml), water (3 ml), and NaOH (1 g). The solution was acidified with dilute HCl and the resultant solid filtered off. Recrystallization from water gave white platelets, mp 92–94° (0.15 g, 82%) (lit.[12b] mp 95–96°).

The mass spectrum showed *m/e* (M$^+$) 148. The ir spectrum gave bands at 3000 (strong and very broad, OH), 1700 (strong, C=O), and 1610 cm^{-1} (weak, C=C); nmr (CCl$_4$) τ −3.0 (s, OH), 1.85 and 2.40 (m, 2, 4, 5, and 6 H), 3.12 (q, *J*$_{trans}$ = 17, *J*$_{cis}$ = 11 Hz, C$_6$H$_4$CH), 4.10 (d, *J*$_{trans}$ = 17 Hz, –C$_6$H$_4$-CH=CH–). Both the latter doublets showed fine splitting (∼1 Hz) due to gem coupling.

***p*-Vinylbenzoic Acid (5a).**—The method of preparation was that of Jäger and Waight.[13] The product was recrystallized from water to yield white crystals, mp 144° (lit.[13] 140°). The ir spectrum agreed with that of Jäger and Waight; nmr (CF$_3$COOH, obscuring acidic proton) τ 1.87 (d, *J* = 8 Hz, 2 and 6 H), 2.45 (d, *J* = 8 Hz, 3 and 5 H), 3.15, 4.09, and 4.55 (vinyl H's with coupling characteristics identical with those of the *m*-vinyl-benzoic acid spectrum).

pK_a Determinations.—Measurements were carried out at 25° using the spectrophotometric method[14a] for all compounds except 3-β-nitrovinylpyridine where coincident free base and conjugate acid uv spectra necessitated use of the potentiometric method.[7,14b]

Uv spectra were scanned on a Perkin-Elmer Ultracord 316 spectrometer, analytical wavelengths selected, and readings at those wavelengths recorded on a Unicam SP 500 spectrometer (see Table II). Table I shows a specimen determination, 4-β-cyanovinylpyridine.

Results and Discussion

Marvel[9] has reported that the synthesis of **2f** and **4f** led also to the formation of Michael-type addition

(11) J. G. Carey, British Patent 1,198,221.

(12) (a) J. A. Landgrebe and R. H. Rynbrandt, *J. Org. Chem.*, **31**, 2585 (1966); (b) W. J. Dale, L. Starr, and C. W. Strobel, *ibid.*, **26**, 2225 (1961).

(13) P. Jäger and E. S. Waight, *J. Chem. Soc.*, 1339 (1963).

(14) A. Albert and E. P. Serjeant, "Ionisation Constants of Acids and Bases," Methuen and Co. Ltd., London, 1962: (a) Chapter 4; (b) Chapter 2.

products. Since those by-products do not arise in the preparation of **3f**, it might be conjectured that the true structures were those arising from β attack on **2f** and **4f** by a second carbanion due to mesomeric withdrawal by the pyridine ring. However, nmr studies revealed that the alternative structures **6** and **7**, as suggested by Marvel, were correct.
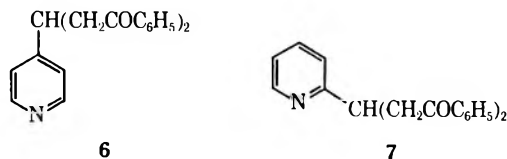
Both spectra showed a triplet at τ 5.5 (area 1) and a doublet at τ 6.0 (area 4), confirming that addition of the second carbanion from acetophenone takes place on the α carbon atoms of **2f** and **4f**.

The conversion of the pK_a's in Table II to σ values involves use of the appropriate ρ value for the pyridinium–pyridine equilibrium. Fischer and Vaughan[8] have demonstrated with a selected number of substituents (H, 3-CH$_3$, 3-Cl, 3-Br, 3-COOCH$_3$, 3-CN, and 3-NO$_2$) that this value is 6.01, and it is not sensibly altered by incorporation of their other substituents values or pK_a's from other workers (with the exception of 4-(−I, −M) groups, which are known to follow σ_I[8,15]).[16] Use of this ρ value leads to the σ values shown in Table III. These indicate that all these substituents are of (−I, +M) type. The M effect arises from the conjugation of the double bond with the aromatic ring. It is of the same order of magnitude as that of the halogens. The −I effect is variable, dependent on the degree of electron withdrawal by the inductive effect of the β-vinyl group.

(15) J. M. Essery and K. Schofield, *J. Chem. Soc.*, 2225 (1963).

(16) It is surprising that pK_a values of pyridine correlate with σ and not σ^+. Perhaps the answer lies in the fact that electron deficiency in the pyridinium ion arises in the N sp^2 orbital which is orthogonal to the p-orbital aromatic system responsible for communication of substituent resonance effects. This situation is different from that of the transition state for solvolysis of *tert*-cumyl chlorides, where the deficit occurs in a p orbital overlapping with the aromatic system, or for electrophilic substitution, where it arises directly in the p orbitals whose interaction is responsible for aromaticity in the ground-state molecule. Some support is given for this from the work of Blanch[17] and Miller.[18] The reaction rate of 4-chloropyridine with sodium methoxide affords a σ^- value for the substituent **10** of 2.32. The σ value for **11** from the ionization of 4-pyridinecarboxylic acid is 2.34;

clearly in this case the positive nitrogen cannot avail itself of additional resonance interaction with excess of negative charge. Conversely, however, the second pK_a's of 3- and 4-aminopyridine do reveal an exalted value in the second case, 4.0.[19]
Moreover this reasoning would suggest that, while the correlation of the pK_a's of pyridine N-oxides[20] with σ^- is explicable in that the system is isoelectronic with phenolate anion, that with σ^+ is not. This latter anomaly might be clarified by further quantitative experiments involving electrophilic reaction at the oxygen atom of such compounds, and incorporation of data in an equation of the Yukawa-Tsuno type[21]

$$\log k/k_0 = \rho[\sigma + r(\sigma^+ - \sigma)]$$

Thus, it is noteworthy that the latter workers report a value of r of 0.55 rather than ~1 for the σ^+ correlation with pK_a values of pyridine N-oxides. Clearly there is much that is not yet fully understood in the application of Hammett-type equations to heteroaromatic systems.
(17) J. H. Blanch, *J. Chem. Soc. B*, 937 (1966).
(18) M. Liveris and J. Miller, *ibid.*, 3486 (1963).
(19) H. H. Jaffé and H. Lloyd Jones, *Advan. Heterocycl. Chem.*, **3**, 209 (1964).
(20) H. H. Jaffé, *J. Org. Chem.*, **23**, 1790 (1958).
(21) Y. Yukawa, Y. Tsuno, and M. Sawada, *Bull. Chem. Soc. Jap.*, **39**, 2274 (1966).

TABLE I

DETERMINATION OF THE pK_a VALUE OF
4-β-CYANOVINYLPYRIDINE[a]

λ, nm	pH	Optical density d	Log $(d_m - d)/(d - d_i)$	pK_a
255	3.45	0.448	0.66	4.11
	3.78	0.466	0.36	4.14
	4.00	0.480	0.12	4.12
	4.25	0.503	−0.11	4.14
	4.60	0.529	−0.46	4.14
	4.85	0.546	−0.79	4.06
	5.15	0.552	−1.06	4.09
270	3.60	0.538	0.53	4.13
	3.90	0.498	0.15	4.05
	4.15	0.468	−0.09	4.06
	4.40	0.442	−0.31	4.07

pK_a 4.10 ± 0.05

[a] Stock solution, 1.50×10^{-3} M in 1% aqueous ethanol (for other compounds stock solution concentrations of up to 25% aqueous ethanol were used, but in all cases analytical solutions contained no more than 1% ethanol); analytical solution, 1.50×10^{-4} M; buffer, 0.01 M acetic acid–0.01 M sodium acetate; analytical wavelengths, 255 and 270 nm; optical density of free base (d_m), 0.566 (255 nm), 0.370 (270 nm); conjugate acid (d_i), 0.422 (255 nm), 0.588 (270 nm).

TABLE II

pK_a DETERMINATIONS

Compd	λ_{max}, nm FB[a]	λ_{max}, nm CA[b]	Method of pK_a detn[c]	Analytical wavelengths, nm	pK_a, 25°
Pyridine	253	255	S	245, 255	5.14[d]
			P		5.13[d]
3f	286	275	S	275, 310	4.05
2f	250	252	S	250	4.83
3g	275	283	S	285	4.25
2g	278	283	S	280, 285	4.82
3e	258	254	S	225	4.02
2e	259	271	S	230, 270	4.96
3d	272	262	S	275, 285	3.88
2d	263	257	S	225	5.19
3b	258	255	S	210, 220, 225, 230	3.69
2b	258	269	S	255, 270	4.10
3a			P		3.44
3c	290	266	S	285, 295	3.71
2c	267	274	S	250, 255, 285	4.33
4-Vinylpyridine	242	265	S	230	5.61
5b	223	222	S	230, 235	4.13
5a	266	271	S	275, 280, 285, 290	4.29
			P		4.34[e]

[a] Free base. [b] Conjugate acid. [c] S, spectrophotometric; P, potentiometric. [d] These values are well within the range reported by other workers; see A. Pietryzyk, R. Wiley, and D. McDaniel, *J. Org. Chem.*, **22**, 83 (1957). [e] Considered less accurate than spectrophotometric determination.

This description may well be the *only* conclusion of genuine significance which can be attached to the results. Nevertheless, it is tempting to define these interactions by a further dissection of the σ values, even if there is some controversy and doubt regarding the validity of such a process,[22] particularly in this case where only a small range of substituent effects is being considered.

(22) See in particular M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill, New York, N. Y., 1969, p 421.

TABLE III
HAMMETT SUBSTITUENT CONSTANTS

Substituent /\ \X	σ^a	σ_I (arom)[b]	σ_I (nmr)[b]
3-CH=CHCOC$_6$H$_5$	0.18	0.30[f]	0.20[h]
4-CH=CHCOC$_6$H$_5$	0.05		
3-CH=CHCOC$_6$H$_4$NO$_2$	0.15		
4-CH=CHCOC$_6$H$_4$NO$_2$	0.05		
3-CH=CHCOOC$_2$H$_5$	0.19	0.34	0.21
4-CH=CHCOOC$_2$H$_5$	0.03		
3-CH=CHCOCH$_3$	0.21	0.32	0.23
4-CH=CHCOCH$_3$	−0.01		
3-CH=CHCN	0.24	0.52	0.53
4-CH=CHCN	0.17		
3-CH=CHNO$_2$	0.28, 0.32[c]	0.68	0.60
4-CH=CHNO$_2$	0.26[c]		
3-CH=CHCHO	0.24	0.33[g]	0.31
4-CH=CHCHO	0.13		
3-CH=CH$_2$	0.08,[d] 0.05[e]	0.00	0.00
4-CH=CH$_2$	−0.08,[d] −0.08, −0.08[e]		

[a] Calculated using $\rho = 6.01$, log $K_0 = 5.14$. [b] Taken from Table I, ref 26. [c] Reference 7. [d] Calculated using $\rho = 1.00$, log $K_0 = -4.21$. [e] See reference in footnote d, Table II. [f] Calculated from $\sigma_m = 0.34$, $\sigma_p = 0.43$: W. N. White, R. Schlitt, and D. Gwynn, *J. Org. Chem.*, 26, 3613 (1961). [g] Calculated from $\sigma_m = 0.36$, $\sigma_p = 0.43$: A. A. Humffray, J. J. Ryan, J. P. Warren, and Y. H. Yung, *Chem. Commun.*, 610 (1965). [h] R. G. Pews, Y. Tsuno, and R. W. Taft, *J. Amer. Chem. Soc.*, 89, 2391 (1967), for methylene chloride solvent; the others are for weakly protonic solvents.

The most generally used procedure is that of Taft,[23] who considers that σ values may be parameterized into inductive and resonance components according to the equations

$$\sigma_m = \sigma_I + \alpha \sigma_R \quad (1)$$

$$\sigma_p = \gamma \sigma_I + \sigma_R \quad (2)$$

Theoretically very similar procedures involving the basic assumption of additivity of mutually independent inductive and resonance effects have been proposed by Yukawa and Tsuno[21] and Swain and Lupton.[24] Equations 1 and 2 have been employed in Table III for evaluation of σ_I values for CHO and COC$_6$H$_5$, using $\gamma = 1$ and $\gamma = 0.29$.

Corresponding application of these equations to the *m*- and *p*-vinylbenzoic acid pK_a values (Table III), taking the value for σ_m as 0.08, yields $\sigma_I = 0.15$ and $\sigma_R = -0.23$ for the vinyl substituent. These results may be compared with those for the ethynyl group ($\sigma_I = 0.20$, $\sigma_R = +0.03$) which is thus seen to have a similar electron-withdrawing capacity by induction, but a negligible resonance interaction.[11,25]

Equations 1 and 2 may be modified to (3) and (4) to accommodate the effect of the substituent considered here on the pyridinium ion–pyridine equilibrium

$$\sigma_m = \sigma_I/\beta(\beta \text{ substituent X}) + \sigma_I(\text{vinyl}) + \alpha \sigma_R(\text{vinyl}) \quad (3)$$

$$\sigma_p = (\gamma/\beta)\sigma_I(\beta \text{ substituent X}) + \sigma_I(\text{vinyl}) + \sigma_R(\text{vinyl}) \quad (4)$$

assuming the vinyl group contributes a constant + M effect independent of the variable −I effect of the β

(23) R. Taft, *J. Phys. Chem.*, **64**, 1805 (1960).
(24) C. G. Swain and E. C. Lupton, *J. Amer. Chem. Soc.*, **90**, 4328 (1968).
(25) C. Eaborn, A. R. Thompson, and D. R. M. Walton, *J. Chem. Soc. B*, 859 (1969).
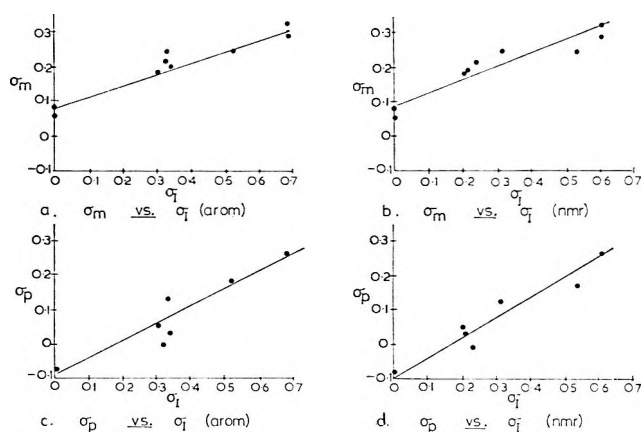
Figure 1.—Correlation of σ (CH=CHX) with σ_I (X).

substituent, X. The σ_I values are taken from Ritchie and Sager's compilation.[26] A list of three different σ_I values are given arising from various modes of estimation, although all generally are similar for a given substituent as theory demands. However, the values are sufficiently different to enable improvement of a correlation by a judicious selection, a difficulty often arising with the use of modified forms of the Hammett equation, particularly when dealing with a set of effects of limited range as here. We have chosen to use σ_I(arom), because these values can be calculated from σ_m and σ_p values as described previously (see Table III), together with σ_I(nmr).

From eq 3, a plot of σ_m against σ_I for the β substituent should be a straight line of slope β^{-1}. Figure 1a shows such a plot, which gives a straight line of correlation coefficient (r) 0.9585, "satisfactory."[27] The value of β^{-1} is a measure of the reduction factor involved in transmission of the inductive effect of the β substituent through the double bond. This has been given previously as 0.21;[7] the value here is 0.34. The equivalent plot using σ_I(nmr) values has slope 0.35 ($r = 0.9331$ "fair,"[27] Figure 1b).

The value for γ in eq 4, the factor by which the effect of induction varies between the meta and para positions, is usually taken as unity. From (4), a plot of σ_p vs. σ_I should thus be a straight line and have the same slope as the plots in Figure 1a and b passing through the y axis at the σ_p value for vinyl. The straight-line correlation of σ_p vs. σ_I(arom) (Figure 1c) has a slope of 0.51, $r = 0.9248$ "fair,"[27] which becomes 0.54, $r = 0.9567$, "satisfactory,"[27] when σ_I(nmr) values are used (Figure 1d).

The correlation of the σ_m and σ_p values to eq 3 and 4 is thus by no means precisely quantitative, but perhaps it is not too optimistic to say that the measure of correlation is encouraging and probably as good as can be expected considering the overall small range of the substituent effects considered, the theoretical approximations involved, and experimental errors.

The discrepancy between the predicted slope, 0.3, and that calculated, 0.5, for eq 4 could arise from a value of γ greater than unity, a circumstance which has been argued for by Exner[28] for benzenoid systems, but

(26) C. D. Ritchie and W. F. Sager *Progr. Phys. Org. Chem.*, **2**, 323 (1964).
(27) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953); however, see J. Shorter, *Chem. Brit.*, **4**, 269 (1968).
(28) O. Exner, *Collect. Czech. Chem. Commun.*, **31**, 65 (1966).

considered unlikely by other groups of workers[24,29] because it places undue emphasis on the I_{π} effect. Indeed, Swain and Lupton[24] believe the value should be less than 1, which is certainly true for the correlation of pK_a values[8] and rates of quaternization of substituted pyridines.[30] As already noted, Fischer and Vaughan have shown that electron-withdrawing groups of potential $(-I, -M)$-type exert only a $-I$ effect in these series, a conclusion amply supported by the work of Schofield,[15] and yet all such groups have a different effect depending on whether they occupy the 3 or 4 position (Table IV).

Another explanation of the increased slope of the σ_p correlation could be a competition between the pyridinium nucleus and the β-vinyl substituent for the π electrons of the double bond, which the former always wins but in varying degrees, so that the assumption of a *constant* negative σ_R(vinyl) value in eq 3 and 4 is incorrect. However, σ_R^0 measurements for the β substituents[31] (NO$_2$, $\sigma_R^0 = 0.17$; CN, 0.09; COOEt, 0.18; COCH$_3$, 0.22; CHO, 0.24; COC$_6$H$_5$, 0.19) show

that the $-M$ effect is not proportional to the $-I$ effect for such substituents. Thus to explain the different slope by this phenomena would involve postulation of interaction between the resonance effect of the vinyl group and the inductive effect of the β substituent, a type of interaction previously suggested[31] and also implicitly assumed,[32] but not widely considered, the mutual independence of M and I effects being the general basis for dual substituent parameter correlations.

Stewart and Walker[7] have measured σ_p^- for the β-nitro vinyl group; it is 0.88. Clearly, for this substituent, and presumably for the others studied here, the $-M$ effect of the β substituent fully reasserts itself as expected when conjugation with excess of electronic charge is possible. Thus, these groups fall into the small category of those that have both σ^+ and σ^- values significantly different from σ. The sign of the σ_R^0 values of such groups, measured as 0.13 for CH=CHNO$_2$ and 0.10 for CH=CHCOOH,[31] therefore appears to be in some doubt.

(29) R. T. C. Brownlee, R. E. J. Hutchinson, A. R. Katritzky, T. T. Tidwell, and R. D. Topsom, *J. Amer. Chem. Soc.*, 90, 1757 (1968).

(30) A. Fischer, W. J. Galloway, and J. Vaughan, *J. Chem. Soc.*, 3596 (1964).

(31) A. Fischer, D. A. R. Happer, and J. Vaughan, *ibid.*, 4060 (1964).

(32) D. W. Farlow and R. B. Moodie, *J. Chem. Soc.*, B, 334 (1970).

Mechanisms of Substitution Reactions at Sulfinyl Sulfur.   VI. The Kinetics of the Reaction of Mercaptans with Aryl Sulfinyl Sulfones[1]

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The kinetics of the reaction of n-butyl mercaptan with p-toluenesulfinyl p-tolyl sulfone (1a) in 60% dioxane containing 0.001-0.40 M perchloric acid have been investigated. In the region 0.001-0.01 M HClO$_4$, reaction of n-BuS$^-$ with 1a is an important contributor to the rate. At higher acidities the only important contributor to the rate is a reaction between the undissociated mercaptan and 1a. Reaction of n-BuSH with 1a is not subject to significant acid catalysis, in marked contrast to the butyl sulfide catalyzed hydrolysis of 1a where nucleophilic attack of n-Bu$_2$S on 1a occurs only if there is accompanying acid catalysis. This difference in the behavior of n-BuSH and n-Bu$_2$S provides evidence of the probable correctness of the explanation advanced earlier[3] for why acid catalysis is necessary in the sulfide-catalyzed hydrolysis but not in the ordinary hydrolysis of 1a.

In acidic aqueous dioxane the hydrolysis of aryl sulfinyl sulfones (eq 1) can be markedly catalyzed by the

$$\underset{\underset{O}{\parallel}}{\overset{\overset{O}{\parallel}}{ArS}}-\underset{\underset{O}{\parallel}}{\overset{}{SAr}} + H_2O \longrightarrow 2ArSO_2H \qquad (1)$$

1

addition of small concentrations of alkyl sulfides such as n-butyl sulfide.[3] While the ordinary hydrolysis of 1 under these conditions is *not* subject to acid catalysis, *i.e.*, rate $= k_h(1)$, the sulfide-catalyzed hydrolysis occurs *only* with acid catalysis, *i.e.*, rate $= k_s(H^+)(R_2S)$-(1). To explain this difference in behavior it was suggested[3] that uncharged nucleophiles like H$_2$O and R$_2$S are unable to displace sulfinate ion (ArSO$_2^-$) as such from 1. In the sulfide-catalyzed hydrolysis (eq 2), if R$_2$S is to effect a substitution on the sulfinyl group of 1,

(1) (a) This research was supported by the National Science Foundation, Grant GP-10732X. (b) Preceding paper in this series: J. L. Kice and G. Guaraldi, *J. Org. Chem.*, 33, 793 (1968).

(2) Department of Chemistry, University of Vermont, Burlington, Vt. 05401.

(3) J. L. Kice and G. Guaraldi, *J. Amer. Chem. Soc.*, 89, 4113 (1967).

$$R_2S + ArS\!-\!SAr + H_3O^+ \xrightarrow[\text{determining}]{\text{rate}}$$

$$\left[R_2S^{\delta+}\text{-}\text{-}\text{-}\underset{Ar}{S}\text{-}\text{-}\text{-}\underset{Ar}{S}\text{-}O\text{-}\text{-}\text{-}H\text{-}\text{-}\text{-}^{\delta+}OH_2 \right] \longrightarrow$$

$$\text{transition state}$$

$$R_2\overset{+}{S}SAr + ArSO_2H + H_2O \quad (2)$$

$$\downarrow \text{H}_2\text{O} \quad \text{fast}$$

$$R_2S + ArSO_2H + H^+$$
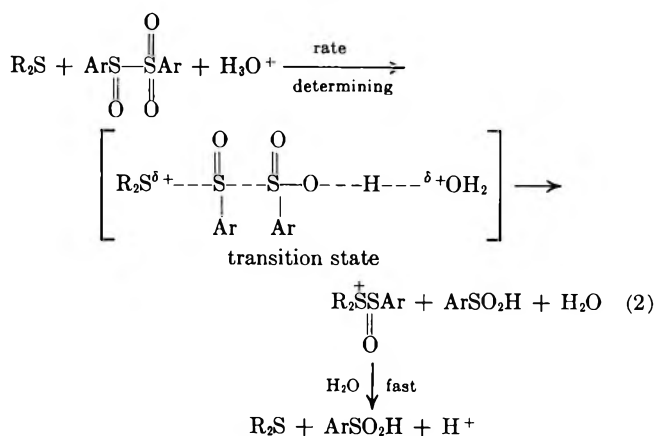
a proton must be transferred to the $ArSO_2$ group coincident with the scission of the $S(O)\!-\!SO_2$ bond, so that the $ArSO_2$ group is displaced as $ArSO_2H$.[4] In the ordinary hydrolysis, on the other hand, where water is the attacking nucleophile, the attacking water molecule itself can supply the proton required by the departing $ArSO_2$ group, either *via* a mechanism (eq 3) in which this pro-

$$H_2O + H_2O + ArS\!-\!SAr \rightleftharpoons ArS\!-\!\!-\!SAr + H_3O^+ \longrightarrow$$

$$ArSO_2H + ArSO_2H + H_2O \quad (3)$$
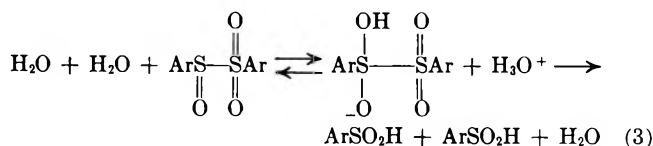
ton is first transferred to another water molecule and then transferred in a second step from there to the $ArSO_2$ group or *via* a mechanism (eq 4) where this same

$$H_2O + H_2O + ArS\!-\!SAr \longrightarrow$$

$$\left[\begin{array}{c} H\!-\!O\text{-}\text{-}S\text{-}\text{-}S\!-\!Ar \\ \underset{H}{|} \quad \underset{Ar}{|} \quad \underset{O}{|} \\ O\text{-}\text{-}H \\ | \\ H \end{array} \right] \longrightarrow ArSO_2H + ArSO_2H + H_2O \quad (4)$$

$$\text{transition state}$$
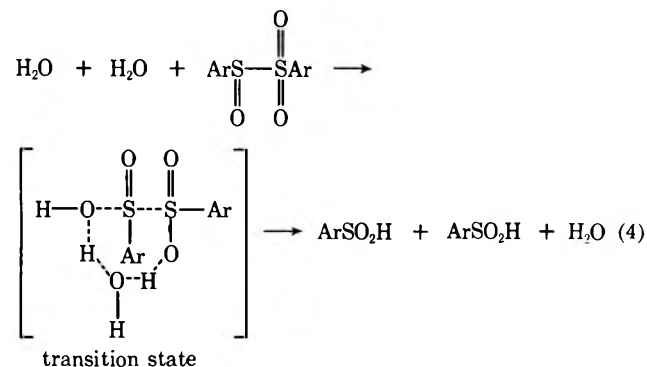
proton transfer is accomplished in a single encounter. For either eq 3 or eq 4 as the mechanism one will, of course, have no dependence of the hydrolysis rate on (H_3O^+).

If the above explanation for the difference in the dependence of the rates of the ordinary hydrolysis and the sulfide-catalyzed one on (H_3O^+) is correct, then the reaction of a mercaptan with **1** in acidic aqueous dioxane (eq 5) should, like the ordinary hydrolysis, *not* be sig-

(4) That the proton is transferred in the rate-determining step rather than in an earlier equilibrium is shown by the solvent–isotope effect of $(k_8{}^{H_2O}/k_8{}^{D_2O}) = 1.4$. Presumably the reason that the mechanism shown in eq 2 is preferred over one involving attack of R_2S on sulfonyl-protonated **1** formed in a prior equilibrium, *i.e.*, eq i, is simply the fact that, due to the extremely

$$R_2S + ArS\!-\!\overset{\overset{OH}{|}{}^+}{S}Ar \longrightarrow {}^+R_2SSAr + ArSO_2H \quad (i)$$

$$\mathbf{2}$$
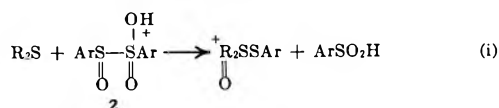
low basicity of sulfonyl groups,[5] the equilibrium concentration of **2** is too small for reaction i to be able to compete effectively with eq 2.

(5) S. K. Hall and E. A. Robinson, *Can. J. Chem.*, **42**, 1113 (1964); E. M. Arnett and C. Douty, *J. Amer. Chem. Soc.*, **86**, 409 (1964).

$$RSH + ArS\!-\!SAr \longrightarrow RSSAr + ArSO_2H \quad (5)$$
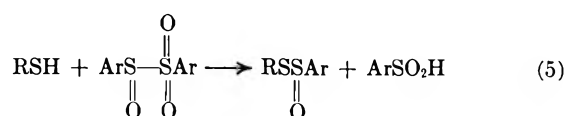
nificantly acid catalyzed, even though the mercaptan represents a neutral sulfur nucleophile of about the same reactivity as the sulfide, since RSH, like H_2O, and unlike R_2S, has a proton attached to the attacking atom which can be transferred to the departing $ArSO_2$ group in the same manner as shown in eq 3 and 4. For this reason it seemed worthwhile to investigate the kinetics of the reaction of a typical mercaptan with an aryl sulfinyl sulfone in acidic aqueous dioxane. The present paper reports the results of such a study.

Results

The particular mercaptan–sulfinyl sulfone combination chosen for study was *n*-butyl mercaptan–*p*-toluenesulfinyl *p*-tolyl sulfone (**1a**, Ar = *p*-$CH_3C_5H_4$). The rate of disappearance of **1a** in the presence of added mercaptan could be followed kinetically by the same spectrophotometric procedure used earlier[3] to follow the kinetics of the hydrolysis of **1a**. All runs were carried out with the added mercaptan (0.10–0.15 *M*) present in huge stoichiometric excess over **1a** ($\sim 10^{-4}$ *M*). The disappearance of **1a** followed good first-order kinetics in every case.

The experimental first-order rate constants, k_1, for the disappearance of **1a** under the various reaction conditions investigated are shown in Table I. Each mea-

TABLE I

KINETICS OF THE DISAPPEARANCE OF *p*-TOLUENESULFINYL
p-TOLYL SULFONE IN THE PRESENCE OF *n*-BUTYL MERCAPTAN
IN 60% DIOXANE AT 21.4°

(LiClO$_4$), *M*	(*n*-BuSH), *M*	(HClO$_4$), *M*	$k_1 \times 10^3$, sec^{-1} [a]	$k_M = \left[\dfrac{k_1 - k_h}{(\text{RSH})}\right]$, M^{-1} sec^{-1}
0.00	0.150	0.0010	11.5	0.049
		0.0012	10.9	0.045
		0.0015	10.6	0.043
		0.0016	10.5	0.042
		0.0020	9.6	0.037
		0.0025	9.0	0.032
		0.0040	8.3	0.028
		0.0050	7.8	0.025
		0.010	7.3	0.021
		0.050	7.2	0.020
		0.10	7.4	0.022
	0.095	0.10	6.2	0.021
	0.146	0.20	8.4	0.028
		0.40	9.3	0.032
0.30	0.146	0.10	16.7	0.082

[a] All rate constants are the average of several runs. Initial concentration of sulfinyl sulfone, $\sim 1 \times 10^{-4}$ *M* in all runs.

sured rate constant k_1 is the sum of the rate constant for the normal hydrolysis of **1a** (k_h) and the pseudo-first-order rate constant [k_M(RSH)] for the mercaptan–**1a** reaction under that particular set of reaction conditions, *i.e.*

$$k_1 = k_h + k_M(\text{RSH})$$

In a separate set of experiments, values of k_h were determined for **1a** for each set of reaction conditions in Table
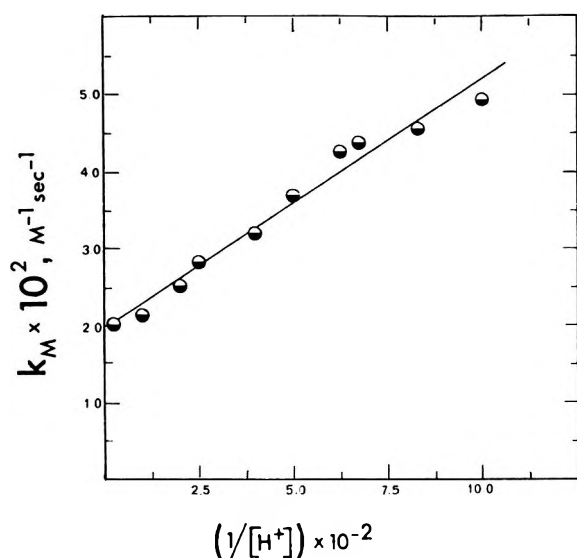
Figure 1.—Plot of k_M, the rate constant for the reaction of 1a with n-BuSH, vs. $1/(H^+)$ for runs in 60% dioxane containing 0.001–0.01 M HClO₄.

I, were found to be effectively independent of perchloric acid concentration, and were found to agree within a few per cent with those measured for 1a earlier[3] under certain of these reaction conditions. Values of k_M calculated from the k_1 values, the k_h values, and the relationship $k_M = [k_1 - k_h/(RSH)]$ are given in the last column of Table I.

Runs in 0.10 M perchloric acid at two different mercaptan concentrations indicate that k_M is independent of mercaptan concentration, showing that, as expected, the 1a–mercaptan reaction is first order in mercaptan.

Discussion

Examination of Table I reveals that in the region 0.001–0.01 M perchloric acid k_M decreases with increasing acid concentration, suggesting that in this region reaction of the mercaptide ion n-BuS⁻ with 1a (eq 6) is also contributing significantly to the rate of

$$n\text{-BuS}^- + \underset{\underset{O}{\overset{O}{\|}}}{ArS}\text{—}\underset{\underset{O}{\overset{O}{\|}}}{S}Ar \xrightarrow{k_{RS^-}} n\text{-BuSSAr} + \underset{\overset{O}{\|}}{ArSO_2}^- \quad (6)$$
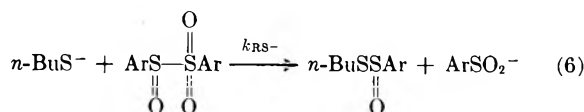
disappearance of 1a. In more acid media (0.01–0.10 M HClO₄) k_M is independent of acid concentration showing that in this region the only significant contributors to k_M are processes whose rates are independent of (H⁺), i.e., either direct reaction of n-BuSH with 1a (eq 7), or an acid-catalyzed reaction of n-BuS⁻ with the same substrate (eq 8). If this assessment of the kinetic

$$n\text{-BuSH} + \underset{\underset{O}{\overset{O}{\|}}}{ArS}\text{—}\underset{\underset{O}{\overset{O}{\|}}}{S}Ar \xrightarrow{k_{RSH}} n\text{-BuSSAr} + \underset{\overset{O}{\|}}{ArSO_2}H \quad (7)$$

$$n\text{-BuS}^- + \underset{\underset{O}{\overset{O}{\|}}}{ArS}\text{—}\underset{\underset{O}{\overset{O}{\|}}}{S}Ar + H^+ \xrightarrow{k'_{RS^-}} n\text{-BuSSAr} + \underset{\overset{O}{\|}}{ArSO_2}H \quad (8)$$
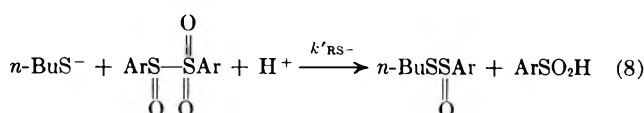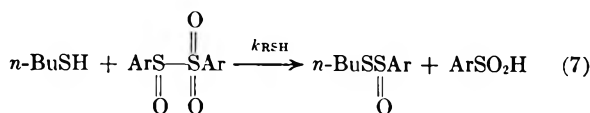
situation is correct, in the range 0.001–0.10 M HClO₄, k_M should be given by

$$k_M = k_{RS^-}\left[\frac{K_a^{RSH}}{(H^+)}\right] + k'_{RS^-}K_a^{RSH} + k_{RSH} \quad (9)$$

where K_a^{RSH} is the acid dissociation constant of the mercaptan, and a plot of k_M vs. $1/(H^+)$ should be linear. Figure 1 shows that this is indeed the case, thereby demonstrating that the increase in k_M with decreasing (H⁺) below 0.01 M HClO₄ is indeed due to the fact that reaction of n-BuS⁻ with 1a becomes significant at low acidities.

The next question to consider is whether eq 7 or 8 is the major contributor to the acid-independent term in eq 9. For other anionic nucleophiles (Cl⁻, Br⁻, etc.) reacting with 1a one has found[3] that the rate constant (k'_{Nu}) for their acid-catalyzed reaction with the sulfinyl sulfone is never larger than five times the rate constant (k_{Nu}) for their uncatalyzed reaction with the same substrate. Assuming the same is true for n-BuS⁻, this means that $(k'_{RS^-}/k_{RS^-}) \le 5$. The slope of the plot in Figure 1 is equal to $k_{RS^-}\text{-}K_a$, the intercept to $k'_{RS^-}\text{-}K_a + k_{RSH}$. Since the intercept (0.02) is about 700 times greater than the slope (3×10^{-5}), this requires, provided $(k'_{RS^-}/k_{RS^-}) \le 5$, that essentially all of the acid-independent term be due to eq 7, the reaction of the undissociated mercaptan with 1a.

Above 0.10 M HClO₄ k_M increases slightly with increasing acid concentration (Table I). Does this represent a contribution to the rate from an acid-catalyzed reaction of the undissociated mercaptan with 1a (eq 10),

$$n\text{-BuSH} + \underset{\underset{O}{\overset{O}{\|}}}{ArS}\text{—}\underset{\overset{O}{\|}}{S}Ar + H^+ \xrightarrow{k'_{RSH}}$$
$$\underset{\underset{H}{\overset{+}{\|}}}{n\text{-BuS}}\text{—}\underset{\overset{O}{\|}}{S}Ar + ArSO_2H \quad (10)$$
$$\downarrow \text{fast}$$
$$n\text{-BuSSAr} + H^+$$
$$\underset{\overset{O}{\|}}{}$$
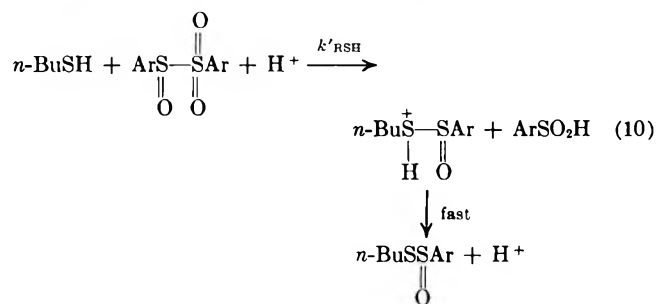
analogous to eq 2 for the reaction of n-Bu₂S with 1a? We think not and that the increase in k_M with (HClO₄) in this region is more likely due to a salt effect on k_{RSH}, since the addition of equivalent amounts of LiClO₄ in place of HClO₄ leads to an even larger increase in k_M (last entry in Table I). However, even if the increase in k_M with (HClO₄) should represent a contribution to the rate from eq 10, such an acid-catalyzed process is *much* less important relative to the rate of the uncatalyzed reaction for the mercaptan reacting with 1a than for the reaction of the sulfide with 1a. This can be seen (Table II) by comparing the variation of k_M in the

TABLE II

DEPENDENCE OF RATES OF REACTION OF BUTYL MERCAPTAN AND BUTYL SULFIDE WITH 1a ON ACID CONCENTRATION[a]

(HClO₄), M	k_M for n-BuSH reaction	k_S for Bu₂S reaction
0.01	0.020	<0.04
0.10	0.021	0.24
0.20	0.028	0.70
0.40	0.032	1.7

[a] All data for 60% dioxane at 21.4°.

region 0.01–0.40 M HClO$_4$ with the variation in k_S for the butyl sulfide catalyzed hydrolysis of 1a over the same range of acid concentrations.

We conclude from this that the explanation previously offered[3] for why the sulfide-catalyzed hydrolysis of 1a requires acid catalysis while the ordinary hydrolysis does not is not apparently the correct one.

Experimental Section

Preparation and Purification of Materials.—p-Toluenesulfinyl p-tolyl sulfone (1a) and dioxane were prepared and/or purified in the manner described in an earlier paper.[3] n-Butyl mercaptan was freshly fractionally distilled under nitrogen, bp 97–98°.

Procedure for Kinetic Runs.—The general procedure for following the kinetics of the disappearance of 1a was the same as that outlined previously.[3] To initiate a run the proper amount of a stock solution of 1a in *anhydrous* dioxane was added to an aqueous dioxane solution containing the appropriate amounts

of perchloric acid, n-butyl mercaptan, etc., both solutions having been brought to 21.4° before mixing. The disappearance of 1a was then followed by monitoring the decrease in the optical density, A, of the solution at 300 mμ in the manner described in an earlier paper.[3] Plots of log ($A - A_\infty$) vs. time were nicely linear. One should note that in those runs in which the reaction of mercaptan with 1a accounts for most of the rate A_∞ is significantly larger than when one is following only the hydrolysis of 1a, because of the fact that the thiolsulfinate product of the mercaptan–1a reaction, n-BuSS(O)Ar, has a significant extinction coefficient at 300 mμ, unlike the sulfinic acid, ArSO$_2$H, which is effectively transparent at this same wavelength. The spectra obtained at the end of the experiments in the presence of mercaptan corresponded to those expected for the formation of a mixture of thiolsulfinate (from the mercaptan–1a reaction) and sulfinic acid (from the normal hydrolysis) in the proportions predicted by comparison of k_1 in the presence of mercaptan and in its absence.

Mechanisms of Substitution Reactions at Sulfinyl Sulfur. VII. General Base Catalysis by a Tertiary Amine of the Hydrolysis of an Aryl Sulfinyl Sulfone[1]

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The hydrolysis of p-anisyl p-methoxybenzenesulfinyl sulfone (2a, eq 2) in aqueous dioxane or glyme can be catalyzed by various tertiary amines. The results for N-benzyldiethylamine, $(k_{R_3N}^{H_2O}/k_{R_3N}^{D_2O}) = 2.4$, clearly indicate that the amine is acting in that case as a general base catalyst and represent the first reported example of general base catalysis of a simple substitution at sulfinyl sulfur. On the other hand, the data for catalysis of the hydrolysis by pyridine point toward that amine acting as a nucleophilic rather than a general base catalyst. This, and the behavior of N-benzylpyrrolidine, both suggest that fairly modest changes in amine structure which merely reduce the steric hindrance around nitrogen can be sufficient to switch one from a situation where the tertiary amine acts as a general base catalyst to one where nucleophilic catalysis is observed to predominate instead. This, of course, means that each future example of tertiary amine catalysis of a substitution at sulfinyl sulfur will have to be examined carefully on an individual basis before decision can be reached as to whether nucleophilic or general base catalysis is involved.

It was shown[3] recently that catalysis of the hydrolysis of aryl α-disulfones (1) by triethylamine in aqueous glyme or dioxane involves general base catalysis (eq 1),

$$\text{Et}_3\text{N} + \text{H}_2\text{O} + \underset{\underset{\text{1}}{\overset{\text{O O}}{\overset{\|\ \|}{\text{ArS—SAr}}}}{\underset{\|\ \|}{\text{O O}}} \xrightarrow{k_{ab}}$$

$$\text{Et}_3\text{NH}^+ + \text{ArSO}_3\text{H} + \text{ArSO}_2^- \quad (1)$$
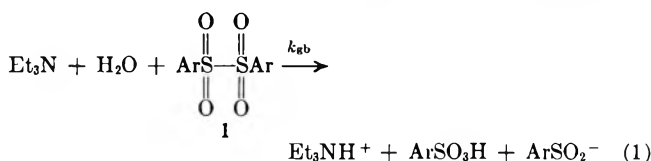
even though n-alkyl primary and secondary amines react with 1 as nucleophiles. This reaction represented the first reported case of general base catalysis of a substitution at sulfonyl sulfur, although another example has subsequently been reported.[4]

We were interested in determining whether general base catalysis by a tertiary amine could also be observed in an analogous substitution at sulfinyl sulfur. We have accordingly investigated the catalysis of the hydrolysis (eq 2) of an aryl sulfinyl sulfone (2) by several tertiary amines under the same conditions. While the rapidity of the catalyzed reaction limited the range of

$$\underset{\underset{\|\ \|}{\underset{\text{O O}}{\text{2}}}}{\overset{\text{O}}{\overset{\|}{\text{ArS—SAr}}}} + \text{H}_2\text{O} \longrightarrow 2\text{ArSO}_2\text{H} \quad (2)$$
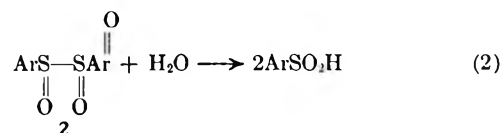
tertiary amines that could be examined, we have still been able to demonstrate that, although certain tertiary amines like pyridine catalyze the hydrolysis by acting as nucleophilic catalysts, the more sterically hindered tertiary alkyl amine, N-benzyldiethylamine, catalyzes the hydrolysis by general base catalysis. To our knowledge this is the first example of general base catalysis of the hydrolysis of a sulfinyl compound, and it shows that this type of catalysis, which has been widely encountered in substitutions of carboxylic acid derivatives[5] and recently observed[3,4] in substitutions at sulfonyl sulfur, can also be important in appropriate substitions at sulfinyl sulfur.

Results

Catalysis of the hydrolysis of p-anisyl p-methoxybenzenesulfinyl sulfone (2a, Ar = p-CH$_3$OC$_6$H$_4$) by various tertiary amines was investigated in either 60% glyme–40% water (v/v) or 60% dioxane–40% water (v/v) as

(1) (a) This research was supported by the National Science Foundation, Grant GP-10732X. (b) Preceding paper in this series: J. L. Kice and J. D. Campbell, *J. Org. Chem.*, **36**, 2288 (1971).

(2) Department of Chemistry, University of Vermont, Burlington, Vt. 05401.

(3) J. L. Kice and G. J. Kasperek, *J. Amer. Chem. Soc.*, **92**, 3393 (1970).

(4) E. T. Kaiser, *Accounts Chem. Res.*, **3**, 145 (1970).

(5) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, New York, N. Y., 1966, pp 27–118.
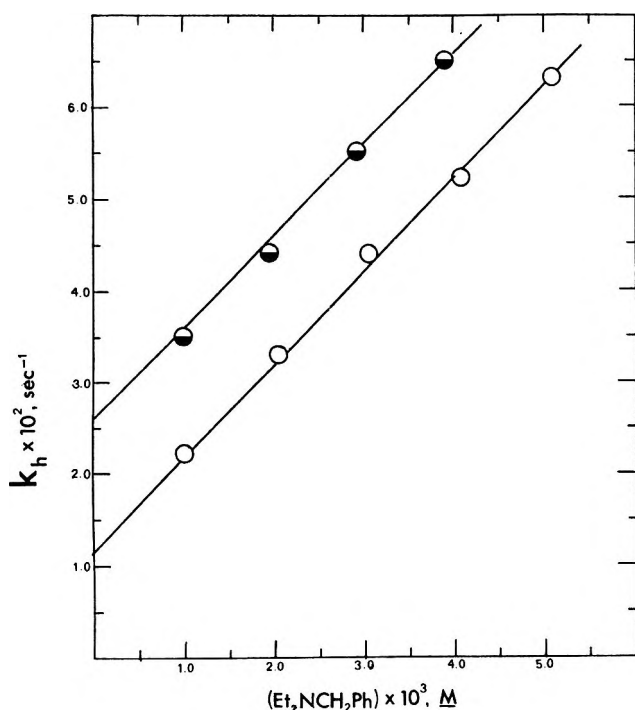
Figure 1.—Rate of hydrolysis of 2a in 60% glyme in *N*-benzyl-diethylamine buffers at 21.4°: ◐, runs in 2.5:1 Et_2NCH_2Ph-$Et_2\overset{+}{N}HCH_2Ph$ buffer; O, runs in 1:1 Et_2NCH_2Ph-$Et_2\overset{+}{N}HCH_2Ph$ buffer.

solvents at 21.4°. Rates were followed spectrophotometrically using previously described procedures.[6] All runs were carried out at constant ionic strength in amine–ammonium ion buffers with both buffer components present in large stoichiometric excess over the sulfinyl sulfone. The disappearance of 2a followed good first-order kinetics under all conditions investigated.

The kinetic results for *N*-benzyldiethylamine as catalyst in 60% glyme are shown in Table I. Those for pyridine as catalyst in 60% dioxane are given in Table II.

We also investigated catalysis by several other tertiary amines, namely, tribenzylamine, triethylamine, and *N*-benzylpyrrolidine. Tribenzylamine was without any catalytic effect at a concentration of 0.01 *M* in a 1:1 $(PhCH_2)_3N$-$(PhCH_2)_3NH^+$ buffer. In either 1:1 or 1:5 Et_3N-Et_3NH^+ buffers rates of hydrolysis of 2a were too fast to measure accurately in either 60% glyme or 60% dioxane, even at the lowest amine concentrations (1×10^{-3} *M*) that could be used if one was to maintain an effectively constant Et_3N-Et_3NH^+ ratio throughout the course of the reaction.[7]

N-Benzylpyrrolidine was also too reactive to permit an accurate determination of its catalytic rate constant and is therefore a significantly better catalyst than *N*-benzyldiethylamine, even though they are presumably of closely comparable base strength.

(6) J. L. Kice and G. Guaraldi, *J. Amer. Chem. Soc.*, **89**, 4113 (1967).

(7) Since an initial 2a concentration of 5×10^{-5} *M* is about as low as one can conveniently go, and since hydrolysis of 2a yields 2 mol of sulfinic acid (eq 2), one is restricted to amine concentrations above 9×10^{-4} *M* if one wants to maintain a constant pH during the course of the reaction. The latter is necessary since with relatively basic tertiary amines, like *N*-benzyldiethylamine and triethylamine, the direct reaction of hydroxide with 2a is a significant contributor to the total rate in 1:1 amine–ammonium ion buffers (see discussion of results with $PhCH_2NEt_2$).

TABLE I

HYDROLYSIS OF *p*-ANISYL *p*-METHOXYBENZENESULFINYL SULFONE IN THE PRESENCE OF *N*-BENZYLDIETHYLAMINE IN 60% GLYME[a]

Et_2NCH_2Ph-$Et_2\overset{+}{N}HCH_2Ph$ buffer ratio	$(Et_2NCH_2Ph) \times 10^3$, *M*	$k_h \times 10^2$, sec^{-1}	$k_{Et_2NCH_2Ph}$, M^{-1} sec^{-1}[b]	$k_{OH}(OH^-) \times 10^2$, sec^{-1}[c]
1:1	1.01	2.2		
	2.04	3.3		
	3.06	4.4	10.2	0.97
	4.08	5.2		
	5.10	6.3		
2.5:1	0.98	3.5		
	1.96	4.4	10.0	2.4
	2.93	5.5		
	3.91	6.5		
1:1	2.0	2.6 (D$_2$O)		
	3.0	3.0 (D$_2$O)	4.2 (D$_2$O)	1.7 (D$_2$O)
	4.0	3.5 (D$_2$O)		
	5.0	3.8 (D$_2$O)		

[a] All runs at 21.4° with ionic strength held constant at 0.01 by addition of $LiClO_4$; initial concentration of 2a, 5×10^{-5} *M*. [b] Calculated from slope of plot of k_h vs. (Et_2NCH_2Ph). [c] Intercept at (Et_2NCH_2Ph) of 0.00 *M* equals 0.19×10^{-2} sec^{-1} + $k_{OH}(OH^-)$.

TABLE II

HYDROLYSIS OF *p*-ANISYL *p*-METHOXYBENZENESULFINYL SULFONE IN THE PRESENCE OF PYRIDINE IN 60% DIOXANE[a]

C_6H_5N-$C_6H_5NH^+$ buffer ratio	$(C_5H_5N) \times 10^3$, *M*	$k_h \times 10^2$, sec^{-1}	$k_{C_5H_5N}$, M^{-1} sec^{-1}[b]
1:1	9.7	4.0	
	4.9	2.1	
	2.9	1.3	3.9
	1.95	0.99	
	0.97	0.64	
1:1	10.0	2.8 (D$_2$O)	
	8.0	2.1 (D$_2$O)	
	6.0	1.7 (D$_2$O)	2.7
	4.0	1.1 (D$_2$O)	
1:1	10.0[c]	3.9	
	10.0[d]	3.5	

[a] All runs at 21.4° with ionic strength held constant at 0.01 by addition of $LiClO_4$; initial concentration of 2a, 5×10^{-5} *M*. [b] Calculated from slope of plot of k_h vs. (C_5H_5N). [c] *p*-MeOC$_6$H$_4$SO$_2$Na, 5×10^{-4} *M*, added initially. [d] *p*-MeOC$_6$H$_4$SO$_2$Na, 1×10^{-3} *M*, added initially.

Discussion

Catalysis by *N*-Benzyldiethylamine.—Figure 1 shows plots of the rate of hydrolysis of 2a, k_h, vs. (amine) for runs with added *N*-benzyldiethylamine in 60% glyme at two different Et_2NCH_2Ph-$Et_2N^+HCH_2Ph$ buffer ratios (1:1 and 2.5:1). The slope of the plots is independent of the buffer ratio while the intercepts of the plots, when corrected for the small contribution to k_h from the spontaneous rate of hydrolysis of 2a under these conditions[6] (0.19×10^{-2} sec^{-1}), show that the intercept for the runs at the 2.5:1 buffer ratio is exactly 2.5 times larger than the intercept for the plot for the 1:1 buffer ratio runs. This behavior shows that under these conditions k_h is given as shown in eq 3 where

$$k_h - k_{spont} = k_{OH}(OH^-) + k_{Et_2NCH_2Ph}(Et_2NCH_2Ph) \quad (3)$$

$k_{Et_2NCH_2Ph}(Et_2NCH_2Ph)$ is the contribution from the amine-catalyzed reaction and $k_{OH}(OH^-)$ is the contribu-

tion from a direct reaction of hydroxide ion with **2a** (eq 4).

$$OH^- + ArS\overset{\overset{O}{\parallel}}{\underset{\underset{O}{\parallel}}{S}}Ar \xrightarrow{k_{OH}} ArSO_2H + ArSO_2^- \quad (4)$$

$$\downarrow OH^-, \text{fast}$$

$$ArSO_2^-$$
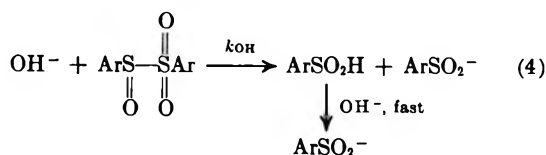
Measurements of the rate of the amine-catalyzed reaction in 60% glyme–40% D_2O (Table I) reveal that $k_{Et_2NCH_2Ph}$ is 2.4 times smaller in this solvent than it is in 60% glyme–40% H_2O. Such a solvent isotope effect of $(k^{H_2O}_{Et_2NCH_2Ph}/k^{D_2O}_{Et_2NCH_2Ph})$ = 2.4 provides clear evidence that the catalysis of the hydrolysis of **2a** by Et_2NCH_2Ph must involve general base catalysis (eq 5) and not nucleophilic catalysis. Thus, hydrolyses in

$$Et_2NCH_2Ph + H_2O + ArS\overset{\overset{O}{\parallel}}{\underset{\underset{O}{\parallel}}{S}}Ar \xrightarrow{k_{gb}^{Et_2NCH_2Ph}}$$

$$Et_2\overset{+}{N}HCH_2Ph + ArSO_2H + ArSO_2^- \quad (5)$$
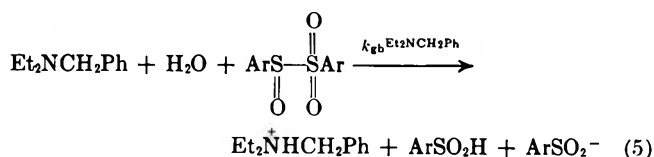
which amines act as nucleophilic catalysts normally exhibit rather small solvent isotope effects (k_{H_2O}/k_{D_2O} = 0.9–1.4) while those where general base catalysis is involved show much larger values of k_{H_2O}/k_{D_2O}, 1.9–4.4.[8]

As far as we can tell this represents the first example of general base catalysis of a hydrolysis of a sulfinyl derivative and shows that this phenomenon can also be observed in substitutions at this oxidation state of sulfur.

That not all tertiary amines, however, catalyze the hydrolysis of **2a** by acting as general base catalysts is indicated by results with several other amines. Let us first consider the results with pyridine.

Catalysis by Pyridine.—Figure 2 shows a plot of k_h vs. (amine) for the pyridine-catalyzed runs of Table II (1:1 C_5H_5N–$C_5H_5NH^+$ buffer). Since the line through the data points for each set of runs intercepts the k_h axis at a value equal to the spontaneous rate of hydrolysis of **2a**, this means that there is no contribution to the rate from the $k_{OH}(OH^-)$ term (eq 4) under these conditions. This is not surprising because, pyridine being a substantially weaker base than Et_2NCH_2-Ph, the hydroxide concentration in a 1:1 C_5H_5N–C_5H_5-NH^+ buffer should be much smaller than in a 1:1 buffer of the other amine.

Figure 2 shows that the slope of the k_h vs. (C_5H_5N) plot is somewhat lower in 60% dioxane–40% D_2O than it is in 60% dioxane–40% H_2O, corresponding to a solvent isotope effect of $(k^{H_2O}_{C_5H_5N}/k^{D_2O}_{C_5H_5N})$ of 1.4. Note that this is significantly smaller than the solvent-isotope effect of 2.4 found in the Et_2NCH_2Ph-catalyzed reaction. Although at the upper end of the range of values normally observed when nucleophilic catalysis by an amine is involved, it is significantly lower than those (1.9–4.4) usually associated with general base catalysis by the same species. We therefore conclude that the solvent isotope effect associated with the pyridine-catalyzed reaction is indicative of its involving nucleophilic catalysis by pyridine.

Two other aspects of the results also point toward the same conclusion. First, one sees that, although pyri-

(8) For a tabulation of most of the pertinent data, see S. J. Johnson, *Advan. Phys. Org. Chem.*, **5**, 281 (1967).
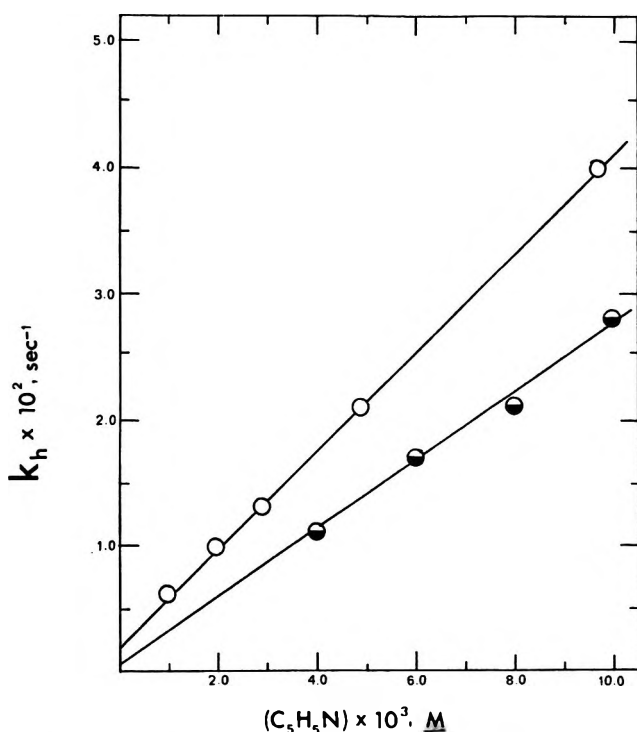
Figure 2.—Rate of hydrolysis of **2a** in pyridine buffers at 21.4°: O, runs in 1:1 C_5H_5N-$C_5H_5NH^+$ buffer in 60% dioxane–40% H_2O; ●, runs in 1:1 C_5H_5N-$C_5H_5ND^+$ buffer in 60% dioxane–40% D_2O.

dine is over four powers of ten weaker base than Et_2-NCH_2Ph,[9] $k_{C_5H_5N}$ in 60% dioxane is only 2.5 times smaller than $k_{Et_2NCH_2Ph}$ in 60% glyme. Although earlier work[3] has shown some increase in the rate constant for the Et_3N-catalyzed hydrolysis of **1** on going from 60% glyme to 60% dioxane, the magnitude of the effect is at most about a factor of ten. Thus, unless the Brønsted β associated with the general base catalyzed hydrolysis of **2a** were quite small, one could not have $k_{C_5H_5N}$ as large as it is and still have pyridine acting as a general base catalyst. It seems more reasonable to assume that $k_{C_5H_5N}$ is as large as it is because pyridine is functioning as a nucleophilic catalyst and is, because the nitrogen atom is much less sterically hindered than the one in an amine like Et_2NCH_2Ph, much more reactive as a nucleophile in relation to its basicity than is Et_2NCH_2Ph.[10] Second, there is the fact that the initial addition of 10^{-3} M sodium p-methoxybenzenesulfinate leads to a small but definite decrease in $k_{C_5H_5N}$ (see last two runs in Table II). This effect of added sulfinate is understandable if the pyridine-catalyzed reaction involves nucleophilic catalysis by C_5H_5N and the mechanism shown in eq 6, since in the presence of sufficient added $ArSO_2^-$ the k_{-1} step becomes competitive with the k_2 step, and $k_{C_5H_5N}$, which is equal to $k_1k_2(H_2O)/[k_2(H_2O) + k_{-1}-(ArSO_2^-)]$, decreases. Were the pyridine-catalyzed reaction to involve general base catalysis by the amine no such effect of added sulfinate would be observed.

(9) M. Bouregeaud and A. Dondelinger, *C. R. Acad. Sci.*, **179**, 1159 (1924).

(10) A referee has suggested that pyridine may exhibit nucleophilic catalysis and N-benzyldiethylamine general base catalysis not for the reasons just cited but because the reversal of the first step in the nucleophilic catalysis mechanism for $PhCH_2NEt_2$ (analogous to step k_{-1} in eq 6) is unusually fast relative to k_2 for this amine as compared to the situation with pyridine, so that any potential nucleophilic catalysis by $PhCH_2NEt_2$ is effectively suppressed and the general base catalyzed mechanism becomes dominant. Although we think it unlikely that a change from pyridine to $PhCH_2NEt_2$ would lead to a change in k_{-1}/k_2 large enough to have an effect of this magnitude, we cannot completely rule out this possibility.

We thus feel that the weight of the evidence points toward the pyridine-catalyzed hydrolysis involving nucleophilic catalysis by pyridine according to the mechanism shown in eq 6.

$$ArS-SAr + C_5H_5N \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ArSN\underset{\|}{\overset{+}{\bigcirc}} + ArSO_2^-$$

$$\downarrow H_2O \: k_2$$

$$ArSO_2H + C_5H_5N + H^+ \tag{6}$$
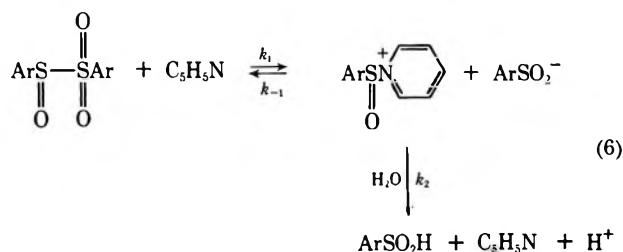
Catalysis by Other Tertiary Amines.—As mentioned earlier, N-benzylpyrrolidine is significantly more reactive as a catalyst for the hydrolysis of **2a** than is N-benzyldiethylamine, being in fact too reactive to permit an accurate determination of its catalytic rate constant. Since the two amines are of almost exactly equal base strength (pK_b of Et$_2$NCH$_2$Ph = 4.4;[9] pK_b of N-benzylpyrrolidine = 4.5[11]), they should be of essentially equal reactivity as general base catalysts for the hydrolysis of **2a**. The fact that N-benzylpyrrolidine is a significantly better catalyst than Et$_2$NCH$_2$Ph suggests that the pyrrolidine is probably catalyzing the hydrolysis by acting not as a general base but rather as a nucleophilic catalyst. Due to two of the substituents on the nitrogen being tied back in a ring, the nitrogen in the pyrrolidine is presumably much less sterically hindered than the one in Et$_2$NCH$_2$Ph, and the pyrrolidine should be considerably more reactive than Et$_2$-NCH$_2$Ph as a nucleophile toward **2a**, even though the two amines are of equal basicity toward a proton.

The results in the present paper thus suggest that tertiary amines can catalyze the hydrolysis of sulfinyl derivatives either by nucleophilic or general base catalysis and that the particular type of catalysis actually observed with a given substrate may change with only a fairly modest change in amine structure. Regrettably this means that in further studies of such catalysis each individual sulfinyl compound–tertiary amine system will have to be examined in detail independently before one can be sure which type of catalysis is involved in that particular system.

Since triethylamine (pK_b = 3.25) is a significantly stronger base than Et$_2$NCH$_2$Ph, one cannot tell from the fact that this amine is also too reactive as a catalyst to permit measurement of k_{Et_3N} whether this is due to its acting as a nucleophilic rather than a general base

(11) L. C. Craig and R. M. Hixon, *J. Amer. Chem. Soc.*, **53**, 4367 (1931).

catalyst. It could equally well be due to the fact that the greater basicity of Et$_3$N makes k_{gb} for this amine significantly larger than k_{gb} for Et$_2$NCH$_2$Ph. (With the Et$_2$NCH$_2$Ph runs we are already close enough to the upper limit of the rates that we can measure accurately that k_{gb} for Et$_3$N would only need to be about four times larger than k_{gb} for Et$_2$NCH$_2$Ph in order for k_{Et_3N} to be too large for us to be able to measure it accurately.)

Experimental Section

Preparation and Purification of Materials. N-Benzylpyrrolidine was prepared by the method of Fery and van Hove.[12] Benzyl chloride (41 ml) was added over a 2-hr period to a rapidly stirred, ice-cooled mixture of 33 g of pyrrolidine, 100 ml of ether, and 50 g of potassium carbonate. The final mixture was stirred for 2 hr more and then allowed to stand overnight. It was then acidified with 200 ml of 6 N HCl and extracted with ether. The aqueous phase was neutralized with concentrated potassium hydroxide solution and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate. Subsequent removal of the ether and distillation gave 52 g (70%) of N-benzylpyrrolidine, bp 45° (0.7 mm), n^{20}D 1.5271. N-Benzyldiethylamine was prepared in essentially the same manner as N-benzylpyrrolidine using 63.3 g of benzyl chloride and 36.5 g of diethylamine. The final distillation gave 30 g (37%) of N-benzyldiethylamine, bp 79–80° (7 mm), n^{25}D 1.4957 [lit.[13] 84–85° (12 mm), n^{25}D 1.5014]. p-Anisyl p-methoxybenzenesulfinyl sulfone was prepared as described by Kice and Guaraldi.[14] Pyridine was purified by refluxing analytical reagent grade material over barium oxide and then fractionally distilling. Dioxane, glyme, and triethylamine were purified by previously published procedures.[3,6] Tribenzylamine (Eastman) was recrystallized from ethanol before use, mp 93–95°.

Procedure for Kinetic Runs.—The various amine-ammonium ion buffers were prepared by adding the calculated amount of standard perchloric acid to a standard solution of the amine. The ionic strength was maintained constant by the addition of lithium perchlorate. To carry out a run 3.0 ml of the appropriate amine buffer in either 60% glyme or 60% dioxane was placed in a 1-cm spectrophotometer cell and brought to 21.4° in a thermostated cell compartment of a Cary Model 15 spectrophotometer. Then 7–8 μl of a freshly prepared 0.02 M solution of sulfinyl sulfone **2a** in either anhydrous glyme or dioxane was introduced into the buffer solution on the flattened end of a glass stirring rod and rapidly and thoroughly mixed with the solution in the cell. The rate of disappearance of **2a** was then followed spectrophotometrically in the manner described by Kice and Guaraldi.[6] The spectra at the conclusion of the hydrolysis corresponded to those that have been obtained in those hydrolyses of **2a** to sulfinic acid studied earlier.[6]

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The Thermal Dissociation of Aryl Carbanilates in Glyme

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Members of a series of meta- and para-substituted phenyl carbanilates were shown to undergo a rapid reversible dissociation in glyme. The equilibrium constants for this dissociation were measured at temperatures between 90.4 and 150° (50 and 90.4° in the case of p-nitrophenyl carbanilate). The reaction followed the Hammett equation and gave the positive ρ values of 1.49–1.66. The significance of the thermodynamic parameters and Hammett correlations is discussed.

It has been known for some time that carbamates undergo an ester interchange reaction with alcohols, amines, and other active hydrogen compounds.[1-5]

$$R_1R_2N\overset{\overset{\displaystyle O}{\|}}{C}OR_3 + YH \longrightarrow R_1R_2N\overset{\overset{\displaystyle O}{\|}}{C}Y + R_3OH \qquad (1)$$
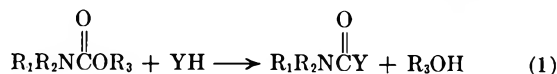
There are several different pathways by which this reaction may proceed, and the choice of a particular pathway appears to depend on the nature of the carbamate, the catalyst, and the temperature. In the alkoxide ion catalyzed transesterification of alkyl N,N-disubstituted carbamates (reaction 1, R_1, R_2, R_3 = alkyl; Y = RO), evidence has been presented for a carbonyl addition intermediate.[2b] In the case of monosubstituted carbamates (reaction 1, R_2 = H) an alternate pathway is available. These compounds may dissociate at elevated temperatures, usually with acid or base catalysis, to form isocyanate and alcohol,[6-9] and the ester interchange may proceed by a two-step process. Mukaiyama and coworkers[3] have carried out kinetic studies on the ester interchange reaction of substituted benzyl carbanilates with several active hydrogen-containing compounds at temperatures of 130–170°, and they assume a mechanism represented by eq 2 and 3.

$$R_1\overset{\overset{\displaystyle H}{|}}{N}-\overset{\overset{\displaystyle O}{\|}}{C}OR_2 \rightleftharpoons R_1NCO + R_2OH \qquad (2)$$

$$R_1NCO + YH \rightleftharpoons R_1\overset{\overset{\displaystyle H}{|}}{N}-\overset{\overset{\displaystyle O}{\|}}{C}Y \qquad (3)$$

Pseudounimolecular rate constants were reported.[10]

The rate constants for the reaction of the substituted benzyl carbanilates with ethanolamine at 150° followed the Hammett relationship and gave a ρ value of +0.538. The substitution was in the anilide ring of the benzyl carbanilate.

Both dissociation (reaction 2) and ester interchange (reaction 1) are facile in the case of aryl N-arylcarbamates,[2] and can take place either in the presence or absence of added catalyst depending on the temperature. Tartakovskaya and coworkers[9] studied the decomposition temperatures of a number of solid aryl carbanilates suspended in mineral oil. These temperatures, the lowest at which phenyl isocyanate could be identified in an infrared spectrum, ranged from 100° for p-nitrophenyl carbanilate to 150° for p-tolyl carbanilate. In dioxane solution, p-nitrophenyl carbanilate has been reported to dissociate at room temperature with an equilibrium constant of about 2×10^{-3} mol/l.[7] The dissociation was catalyzed by trimethylamine.

The rates of aminolysis of aryl carbanilates with aniline in dioxane, catalyzed by triethylamine at 80°, were studied by Furuya and coworkers.[4] The reactions of phenyl, p-tolyl, and p-methoxyphenyl carbanilates with aniline were first order in urethane and first order in triethylamine. Evidence was presented that suggested the formation of a cationic complex as the rate-determining step. p-Chlorophenyl carbanilate and p-nitrophenyl carbanilate gave more complex kinetics, and the latter also underwent aminolysis in the absence of triethylamine.

Sal'nikova and coworkers[5] have studied the ester interchange between aryl carbanilates and 1-hexanol in o-dichlorobenzene. The reactions were carried out without added catalyst at 160–180°. Phenyl isocyanate was identified as an intermediate, but the overall ester interchange was interpreted as a bimolecular nucleophilic displacement involving a carbonyl addition intermediate. Second-order rate constants were reported for this reaction, which was said to compete with the dissociation of aryl carbanilates.

The evidence bearing on the mechanisms of the carbamate ester interchange presents a rather confusing picture. As part of an effort to clarify the mechanism of the overall ester interchange reaction, we have studied the thermal dissociation of aryl carbanilates in ethylene glycol dimethyl ether (glyme). The dissociation was very rapid and reversible and did not require the addition of a catalyst. Phenyl carbanilate (0.09 mol/l. in glyme) dissociated to the extent of 23% at 90.4° and

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(2) (a) N. G. Gaylord and C. E. Sroog, *J. Org. Chem.*, **18**, 1632 (1953); (b) N. G. Gaylord, *ibid.*, **25**, 1874 (1960).

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(10) These workers[3] assumed that reaction 2 was the rate-determining step and therefore that their first-order rate constants referred to the rate of this dissociation. If this were the case, then the first-order rate plots should have an intercept at zero time equal to the logarithm of the initial amine concentration. The published rate plots for the reaction of N-p-nitrophenyl benzyl carbamate with ethanolamine in benzyl alcohol[3d] have intercepts smaller than this value, and the extrapolated concentration of amine at zero time decreases with decreasing temperature. This behavior strongly suggests that an intermediate was present in high concentration and is inconsistent with reaction 2 as the rate-determining step. Reaction 3 may

have been rate determining in which case the observed rate constant would be equal to K_2k_3X, where K_2 is the equilibrium constant for reaction 2, k_3 is the second-order rate constant for reaction 3, and X is the ratio of ethanolamine concentration to benzyl alcohol concentration. The value of X would be constant since both reagents were present in excess.

63% at 150°. Equilibrium was reached within 10 min at 90.4° and within 2 min at 150°.

Experimental Section

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Carbon–hydrogen analyses were performed by Crobaugh Laboratories, Cleveland, Ohio. Infrared absorption measurements were made with a Beckman IR-12 double-beam spectrophotometer, using a 0.1-mm Irtran cell.

Materials.—Aryl carbanilates were prepared from phenyl isocyanate and the corresponding phenols in benzene solution, using a catalytic amount of pyridine. The resulting colorless solids were recrystallized from hexane in a Soxhlet apparatus and dried under vacuum. The melting points and carbon–hydrogen analyses are shown in Table I.

TABLE I
MELTING POINTS FOR SUBSTITUTED PHENYL CARBANILATES

Compd[a]	Registry no.	Mp, °C	Lit. mp, °C
Unsubstituted	4930-03-4	126–127	123[b]
p-CH₃	16323-13-0	111.5–112.5	113[b]
p-F	29913-14-2	150–151	
m-F	29913-15-3	114–115.5	
p-Cl	16400-09-2	144–146	139,[b] 138.5[c]
p-Br	16323-16-3	142.5–144	138[c]
p-OCH₃	19219-48-8	135–137	135[c]
m-OCH₃	21123-19-3	120–122.5	123–124[d]
p-NO₂	6320-72-5	153–155	147[b]
			149–150[e]
			93.5–94[c]

[a] Satisfactory analyses (±0.4%) for C and H were provided for this compound: Ed. [b] Reference 4. [c] Reference 9. [d] M. T. Leffler and E. J. Matson, *J. Amer. Chem. Soc.*, **70**, 3439 (1948). [e] Reference 7.

Solvent purification and solution preparation were carried out in a self-contained apparatus under an atmosphere of dry prepurified nitrogen. The glyme was distilled once from sodium ribbon and again from lithium aluminum hydride. Both distillations used an 86-cm vacuum-jacketed column operated at a reflux ratio of 10:1. Only the center cut was retained in each distillation. The distillate was then drained into a volumetric flask containing the requisite amount of aryl carbanilate. This flask was provided with a magnetic stirrer for mixing and with a Teflon stopcock and exit tube for filling the reaction vessels. The distillation receiver and volumetric flask were dried before starting the distillation by heating with a flame in a current of dry nitrogen.

Solutions of phenyl isocyanate, for use in calibration of absorbance, were prepared by distilling phenyl isocyanate into a volumetric flask under dry nitrogen. The flask was then weighed, transferred to the distillation receiver described above, and filled with freshly purified glyme under nitrogen.

Procedure.—The reaction was carried out in sealed Pyrex tubes of 2.2-ml capacity charged with 1 ml of solution. Each tube was dried before filling by heating with a flame in a current of dry nitrogen, and the nitrogen current was maintained until the tube was filled. After each tube was filled, it was immediately sealed under vacuum and stored in a Dry Ice-acetone bath.

The reaction was carried out in a thermostated oil bath which maintained the stated temperatures within 0.1°. Tubes were withdrawn at intervals, cooled in a Dry Ice-acetone bath, warmed to room temperature, and opened. The infrared cell was filled and the absorbance measured as rapidly as possible. Typically the isocyanate absorbance was measured within 6 min after removing the reaction tube from the oil bath, and the urethane carbonyl absorbance was measured 1 min later. In all runs involving phenyl carbanilate, the infrared spectrum of the solution was scanned between 1500 and 4000 cm⁻¹ after the initial absorbance measurements were made. Extraneous peaks were not observed. The reversal of the reaction took place slowly within the infrared cell. In one case, involving an equilibrium sample of phenyl carbanilate, the concentration of isocyanate decreased to 87.5% of its initial value after 40 min in the cell,

while the concentration of phenyl carbanilate increased correspondingly.

The concentration of phenyl isocyanate was determined from its strong, sharp absorbance at 2262.5 cm⁻¹, after subtracting the solvent absorbance of 0.129–0.131 absorbance units. The solvent absorbance was rechecked periodically. The isocyanate absorbance was calibrated at ten concentrations covering the range of interest and followed Beer's law with an extinction coefficient of 1314 ± 48. The concentration of phenyl carbanilate was determined from its carbonyl absorbance at 1757 cm⁻¹, after subtracting the solvent absorbance of 0.056–0.060 absorbance units. A separate calibration chart was prepared for each aryl carbanilate. The absorption maxima and extinction coefficients are shown in Table II. p-Nitrophenyl carbanilate underwent dissociation within the infrared cell, and so an accurate calibration chart could not be prepared.

TABLE II
INFRARED MAXIMA AND EXTINCTION COEFFICIENTS FOR SUBSTITUTED PHENYL CARBANILATES

Compd	ν_{max}, cm⁻¹	ϵ_{max}[a]	n[b]
Unsubstituted	1757	1004 ± 10	8
p-CH₃	1755	1060 ± 5	5
p-F	1757	1111 ± 17	5
m-F	1759	1104 ± 25	5
p-Cl	1755.5	1085 ± 16	8
p-Br	1754	957 ± 5	4
p-OCH₃	1753	1015 ± 38	5
m-OCH₃	1757	1055 ± 10	5
p-NO₂	1759		

[a] By least-squares correlation including the origin ± standard deviation in slope. [b] Number of measurements, not including the origin.

The concentrations of phenyl isocyanate and aryl carbanilate were measured at various time intervals. The results of a typical run are shown in Figure 1. In all cases, the concentration of phenyl isocyanate rose rapidly and quickly reached an equilibrium value, while the aryl carbanilate concentration decreased correspondingly to an equilibrium value. The equilibrium concentration was taken as the concentration which did not change during three measurements over a period of at least 30 min. The time required to reach equilibrium was about 10 min in most cases. The shortest time was 2 min for phenyl carbanilate at 150°, and the longest time was 45 min for p-nitrophenyl carbanilate at 50°. A reaction requiring 2–10 min (Figure 1) is much faster than it appears to be, since most of the reaction occurs during the period necessary to bring the sample to thermal equilibrium in the constant temperature bath.

The equilibrium constants were calculated as the square of isocyanate concentration divided by the urethane concentration. In the case of p-nitrophenyl carbanilate only the isocyanate concentration was measured.

Results and Discussion

Under certain conditions, it appears likely that the exchange reaction between phenyl carbanilate and alcohols may occur in two major steps, as shown in eq 4 and 5.

$$\underset{\text{H}}{\text{C}_6\text{H}_5\text{N}}{-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{OC}_6\text{H}_5 \rightleftharpoons \text{C}_6\text{H}_5\text{NCO} + \text{C}_6\text{H}_5\text{OH} \qquad (4)$$

$$\text{C}_6\text{H}_5\text{NCO} + \text{ROH} \rightleftharpoons \underset{\text{H}}{\text{C}_6\text{H}_5\text{N}}{-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{OR} \qquad (5)$$
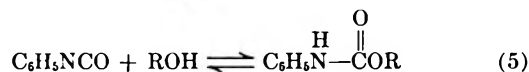
The study of these reactions independently should provide valuable information concerning the overall exchange reaction. Reaction 5 has been studied extensively. It is relatively slow in ether solvents and approximates second-order kinetics. The apparent

second-order rate constant is reported as 1.33×10^{-6} l. mol^{-1} sec^{-1} for 0.15 M butanol–phenyl isocyanate at 25° in dioxane, and the reaction is still slower in diglyme.[11] Reaction 4, on the other hand, is very fast relative to the overall ester interchange reaction. Preliminary experiments with octanol and phenyl carbanilate in glyme[12] suggest that the overall transesterification (reactions 4 and 5) requires several hours to reach completion at 150°. On the other hand, reaction 4 reaches equilibrium within 2 min. We were unable to determine the kinetic order of reaction 4 because of the time necessary for the mixture to reach thermal equilibrium. Furuya and coworkers[4] have observed an induction period of 200 min for the uncatalyzed reaction of p-nitrophenyl carbanilate with aniline in dioxane at 80°. We have not observed induction periods in the present work, and there is no evidence for inhibition phenomena in reaction 4. The precise mechanism of this reaction remains in doubt.

The equilibrium constants and thermodynamic parameters for the dissociation of aryl carbanilates are shown in Table III. Most of the $\Delta H°$ and $\Delta S°$ values are of the order of magnitude expected for a thermal dissociation, but the $\Delta S°$ value for p-nitrophenyl carbanilate is surprisingly high. This value possibly may reflect a high degree of association of the starting urethane in the solvent. It should be noted that the log K vs. $1/T$ correlation for p-nitrophenyl carbanilate was obtained over a different temperature range than those for the other aryl carbanilates and is also subject to a greater degree of uncertainty. Extrapolation gives an equilibrium constant of about 2×10^{-4} mol l.$^{-1}$ for the dissociation of p-nitrophenyl carbanilate in glyme at 25°, as compared to a value of about 2×10^{-3} mol l.$^{-1}$ reported by Kopple[7] for the same dissociation in dioxane at room temperature catalyzed by trimethylamine.

Figure 1.—Dissociation of phenyl carbanilate at 100°. Concentration of phenyl isocyanate (circles) and phenyl carbanilate (squares) vs. time.

TABLE III
DISSOCIATION OF SUBSTITUTED PHENYL CARBANILATES IN GLYME

Substituent[a]	K, mol. l.$^{-1}$ $\times 10^2$				$\Delta H°$,[b] kcal	$\Delta S°$,[b] eu
	150°	125°	100°	90.4°		
H[c]	9.39	3.48	1.08	0.629	13.9 ± 0.1	28.0
H[d]			1.05			
p-CH$_3$	5.67	1.93	0.542	0.277	15.4 ± 0.2	30.7
p-F	10.1	3.20	0.914	0.429	15.9 ± 0.2	33.2
m-F	33.1	11.0	3.19		14.7 ± 0.01	32.5
p-Cl	13.1	5.66	1.82	0.960	13.4 ± 0.4	27.7
p-Br	14.6	4.56	1.58	1.01	13.6 ± 0.3	28.3
p-OCH$_3$	3.91	1.26			15.1	29.3
m-OCH$_3$	13.4	4.76	1.43	0.890	14.0 ± 0.03	29.0
p-NO$_2$				11.1[e]	21.3 ± 1.4	54.7

[a] Initial concentration 0.075 mol/l. except where otherwise noted. [b] From least-squares correlation of log K vs. $1/T$. Standard deviations in slope are shown. [c] Initial concentration 0.09 mol/l. [d] Initial concentration 0.0831 mol/l. [e] $K \times 10^2$ was 4.75 at 75°, 1.02 at 60°, and 0.306 at 50°.

Electron-withdrawing meta and para substituents on the phenolic ring increase the extent of dissociation, and electron-releasing substituents decrease the extend of dissociation. The reaction approximately followed the Hammett equation (Figure 2). The points for para halogen substituents fell below the line at all tem-

Figure 2.—Dissociation of aryl carbanilates at 150.0°. Correlation of equilibrium constants with Hammett σ values.

peratures. The values of ρ, estimated by least-squares correlation omitting the para halogens, were +1.66 at

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90.4°, +1.49 at 100°, +1.53 at 125°, and +1.50 at 150°.

The values of ρ in the present case are rather similar to the ρ value of +1.63 reported by Furuya and coworkers[4] for the aryl carbanilate–aniline interchange reaction in dioxane. However, there are obvious differences between the present products and the transition state postulated[4] for the interchange. A ρ value of +0.272 was reported for the second-order rate of the ester interchange between aryl carbanilates and 1-hexanol in o-dichlorobenzene.[5] The mechanism of this reaction presumably did not involve dissociation, and in any case the effect of substituents on the equilibrium constant for dissociation in dichlorobenzene may not be similar to that in ether solvents.

Previous workers have interpreted the positive ρ values in urethane interchange reactions in terms of an increase of the positive charge on carbonyl carbon[4] or amide nitrogen[3d] caused by electron-withdrawing substituents. In the present case, the data in Table III suggest that any correlation between log K and σ would result from a balance between the enthalpies and entropies of formation, solution, and association in the reactants and products. Since neither $\Delta H°$ nor $\Delta S°$ for the dissociation appears to correlate with σ, it would be difficult to interpret a linear free-energy correlation in terms of internal electronic effects within the urethane and phenol molecules.

A large number of reactions are known in which a Hammett linear free-energy correlation appears to exist, but in which both $\Delta H°$ and $\Delta S°$ change in a nonlinear manner with changes in σ.[13] In such reactions there appears to be a reasonable linear correlation between $\Delta H°$ and $\Delta S°$. These correlations have been interpreted in various ways,[13-16] but their significance

is not established. Recently an effort has been made to rationalize correlation between enthalpy and entropy of activation in a qualitative manner, by reference to the effect of σ on the enthalpy and energy of solvation.[17] Such a rationalization would be difficult to apply to the present case, since there is no discernable trend in the value of log K with increasing $\Delta H°$. It has been suggested[18,19] that most or all of the linear enthalpy–entropy correlations reported in the literature are fallacious, at least when these correlations are based in kinetic measurements. By this interpretation, such correlations are fundamentally derived from experimental errors in the original measurements and from improper statistical treatment of the data.

The present equilibrium studies provide a basis for the further study of rates and mechanisms in the transesterification of aryl carbanilates. The mechanisms of this reaction may change fundamentally with changes in temperature, solvent, and catalyst. The reaction of alcohols with isocyanate (reaction 5) is much faster in alcohol or hydrocarbon solvents than in ether solvents,[12] and the rate changes much less rapidly with temperature than does the equilibrium constant for dissociation (reaction 4). The activation energy for the reaction of phenyl isocyanate with 1-butanol in toluene was reported as 3.1 kcal mol^{-1} at 24–40°.[20] The rate of bimolecular nucleophilic attack may also be very sensitive to solvent, catalyst, and temperature. In order to examine the above factors more closely, we are presently investigating urethane dissociation equilibria in other aprotic solvents, and the kinetics of the urethane transesterification reaction in ether and alcohol solvents.

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Base-Catalyzed Reactions. XXXIX.[1] Kinetic Studies of Homogeneous Base-Catalyzed Addition Reactions of Alkylaromatics to Conjugated Hydrocarbons

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A large variety of alkylaromatic compounds were found to undergo nucleophilic addition to conjugated olefins at room temperature when the reaction was performed in a dipolar aprotic solvent using potassium *tert*-butoxide as a catalyst. The effectiveness of each of the solvents was determined from pseudo-first-order rate constants for the addition of 4-isopropylpyridine to isoprene in a variety of solvents and it was found to be DMSO > HMPA > NM2P > DMF > TMSO ≈ TMU (NM2P = *N*-methyl-2-pyrrolidone, TMSO = tetramethylene sulfoxide, TMU = tetramethylurea). The rates of reaction were also measured when the conjugated olefin used was styrene, α-methylstyrene, and β-methylstyrene. The mechanism of nucleophilic addition is discussed with regard to the effect of solvent and olefins used. Some selected reactions were run at different temperatures and their activation parameters were calculated.

Pseudohomogeneous alkylation reactions using organoalkali metals as catalysts have been studied extensively in this laboratory and have been shown to be synthetically useful for a variety of reactions.[3] The alkylation reactions were limited mainly to alkylation of alkylbenzenes[3] and alkylpyridines but more recently were also extended to alkylnaphthalenes.[4]

Although high temperatures are necessary for the addition of ethylene to aromatic compounds,[3] it has been found that by substituting conjugated dienes such as butadiene[5] and isoprene[6] or styrenes[7] for ethylene the addition reaction proceeds at room temperature or lower, especially when 2- or 4-alkylpyridines are used as the aromatics. It was thought, therefore, that weaker bases, such as potassium *tert*-butoxide in aprotic solvents, might act as catalysts for the alkenylation or aralkylation of pyridines and of other aromatic compounds. The success of this type of reaction has been reported in a preliminary communication.[8]

The present paper describes the effect of various aprotic solvents on the rate of the homogeneous addition reaction and the activation parameters of some of the reactions in various solutions.

An examination of dipolar aprotic solvents has shown that the negatively charged end of the solvent molecule dipole is more exposed to the molecular environment, and thus the strongest interactions occur with cations.[9] The anions are then free to participate actively in reactions without the stabilizing influence of ion-pair formation; the enhanced reactivity in dipolar aprotic solvents is in many cases quite dramatic. A good review has been written regarding the rates of bimolecular substitution reactions in protic and dipolar aprotic solvents.[10]

Studies have recently been made comparing reactions in various aprotic solvents. Zaugg[11a] investigated the effect of aprotic solvents upon the rate of reaction of sodio-*n*-butylmalonic ester with *n*-butyl bromide and the relative rates follow: benzene, 1; tetrahydrofuran (THF), 14; dimethoxyethane (DME), 80; dimethylformamide (DMF), 970; and dimethyl sulfoxide (DMSO), 1420. The suggested reason for the rate increase is that ionic aggregates are formed in solvents of low dielectric constants, but as the solvent becomes more polar a larger number of very slightly solvated reactive anions are formed that then participate rapidly in the reactions.[11b] In another study of reaction rates in various solvents, it was found that HMPA was a much better solvent than DMSO for the reaction of sodium azide with 1-bromobutane.[12]

Results and Discussion

The variety of alkylaromatics which were alkenylated or aralkylated in a homogeneous solvent-potassium *tert*-butoxide system is given in Table I, and the reactions can be represented by eq 1 and 2.[13]

Several interesting observations can be made from Table I. First, 4-ethyl- and 4-isopropylpyridine (expt 2 and 3) reacted with isoprene rapidly and gave quantitative yields of products in about 15 min. The rate of reaction of 4-picoline was slower than that of the higher 4-alkylpyridines, which is in agreement with the rates of reaction observed previously.[14] It is of interest to note that 2-picoline did not react with isoprene, and the rate of addition of 2-ethylpyridine was substantially slower than that of the 4 isomers in accordance with previous findings.[7]

The use of potassium *tert*-butoxide in a homogeneous system has an advantage in certain cases over the organoalkali metal catalyst systems, insofar as some of the heteroaromatic compounds that failed to react using the organoalkali metal catalysts were found to undergo reaction in a homogeneous medium. One notable example is the reaction of 2-methylthiophene with sty-

(1) (a) For paper XXXVIII, see W. M. Stalick and H. Pines, *J. Org. Chem.*, **35**, 1712 (1970). (b) Paper X of the series Alkylation of Heteroaromatics; for paper IX, see ref 1a.

(2) (a) Monsanto Predoctoral Fellow, 1965-1966; Ethyl Corp. Predoctoral Fellow, 1967-1968. (b) NSF Undergraduate Research Participant, 1966-1967. (c) Postdoctoral Fellow, on leave of absence from Czechoslovak Academy of Science.

(3) H. Pines and L. A. Schaap, *Advan. Catal.*, **12**, 117 (1960).

(4) B. Stipanovič and H. Pines, *J. Org. Chem.*, **34**, 2106 (1969).

(5) H. Pines and J. Oszczapowicz, *ibid.*, **32**, 3183 (1967).

(6) W. M. Stalick and H. Pines, *ibid.*, **35**, 415 (1970).

(7) H. Pines and N. E. Sartoris, *ibid.*, **34**, 2113 (1969).

(8) H. Pines and W. M. Stalick, *Tetrahedron Lett.*, 3723 (1968).

(9) E. M. Kosower, "An Introduction to Physical Organic Chemistry," Wiley, New York, N. Y., 1968, pp 334-342.

(10) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).

(11) (a) H. Zaugg, *J. Amer. Chem. Soc.*, **83**, 837 (1961); (b) H. Zaugg, *ibid.*, **82**, 2903 (1960).

(12) J. J. Delpuech, *Tetrahedron Lett.*, 2111 (1965).

(13) While this research was in progress, a condensation of butadiene with compounds of the general structure X-CH₃ (X = NO₂, CN, CHO) was reported: J. E. Hofmann and A. Schriesheim, *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, 16 (1967).

(14) W. M. Stalick and H. Pines, *J. Org. Chem.*, **35**, 422 (1970).

COMPOUNDS THAT UNDERGO BASE-CATALYZED ADDITIONS IN HOMOGENEOUS SYSTEMS[a]

Expt no.	Base concn,[b] mol/l.	Alkylaromatic	Alkylaromatic concn, mol/l.	Olefin	Olefin concn, mol/l.	% conversion[c,d]
1	0.5	4-Picoline	3	Isoprene	5	100
2	0.5	4-Ethylpyridine	3	Isoprene	5	100
3	0.5	4-Isopropylpyridine	3	Isoprene	5	100
4	0.5	2-Picoline	3	Isoprene	5	0
5	0.5	2-Ethylpyridine	3	Isoprene	6	15
6	0.5	2-Methylpyrazine	10	Isoprene	10	24
7	0.7	4-Picoline	3	Piperylene	5	77
8	0.7	4-Picoline	3	Butadiene	e	51
9	0.5	4-Picoline	10	Styrene	9	76[f]
10	0.5	4-Picoline	10	α-Methylstyrene	8	91[f]
11	0.7	4-Picoline	3	β-Methylstyrene	2.4	65[f]
12	0.7	2-Methylthiophene	3	Styrene	5	10[g]
13	0.7	1-Methylnaphthalene	3	Styrene	5	26[h]
14	0.7	3-Picoline	3	Styrene	5	46[i]

[a] The solvent was HMPA in all cases, and reactions were run at either 20° or room temperature. [b] The catalyst in all cases was potassium *tert*-butoxide. [c] Per cent conversion was based on the amount of alkylaromatic reacted after 3 hr. [d] The products formed were the mono-, di-, and triaddition products produced by adding one, two, or three olefin units to the side chain of the alkylaromatic. [e] Butadiene was bubbled through the reaction mixture as a gas. [f] Per cent conversion in this case is based on the amount of olefin reacted. [g] Yield after 165 hr. [h] Yield after 72 hr. [i] Yield after 50 hr.

$$ArCH_3 + CH_2=CHC=CHR' \xrightarrow[\text{solvent}]{K^+tert\text{-BuO}^-}$$

$$ArCH_2CH_2CH=CCH_2R' \quad (1)$$

$$ArCH_3 + \xrightarrow[\text{solvent}]{K^+tert\text{-BuO}^-}$$

$$ArCH_2CHCH- \quad (2)$$

$$Ar = \quad , \quad , \quad ,$$

$$R, R' = H, CH_3$$

$$ (3) $$

1

2
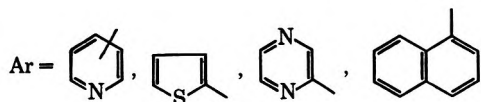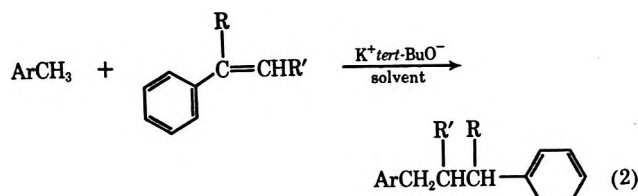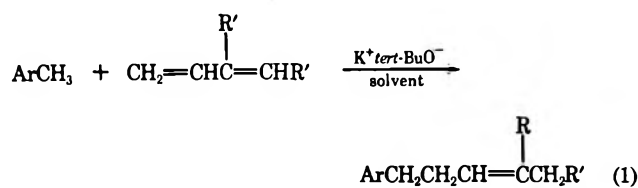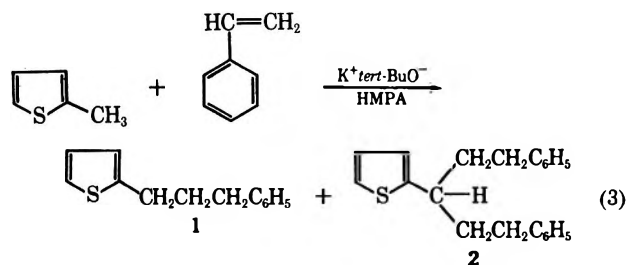
rene (eq 3). Literature reports state that metal hydrogen exchange occurs with the ring hydrogens and not with those of the alkyl side chain.[15] This example seems to be the first report of side chain metalation of one of the five-membered π-excessive heteroaromatic systems. In a like manner, it was possible to alkenylate 2-methylpyrazine (expt 6) and aralkylate 1-methylnaphthalene (eq 4).

The reactions of styrene with 1-methylnaphthalene and 2-methylthiophene were preceded by polymerization of styrene, and only after the styrene slowly de-

3

4

2 minor products (unidentified) (4)
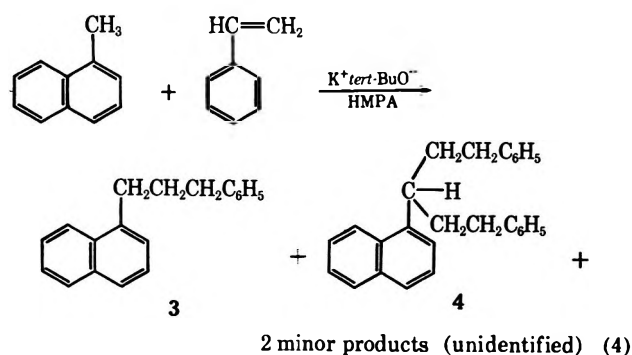
polymerized, after 1 day or longer, was a reaction product formed. Similar observations have been made during aralkylation of alkylpyridines with vinylpyridines.[16]

Finally, all of the conjugated olefins that have been used in the pseudohomogeneous media were found to react in the present system, including isoprene (expt 1), piperylene (expt 7), butadiene (expt 8), α-methylstyrene (expt 10), and β-methylstyrene (expt 11). Some of the yields given in Table I are probably far from optimum, since many of these reactions were run before the best techniques were found.

Kinetic Studies. A. Effect of Solvent on Reaction Rate.—Kinetic studies were made on the reaction of 4-isopropylpyridine with isoprene in a variety of solvents in order to determine their effect on the rate of reaction and product distribution (Table II). As has been reported previously[6] both tail and head addition occur (eq 5). Inspection of Table II shows that the reaction proceeds fastest in DMSO. The solvents were found to support the reaction in the following decreasing order: DMSO > HMPA > NM2P > DMF > TMSO > TMU ≫ ether solvents (NM2P = *N*-methyl-2-pyrrolidone, TMSO = tetramethylene sulfoxide, TMU = tetramethylurea). The present results are in agreement with the data reported for the base-catalyzed isomerization of olefins,[17] but the results are in contradiction with those found by Delpuech[12] who has reported that HMPA was the best

(15) S. Gronowitz, *Advan. Heterocycl. Chem.*, 73 (1963), and references therein.

(16) N. E. Sartoris and H. Pines, *J. Org. Chem.*, **34**, 2119 (1969).

(17) (a) S. Bank, A. Schriesheim, and C. A. Rowe, Jr., *J. Amer. Chem. Soc.*, **87**, 3244 (1965); (b) A. Schriesheim, *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, **14**, D9 (1969).

TABLE II

EFFECT OF SOLVENT ON REACTION RATE AND
PRODUCT RATIO[a] OF 4-ISOPROPYLPYRIDINE WITH ISOPRENE

Expt no.	Solvent[b]	$t_{1/2}$, min	Rate constant[c] × 10^5, sec^{-1}	Products[d] % head addition (5)	% tail addition (6)
15	DMSO	1.15	1010	59	41
16	HMPA	1.89	612	41	59
17	NM2P	32.8	35.2	52	48
18	NM2P[e]	36.6	32.0		
19	DMF	70.7	16.4	54	46
20	TMSO	240	4.8	51	49
21	TMU	250	4.66	51	49
22	THF	>1000[f]			
23	p-Dioxane	>1000[f]			
24	DME	>1000[f]			

[a] Concentrations used were 4-isopropylpyridine 4.8 mol/l. and isoprene 0.6 mol/l. [b] The catalyst was potassium *tert*-butoxide, concentration 0.45 mol/l. [c] The pseudo-first-order rate contants were determined at 20°. [d] The numbers 5 and 6 refer to the products shown in eq 5. [e] The 4-alkylpyridine used in this case was 4-ethylpyridine. [f] There was no noticeable change in the isoprene concentration after 5 hr.

(5)

5 head addition

6 tail addition
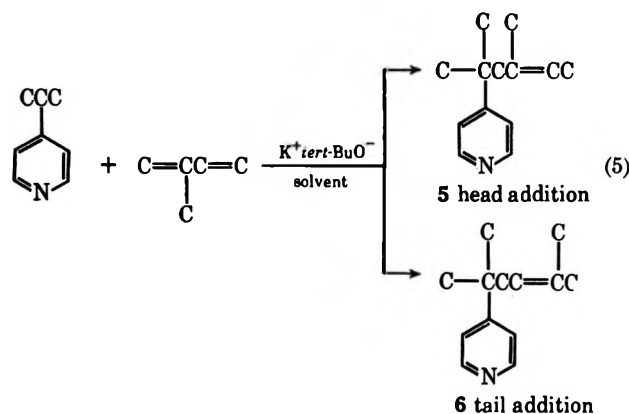
dipolar aprotic solvent. This was further corroborated by other researchers who observed higher yields for the base-induced alkylation of ethyl acetoacetate in HMPA than in DMSO or NM2P.[18] In the proton exchange reaction of toluene, HMPA is vastly more active than DMSO or TMSO,[19] and again in the base-catalyzed autoxidation of thiols and disulfides HMPA is found to be superior to DMF or TMU.[20] Similar results have led Normant to state that HMPA appears to be the most remarkable of the polar aprotic solvents.[21]

The greater rate enhancement in DMSO over that in HMPA can be explained by considering the free energy *vs.* reaction coordinate of the reaction being studied. The reaction is assumed to proceed from the starting materials through an addition transition state to an intermediate, which will then proceed through a second transition state upon protonation before going to product. It was reported previously from this laboratory[14] that the rate of addition to isoprene was increased in the addition step by metal–double bond complexation and in the protonation step by intramolecular protonation. Any factor that would increase either of these steps would then increase the overall rate of addition.

It is known that, when potassium *tert*-butoxide is employed as a base in DMSO, the latter readily undergoes a proton exchange with alkylaromatics.[22] HMPA, however, does not undergo such an exchange reaction with the surrounding weakly acidic hydrocarbons such as toluene.[19] Considering the addition of the 4-isopropylpyridine anion to isoprene, it is obvious that both DMSO and HMPA are excellent solvents for cation solvation, thus essentially removing the cation from the ion pair. The anion in both of these solvents will therefore readily add to isoprene, but in HMPA the protonation will occur mainly from the excess isopropylpyridine molecules, since *tert*-butyl alcohol generated in the reaction is present only in minute quantities. On the other hand, in DMSO the protonation of the allylic anion can occur not only from isopropylpyridine but also from the solvent itself, thus giving the overall result that DMSO is the best solvent for this reaction.

B. Effect of Solvents on Product Distribution.— The product distribution noted in Table II can also be explained by the ease of protonation of the anion adduct. The addition of the anion to isoprene is

primary ⟷ secondary (tail addition)

primary ⟷ tertiary (head addition)
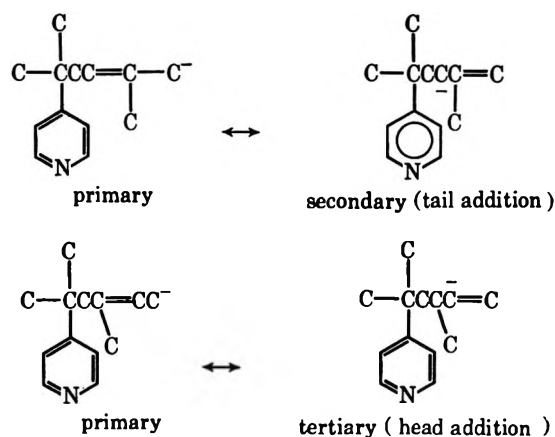
assumed to be relatively nonselective in both DMSO and HMPA owing to the absence of ion pairing. Protonation of the anion is, however, sterically more favorable for the head addition isomer. In HMPA, protonation of the anion occurs by the excess 4-isopropylpyridine, and this is a sterically hindered process. In DMSO, however, the intermediate anions can also be protonated by the solvent DMSO, snd these solvent protons are more accessible for protonation. Thus, the product contains more of the tail addition isomer (59%), which, although more sterically hindered for protonation than the head addition isomer, is nevertheless more electronically stable having primary ⟷ secondary *vs.* primary ⟷ tertiary anions in its resonance state. The other solvents used are intermediate in their abilities to exchange hydrogens, and the product ratios in these solvents are about 50% tail addition and 50% head addition.

C. Effect of Steric Factors on Reaction Rate.—The effects of steric factors on reaction rates were determined using 4-ethyl- and 4-isopropylpyridine as the aromatics and styrene, α-, and β-methylstyrene as the olefins. All rate determinations were made using the 4-alkylpyridine in large excess over the diolefin. Good

(18) W. J. Le Noble and H. F. Norris, *J. Org. Chem.*, **34**, 1969 (1969).
(19) J. E. Hofmann, A. Schriesheim, and D. D. Rosenfeld, *J. Amer. Chem. Soc.*, **87**, 2523 (1965).
(20) T. J. Wallace and A. Schriesheim, *Tetrahedron*, **21**, 2271 (1965).
(21) H. Normant, *Angew. Chem., Int. Ed. Engl.*, **6**, 1046 (1967).

(22) N. Kharasch and B. S. Thyagarajan, *Quart. Rep. Sulfur Chem.*, **1**, 61 (1966).

pseudo-first-order kinetic plots were obtained in all cases.

From Table III it can be seen that the reactions occur

TABLE III
RATES OF REACTION OF ALKYLPYRIDINES WITH STYRENES[a]

Expt no.	z =	R = (z-Alkylpyridine)	R₁ (Styrene)	Solvent	$t_{1/2}$, min	Rate constant[b] × 10^4, sec^{-1} / 10^2
25	4	-C<C,C	-C=C	NM2P	0.84	136
26	4	-C<C,C	-C=C	TMU	4.60	25.0
27	4	-C<C,C	-C=C	TMSO	4.56	25.3
28	4	-C<C,C	-C<C,C	NM2P	82.4	1.40
29	4	-C<C,C	-C<C,C	DMSO	5.64	20.5
30	4	-C<C,C	-C=C-C	DMSO	20.9	5.53
31	4	-C<C,C	-C=C-C	HMPA	19.1	6.04
32	4	-C-C	-C<C,C	DMSO	3.36	34.0
33	4	-C-C	-C=C-C	DMSO	3.02	38.3
34	4	-C-C	-C=C	NM2P	1.38	83.7
35	2	-C-C	-C=C	NM2P	40.64	2.82
36	2	-C-C	-C=C	DMSO	4.17	27.4
37	3	-C-C	-C=C	DMSO	17.03	6.78

[a] The catalyst was potassium *tert*-butoxide, concentration 0.45 mol l.$^{-1}$; other concentrations used were 4-isopropylpyridine 4.8 mol l.$^{-1}$, 4-ethylpyridine 5.2 mol l^{-1}, and styrenes 0.6 mol l^{-1}. [b] The pseudo-first-order rate constants were determined at 20.0 ± 0.1°.

fastest in DMSO and HMPA, slower in NM2P, and the slowest in TMU and TMSO. The 4-alkylpyridines added too rapidly to styrene in DMSO or HMPA for the rate of reaction to be measured by the techniques used in this study. The addition of alkylpyridine to pure *cis*- and *trans*-β-methylstyrene could not be studied as these olefins undergo rapid isomerization to a mixture of 95% trans and 5% cis isomer in less than 1 min after contact with the solvent–base system at 20°.

Some interesting conclusions can be drawn from the experiments in Table III. 4-Ethylpyridine adds to α-methylstyrene in DMSO 1.7 times as fast as and to β-methylstyrenes 7 times as fast as does 4-isopropylpyridine (expt 29, 30, 32, and 33). This is in contradiction to the results obtained previously from a competitive reaction whereby the 4-isopropylpyridine anion adds to isoprene 1.1 times as fast as does the 4-ethylpyridine anion.[14] The data thus obtained imply that addition to isoprene is the least sterically hindered reaction, whereas the addition to α-methylstyrene must thus be somewhat hindered, and steric hindrance seems to be a major factor in the rate of addition to β-methylstyrene.

The addition of the 4-isopropylpyridine anion to isoprene in DMSO is 1.6 times as fast as that in HMPA, presumably because DMSO aids in the protonation of the product (expt 15 and 16, Table II). When a similar comparison is made for the addition to β-methylstyrene (expt 30 and 31), the reaction rates are about equal with the reaction occurring 1.1 times as fast as that in HMPA, probably because steric hindrance has made the addition step rate controlling.

D. Effect of Acidity on Reaction Rate.—It was found that the rate of addition of the isomeric ethylpyridines to styrene depends on the acidity of the alkylpyridines (Table III). The relative acidities of pico-

lines have been recently determined from the sodium methoxide exchange rates between methanol and ω-tritium-substituted picolines.[23] They were ($K_2 \times 10^6$ l. mol^{-1} sec^{-1}) 3-picoline 0.42, 2-picoline 54, and 4-picoline 760. In the present experiments it was found that the rate of addition of 2-ethylpyridine to styrene is 4 times as great as that of 3-ethylpyridine, although there must be greater hindrance in the addition of 2 over the 3 isomer (Table III, expt 36 and 37).

4-Ethylpyridine adds to styrene in DMSO too fast to be measured, while in NM2P the rate of addition of 4- and 2-ethylpyridine is 83.8 vs. 2.84 at 20° (expt 34 and 35). 3-Ethylpyridine is not acidic enough to add to styrene in NM2P; instead the NM2P adds to the olefin to form 3-β-ethyl- and di(3-β-ethyl)-N-methyl-2-pyrrolidone.[24]

Activation Parameters.—Table IV summarizes the average rate constants found at the different temperatures and the derived activation parameters as calculated by means of standard expressions. The $\Delta S^{\ddagger}$ values are all negative and show a continuous trend of becoming more negative as the unsaturated hydrocarbons become less sterically hindered to addition in a given solvent, NM2P.

The entropy of activation for the addition of 2- and 4-ethylpyridine to styrene being the same indicates that the lower enthalpy of activation of the 4 isomer is due mainly to its greater acidity and not to a lower steric effect. When a change is made in the solvent for the same reaction, as shown in the first two cases of Table IV, again it is noted that the change in the rate of the reaction is due to the enthalpy of activation. As expected in this study, HMPA has a lower enthalpy of activation and the reaction proceeds faster in this solvent than in NM2P.

Experimental Section

General Reaction Procedure.—The general reaction procedure followed was similar to that used for the isomerization of olefins.[25] All of the needed reagents and solvents were distilled immediately before use and transferred to a drybox where the catalyst solutions were prepared. It has been reported that carbanions in this type of system are relatively stable if oxygen is excluded;[26] these reports were well verified by this study. The alkylaromatic was then added to the catalyst solution contained in a small vial and sealed with a self-sealing neoprene stopper. The sealed vial was

(23) W. N. White and D. Lazdins, *J. Org. Chem.*, **34**, 2756 (1969).
(24) H. Pines, S. V. Kannan, J. Simonik, and B. Stipanović, unpublished results.
(25) S. Bank, C. A. Rowe, Jr., A. Schriesheim, and L. A. Naslund, *J. Amer. Chem. Soc.*, **89**, 6897 (1967).
(26) A. J. Parker, *Advan. Org. Chem.*, **5**, 1 (1965).

TABLE IV
ACTIVATION PARAMETERS FOR THE ADDITION OF ALKYLPYRIDINES TO ISOPRENE AND STYRENES

x-Alkylpyridine

Olefin	x =	R =	K_ψ, sec^{-1}	Temp, °C	Solvent	E_a, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/deg/mol
Isoprene	4	$-\text{C}<^{\text{C}}_{\text{C}}$	3.51×10^{-4} 7.70×10^{-4}	20 30	NM2P	13.8 ± 0.3	13.2 ± 0.3	-29.1 ± 1.1
Isoprene	4	$-\text{C}<^{\text{C}}_{\text{C}}$	3.22×10^{-3} 6.12×10^{-3}	10 20	HMPA	10.6 ± 0.6	10.0 ± 0.6	-34.4 ± 2.3
α-Methylstyrene	4	$-\text{C}<^{\text{C}}_{\text{C}}$	1.40×10^{-4} 3.30×10^{-4}	20 30	NM2P	15.1 ± 0.5	14.5 ± 0.5	-26.6 ± 1.7
Styrene	4	$-\text{C}<^{\text{C}}_{\text{C}}$	8.48×10^{-3} 1.35×10^{-2}	10 20	NM2P	7.8 ± 0.8	7.3 ± 0.8	-42.3 ± 2.7
Styrene	2	$-\text{C-C}$	2.82×10^{-3} 6.06×10^{-3}	20 30	NM2P	13.4 ± 0.2	12.83 ± 0.23	-31.0 ± 0.8
Styrene	4	$-\text{C-C}$	5.03×10^{-3} 8.38×10^{-2}	10 20	NM2P	8.7 ± 0.02	8.20 ± 0.02	-31.8 ± 0.1
Styrene	3	$-\text{C-C}$	2.24×10^{-4} 6.78×10^{-4}	10 20	DMSO	9.6 ± 0.2	9.06 ± 0.21	-33.9 ± 0.8

then removed either to the laboratory or placed in a thermostated constant temperature bath. The olefin was injected through the neoprene cap and reaction samples were removed at various intervals and quenched in methanol. The samples were then analyzed for products by vpc. When preparative samples were prepared, the reactions were quenched with methanol and extracted with water and ether. The ether fractions were combined and dried over MgSO$_4$, and the ether was removed by rotary evaporation before the residue was distilled for a crude separation of products. Further purifications were made by preparative vpc.

Characterization of Compounds in Table I.—1-Phenyl-3-(2-thienyl)propane (1) and 1,5-diphenyl-3-(2-thienyl)pentane (2) were synthesized by the general reaction procedure given above. After the solvent had been removed, compound 1 distilled over as a light yellow fraction at 124° (5 mm). Compound 2 was left in the brown residue after distillation. Further purification of compound 1 was made by vpc using an 8 ft × ³/₈ in. column packed with 15% silicone gum rubber SE-30 on 60–80 mesh Gas-Pack WAB at 220°. The nmr spectrum was taken and found to be consistent with the proposed structure. Compound 2 was purified on the same preparative pvc column at 250°, and after two recyclings a clear, viscous liquid was obtained in 99.5+% purity. The spectrum was taken using a micro nmr tube and found to be consistent with the proposed structure.

In a like manner 1-phenyl-3-(1-naphthyl)propane (3) and 1,5-diphenyl-3-(1-naphthyl)pentane (4) were synthesized and identified. Purification was made on the vpc column described above. Compound 3 was purified at 240° and compound 4 at 270°. Two other higher boiling minor products were evident but were not separated for identification. The nmr spectra of both 3 and 4 were consistent with the proposed structures.[27]

The other reactions described in Table I were not run on a preparative scale since the products of reaction have previously been reported. Product identifications were for the most part made by comparative vpc with compounds of known structure. The products from the following reactants are reported: 4-picoline with piperylene,[28] butadiene,[5,14] styrene,[7] α-methylstyrene,[7] and β-methylstyrene;[7] 4-picoline, 4-ethylpyridine, and 4-isopropylpyridine with isoprene;[6] and 3-picoline with styrene.[29]

Calculations.—After the samples taken from the reactions studied at different time intervals were analyzed, the data were transferred to computer cards. The reaction rate constant and half-life were then calculated by means of the FORTRAN program TXNRAT, using standard least-squares techniques.[30] Activation parameters were then calculated by means of standard expressions. All calculations were carried out on the Northwestern University CDC 6400 computer.

Equipment.—Nmr analyses were performed on a Varian Model A-60 spectrophotometer using tetramethysilane as an internal standard in a CCl$_4$ solvent. The micro nmr tube was from NMR Specialties, Inc. Some studies were performed at a constant temperature in a Lo-Temptrol 154 constant temperature bath from Precision Scientific Co. thermostated to ±0.10°. Vpc separations and identifications were made using an F & M Model 270 dual-column gas chromatograph equipped with a thermal conductivity detector and using helium as a carrier gas. Product compositions, separations, and identifications were performed using 7 ft × 0.25 in. or 8 ft × ³/₈ in. columns packed with 15% silicone gum rubber SE-30 on 60–80 mesh Gas-Pack WAB and a 10.5 ft × 0.25 in. column packed with 15% Versamid 900 on 60–80 mesh Gas-Pack WAB at various temperatures.

(27) By vpc compounds 1–4 were found to be of greater than 95% purity. Using nmr it was then possible to determine accurately the number of styrene moieties that had been added to the alkyl side chain.

(28) H. Pines and B. Stipanović, unpublished results.
(29) Yu. I. Chumakov and V. M. Ledovskikh, *Tetrahedron*, **21**, 937 (1965).
(30) A modification of a program reported earlier: J. P. Day, F. F. Basolo, and R. G. Pearson, *J. Amer. Chem. Soc.*, **90**, 6927 (1968).

Base-Catalyzed Reactions. XL.[1]   Sodium- and Potassium-Catalyzed Reactions of 3-Methyl- and 3-Ethylpyridine with Olefinic Hydrocarbons.   Cyclialkylation of 3-Alkylpyridines

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The lower acidity of 3-alkylpyridines compared to the 2 and 4 isomers is manifested in their reactivities, especially in base-catalyzed reactions. They require more vigorous conditions for reactions to occur. A novel cyclialkylation occurs when 3-ethylpyridine or 3-sec-butylpyridine reacts with ethylene in the presence of sodium or potassium. Under the same conditions, 3-methylpyridine fails to react. The cyclialkylation is confined to ethylene among the olefins studied. With conjugated olefins such as butadiene, isoprene, and styrene, the norml addition products are formed. A mechanism consistent with the results is proposed.

Base-catalyzed reactions of alkylbenzenes,[2] alkylnaphthalenes,[3] and alkylpyridines[2,4] have been the subjects of extensive investigations in this laboratory. In the presence of sodium, toluene has been shown to form normal addition products with olefins but cyclic products accompany the normal products in the presence of potassium,[2,3] while the more acidic 2- and 4-alkylpyridines gave rise to only normal addition products.[2,4] With their acidities comparable to that of toluene and with the 2 positions of their rings highly susceptible to nucleophilic attack, 3-alkylpyridines were found to behave differently from their 2 and 4 isomers.[5] The present investigation was undertaken to extend the scope of the reaction.

the benzylic hydrogens are successively displaced to give normal addition products. In addition to requiring longer reactions times and higher temperatures, 3-ethylpyridine (1) reacts differently with ethylene as can be seen from Table I. The two primary products from the reaction in the presence of sodium are 3-sec-butylpyridine (4) and 6,7-dihydro-7,7-diethyl-5-methyl-5H-1-pyridine (7). Further ethylation occurs with a longer reaction time to yield 6,7-dihydro-5,7,7-triethyl-5-methyl-5H-1-pyridine (8). The reaction sequence is summarized in Scheme I.

A carbanion mechanism has been proposed for the reactions catalyzed by alkali metals.[2,6] Extending this mechanism to the present reaction, the carbanion

SCHEME I
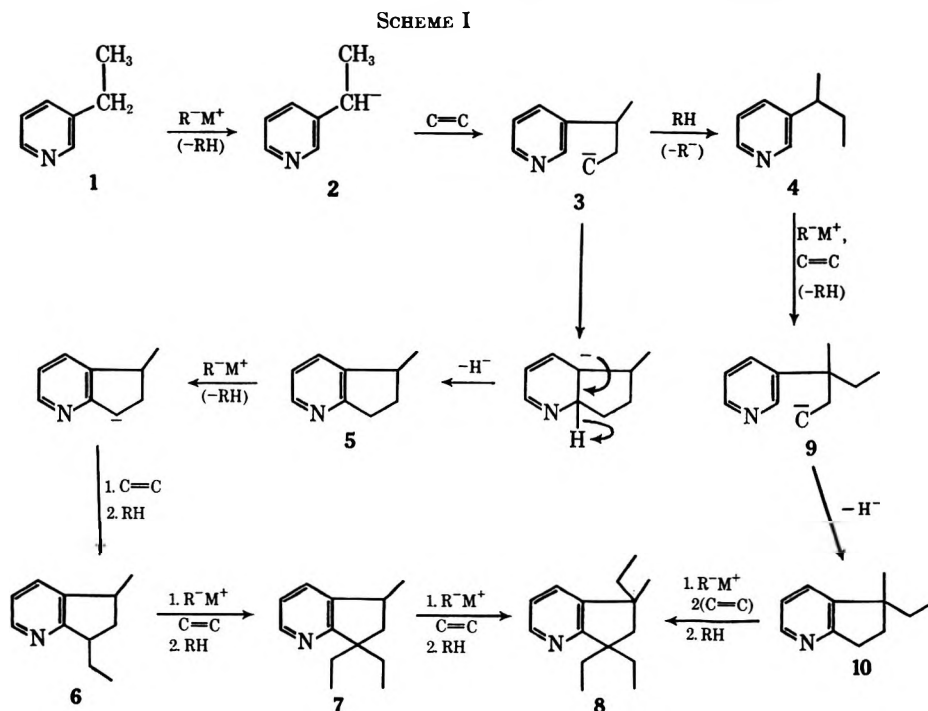
Results and Discussion

A.   Ethylene.

When 2- or 4-alkylpyridines react with ethylene in the presence of sodium or potassium,

formed from 1, through a mechanism similar to the one described previously,[7] can add to ethylene to form carbanion 3, which has two courses open for reaction: it can transmetalate to give 4 or attack the 2 position of the ring in the same molecule to give a cyclic product 5. This new type of cyclization is consistent with our knowledge of the high electrophilicity of the 2 position

(1) (a) For paper XXXIX, see H. Pines, W. M. Stalick, T. G. Holford, J. Golab, H. Lazar, and J. Simonik, *J. Org. Chem.*, **36**, 2299 (1971). (b) Paper XI of the series, Alkylation of Heteroaromatics; for paper X, see ref 1a.

(2) H. Pines and L. A. Schapp, *Advan. Catal.*, **12**, 116 (1960).

(3) B. Stipanovič and H. Pines, *J. Org. Chem.*, **34**, 2106 (1969).

(4) H. Pines and B. Notari, *J. Amer. Chem. Soc.*, **82**, 2209 (1960).

(5) S. V. Kannan and H. Pines, *Chem. Commun.*, 1360 (1969).

(6) H. Pines and N. C. Sih, *J. Org. Chem.*, **30**, 280 (1965).

(7) Reference 3; see Discussion.

TABLE I

REACTIONS OF 3-ETHYLPYRIDINE WITH ETHYLENE[a] IN THE PRESENCE OF ALKALI METALS

Expt no.	Temp, °C	Duration of reaction, hr	Conversion, %[b]	Composition of product,[c] wt %			
				4	7	8	Others
Sodium							
1	160	2.5	17	42	58	0	
2	160	7.0	41	42	47	11	
3	160	15.0	64	34	49	18	
4	160	26.0	82	25	33	35	
Postassium							
5	120	4.5	12	25	26	20	29
6	120	11.5	44	27	26	17	30
7	120	24.0	64	25	24	21	30
8	160	3.0	26	29	24	15	32
9	160	12.0	60	32	28	19	21
10	160	18.0	78	35	24	22	17

[a] Initial pressure of ethylene at room temperature was 40 atm. [b] Based on 3-ethylpyridine. [c] From vpc peak areas uncorrected for thermal conductivity.

in the pyridine ring.[5] The proportions of the normal and cyclic products in the reaction will depend on the relative rates of transmetalation and cyclization. A consequence of cyclization is the liberation of hydride anion which adds to ethylene, the ultimate product being ethane which was found to be present in the product.

Obviously because of its high reactivity compared with 1 and 4, the cyclic product 5 could not be detected in the products. Hence, it is presumed that 5 is converted to its carbanion and then to 6 as shown in Scheme I as soon as it is formed. Although the carbanion derived from 6 is tertiary, it appears to be more readily formed than those from 1 or 4; it reacts with ethylene to form 7. The relative proportions of 4 and 7 should be a measure of the relative rates of transmetalation and cyclization of the carbanion 3.

As the reaction progresses, the concentration of 1 decreases and that of 4 and 7 increases. The latter two start competing for ethylene through their anions, which are both tertiary. By starting with pure 4 and allowing it to react with ethylene in the presence of sodium, it was found that it gave rise to only one product in 39% yield, viz., 8. The reaction took a long time (14 hr), which is to be anticipated for a sec-butyl group.[2] As can be seen from Scheme I, 8 can arise both from 4 and 7. Whereas it is a one-step process for 7, it is a multi-step process for 4. Of these many steps, only the cyclization is expected to be slow, the displacement of benzylic hydrogens in the 2 position being necessarily faster. The absence of 11 in the reaction products,

11
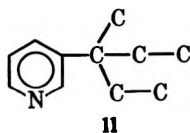
which can be formed from either 1 or 4, shows that, once the anion 9 is formed, its transmetalation to give 11 is slower compared to its cyclization to 10.

Potassium has previously been found to bring about such alkylation reactions at lower temperatures, about 120° compared to about 160° for sodium.[3] From Table I it can be seen that side reactions are promoted by potassium accounting for a considerable percentage of other products which were not identified. There were at least eight products at lower conversions which could not be separated by gas chromatography. At higher

conversions, the products 4, 7, and 8 predominated over others. In all likelihood, potassium is catalyzing nuclear alkylation in addition to cyclization reactions. Potassium-catalyzed nuclear alkylation has already been reported in the case of alkylnaphthalenes.[3]

Lithium failed to bring about the same reaction even at 200°. The black material obtained after decomposition of the product with methanol probably indicates that dimerization and polymerization of 3-ethylpyridine occurred in preference to reaction with ethylene.

Cyclization does not occur in the cases of 2- and 4-ethylpyridine under he influence of the same catalysts, because such a reaction would necessarily involve nucleophilic attack on the 3 position of the ring and that position is resistant to such reactions.

It was found that 3-methylpyridine fails to react with ethylene in the presence of sodium, potassium, and lithium under the same conditions. Varying the temperature and the amount of the catalyst had no effect. It is presumed that the black residue invariably obtained after decomposition of the reaction product at the end of each experiment is an indication that the catalyst is being consumed for dimerization and polymerization reactions of the starting material. Alkali metals are known to catalyze such reactions.[8] It appears that, in the case of 3-methylpyridine, these side reactions are faster than addition to ethylene.

Attempts were made to react propylene with 3-methyl- and 3-ethylpyridine in the presence of sodium and potassium. Propylene being less reactive than ethylene would require high temperatures for the reaction to occur.[2] At temperatures of 200° and higher, however, a self-condensation of alkylpyridines occur,[8] accompanied by the destruction of the catalyst. The product from these reactions consisted of a black residue.

B. Styrene and α-Methylstyrene.—With a more reactive olefin like styrene or α-methylstyrene, both 3-methyl- and 3-ethylpyridine react. Cyclization products were not formed in the reactions. Styrene reacts with 3-ethylpyridine to form only the monoadduct 12, whereas 3-methylpyridine has been reported to form both mono- and diadducts.[9] A 3% yield of ethylbenzene was also obtained in the former reaction. The re-

(8) R. M. Acheson, "The Chemistry of Heterocyclic Compounds," Wiley, New York, N. Y., 1967, p 198.
(9) Y. I. Chumakov and V. M. Ledovskikh, *Tetrahedron*, **21**, 937 (1965).

actions of 3-methylpyridine and 3-ethylpyridine with α-methylstyrene are complex, giving at least five products, respectively, at low conversions which could not be separated by gas chromatography. Obviously, side reactions are competing with the normal addition reactions.

C. Butadiene and Isoprene.—The reaction of 3-methylpyridine with butadiene has been reported to tive 3-(trans-3-pentenyl)pyridine with traces of 1 olefin.[9] Under the vigorous conditions used for the reaction, it is probable that the authors had obtained the thermodynamically more stable trans adduct due to equilibration. Reinvestigation of this reaction under milder conditions (60° vs. 150°) yielded the cis adduct 13 in predominance over the trans adduct 14 (Table II). The

TABLE II

REACTION OF 3-ALKYLPYRIDINES WITH BUTADIENE[a]
IN THE PRESENCE OF SODIUM AT 60°

3-Methylpyridine

Reaction time, hr	Conversion, %[b]	Wt % of total adducts[c]				Cis/trans
		Mono-				
		cis-13	trans-14	Di-	Tri-	
0.5	39	55	33	12		1.67
1.7	70	50	31	19		1.61
2.0	100	32	23	45	Trace	1.39
8.0	100	18	14	63	5	1.29

3-Ethylpyridine

Reaction time, hr	Conversion, %	Wt % of total adducts				Cis/trans
		15	16	Di-	Tri-	
1.0	15	49	34	17		1.44
3.0	44	45	33	22		1.33
6.0	77	39	34	27		1.15
2.0[d]	100	29	29	42		1.00

[a] 0.05 mol of 3-alkylpyridine and 0.15 mol of butadiene used. [b] Based on alkylpyridine charged. [c] From vpc peak areas, uncorrected for thermal conductivity. [d] Reaction conducted at 90°.

cis/trans ratio, however, decreases with increasing conversion indicating that either the cis adduct reacts faster than the trans adduct with butadiene to form the diadduct or that the former isomerizes to the thermodynamically more stable trans adduct. The same trend is observed in the reaction of 3-ethylpyridine with butadiene when cis-15, trans-16, and diadducts are formed. A total gas chromatographic separation of the diadducts to determine their geometry around the double bond could not be accomplished. In the present reactions also, the presence of the terminal olefin was detected by infrared spectroscopy in both mono- and diaddition products. Under comparable conversions, 3-ethylpyridine formed more diadduct than 3-methylpyridine. This probably indicates the greater reactivity of the tertiary anion from the former compared to the secondary anion from the monoadduct of the latter. The formation of diadducts from dienes even at low conversions has also been observed in earlier studies and was interpreted as being due to the intramolecular proton transfer reaction to form a new picolyl anion.[10,11]

The reaction of isoprene with 3-ethylpyridine was carried out to determine the head/tail addition ratio in the formation of the monoadducts 17 and 18 (Table III). The ratio was 1 to 3 indicating that tail addition is preferred.

TABLE III

REACTION OF 3-ETHYLPYRIDINE WITH STYRENE AND ISOPRENE[a]

Reactant	Temp, °C	Conversion, %[b]	Wt % of monoadduct[c]
Styrene	135	100	97[d] (12)
Isoprene	80	100	100[e] (17, 18)

[a] 0.03 mol of 3-ethylpyridine and 0.015 mol of olefinic hydrocarbon were used. [b] Based on olefins used. [c] From vpc peak areas uncorrected for thermal conductivity. [d] The other 3% was identified as ethylbenzene. [e] Nmr showed 25% 17 and 75% 18.

The absence of cyclialkylation in the reactions of styrene, butadiene, and isoprene has to be accounted for. From previous studies,[12] it is known that only anion 19 is generated by the addition of styrene to an alkylpyridine. Being a secondary anion and being

$$PyCHCH_2\overset{|}{\underset{R}{C}}HC_6H_5$$

19, R = H, CH$_3$, etc.
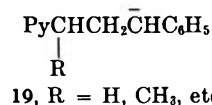
stabilized by resonance with the phenyl ring, it is not expected to be as nucleophilic as the primary anion 3, which has all the negative charge localized on one carbon atom. Hence, it is not able to attack the 2 position of the ring as effectively as the latter. Also, the transmetalation step may be expected to be faster with a secondary anion than a primary one.

In the addition of 3-alkylpyridines to butadiene, allylic anion is generated. This delocalized anion 20 is

$$PyCHCH_2\overset{|}{\underset{R}{C}}CH=CH_2 \longleftrightarrow PyCHCH_2\overset{|}{\underset{R}{C}}=CH\bar{C}H_2$$

20
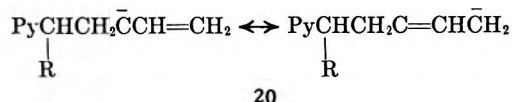
sufficiently stable that transmetalation is energetically preferred over cyclialkylation. For the same reason isoprene is also reluctant to form cyclic products.

Summary

3-Alkylpyridines form cyclialkylated products on reaction with ethylene; this is in contrast to their 2 and 4 isomers. The cyclialkylation is a consequence of the high electrophilicity of the 2 position of the ring. With vinyl- or aryl-substituted ethylenes, the "normal" mono- and diadditions take place.

Experimental Section

Reagents.—3-Methyl- and 3-ethylpyridine were purchased from Reilly Tar and Chemical Co. The material was dried over barium oxide and distilled in a nitrogen atmosphere. sec-Butylpyridine was obtained by reacting 3-ethylpyridine with ethyl-bromide, according to the procedure described in the literature.[13] All the alkylpyridines used in the reaction were over 99.5% pure as adjudged by gas chromatography.

Butadiene was obtained from Matheson Co. Isoprene (Aldrich Co.) was dried over Linde 3A molecular sieves and distilled just before use. Isopropylcyclohexane (internal standard) was obtained by catalytic hydrogenation of isopropylbenzene under 100 atm of hydrogen pressure at 150°, using nickel kieselguhr (Harshaw Chemical Co.) catalyst. Styrene and α-methylstyrene were purchased from Matheson Co.

Alkylation Procedure.—The following general procedure was used for alkylations with ethylene, butadiene, and isoprene. The alkylpyridine, about 1% by weight of the alkali metal, and an internal standard (usually isopropylcyclohexane) were stirred in a flask equipped with a high-speed stirrer[6] under an atmosphere

(10) H. Pines and J. Oszczapowicz, J. Org. Chem., 32, 3183 (1967).
(11) W. M. Stalick and H. Pines, ibid., 35, 422 (1970).
(12) H. Pines and N. E. Sartoris, ibid., 34, 2113 (1969).
(13) H. C. Brown and W. A. Murphey, J. Amer. Chem. Soc., 73, 3308 (1951).

Table IV

Chemical Shifts in Nmr Spectra

Compd	Group	Multiplicity (no. of protons)	δ, ppm
7, R_1 = H	a	Doublet (3)	1.23
(b)	b	Multiplet (1)	3.10
	c	Multiplet (6)	2.06
	d	Triplet (3)	0.70
	e	Triplet (3)	0.72
8, R_1 = CH_2CH_3	a	Singlet (3)	1.23
(c) (d)	b		
	c	Multiplet (8)	1.67
	d, e	Multiplet (9)	0.8

13, 14, R_1 = R_2 = R_3 = H	a, b, c	Multiplet (4)	2.50
	d, e	Multiplet (2)	5.41
	f, *cis*-13	Doublet (3)	1.51
	f, *trans*-14	Doublet (3)	1.61
15, 16, R_1 = CH_3;	a	Multiplet	2.70
R_2 = R_3 = H	b	Doublet	1.24
	c	Multiplet	2.29
	d, e	Multiplet	5.30
	f, *cis*-15	Doublet	1.53
	f, *trans*-16	Doublet	1.60
17, R_1 = R_2 = CH_3;	a	Multiplet (1)	2.83
R_3 = H	b	Doublet (3)	1.38
	c	Doublet (2)	2.31
	d, f	Doublet (6)	1.62
	e	Quartet (1)	5.14
18, R_1 = R_3 = CH_3;	a	Multiplet (1)	2.83
R_2 = H	b	Doublet (3)	1.27
	c	Multiplet (2)	2.31
	d	Triplet (1)	5.14
	e, f	Singlet (6)	1.75

12

	a	Doublet (3)	1.23
	b	Multiplet (1)	2.46
	c	Multiplet (2)	1.85
	d	Triplet (2)	2.46

of nitrogen. After 2.5 hr the black solution was transferred to a Magne-Dash autoclave,[14] olefin was added, and the reaction was conducted for a prescribed length of time at the desired temperature. At the end of the reaction, the contents were cooled, decomposed with methanol, and analyzed directly by gas chromatography. Samples for nmr and ir were obtained by washing the solution with water, distilling, and separating by preparative gas chromatography.

In the case of styrene and α-methylstyrene, these were added to the heated catalyst solution at 135° dropwise and the reaction was quenched 15 min after the addition was finished.

Analytical Procedure.—Analysis of the products formed was conducted on either a 10% Versamide 900 (6 ft) on 60–80 mesh Gas-Pack WAB or on a 20% silicone DC 550 (6 ft) on 60–80 mesh Gas-Pack W column with the temperature programmed between 100 and 250°. Preparative gas chromatography was performed on 10 ft × $^3/_8$ in. 20% silicone DC 550 on 60–80 mesh Gas-Pack W and on 8 ft × $^3/_8$ in. 10% Versamid 900 on 60–80 mesh Gas-Pack WAB columns. The compounds were identified by a combination of ir, nmr, and microanalysis where needed.

Identification of the Products.—The products were identified by a combination of nmr, ir, and vpc (Table IV). In the nmr spectrum of compounds **7** and **8**, one of the α protons was found to be absent but the γ proton was intact showing that the addition had occurred in the α position. The retention times by gas chromatography indicate that **7** is a triadduct and **8** is a tetraadduct. Infrared spectra showed the absence of unsaturation and only the proposed structure fits the facts.

Microanalyses[a]

Compd	Calcd, %			Found %		
	C	H	N	C	H	N
7	82.48	10.12	7.40	82.41	10.10	7.40
8	82.87	10.67	6.46	82.45	10.97	6.72

[a] W. H. W. Laboratories, Garden City, Mich.

The cis and trans compounds obtained from the reaction of 3-methyl- and 3-ethylpyridine with butadiene were separated by preparative vpc. The ir of the cis adducts had a characteristic peak at 675 cm⁻¹, the trans adducts at 966 cm⁻¹, and the terminal olefin at 909 cm⁻¹. From the extinction coefficients, the terminal olefin was calculated to be present in quantities of <5%. The protons in the vinylic methyl in cis adducts appear at a higher field compared to trans adducts probably due to shielding afforded by the π-electron cloud of the pyridine ring. Also, the J_{cis} for **13** and **15** were 4.4 and 7 cps, respectively, and J_{trans} for **14** and **16** were 2.2 and 3.3 cps, respectively. The hydrogens in the methyl group in the benzylic positions of compounds **17** and **18** have different chemical shifts in nmr (see Table IV). Also, the hydrogens in the allylic methyl groups in **17** appear as a doublet at δ 1.62 and those of **18** appear as a singlet at δ 1.75. Both the peaks were used to compute the relative ratios of the two formed in the reaction of 3-ethylpyridine with isoprene. Compounds **11** and **4** were identified by their relatively simple nmr spectrum.

(14) Autoclave Engineers Inc., Erie, Pa.

Base-Catalyzed Reactions. XLI.[1] Novel Intramolecular Nucleophilic Cyclizations of Alkenylpyridines

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A novel cyclization reaction has been found to occur when ω-(3-pyridyl)-1-alkenes, such as 6-(3-pyridyl)-1-hexene or 7-(3-pyridyl)-1-heptene, are reacted in the presence of alkali metal catalysts. The final tricyclic products obtained from this reaction are formed by a facile intramolecular nucleophilic attack onto the electron-deficient α or γ positions of the pyridine ring. From 6-(3-pyridyl)-1-hexene (1) it is thus possible to produce both 4b,5,6,7,7a,8-hexahyropentaleno[2,1-*b*]pyridine (5) and 5,5a,6,7,8,8a-hexahydropentaleno[1,2-*c*]pyridine (6), depending if cyclization occurs in the 2 or 4 position of the pyridine ring. When ω-(4-pyridyl)-1-alkenes are subjected to the same reaction conditions, only monocyclizations occur. For example, 6-(4-pyridyl)-1-hexene (3) cyclizes to yield both *trans*- and *cis*-1-methyl-2-(4-pyridyl)cyclopentane (9 and 10). No double cyclization occurs in the case of 4-alkenylpyridines because nucleophilic attack would have to take place in the electron-rich β position of pyridine. Changing the alkali metal catalyst from potassium to sodium has no marked effect upon the course of the reaction.

During the last 15 years, we have demonstrated the use of sodium and potassium as catalysts for a number of reactions of hydrocarbons such as isomerization of olefins, dehydrogenation of olefins to aromatics, hydrogen transfer, alkylation of arylalkanes, etc.[2] Previous studies have included the alkali metal catalyzed side chain alkylation,[2] alkenylation,[3] and aralkylation[4] of 2- and 4-alkylpyridines. The formation of the majority of the products from these base-catalyzed reactions has been explained *via* a carbanion intermediate.

The present investigation has been extended to include reactions of ω-pyridyl-1-alkenes which contain both intrinsic acidic picolyl hydrogens[5] and double bonds. When 3-alkenylpyridines are reacted, intramolecular cyclizations occur to give pyrindan derivatives. However, when the 4-pyridylalkenes are subjected to the same reaction conditions, no intramolecular cyclization onto the pyridine ring is noticed. Although pyridines are known to undergo facile nucleophilic substitution in the α and γ positions, intramolecular nucleophilic cyclizations have not been reported until recently. The only example found in the literature was the cyclization of a 2-substituted 3-(3-pyridyl)-propylamine to a tetrahydro-1,8-naphthyridine in a 54% yield,[6] a reaction similar to a Chichibabin reaction in that an amine is the attacking nucleophile. A preliminary report from our laboratory appears to be the first cited example of an intramolecular cyclization where a carbanion is the attacking species.[7]

Even though alkali metals are known to disperse quite readily in 4-alkenylpyridines,[3a] it was found in this study that sodium dispersed very sluggishly in 3-alkenylpyridines under the reaction conditions used. So that all reactions could be performed under the same conditions, *o*-chlorotoluene was used as a chain initiator.[8] The *o*-chlorotoluene reacts readily with the alkali

metal to give an organoalkali metal complex which then initiates the reaction. It has been reported previously[9] that potassium and cesium initiate cyclizations reactions onto benzene, but that sodium and lithium are ineffective as catalysts for the same nucleophilic cyclizations. Consequently, the present study examines the catalytic effect of both sodium and potassium on the intramolecular cyclizations onto the pyridine ring.

Results and Discussion

Intramolecular cyclization reactions were found to occur when ω-pyridyl-1-alkenes, in an inert solvent such as *sec*-butylcyclohexane, were heated to 160° in the presence of an organoalkali metal catalyst. The degree of cyclization was found to be dependent upon which position of the pyridine ring carried the substituent.

When 6-(3-pyridyl)-1-hexene (1) was allowed to react under the conditions described, two tricyclic products, 5 and 6, were isolated from the reaction mixture in better than 30% yield (Table I, expt 1-4). The ratio greatly favors the formation of product 5, where cyclization onto the pyridine ring occurs in the 2 position. Scheme I outlines a reaction mechanism that can explain the products formed. In the initial step the alkenylpyridine loses the picolyl proton, the most acidic one in the compound, to form intermediate 1a. Owing to the close proximity of the picolyl carbon to the terminal double bond, intermediate 1a will cyclize in such a way as to form the most stable carbanion, giving intermediate 1b. (The formation of 1b is favored over a cyclohexylpyridine intermediate which would necessitate the formation of a less stable secondary carbanion.) The next step of the reaction is intramolecular alkylation (cyclialkylation) of the anion onto the pyridine nucleus. The most common nycleophilic attack on pyridine is addition across the azomethine linkage; when this occurs, compound 5 is formed. The 4 position of pyridine is also susceptible to nucleophilic attack, and addition here forms compound 6. The pronounced reactivity of the 2 and 4 positions can be attributed to the fact that addition at these sites permits the negative charge to reside partially on the electronegative nitrogen atom, as shown for intermediates 1c and 1d.

(1) (a) For paper XL, see S. V. Kannan and H. Pines, *J. Org. Chem.*, **36**, 2304 (1971). (b) Paper XII of the series Alkylation of Heteroaromatics; for paper XI, see ref 1a.

(2) H. Pines and L. A. Schaap, *Advan. Catal.*, **12**, 117 (1960).

(3) (a) W. M. Stalick and H. Pines, *J. Org. Chem.*, **35**, 415 (1970); (b) H. Pines and J. Oszczapowicz, *ibid.*, **32**, 3183 (1967).

(4) N. E. Sartoris and H. Pines, *ibid.*, **34**, 2119 (1969).

(5) Picolyl hydrogens throughout the paper are defined as those hydrogens on the α-carbon atom of an alkyl group on pyridine.

(6) E. M. Hawes and D. G. Wibber ey, *J. Chem. Soc. C*, 315 (1966).

(7) H. Pines and S. V. Kannan, *Chem. Commun.*, 1360 (1969).

(8) H. Pines, J. A. Vesely, and V. N. Ipatieff, *J. Amer. Chem. Soc.*, **77**, 554 (1955).

(9) H. Pines, N. C. Sih, and T. Lewicki, *J. Org. Chem.*, **30**, 1457 (1965).

TABLE I
PRODUCTS OF CYCLIZATION OF ω-PYRIDYL-1-ALKENES

Expt no.	Reactant No.	Reactant Structure	Catalyst	Reaction time, hr	% yield	Products No.	A structure	No.	B structure	Product ratio % A	% B
1	1	CCCCC=C (3-pyridyl)	Na	7.8	33.3	5		6		88	12
2	1		Na	21	33.6	5		6		88	12
3	1		K	7.8	24.1	5		6		86	14
4	1		K	21	32.5	5		6		82	18
5	2	CCCCCC=C (3-pyridyl)	Na	10.3	37	7		8		~100	Traces
6	2		K	10.3	37	7		8		86	14
7	3	CCCCC=C (4-pyridyl)	Na	7.5	71.1	9	trans CH₃	10	cis CH₃	87	13
8	3		K	7.5	11	9	trans	10	cis	~100	Traces
9	4	CCCCCC=C (4-pyridyl)	Na	11.5	85.1	11	trans CH₃	12	cis CH₃	95	5
10	4		Na	22.5	87	11	trans	12	cis	95	5
11	4		K	11.5	26	11		12		~100	Traces
12	4		K	22.5	27.5	11		12		~100	Traces

SCHEME I

$$1 \underset{RH}{\overset{R^-M^+}{\rightleftarrows}} \text{1a}$$

1d + 1c ← 1b

1c and 1d → -H⁻ → 5 + 6

1b → RH (blocked)

$$1 \xrightarrow{+H^-} \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2^- \quad \text{1e}$$

1e + 1 → 1a + CH₂CH₂CH₂CH₂CH₂CH₃ (3-pyridyl)
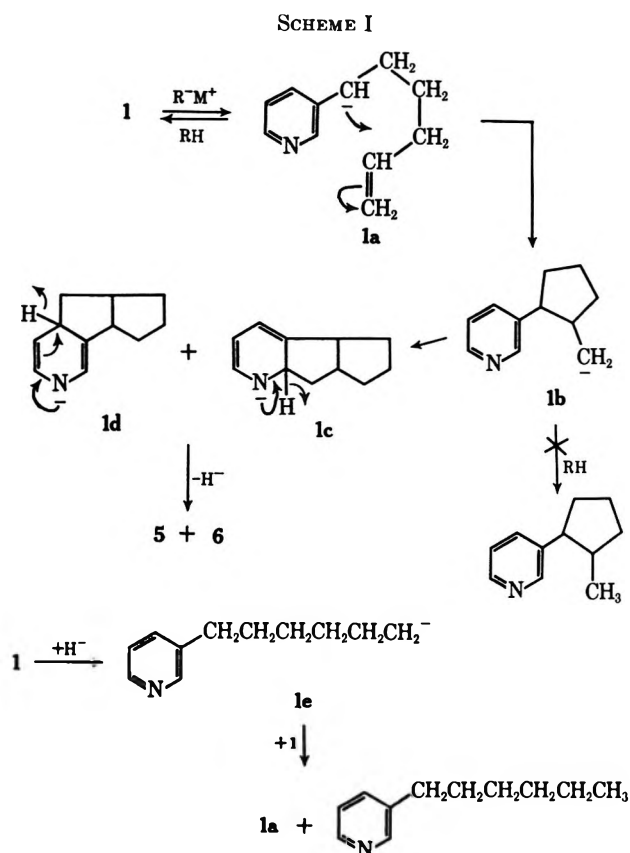
Since hydride addition and double bond migration are the two most common reactions of olefins in the presence of alkali metal catalysts,[2,10] it is reasonable to assume that the hydride ion produced from intermediates 1c and 1d probably reacts with a second molecule of the starting alkenylpyridine (1) to produce a primary carb-

(10) (a) L. H. Slaugh, *J. Org. Chem.*, **32**, 108 (1967); (b) J. E. Germain, L. Bassery, and R. Maurel, *C. R. Acad. Sci.*, Ser. C, **260**, 560 (1965); (c) J. E. Hofmann, P. A. Argabright, and A. Schriesheim, *Tetrahedron Lett.*, 1005 (1964).

anion 1e. This carbanion can then abstract a picolyl proton from yet a third molecule of 1, yielding intermediate 1a and a saturated alkylpyridine. The vpc analysis of products did indeed indicate the formation of alkylpyridine and tricyclic products. This results in a net stoichiometry of two molecules of 1 reacting to form one of the tricyclic product.

The extent of cyclization depends largely on the relative rate of intramolecular alkylation *vs.* the rates of the competing reactions, such as isomerization of the double bond, hydride addition, intermolecular alkylation, etc. The total per cent conversion of reactants is not reported in Table I, as it could not be calculated for these reactions because the double bond isomers were inseparable from reactant by vpc. By hydrogenation of the reaction mixture it was found that double bond isomerizations were one of the major side reactions, assuming that the majority of the starting material was consumed. The absence of monocyclized product which could arise by protonation of intermediate 1a clearly demonstrates that the rate of nucleophilic attack on pyridine is much faster than is transmetalation of the intermediate anion in the case of 2-alkenylpyridines.

The homolog of 1, 7-(3-pyridyl)-1-heptene (2), undergoes a set of reactions that is analogous to those just described (expt 5 and 6, Table I). In this case the tricyclic products formed are 4b,6,7,8,8a,9-hexahydro-5H-indeno[2,1-b]pyridine (7) and 5a,6,7,8,9,9a-hexahydro-5H-indeno[1,2-c]pyridine (8). As in the preceding case, the monocyclized product was not produced and the major dicyclized product was that one arising from nucleophilic attack at the α position of the pyridine ring.

Under the same conditions that give rise to tricyclic products from 3-alkenylpyridines, the corresponding 4-alkenylpyridines undergo only monocyclization. Examination of Table I shows that 6-(4-pyridyl)-1-hexene (3) (expt 7 and 8) and 7-(4-pyridyl)-1-heptene (4) (expt 9-12) undergo but one intramolecular cyclization to

produce *cis*- and *trans*-1-methyl-2-(4 pyridyl)cyclopentane (**10** and **9**) and *cis*- and *trans*-1-methyl-2-(4-pyridyl)cyclohexane (**12** and **11**), respectively. The mechanism for this reaction would be the same as that described for the 3-alkenylpyridines, but in this case transmetalation of an intermediate similar to **1b** (Scheme I) is a much more facile reaction than is nucleophilic attack at the electron-rich 3 position of the pyridine ring. The trans to cis ratio found in all cases was much in favor of the more thermodynamically stable trans isomer. The cis and trans compounds were distinguished from one another by nmr, relative retention times on vpc, and by refractive indices, where the cis isomers were found to have higher refractive indices than the trans isomers, in agreement with the von Auwers–Skita rule.[11]

The fact that 3-alkenylpyridines cyclized onto the α or γ positions whereas the 4-alkenylpyridines did not undergo a cyclialkylation reaction agrees with an anionic mechanism. The anions formed would be expected to attack the electron-deficient α and γ positions of the pyridine ring and not the relatively electron-rich β position, as is found. On the other hand, if the intermediate were a radical in nature, it would be just as likely to cyclize in the β as in the α or γ position since radicals are fairly indiscriminate in the position of attack.[12]

In an earlier study on the alkali metal catalyzed cyclizations of ω-phenyl-1-alkenes, it was found that potassium caused cyclization where sodium failed to yield dicyclized products.[9] As can be seen in Table I, sodium and potassium reacted similarly in this study. In the case of 3-alkenylpyridines (expt 1–6), potassium causes slightly more cyclization to occur in the 4 position than does sodium; this is probably due to the greater ionic character of the potassium–carbon bond.[13] The carbanion formed when potassium is used as the catalyst is electrostatically less stabilized by its cation and thus reacts less discriminately. Sodium was found to yield a greater per cent of monocyclized product from 4-alkenylpyridines than potassium (expt 7–12). Under the conditions used in this study, it is reasonable to assume that the 4-alkenylpyridines easily form the picolyl anions with sodium and then cyclize to form the corresponding products (expt 7, 9, 10), whereas the more reactive potassium initiator is less discriminate and abstracts allylic protons more easily, leading to much more double bond isomerization and consequently less cyclized product (expt 8, 11, 12).

Examination of Table I (expt 1 and 4 *vs.* 7 and 9, sodium catalyst) indicates that the 4-alkenylpyridines give about 85% yield of cycliisomerized products **9–12**, whereas the 3-alkenylpyridines give a 35% yield of cyclialkylated products **5–8** which, however, is equivalent to a 70% yield. In the case of cyclialkylation a hydride is liberated which reacts with another molecule of the starting material to produce an alkylpyridine, as shown in Scheme I. A further possibility that might also contribute, to a minor extent, to the still relatively

higher yields of cyclized product from 4-alkenylpyridines is the ease of removal of 4-picolyl protons. Since 4-picolyl protons are much more acidic than 3-picolyl protons,[14] more intermediates (such as **1a**, Scheme I) are formed that initiate the cycliisomerization reaction.

Experimental Section

Reagents.—3-Picoline and 4-picoline were purchased from Reilly Tar and Chemical Co. The alkylpyridines were distilled, dried over Linde 5A molecular sieves, and redistilled immediately before use. *sec*-Butylcyclohexane was obtained by catalytic hydrogenation of *sec*-butylbenzene. 1-Bromo-4-pentene (Pfaltz & Bauer) and 1-bromo-5-hexene (Columbia) were used as received.

Synthesis of Alkenylpyridines.—The alkenylpyridines were prepared in liquid ammonia from the corresponding picoline, alkenylbromide, and sodium amide according to the general procedure of Brown and Murphey.[15] Physical constants for these alkenylpyridines are given in Table II.

TABLE II
PHYSICAL CONSTANTS OF REACTION COMPOUNDS

Compd no.	n^{20}D	Relative retention time[a]	Bp, °C (mm)[b]
1	1.5036	1.33	75–77 (2)
2	1.5015	1.93	83–85 (2)
3	1.5052	1.36	73 (1.5)
4	1.5005	2.01	99 (3)
5	1.5483	2.16[c]	
6[d]	1.5502	2.75[c]	
7	1.5480	3.07	
8		3.99	
9	1.5175	1.36	
10	1.5258	1.70	
11	1.5188	2.01	
12[e]	1.5271	2.81	

[a] Retention times were obtained using a 4 ft × 0.25 in. column packed with 20% Carbowax 20M + 5% KOH on 60–80 mesh Gas-Pack WAB. Conditions used were 175° and a flow rate of 100 ml/min. The internal standard was naphthalene, retention time = 1.00. [b] Boiling point values are uncorrected. [c] Flow rate used was 85 ml/min. [d] *Anal.* Calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.16; N, 8.80. Found: C, 82.61; H, 8.37; N, 8.98. [e] The relative retention times of the following compounds were also determined under the same conditions described in footnote a: 3-*n*-hexylpyridine = 1.08; 3-*n*-heptylpyridine = 1.56; 4-*n*-hexylpyridine = 1.09; 4-*n*-heptylpyridine = 1.60.

The following compounds were synthesized by this method.

(1) 6-(3-Pyridyl)-1-hexene (1) was made from 3-picoline and 1-bromo-4-pentene in a 90% yield.

(2) 7-(3-Pyridyl)-1-heptene (2) was isolated from the reaction of 3-picoline with 1-bromo-5-hexene in a 69% yield.

(3) 6-(4-Pyridyl)-1-hexene (3) was synthesized from 4-picoline and 1-bromo-4-pentene. The product was isolated in an 88% yield.[16]

(4) 7-(4-Pyridyl)-1-heptene (4) was isolated in an 89% yield from the reaction of 1-bromo-5-hexene with 4-picoline.

Preparation of Catalyst Solution and General Reaction Procedure.—The apparatus used was that described previously.[9] The catalyst solution was prepared by mixing 0.3 ml of *o*-chlorotoluene, 3 ml of *sec*-butylcyclohexane, and about 0.2 g of alkali metal in a reaction flask. Upon heating the contents for 2–3 hr at 160° under a nitrogen atmosphere, a black finely dispersed suspension of the catalyst was formed. About 2 ml of the appropriate alkenylpyridine was slowly introduced by a syringe through a rubber septum. The reaction mixture was then heated for the desired length of time at 160°. When desired, samples

(11) (a) K. von Auwers, *Justus Liebigs Ann. Chem.*, **420**, 84 (1920); (b) A. Skita, *ibid.*, **431**, 1 (1923).

(12) (a) D. H. Hey, D. A. Shingleton, and G. H. Williams, *J. Chem. Soc.*, 5612 (1963); (b) R. A. Abramovitch and J. G. Saha, *ibid.*, 2175 (1964); (c) J. M. Bonnier, J. Court, and M. Gelus, *Bull. Soc. Chim. Fr.*, 139 (1973).

(13) E. G. Rochow, D. T. Hurd, and K. N. Lewis, "The Chemistry of Organometallic Compounds," Wiley, New York, N. Y., 1957, p 65.

(14) W. N. White and D. Lazdins, *J. Org. Chem.*, **34**, 2756 (1969).

(15) H. C. Brown and W. A. Murphey, *J. Amer. Chem. Soc.*, **73**, 3308 (1951).

(16) Previously synthesized in this laboratory: W. M. Stalick and H. Pines, *J. Org. Chem.*, **35**, 422 (1970).

were removed from the mixture, quenched with methanol, and analyzed by vpc to determine the extent of reaction. The reaction material was then cooled and decomposed with 3 ml of methanol. Analysis was made on this material by vpc or on the hydrogenated products obtained over a 10% palladium/charcoal catalyst.

Reaction Products.—The liquid, cyclized reaction products that were isolated from the general reactions described above were separated from one another by means of preparative vpc. When separation of product from starting material was impossible because of identical relative retention times, e.g., 3 and 9 or 4 and 11 (Table II), the reaction mixture was first hydrogenated and separations were then performed. All products were shown to be of greater than 95% purity by vpc. The products were identified by means of nmr and ir spectral analyses. It is possible to assign the direction of cyclization in the case of the tricyclic products 5–8 by examination of the pyridine ring protons. Compounds 5 and 7 show three different protons at δ 8.20–8.26, 7.26–7.39, and 6.90–6.96 ppm corresponding to the α, γ, and β protons, thus indicating that cyclization occurred in the α position. Similarly, with compounds 6 and 8, the presence of two α protons a δ 8.20–8.26 ppm and one β proton at δ 6.93–7.00 ppm denotes that cyclization occurred in the γ position. For compounds 5–8 no methyl groups were present, only methylene and methine protons were present as indicated by a broad band at δ 1.00–2.34 ppm that correctly integrated for the proposed number of protons. Com-

pounds 9–12 all had spectra similar to one another. The stereochemistry was determined from nmr by examining the chemical shift fo the methyl group and by coupling constants. Integration again was consistent with the proposed structures. No unsaturation was found by nmr or ir in any of the compounds 5–12. Refractive indices also indicate cyclic compounds (see Table II).

Analyses.[17]—The nmr spectra of the pure samples in carbon tetrachloride were taken with a Varian T-60 spectrophotometer using tetramethylsilane as an internal standard. The microanalysis was done by M-H-W Laboratories, Garden City, Mich. Vapor phase chromatographic analyses and separations were performed on an F & M Model 720 dual-column instrument equipped with a thermal conductivity detector and using helium as a carrier gas. The separation of products for identification was accomplished with a 6 ft × ³/₈ in. column packed with Versamid 900 on Gas-Pack WAB.

Registry No. −1, 29883-73-6; **2**, 29883-74-7; **3**, 22241-43-6; **4**, 29883-76-9; **5**, 29883-77-0; **6**, 29883-78-1; **7**, 29883-79-2; **8**, 29905-80-5; **9**, 29864-45-7; **10**, 29864-46-8; **11**, 29864-47-9; **12**, 29868-59-5.

(17) The inclusion of elemental analyses for all the new compounds, suggested by the reviewers, would have been desirable in order to confirm their purity, although the nmr spectra and vpc indicate that all the isolated compounds were of at least 95% purity.

Base-Catalyzed Reactions. XLII.[1] Reactions of N-Methyl-2-pyrrolidinone and N-Methyl-2-piperidone with Olefins and Diolefins in the Presence of Potassium tert-Butoxide as Catalyst

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N-Methyl-2-pyrrolidinone (NM-2-Py) and N-methyl-2-piperidone (NM-2-Pi), the so-called "aprotic" dipolar solvents, were found to undergo reactions involving protons in the 3 position of their rings, with styrenes and conjugated diolefins. In the reactions studied, NM-2-Py was found to react only half as fast as NM-2-Pi. Also, the reaction of NM-2-Py was found to proceed faster in dimethyl sulfoxide than in hexamethylphosphoramide. Under the same conditions N-methylcaprolactam failed to react. A mechanism consistent with the results is proposed.

The reactions of olefins and diolefins with alkylaromatics and alkylpyridines was the subject of intensive research in this laboratory.[2] The experiments were made using sodium and potassium as catalysts. It has been recently observed that with the alkyl heterocyclic compounds the addition to conjugated hydrocarbons can also occur using potassium *tert*-butoxide as catalyst.[3] As an extension of this study the reaction of 3-ethylpyridine with styrene in the "aprotic" solvent N-methyl-2-pyrrolidinone (NM-2-Py) and in the presence of potassium *tert*-butoxide was investigated, and it was found that the "solvent" preferentially reacted with the olefins to form mono- and diadducts. The nmr spectrum of the monoadduct 1 conforms with the structure shown.

Among widely used dipolar aprotic solvents, only dimethyl sulfoxide (DMSO) has been reported to undergo reactions with olefins,[4] dienes,[5] aldehydes,[6] ketones,[6]

1
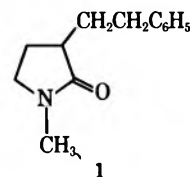
and esters[7] in the presence of bases like alkali metal amides, hydrides, and alkoxides through its carbanion. This seems to be the first time that the addition reaction of NM-2-Py to an olefinic double bond is reported. This study was extended to the homologs, namely to N-methyl-2-piperidone (NM-2-Pi) and N-methylcaprolactam (NMC).

Results and Discussion

The results of the reactions of various olefins with NM-2-Py and NM-2-Pi in the presence of a potassium *tert*-butoxide catalyst are presented in Table I. These reactions are straightforward and occur without opening of the rings of the lactams. The structures of the compounds were assigned on the basis of nmr and ir. The addition of lactams in their 3 position to the olefins

(1) For paper XLI of the series, see H. Pines, S. V. Kanna, and W.M. Stalick, *J. Org. Chem.*, 2308 (1971).

(2) (a) H. Pines and L. A. Schapp, *Advan. Catal.*, **12**, 117 (1960); (b) H. Pines and N. C. Sih, *J. Org. Chem.*, **30**, 280 (1965).

(3) H. Pines and W. M. Stalick, *Tetrahedron Lett.*, **34**, 3723 (1965).

(4) M. Feldman, S. Danishefsky, and R. Levine, *J. Org. Chem.*, **31**, 4322 (1966).

(5) P. A. Argabright, J. E. Hofmann, and S. Schriesheim, *ibid.*, **30**, 3233 (1965).

(6) E. J. Corey and M. Chaykovski, *J. Amer. Chem. Soc.*, **84**, 866 (1962).

(7) G. A. Russell, E. Sabourin, and G. J. Mikol, *J. Org. Chem.*, **31**, 2854 (1966).

TABLE I

REACTION OF N-METHYL-2-PYRROLIDINONE AND N-METHYL-2-PIPERIDONE WITH OLEFINS[a]

Expt no.	Olefin (mol)	Solvent[b]	Reaction time hr	Conversion, %[c]	Wt % of product[d] Adducts Mono-[e]	Di-[e]
			N-Methyl-2-pyrrolidinone			
1	$C_6H_5CH=CH_2$ (0.01)		24	100	72 (1)	28 (2)[f]
2	$C_6H_5CH=CH_2$ (0.005)		24	100	100 (1)	
3	$C_6H_5C(CH_3)=CH_2$ (0.01)		24	47	100 (3)	
4	$C_6H_5C(CH_3)=CH_2$ (0.01)	DMSO	24	100	100 (3)	
5	$(CH_3)_3SiCH=CH_2$ (0.025)		24		No reaction	
6	$(CH_3)_3SiCH=CH_2$ (0.025)	DMSO	24	100[g]	67 (4)	33 (5)
7	$(CH_3)_3SiCH=CH_2$ (0.025)	HMPA	24		No reaction	
8	$CH_2=CHCH=CH_2$[h]		15	82[i] (6)	18[i] (7)	
9	$CH_2=CHC(CH_3)=CH_2$ (0.025)	DMSO	3	14[g]	100[i] (8, 9)	
10	$CH_2=CHC(CH_3)=CH_2$ (0.025)	DMSO	6	21[g]	60[i] (8, 9)	40
11	$CH_2=CHC(CH_3)=CH_2$ (0.025)	DMSO	24	100	30[i] (8, 9)	70
			N-Methyl-2-piperidone			
12	$C_6H_5CH=CH_2$ (0.005)		24	100	100 (10)	
13	$C_6H_5C(CH_3)=CH_2$ (0.005)	DMSO	24	100	100 (11)	
14	$(CH_3)_3SiCH=CH_2$ (0.005)	DMSO	24	100[g]	64 (12)	36 (13)
15	$CH_2=CHC(CH_3)=CH_2$		19	100[g]	62 (14a, 14b)[j]	

[a] 0.02 mol of the reactant and 0.005 M of catalyst were used, except in expt 1 and 2 where 0.01 M of the former and 0.02 M of the latter were used. The reactions were made at room temperature. [b] DMSO, dimethyl sulfoxide; HMPA, hexamethylphosphoramide. [c] Based on olefin. [d] Based on vpc peak areas, uncorrected for thermal conductivities. [e] The numbers in parentheses refer to the compound numbers that are used in this paper. [f] Mp (of the diadduct) 103°, after recrystallization from *n*-heptane. [g] Based on lactam. [h] Quantity not known. [i] After hydrogenation the product consisted of 85% tail addition (8) and 15% head addition (9). [j] After hydrogenation the product consisted of 85% tail addition (14a) and 15% head addition (14b).

8　**9**　**14a**　**14b**
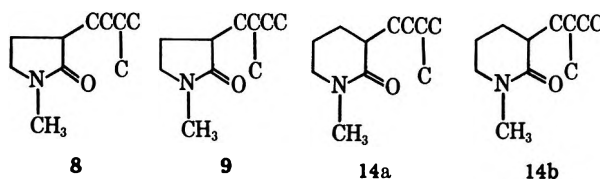
is to be expected since hydrogens in this position are activated to proton abstraction by the neighboring carbonyl group. The resulting carbanion can attack the olefin to generate another resonance-stabilized carbanion which can transmetalate with the parent lactam to form the monoadduct. The reaction sequence using styrene as the olefin is shown in Scheme I.

Efforts to make NMC react with any of the olefins in the presence of potassium *tert*-butoxide were unsuccessful.

Styrenes.—Even in the absence of a solvent, styrene reacts with NM-2-Py to form both mono- (1) and diaddition (2) products. At low concentrations, it forms only the monoadduct 10 with NM-2-Pi. The reaction of NM-2-Py with α-methylstyrene (αMS) is slower and this can be ascribed to the greater stability of a secondary over a tertiary anion formed in the addition reactions (eq 1 and 2).

$$NM\text{-}2\text{-}Py^- + PhC \overset{C}{\underset{C}{\diagup}} \longrightarrow NM\text{-}2\text{-}Py\overset{C}{\underset{C}{C}}CPh \text{ (tertiary)} \quad (1)$$

$$NM\text{-}2\text{-}Py^- + PhC=C \longrightarrow NM\text{-}2\text{-}Py\overset{}{C}CPh \text{ (secondary)} \quad (2)$$
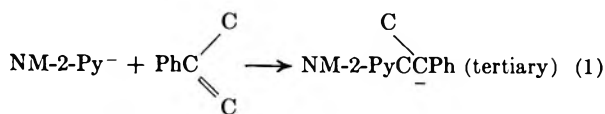
The direction of addition to the styrenes is to generate a carbanion resonance stabilized by the phenyl group, which is consistent with previous observations.[8–10]

(8) H. Pines and N. E. Sartoris, *J. Org. Chem.*, **34**, 2113 (1969).
(9) J. Shabtai and N. Pines, *ibid.*, **26**, 4225 (1961).
(10) J. Shabtai, E. M. Lewicki, and H. Pines, *ibid.*, **27**, 2618 (1962).

SCHEME I

1, $n = 2$
2, $n = 3$
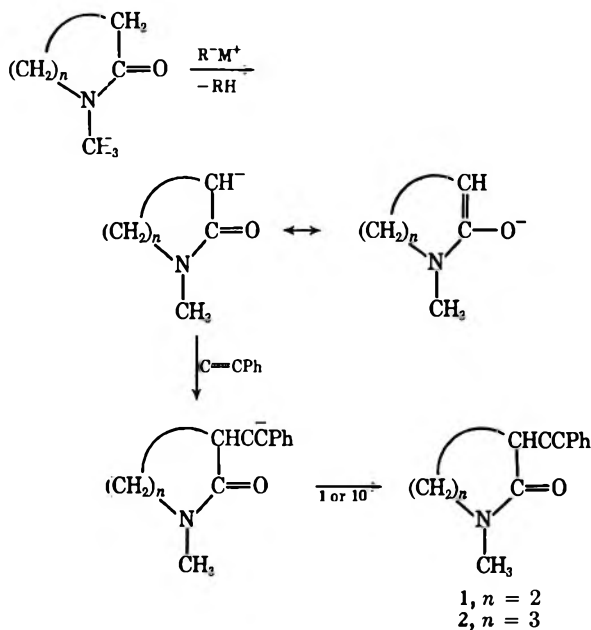
Trimethylvinylsilane.—Both NM-2-Py and NM-2-Pi add to trimethylvinylsilane in such a manner as to produce a carbanion adjacent to the silicon atom as shown in eq 3. This occurs in preference to the addition which will generate a primary carbanion showing that the silicon atom is exerting a stabilizing effect on the carbanion, thus favoring its formation.[11]

(11) (a) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 71 ff; (b) B. Stipanović and H. Pines, *Chem. Commun.*, 1361 (1969).

$$(n = 2 \text{ or } 3)$$
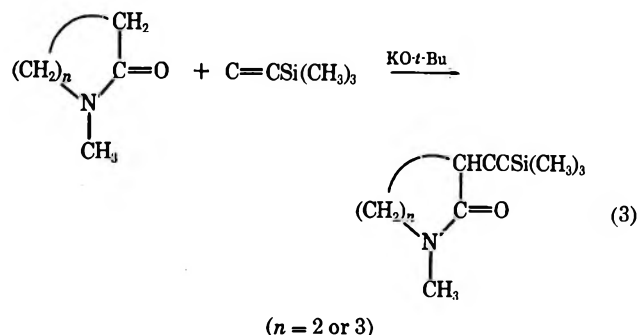
Butadiene.—This diolefin on reaction with NM-2-Py can be expected to form both cis and trans mono-adducts, which it does (see Experimental Section). The relative ratios of the two could not be determined with accuracy from the ir spectrum. Diadduct is also formed in this reaction.

Isoprene.—The reaction of isoprene with NM-2-Py and NM-2-Pi results in the formation of a mixture of tail- and head-addition isomers, compounds **8, 14a** and **9, 14b**, respectively. In the monoaddition product, the tail-addition product ($\sim$85%) predominates over the head-addition ($\sim$15%) product in both reactions. This can be attributed to the greater stability of the intermediate tail-addition anions as discussed previously in the case of reactions of isoprene with δ-alkyl-pyridines[12,13] and with alkylbenzenes.[2b]

Relative Reactivities of NM-2-Py and NM-2-Pi.—In an effort to determine whether NM-2-Py or NM-2-Pi reacted faster with olefins in the presence of potassium *tert*-butoxide, they were allowed to compete for a small amount of styrene or α-methylstyrene. In both reactions, NM-2-Pi was found to react about twice as fast as NM-2-Py. In the case of styrene, NM-2-Py had a half-life of 52 min compared to 23 min for NM-2-Pi.

In a competitive reaction made at 25° using styrene and an equimolal solution of *N*-methyl-2-piperidone and *N*-methyl-2-pyrrolidinone, it was found that the monoadduct from NM-2-Pi predominated over that from NM-2-Py by 1.8 times. In a similar experiment with α-methylstyrene, it was found that NM-2-Pi formed 1.9 times more product than did NM-2-Py.

The above results are in contrast to the relative rates of base-catalyzed bromination of cyclopentanone and cyclohexanone in which the five-membered ring brominates almost ten times as fast as the six-membered ring.[14] Similarly, in the ionization of cyclopentanone and cyclohexanone as shown by the relative rates of hydrogen–deuterium exchange, the five-membered ring is about seven times as reactive as the six-membered one.[15]

Reaction of NM-2-Py with Olefins in DMSO and in HMPA.—Studies on the influence of solvents on the reaction of alkylpyridines with olefins have been conducted in this laboratory.[16] The results indicated that in addition to increasing the polarity of the medium, dimethyl sulfoxide (DMSO) is involved in the reaction in some other manner, probably by donating a proton

in the transmetalation step. This would account for the larger reaction rates observed in DMSO compared to hexamethylphosphoramide (HMPA) contrary to earlier reports where HMPA has been observed to bring about faster reactions.[17] In the present study, DMSO was found to enhance the rates of the addition of NM-2-Py or NM-2-Pi to olefins. Further, the reaction of NM-2-Py with α-methylstyrene was found to have a half-life of 6 hr in HMPA but only 3.3 hr in DMSO.

Effect of Unsaturation on the Relative Reactivities of 3-Substituted NM-2-Py.—It was previously observed that the presence of a side-chain double bond increases the rate of alkenylation of substituted pyridines.[12,13] It was therefore of interest to determine whether a similar effect exists in the reactions of NM-2-Py. To accomplish it a mixture of monoadducts of isoprene with NM-2-Py (85% of **15** and 15% of **16**) and the mixture of their hydrogenated derivatives (**8** and **9**, Table I, footnote *i*) were alkenylated with isoprene under the same experimental conditions.
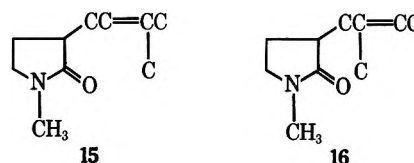
Their half-lives were found to be 149 min for the mixture of **15** and **16** and 324 min for the mixture of the saturated compounds **8** and **9**. These results demonstrate clearly that the presence of a double bond in the side chain increases the rate of alkenylation of lactams, and this can be ascribed to a complexation of the olefinic bond with the catalyst as discussed previously.[13,16]

Experimental Section

Reagents.—*N*-Methyl-2-pyrrolidinone, *N*-methyl-2-piperidone, styrene, α-methyl- and β-methylstyrene, trimethylvinylsilane, isoprene (all from Aldrich), DMSO (Matheson Coleman and Bell), and HMPA (Fischer) were all distilled and stored over Linde 13A molecular sieves and distilled again before use. *N*-Methylcaprolactam was prepared by the method of Benson and Cairns[18] from ϵ-caprolactam in 72% yield. Potassium *tert*-butoxide (K & K Laboratories) was sublimed just before use.

General Reaction Procedure.—In a 50-ml reaction bottle, potassium *tert*-butoxide was dissolved in the solution of lactam and isopropylcyclohexane, used as an internal standard, by vigorous shaking. *N*-Methyl-2-pyrrolidinone dissolved the catalyst easily forming a dark brown solution; *N*-methyl-2-piperidone dissolved less readily forming a dark green solution. The dissolution of the potassium *tert*-butoxide in *N*-methylcaprolactam was very slow, ultimately resulting in a pale yellow liquid. The bottle was sealed with a self-sealing neoprene stopper. All these operations were carried out in a drybox. The reaction bottle was then removed to the laboratory or placed in a thermostated constant temperature bath, the olefin injected from a syringe through the neoprene septum, and the reaction allowed to proceed for the desired period of time. Samples were withdrawn at intervals, quenched with methanol, and analyzed by vpc. At the end of the experiment the product was quenched with methanol and analyzed by vpc. For separation of products by preparative vpc, the solution was combined with ethyl acetate and washed with water and the ethyl acetate was removed by distillation.

In the experiments where a solvent was used, the catalyst was dissolved in the solvent, the lactam and internal standard were added to it, and the reaction was conducted the usual way.[16]

For successful and reproducible results it is imperative to use

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TABLE II

NMR SPECTRA OF THE PRODUCTS
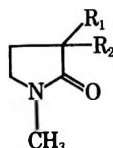
Compd no.	R₁	R₂	Group (no. of protons)	Multiplicity	δ, ppm
1	$-H$	$-CH_2CH_2C_6H_5$ (a) (b)	a (2), b (2)	Broad band of peaks	1.40–2.30
2	$-CH_2CH_2C_6H_5$ (a) (b)	$-CH_2CH_2C_6H_5$ (a) (b)	a (4), b (4)	Multiplet	1.86
3	$-H$	$-CH_2CHC_6H_5$ | CH₃ (c)	a (2), b (1) c (3)	Broad band of peaks Doublet	1.60–2.40 1.20
4	$-H$	$CH_2CH_2Si(CH_3)_3$ (a) (b) (c)	a (2) b (2) c (9)	Multiplet Multiplet Singlet	1.56 0.53 0
5	$CH_2CH_2Si(CH_3)_3$ (a) (b) (c)	$CH_2CH_2Si(CH_3)_3$ (a) (b) (c)	a (4) b (4) c (18)	Multiplet Multiplet Singlet	1.36 0.40 0
6	$-H$	$-CH_2CH_2CH_2CH_3$ (a) (a) (a) (b)	a (6) b (3)	Broad band of peaks Triplet	1.30 0.92
7	$-CH_2CH_2CH_2CH_3$ (a) (a) (a) (b)	$-CH_2CH_2CH_2CH_3$ (a) (a) (a) (b)	a (12) b (6)	Broad band Triplet	1.26 0.90

10	$-H$	$-CH_2CH_2C_6H_5$ (a) (b) (a) (b)	a (2), b (2)	Broad band of peaks	1.60–2.60
11	$-H$	$-CH_2CHC_6H_5$ | CH₃ (c)	a (2), b (1) c (3)	Broad band of peaks Doublet	1.60–2.30 1.18
12	$-H$	$CH_2CH_2Si(CH_3)_3$ (a) (b) (c)	a (2) b (2) c (9)	Multiplet Multiplet Singlet	1.70 0.43 0
13	$CH_2CH_2Si(CH_3)_3$ (a) (b) (c)	$CH_2CH_2Si(CH_3)_3$ (a) (b) (c)	a (4) b (4) c (18)	Multiplet Multiplet Singlet	1.40 0.36 0
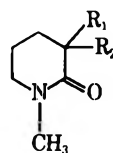
freshly sublimed potassium *tert*-butoxide and to keep all the reagents completely dry.

Competitive Reactions of NM-2-Py and NM-2-Pi.—In a 50-ml capacity reaction bottle, 0.005 mol of potassium *tert*-butoxide was dissolved in 0.02 mol each of the lactams and 0.2 ml of isopropylcyclohexane, and the bottle was sealed with a neoprene stopper and placed in a thermostated bath at 25°. Styrene, 0.05 mol, was injected into the bottle. At the end of the reaction (24 hr), the product was quenced with methanol and analyzed by vpc. A similar experiment was made with α-methylstyrene.

Effect of Double Bond on Substitution.—In separate reaction bottles, 0.11 mol of the monoadduct from the reaction of NM-2-Py and isoprene (a mixture of about 85% of tail- and 15% of head-addition products) and their hydrogenated isomers were allowed to react with 0.01 mol of isoprene and 0.005 mol of potassium *tert*-butoxide in 5 ml of DMSO. The reaction was followed by vpc and quenched after 16 hr.

Analytical Procedure.—The products were all analyzed on a 5 ft × 0.25 in. column of 20% silicone oil DC 550 on Gas-Pack WAB (60–80 mesh), temperature programmed from 100–220°.

Identification of Products.—The products obtained in the described reactions are reported for the first time. They were all purified by separation by preparative vpc on an 8 ft × 0.25 in.

column of 10% Versamid 900 on 60–80 mesh Gas-Pack WAB. These samples were then identified by nmr (Table II) and ir.[19]

Both NM-2-Py and NM-2-Pi have characteristic nmr spectra. The protons on the carbon adjacent to nitrogen in this ring appear at a lower field, δ 3.38 ppm in NM-2-Py and δ 3.32 ppm in NM-2-Pi, compared to the other protons. Substitution of these two protons would be reflected in the nmr spectra of the product. In all of the products obtained in these reactions these two protons were found to be present. The only other protons that could resonably be expected to be affected by the base catalyst are the ones adjacent to the carbonyl group. These do not possess a distinct chemical shift in nmr. In all the nmr spectra of the products, the basic spectrum of NM-2-Py and NM-2-Pi were intact. Also, the characteristic carbonyl frequency for both lactams (at 1676 cm⁻¹) was not displaced in the products. These two facts demonstrate that the ring is not opened during the reactions. It was thus concluded that in the reaction the 3

(19) The inclusion of elemental analyses for all the new compounds, suggested by the reviewers, would have been desirable in order to confirm their purity, although the nmr spectra and vpc, however, indicate that all the isolated compounds were of at least 95% purity.

position of the rings is involved and compounds 1, 2, and 3 were identified by their relatively simple nmr spectra.

The direction of addition in 4, 5, 12, and 13 was decided by the absence of terminal methyl group protons in their nmr spectra, which would have been present had the addition taken place in the opposite direction.

The monoaddition product of the reaction of butadiene with NM-2-Py showed the presence of both cis (675 cm^{-1}) and trans (966 cm^{-1}) double bonds. It was also identified by the nmr spectrum of its hydrogenated analog 6. The diadduct of the reaction was also identified in the same fashion. The monoaddition products from the reaction of isoprene with NM-2-Py and NM-2-Pi were found by vpc and nmr to be a mixture of both head- and tail-addition products in an approximate ratio of 15:85. The assignment of the structures are based on an earlier report.[12]

They were confirmed by hydrogenating the double bonds and studying the nmr of the saturated analogs.

Stereospecific Syntheses of the Seven Dimethylcycloheptanes[1a]

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Unequivocal stereospecific syntheses of the seven possible dimethylcycloheptanes are reported. Separate preparation of the two (inseparable) 1,4 isomers to assure isomer purity involved synthetic problems of special interest.

In order to apply experimental tests to the theoretical predictions about the conformational behavior of seven-membered rings,[2,3] we required stereochemically pure samples of the seven possible dimethylcycloheptanes. Inasmuch as the likelihood of reasonable separation of cis and trans isomers was remote, we were obliged to synthesize each one separately by an unambiguously stereospecific route. The four 1,2 and 1,3 isomers could be prepared by diazomethane ring expansion of the appropriate dimethylcyclohexanones, which were known. In order to eliminate the possibility of epimerization, none of the dimethylcyclohexanones were acceptable with methyl α to the ketone. For this reason the 1,4-dimethylcycloheptanes required other syntheses, and these presented an interesting problem in unequivocal stereospecificity. The *cis*-4,4-dimethylcycloheptane was created by cleaving a 1,4 bridge across a cycloheptane ring (Scheme II). The trans 1,4 isomer was created by initial synthesis of an authenticated 1,4-cis derivative followed by S$_N$2 displacement of one substituent by a methyl anion (Scheme III).

While our work was in progress, a report appeared on the preparation of the dimethylcycloheptanes by diazomethane ring expansion.[4] We felt, however, that their preparations did not satisfy our needs for purity and unambiguous stereochemistry. The 1,2 isomers were separated chromatographically, but their relative stereochemistry was not independently assigned. The 1,4 isomers, inseparable chromatographically, may have involved epimerization in the ring expansion. Since their physical properties for the 1,4 isomers are completely identical,[4] only different chemical routes can guarantee their purity.

Our routes to the 1,1, 1,2, and 1,3 isomers are shown in Scheme I. The cyclopropane route to the *gem*-di-

SCHEME I
PREPARATION OF THE FIVE 1,1-, 1,2-, AND
1,3-DIMETHYLCYCLOHEPTANES
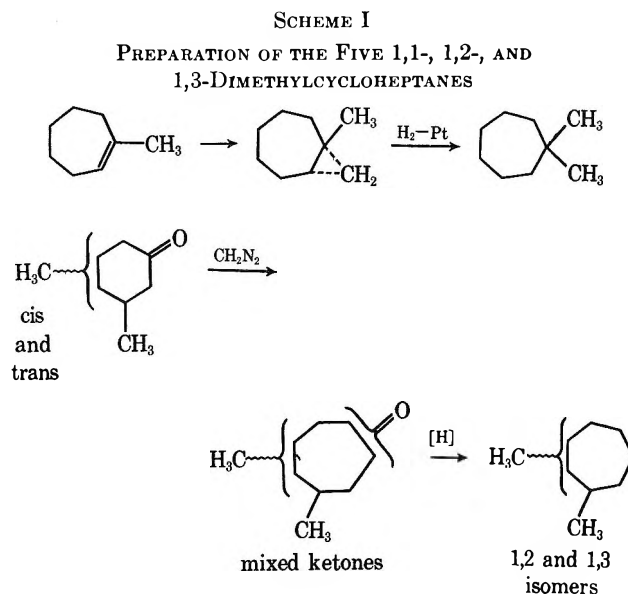
methyl compound is briefer than ring expansion.[5] The commercial *cis*- and *trans*-3,4-dimethylcyclohexanones were purified and confirmed first as to identity by Clemmensen reduction and vpc comparison with authentic samples of the two 1,2-dimethylcyclohexanes. The *cis*- and *trans*-1,2-dimethylcycloheptanes produced from them (Scheme I) were identical in vpc retention time with the two components (4:1 = cis:trans) of the mixture formed on hydrogenation of 1,2-dimethylcycloheptenes. The latter was a mixture of three isomeric olefins produced by the action of methyllithium on 2-

(1) (a) Financial Assistance from the National Institutes of Health (Grant No. GM-10714) is gratefully acknowledged; (b) taken from the doctoral thesis of R. K. B., National Institutes of Health Predoctoral Fellow, 1969–1970.

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methylcycloheptanone followed by iodine dehydration.[6]

For the 1,3 isomers, the commercial mixture of 3,5-dimethylcyclohexanones served as a source of pure cis ketone *via* its crystalline oxime[7] and pyruvic acid regeneration. The trans ketone was prepared by conjugate addition of methylmagnesium iodide to 5-methyl-2-cyclohexenone,[8] a reaction previously shown to give essentially pure trans isomer by an independent synthesis.[9] These ketones were then separately ring enlarged and reduced (Scheme I).

The 1,4 isomers presented a much more serious synthetic challenge since hydrogenation of 1,4-dimethylcycloheptene produced a mixture inseparable by preparative vpc and hardly resolved in analytical vpc. The synthetic scheme elected for the stereospecific synthesis of the cis isomer depended on bridging cycloheptadiene with a two-carbon bridge *via* the Diels–Alder reaction and then cleaving this unequivocally cis bridge, as outlined in Scheme II. Cycloheptadiene[10] was al-

SCHEME II

SYNTHESIS OF *cis*-1,4-DIMETHYLCYCLOHEPTANE
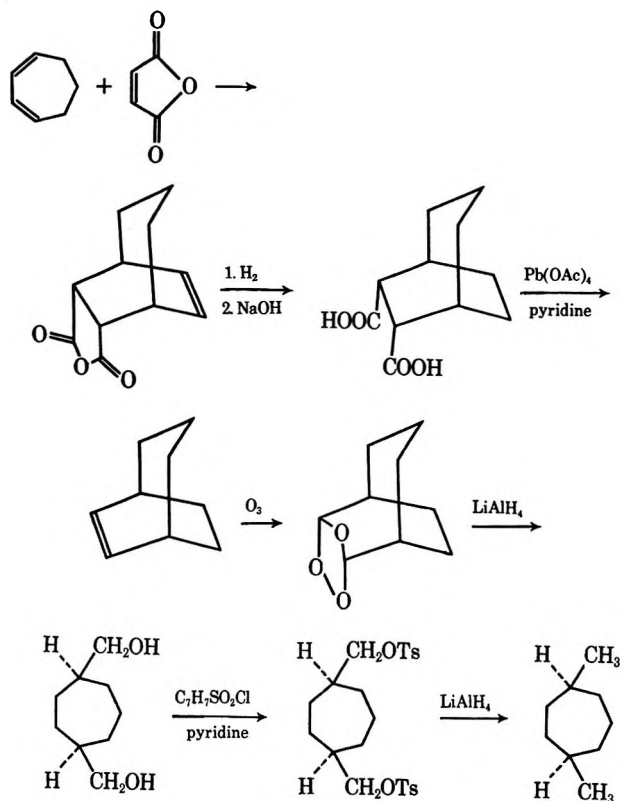
lowed to react with maleic anhydride[11] and the adduct was hydrogenated and saponified. Treatment with lead tetraacetate and pyridine at 60° led to vigorous evolution of carbon dioxide and produced an olefin with a two-proton doublet at τ 3.83 ($J_1 = 8.5$, $J_2 = 3$ cps) in the nmr spectrum. This olefin was ozonized at $-78°$

and the crude ozonide reduced directly to a diol with lithium aluminum hydride; the viscous diol exhibited a four-proton doublet at τ 6.69 ($J = 5$ cps). The corresponding ditosylate was crystalline and reduced to pure *cis*-1,4-dimethylcycloheptane.

To obtain two functional groups across a seven-membered ring, we relied on cleavage of a bicyclic system. The two groups, hydroxymethylene and epoxide, were shown to be cis through their interaction, and the epoxide was displaced by methyl (Scheme III). Creation and cleavage of the bicyclooctanone to 4-cycloheptene-carboxylic acid was reported by Stork,[12] and reduction of the crystalline acid yielded the unsaturated alcohol exhibiting in the nmr spectrum a two-proton multiplet at τ 4.31 (olefin) and a two-proton doublet at τ 6.63 (hydroxymethylene).

Epoxidation yielded a mixture of hydroxy epoxides in a favorable ratio (72:28 = cis:trans) owing presumably to hydrogen-bonded assistance to cis approach of the peracid.[13] Assignment of relative configuration, as well as separation of the pure cis isomer, was achieved by treatment with toluenesulfonic acid in boiling benzene, which converted the trans isomer cleanly to a bicyclic ether without affecting the cis isomer. The cis isomer, separated by chromatography and refluxed with dimethylmagnesium[14] in dioxane,[15] was transformed into the diol, characterized in the nmr spectrum by a three-proton doublet at τ 8.97 ($J = 5$ cps), a three-proton multiplet at τ 5.87–7.15 (–CH$_2$OH + –CH-OH), and a two-proton singlet at τ 7.37 (–COH). The subsequent tosylation and reduction was carried out without intermediate isolation and afforded pure *trans*-1,4-dimethylcycloheptane.

All seven hydrocarbons were shown to be >98% pure by vpc analysis and exhibited mass spectra or elemental analyses consistent with C_9H_{18}. Their detailed nmr spectra will be reported elsewhere.[3]

Experimental Section[16]

1-Methylbicyclo[5.1.0]octane.—Active Zn·Cu[17] dried/vac/-P$_2$O$_5$ overnight. 20 g (305 mmol) suspended/150 ml anhyd Et$_2$O; several crystals/I$_2$ added, stirred to color discharge. Mixture of CH$_2$I$_2$ (79 g, 295 mmol) and 1-methylcycloheptene (Aldrich Chemical Co.) (27.5 g, 250 mmol) added, heated, and stirred. Monitored/vpc (5 ft 3% SE-30/75°): 84% conversion after 72 hr reflux. Cooled, filtered, washed residues 2×/Et$_2$O and combined Et$_2$O with satd aq NH$_4$Cl (100 ml), then aq NaHCO$_3$ and H$_2$O. Dried, evap Et$_2$O/room temp and distilled oil/24-in. Teflon spinning band column. Major = 17 g (55%) 1-methylbicyclo[5.1.0]octane, bp 149–150°, $n^{21.5}$D 1.4580, 98% pure vpc (3% SE-30/75°). Ir (λ_{max}) 3.21, 3.37, 7.24, 9.78, 11.43 μ; nmr (τ) 7.57–8.33 (m, 10), 8.95 (s, 3), 9.30–9.92 (m, 3).

(6) Rearrangement to 1-methyl-1-vinylcyclohexane has been reported[4] in this dehydration, but we observed none of this product.

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(13) H. B. Henbest, *Proc. Chem. Soc., London* 159 (1963).

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(16) Melting points were determined on a Fisher-Johns apparatus and are accurate to within ±1.0°; boiling points are uncorrected. The ir spectra were determined on Perkin-Elmer 137 or DR-69 spectrophotometers, solid samples in KBr, liquids as neat films unless otherwise noted. All nmr spectra were determined on Varian A-60D instrument, in CCl$_4$ or CDCl$_3$ solution unless otherwise noted and reported in "τ (multiplet size, no. of hydrogens, coupling constant)." Mass spectra were determined on the AEJ MS-12 mass spectrometer, purchased under NSF research instrument Grant No. GP-3644. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

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SCHEME III

SYNTHESIS OF *trans*-1,4-DIMETHYLCYCLOHEPTANE
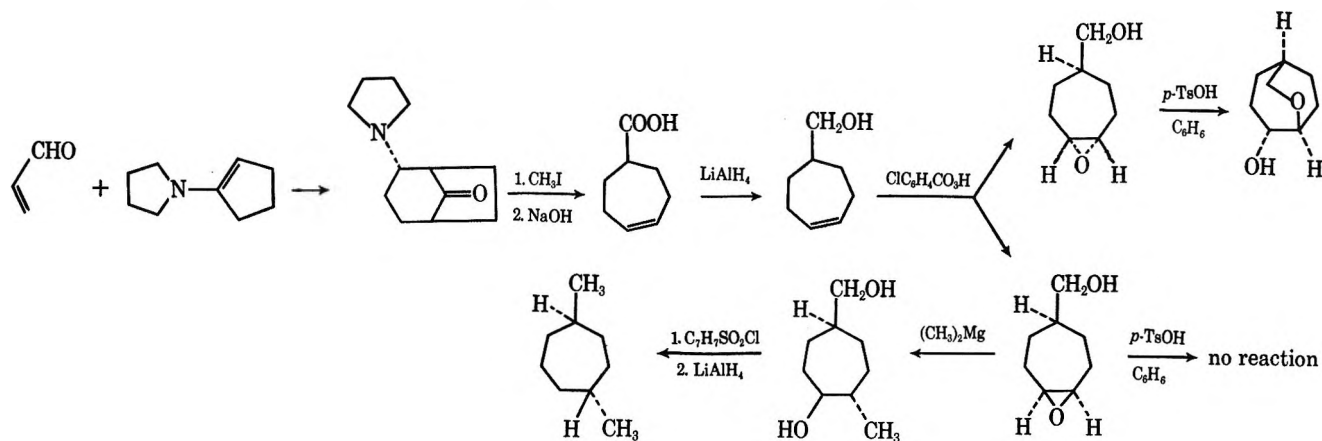
Anal. Calcd for C$_9$H$_{16}$: C, 87.02; H, 12.98. Found: C, 87.11; H, 12.88.

1,1-Dimethylcycloheptane.—1-Methylbicyclo[5.1.0]octane (1.24 g, 10 mmol) in 25 ml glac HOAc, added 224 mg PtO$_2$ and shook/H$_2$/60 psi 48 hr. Filtered, diluted/H$_2$O (200 ml), extracted 3×/hexane (25 ml). Hexane soln washed/aq NaHCO$_3$, dried and evap. Distillation of residue gave 900 mg (71%) 1,1-dimethylcycloheptane, bp 147–148°, n^{24}D 1.4416 (lit.[4] bp 152°, n^{20}D 1.4439), 98% pure (vpc as above). Ir (λ_{max}) 3.43, 6.93, 7.23, 7.35 μ; nmr (τ) 8.25–8.78 (m, 12), 9.07 (s, 6).

Anal. Calcd for C$_9$H$_{18}$: C, 85.63; H, 14.37. Found: C, 85.40; H, 14.37.

***cis*-3,4- (and 4,5-) Dimethylcycloheptanones.**—*cis*-3,4-Dimethylcyclohexanone (Chemical Samples Co.) (17.2 g, 136 mmol) in 70 ml of 95% EtOH + 5 ml H$_2$O. Added Diazald (Aldrich Chemical Co.) (32.1 g, 150 mmol), cooled to 0–5°/ice-salt. Slow mechanical stirring and dropwise addition of soln/KOH (5 g, 75 mmol) in 15 ml 1:1 H$_2$O–EtOH. Temp <10° (50 min). Stirred 30 min more, added concd HCl (10 ml), then added soln/KOH (15 g) in 40 ml H$_2$O and refluxed 1 hr. Diluted/300 ml H$_2$O, extracted 3×/hexane (75 ml). Combined extracts washed (H$_2$O, dil HCl, dried and evap to oil. Vpc (as above) showed 75% conversion to two products. Teflon spinning band distillation yielded 1.4 g starting ketone, bp 74–76° (12 mm), mixed fractions and 8.22 g of ~1:1 mixture of product dimethylcycloheptanones, bp 91–95° (12 mm) (47%). Ir (λ_{max}) 3.37, 5.83, 7.23 μ.

***cis*-1,2-Dimethylcycloheptane.**—Mixture/last preparation (8.2 g, 58 mmol) added to 42.5 g (650 mmol) mossy Zn amalgam.[18] Added soln: concd HCl (20 ml), H$_2$O (10 ml), glac HOAc (20 ml). Refluxed stirred 24 hr. Additional 10 ml portions/HCl every hour/1st 4 hr. Cooled, diluted/H$_2$O, extracted 2×/hexane (75 ml). Washed hexane/H$_2$O, 10% aq NaOH dried, and evap. Residual liquid distilled: major = 4.68 g (62%) *cis*-1,2-dimethylcycloheptane, bp 157–159°, containing 10% *trans*/vpc (above). Preparative vpc (20 ft 30% SE-30/125° at 150 ml flow): retention times = cis, 60 min; trans, 47 min. Pure *cis*-1,2-dimethylcycloheptane: bp 161°, $n^{24.5}$D 1.4481 (lit.[4] bp 161°, n^{20}D 1.4491). Ir (λ_{max}) 3.37 3.40, 6.86, 7.21 μ; nmr (τ) 8.0–9.0 (m, 12), 9.17 (d, 6, J = 6 cps).

Anal. Calcd for C$_9$H$_{18}$: C, 85.63; H, 14.37. Found: C, 85,41; H, 14.20.

***trans*-3,4- (and 4,5-) Dimethylcycloheptanones.**—*trans*-3,4-Dimethylcyclohexanone (Chemical Samples Co.) fractionated/Teflon spinning band column to 99% pure (vpc, above) ketone, $n^{24.5}$D 1.4451; 2,4-DNP (rexld/EtOH), mp 132–134°. Ketone (33.2 g, 290 mmol) in EtOH (50 ml) + H$_2$O (10 ml) and added Diazald (Aldrich Chemical Co.) (63 g, 290 mmol), cooled to 0°/ice-salt. As above with KOH (12 g in 40 ml 1:1 EtOH–H$_2$O) and work-up. Distillation as above yielded 4.14 g recovered starting ketone and 14.51 g (45%) of product dimethylcycloheptanone mixture (~1:1), which was redistilled, bp 81–85° (6–8 mm), $n^{24.5}$D 1.4594, >98% pure (vpc). Ir (λ_{max}) 3.40, 6.84, 7.25, 7.29, 11.57 μ.

***trans*-1,2-Dimethylcycloheptane.**—As with the *cis*-dimethyl-

cycloheptanones above, the trans mixture (13.2 g, 95 mmol) was reduced with fresh mossy Zn amalgam[18] in 50 ml 75% aq HOAc + 70 ml concd HCl for 18 hr/reflux. Similar work-up afforded *trans*-1,2-dimethylcycloheptane (6.38 g, 53%), bp 154–155°, n^{23}D 1.4461 (lit.[4] bp 157°, n^{20}D 1.4439). Ir (λ_{max}) 3.45, 6.85, 7.27, 7.33 μ; nmr (τ) 7.67–9.00 (m, 12), 9.04 (d, 6, J = 6 cps). Purity >99% vpc.

Anal. Calcd for C$_9$H$_{18}$: C, 85.63; H, 14.37. Found: C, 85.42; H, 14.27.

***cis*-3,5-Dimethylcyclohexanone.**—3,5-Dimethylcyclohexanone (Aldrich Chemical Co.) (4:1 = cis:trans/vpc on 20% SE-30/75) converted to oxime with H$_2$NOH·HCl and 10% NaOH. Crystalline oxime[7] washed/H$_2$O, dried. Oxime (55 g, 390 mmol) in 800 ml 50% aq HOAc, pyruvic acid (320 g, 3.64 mol) added and refluxed 18 hr. Cooled, diluted/H$_2$O (950 ml), extracted 3×/hexane (350 ml). Hexane washed/aq NaHCO$_3$, aq NaCl, dried, and evap. Distillation of residue gave 37.4 g (77%) *cis*-3,5-dimethylcyclohexanone, bp 86° (33 mm), n^{24}D 1.4407 (lit.[7] n^{20}D 1.4407). Ir (λ_{max}) 3.36, 3.42, 5.80, 7.25, 7.33 μ. Purity >99%/vpc.

***cis*-3,5-Dimethylcycloheptanone.**—*cis*-3,5-Dimethylcyclohexanone (36.0 g, 280 mmol) in EtOH (100 ml) + H$_2$O (8 ml) and added Diazald as before (64.2 g, 300 mmol). Same procedure afforded 5.36 g recovered starting ketone and 19.71 g (58%) of *cis*-3,5-dimethylcycloheptanone, bp 94–96° (44 mm), $n^{23.5}$D 1.4532 (lit.[19] n^{23}D 1.4524), 98% pure/vpc (20% SE-30/70°). Ir (λ_{max}) 3.32, 5.79, 7.19, 7.26 μ; nmr (τ) 7.30–7.90 (m, 4), 7.90–8.78 (m, 6), 9.03 (d, 3, J = 5 cps), 9.03 (d, 3, J = 6 cps). Semicarbazone, mp 163–164° (aq MeOH) (lit.[19] mp 165.7–166.6°).

***cis*-1,3-Dimethylcycloheptane.**—*cis*-3,5-Dimethylcycloheptanone semicarbazone (1.0 g, 5.1 mmol) was fused with 5 g KOH in a short-path still and distillate collected at 120°. Distillate in Et$_2$O washed/10% HCl, 5% NaHCO$_3$, dried, and evap to clear oil (237 mg, 37%). Further purified by passing through silica gel in petrol (20–40°) and distillation to *cis*-1,3-dimethylcycloheptane, bp 151°, n^{21}D 1.4410 (lit.[4] bp 153°, n^{20}D 1.4408), >99% pure/vpc (3% SE-30/85°). Ir (λ_{max}) 3.42, 6.87, 7.29, 7.35 μ; nmr (τ) 9.13 (d, 6, J = 6.5 cps).

Anal. Calcd for C$_9$H$_{18}$: C, 85.63; H, 14.37. Found: C, 85.51; H, 14.21.

***trans*-3,5-Dimethylcyclohexanone.**—5-Methylcyclohex-2-en-1-one, prepared by ref 8, had bp 82° (30 mm), n^{20}D 1.4745 (lit.[8] 1.4739), 2,4-DNP mp (MeOH) 148–150° (lit.[8] 152°). This ketone (8.8 g, 80 mmol) in Et$_2$O (100 ml) added dropwise/10–12° to metal-free Grignard from 2.46 g (100 mmol) Mg + 17.1 g (120 mmol) CH$_3$I + 100 mg Cu$_2$Cl$_2$. After addition, refluxed 1.5 hr and stirred overnight. Soln decomposed with ice + 12 g glac HOAc, extracted/Et$_2$O. Et$_2$O washed/5% NaHCO$_3$, aq NaCl, dried, and evap to yellow oil. Distillation gave 7.27 g (72%) *trans*-3,5-dimethylcyclohexanone, bp 78–80° (25 mm), n^{25}D 1.4474 (lit.[9] 1.4467), contaminated with 9% cis isomer by vpc (3% SE-30/85°). 2,4-DNP mp (EtOH) 108–109° (lit.[9] 109–110°). The pure trans isomer was originally prepared by recovery from the ring enlargement (next procedure), but later

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(18) Amalgamation/Zn: 2 short washings s/5% HCl, then shaken/HgCl$_2$ (10% by weight of Zn) in 10× (w/v) volume/H$_2$O.

(19) N. L. Allinger, *J. Amer. Chem. Soc.*, **81**, 232 (1959).

could be separated (>99% pure/vpc) by careful spinning band distillation.

trans-3,5-Dimethylcycloheptanone.—Ring enlargement procedure as with the other isomers: 22.2 g (176 mmol) pure *trans*-3,5-dimethylcyclohexanone, 40.8 g (190 mmol) Diazald, 5.3 g (94 mmol) KOH, and addition over 2 hr/10–15°. Final oil distilled to a fraction 60–100° (20 mm) which was redistilled/spinning band column to 5.25 g (28%) *trans*-3,5-dimethylcycloheptanone, bp 89–91° (10 mm), n^{23}D 1.4573 (lit.[19] 1.4572), >99% pure/vpc, and 5.43 g recovered *trans*-3,5-dimethylcyclohexanone. Product ir (λ_{max}) 3.38, 5.85, 6.85, 7.25, 7.39, 7.99, 8.48, 12.24 μ; nmr (τ) 7.17–8.60 (m, 10), 9.05 (d, 6, J = 6 cps); semicarbazone, mp (aq MeOH) 163.5–164° (lit.[19] mp 164.5–165.5°).

trans-1,3-Dimethylcycloheptane.—Clemmensen reduction on *trans*-3,5-dimethylcycloheptanone (4.8 g, 34 mmol) with 22 g (343 mmol) fresh Zn·Hg[18] as for 1,2-dimethylcycloheptanes above. Product oil passed through silica gel column in petrol (20–40°) and distilled to 2.17 g (50%) *trans*-1,3-dimethylcycloheptane, bp 147–148°, n^{23}D 1.4476, >98% pure/vpc (3% SE-30/85°). Ir (λ_{max}) 3.37, 6.81, 7.22, 7.25 μ; nmr (τ) 7.69–9.00 (m, 12), 9.14 (d, 6, J = 6 cps).

Anal. Calcd for C_9H_{18}: C, 85.63; H, 14.37. Found: C, 85.91; H, 14.30.

Bicyclo[3.2.2]nonane-2,2-dicarboxylic Acid.—Unsaturated analog (Scheme I), prepared by ref 11 (4.30, 22.4 mmol), in 50 ml 4:1 glac HOAc-Ac₂O. Added PtO₂ (430 mg) and stirred/H₂ (1 atm) until theoretical uptake. Filtered and evap/vac. Residue in CHCl₃ washed/H₂O, 5% NaHCO₃, dried, and evap to 4.36 g pale yellow solid, rexld 2×/petrol (60–110°) to saturated anhydride, mp 136–138°. Ir (λ_{max}) 3.37, 3.45, 5.35, 5.59, 8.08, 8.22, 9.28, 10.96, 10.53, 13.22 μ; nmr (τ) 6.70 (s, 2), 7.48 (m, 2), 7.83–8.55 (m, 10).

The anhydride (3.18 g, 16.4 mmol) suspended in 75 ml 10% aq NaOH and stirred/room temp until dissolved, cooled/ice and acidified to pH 1/concd HCl. Thick ppt filtered, washed/H₂O, and air-dried to 3.13 g (90%) of bicyclo[3.2.2]nonane-2,3-dicarboxylic acid. Although used without further purification, rexln/acetone gave mp 133–135° (hydrate) (lit.[11] 132–134°). Ir (KBr) (λ_{max}) 2.9–4.0, 5.83, 8.14 μ; nmr (τ) 4.28 (s, broad, 2) due to hydrate, 6.99 (s, 2), 7.52 (m, 2), 8.00–8.77 (m, 10).

Bicyclo[3.2.2]non-2-ene.—Bicyclo[3.2.2]nonane-2,3-dicarboxylic acid (2.89 g, 13.6 mmol) suspended in 48 ml dry C₆H₆ under N₂. Dry pyridine (1.62 g, 20.6 mmol) added, then 688 mg (13.6 mmol) 90% Pb(OAc)₄ with stirring. Clear yellow soln heated/50°, gas evolved vigorously, and temp rose to 60–65°. Then refluxed 2 hr, cooled, filtered, washed/H₂O, 5% NaHCO₃, 10% HCl, and aq NaCl, and dried. Solvent carefully removed/room temp/vac to red oil. Chromatography/silica gel in petrol (20–40°); first 100 ml eluate evap at or below room temp to 550 mg (33%) bicyclo[3.2.2]non-2-ene, mp 67–69° (subl). Ir (λ_{max}) 6.05, 14.18 μ; nmr (τ) 3.83 (dd, z, J = 3, 8.5 cps), 7.58 (m, 2), 7.83–8.90 (m, 10); m/e 122 (parent ion).

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.40; H, 11.77.

cis-1,4-Bis(hydroxymethylene)cycloheptane.—Bicyclo[3.2.2]-non-2-ene (488 mg, 4.0 mmol), in 50 ml CH₂Cl₂ cooled to −78° and ozonized until excess O₃ showed in KI trap. Soln dried and evap to gum and placed in extraction thimble. LiAlH₄ (1.9 g, 50 mmol) suspended in 100 ml dry THF and refluxed in soxhlet overnight (no residue in thimble). Diluted/Et₂O and decomposed/H₂O (2 ml), 15% NaOH (2 ml), and H₂O (6 ml). White ppt filtered and washed/Et₂O. Soln evap to 609 mg (96%) *cis*-1,4-bis(hydroxymethylene)cycloheptane as pale yellow oil, pure by tlc (EtOAc). Distillation to clear, viscous liquid, bp 120–122°. Ir (λ_{max}) 2.98, 3.43, 9.40, 9.70, 9.93 μ; nmr (τ) 6.23 (s, 2), 6.27–6.95 (m, 4), 7.72–9.42 (m, 12). Bis-3,5-dinitrobenzoate prepared and xld 2×/EtOH to mp 158–160°.

Anal. Calcd for $C_{23}H_{22}N_4O_{12}$: C, 50.55; H, 4.06. Found: C, 50.68; H, 3.97.

cis-1,4-Bis(tosyloxymethylene)cycloheptane.—Diol/last preparation (600 mg, 3.8 mmol) in 5 ml dry pyridine. Cooled to 0° and added 3.2 g (16.8 mmol) freshly rexld TsCl in 20 ml pyridine, dropwise. Yellow soln stood 72 hr/6°, then poured onto ice-concd HCl (10 ml) and extracted 3×/Et₂O. Et₂O soln washed/50% HCl (2×), H₂O, dried (MgSO₄–K₂CO₃), and evap to pale yellow oil which xld from petrol (20–40°) at −78° to 828 mg (47%) of ditosylate. Ir (λ_{max}) 6.23, 8.40, 8.50, 9.12 μ. Rexld/Et₂O-petrol to mp 78.5–79.5°.

Anal. Calcd for $C_{23}H_{30}S_2O_6$: C, 59.22; H, 6.48. Found: C, 59.28; H, 6.55.

cis-1,4-Dimethylcycloheptane.—*cis*-Ditosylate (last preparation) (16.3 g, 35 mmol) in 75 ml dry THF and added dropwise to stirred suspension of LiAlH₄ (12.16 g, 320 mmol) in 100 ml THF. After addn, refluxed 6 hr, cooled, diluted/Et₂O, and decomposed/H₂O, NaOH, filtered, washed/Et₂O. Et₂O soln dried and evap to clear oil which was passed through silica gel in petrol (20–40°). First 100 ml of eluate evap to 313 mg *cis*-1,4-dimethylcycloheptane, bp 153°, n^{20}D 1.4395 (lit.[4] on mixed 1,4 isomers: bp 154°, n^{20}D 1.4398). Ir (λ_{max}) 3.39, 3.42, 6.90, 7.27, 7.35 μ; m/e 126 (parent ion); purity >99%/vpc.

5-Hydroxymethylcycloheptene.—Cyclohept-4-enecarboxylic acid[13] (280 mg, 2.0 mmol) in 19 ml Et₂O added dropwise rapidly to suspension of 152 mg (4.0 mmol) LiAlH₄/25 ml Et₂O and refluxed 1 hr. Excess decomposed/H₂O, NaOH and salts filtered, washed/Et₂O. Et₂O dried and evap to 212 mg (84%) 5-hydroxy-methylcycloheptene as clear oil, bp 98–99° (20 mm). Ir (λ_{max}) 2.9–3.1, 3.29, 3.42, 6.01, 14.35 μ; nmr (τ) 4.31 (t, 2, J = 3 cps), 5.90 (s, 1), 6.63 (d, 2, J = 6 cps), 7.33–9.33 (m, 9).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.01; H, 11.35.

Epoxidation of 5-Hydroxymethylcycloheptene.—5-Hydroxy-methylcycloheptene (1.015 g, 8.05 mmol) in 15 ml C₆H₆ cooled to 5°/ice and added 1.82 g (9.0 mmol) 85% *m*-chloroperbenzoic acid/30 ml C₆H₆ dropwise. To room temp, stirred overnight. Soln washed/10% NaOH, dried, and evap to mixed epoxides, oil, 709 mg (62%). Vpc (Carbowax 20M/156°) = 72:28 mixture/epoxides and 1.4% bicyclic ether–alcohol (below). On prep vpc (20 ft 30% SE-30/180°) minor component completely converted to bicyclic ether–alcohol.

Epoxide mixture (1.04 g, 7.04 mmol) in 20 ml C₆H₆ and 100 mg *p*-TsOH refluxed 2 hr to complete conversion vpc. Soln washed/10 NaOH, H₂O, dried, and evaporated to 987 mg, separated by silica gel chromatography/EtOAc. First eluate = *cis*-5-hydroxymethylcycloheptene oxide, bp 85–86° (0.5 mm). Ir (λ_{max}) 2.83, 3.44, 9.26, 9.59, 9.92, 10.84, 11.55, 12.44 μ; nmr 6.68 (d, 2, J = 5 cps), 6.87 (d, 2, J = 5 cps), 7.33–9.40 (m, 9); m/e 142 (parent ion).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.38; H, 9.94.

Second eluate, 2-hydroxy-7-oxabicyclo[3.2.2]nonane crystallized on evaporation. Sublimed/70° (20 mm) to mp 130° (subl); ir (λ_{max}) 2.92, 3.42, 9.54 μ; nmr (τ) 5.83–6.73 (m, 4), 6.93 (s, 1), 7.50–9.17 (m, 9).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.27; H, 10.17. 3,5-Dinitrobenzoate (EtOH) mp 136–137°.

trans-2-Methyl-*cis*-5-hydroxymethylcycloheptanol.—Soln/(CH₃)₂Mg in Et₂O[15] and solvent exchanged for dry dioxane (same white ppt), approx 1 mmol/ml. To 30 ml soln added dropwise 1.42 g (10.0 mmol) *cis*-epoxy alcohol (above) in 10 ml dry dioxane and refluxed (101°) for 44 hr. Cooled, decomposed excess carefully with satd NH₄Cl solution, diluted/H₂O and extracted/Et₂O (8 × 50 ml). Et₂O dried and evap to pale yellow oil (1.49 g, 94%), one spot/tlc. Distillation yielded *trans*-2-methyl-*cis*-5-hydroxymethylcycloheptanol, bp 118° (0.5 mm). Ir (λ_{max}) 2.95, 3.41, 6.87, 9.51, 10.00 μ; nmr (τ) 5.87–7.15 (m, 3), 7.37 (s, 2), 7.58–9.48 (m, 10), 8.97 (d, 3, J = 5 cps); m/e 158 (parent ion).

trans-1,4-Dimethylcycloheptane.—Diol above (475 mg, 3.0 mmol) in 15 ml dry pyridine and added 2.30 g (12.0 mmol) freshly rexld tosyl chloride and left at 6°/44 hr. Diluted/H₂O and extracted/Et₂O. Et₂O washed/1:1 HCl, H₂O, and dried over K₂CO₃–Na₂SO₄, and evaporated to 1.306 g (93%) oil which could not be crystallized and decomposed on silica gel chromatography, but ir and nmr in accord with expectation. Oil dissolved in 5 ml dry DME, added to suspension of 550 mg (15 mmol) LiAlH₄ in 15 ml DME, and refluxed 24 hr. Excess decomposed/H₂O and sais dissolved/10% HCl. Extracted/Et₂O, dried, and evaporated carefully to oil and passed through silica gel in petrol (20–40°). First 100 ml/eluate evaporated and distilled to 61 mg *trans*-1,4-dimethylcycloheptane, bp 152°, n^{23}D 1.4381. Ir (λ_{max}) 3.39, 3.42, 6.87, 7.28, 7.35 μ; m/e 126 (parent ion); purity >99%/vpc.

Registry No.—1-Methylbicyclo[5.1.0]octane, 13388-61-9; 1,1-dimethylcycloheptane, 13151-49-0; *cis*-3,4-dimethylcycloheptanone, 29584-58-5; *cis*-4,5-dimethylcycloheptanone, 29584-59-6; *cis*-1,2-dimethylcycloheptane, 13151-51-4; *trans*-3,4-dimethylcyclo-heptanone, 29577-66-0; *trans*-4,5-dimethylcyclohep-

tanone, 29577-67-1; trans-1,2-dimethylcycloheptane, 13151-50-3; cis-1,3-dimethylcycloheptane, 13151-53-6; trans-1,3-dimethylcycloheptane, 13151-52-5; bicyclo-[3.2.2]nonane-2,2-dicarboxylic anhydride, 29577-71-7; bicyclo[3.2.2]non-2-ene, 7124-86-9; cis-1,4-bis(hydroxymethylene)cycloheptane, 29577-72-8, 29577-73-9 (bis-3,5-dinitrobenzoate); cis-1,4-bis(tosyloxymethylene)-cycloheptane, 29577-74-0; cis-1,4-dimethylcycloheptane, 14190-15-9; 5-hydroxymethylcycloheptene, 17328-87-9; cis-5-hydroxymethylcycloheptene oxide, 29577-76-2; 2-hydroxy-7-oxabicyclo[3.2.2]nonane, 17328-88-0, 29577-78-4 (3,5-dinitrobenzoate); trans-2-methyl-cis-5-hydroxymethylcycloheptanol, 17328-91-5; trans-1,4-dimethylcycloheptane, 13151-54-7.

The Synthesis and Stereochemistry of the Four Isomeric Pinane-2,3-diols

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The synthesis of the four possible pinane-2,3-diols, 1–4, is described and rigorous stereochemical assignments are made. Several anomalous reactions were observed in which an attacking species reacts preferentially on the pinane ring system from the same side as the gem-dimethyl bridge.

In connection with our study of the base-catalyzed rearrangement of 2,3-pinanediol monotosylates,[3] we required synthetic routes to the four possible pinane-2,3-diols 1–4. At the time this study was initiated,
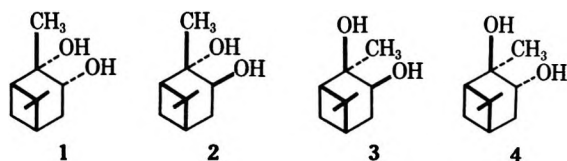
two of these diols (1 and 2) had been reported in the literature but there was confusion and disagreement as to the stereochemistry of these diols.[4-9] We have presented evidence which clarified the stereochemistry of these diols[10] and these assignments have been independently confirmed by other workers.[11-13]

Diols 1 and 2.—Oxidation of α-pinene (5) with potassium permanganate under neutral conditions gives a modest yield of the ketol 6, whereas oxidation
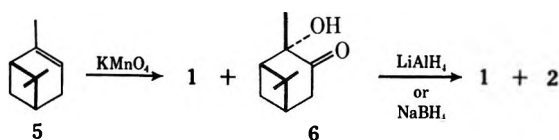
under basic conditions gives the diol 1 in low yield. None of the diol 3 can be detected by spectral methods or by thin layer chromatography (tlc) in the crude product from this reaction. Thus, the reaction of 5

with permanganate ion is highly stereoselective and the attack of the oxidant occurs from the side opposite the gem-dimethyl bridge. The expectation that attack of external reagents on the pinane skeleton should occur from this direction has been widely used in assigning stereochemistry to various pinane derivatives, but, as will be shown below, it is not an unfailing guide to stereochemical assignments in this system.

Because the metal hydride reduction of both isopinocamphone (7) and pinocamphone (8) have been
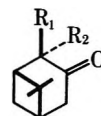
7, R_1 = Me; R_2 = H
8, R_1 = H; R_2 = Me

reported[14] to be highly stereoselective with attack of the reagent from the side opposite the gem-dimethyl bridge, it was expected that the reduction of ketol 6 with lithium aluminum hydride (LiAlH$_4$) would give mainly diol 2. Surprisingly, this reduction produced the readily separable diols 1 and 2 in the ratio 54:46. Two previous reports of the reduction of ketol 6 with LiAlH$_4$ had claimed that only diol 2 was produced,[6,15] whereas Suga[8] reports that diols 1 and 2 are formed in the ratio 63:37 in reasonable agreement with our results. This seemingly anomalous stereochemical result might be rationalized by assuming that a complex of the type 9 is formed. In such a complex C-3 is pulled

9
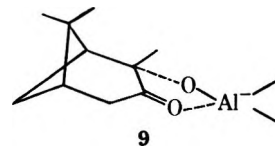
downward in order to obtain coplanarity in the five-membered complex ring and molecular models indicate that in such an arrangement attack of hydride from the top side would be favored. In order to determine

(1) Alfred P. Sloan Foundation Research Fellow, 1970–1972.
(2) Gulf Fellow, 1968–1969; NSF Summer Fellow, 1969; NSF Trainee, 1969–1970.
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whether this was a tenable hypothesis, two further experiments were conducted. The ketol 6 was reduced with sodium borohydride in methanol with the expectation that because of the hydroxylic nature of the solvent, complexation similar to 9 would not occur and, indeed, this reduction gave the diols 1 and 2 in the ratio 17:83. The ketol was also converted to acetoxy ketone 10 and reduction of 10 with LiAlH₄ gave 1 and 2 in the

10
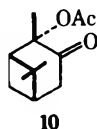
ratio 6:94. This result is also consistent with the above postulate because if ketone reduction precedes ester reduction a complex of the type 9 cannot be formed.

Diols 3 and 4.—The introduction of the oxygen substituent at C-2 on the same side as the *gem*-dimethyl bridge makes the synthesis of diols 3 and 4 somewhat more complicated than the preparation of 1 and 2 and requires a different synthetic strategy. One approach to systems with this stereochemistry is outlined in Scheme I. Conversion of the known[16] enol acetate 11

SCHEME I
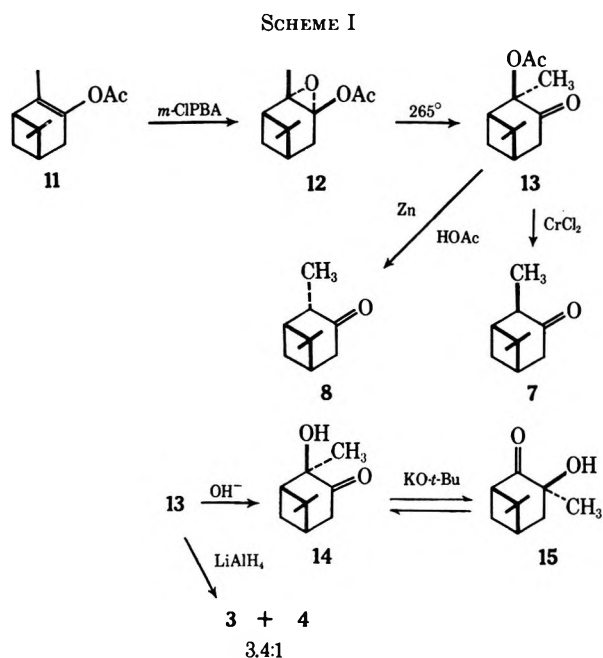
to the epoxy acetate 12 was easily accomplished with *m*-chloroperbenzoic acid, but the thermal rearrangement of 12 to the acetoxy ketone 13 proved to be surprisingly difficult. Such rearrangements usually occur very readily and epoxy acetates of this type are often difficult to isolate and purify. For example, 1-acetoxy-1,2-epoxycyclohexane undergoes rearrangement when heated for a few minutes at 100°.[17] In contrast, 12 could be heated at 150° for 5 min with no rearrangement and the use of higher temperatures and longer reaction times gave mainly decomposition products. Attempts to bring about the rearrangement by chromatography on silica gel[18] or by catalysis with

boron trifluoride etherate[19] led to incomplete reaction and the formation of a large number of by-products. It was finally found that the rearrangement of 12 to 13 could be cleanly effected by passing 12 in a stream of nitrogen through a column of glass beads maintained at 265°. Although rearrangements of this type are known to proceed with clean inversion of configuration at the migration terminus,[20] the rather drastic conditions necessary for the rearrangement of 12 required proof that the pinane skeleton was still intact. Reduction of 13 with zinc and acetic acid gave pinocamphone (8), presumably arising by isomerization of 7 to 8. In contrast, reduction of 13 with chromium(II) chloride[21] gave isopinocamphone 7 indicating that the conditions for this reduction are sufficiently mild to give the ketone produced by initial kinetically controlled protonation. The difficulty encountered in bringing about the rearrangement of 12 to 13 reflects the severe interaction between the acetoxy group and the C-9 methyl group in the transition state for the rearrangement.

Reduction of 13 with LiAlH₄ produced the noncrystalline *cis*-diol 3 and the crystalline *trans*-diol 4 in the ratio 3.4:1. The stereochemistry of these diols is unambiguously established by the experiments described below. Our initial plan for the synthesis of diol 4 was based on the assumption that Meerwein–Ponndorf–Verley (MPV) reduction of 13 or 14 would lead to the more stable diol 4 by analogy with the work of Schmidt[6] who showed that MPV reduction of ketol 6 gave exclusively diol 2. When ketol 14 was subjected to reduction with aluminum isopropoxide in isopropyl alcohol, a diol was obtained which, by virtue of its nmr spectrum, was clearly neither of the diols 3 or 4. The new diol showed an absorption in its nmr spectrum for a proton on a carbon bearing a hydroxyl group as a doublet at δ 3.85 (*J* = 5.0 Hz). This suggested that 14 had undergone a ketol rearrangement[22] to give 15 under the strongly basic conditions of the MPV reduction prior to reduction and that the new diol was derived from reduction of 15. Indeed, when ketol 14 was treated with potassium *tert*-butoxide in *tert*-butyl alcohol it was gradually converted to the isomeric ketol 15 and an equilibrium was established which consisted of 58% 15 and 42% 14. The new ketol 15 was identical with the ketol obtained by oxidation of the diol from the MPV reduction of 14.

In contrast to the ready rearrangement of ketol 14, the isomeric ketol 6 could be recovered unchanged after prolonged treatment with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol. The stability of 6 reflects the fact that in the transition state for a similar ketol rearrangement the migrating methyl group would interact very severely with the C-9 methyl group. Such an interaction is not developed in the rearrangement of 14 to 15.

Because of the failure of this route to cleanly produce *trans*-diol 4, an alternative route to this compound was devised based upon the proposition that addition of methyllithium or methylmagnesium iodide to a suitably substituted nopinone would lead to diol 4. For this

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purpose the keto acetate **18** was prepared as outlined in Scheme II. Surprisingly, addition of methyllithium

SCHEME II
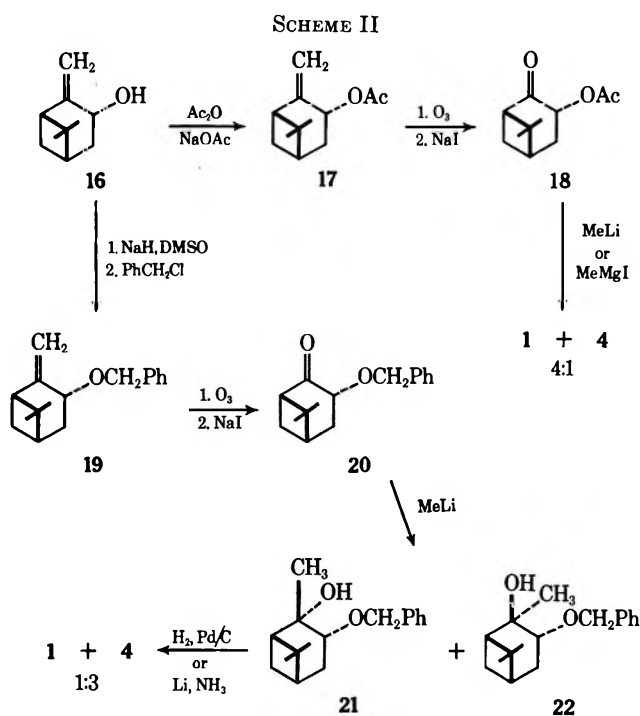
to **18** gave a mixture of the diols **1** and **4** in the ratio 4:1. Essentially the same product distribution was obtained when methylmagnesium iodide was used in place of methyllithium. Thus, the attack of the organometallic reagents occurs overwhelmingly from the same side as the *gem*-dimethyl bridge. Subsequent to our studies Schmidt[23] reported that inverse addition of methylmagnesium iodide to **18** followed by hydrolysis gave only *trans*-diol **4** in 28% yield. In our hands, this procedure gave the diol **4** in 24% yield as well as the *cis*-diol **1** in 20% yield.[24] Thus, the order of addition of the Grignard reagent also affects the stereochemical outcome of this reaction in a manner which remains unclear.

Our initial postulate to rationalize the "wrong" stereochemical outcome of the organometallic reactions with acetoxy ketone **18** was based on the possibility that the organometallic reagent attacked the acetoxy group first to produce the salt **23** and that attack on this
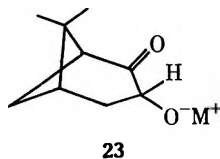
salt occurred preferentially from the top side because of charge repulsion. This suggested that replacement of the acetoxy group by a benzyl group might reverse the stereochemical outcome. The corresponding benzyloxy ketone **20** was prepared as shown in Scheme II. Addition of methyllithium produced the hydroxy ethers **21** and **22** in the ratio 1:3. Hydrogenolysis of

the benzyl protecting groups in a carefully base-washed apparatus or cleavage with lithium in liquid ammonia gave the diols **1** and **4** in the ratio 1:3. Thus, the change in protecting group reverses the stereochemical outcome of the addition to the C-2 carbonyl group.

Experimental Section[25]

Preparation of Ketol 6.—To a cold (ice bath) solution of 100 g (0.734 mol) of α-pinene {Aldrich, $[\alpha]^{25}$D +37.32° (c 2.7, CHCl₃)} in 883 g of 90% aqueous acetone was added with stirring 200 g (1.265 mol) of pulverized potassium permanganate over a period of 10 hr. The reaction mixture was stirred at 0–5° for an additional 24 hr, filtered, evaporated to *ca.* 250 ml, and extracted with ether. The combined ethereal extracts were washed with water and saturated aqueous sodium bicarbonate, dried, and concentrated to give 64.07 g of an oil which was distilled to give 58.55 g (48%) of ketol **6**, bp 113–115° (17 mm). A small portion of the distillate was recrystallized from pentane to afford pure ketol **6**: mp 34–35°; n^{28}D 1.4877; $[\alpha]^{25}$D −27.50° (c 2.5, CHCl₃) {lit.[4,6] mp 35.5–36.6°; bp 96.5–96.7 (5 mm); n^{20}D 1.490; $[\alpha]^{20}$D −18.56° (c 14.44, EtOH)}; ir (CCl₄) 3610 (free OH), 3500 (bonded OH), and 1720 cm⁻¹ (C=O); nmr (CCl₄) δ 2.60–1.65 (m, 7), 1.38 (s, 3, CH₃), 1.32 (s, 3, CH₃), and 0.88 (s, 3, CH₃).

Preparation of Diol 1.—A solution of 23.4 g (0.148 mol) of potassium permanganate and 5 g (0.125 mol) of sodium hydroxide in 800 ml of water cooled to 0° was added quickly with vigorous stirring to a cold (−5°) mixture of 1.0 l. of *tert*-butyl alcohol, 200 ml of water, and 500 g of cracked ice containing 13.27 (0.0974 mol) of α-pinene {$[\alpha]^{25}$D −22.46° (c 3, CHCl₃)}. After 3.0 min of reaction, sulfur dioxide was bubbled through the solution to ensure complete reduction of the permanganate. The precipitated manganese dioxide was removed by filtration through a layer of Celite 512. The filtrate was evaporated under reduced pressure to *ca.* 250 ml and continuously extracted with ether for 48 hr. Concentration of the ether layer afforded 7.27 g of a viscous yellow oil. This oil was chromatographed on 400 g of Silicar CC-7, 100–200 mesh silica gel. The early fractions eluted with ether–pentane mixtures gave 1.08 g (7%) of ketol **6** {$[\alpha]^{25}$D +5.66 (c 2, CHCl₃)}. Later fractions yielded 5.73 g of a mixture of diol **1** and a carboxylic acid. The mixture was dissolved in 150 ml of ether, washed with five 50-ml portions of saturated aqueous sodium bicarbonate, dried, and concentrated to give 3.07 g (18%) of a clear oil. A small portion of this oil was recrystallized from hexane to afford the pure diol **1**: mp 55–56°; $[\alpha]^{25}$D −0.71 (c 2, CHCl₃) (lit.[6,8] mp 55.5–56.0°); ir (CCl₄) 3610 (free OH) and 3420 cm⁻¹ (bonded OH); nmr (CDCl₃) δ 3.96 (dd, 1, J = 9.0 and 5.0 Hz, CHOH), 2.65–1.33 (m, 6), 1.29 (s, 3, CH₃), 1.26 (s, 3, CH₃), and 0.93 (s, 3, CH₃).

Preparation of Keto Acetate 10.—To a solution of 5.00 g (28.8 mmol) of ketol **6** in 11.6 g (115 mmol) of anhydrous triethylamine and 20 ml of anhydrous ether cooled to 0° was added with stirring under nitrogen over a period of 0.5 hr a solution of 6.80 g (86.5 mmol) of acetyl chloride in 20 ml of ether. The mixture was stirred at 0° for 4 hr, allowed to warm to room temperature, and stirred for 20 hr. The reaction mixture was diluted with 200 ml of ice water and extracted with ether. The combined extracts were washed with cold 1 N hydrochloric acid, saturated sodium carbonate, and brine and dried. Removal of the solvent gave 5.38 g of an orange oil which was chromatographed on 425 g of silica gel (100–200 mesh). Elution with ether–hexane mixtures afforded in middle fractions 4.60 g (76%) of a viscous, colorless oil which was recrystallized from hexane to afford 2.68 g (45%) of **10** as colorless needles: mp 42–44°; $[\alpha]^{24}$D +2.08° (c 2, CHCl₃); ir (CCl₄) 2950 (CH), 1740 (ester C=O), 1720 cm⁻¹ (ketone C=O); nmr (CCl₄) δ 3.00–1.95 (m, 6), 1.91 (s, 3, CH₃COO), 1.51 (s, 3, CH₃), 1.36 (s, 3, CH₃), 0.86 (s, 3, CH₃).

Anal. Calcd for C₁₂H₁₈O₃: C, 68.54; H, 8.63. Found: C, 68.43; H, 8.92.

(23) H. Schmidt, M. Muhlstadt, and H. C. Flemming, *Chem. Ber.*, **102**, 118 (1969).

(24) Diol **4** is highly crystalline and easily isolated from the crude products of these reactions. In contrast the *cis*-diol **1** is a very low-melting solid and is easily discarded with mother liquors from the crystallization of **4** unless great care is exercised.

(25) All boiling points are uncorrected and all melting points are corrected. The infrared spectra were recorded on a Beckman IR-8 spectrophotometer and the nuclear magnetic resonance spectra were recorded on a Varian A-60, A-60A or HA-100 instrument using tetramethylsilane as an internal standard. Gas chromatography studies utilized an Aerograph A-90P or F & M Model 700 gas chromatograph and a Beckman 10-in. recorder equipped with a Disc Integrator. Unless otherwise stated, magnesium sulfate was employed as the drying agent.

Reduction of Ketol 6 with Sodium Borohydride.—A cold (0°) solution of 483.9 mg (2.88 mmol) of ketol 6 {mp 34–35°, $[\alpha]^{25}$D −21.98° (c 2.5, ethanol)} and 146.1 mg (3.86 mmol) of sodium borohydride in 10 ml of dry methanol was stirred under nitrogen at 0° for 2 hr. The methanol was removed under reduced pressure and the residue partitioned between water and ether. The aqueous layer was extracted with several portions of ether and the combined extracts were dried and concentrated to give 287 mg (59%) of crude 2, mp 147–153°. Several recrystallizations from diethyl ether afforded the pure *trans*-diol 2 as fine, colorless needles: mp 169–170° (lit.[6,8] mp 159–160°); ir (KBr) 3500–3100 (broad, bonded OH), 1160, 1080, and 1052 cm^{-1}; nmr (CDCl$_3$) δ 4.18 (dd, 1, J = 6.0 and 10.0 Hz, CHOH), 2.50–1.50 (m, 8), 1.35 (s, 3, CH$_3$), 1.25 (s, 3, CH$_3$), and 0.95 (s, 3, CH$_3$).

Reduction of 0.405 g (2.41 mmol) of ketol 6 in 10 ml of absolute methanol by 0.122 g (3.22 mmol) of sodium borohydride as described above afforded 0.240 g of a colorless solid which was chromatographed through 24 g of neutral silica gel (100–200 mesh) contained in a 30 cm × 15.5 mm glass column. Elution with ether–hexane mixtures afforded in the early fractions 0.113 g (28%) of unreacted ketol 6. Middle fractions afforded 0.022 g (5%) of *cis*-diol 1. The last fractions furnished 0.111 g (27%) of *trans*-diol 2.

Lithium Aluminum Hydride Reduction of Ketol 6.[6]—To a solution of 0.122 g (3.22 mmol) of powdered lithium aluminum hydride in 7 ml of ether was added dropwise under nitrogen with stirring a solution of 0.405 g (2.41 mmol) of ketol 6 in 5 ml of ether at such a rate as to maintain a gentle reflux. After addition was complete the mixture was heated at reflux for 0.5 hr and allowed to cool. To the mixture was added 0.11 ml of water, 0.11 ml of aqueous 15% sodium hydroxide, and 0.33 ml of water and the mixture was stirred for 1 hr to ensure decomposition of the reduction complex. The mixture was filtered and the granular precipitate was washed with several portions of ether. The combined extracts were washed with water, dried, and concentrated to give 0.370 g of a colorless solid which was chromatographed through 24 g of neutral silica gel (100–200 mesh) contained in a 30 cm × 15.5 mm glass column. Elution with ether–petroleum ether mixtures afforded in the early fractions 0.033 g (8%) of ketol 6. Middle fractions afforded 0.177 g (43.3%) of *cis*-diol 1. The last fraction furnished 0.151 g (36.8%) of *trans*-diol 2.

Lithium Aluminum Hydride Reduction of Keto Acetate 10.—Following the procedure described for lithium aluminum hydride reduction of ketol 6, 0.506 g (2.41 mmol) of acetoxy ketone 10 was reduced with 0.200 g (5.27 mmol) of lithium aluminum hydride to a colorless solid, 0.277 g, which was chromatographed as previously described to give 0.015 g (4%) of *cis*-diol 1 and 0.249 g (61%) of *trans*-diol 2.

Preparation of Epoxy Acetate 12.—In a 2-l. flask equipped with dropping funnel, Trubore stirrer, and condenser was placed 41.50 g (0.247 mol) of enol acetate 11[26] {$[\alpha]^{25}$D +31.49° (c 10, CHCl$_3$)} and 140 ml of methylene chloride. The flask and contents were cooled to 0° and a solution of 60.5 g (0.309 mol, 90% assay, FMC) of *m*-chloroperbenzoic acid in 975 ml of methylene chloride was added dropwise with stirring over a period of 1.0 hr. At intervals, 1-ml aliquots were removed from the reaction mixture and diluted with 10 ml of water and 10 ml of 10% potassium iodide solution; the iodine liberated was titrated with a starch indicator end point with 0.01 N sodium thiosulfate. After 13 hr of reaction at 0° 10% of the initial peracid remained. At this time the ice-cold reaction mixture was filtered and the filtrate was washed with 10% sodium bisulfite solution until neutral to starch-iodide paper, then with saturated sodium bicarbonate until neutral to litmus, and with one portion of brine. The methylene chloride solution was dried (Na$_2$SO$_4$), concentrated, and distilled giving 29.14 g of a colorless oil which contained[27] 60% of epoxy acetate 12. Fractional distillation afforded a clear oil which solidified to a white solid, mp 30–51°. Recrystallization from hexane followed by sublimation afforded pure epoxy acetate 12: mp 59–61°; bp 72–76° (0.15 mm); $[\alpha]^{25}$D +48.64° (c 3.5, CHCl$_3$); ir (CCl$_4$) 1755 cm^{-1} (ester C=O); nmr (CCl$_4$) δ 2.04 (s, 3, COCH$_3$), 1.33 (s, 3, CH$_3$), 1.29 (s, 3, CH$_3$), and 0.95 (s, 3, CH$_3$).

Anal. Calcd for C$_{12}$H$_{18}$O$_3$: C, 68.55; H, 8.63. Found: C, 68.45; H, 8.57.

Pyrolysis of Epoxy Acetate 12.—Crude epoxy acetate 12 (29.14 g, containing 60% 12) was passed through a 0.75 × 30 in. Pyrex tube filled with 0.25-in.-diameter glass beads at a rate of 1 drop per 5 sec. The tube was held vertically and heated to 265°. Nitrogen was passed through the tube simultaneously at a rate of 120 ml/min. The gaseous and liquid effluent from the bottom of the tube was collected in two successive traps cooled to 0°. The column was cooled after all the material had passed through and was rinsed with three 100-ml portions of ether and the material in the traps was dissolved in 200 ml of ether. The combined etheral solutions were washed with aqueous saturated sodium bicarbonate, dried, and concentrated. Vpc analysis[27] of the crude product demonstrated that approximately 10% of the original epoxy acetate 12 remained; therefore, the above procedure was repeated. The crude product (28.99 g) was distilled through a spinning band annular still giving a fraction [14.62 g, bp 76–78° (0.20 mm)] which crystallized when scratched with a glass rod. The crystals were recrystallized from pentane to afford 7.43 g (45%) of pure keto acetate 13: mp 50–51°; $[\alpha]^{25}$D −0.33° (c 12, chloroform); ir (CCl$_4$) 1740 (ester C=O), 1710 cm^{-1} (ketone CO); nmr (CCl$_4$) δ 3.17 (m, 1), 2.57 (m, 3), 2.08 (m, 1), 1.95 (s, 3, COOCH$_3$), 1.52 (s, 3, CH$_3$), 1.35 (s, 3, CH$_3$), 1.25–1.08 (m, 10), and 0.97 (s, 3, CH$_3$).

Anal. Calcd for C$_{12}$H$_{18}$O$_3$: C, 68.54; H, 8.63. Found: C, 68.55; H, 8.42.

Reductive Cleavage of Keto Acetate 13. A. With Chromous Chloride.—In a 50-ml flask was placed 10 g of zinc dust, 0.8 g of mercuric chloride, 0.5 ml of concentrated hydrochloric acid, and 10 ml of water. The mixture was shaken for 5 min, the supernatant liquid was decanted, and 20 ml of water and 5 ml of concentrated hydrochloric acid were added to the residue. Carbon dioxide was bubbled through the solution for 3 min and 5 g of chromic chloride hexahydrate was added. Of the resulting blue solution, 15 ml was added dropwise over a period of 10 min to 108 mg (0.5 mmol) of keto acetate 13 in 20 ml of acetone with stirring under CO$_2$ at room temperature. The mixture was stirred at room temperature for 1.0 hr, diluted with 50 ml of brine, and extracted with ether. The combined extracts were washed with saturated sodium bicarbonate solution, dried, and concentrated to give 80 mg of a clear oil which was composed[28] of 96% ketone 7 and 4% ketone 8.

B. With Zinc and Acetic Acid.—In a 50-ml flask equipped with magnetic stirrer and reflux condenser was placed 105 mg (0.5 mmol) of keto acetate 13, 10 g of zinc dust, and 35 ml of glacial acetic acid. The reaction mixture was refluxed for 24 hr, allowed to cool, and filtered. The zinc residue was washed with ether and the combined filtrate and washings were evaporated to a small volume and diluted with 50 ml of ether. The ether solution was washed with 5% sodium hydroxide solution and brine, dried, and concentrated to give 80 mg of a light brown oil which was composed[28] of 80% ketone 8 and 20% ketone 7.

Lithium Aluminum Hydride Reduction of Keto Acetate 13.—Following the procedure described for lithium aluminum hydride reduction of ketol 6, 4.29 g (20.4 mmol) of keto acetate 13 was reduced with 1.70 g (44.7 mmol) of lithium aluminum hydride. The crude product was a colorless semisolid (3.15 g, 91%) which was chromatographed through 200 g of neutral silica gel (100–200 mesh) contained in a 60 cm × 33 mm glass column. Elution with ether–hexane mixtures afforded in early fractions 2.33 g (67%) of *cis*-diol 3 as a viscous, colorless oil: $[\alpha]^{25}$D +25.03° (c 1.5, CHCl$_3$); ir (CCl$_4$) 3670, (free OH), 3430 cm^{-1} (bonded OH); nmr (CDCl$_3$) δ 3.86 (dd, 1, J = 9.0 and 7.0 Hz, CHOH), 3.00–1.40 (m, 8), 1.23 (s, 6, 2CH$_3$), and 1.06 (s, 3, CH$_3$).

Anal. Calcd for C$_{10}$H$_{18}$O$_2$: C, 70.55; H, 10.65. Found: C, 70.62; H, 10.94.

Later fractions afforded 0.70 g (20%) of a colorless, crystalline material which was recrystallized from ethyl acetate to afford pure *trans*-diol 4: mp 152–153°; $[\alpha]^{30}$D −29.10° (c 1, CHCl$_3$); ir (CHCl$_3$) 3600 (free OH), 3550–3100 cm^{-1} (bonded OH); nmr (CDCl$_3$) δ 4.28 (dd, 1, J = 4.5 and 9.5 Hz, CHOH), 3.20 (s, 1, broad, OH), 2.65 (s, 1, OH), 2.60–1.32 (m, 6), 1.28 (s, 3, CH$_3$), 1.25 (s, 3, CH$_3$), and 1.06 (s, 3, CH$_3$).

Anal. Calcd for C$_{10}$H$_{18}$O$_2$: C, 70.55; H, 10.65. Found: C, 70.33; H, 10.44.

Preparation of Ketol 14.—A solution of 0.72 g (3.43 mmol) of keto acetate 13 in 50 ml of water and 50 ml of methanol containing 5.0 mmol of sodium hydroxide was stirred at room temperature

(26) M. P. Hartshorn and A. F. A. Wallis, *Tetrahedron*, **21**, 273 (1965).

(27) A vpc column packed with 10% SF-96 on 60–80 mesh Chromosorb W was employed for this analysis.

(28) A vpc column packed with Carbowax 20M on 60–80 mesh Chromosorb W was employed for this analysis.

for 5.5 hr. The reaction mixture was diluted with 50 ml of water and extracted three 50-ml portions of ether. The combined ether extracts were washed with water, dried, and concentrated to give ketol 14 as a colorless oil, 0.48 g (84%), which was shown by vpc analysis[27] to consist of a single component: bp 53–55° (0.15 mm); $[\alpha]^{25}$D +90.41° (c 5, CHCl₃); 3600 (free OH), 3500 (bonded OH), 1710 (ketone C=O), 1385 and 1370 cm⁻¹ (gem-dimethyl); nmr (CCl₄) δ 3.10 (s, 1, OH), 2.55 (m, 3) 2.10 (m, 3), 1.33 (s, 3, CH₃), 1.21 (s, 3, CH₃), and 0.95 (s, 3, CH₃).

Anal. Calcd for C₁₀H₁₆O₂: C, 71.39; H, 9.59. Found: C, 71.67; H, 9.68.

In order to ensure that no rearrangement had occurred during this hydrolysis, a sample of ketol 14 was acetylated using acetyl chloride and triethylamine in ether to regenerate keto acetate 13.

Aluminum Isoproxide Reduction of Ketol 14.—To 2.01 g (11.9 mmol) of ketol 14 was added 80 ml of absolute isopropyl alcohol, and 9.0 g (44 mmol) of freshly prepared, distilled aluminum isopropoxide.[29] The reaction mixture was stirred and distilled through a 2-in. fractionating Claisen head at the rate of 3 ml/hr. At the end of 12 hr there was a negative 2,4-dinitrophenylhydrazine test[29] for the distillate and the distillation was halted. The contents of the flask were allowed to cool and were stirred with 80 ml of 2% sodium hydroxide solution for 2 hr. The resultant sludge was filtered and the filtrate was extracted with three 100-ml portions of ether. The combined extracts were washed with water and brine, dried, and concentrated to give 1.35 g (66%) of a yellow oil which was shown by tlc analysis to contain unreacted ketol 14 and one other component. The crude product was eluted with ether–hexane solutions through 120 g of neutral silica gel (100–200 mesh) contained in a 60 cm × 25 mm glass column. Late fractions afforded a diol as a clear, homogeneous oil: 1.01 g (50%); $[\alpha]^{25}$D −12.00° (c 3, CHCl₃); ir (CHCl₃) 3600 (free OH), 3400 cm⁻¹ (broad, bonded OH); nmr (ClDCl₃) δ 3.85 (d, 1, J = 5.0 Hz, CHOH), 3.42 (broad s, 2, 2 OH), 2.50–1.80 (m, 6), 1.43 (s, 3, CH₃), 1.21 (s, 3, CH₃), and 1.10 (s, 3, CH₃).

Anal. Calcd for C₁₀H₁₈O₂: C, 70.55; H, 10.66. Found: C, 70.78; H, 10.44.

Based on the above spectral data and its oxidation to ketol 15 this diol is one of the isomeric diols 24.
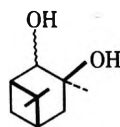
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Oxidation of Diol 23.—A solution of 100 mg (0.588 mmol) of diol 23 and 1.0 ml of ether was cooled to 0° and stirred while a solution of 59 mg (0.196 mmol) of sodium dichromate dihydrate, 0.04 ml (0.783 mmol) of 96% sulfuric acid, and 1.0 ml of water was added dropwise over a period of 5 min. The reaction mixture was stirred at 0° for 0.5 hr, allowed to warm to room temperature, and stirred for 2.0 hr. The reaction mixture was diluted with 10 ml of water, saturated with sodium chloride, and extracted with ether. The combined ether extracts were washed with aqueous saturated sodium bicarbonate, water, and aqueous saturated sodium chloride, dried, and concentrated to give a pale green oil, 51 mg (51%), which had an ir spectrum and vpc retention time[27] identical with ketol 15.

Equilibration of Ketols 14 and 15.—A solution of 0.91 g (5.40 mmol) of ketol 14 in 35 ml of dry *tert*-butyl alcohol was added under nitrogen with stirring to a solution of potassium *tert*-butoxide prepared from 0.30 g (7.78 mmol) of potassium and 30 ml of *tert*-butyl alcohol. The reaction mixture was heated at 65° for 9 hr and stirred and then concentrated under reduced pressure to near dryness, diluted with 250 ml of water, and extracted with ether. The combined extracts were washed with water and brine, dried, and concentrated to give a yellow oil, 0.74 g (84%), which contained 42.4% unreacted ketol 14 and 57.6% of a new ketol characterized as 15. Further heating with base led to no change in the composition of the mixture. This mixture was separated into individual components by preparative vpc.[30] The minor component displayed ir and nmr spectra identical with the starting ketol 14. Ketol 15, the major component, was a clear viscous

oil: ir (CCl₄) 3580 (free OH), 3450 (bonded OH), 1710 cm⁻¹ (ketone C=O); nmr (CCl₄) δ 3.30–1.60 (m, 7), 1.40 (s, 3, CH₃), 1.38 (s, 3, CH₃), 0.91 (s, 3, CH₃).

Anal. Calcd for C₁₀H₁₆O₂: C, 71.39; H, 9.59. Found: C, 71.53; H, 9.78.

Treatment of Ketol 6 with Potassium *tert*-Butoxide.—A solution of 1.82 g (10.80 mmol) of ketol 6 in 60 ml of *tert*-butyl alcohol was added in one portion under nitrogen with stirring to a solution of potassium *tert*-butoxide in *tert*-butyl alcohol prepared from 0.60 g (16 g-atoms) of potassium and 70 ml of *tert*-butyl alcohol. The reaction was stirred at 65° for 10 hr during which time the solution became dark red. The reaction mixture was worked up as above to afford 1.62 g (84%) of a yellow oil which had ir, nmr, and vpc spectra identical with starting ketol 6.

Preparation of Keto Acetate 18.—A solution of 9.01 g (47 mmol) of acetate 17[31] {$[\alpha]^{25}$D +7.78°, (c 2, CHCl₃)} in 100 ml of absolute methanol was exhaustively ozonized at −70°. The ozonized solution was added to a solution of 4 ml of absolute methanol, 12 ml of glacial acetic acid, and 24 g of sodium iodide, and the mixture was stirred at 25° for 7 hr and then added to 300 ml of water and 15 ml of saturated sodium bisulfite solution. The solution was made basic with solid sodium bicarbonate and extracted with ether. The combined extracts were washed with water and brine, dried, and concentrated to give 8.27 g (91%) of a light yellow oil. Distillation afforded pure 18: bp 80.5–81° (0.22 mm); ir (CCl₄) 1750 (ester C=O), 1730 cm⁻¹ (ketone C=O); nmr (CCl₄) δ 5.13 (dd, 1, J = 9 and 3 hz, CHOAc), 2.04 (s, 3, COOCH₃), 1.38 (s, 3, CH₃), and 0.94 (s, 3, CH₃).

Anal. Calcd for C₁₁H₁₆O₃: C, 67.32; H, 8.22. Found: C, 67.20; H, 8.41.

Addition of Methyllithium to Keto Acetate 18.—To 23 ml (15 mmol) of 0.67 N methyllithium in ether cooled to −70° was added in one portion a solution of 0.50 g (2.6 mmol) of keto acetate 18 in 5 ml of ether. The resulting solution was allowed to warm to room temperature and stirred under nitrogen for 24 hr. The reaction mixture was poured into 150 ml of water and extracted with two 50-ml portions of ether and one 50-ml portion of methylene chloride. The combined extracts were dried and concentrated to give a yellow oil, 0.42 g (96%), which was chromatographed over 24 g of neutral silica gel (100–200 mesh) contained in a 30 cm × 15.5 mm glass column. Elution with ether–hexane mixtures afforded in early fractions 0.28 g (65%) of viscous, colorless *cis*-diol 1. Later fractions afforded 0.075 g (17%) of crystalline *trans*-diol 4.

Addition of Methylmagnesium Iodide to Keto Acetate 18. A. Normal Addition.—To a solution of methylmagnesium iodide prepared from 0.37 g (15 mg-atoms) of magnesium turnings, and 2.19 g (15 mmol) of methyl iodide in 15 ml of absolute ether was added at 0° under nitrogen with stirring over a period of 5 min 0.50 g (2.6 mmol) of keto acetate 18 in 5 ml of anhydrous ether. The resulting solution was allowed to warm to room temperature and was stirred for 16 hr. The reaction mixture was heated at reflux for 3 hr, cooled, poured into 150 ml of water, and extracted with ether and methylene chloride. The combined extracts were washed with water and brine, dried, and concentrated to give 0.36 g (84%) of a clear, colorless oil which was chromatographed through 24 g of neutral silica gel (100–200 mesh) contained in a 30 cm × 15.5 mm glass column. Elution with ether–hexane mixtures afforded in early fractions 0.18 g (42%) *cis*-diol 1. Later fractions afforded 0.04 g (10%) of *trans*-diol 4.

B. Inverse Addition.—To a solution of 0.50 g (2 mmol) of keto acetate 18 in 2.5 ml of anhydrous ether cooled to 0° was added under nitrogen with stirring over a period of 2 hr a solution of methylmagnesium iodide prepared from 0.18 g (7.7 mg-atoms) of magnesium turnings, 1.08 g (7.7 mmol) of methyl iodide, and 2.5 ml of ether. The reaction mixture was refluxed for 2 hr and then the reaction was quenched by the addition of 5.0 g of ice. The precipitated magnesium hydroxide was dissolved in a minimum amount of saturated ammonium chloride solution, and the mixture was extracted with ether. The combined extracts were washed with water and brine, dried, and concentrated to afford 0.45 g of a viscous yellow oil which was stirred for 20 hr at room temperature with 25 ml of 1 N methanolic potassium hydroxide. The reaction mixture was diluted with 60 ml of water and extracted with chloroform. The combined chloroform extracts were washed with water and brine, dried, and concentrated to give 0.27 g (63%) of a semisolid which was chromatographed as

(29) A. L. Wilds, *Org. React.*, **2**, 178 (1944).

(30) A 10 ft × ⅜ in. vpc column packed with 30% DEGS on 30–60 mesh Chromosorb W was employed for this separation.

(31) H. Schmidt, *Chem. Ber.*, **77**, 167 (1944).

described above to give 0.08 g (20%) of *cis*-diol 1 and 0.10 g (24%) of *trans*-diol 4.

Preparation of Benzyl Ether 19.—A dispersion of 53% sodium hydride in mineral oil (3.24 g of sodium hydride, 0.135 mol) was washed with three 50-ml portions of dry pentane under nitrogen. After the final wash the residual pentane was evaporated *in vacuo* and 60 ml of dimethyl sulfoxide was added dropwise under nitrogen. The resulting solution was stirred at room temperature for 0.5 hr. To this solution was added dropwise over a period of 5 min a solution of 13.70 g (0.090 mol) of 16[12] {[α]^{25}D −26.26° (*c* 2, CHCl₃)} in 40 ml of dimethyl sulfoxide, and the mixture was stirred at room temperature for 10 hr. To this mixture was added 17.0 g (0.135 mol) of benzyl chloride with stirring over a period of 0.5 hr. The reaction mixture was stirred for 1.0 hr, diluted with 350 ml of ice water, and extracted with pentane. The combined extracts were washed with brine, dried, and concentrated to give 26.87 g of a pale yellow oil from which crystallized 0.46 g of *trans*-stilbene. The remaining material was distilled to give 14.55 g (67%) of 19: bp 115–116° (0.25 mm); [α]^{25}D −21.79° (*c* 3.5, CHCl₃); ir (CCl₄) 3090 (C=CH), 3050 (aromatic CH), 1640 (C=C), 1380 and 1360 (*gem*-dimethyl), 1055 (CO), 897 (C=CH₂), and 692 cm⁻¹ (aromatic); nmr (CCl₄) δ 7.23 (s, 5, C₆H₅), 4.86 (s, 2, C=CH₂), 4.62 (d, 1, *J* = 12.0 Hz), 4.35 (d, 1, *J* = 12.0 Hz) (AB system, OCH₂Ph), 3.97 (m, 1, CHOCH₂Ph), 2.60–1.50 (m, 6), 1.30 (s, 3, CH₃), and 0.82 (s, 3, CH₃).

Anal. Calcd for C₁₇H₂₂O: C, 84.25; H, 9.15. Found: C, 83.98; H, 9.31.

Preparation of Keto Benzyl Ether 20.—A solution of 14.31 g (59 mmol) of olefin 19 in 150 ml of absolute methanol was ozonized for 1.0 hr at −70°. The ozonized solution was stirred vigorously with a mixture of 55 ml of methanol, 15 ml glacial acetic acid, and 29.6 g, (0.198 mol) of sodium iodide under nitrogen at room temperature for 7.0 hr. The resultant iodine-colored solution was diluted with 450 ml of water and treated with 25 ml of saturated sodium bisulfite solution. The solution was made basic by addition of solid sodium bicarbonate and was extracted with ether. The combined ethereal extracts were washed with water and brine, dried, and concentrated to give 14.22 g of a pale yellow oil which was recrystallized from hexane to afford 5.64 g (39%) of colorless, crystalline keto ether 20: mp 51–52°; [α]^{25}D +1.01° (*c* 3.5, CHCl₃); ir (CCl₄) 3040 (aromatic CH), 2950 (CH), 1715 (ketone C=O), 1385 and 1370 (*gem*-dimethyl), 1055 (CO), and 695 cm⁻¹ (aromatic); nmr (CCl₄) δ 7.21 (s, 5, C₆H₅), 3.90 (d, 1, *J* = 12.0 Hz), 3.74 (d, 1, *J* = 12.0 Hz) (AB system, OCH₂Ph), 2.70–1.60 (m, 6), 1.35 (s, 3, CH₃), and 0.77 (s, 3, CH₃).

(32) J. K. Crandall and L. Chang, *J. Org. Chem.*, **32**, 435 (1967).

Anal. Calcd for C₁₆H₂₀O₂: C, 78.65; H, 8.25. Found: C, 78.87; H, 8.48.

Treatment of 20 with Methyllithium.—To 57 ml (38 mmol) of 0.67 *N* ethereal methyllithium cooled to −70° was added under nitrogen 4.20 g (17.2 mmol) of crystalline keto ether 20 in 30 ml of anhydrous ether. The solution was allowed to warm to room temperature and was stirred for 25 hr. The reaction mixture was poured into 300 ml of water and extracted with ether. The ethereal extracts were dried and concentrated to give 4.57 g of a mixture of alcohols 21 and 22 as a pale yellow oil. Without further purification the benzyl group was reductively cleaved as described below.

Hydrogenolysis of Alcohols 21 and 22. A. By Catalytic Hydrogenation.—In an alcoholic potassium hydroxide washed Paar hydrogenation bottle was placed 0.80 g (3.08 mmol) of the mixture of alcohols 21 and 22 contained above in 50 ml of absolute ethanol and 0.3 g of 5% palladium-on-charcoal catalyst. The mixture was shaken under a 60-psi atmosphere of hydrogen for 24 hr, filtered, and concentrated to give a 0.61 g of a colorless semisolid which was chromatographed through 24 g of neutral silica gel (100–200 mesh) contained in a 30 cm × 15.5 mm glass column. Elution with ether–hexane mixtures afforded in the earlier fractions 0.09 g (16.9%) of *cis*-diol 1. Later fractions afforded 0.25 g (48.5%) of *trans*-diol 4.

B. By Reduction with Sodium in Liquid Ammonia.—To 150 ml of liquid ammonia which had been distilled through a potassium hydroxide tower was added 1.00 g (3.9 mmol) of the mixture of alcohols 21 and 22 in 6 ml of absolute ethanol. To this solution was added 0.44 g (19 mg-atoms) of sodium in small pieces. When all of the sodium was added, the solution maintained a dark blue color for *ca.* 3 min and then spontaneously became colorless. The mixture was allowed to stir an additional 1 hr and the ammonia was allowed to evaporate. The residue was diluted with 150 ml of water and extracted with chloroform. The combined extracts were washed with water and brine, dried, and concentrated to give 0.41 g of a pale yellow semisolid which was chromatographed through 17 g of neutral silica gel (100–200 mesh) contained in a 38 cm × 11.5 mm glass column. Elution with petroleum ether–ether mixtures afforded in the early fractions 88 mg (13.5%) of *cis*-diol 1. Later fractions afforded 150 mg (23%) of *trans*-diol 4.

Registry No.—1, 18680-27-8; **2**, 21803-49-6; **3**, 29333-10-6; **4**, 20536-52-1; **6**, 1845-25-6; **10**, 29333-13-9; **12**, 29333-14-0; **13**, 29333-15-1; **14**, 22419-98-3; **15**, 29333-17-3; **18**, 22419-94-9; **19**, 29333-19-5; **20**, 29333-20-8; **23**, 29333-21-9.

An Efficacious Methyl-Labeled (±)-Camphor Synthesis[1]

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A nine-step (±)-camphor synthesis is reported which allows the individual labeling of each of the three methyl groups, all steps proceeding in high yield. Norcamphor is methylated, carboxylated, and then treated with methylmagnesium bromide, leading to 2-*endo*,3-*exo*-dimethyl-3-*endo*-hydroxy-2-*exo*-norbornanecarboxylic acid. This acid was rearranged in 85% sulfuric acid to 1,7-dimethylnorbornane-7-carbo-2-lactone, which was reduced with lithium aluminum hydride and monotosylated with tosyl chloride to give 8-tosyloxyisoborneol. Chromic acid–pyridine oxidation to 8-tosyloxycamphor, followed by tosyl group displacement with iodide ion and catalytic hydrogenolysis, led to (±)-camphor.

We wish to report a convenient synthesis of (±)-camphor which allows the specific labeling of each of the three methyl groups. The sequence approximates one reported earlier by Finch and Vaughan[3] with, however,

some important variances (Chart I) and all steps proceeding in good yield.

The procedure commences from norcamphor (1), which was methylated essentially by the method described by Corey and coworkers,[4] yielding the exo methyl ketone 2. This ketone was converted to the corresponding enolate anion using triphenylmethylsodium,

(3) A. M. T. Finch and W. R. Vaughan, *J. Amer. Chem. Soc.*, **87**, 5520 (1965); **91**, 1416 (1969).

(4) E. J. Corey, R. Hartmann, and P. A. Vatakencherry, *ibid.*, **84**, 2611 (1962); J. Wolinsky, D. R. Dimmel, and T. W. Gibson, *J. Org. Chem.*, **32**, 2087 (1967).

Chart I

The Synthesis of (±)-Camphor
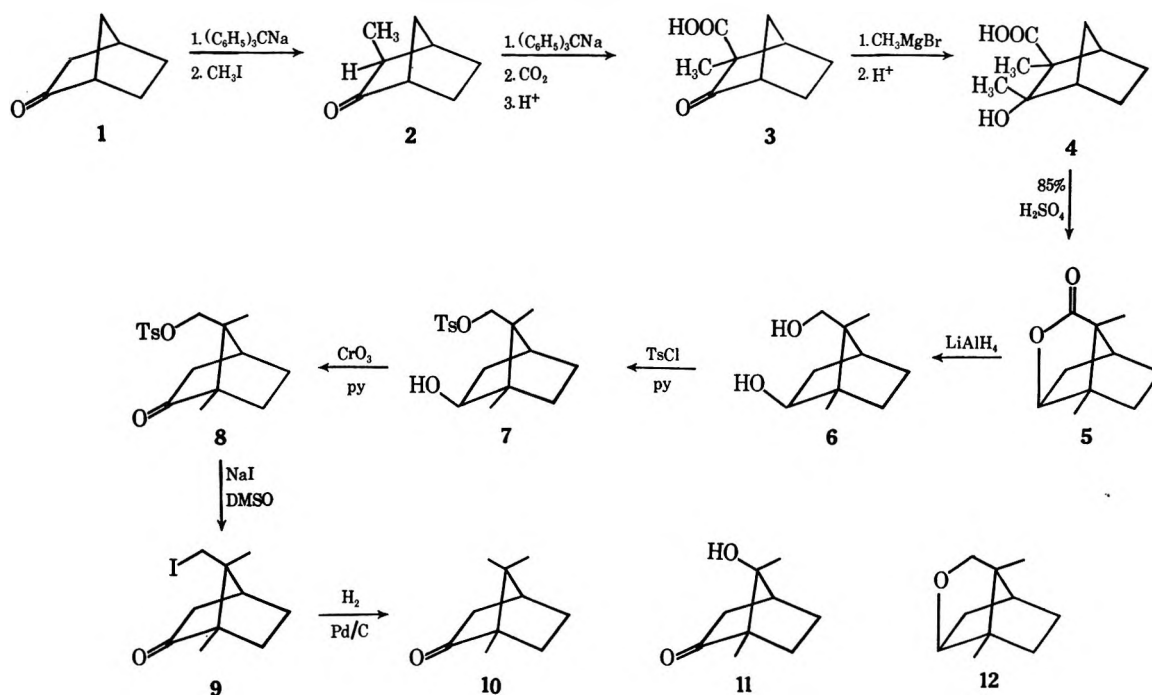
which was allowed to react with carbon dioxide to give the 3-*exo*-carboxylic acid **3**.

The reaction of the keto acid **3** with methylmagnesium bromide gave the hydroxy acid **4**, the newly introduced methyl group having previously been assigned the exo configuration on the basis of the known direction of preferred attack on the norbornane enolate system.[3] The acid **4** was rearranged in 85% sulfuric acid to the lactone **5**,[3,5] which, in turn, was reduced with lithium aluminum hydride to 8-hydroxyisoborneol (**6**).[3,6] The previously reported selective oxidation of the secondary hydroxyl group in **6** yielding 8-hydroxycamphor (**11**) in relatively poor yield was also found to be the case in our hands, and we explored instead an alternate route to camphor.

Monotosylation of 8-hydroxyisoborneol was successfully accomplished at low temperature[7] and the hydroxy tosylate **7** was smoothly oxidized to 8-tosyloxycamphor (**8**) by the Sarett method.[7,8] The keto tosylate was readily converted to the iodo derivative **9** using sodium iodide in dimethyl sulfoxide, and catalytic hydrogenolysis of the iodide yielded (±)-camphor. In the present case, (±)-camphor-8-[14]*C* and (±)-camphor-9-[14]*C* were prepared by the described route.

Experimental Section

The melting points are uncorrected and were determined with a Thomas-Hoover melting point apparatus. The infrared spectra were recorded on a Perkin-Elmer Model 257 grating infrared spectrophotometer, nmr spectra were carried out on a Perkin-Elmer Hitachi R-20 spectrometer using tetramethylsilane as an internal standard, mass spectra were obtained using a Perkin-

Elmer RMU-6E low-resolution mass spectrometer, and vapor phase chromatograms were carried out on a Varian Aerograph Series 200 instrument. Microanalyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, 5251 Elbach über Engelskirchen, West Germany, and by Spang Microanalytical Laboratory, Ann Arbor, Mich. The purity of the initially obtained reaction product was always checked by tlc (Merck silica gel F-254,[9] methanol, ether, *n*-heptane, 1:5:5) and/or by vpc (5% SE-30 on Chromosorb W). In all cases the product was found to contain not more than trace amounts of impurities, which were readily removed by the final recrystallization.

3-*exo*-Methyl-2-norbornanone (2).—The methylation of norcamphor[10] was carried out by the method described by Corey, Hartmann, and Vatakencherry.[4] For the preparation of 3-*exo*-methyl-[14]*C*-2-norbornanone, 0.10 mCi of methyl-[14]*C* iodide (sp act. 5.54 mCi/mmol) was diluted with 28.40 g of nonradioactive methyl iodide and added to the sodium enolate prepared from 5.50 g (0.050 mol) of norcamphor as previously described.[4]

3-*endo*-Methyl-2-norbornanone-3-*exo*-carboxylic Acid (3).—A three-necked flask fitted with a rubber septum, a pressure-equalizing dropping funnel, and a nitrogen inlet system was filled with nitrogen, and 38 ml of a 0.53 N ethereal solution of triphenylmethylsodium[11] was added through the septum with the aid of a syringe. The stirred reagent was cooled in an ice bath and an ethereal solution of 3-*exo*-methyl-2-norbornanone (2) was added dropwise until the mixture turned bright yellow, occurring after 2.39 g (0.019 mol) of ketone had been introduced. The reaction mixture was transferred with a syringe to a flask containing 22 g (0.50 mol) of powdered Dry Ice and allowed to stir under a carbon dioxide atmosphere for 1 hr. Water was added and the ether was extracted with cold 10% potassium hydroxide solution. The combined basic extracts were washed with ether to remove any nonacidic material, cooled in an ice bath, and acidified with 6 N hydrochloric acid. The keto acid was removed by extraction with chloroform and the combined chloroform extracts were washed with water and dried. Removal of the solvent left 2.70 g (83%) of 3-*endo*-methyl-2-norbornanone-3-*exo*-carboxylic acid as a white solid, mp 94–96°. A small portion of the acid was recrystallized from pentane-ether, followed by sublimation (0.10 mm, 60°): mp 102.5–103.5°; ir (KBr) 1760 (ketone C=O) and 1690 cm⁻¹ (acid C=O); nmr (CDCl₃) δ 8.75 [broad s (exchanged with D₂O), 1, COOH] and 1.36 ppm (s, 3,

(5) S. Beckmann and H. Geiger, *Ber.*, **92**, 2411 (1959).

(6) S. Beckmann, H. Geiger, and M. Schaber-Kiechle, *ibid.*, **92**, 2419 (1959).

(7) W. S. Johnson, J. C. Collins, Jr., R. Pappo, M. B. Rubin, P. J. Kropp, W. F. Johns, J. E. Pike, and W. Bartmann, *J. Amer. Chem. Soc.*, **85**, 1409 (1963).

(8) G. I. Poos, B. E. Arth, R. E. Beyler, and L. H. Sarett, *ibid.*, **75**, 425 (1953); J. R. Holum, *J. Org. Chem.*, **26**, 4814 (1961).

(9) EM Reagents Division, Brinkmann Instruments, Inc., Westbury, N. Y. 11590.

(10) Aldrich Chemical Co., Inc., Milwaukee, Wis. 53233.

(11) W. B. Renfrow, Jr., and C. R. Hauser, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 607.

CH₃); mass spectrum (70 eV) m/e (rel intensity, fragment ion) 168 (2, M⁺), 124 (35, M⁺ − CO₂), 44 (100, CO₂⁺).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.19; H, 7.34.

When the ketone 2 was added to a suspension of sodium amide in ether and the resulting enolate carbonated with CO₂ gas or Dry Ice, the keto acid was isolated according to the procedure described above in only low yields. The use of sodium naphthalide also proved to be less satisfactory.

To prepare 3-*endo*-methyl-2-norbornanone-3-*exo*-carboxylic acid-¹⁴*C*, gaseous carbon dioxide was generated in a 300-ml three-necked flask equipped with a magnetic stirrer, a dropping funnel, and a delivery tube which was connected through a drying tube to the flask containing the sodium enolate of 3-*exo*-methyl-2-norbornanone. Barium carbonate-¹⁴*C* (1.0 mCi, sp act. 59.6 mCi/mmol), diluted with a tenfold molar excess of nonradioactive barium carbonate, was placed in the carbon dioxide generating flask as an aqueous slurry and concentrated sulfuric acid was used to liberate the carbon dioxide. This method gave a 70% yield of the labeled keto acid.

2-*endo*,3-*exo*-Dimethyl-3-*endo*-hydroxy-2-*exo*-norbornanecarboxylic Acid (4).—A solution of 4.90 g (0.029 mol) of 3-*endo*-methyl-2-norbornanone-3-*exo*-carboxylic acid (3) in 90 ml of dry ether was added to a three-necked flask equipped with a magnetic stirrer, reflux condenser, pressure-equalizing dropping funnel, and nitrogen inlet system. The reaction flask was placed under nitrogen and 24 ml of 2.95 M methylmagnesium bromide¹² in ether was added dropwise with stirring. Stirring was continued at room temperature for 2 hr and the mixture was acidified with dilute hydrochloric acid. The aqueous phase was separated and extracted with chloroform. The combined organic layers were washed with water and dried, and the solvent was removed by distillation under reduced pressure. There remained 5.35 g (100%) of the hydroxy acid 4 as a white solid, mp 157–161°. For analysis a sample from another run was recrystallized from pentane–ether: mp 160–164°; ir (KBr) 3420 and 3315 (OH), 1700 cm⁻¹ (C=O); nmr (CDCl₃) δ 6.55 [broad s (exchanged with D₂O), 2, COOH and OH], 1.39 (s, 3, CH₃), and 1.24 ppm (s, 3, CH₃); mass spectrum (70 eV) m/e (rel intensity, fragment ion) 166 (5, M⁺ − H₂O), 138 (100, 166 − C₂H₄), 123 (28, 138 − CH₃), 116 (49).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.09; H, 8.68.

1,7-Dimethylnorbornane-7-carbo-2-lactone (5).—This substance was prepared by an adaptation of the method of Finch and Vaughan.³ A cold aqueous sulfuric acid solution, prepared from 23 ml of concentrated sulfuric acid and 7.5 ml of water, was added dropwise to a flask containing 5.35 g (0.029 mol) of 2-*endo*,-3-*exo*-dimethyl-3-*endo*-hydroxy-2-*exo*-norbornanecarboxylic acid (4), cooled in an ice bath. The solution was stirred at room temperature for 17 hr, poured over 30 g of ice, and extracted with ether. The combined ether extracts were washed with 5% aqueous potassium hydroxide and brine and dried, and the solvent was removed *in vacuo*, yielding 4.25 g (88%) of the lactone 5 as a white solid. A small portion of the product was recrystallized from heptane–ether: mp 192–194° (lit.⁵ mp 192–194°); ir (KBr) 1770 cm⁻¹ (C=O); nmr (CDCl₃) δ 4.31 (d, 1, H at C-2), 1.10 (s, 3, CH₃), and 1.07 ppm (s, 3, CH₃); mass spectrum (70 eV) m/e (rel intensity, fragment ion) 138 (73, M⁺ − C₂H₄), 123 (36, 138 − CH₃), 105 (73), 79 (82), 44 (100, CO₂⁺).

8-Hydroxyisoborneol (6).—A solution of 4.21 g (0.025 mol) of 1,7-dimethylnorborane-7-carbo-2-lactone (5) in 20 ml of dry ether was added slowly *via* a pressure-equalizing dropping funnel to a magnetically stirred slurry of 0.96 g (0.025 mol) of lithium aluminum hydride in 65 ml of dry ether under a nitrogen atmosphere in a three-necked flask also equipped with a reflux condenser. The reaction mixture was stirred at room tmperature for 4.5 hr and at reflux for 1 hr. The reaction mixture was worked up as previously described,³ yielding 3.98 g (92%) of 8-hydroxyisoborneol (6) as a white solid. The diol was recrystallized from ethyl acetate and then sublimed (0.15 mm, 100°): mp 273–275° (lit.³ 275–276°); ir (KBr) 3320 cm⁻¹ (broad, OH); nmr (CDCl₃) δ 2.79 [s exchanged with D₂O), 2, OH], 0.97 (s, 3, CH₃), and 0.92 ppm (s, 3, CH₃); mass spectrum (70 eV) m/e (rel intensity, fragment ion) 152 (22, M⁺ − H₂O), 137 (26, 152 − CH₃), 124 (26, 152 − C₂H₄), 108 (79), 67 (100), 31 (40, CH₂= ⁺OH).

8-Tosyloxyisoborneol (7).—To a solution of 1.02 g (0.006 mol)

of 8-hydroxyisoborneol (6) in 6.0 ml of dry pyridine was added 1.20 g (0.0063 mol) of *p*-toluenesulfonyl chloride with stirring. The solution was stirred at −10° (cold room) under nitrogen for 19 hr, water was added, and the mixture was extracted with ether. The combined ether extracts were washed with 6 N hydrochloric acid and brine and dried, and the solvent was removed under reduced pressure, leaving 1.67 g (86%) of the 8-tosyloxyisoborneol (7) as a white solid. The tosylate was recrystallized from hexane–ether: mp 97–98°; ir (KBr) 3515 (OH), 1181 and 1174 cm⁻¹ (tosylate); nmr (CDCl₃) δ 7.88 (d, 2, ArH), 7.41 (d,2, ArH), 4.70 (d, 1, H at C-2), 3.90 (d, 2, CH₂OTs), 2.56 (s, 3, ArCH₃), 1.97 [s (exchanged with D₂O), 1, OH], 0.91 (s, 3, CH₃), and 0.88 ppm (s, 3, CH₃).

Anal. Calcd for $C_{17}H_{24}O_4S$: C, 62.93; H, 7.46; S, 9.88. Found: C, 62.91; H, 7.54; S, 9.82.

8-Tosyloxycamphor (8).—A solution of 1.39 g (0.0043 mol) of 8-tosyloxyisoborneol (7) in 14 ml of dry pyridine was added in one portion to an ice-cold slurry of 1.29 g (0.013 mol) of anhydrous chromium trioxide in 13 ml of dry pyridine. The mixture was placed under a nitrogen atmosphere and stirred at room temperature for 5 hr, poured into water, and extracted with ether. The combined ether extracts were washed successively with 6 N hydrochloric acid and brine and dried, and the solvent was removed under reduced pressure to yield 1.30 g (94%) of the ketotosylate (8) as a pale yellow oil. Crystallization occurred in pentane–ether to give a colorless solid: mp 73–74°; ir (neat) 1745 (C=O), 1191 and 1180 cm⁻¹ (tosylate); nmr (CDCl₃) δ 7.83 (d, 2, ArH), 7.41 (d, 2, ArH), 3.69 (s, 2, CH₂OTs), 2.44 (s, 3, ArCH₃), 1.01 (s, 3, CH₃), and 0.82 ppm (s, 3, CH₃); mass spectrum (70 eV) m/e (rel intensity, fragment ion) 322 (5, M⁺), 167 (100, M⁺ − Ts), 108 (64), 107 (95), 95 (80), 91 (48, C₇H₇⁺).

Anal. Calcd for $C_{17}H_{22}O_4S$: C, 63.33; H, 6.88; S, 9.95. Found: C, 63.06; H, 7.40; S, 9.73.

8-Iodocamphor (9).—A solution of 0.720 g (0.0022 mol) of 8-tosyloxycamphor (8) in 17 ml of dimethyl sulfoxide containing 1.68 g (0.0112 mol) of sodium iodide was heated at 120° under nitrogen for 24 hr. The reaction mixture was cooled to room temperature, diluted with water, and extracted with pentane. The combined pentane extracts were washed with sodium thiosulfate solution and brine and dried, and the solvent was removed under reduced pressure to give 0.534 g (86%) of 8-iodocamphor (9) as a pale yellow oil. Crystallization occurred in pentane to yield the product as a colorless solid: mp 40–42° (lit.¹³ mp 79°); ir (KBr) 1740 cm⁻¹ (C=O); nmr (CDCl₃) δ 3.01 (s, 2, CH₂I), 1.15 (s, 3, CH₃), and 0.96 ppm (s, 3, CH₃); mass spectrum (70 eV) m/e (rel intensity, fragment ion) 278 (30, M⁺), 151 (58, M⁺ − I), 109 (74), 107 (100), 94 (21), 81 (79).

(±)-Camphor (10).—A solution containing 0.380 g (0.0014 mol) of 8-iodocamphor (9) in 20 ml of ethanol was added to a slurry of 0.760 g of 5% palladium on charcoal in 2.0 ml of water containing 0.090 g (0.0014 mol) of potassium hydroxide (85%). The mixture was shaken under 46 psi of hydrogen for 6 hr on a Parr apparatus, the catalyst then removed by filtration, water added, and the solution extracted with pentane. The combined pentane extracts were washed with brine and dried, and the solvent was removed under reduced pressure. There remained 0.160 g (77%) of (±)-camphor (10) as a white solid which was sublimed (18 mm, steam bath): mp 177–178° (lit.¹⁴ mp 178–178.5°); ir (KBr) 1740 cm⁻¹ (C=O); nmr¹⁵ (CDCl₃) δ 0.98 (s, 3, H₃ at C-9), 0.93 (s, 3, H₃ at C-10), and 0.85 ppm (s, 3, H₃ at C-8); mass spectrum¹⁶ (70 eV) m/e (rel intensity, fragment ion) 152 (36, M⁺), 137 (9, M⁺ − CH₃), 110 (18, M⁺ − C₂H₂O), 109 (41, C₈H₁₃⁺), 108 (55, C₈H₁₂⁺), 95 (100, C₇H₁₁⁺), 83 (23, C₆H₁₁⁺), 81 (82, C₆H₉⁺).

Purification of (±)-Camphor Using Girard Reagent T.—In several runs using larger amounts of materials, the (±)-camphor obtained contained some 2,8-epoxybornane (12), identified by comparing its vpc retention times on 5% SE-30 on Chromosorb W (95°) and 5% Apiezon L, 5% KOH on Chromosorb G (170°) columns with those of an authentic sample. This cyclic ether, reported as a product in the attempted reduction of 8-tosyloxyisoborneol (7) with lithium aluminum hydride,³ was prepared by

(12) Alfa Inorganics, Inc., Beverly, Mass. 01915.

(13) H. Nishimitsu, M. Nishikawa, and H. Hagiwara, *Proc. Jap. Acad.*, **27**, 285 (1951); *Chem. Abstr.*, **46**, 6112a (1952). M. Nishikawa, *J. Pharm. Soc. Jap.*, **72**, 303 (1952); *Chem. Abstr.*, **47**, 2145i (1953).

(14) J. Simonsen, "The Terpenes," Vol. III, 2nd ed, Cambridge University Press, London, 1949, p 384.

(15) J. D. Connolly and R. McCrindle, *Chem. Ind.* (London), 379 (1965); C. C. Hinckley, *J. Org. Chem.*, **35**, 2834 (1970).

(16) D. S. Weinberg and C. Djerassi, *ibid.*, **31**, 115 (1966).

us in this manner in high yield (see below). In the camphor synthesis it was presumably formed in the tosylation and/or oxidation step(s) and could be effectively removed by employing the following procedure.[17]

A solution of 790 mg of impure product (consisting of 90% camphor and 10% 2,8-epoxybornane), 863 mg (5.20 mmol) of Girard Reagent T,[9] and 0.80 ml of acetic acid in 8.0 ml of 95% ethanol was heated at reflux for 48 hr. The reaction mixture was cooled, diluted with equal volumes of water and brine, and extracted with pentane.

Purified camphor was recovered by treating the aqueous layer with 1.5 ml of concentrated hydrochloric acid and heating for 2 hr to effect hydrolysis of the Girard derivative. After cooling the camphor was removed by extraction with pentane; the combined pentane extracts were dried, and the solvent was removed under vacuum to yield 513 mg of (±)-camphor of >99% purity as determined by vpc analysis using a 5% SE-30 on Chromosorb W column.

The combined pentane extracts from the initial work-up of the reaction mixture were dried and the solvent was removed under reduced pressure to yield 215 mg of a white solid consisting of 41% camphor and 59% 2,8-epoxybornane (vpc). This mixture

was recycled as described above, yielding an additional 108 mg of purified camphor. The combined weights of isolated camphor represent a recovery of 87% of purified product which was sublimed (18 mm, steam bath) to yield a white solid, mp 177–178°. Synthetically prepared (±)-camphor-*8*-[14]*C* and (±)-camphor-*9*-[14]*C* were both purified in this manner.

2,8-Epoxynorbornane (12).—A solution of 200 mg (0.60 mmol) of 8-tosyloxyisoborneol (7) in 5.0 ml of dry ether was added dropwise to a slurry of 23 mg (0.60 mmol) of lithium aluminum hydride in 6.0 ml of dry ether. The reaction mixture was stirred under nitrogen for 1 hr and then heated at reflux for an additional hour. The mixture was cooled, acidified with 10% sulfuric acid, and extracted with ether. The combined ether extracts were washed with 5% aqueous sodium bicarbonate and dried, and the solvent was removed under reduced pressure to yield 89 mg (95%) of 2,8-epoxynorbornane (12) as a white solid which was sublimed (16 mm, 50°): mp 172–174° (lit.[3] mp 164–167°); the infrared spectrum showed no peaks characteristic of hydroxyl or tosyl groups; mass spectrum (70 eV) *m/e* (rel intensity, fragment ion) 152 (7, M[+]), 108 (100, M[+] − C_2H_4O or − C_3H_8), 93 (70, 108 − CH_3), 79 (30), 67 (30).

Registry No.—**3**, 29908-22-3; **4**, 29908-23-4; **7**, 29908-24-5; **8**, 29908-25-6; **10**, 21368-68-3.

(17) D. J. Pasto and C. R. Johnson, "Organic Structure Determination," Prentice-Hall, Englewood Cliffs, N. J., 1969, p 393.

Addition of Active Methylene and Methine Compounds to 9-Nitroanthracene[1]

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Addition of 9-nitroanthracene to solutions of sodio malonic ester, sodio methylmalonic ester, sodium 2-propane-nitronate, and sodio malononitrile in dimethyl sulfoxide and subsequent dilution with water and acidification afford 10-dicarbethoxymethyl-, 10-(1,1-dicarbethoxyethyl)-, 10-(2-nitro-2-propyl)-, and 10-dicyanomethyl-9-nitro-9,10-dihydroanthracenes (7a–d), respectively. The results of nmr studies of 7a are consistent only with the diaxially substituted cis isomer. Addition of benzyl halide to dimethyl sulfoxide solutions of the sodium salts of adducts 7a–c, followed by aqueous work-up, produces 10-substituted 9-anthrone oximes 10a–c. Treatment of adducts 7a and 7b with acid causes loss of the elements of nitrous acid with the formation of diethyl (9-anthryl)malonate (12a) and diethyl methyl(9-anthryl)malonate (12b), respectively.

The stable σ complexes formed by nucleophilic attack of certain alkyl nitroaryl ethers by alkoxide ion are known as Jackson–Meisenheimer complexes.[3] These complexes, and structurally similar species, are of theoretical interest because they are possible intermediates in nucleophilic aromatic substitution.[3,4] In some cases the intermediacy of the complex may be shown by spectrometric methods, and some of the complexes are sufficiently stable to permit isolation.[5]

Acidification of Jackson–Meisenheimer complexes (and structurally similar species) normally causes regeneration of the aromatic system; the only exception of which we are aware is reported in the work of Meisenheimer.[6] Complex 2 was prepared by treatment of 9-nitroanthracene (1) with methanolic potassium hydroxide. Acidification produced a material for which Meisenheimer suggested structure 3. It is the purpose of this paper to report the preparation, characteriza-

tion, and reactions of a series of conjugate acids of anions which structurally resemble Jackson–Meisenheimer complexes.
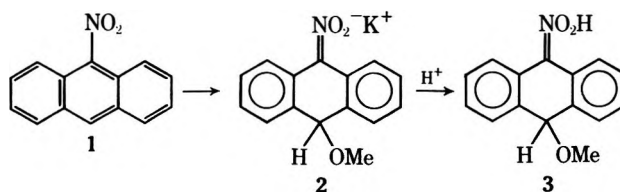
Landolt and Snyder[7] examined the reaction of 9-nitroanthracene with cyanide ion in dimethylformamide. Isolated reaction products included 9-nitro-10-cyanoanthracene (5a) and 9,10-dicyanoanthracene (5b).

Dicyanoanthracene 5b is produced upon treatment of 5a with cyanide ion under the conditions of the reaction.[7] The mechanism which was proposed for the formation of 5a involves one-electron transfer from ini-
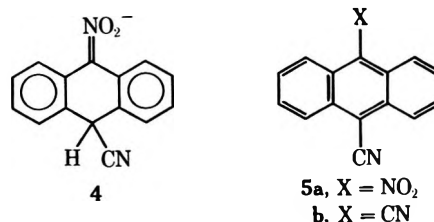
(1) Grateful acknowledgment is made to the U. S. Army Research Office for partial support of this work [Grants DA-ARO(D)-G679 and G857].

(2) NSF Predoctoral Fellow, 1967–1971.

(3) M. J. Strauss, *Chem. Rev.*, **70**, 677 (1970); J. A. Orvik and J. F. Bunnett, *J. Amer. Chem. Soc.*, **92**, 2417 (1970).

(4) (a) E. Buncel, A. R. Norris, and K. E. Russell, *Quart. Rev. (London)*, **22**, 123 (1968); (b) J. Sauer and R. Huisgen, *Angew. Chem.*, **72**, 294 (1960).

(5) J. H. Fendler, E. J. Fendler, and C. E. Griffin, *J. Org. Chem.*, **34**, 689 (1969); J. H. Fendler, E. J. Fendler, W. E. Byrne, and C. E. Griffin, *ibid.*, **33**, 977 (1968); R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966).

(6) J. Meisenheimer, *Ann. Chem.*, **323**, 205 (1902).

(7) R. G. Landolt and H. R. Snyder, *J. Org. Chem.*, **33**, 403 (1968).

tially formed anion **4** and subsequent oxidation of the resulting radical. The overall result of the reaction is the replacement of an aromatic hydrogen atom by a cyano group. The possibility of extending this reaction to other nucleophiles prompted this study.

Adducts.—Addition of 9-nitroanthracene (**1**) to a solution of sodio malonic ester in dimethyl sulfoxide (DMSO) produces an intensely colored solution. Aqueous work-up affords 9-nitro-10-dicarbethoxy-methyl-9,10-dihydroanthracene (**7a**) in 68% yield. Analogously, reaction with the anions of diethyl methylmalonate, 2-nitropropane, and malononitrile provides 9-nitro-10-(1,1-dicarbethoxyethyl)-9,10-dihydroanthracene (**7b**, 75%), 9-nitro-10-(2-nitro-2-propyl)-9,10-dihydroanthracene (**7c**, 76%), and 9-nitro-10-dicyanomethyl-9,10-dihydroanthracene (**7d**, 70%), respec-

6a, R = CH(CO₂Et)₂   **7a**, R = CH(CO₂Et)₂
b, R = CMe(CO₂Et)₂   **b**, R = CMe(CO₂Et)₂
c, R = CMe₂NO₂   **c**, R = CMe₂NO₂
d, R = CH(CN)₂   **d**, R = CH(CN)₂
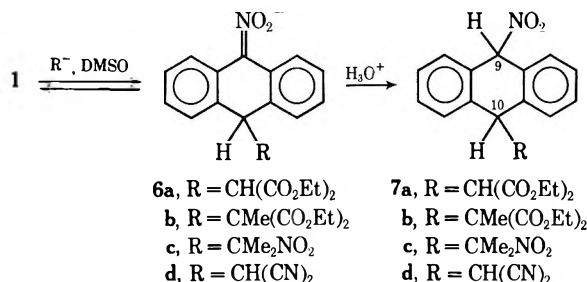
tively. Dilution of the reaction mixture with water followed by acidification causes precipitation of the crude product as a light yellow solid. The yellow color is removed by recrystallization; the use of 2 equiv of nucleophile in the reactions facilitates purification by reducing the amount of unreacted nitroanthracene.

The ir spectra of the adducts contain, in addition to peaks characteristic of R, peaks of medium to strong intensity at ca. 1550 and 1360 (NO_2), 750 (ortho disubstituted benzene), and 1450 cm⁻¹. The nmr spectra of the adducts are summarized in Table I. Chemical shift is strongly dependent upon solvent: the AB system of **7d** collapses to a singlet (4.66 ppm) when $CDCl_3$ is used as the solvent. As shown in Figure 1, the CH-$(CO_2Et)_2$ doublet is superimposed upon the methylene proton multiplet in the nmr spectrum of a solution of **7a** in acetone-d_6, but, upon change of solvent to C_6D_6, the resonances no longer overlap. Potential magnetic nonequivalence[8] of the methylene protons of **7a**, unlike that of **7b**, is manifest. Analysis of the 220-MHz spectrum[9] of **7a** indicates that the multiplet observed at 3.9 ppm in the 60-MHz spectrum consists of a doublet ($J = 10.0$ Hz) centered at 3.85 ppm superimposed upon an AB system of quartets centered at 3.96 ppm. Parameters of the AB system are $J_{AB} = 10.0$ Hz, $\Delta\delta = 0.089$ ppm, $J_{HMe} = 7.0$ Hz.

The central ring of the dihydroanthracene system is constrained to the boat form by the two fused benzene rings. A cis diaxially substituted isomer (**8**), a cis diequatorially substituted isomer (**9**), and two trans disubstituted isomers are possible. In addition, the two cis isomers are interconvertible by a boat–boat ring inversion, as are the two trans isomers. Nmr studies of 9-alkyl- and 9,10-dialkyl-9,10-dihydroanthracenes indicate that the equatorial position is more crowded

(8) M. van Gorkom and G. E. Hall, *Quart. Rev. (London)*, **22**, 14 (1968).

(9) We gratefully acknowledge a grant to the Department of Chemistry and Chemical Engineering of the University of Illinois from the National Science Foundation, which helped to make purchase of the HR 220 possible.

TABLE I
60-MHz NMR SPECTRA OF ADDUCTS AND OXIMES[a]

Compd	δ[b]	Multiplicity[c] (J, Hz)	Proton assignment
7a	1.0	t (7)	CH_2CH_3
	3.9	m	$CH_2CH_3 + CH(CO_2Et)_2$
	4.9	d (10) b	H-10
	6.9	s b	H-9
	~7.5	m	Aromatic
7b	0.9	s	$C(CH_3)(CO_2Et)_2$
	1.2	t (7)	CH_2CH_3
	4.1	q (7)	CH_2CH_3
	5.4	s b	H-10
	6.7	s b	H-9
	~7.5	m	Aromatic
7c[d]	1.3	s	CH_3
	4.9	s b	H-10
	6.4	s b	H-9
	~7.5	m	Aromatic
7d	4.9	AB (10.8) ($\Delta\delta$ = 0.106 ppm)[e]	$CHCH(CN)_2$
	7.2	s b	H-9
	~7.8	m	Aromatic
10a	1.0	t (7)	CH_2CH_3
	3.4	d (10)	$CH(CO_2Et)_2$
	4.0	q (7)	CH_2CH_3
	4.8	d (10)	H-10
	7.3–8.5[f]	m	Aromatic
	10.9	s b	NOH
10b	1.1[g]	s	$C(CH_3)(CO_2Et)_2$
	1.2	t (7)	CH_2CH_3
	4.2	q (7)	CH_2CH_3
	5.3	s b	H-10
	7.5–8.6[f]	m	Aromatic
	10.8	s b	NOH

[a] Solvent is acetone-d_6 unless otherwise specified. [b] In parts per million downfield from TMS. [c] Abbreviations: s, singlet; d, double; t, triplet; q, quartet; m, multiplet; b, broad. [d] In $CDCl_3$ solution. [e] The upfield half is due to $CH(CN)_2$. [f] See text. [g] Superimposed upon triplet in 60-MHz spectra.

8   **9**
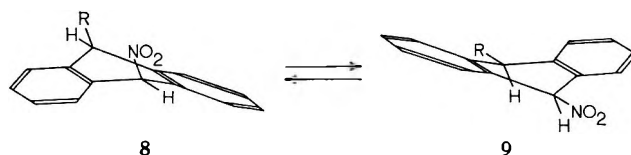
than the axial position, presumably because of steric interaction of the equatorial substituent and the peri protons.[10] Temperature invariance of the nmr spectrum of 9-isopropyl-9,10-dihydroanthracene from 37 to −37° led Brinkmann, *et al.*,[10a] to conclude that the compound is conformationally homogeneous within this temperature range, and only the axially substituted conformer is consistent with the nuclear Overhauser enhancements which they observed. The resonance signals assigned to the benzylic protons of adduct **7a** do not change significantly when the temperature of an acetone-a_6 solution is decreased from 42 to −95°. Temperature invariance of the nmr spectrum indicates either that the adduct is not a rapidly equilibrating mixture of inversional isomers below 42° or that equilibrium is rapid at −95°, which is unlikely.[10a,11a]

(10) (a) A. W. Brinkmann, M. Gordon, R. G. Harvey, P. W. Rabideau, J. B. Stothers, and A. L. Ternay, Jr., *J. Amer. Chem. Soc.*, **92**, 5912 (1970); (b) R. G. Harvey, L. Arzadon, J. Grant, and K. Urberg, *ibid.*, **91**, 4535 (1969); J. E Anderson, *Quart. Rev. (London)*, **19**, 426 (1966).

(11) (a) P. T. Lansbury, *Accounts Chem. Res.*, **2**, 210 (1969); (b) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).
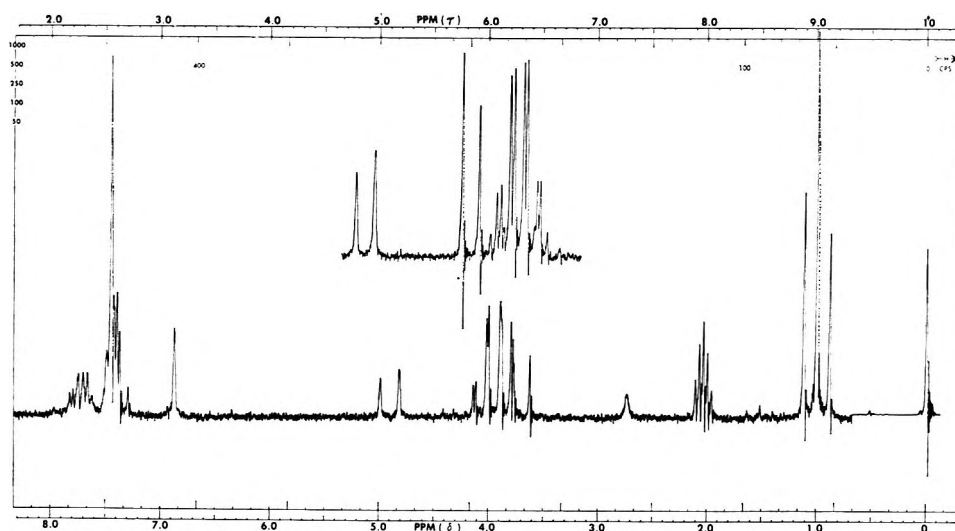
Figure 1.—The 60-MHz nmr spectrum of 9-nitro-10-dicarbethoxymethyl-9,10-dihydroanthracene (**7a**) in acetone-d_6 (lower trace) and in C_6D_6 (upper trace). Solvent impurities (acetone-d_5 and HDO) are responsible for resonances at 2.05 and 2.8 ppm.

Resonance signals arising from benzylic protons of the adducts are broadened by long-range benzylic coupling with ortho and para ring protons. The magnitude of the benzylic coupling constant is dependent upon the dihedral angle between the ring plane and the plane defined by the Ar–C–H bonds; a larger coupling constant should be observed for an axial than for an equatorial proton.[11] In addition, the appearance of these resonance signals will be altered by coupling between the benzylic protons. The magnitude of the homoallylic coupling constant is dependent upon the positions occupied by the benzylic protons; typical values of the homoallylic coupling constant for the dihydroanthracene system are $J_{a,a} = 2.5$ Hz, $J_{a,e} = 1.5$ Hz, and $J_{e,e} = 0.5$ Hz.[10a,12]

Resonance of the C-9 proton of adduct **7a** (C_6D_6 solution) gives rise to a singlet at 6.10 ppm (width at half-height, 1.4 Hz), and resonance of the C-10 proton gives rise to a doublet ($J = 10$ Hz) centered at 5.17 ppm (width of each peak at half-height, 1.4 Hz). Observed line widths of the benzylic resonances preclude the diequatorially substituted isomer, and consideration of a trans isomer would require an atypically small homoallylic coupling constant. In addition, line widths of the two benzylic resonances of a trans isomer would differ as a result of distinct benzylic coupling constants for axial and equatorial protons.

The resonances of equatorial, but not axial, benzylic protons of dihydroanthracenes are enhanced upon irradiation of aryl resonance signals[10a] (nuclear Overhauser effect[13]). Irradiation of a deoxygenated solution of **7a** in C_6D_6 at 7.50 ppm causes an enhancement of the C-10 proton resonance of 15%, and irradiation at 7.10 ppm causes an enhancement of the C-9 proton resonance of 10%. These data are consistent only with the diaxially substituted cis isomer.

Complex formation proceeds poorly in conventional protic solvents; only nitroanthracene was recovered from an attempted preparation of **7a** in ethanol. Reaction fails to occur in DMSO when a catalytic quantity

of base is used, and at least 67% of a sample of adduct **7d** reverted to nitroanthracene upon standing for 2 hr at room temperature in DMSO containing a catalytic amount of dimsyl ion. Reversal of adduct formation also takes place upon dissolution of **7d** in pyridine.

Two factors contribute to the increased rate of nucleophilic substitution reactions in dipolar aprotic media: enhanced reactivity of nucleophile and greater stabilization of the transition state. Haberfield, Clayman, and Cooper[14] have reported that the change in enthalpy of solvation of the nucleophile, on going from polar protic to dipolar aprotic solvent, is not always the primary factor in determining the much smaller activation enthalpies of S_N2 and S_NAr reactions in dipolar aprotic solvents.

Grunwald and Price[15] have emphasized the importance of the contribution to solvation energy made by the dispersion interaction. The dispersion interaction is particularly strong when both solvent and solute are highly polarizable, and its contribution to solvation energy may be dominant. The intense color observed upon treatment of nitroaromatic compounds with base has been ascribed to species similar to Jackson–Meisenheimer complexes[4a,5] and is an indication of the high polarizability expected for a highly delocalized anion (represented in structure **6** by only one of the many limiting resonance forms).

Although the adducts are thermodynamically less stable than the compounds from which they are prepared, the conjugate bases of the adducts are stable in the highly polarizable, dipolar aprotic solvents. Anionic character of the aromatic system, which develops in the transition state and is realized in the complex, increases the strength of the dispersion interaction, and, consequently, the energy of solvation.

Upon protonation of the anion of 9-nitrofluorene, Kerber and Hodos[16] obtained a nitronic acid which is stable in hydroxylic solvents but tautomerizes to 9-nitrofluorene in nonpolar solvents. Protonation of complex **6** may proceed through a nitronic acid (*vide infra*),

(12) Note that $J_{e,e}$ is the coupling constant between two equatorial protons and that it is this coupling constant that is expected for a *diaxially* substituted dihydroanthracene.

(13) A. Carrington and A. McLachlan, "Introduction to Magnetic Resonance," Harper and Row, New York, N. Y., 1967, p 229.

(14) P. Haberfield, L. Clayman, and J. S. Cooper, *J. Amer. Chem. Soc.*, **91**, 787 (1969).

(15) E. Grunwald and E. Price, *ibid.*, **86**, 4517 (1964).

(16) R. C. Kerber and M. Hodos, *J. Org. Chem.*, **33**, 1169 (1968).
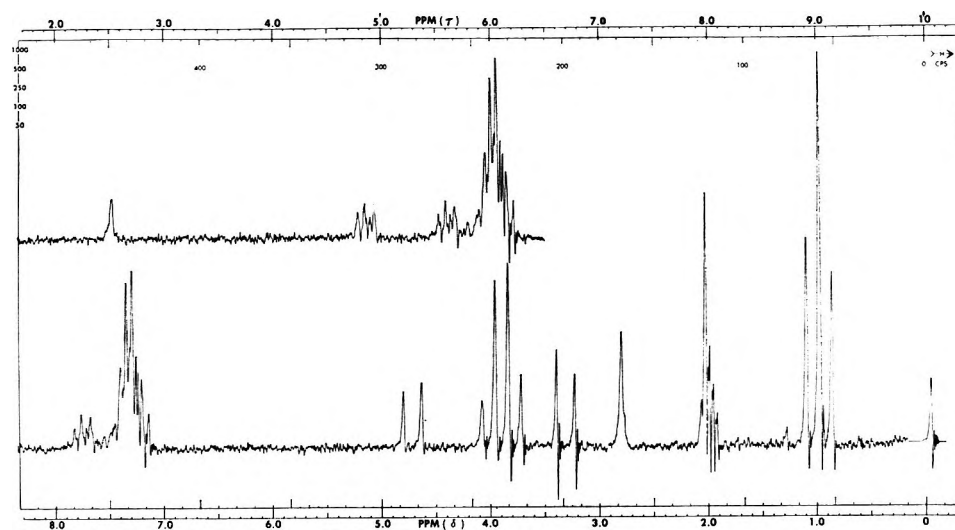
Figure 2.—The 60-MHz nmr spectrum of 10-dicarbethoxymethyl-9,10-dihydro-9-oximinoanthracene (10a) in acetone-d_6; upper trace, offset 200 Hz. Solvent impurities (acetone-d_5 and HDO) are responsible for resonances at 2.05 and 2.8 ppm.

but spectral data clearly establish that the adducts isolated are nitro compounds.

Oximes.—Treatment of solutions of 6a, 6b, and 6c in DMSO with benzyl halide, followed by aqueous work-up, affords 10-dicarbethoxymethyl-9,10-dihydro-9-oximinoanthracene (10a, 63%), 10-(1,1-dicarbethoxyethyl)-9,10-dihydro-9-oximinoanthracene (10b, 68.5%), and 10-(2-nitro-2-propyl)-9,10-dihydro-9-oximinoanthracene (10c, 59%), respectively. Attempted preparation of oxime 10d by this procedure

10a, R = CH(CO₂Et)₂
b, R = CMe(CO₂Et)₂
c, R = CMe₂NO₂
d, R = CH(CN)₂
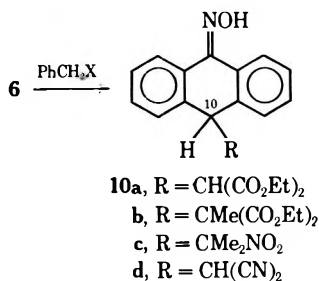
failed; addition of benzyl chloride to a DMSO solution of 6d evidently reversed complex formation, for only nitroanthracene was isolated. Some reversion may also have occurred in the preparation of 10b, since 26% of the nitroanthracene used to prepare the solution of 6b was recovered upon recrystallization of the crude oxime. Substantial quantities of nitroanthracene are not encountered in the preparation of the adducts (7a–d) or the other oximes (10a and 10c).

The ir spectra of the oximes contain, in addition to peaks characteristic of R, peaks of medium to strong intensity at ca. 1000, 935, and 785 cm⁻¹. The nmr spectra of 10a and 10b are summarized in Table I. Because of the low solubility of 10c, nmr data have not been obtained. Nonequivalence of the methylene protons is not observed for either 10a or 10b. Multiplets assigned to aromatic protons of 10a appear at 8.5 (1 H), 7.8 (1 H), and 7.3 ppm (6 H) (see Figure 2); similarly, multiplets appear at 8.6 (1 H) and 7.5 ppm (7 H) in the spectrum of 10b.

The mechanism of oxime formation involves base-catalyzed decomposition of the initially formed

benzyl nitronate (11).[17] Kerber and Hodos[16] have reported that protonation and benzoylation of the anion
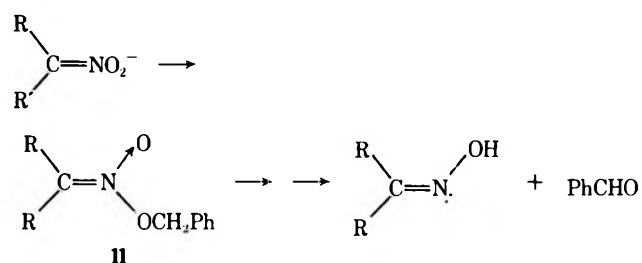
of 9-nitrofluorene form the nitronic acid and *O*-benzoyl derivative, respectively. Since oxime formation from 6 (which proceeds through an *O*-alkylated derivative) is observed, it seems likely that protonation initially occurs at an oxygen atom. C-Alkylation of 2-propanenitronate by 9-nitroanthracene occurs in preference to *O*-alkylation. Thermodynamic, rather than kinetic, factors may be significant here.

Reaction of Adducts with Acid.—Exposure to boiling aqueous ethanolic HCl converts 7a to 9-(dicarbethoxymethyl)anthracene (12a) in 93% yield. Analogously,

12a, R = CH(CO₂Et)₂
b, R = CMe(CO₂Et)₂
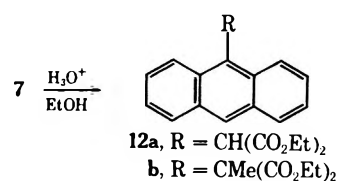
9-(1,1-dicarbethoxyethyl)anthracene (12b) is available from 7b. Attempted preparation of 9-(2-nitro-2-propyl)anthracene from 7c failed; the products obtained were oxime 10c and the corresponding ketone, 10-(2-nitro-2-propyl)-9,10-dihydro-9-oxoanthracene (13). The identity of 12a was confirmed by hydrolysis and decarboxylation to the known[18] (9-anthryl)acetic acid. The identity of 13 was confirmed by conversion to 10c (95% yield) upon treatment with hydroxylamine hydrochloride in pyridine.

(17) N. Kornblum and R. A. Brown, *J. Amer. Chem. Soc.*, **86**, 2681 (1964).

(18) N. Acton and E. Berliner, *ibid.*, **86**, 3312 (1964).
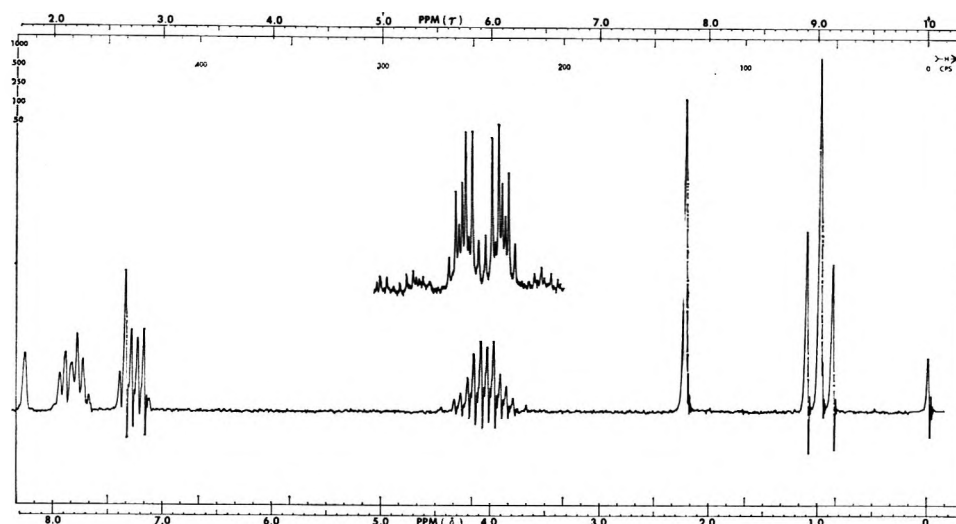
Figure 3.—The 60-MHz spectrum of 9-(1,1-dicarbethoxyethyl)anthracene (12b) in CCl₄ (lower trace) and 220-MHz partial spectrum of the methylene proton region (upper trace).
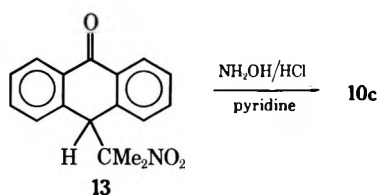
As may be seen from Figure 3, the 60-MHz nmr spectrum of **12b** contains a complex multiplet (arising from resonance of nonequivalent methylene protons) at 4 ppm, which is resolved at 220 MHz into an AB system of quartets.[9] The parameters are $J_{AB} = 11$ Hz, $\Delta\delta = 0.12$ ppm, $J_{HMe} = 7$ Hz. The methylene protons of adducts **7a** and **7b**, oximes **10a** and **10b**, and substituted anthracenes **12a** and **12b** are potentially magnetically nonequivalent. The nonequivalence is manifest for **7a**, though not for **10a** or **12a**, and for **12b**, though not for **7b** or **10b**.

Mass spectra have been recorded for each of the new compounds reported, and in each case a fragmentation scheme has been proposed[19] which is consistent with the mass spectral data and which supports the structural assignment. The compositions of key fragments were confirmed by exact mass measurements.[20]

Experimental Section[21]

9-Nitro-10-dicarbethoxymethyl-9,10-dihydroanthracene (7a).— A solution of sodio malonic ester was prepared by stirring diethyl malonate (36 mmol, 5.5 ml) with sodium hydride (36 mmol) in DMSO (50 ml) for 1 hr. To the resulting solution was added a solution of 9-nitroanthracene (18 mmol, 4.02 g) in warm DMSO (75 ml). Stirring was continued for 1 hr, the reaction mixture

(19) R. H. Williams, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1971.

(20) Exact mass measurements were obtained by the peak-matching technique by Mr. J. Carter Cook on an MAT SM-1B high resolution mass spectrometer and are within 0.0004 amu of values calculated for the indicated ion composition. We gratefully acknowledge NIH grants GM-16864 and CA-11388 to the Department of Chemistry and Chemical Engineering, University of Illinois, which helped make purchase of the SM-1B possible.

(21) Commercially available reagents were used as received. Melting points were determined with a Kofler micro stage apparatus and are uncorrected. A Perkin-Elmer 521 ir spectrophotometer was used for ir spectra, which were run in KBr. Microanalyses were performed by Mr. J. Nemeth and associates. Routine nmr spectra were recorded on a Varian A-56/60 or A-60A spectrometer; 100-MHz and 220-MHz spectra were recorded by Mr. R. L. Thrift and associates on Varian HA-100 and HR-220⁹ spectrometers, respectively. Mass spectra were recorded by Mr. J. Wrona and associates on an Atlas CH4 mass spectrometer at 70 eV.

was poured into 300 ml of water, and concentrated hydrochloric acid was added to reduce the pH to *ca.* 3. The precipitate was collected by filtration and dissolved in 150 ml of 50:50 CH₂Cl₂-ethanol. After treatment with activated charcoal, the solution was concentrated to 50 ml. Upon standing at −15°, the solution deposited 4.76 g (68%) of off-white crystals. Recrystallization from CH₂Cl₂-hexane gave **7a** as white crystals: mp 123.5–124.5°; ir 1745, 1550, 1310, 1260, 1143, 760 cm⁻¹; mass spectrum *m/e* (*I*)[22] 351 (47), 263 (47), 233 (60), 191 (60), 178.0784 (100, C₁₄H₁₀), 176 (47).

Anal. Calcd for C₂₁H₂₁NO₆: C, 65.79; H, 5.52; N, 3.65. Found: C, 65.72; H, 5.44; N, 3.60.

9-Nitro-10-(1,1-dicarbethoxyethyl)-9,10-dihydroanthracene (7b).—A solution of sodio methylmalonic ester was prepared by stirring diethyl methylmalonate (36 mmol, 6.15 ml) with sodium hydride (36 mmol) in DMSO (75 ml) for 1 hr. 9-Nitroanthracene (18 mmol, 4.02 g) and DMSO (50 ml) were added, and after 1 hr the reaction mixture was poured over 500 ml of ice–water and acidified. Crude product was collected by filtration and dissolved in CH₂Cl₂ (75 ml). The solution was washed twice with water, dried (Na₂SO₄), decolorized, and concentrated to 30 ml. The volume of the solution was then maintained by the addition of ethanol as CH₂Cl₂ was removed at the steam bath. After several hours at −15°, 5.40 g (75%) of slightly yellow crystals had been deposited. Recrystallization from CH₂Cl₂-ethanol gave **7b** as white crystals:[23] mp 113–114°; ir 1733, 1555, 1292, 1258, 1108, 742 cm⁻¹; mass spectrum *m/e* (*I*) 223.0632 (75, C₁₄H₉NO₂), 193 (60), 178.0784 (100, C₁₄H₁₀), 129 (73), 74 (65).

Anal. Calcd for C₂₂H₂₃NO₆: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.49; H, 5.85; N, 3.39.

9-Nitro-10-(2-nitro-2-propyl)-9,10-dihydroanthracene (7c).—A solution of sodium methylsulfinylmethide was prepared by stirring sodium hydride (36 mmol) with DMSO (50 ml) at 70° until gas evolution had subsided. 2-Nitropropane (36 mmol, 3.2 ml) was added in portions while the temperature was maintained at 70°, and stirring was continued for 30 min after addition was complete. The thick paste which resulted upon cooling was diluted with a solution of 9-nitroanthracene (18 mmol, 4.02 g) in warm DMSO (75 ml), and nearly all of the solid dissolved within the first few min. After 1 hr the reaction mixture was poured over 300 ml of ice–water, and concentrated HCl was added until a persisting green color was produced (pH *ca.* 4). The precipitate was collected by filtration and dissolved in CH₂Cl₂; the solution was washed, dried, decolorized, and concentrated.[24] Hexane was added as the last of the CH₂Cl₂ was removed at the steam bath. The pink crystals obtained upon cooling of the solution weighed 4.29 g (76%). Two more recrystallizations gave **7c** as white crystals: mp 130–140° dec (with gas evolution); ir 1550, 1530,

(22) Intensities are reported as per cent of base peak.

(23) Highly purified samples of crystalline **7b** decompose upon standing at room temperature for several weeks. The rate of decomposition can be retarded by storing adduct **7b** at −15°.

(24) Alternatively, washing the crude material with several portions of ethanol affords product of purity which is adequate for most purposes.

1370, 1350, 1340, 725 cm^{-1}; mass spectrum *m/e* (*I*) 208.0763 (24, $C_{14}H_{10}NO$), 91 (32), 60 (100), 58 (84), 55 (26).

Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.15; H, 5.01; N, 8.89.

9-Nitro-10-dicyanomethyl-9,10-dihydroanthracene (7d).—A solution of sodio malononitrile was prepared by adding a solution of malononitrile (36 mmol, 2.38 g) in DMSO (5 ml) to a magnetically stirred suspension of sodium hydride (36 mmol) in DMSO (45 ml). After gas evolution had ceased (*ca.* 1 hr), 9-nitroanthracene (18 mmol, 4.02 g) and DMSO (75 ml) were added. The reaction mixture was stirred for 2 hr prior to aqueous work-up. The crude product was dissolved in CH_2Cl_2 (75 ml), and the solution was washed, dried, decolorized, and concentrated on the steam bath until crystallization began. The light yellow product (2 crops) weighed 3.68 g (70%). Recrystallization from CH_2Cl_2–cyclohexane gave 7d as white crystals: mp 166–170° dec (with gas evolution); ir 2910, 1555, 1490, 1360, 755, 705 cm^{-1}; mass spectrum *m/e* (*I*) 223.0632 (79, $C_{14}H_9NO_2$), 178.0784 (55, $C_{14}H_{10}$), 176 (50), 84 (58), 66 (100).

Anal. Calcd for $C_{17}H_{11}N_3O_2$: C, 70.57; H, 3.83; N, 14.53. Found: C, 70.53; H, 3.79; N, 14.70.

10-Dicarbethoxymethyl-9,10-dihydro-9-oximinoanthracene (10a).—The preparation of 7a was repeated, but, 1 hr after the addition of 9-nitroanthracene, benzyl chloride (72 mmol, 8.3 ml) was added, and the reaction mixture was stirred at room temperature for an additional 15 hr before aqueous work-up. The yellow precipitate was collected by filtration, washed with cold ethanol (three 40-ml portions) and recrystallized from CH_2Cl_2–hexane. The light yellow product weighed 4.18 g (63%). Recrystallization from ethanol gave 10a as white crystals: mp 196–199° dec; ir 1750, 1727, 1305, 1252, 1181, 977 cm^{-1}; mass spectrum *m/e* (*I*) 208.0758 (100, $C_{14}H_{10}NO$), 207 (95), 190 (22), 177 (21), 121 (36), 120 (56), 117 (28).

Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.61; H, 5.60; N, 3.99.

10-(1,1-Dicarbethoxyethyl)-9,10-dihydro-9-oximinoanthracene (10b).—To a magnetically stirred solution of sodio methylmalonic ester (prepared from diethyl methylmalonate (18 mmol) and sodium hydride (18 mmol)) in DMSO (25 ml) were added 9-nitroanthracene (18 mmol, 4.02 g) and DMSO (25 ml). After 1 hr, benzyl bromide (18 mmol, 2.14 ml) was added, and stirring was continued for 2 hr before aqueous work-up. The precipitate was dissolved in CH_2Cl_2, and the solution was washed, dried, decolorized, and concentrated to a volume of 30 ml. Volume of the solution was then maintained by the addition of ethanol as remaining CH_2Cl_2 was removed at the steam bath. The ethanol solution was allowed to cool slowly and maintained at −15° for 4 hr. The supernatant liquid was decanted, and the crystals were washed twice with cold ethanol (10-ml portions). The yellow crystalline product, which weighed 1.05 g, was identified as 9-nitroanthracene by melting point (147–149.5°), mixture melting point and tlc (recovery, 26%). The combined mother liquor and washings were concentrated to the original volume (30 ml) and cooled to −15°. Crystallization was initiated by scratching and after 5 hr the product was collected by filtration and washed with cold ethanol. The slightly yellow crystals weighed 3.40 g (68.5%, based on unrecovered nitroanthracene) and melted at 161–163.5°. Recrystallization from CH_2Cl_2–ethanol gave 10b as white crystals: mp 162.5–163.5°; ir 1730, 1250, 1230, 1112, 1100, 780 cm^{-1}; mass spectrum *m/e* (*I*) 209 (11), 208.0763 (100, $C_{14}H_{10}NO$), 207 (11), 191 (14), 190 (25), 180 (13).

Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.27; H, 6.08; N, 3.67. Found: C, 69.14; H, 5.98; N, 3.62.

10-(2-Nitro-2-propyl)-9,10-dihydro-9-oximinoanthracene (10c).—A solution of 9-nitroanthracene (18 mmol, 4.02 g) in warm DMSO (75 ml) was added to a magnetically stirred suspension of sodium propanenitronate (prepared from 36 mmol each of 2-nitropropane and sodium hydride) in 100 ml of DMSO. After 30 min of reaction, benzyl chloride (36 mmol, 4.15 ml) was added, and the reaction mixture was stirred for 15 hr before aqueous work-up. The precipitate was collected by filtration and washed with three 40-ml portions of ethanol and one 40-ml portion of CH_2Cl_2. The white crystals of 10c weighed 3.15 g (59%) and decomposed at 230–240°: ir 1535, 1395, 1350, 1000, 935, 750 cm^{-1}; mass spectrum *m/e* (*I*) 209 (16), 208.0763 (100, $C_{14}H_{10}NO$), 191 (11), 190 (18), 180 (10).

Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 69.00; H, 5.44; N, 9.23.

9-(Dicarbethoxymethyl)anthracene (12a).—Hydrochloric acid (24 mmol, 2 ml) was added to a magnetically stirred solution of 7a (1.0 mmol, 383 mg) in 33% aqueous ethanol (60 ml) at the boiling point. The volume of the reaction mixture was maintained by the addition of water as ethanol was distilled during 1 hr. The reaction mixture was cooled to room temperature, and the precipitate was collected by filtration. The light yellow crystals weighed 311 mg (93%). Recrystallization from methylcyclohexane gave 12a as light yellow crystals: mp 121–123°; ir 1750, 1705, 1250, 1200, 1032, 740 cm^{-1}; nmr (CS_2) δ 7.4–8.5 (m, aromatic), 5.9 [s, CH(CO$_2$Et)$_2$], 4.1 (q, *J* = 7 Hz, CH$_2$CH$_3$), 1.1 (t, *J* = 7 Hz, CH$_2$CH$_3$); mass spectrum *m/e* (*I*) 336 (100), 236 (91), 235 (41), 191 (57), 189 (43).

Anal. Calcd for $C_{21}H_{20}O_4$: C, 74.98; H, 5.99. Found: C, 75.13; H, 6.15.

(9-Anthryl)acetic Acid.—Water (20 ml) was added to a refluxing solution of 12a (1.0 mmol, 336 mg) and sodium hydroxide (5.0 mmol, 200 mg) in ethanol (30 ml). The solution was heated under reflux for 4 hr, and the volume of the solution was maintained by addition of water as ethanol was boiled off during a fifth hour of heating. Hydrochloric acid (12 mmol, 1.0 ml) was added to the aqueous solution, and the reaction mixture was heated under reflux for 1 hr to complete decarboxylation. The product was collected by filtration and recrystallized from acetic acid. The light yellow crystals weighed 193 mg (82%). Recrystallization from benzene gave (9-anthryl)acetic acid as light yellow crystals: mp 227–229° dec (lit.[18] mp 229–231.4°); ir 1700, 1305, 728 cm^{-1}.

Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.43; H, 5.31.

9-(1,1-Dicarbethoxyethyl)anthracene (12b).—Hydrochloric acid (48 mmol, 4 ml) was added to a refluxing solution of 7b (2.0 mmol, 794 mg) in ethanol (40 ml). After 1 hr, the reaction mixture was poured into 300 ml of water, and the resulting suspension was extracted with CH_2Cl_2 (three 50-ml portions). The extract was washed, dried, decolorized, and concentrated. The last of the CH_2Cl_2 was replaced with ethanol (95%) at the steam bath, and the volume of the solution was reduced to 4 ml. After 12 hr at −15°, 326 mg (46.5%) of yellow crystals had been deposited. Recrystallization from CH_2Cl_2–ethanol gave 12b as yellow crystals: mp 155–156.5°; ir 1740, 1700, 1380, 1268, 1117, 741 cm^{-1}; nmr (CS_2) δ 7.2–8.3 (m, aromatic), 4.0 (m, CH$_2$CH$_3$), 2.1 [s, C(CH$_3$)(CO$_2$Et)$_2$], 1.0 (t, *J* = 7 Hz, CH$_2$CH$_3$); mass spectrum *m/e* (*I*) 350 (100), 277 (62), 203 (100), 202 (32), 138 (32).

Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.40; H, 6.22.

10-(2-Nitro-2-propyl)-9,10-dihydro-9-oxoanthracene (13).—Dilute hydrochloric acid (3.0 ml concentrated hydrochloric acid and 40 ml of water) was added to a magnetically stirred solution of 7c (2.0 mmol, 624 mg) in refluxing ethanol (40 ml). After 2 hr at reflux, the reaction mixture was poured over 100 ml ice-water, and the resulting suspension was filtered. The filtrate was extracted with CH_2Cl_2 (four 25-ml portions), the extract was washed twice with water, and the precipitate was washed with the extract. The precipitated weighed 166 mg (28%), and was identified as oxime 10c by tlc and ir. The filtrate was concentrated to a volume of 4 ml, and the remaining CH_2Cl_2 was replaced with ethanol at the steam bath. After the solution had stood for several hr at −15°, 180 mg (32%) of 13 was deposited. Recrystallization from CH_2Cl_2–ethanol gave 13 as white crystals: mp 185.5–187°; ir 1665, 1600, 1525, 1305, 1285, 730 cm^{-1}; nmr (CDCl$_3$) δ 7.3–8.3 (m, aromatic), 4.9 (s b, CHCMe$_2$NO$_2$), 1.3 [s, C(CH$_3$)$_2$NO$_2$]; mass spectrum *m/e* (*I*) 194 (18), 193.0656 (100, $C_{14}H_9O$), 165 (13).

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.38; N, 4.98. Found: C, 72.83; H, 5.39; N, 4.94.

Intermediates in Nucleophilic Aromatic Substitution. XI.[1,2]
Kinetic and Proton Magnetic Investigations of the Interaction of
Lyate Ions with 1-Substituted 2,4,6-Tricyanobenzenes

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Rate constants for the formation, k_1, and those for the decomposition, k_{-1}, of the methoxyl complex of 2,4,6-tricyanoanisole (6) have been determined in DMSO-rich methanolic solutions. The equilibrium constant for the formation of 6 in methanol, determined from linear Benesi-Hildebrand plots, is 42,500-fold smaller than that for the formation of the 1,1-dimethoxy-2,4,6-trinitrocyclohexadienylide ion. No accumulation of complexes analogous to 6 have been observed in the interaction of hydroxide ion in aqueous solutions with 1-bromo-2,4,6-tricyanobenzene or with 2,4,6-tricyanoanisole in which case the rate-determining step is the formation of the complex. The structure of 6 has been established from its pmr spectrum. A linear relationship between the H-3,5 chemical shifts of the methoxyl Meisenheimer complexes of trinitro-, tricyano-, and the isomeric cyanodinitro- and dicyanonitroanisole in DMSO-d_6 and the equilibrium constants for their formation in methanol at 25.0° has been found.

In the previous parts of this series we have examined the stabilities of Meisenheimer complexes 1–5 quanti-
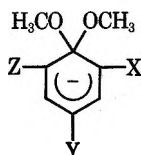
1, X = Y = Z = NO$_2$
2, X = CN; Y = Z = NO$_2$
3, Y = CN; X = Z = NO$_2$
4, X = Z = CN; Y = NO$_2$
5, X = Y = CN; Z = NO$_2$
6, X = Y = Z = CN

tatively.[4,5] The obtained equilibrium constants for the formation of these complexes in methanol at 25.00°, $K_1 = 17,000$, $K_2 = 2600$, $K_3 = 280$, $K_4 = 34$, $K_5 = 10$ l. mol^{-1}, parallel the extent of the electron-withdrawing power of the substituents. More importantly, replacement of a para nitro group by a cyano group causes a considerably more dramatic effect than the corresponding replacement in the ortho position. In order to assess the relative importance of steric and resonance effects on these nucleophilic aromatic substitutions, we have investigated the interaction of methoxide ions with 2,4,6-tricyanoanisole (7) in methanol and methanolic dimethyl sulfoxide. The structure of the methoxyl complex of 7 (6) which results from this interaction has been established from the pmr parameters of the isolated and *in situ* generated complex. In addition, kinetic and thermodynamic investigations of the reaction of hydroxide ion with 1-bromo-2,4,6-tricyanobenzene (8) and 2,4,6-tricyanoanisole (7) in water afford additional comparisons between the nucleophilic reactivities of tricyano- and trinitro-substituted arenes.

Experimental Section

The solvents and reagents were prepared, purified, and standardized as previously described.[4–6]

1-Bromo-2,4,6-tricyanobenzene (8) was prepared from 2-bromomesitylene according to a modified procedure of Wallenfels, *et al.*[7] 2-Bromomesitylene (40 g, 0.201 mol) (Aldrich Chemical Co.) in a solution of 10 g of sodium hydroxide in 1 l. of water was heated to boiling and *ca.* one-half of 210 g of potassium permanganate was added. After refluxing the mixture for 15 hr, the remainder of the potassium permanganate was added and the mixture was refluxed for 24 hr. The hot reaction mixture was filtered, the manganese dioxide was washed three or four times with 150 ml of hot water, and the filtrate was concentrated to *ca.* 300 ml by distillation. The warm pot residue was acidified with concentrated nitric acid until the first thick white precipitate redissolved. After being cooled and allowed to stand, filtration yielded 2-bromomesitylenic acid (9), mp 275–278° (lit.[7] mp 260–275°), after drying *in vacuo*. Additional product was recovered by extracting the filtrate with isopropyl ether four or five times followed by rotary evaporation of the combined extracts with 100 ml of water added to decompose peroxides. 2-Bromomesitylenic triamide (10) was prepared by refluxing 17.0 g (58.8 mmol) of crude 9 in 48.1 ml of thionyl chloride for 22 hr, followed by vacuum rotary evaporation of the clear reaction solution to dryness. The residue was dissolved in 450 ml of dry benzene and ammonia was bubbled through the stirred reaction mixture for *ca.* 4 hr. The white precipitate of ammonium chloride and 10 was filtered, dried at 105–110°, and suspended in 200 ml of water. Filtration gave white crystalline 10, which was washed with water and dried at 105–110°, mp >300°. 1-Bromo-2,4,6-tricyanobenzene (8) was prepared by refluxing a mixture of 10.69 g (37.2 mmol) of 10, 7.5 g of sodium chloride, and 75 ml of phosphorus oxychloride for 6 hr. The excess phosphorus oxychloride was removed by rotary evaporation at 0.1 mm and the residue was pulverized and poured into 113 ml of ice water. The precipitate was filtered, washed with water, and dried *in vacuo* over phosphorus pentoxide. After recrystallization from benzene and drying *in vacuo*, the white crystals of 8 melted at 214–215° (lit.[7] 212–215°).

2,4,6-Tricyanoanisole (7) was prepared by the addition of 1.00 ml (6 mmol) of 5.95 M potassium methoxide in methanol to a warm solution of 1.09 g (5 mmol) of 8 in 10 ml of methanol. The reaction mixture was refluxed for 30 min, cooled, and poured onto *ca.* 25 g of ice. The white, crystalline precipitate was filtered, washed with distilled water, and dried *in vacuo* over phosphorus pentoxide, mp 147–148°.

Anal.[8] Calcd for C$_{10}$H$_5$N$_3$O: C, 65.7; H, 2.75; N, 23.0. Found: C, 65.4; H, 2.90; N, 22.7.

(1) Part X: J. H. Fendler, E. J. Fendler, and L. M. Casilio, *J. Org. Chem.*, **36**, 1749 (1971).

(2) For recent reviews on Meisenheimer complexes and their relevance in nucleophilic aromatic substitution, see (a) R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966); (b) E. Buncel, A. R. Norris, and K. E. Russell, *Quart. Rev., Chem. Soc.*, **22**, 123 (1968); (c) P. Buck, *Angew. Chem., Int. Ed. Engl.*, **8**, 120 (1969); (d) J. Miller, "Aromatic Nucleophilic Substitutions," Elsevier, Amsterdam, 1968; (e) M. R. Crampton, *Advan. Phys. Org. Chem.*, **7**, 211 (1969); (f) F. Pietra, *Quart. Rev., Chem. Soc.*, **23**, 504 (1969); (g) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).

(3) Address to which inquiries should be sent.

(4) J. H. Fendler, E. J. Fendler, and C. E. Griffin, *J. Org. Chem.*, **34**, 689 (1969).

(5) E. J. Fendler, J. H. Fendler, C. E. Griffin, and J. W. Larsen, *ibid.*, **35**, 287 (1970).

(6) W. E. Byrne, E. J. Fendler, J. H. Fendler, and C. E. Griffin, *ibid.*, **32**, 2506 (1967).

(7) K. Wallenfels, F. Witzler, and K. Friedrich, *Tetrahedron*, **23**, 1353 (1967).

(8) The analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

2,4,6-Tricyanoanisole ($O^{14}CH_3$) was prepared by the addition of 1.09 g (5 mmol) of **8** to a solution containing 1 ml of methanol-^{14}C (200 μCi), 1 ml of methanol, and 1.00 ml (6 mmol) of 5.95 M potassium methoxide in methanol. Dry dioxane (3 ml) was added, and the reaction mixture was refluxed for *ca.* 10 min followed by stirring at room temperature for 5 hr. After cooling to *ca.* 0°, the reaction mixture was poured into 25 ml of ice water, filtered, washed with ice water, and dried *in vacuo* over phosphorus pentoxide. After recrystallization from aqueous methanol using decolorizing charcoal, the white needles melted at 146–147°. The pmr spectrum in DMSO-d_6 was identical with that of the unlabeled ether **7**.

Potassium 1,1-dimethoxy-2,4,6-tricyanocyclohexadienylide (**6**) was prepared by the addition of 0.192 ml (0.972 mmol) of 5.05 M potassium methoxide in methanol to a solution of 0.1668 g (0.985 mmol) of **7** in 0.60 ml of dry dioxane. The yellow crystals, which formed upon evaporation of a small amount of the solvents with dry nitrogen, were filtered and washed with dry benzene and anhydrous ether in an atmosphere of dry nitrogen. The yellow crystals were pulverized and dried *in vacuo* over phosphorus pentoxide.

Anal.[8] Calcd for $C_{11}H_8N_3O_2K$: C, 52.2; H, 3.18; N, 16.6; K, 15.4. Found: C, 50.3; H, 2.70; N, 16.3; K, 15.6.

Absorption spectra of **7** and **8** in several media were recorded on a Cary 14 spectrophotometer. Absolute absorbance measurements were obtained using a Beckman DU-2 spectrophotometer. The attainment of the equilibrium for the formation of **6** was followed at 400 nm in the thermostated cell compartment of the latter instrument. The temperature was measured inside the cells and was maintained within ±0.02°. The mixing techniques for the fast reactions have been described previously.[4] Since the concentration of **7** was at least 50-fold smaller than that of the methoxide ion, good pseudo-first-order kinetics were observed for the equilbrium formation of **6**. The rate constants, k_ψ, for the reaction of the hydroxide ion with **7** and **8** in aqueous solution were obtained by monitoring the increase in the absorbance at 360 nm. Good first-order plots for these reactions were obtained.

The 60-MHz pmr spectra were obtained with a Varian Associates A-60 spectrometer at ambient probe temperature or at 25° (probe temperature maintained with a V6040 variable-temperature controller). Unless otherwise noted, all spectra were determined on solutions in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard; chemical shifts are given on the τ scale in parts per million relative to TMS (τ 10.00 ppm) and are accurate to ±0.03 ppm. Chemical shift data were taken from spectra determined at sweep widths of 500 Hz.

Results

The addition of nucleophiles to **7** and **8** results in the development of new absorption bands (Table I). When sodium methoxide (up to 2.1 M) is added to a methanolic solution of **7**, a fairly sharp new absorption band develops at 280 nm. At higher methoxide ion concentrations, or alternatively in DMSO-methanol solutions, a second band, with a maximum at 400 nm, appears (Figure 1). These two absorption bands are due to the formation of the methoxyl complex of 2,4,6-tricyanoanisole (**6**) since the isolated complex **6** shows the same absorption bands and since the equilibrium constants for the formation of **6** obtained from Benesi–Hildebrand plots at 280 and 400 nm agree within exerimental error (Table II).

The addition of sodium hydroxide to aqueous solutions of **7** and **8** results in the development of a new band at 360 nm, while absorption bands at 280 and 400 nm, characteristic of **6** and its possible hydroxyl analog, are absent (Table I). In aqueous sodium hydroxide solutions (up to 2.0 M) of **7** and **8** no evidence can be adduced, therefore, for the formation of σ-type addition complexes. The absorption at 360 nm is due to the formation of the 2,4,6-tricyanophenoxide ion. Supporting this interpretation is the fact that the absolute

TABLE I
ABSORPTION SPECTRA OF 1-SUBSTITUTED 2,4,6-TRICYANOBENZENES

Substituent	Condition[a]	λ_1 (ϵ_1), nm (cm^{-1} l. mol^{-1})	λ_2 (ϵ_2), nm (cm^{-1} l. mol^{-1})
Br	Methanol	250 (12,400)	310 (6250)
Br	2.00 M NaOH		360 (2250), 400 (50)
OCH₃	Methanol	225 (32,900)	310 (2060)
OCH₃	2.11 M NaOCH₃, methanol	280 (18,000)	
OCH₃	5.73 M KOCH₃, methanol	280 (17,600)	400 (14,800)
OCH₃	DMSO-methanol, 70:30 (v/v)	260 (7000)	320 (2000)
OCH₃	0.024 M NaOCH₃, DMSO-methanol, 70:30 (v/v)	280 (17,300)	400 (18,900)
OCH₃	2.00 M NaOH		360 (2600), 400 (40)

[a] At 25.00°, [1-(X)-2,4,6-tricyanobenzene] $\simeq$ 5.0 $\times$ 10^{-5} M, using a pair of 1.0-cm matched cells and blanks identical in composition with the samples with the exception of the aromatic compound.

TABLE II
INTERACTION OF 2,4,6-TRICYANOANISOLE (5.0 $\times$ 10^{-5} M) WITH SODIUM METHOXIDE IN METHANOLIC DIMETHYL SULFOXIDE AT 25.00°

[DMSO], M	10³ × [NaOCH₃], M	10³k_{obsd}, sec^{-1}	k_1, l. mol^{-1} sec^{-1}	10⁴k_{-1}, sec^{-1}	K, l. mol^{-1}
0					0.4[a]
4.23					280,[a] 320[b]
7.03	5.24	2.30	0.33	6.0	550
	7.86	3.13			
	10.48	4.00			
	13.10	4.80			
	15.75	5.90			
	22.00	7.65			
8.44	2.00	1.45	0.57	3.0	1890
	4.15	2.57			
	5.20	3.15			
	8.30	4.80			
	10.4	6.16			
	14.00	8.20			
10.55	1.3	2.69	1.75	2.0	8000
	2.6	5.52			
	4.12	7.56			
	5.20	9.77			
	8.24	14.7			
11.25	1.04	4.90	4.00		
	1.30	5.92			
	2.08	8.50			
	2.60	11.0			
	4.16	16.9			
	8.32	32.4			
	10.4	42.0			

[a] From Benesi–Hildebrand plots at 280 nm (eq 1). [b] From Benesi–Hildebrand plots at 400 nm (eq 1).

absorbances of **7** and **8** in alkaline solutions did not diminish upon neutralization to pH 3.[9]

In the absence of alkoxide ions, **7** is quite stable in methanol or in methanolic dimethyl sulfoxide solutions. Toluene–water extracted samples[11] of carbon-14 labeled

(9) The pK of 2,4,6-tricyanophenol is *ca.* 1[10] and hence would be completely ionized, whereas a σ complex would unquestionably decompose in acidic solution.

(10) K. Dimroth and K. J. Kraft, *Angew. Chem., Int. Ed., Engl.*, **3**, 384 (1964).

(11) J. H. Fendler, *J. Amer. Chem. Soc.*, **88**, 1237 (1966).

7 ($O^{14}CH_3$) in methanol did not show any loss of activity at 45.00° over a period of 1 week and no absorbance changes were observed for the methanol solutions over the same time period. However, subsequent to the formation of **6**, especially under pmr conditions, a slow decomposition was observed (*vida supra*).

Rate constants for the formation, k_1, and the decomposition, k_{-1}, of **6** in methanol are too high to be kinetically determined by our techniques.[4,5] The equilibrium constant, K, for the formation of **6** in methanol has been obtained, however, from the slope and intercept of linear Benesi–Hildebrand[12] plot (eq 1) where A

$$\frac{[7]}{A} = \frac{1}{\epsilon} + \frac{1}{K\epsilon}\left(\frac{1}{[CH_3O^-]}\right) \qquad (1)$$

is the absorbance in a 1.0-cm cell and ϵ is the molar extinction coefficient (Figure 2). The stability of complex **6** increases in DMSO-rich methanolic solutions to such an extent that pseudo-first-order rate constants for its equilibrium attainment, k_{obsd}, could be determined at 400 nm. Since the absorbance remains essentially constant over a large range of methoxide ion concentration, the equilibrium (eq 2) is complete. The ob-

$$7 + CH_3O^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 6 \qquad (2)$$

served rate constants, k_{obsd}, for solutions of $(1.0–22.0) \cdot 10^{-3}$ M sodium methoxide in 7.03, 8.44, 10.55, and 11.25 M DMSO in methanol are given as shown in eq 3 where

$$k_{obsd} = k_1[OCH_3^-] + k_{-1} \qquad (3)$$

k_1 is the second-order rate constant for the formation of **6** and k_{-1} is the first-order rate constant for its decomposition. Table II contains the data for k_{obsd}, k_1, and k_{-1} in methanol at 25.00° and in several dimethyl sulfoxide–methanol solutions. Errors in k are ±4% and those in k_{-1} are ±10%.

Tables III and IV summarize the kinetic and thermodynamic parameters for the reactions of **7** and **8** with

TABLE III

INTERACTION OF 2,4,6-TRICYANOANISOLE (3×10^{-4} M) WITH HYDROXIDE ION IN WATER[a]

[NaOH], M	$10^3 k_\psi$, sec⁻¹, at 25.00°	$10^3 k_\psi$, sec⁻¹, at 45.00°
0.010		4.50
0.015		6.90
0.020		9.20
0.025		11.3
0.030	2.73	13.8
0.050	3.97	
0.10	8.05	
0.15	11.9	
0.20	15.2	
0.25	17.3	

[a] $k_{OH} = 6.71 \times 10^{-2}$ and 4.33×10^{-1} l. mol⁻¹ sec⁻¹ at 25.00 and 45.00°, respectively; $E = 17.6 \pm 0.8$ kcal mol⁻¹; $\Delta S^{\ddagger}$ at 25.00° $= -7.0 \pm 2.0$ eu.

hydroxide ion in aqueous solution. Errors in k_{OH} are ±5%.

The pmr data for **7** and **8** and for isolated and *in situ* generated **6** in DMSO-d_6 solutions are collected in Table V.

(12) H. A. Benesi and J. H. Hildebrand, *J. Amer. Chem. Soc.*, **71**, 2703 (1949).
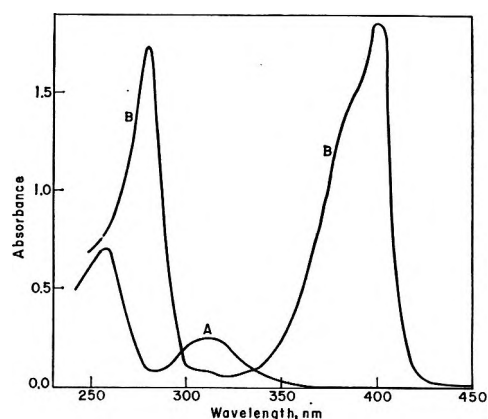
Figure 1.—Absorption spectra of 2,4,6-tricyanoanisole in 75:25 DMSO-MeOH (v/v) at 25.00°, using a pair of matched 1.00-cm cells. [NaOCH₃] = 0 M (A) and 0.024 M (B).
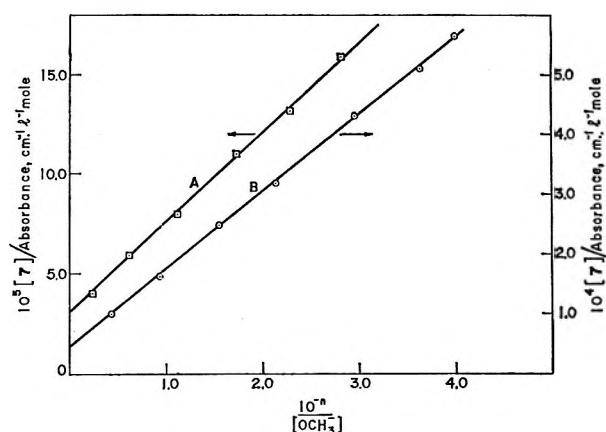
Figure 2.—Benesi-Hildebrand plots for the formation of **6**: A, in 4.23 M DMSO, $n = 3$, determined at 400 nm; B, in MeOH. $n = 0$, determined at 280 nm.

TABLE IV

INTERACTION OF 1-BROMO-2,4,6-TRICYANOBENZENE (3×10^{-4} M) WITH HYDROXIDE ION IN WATER[a]

[NaOH], M	$10^2 k_\psi$, sec⁻¹, at 25.00°	$10^2 k_\psi$, sec⁻¹, at 45.00°
0.01	2.49	5.43
0.02	3.81	11.1
0.04		20.5
0.05	5.45	26.7
0.10	8.54	
0.15	13.5	
0.20	16.8	

[a] $k_{OH} = 7.30 \times 10^{-2}$ and 5.00×10^{-1} l. mol⁻¹ sec⁻¹ at 25.00 and 45.00°, respectively; $E = 18.1 \pm 0.6$ kcal mol⁻¹; $\Delta S^{\ddagger}$ at 25.00° $= -8.7 \pm 2.0$ eu.

Discussion

The stability of the methoxyl complex of 2,4,6-tricyanoanisole (**6**) in methanol is 42,500-fold smaller than that of its trinitro-substituted analog **1**. Significantly, the presence of one and two nitro groups in the isomeric 2,4,6-dicyanonitroanisole (**5** and **6**) and cyanodinitroanisole (**2** and **3**) Meisenheimer complexes results in 25- to 85-fold and 700- to 6500-fold, respectively, greater equilibrium constants for complex formation than that for **6**. These results are in agreement with quantum mechanical calculations which have demonstrated that

TABLE V

PMR SPECTRA OF 1-SUBSTITUTED 2,4,6-TRICYANOBENZENES
AND THE POTASSIUM 1,1-DIMETHOXYCYCLOHEXADIENYLIDE[a]

	8	7	6[b]
			7.12
τ_{OCH_3}		5.68,[c] 5.86	(7.08),[c] (7.23)
			2.82
$\tau_{H-3,5}$ 1.00,[c] 1.50		1.52,[c] 1.88	(2.83),[c] (3.15)

[a] At 25° unless specified otherwise. [b] Values in parentheses have been obtained for the complex generated *in situ* by the dropwise addition of 5.95 M potassium methoxide in methanol to a ca. 2 M solution of **7** in DMSO-d_6. [c] At 42°.

the negative charge resides largely on the nitro groups.[13] The equilibrium constants for the formation of complexes **1-6** are manifestations of the extent of electron delocalization at the site of nucleophilic attack by the substituents.

Increasing the concentration of dimethyl sulfoxide as the cosolvent in methanol considerably enhances the stability of **6**. The equilibrium constant for its formation in 30% DMSO (4.23 M) is greater by a factor of 750 than that in pure methanol (Table II). A similar, although somewhat less significant, rate enhancement by dipolar aprotic dimethyl sulfoxide has been observed for the formation of **1**[14] and **4**.[5] In all these cases, the increase in the equilibrium constant with increasing dimethyl sulfoxide concentration is a composite effect of an increase in k_1 and a decrease in k_{-1}. Furthermore, the magnitude of the rate-constant enhancement by DMSO is greater for the forward reaction, k_1, than for the retardation of the reverse reaction, k_{-1}. In the case of **4** a linear relationship has been obtained between log k_1 and log k_{-1} *vs.* molar dimethyl sulfoxide concentration. Similarly, log k_1 values for the formation of **6** increase linearly with increasing molar concentrations of DMSO in the 7.03 to 11.25 M range (not shown). If this linear plot is extrapolated to zero dimethyl sulfoxide concentration, a value of $k_1 = 4.7 \times 10^{-3}$ l. mol^{-1} is obtained for the formation of **6**. Combining this value with that for the equilibrium constant for the formation of **6** in methanol, 0.4 l. mol^{-1}, the rate constant for the decomposition of **6** in methanol is found to be $k_{-1} = 1 \times 10^{-3}$ sec^{-1}. However, due to the possible invalidity of a linear extrapolation, this value should only be considered to be accurate within an order of magnitude. Indeed, the linear relationship between the rate enhancement of k_1 and the DMSO concentration may be fortuitous. Rate constants for the formation of complex **6** in DMSO-MeOH solutions, $k_1^{DMSO-MeOH}$, are related to that in pure methanol, k_1^{MeOH}, and to the activity coefficents of **7** and of sodium methoxide in the DMSO-MeOH solutions as shown in eq 4. Similarly, the rate

$$k_1^{DMSO-MeOH} = k_1^{MeOH} \frac{f'_7 f'_{NaOCH_3}}{f'^{\ddagger}} \quad (4)$$

constants for the decomposition of **6** in DMSO-MeOH solutions, $k_{-1}^{DMSO-MeOH}$, are expressed as shown in eq 5

(13) P. Caveng, P. B. Fischer, E. Heilbronner, A. L. Miller, and H. Zollinger, *Helv. Chim. Acta*, **50**, 848 (1967).

(14) J. H. Fendler, and J. W. Larsen, unpublished results.

$$k_{-1}^{DMSO-MeOH} = k_{-1}^{MeOH} \frac{f'_6}{f'^{\ddagger}} \quad (5)$$

where $f'^{\ddagger}$ and $f''^{\ddagger}$ in eq 4 and 5 represent the activity coefficients for the transition states of the forward and reverse reactions relative to methanol, respectively. From determinations of the rate constants for the formation and decomposition of **1** in DMSO-MeOH mixtures and the relative solubilities of **1** and 2,4,6-trinitroanisole (**11**) in these solvents, we demonstrated recently[14] that DMSO stabilized both the initial and transition states for the *formation* of complex **1** and that the stabilization is greater for the transition state than for the ether **11**. DMSO also stabilizes both the initial and transition states for the *decomposition* of the complex. Conversely, complex **1** is stabilized to a greater extent than the transition state through which the ether **11** is reformed.[14] These results, of course, substantiate the accepted mechanism for bimolecular nucleophilic aromatic substitution[2] and imply that due care should be taken in interpreting solvent effects.

Since no detectable intermediates are observed in the interaction of hydroxide ion with **7** or **8** in aqueous solutions and by analogy with the interaction of hydroxide ion with **11**,[15] the rate-determining step in these reactions is the formation of the hydroxyl Meisenheimer complexes. The rate constant for the formation of the hydroxyl Meisenheimer complex of **7** in water is roughly 15 times greater than that for the formation of **6** in methanol. Differences in the media as well as the uncertainties in the k_1 value in methanol do not allow, however, meaningful comparisons of the reactivities of hydroxide and methoxide ions toward **7**. The greater activating power of the nitro group as compared to the cyano group is, once again, manifested in the twofold smaller value of k_{OH} for the formation of the hydroxyl adduct of **7** than that of **11**. The corresponding difference in the reactivity of methoxide ion in methanol toward **7** and **11** (k_1 for **1** = 17 l. mol^{-1} sec^{-1},[15] k_1 for **6** $\simeq$ 4.7 $\times$ 10^{-3} l. mol^{-1} sec^{-1}) is considerably greater. These relative reactivity differences are due to the solvation requirements of the respective initial and transition states. The determined enthalpies and entropies of activation for the interaction of hydroxide ion with **7** and **8** correspond to those available for the hydroxydehalogenation of nitro-substituted arenes.[2] Lack of data for **11** prohibits a more direct comparison of the enthalpy and entropy values for trinitro- and tricyanosubstituted benzenes.

We have again used proton magnetic resonance spectroscopy to substantiate the postulated structure of complex **6** and to investigate the possible existence of other intermediates or transients. No pmr data has been reported previously for tricyano-substituted benzenes. The spectrum of complex **6** consists of a singlet at τ 7.08 ppm (relative intensity 6) and a singlet at τ 2.83 ppm (relative intensity 2) attributable to the methoxyl and ring proton resonances, respectively. This spectrum is completely consistent with a 1:1 σ complex and eliminates the possibility of a charge-transfer or π complex. In addition, the strong shielding of the complex protons relative to those of the parent ether **7** (see Table V) is characteristic of Meisenheimer complexes[1,2,4-6] and is the consequence of the rehybridization of C-1 from sp^2 to sp^3 and the increased electron

(15) V. Gold and C. H. Rochester, *J. Chem. Soc.*, 1710 (1964).

density in the ring. Not unexpectedly both the chemical shifts of the methoxyl resonances of complexes 1–6 (τ 6.92–7.08 ppm) and the magnitude of the upfield shifts ($\Delta\delta$ 1.00–1.49 ppm)[4,5] are relatively insensitive to the position or nature of the aromatic substituents. However, the chemical shift of the H-3,5 resonances and the difference in the chemical shifts ($\Delta\delta$)[4,5] increase as a function of increasing substitution of cyano groups in the ring. HMO calculations have shown that the negative charge of Meisenheimer complexes is primarily delocalized over the nitro groups.[13] Since charge delocalization by cyano groups should be less than that by nitro groups, an increase in π-electron density, and hence in the upfield shifts, as a function of increasing cyano substitution is quite reasonable. Indeed, we have found a linear relationship between the H-3,5 chemical shifts of complexes 1–6 and the respective equilibrium constants for complex formation, K (Figure 3). No linear relationship exists, however, between the H-3,5 chemical shifts of the anisoles and K and thus the corresponding plot for $\Delta\delta$ and K exhibits a poor linear relationship. These results suggest that contributions other than electron density to the H-3,5 chemical shifts of complexes 1–6, such as anisotropy, are either constant or relatively small and that approximate equilibrium constants for complexes containing other substituents at C-2, -4, and -6, e.g., CF_3, could be predicted from the pmr spectra of the complex.

In the case of 2,4,6-trinitroanisole,[4,16] 2-cyano-4,6-dinitro- and 4-cyano-2,6-dinitroanisole,[4] and 2,4-dicyano-6-nitroanisole,[5] initial attack of methoxide ion

(16) K. L. Servis, *J. Amer. Chem. Soc.*, **89**, 1508 (1967).
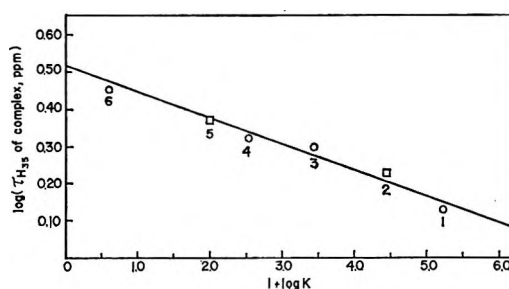
Figure 3.—Plot of log ($\tau_{H_{35}}$, ppm) for complexes 1–6 in DMSO-d_6 vs. log K for complex formation in methanol at 25.00°: O, $\tau_{H_{35}}$; □, ($\tau_{H_3} + \tau_{H_5}$)/2.

was found to occur at C-3, an unsubstituted aromatic carbon atom para to a nitro group. In order to investigate this possibility and the existence of any other fairly stable transients involved in the interaction of methoxide ions with 7, we examined the formation of 6 *in situ* in DMSO-d_6 using pmr spectroscopy. On the time scale necessitated by this technique,[4,5] no transients could be detected prior to or concurrent with the formation of 6. On a much longer time scale (>24 hr at 42°), partial decomposition of 6 was found to occur.

Kinetics and Mechanism of Methyl Transfer from Sulfonium Compounds to Various Nucleophiles

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A series of substituted phenyldimethylsulfonium perchlorates has been prepared and the reaction of these compounds with various nucleophiles has been investigated. With oxygen nucleophiles in water, elevated temperatures are required to effect methylation, whereas a slow reaction is observed with amines in water at 25°. A large solvent effect associated with these reactions permits the convenient study of the methylation of amine nucleophilies in acetonitrile at 25°. The values of ρ obtained from Hammett plots of the kinetic data are quite similar, using either hydroxide ion, pyrrolidine, or *n*-butylamine as the added nucleophile. Activation parameters and data derived from various linear free-energy relationships for the reaction of methylsulfonium compounds with nucleophiles are compared with data for the analogous reactions in which methyl iodide acts as the methylating agent. These data are discussed in relation to enzyme-catalyzed transmethylations which use the sulfonium compound S-adenosylmethionine as the methyl donor.

The process of transferring one-carbon moieties is ubiquitous in biological systems.[1] A considerable amount of information has been accumulated concerning the mechanism by which the folate enzymes activate formaldehyde and effect one-carbon transfer.[2] Equally important and even more widespread in their distribution in metabolic pathways are the reactions involving transfer of intact methyl or methylene groups.[3] Ac-

ceptors of these one-carbon moieties include such diverse molecules as catecholamines,[4] nucleic acids,[5] histones,[6] quinones and fatty acids,[7] to name but a few. The remarkable feature of biological transmethylations, involving such a wide variety of acceptor molecules, is that the donor of the "activated" methyl group is universally (−)-S-adenosyl-L-methionine[1] (1), hereafter referred to as SAM. The reaction of SAM with a nucleophilic acceptor results in the formation of S-adeno-

(1) (a) S. H. Mudd and G. L. Cantoni in "Comprehensive Biochemistry," Vol. 15, M. Florkin and E. H. Stotz, Ed., Elsevier, New York, N. Y., 1964, p 1; (b) D. M. Greenberg, *Advan. Enzymol.*, **25**, 395 (1963).

(2) R. L. Blakley, "The Biochemistry of Folic Acid and Related Pteridines," Wiley-Interscience, New York, N. Y., 1969.

(3) S. K. Shapiro and F. Schlenk, Ed., "Transmethylation and Methionine Biosynthesis," University of Chicago Press, Chicago, Ill., 1965.

(4) J. Axelrod, *Recent Progr. Horm. Res.*, **21**, 597 (1965).

(5) E. Borek, *Annu. Rev. Biochem.*, **35**, 275 (1966).

(6) E. L. Gershey, G. W. Haslett, G. Vidali, and V. G. Allfrey, *J. Biol. Chem.*, **244**, 4871 (1969).

(7) E. Lederer, *Quart. Rev. Chem. Soc.*, **4**, 453 (1969).

1
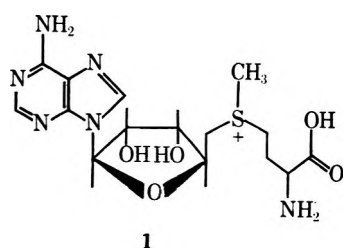
sylhomocysteine plus the methylated acceptor.[3] *A priori*, it would appear that this results from a simple nucleophilic attack on the methyl group in the same manner as nucleophilic attack occurs on the more common methylating agent, methyl iodide.[8] However, as discussed by Schlenk in a comprehensive review,[9] the chemistry of SAM and related sulfonium compounds is obviously more complex than methyl iodide.

In order to have a chemical basis for understanding the specificity of enzyme-catalyzed transmethylation reaction between SAM and various acceptor molecules, a detailed mechanistic description of the nonenzymic process, similar to that which has been described for pyridoxal and related compounds,[10,11] is desirable. However, the chemical instability of SAM in aqueous media at pH > pK_a of the COOH group[12] renders this type of approach more difficult for SAM than for the less labile cofactors. The use of more stable sulfonium salts for kinetic studies of nonenzymic transmethylation can provide information about the chemistry of trivalent sulfur compounds, which is presently unavailable. A survey of the literature indicates that nucleophilic attack on sulfonium compounds takes place only under forcing conditions and that attack on the methyl group is rarely observed (see Discussion section). Furthermore, no detailed kinetic study of such a reaction has been undertaken. In order to study exclusive methyl transfer with a wide variety of nucleophiles, and to study substituent effects on the trivalent sulfur atom of the sulfonium compound, a series of 13 substituted phenyldimethylsulfonium compounds (2) were

2a, X = H	**3a**, X = H;
b, X = p-NO₂	R = C₆H₅;
c, X = p-Cl	Y = ClO₄⁻
d, X = p-COOH	**b**, X = H;
e, X = p-OH	R = OCH₃;
f, X = p-OCH₃	Y = BF₄⁻
g, X = p-CH₃	
h, X = p-CO₂CH₃	
i, X = o-CH₃	
j, X = o-CO₂H	
k, X = o-COCH₃	
l, X = o-CH₂NH₂·HClO₄	

synthesized, and a kinetic investigation of the reaction of these compounds with oxygen and nitrogen nucleo-

philes according to eq 1 was carried out in water and acetonitrile.

2
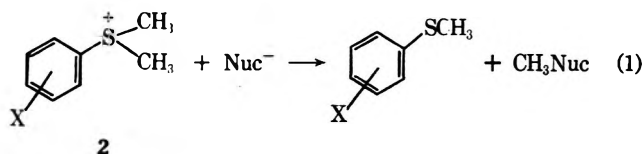
Experimental Section

Materials.—The sulfonium salts used in this study together with their physical properties are listed in Table I. Except as noted below, all of these compounds were prepared by reacting the corresponding thioether with a slight excess of methyl iodide in the presence of anhydrous silver perchlorate, using ethylene chloride or acetonitrile as the solvent.[13] The precipitated silver iodide was removed from the reaction mixture by filtration. The filter cake was washed with solvent, and the combined filtrates were concentrated *in vacuo* to give the product either as a crystalline solid or as an oily residue, which readily crystallized from alcohol or alcohol–ether. The precursor thioethers were either commercially available or were prepared by literature methods. In the case of 2l (X = o-CH₂NH₂), methylation of the corresponding o-(aminomethyl)thioanisole would presumably result in a mixture of products due to competing N- and S-methylation; therefore, the amino group was blocked as the carbobenzyloxy derivative by treatment with carbobenzyloxy chloride in the usual manner.[14] The crude crystalline product, obtained on work-up of the reaction mixture (mp 56–59°), was suitable for use in further transformations. Methylation of this material with methyl iodide, as described above, gave an oily product which could not be crystallized. Cleavage of the carbobenzyloxy group with 70% perchloric acid gave the desired compound (2l), as the bisperchlorate, mp 211–212.5° dec.

All attempts to prepare molecules of type 3, in which the methyl group would be more susceptible to nucleophilic attack than in 3a or 3b, failed to give the desired materials. Thus, treatment of phenyl trifluoromethyl sulfide or bis(p-nitrophenyl) sulfide with either methyl iodide or dimethyl sulfate, under a variety of conditions, gave only unchanged thioethers on work-up of the reaction mixtures, and afforded none of the desired 3, X = H and R = CF₃, or X = NO₂ and R = p-O₂NC₆H₄, respectively. Apparently the strong electron-withdrawing properties of the substituent group, which were expected to facilitate the transmethylation reaction by rendering the sulfur atom more electron poor, prevents the formation of the sulfonium compound *via* nucleophilic attack on the methylating agent by the sulfur atom.

Sodium hydroxide (Fisher) and all other inorganic salts were reagent grade and were used without further purification. All amines, except 1-phenylethanolamine (*vide supra*), were refluxed over calcium hydride or sodium and sodium hydroxide, and then distilled to give pure, anhydrous amines with boiling points and refractive indices in agreement with literature values. 1-Phenylethanolamine (Aldrich) could not be recrystallized or distilled without decomposition, and was used without further purification. It was shown to be a pure compound as judged by its chromatographic behavior, R_f 0.73 [2-propanol–acetic acid–H₂O (70:5:25)].[15] Acetonitrile (Fisher certified 99+%) was used without further purification, as it has been shown to be free of trace contaminants by polarography.[16]

Spectral Characteristics.—The infrared spectrum of all sulfonium compounds described in Table I showed a broad band centered at *ca.* 9 μ and extending from 8.5 to 10 μ. This enables one to readily distinguish the starting thioether from the desired sulfonium salt. Attempts to obtain meaningful nuclear magnetic resonance spectra (60 MHz) of these compounds were not successful in aqueous medium, since the maximum solubility of the compounds in water is only *ca.* 10⁻¹ M. The ultraviolet spectra of the sulfonium compounds are quite different from the parent thioether as shown in Table II. In addition, the sulfonium com-
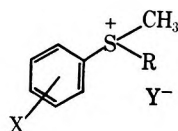
(8) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, Chapter VII.

(9) F. Schenk, *Fortschr. Chem. Org. Naturst.*, **23**, 61 (1965).

(10) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. II, W. A. Benjamin, New York, N. Y., 1966, Chapter 8.

(11) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 133.

(12) (a) L. W. Parks and F. Schlenk, *J. Biol. Chem.*, **230**, 295 (1958); (b) J. Baddiley, W. Frank, N. A. Hughes, and J. Wieczorkowski, *J. Chem. Soc.*, 1999 (1962).

(13) T. Hashimoto, K. Ohkuho, H. Kitano, and K. Fukui, *Nippon Kagaku Zasshi*, **87**, 456 (1966); *Chem. Abstr.*, **65**, 15259h (1966).

(14) D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

(15) Lit. R_f 0.73: W. Drell, *J. Amer. Chem. Soc.*, **77**, 5429 (1955).

(16) J. F. Coetzee, G. P. Bunningham, D. K. McGuire, and G. R. Padmanabhan, *Anal. Chem.*, **34**, 1139 (1962).

Sulfonium salt	X	Mp, °C	Lit mp, °C	Calcd, %			Found, %		
				C	H	Cl	C	H	Cl
2a	H	160–161.5	158–160[b]						
2b	p-NO₂	126–128		33.87	3.56	12.51	34.04	3.54	12.41
2c	p-Cl	153–155		35.19	3.70	25.96	35.40	3.90	25.81
2d	p-COOH	175–176		38.24	3.93	12.56	38.46	3.94	12.44
2e	p-OH	157–159	155–157[c]						
2f	p-OCH₃	84–86	84–86[c]						
2g	p-CH₃	123–124.5		42.78	5.18	14.05	42.88	5.38	14.29
2h	p-CO₂CH₃	131–134		40.48	4.42	11.96	40.63	4.30	11.92
2i	o-CH₃	101–103		42.78	5.18	14.05	42.89	5.19	14.27
2j	o-CO₂H	164–168		38.24	3.93	12.56	38.35	3.86	12.59
2k	o-COCH₃	179–181		42.79	4.67	12.65	43.01	4.75	12.59
2l	o-CH₂NH₂·HClO₄	211–212.5		29.37	4.10	19.26	29.37	3.90	19.15
3a	H (R = C₆H₅)	76–78.5	73–74[d]						
3b	H (R = OCH₃)	98–101	92–94[e]						

[a] Melting points are uncorrected. All analyses were performed by A. Bernhardt, 5251 Elbach über Engelskirchen, West Germany. [b] F. G. Bordwell and P. J. Boutan, *J. Amer. Chem. Soc.*, **78**, 87 (1956). [c] K. Hirose and S. Ukai, *Yakagaku Zasshi*, **86**, 187 (1966); *Chem. Abstr.*, **64**, 19466t (1966); compound prepared *via* different procedure. [d] See ref 13. [e] C. R. Johnson and W. G. Phillips, *J. Org. Chem.*, **32**, 1926 (1967).

TABLE II

ABSORPTION MAXIMA OF SULFONIUM COMPOUNDS
AND THE CORRESPONDING DEMETHYLATED THIOETHERS

Compd	λ_{max}^{S}, nm[a]	λ_{max}^{T}, nm[b]
2a	218	253
2b	248	342
2c	232	258
2d	230[c]	275
2e	242[d]	260
2f	243	253[e]
2g	227	255
2h	232	288
2i	222	247
2j	...[f]	255
2k	245	235
2l	222	250
3a	233	249

[a] Absorption maximum for sulfonium compound; $c = ca.\ 10^{-4}$ M in water. [b] Absorption maximum for thioether product arising from demethylation of the numbered sulfonium compound; $c = ca.\ 10^{-4}$ M in 1% acetonitrile:1 M NaOH (v:v). Nearly identical values of λ_{max}^{T} were obtained in 100% acetonitrile for compounds with no ionizable substituent. [c] In basic medium, no maximum with $\epsilon > 10^3$ was observed above the cutoff point of 230 nm. [d] In basic medium, λ_{max} 268 nm. [e] Reaction followed at 260 nm, the wavelength of maximum difference between the absorption spectra of 2f and the product, p-methoxythioanisole. [f] In both neutral and basic media, no maximum of $\epsilon > 10^3$ was observed above the cutoff point of 230 nm.

pounds characteristically exhibit a weak doublet ($\epsilon < 10^2$) in the region ca. 50 nm above the λ_{max} (i.e., generally ca. 265–275 nm).

Kinetics.—The kinetic measurements described herein were carried out in aqueous media and in pure acetonitrile solutions. The reactions in water were studied at 57.1 ± 0.3, 68.5 ± 0.3, and 78.8 ± 0.5°, and the temperature was maintained by allowing the reaction to proceed in sealed ampoules in a large round-bottom flask containing either acetone, n-hexane, or ethanol, respectively, at reflux. Because of the high temperatures involved, the strongly basic solutions attacked the glass of all sealed ampoules which were available commercially. Therefore, ampoules were made from Corning alkali-resistant tubing (no. 79900). These ampoules were not degraded by 1 M sodium hydroxide solution at 78° for a period of at least 1 week. The reactions in water were sufficiently slow so that the following experimental procedure was employed. A solution of sodium hydrxide of known normality was mixed with an aqueous solution (ca. 10^{-2} M) of the sulfonium salt, in a ratio which gave a final substrate concentration of ca. 10^{-4} M. Since the concentration of hydroxide was always at least 0.5 M, pseudo-first-order kinetics were obtained in all cases. The solution of substrate

and hydroxide was then divided into 12–15 ampoules, which were sealed and placed in the refluxing solvent. Within 3–5 min, the bath temperature returned to the desired point (solvent reflux temperature), and the ampoules were allowed to equilibrate in the system for a total of 20 min. The first ampoule was then removed and opened, and the absorbance of the solution was recorded at 25.0 ± 0.1° as the initial data point. Additional samples were removed periodically and their absorbances recorded in a similar manner.

The measurements made in acetonitrile were carried out at 25.0 ± 0.1°. Since the reaction rates were considerably faster in this system than in the aqueous solutions described above, a slightly different procedure was employed to initiate the reactions and to monitor their progress. A solution (ca. 10^{-2} M) of the substrate in acetonitrile was added from a 20-μl pipet to a cuvette containing 3.0 ml of a solution of the amine nucleophile in acetonitrile, previously equilibrated at 25.0 ± 0.1°. The cuvette was inverted several times and immediately returned to the thermostated cell housing of the spectrophotometer for recording the change in absorbance. A similar procedure was employed to study the reaction of 2b with inorganic anions in water except that the temperature of the cell housing was maintained at 78.5 ± 0.5°. The concentration of the sulfonium compound in the cuvette was ca. 6×10^{-5} M, and the concentration of added nucleophile was at least 0.01 M, so that pseudo-first-order kinetics were obtained in all cases.

The appearance of the thioether product was followed spectrophotometrically by recording the increase in optical density with time at the λ_{max} of the particular thioether (Table II). Repetitive scans of the ultraviolet and/or visible region of the spectrum showed clean isosbestic points, indicating no buildup of an intermediate which absorbed in the region scanned. The values of pseudo-first-order rate constants (k_{obsd}) were calculated from plots of log ($OD_\infty - OD_t$) vs. time.[17] First-order plots were linear for a minimum of two half-lives, and in most cases for more than three half-lives.

Apparatus.—Ultraviolet and visible spectra were measured on a Cary 15 recording spectrophotometer, which was used for all repetitive scans of the initial kinetic runs. Infrared spectra were recorded with a Perkin-Elmer Model 21 spectrophotometer. All kinetic measurements were carried out on a Gilford 2400 recording spectrophotometer (or a Beckman DU monochromator equipped with a Gilford automatic cuvette positioner and photometer). The temperature in the spectrophotometer cell compartments was maintained with water from a large thermostated circulating bath.

Results

The reaction of sulfonium compounds 2 with nucleophiles follows the rate law of eq A, which yields eq B

(17) Reference 11, p 558.

$$dP/dt = v = k_2[S][Nuc] \qquad (A)$$

$$k_{obsd} = k_{OH}[OH] \qquad (B)$$

when hydroxide is used as the nucleophile under the pseudo-first-order conditions employed. A plot of the data of Table III shows the dependence of k_{obsd} on hy-

TABLE III

EFFECT OF HYDROXIDE ION CONCENTRATION ON THE RATE OF DECOMPOSITION OF 2c[a]

[OH$^-$], M	$k_{obsd} \times 10^4$, sec^{-1} [b]	$k_{OH} \times 10^4$, M^{-1} sec^{-1}
1.0	2.45 ± 0.10	2.45 ± 0.10
0.75	1.54 ± 0.06	2.05 ± 0.08
0.5	0.85 ± 0.07	1.70 ± 0.14

[a] Temperature 78.8 ± 0.5°; μ = 1.0 with NaClO$_4$. [b] Average of at least three determinations.

droxide ion concentration for the decomposition of 2c. The observed rate constants in 1 M hydroxide are given in Table IV. Unfortunately, the slow rates of reaction

TABLE IV

OBSERVED RATE CONSTANTS FOR HYDROXIDE ION CATALYZED DECOMPOSITION OF 2[a]

Compd	X	σ_{para} [b]	$k_{obsd} \times 10^4$, sec^{-1}
2a	H	0	1.14 ± 0.10
2c	p-Cl	0.23	2.45 ± 0.10
2d	p-COO$^-$	0.13[c]	2.20 ± 0.14
2f	p-OCH$_3$	−0.27	0.39 ± 0.00
2g	p-CH$_3$	−0.17	0.58 ± 0.06
2i	o-CH$_3$		1.01 ± 0.08
2j	o-COO$^-$		0.72 ± 0.04
2l	o-CH$_2$NH$_2$		1.68 ± 0.09

[a] Temperature 78.8°; μ = 1.0. [b] σ values from C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, 2, 323 (1964) except for p-COO$^-$. [c] H. Jaffé, *Chem. Rev.*, 53, 191 (1953).

of these compounds with hydroxide ion precluded measurement of rates in solutions containing less than 1 M hydroxide for compounds other than 2c. A Hammett plot[18] of the data for the para-substituted compounds in Table IV is shown in Figure 1. The value for ρ is 1.60; only the sulfonium compound containing the charged p-carboxylate substituent (2d) deviates from the line. Similarly, the effect of temperature on the rate of decomposition of 2c by hydroxide ion is shown in Table V. An Arrhenius plot of these data (Figure 2)

TABLE V

EFFECT OF TEMPERATURE ON THE RATE OF DECOMPOSITION OF 2c BY HYDROXIDE ION

Temp, °C	$k_{obsd} \times 10^5$, sec^{-1}
57.1 ± 0.3	2.35 ± 0.16
68.5 ± 0.3	7.58 ± 0.25
78.8 ± 0.5	24.5 ± 1.0

allows the calculation of E_a = 25.6 kcal/mol. From these data, the values of $\Delta F^\ddagger$ = 26.3 kcal/mol, $\Delta H^\ddagger$ = 24.8 kcal/mol, and $\Delta S^\ddagger$ = −5.0 eu can be obtained.

The reaction of several sulfonium ions of type 2 failed to give the products expected from eq 1. For example, the p-hydroxy compound (2e) is almost totally unreactive under the conditions used in this study. The fact that the p-methoxy derivative (2f) reacts with hydroxide, as expected, to form the corresponding thio-

ether and methanol indicates that the oxyanion of 2e is particularly resistant to hydrolysis. This is presumably due to the large contribution of the inert quinoid form in the resonance hybrid shown below. This type
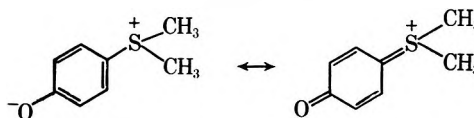
of hybrid has been proposed previously[19] on the basis of pK_a and ultraviolet absorption spectral measurements. Similarly, the reaction of 2k with hydroxide failed to give the corresponding thioether but, rather, led to a thianaphthene derivative. This reaction is not without precedent, having been observed previously for the corresponding p-methyl derivative.[20]

The reaction of the p-nitro compound (2b) with hydroxide ion leads to the formation of p-nitrophenolate ion and dimethyl sulfide, indicated by the development of an intensely yellow colored solution during reaction and an ultraviolet spectrum with λ_{max} 400 nm. No reaction of 2b with other oxygen nucleophiles could be detected at 25° in aqueous media. However, at 78° a slow reaction was observed with carbonate ion according to eq 1 to give p-nitrothioanisole (λ_{max} 350 nm). Only when a nucleophile is employed which has an appreciable degree of polarizability (*i.e.*, a soft nucleophile[21]) does transmethylation occur as in eq 1. This type of reaction was originally observed with thiocyanate as the nucleophile[22] and was referred to as an "abnormal reaction," in that the nucleophile attacked the methyl group in a simple SN2 reaction rather than the aromatic nucleus *via* an addition–elimination mechanism. It is well known[23] that nucleophiles such as iodide, thiocyanate, etc., attack a saturated sp^3 carbon in preference to an sp^2-hybridized carbon atom. For this reason, the reaction of 2b with several inorganic nucleophiles was studied and the rate data are shown in Table VI. A plot of these data by the Swain–Scott proce-

TABLE VI

REACTION OF 2b WITH VARIOUS INORGANIC NUCLEOPHILES IN WATER[a]

Nucleophile	n [b]	k_2, M^{-1} sec^{-1}
SCN$^-$	4.77	1.35 × 10^{-3}
I$^-$	5.04	2.21 × 10^{-3}
S$_2$O$_3$$^{2-}$	6.36	8.58 × 10^{-2}

[a] Temperature 78.5 ± 0.5°; reaction run in 0.2 M HCO$_3$$^-$–CO$_3$$^{2-}$ buffer (1:1), pH 9.66; μ = 1.0 with NaClO$_4$. Added nucleophile concentration = 3.3 × 10^{-2} to 6.0 × 10^{-1} M. [b] Nucleophilicity constant of Swain and Scott.[24]

dure[24] is shown in Figure 3. The slope of the line of this plot is equal to 1.14.

The inability to observe facile transmethylations in aqueous media prompted investigation of the reactions of 3 containing strongly electron-withdrawing R groups. All attempts to isolate such compounds failed (see

(18) L. P. Hammett, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1970, Chapter II.

(19) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1962, p 152.

(20) (a) F. Krollpfeiffer, H. Hartmann, and F. Schmidt, *Justus Liebigs Ann. Chem.*, 563, 15 (1949). (b) R. A. Guerra, *Acta Salmanticensia, Ser. Cienc.*, 6, 7 (1963); *Chem. Abstr.*, 63, 5581h (1965).

(21) R. G. Pearson, *Surv. Progr. Chem.*, 5, 1 (1969).

(22) B. A. Bolto and J. Miller, *J. Org. Chem.*, 20, 558 (1955).

(23) (a) Reference 10, Vol. I, p 42; (b) ref 11, p 85.

(24) C. G. Swain and C. B. Scott, *J. Amer. Chem. Soc.*, 75, 141 (1953).

Figure 1.—Hammett plot for the hydroxide ion catalyzed hydrolysis of 2 in water at 78.5 ± 0.5°.

Figure 2.—Arrhenius plot for the hydroxide ion catalyzed hydrolysis of 2c in water.

Experimental Section). We attempted to generate a more reactive sulfonium ion *in situ*, by reaction of a thioether with cyanogen bromide, a method which has been used extensively for selective cleavage of methionine-containing peptides.[25] The reaction anticipated in the current work is shown in eq 2.

(2)

Figure 3.—Swain–Scott plot for the reaction of 2b with nucleophiles in water at 78.5 ± 0.5°.

Repetitive scanning of the solution of 4 in 0.1 *M* CNBr and 0.1 *M* HCl[26] showed no change in the ultraviolet spectrum at ambient temperature over a period of up to 6 hr. The ultraviolet absorption spectrum of 4 had λ_{max} 257 nm, whereas the ultraviolet absorption spectrum of 5, synthesized by an independent route,[27] had λ_{max} 245 and 222 nm. Thus, in contrast to the facile cleavage under these conditions of methionine-containing peptides, no analogous conversion of 4 to 5

was detectable. The reactions of 2j and 2l were also investigated in an attempt to effect transmethylation from a methylsulfonium compound to an adjacent carboxylate or amine nucleophile. No evidence for a facile intramolecular reaction could be obtained. Studies in this area are continuing and the results will be reported in a future paper.

Large solvent effects in reactions involving decomposition of formally charged molecules to neutral molecules have been noted for some time.[28] In order to investigate the reaction of sulfonium compounds with nucleophiles in a nonaqueous medium, it was decided to work with amine nucleophiles in acetonitrile. A major factor in this decision was the fact that the pK_a of many representative amines have been determined in aceto-

(25) B. Witkop, *Advan. Protein Chem.*, **24**, 91 (1970), and references therein

(26) E. Gross and B. Witkop, *J. Biol. Chem.*, **237**, 1856 (1962).

(27) R. K. Olsen and H. R. Snyder, *J. Org. Chem.*, **30**, 187 (1965).

(28) Reference 8, p 457.

Figure 4.—Brønsted plot for the reaction of **2b** with various amine nucleophiles in acetonitrile at 25 ± 0.1°.

nitrile.[29] The second-order rate constants for reaction of the *p*-nitrophenyldimethylsulfonium compound, **2b**, with various amines are given in Table VII. A Brøn-

TABLE VII
REACTION OF 2b WITH AMINES IN ACETONITRILE[a]

Amine	$pK_a^{CH_3CN}$ [b]	k_2, M^{-1} sec^{-1}
n-Butylamine	18.26	1.43×10^{-2}
Di(*n*-butyl)amine	18.31	2.74×10^{-2}
Tri(*n*-butyl)amine	18.09	5.71×10^{-3}
Ethanolamine	17.53	4.88×10^{-3}
Benzylamine	16.76	4.36×10^{-3}
β-Phenylethylamine	17.5 ± 0.5[c]	8.65×10^{-3}
Phenylethanolamine	16.5 ± 0.5[c]	5.17×10^{-3}
Morpholine	16.61	1.85×10^{-2}
Piperidine	18.92	1.45×10^{-1}
Pyrrolidine	19.58	2.20×10^{-1}

[a] Temperature 25 ± 0.1°. [b] $pK_a^{CH_3CN}$ from ref 29, unless noted otherwise. [c] $pK_a^{CH_3CN}$ estimated from a plot of $pK_a^{H_2O}$ vs. $pK_a^{CH_3CN}$ for those amines whose pK_a's were known in both solvents. There is considerable uncertainty in these values.

sted plot[30] of these data is shown in Figure 4, and a value $\beta = 0.36$ is obtained from the slopes of the lines, primary and secondary amines being clearly separated. Two representative amines, namely, pyrrolidine and *n*-butylamine, were used as nucleophiles in order to study most of the sulfonium ions of types **2** and **3**. These data are presented in Table VIII and the Hammett plots[18] given in Figure 5. It can be seen that the slopes of the lines ($\rho = 1.74 \pm 0.05$) for both sets of data are quite similar and are in good agreement with the value obtained for the reaction of hydroxide ion with **2** in water (Figure 1).

Discussion

It has been known for some time that sulfonium compounds are extremely resistant to attack by oxygen nu-

(29) J. F. Coetzee, *Progr. Phys. Org. Chem.*, **4**, 45 (1967).
(30) Reference 11, p 170.

TABLE VIII
EFFECT OF SUBSTITUENTS ON THE RATE OF REACTION OF SULFONIUM COMPOUNDS WITH *n*-BUTYLAMINE AND PYRROLIDINE IN ACETONITRILE[a]

Compd (X)	σ_{para} [b]	$k_{2p} \times 10^2$,[c] M^{-1} sec^{-1}	$k_{2b} \times 10^4$,[d] M^{-1} sec^{-1}
2a (H)	0	1.04	0.55
2b (NO₂)	0.78	22.0	14.3
2c (Cl)	0.23	2.46	1.61
2g (CH₃)	−0.17	0.54	
2h (CO₂CH₃)	0.45	5.68	3.38
2i (*o*-CH₃)		1.05	
3a		22.5	11.8

[a] Temperature 25 ± 0.1°. [b] See footnote *b*, Table IV. [c] Second-order rate constant using pyrrolidine as added nucleophile over the concentration range 10^{-2} to 10^{-1} *M*. [d] Second-order rate constant using *n*-butylamine as added nucleophile over the range 10^{-2} to 10^{-1} *M*.

cleophiles.[31] The sulfonium compounds employed in the present study also require vigorous conditions to effect transmethylation with oxygen nucleophiles in water but, as will be discussed below, changes in solvent and/or nucleophile drastically alter the rate of non-enzymic transmethylation. The acidity of protons attached to the α carbon of sulfonium compounds permits the formation of sulfonium ylides.[32] In the present work this ylide would not be reactive and the reaction scheme of eq 3 would apply. This is a system of the

$$(3)$$

general type shown below, *i.e.*, preequilibrium ioniza-

$$E^- \underset{-H^+}{\overset{+H^+}{\rightleftharpoons}} EH \xrightarrow{k_{rate}} product$$

tion of an acidic group to give an unreactive moiety at the expense of the reactive species. This type of kinetic scheme predicts that k_{obsd} will be insensitive to increasing concentrations of hydroxide ion at pH > pK_a of EH since the enhanced rate of reaction due to the increased concentration of OH⁻ will be equally offset by the decreased concentration of the reactive species, EH.[33] As can be seen by the data of Table III, the values of k_{obsd} are strongly dependent on the concentration of hydroxide ion, and there is no indication of a hydroxide-independent rate in the region studied. This indicates that the pK_a of compounds of type **2** is considerably higher than 14. Johnson[32] has estimated the pK_a of the methyl protons of **6** to be >17.3 based on the

(31) (a) J. L. Gleave, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 236 (1935); (b) F. Challenger, R. Bywood, P. Thomas, and B. J. Hayward, *Arch. Biochem. Biophys.*, **69**, 514 (1957).
(32) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, Chapter 9.
(33) Reference 10, Vol. I, Chapter 1.

6

assumption that the tertiary proton at the peri positive of **6** (measured pK_a in aqueous dioxane $= 7.3$[34]) is at least 10^{10} more acidic than the methyl protons.

Franzen and Driessen[35] have shown that the preparation of ylides from dimethylphenylsulfonium salts requires strong bases (*e.g.*, *tert*-butoxide) in rigorously anhydrous dimethyl sulfoxide. In the work reported herein, the presence of the relatively strong acid, water, would result in immediate protonation of any ylide formed. In deuterated water, this would result in exchange of the acidic protons. Attempts to measure this rate of exchange by nuclear magnetic resonance spectroscopy were unsuccessful owing to the low solubility of **2** in D_2O (see Experimental Section). Although there are several references in the literature to the facile exchange of α protons of sulfonium compounds in aqueous media,[36] the conclusion from the present work is that these exchange processes involve kinetically insignificant amounts of the ylide in a rapid equilibrium at pH 14. Thus, the data of Table IV is unencumbered by any preequilibria considerations, and the ρ value of 1.55 obtained from Figure 1 is a direct measure of the effect of the substituent group on the rate of hydrolysis.

The activation parameters derived from the data of Table V and Figure 2 afford insight into the reasons for resistance of **2** to hydrolytic decomposition. The thermodynamic parameters ΔG, ΔH, and ΔS for the process of transforming a sulfonium compound to a thioether have been known for some time.[37] Although the values have been revised on several occasions, the free energy of reaction is *ca.* -7 to -10 kcal/mol, which is of the same order as the so-called high-energy bond of ATP. However, it can be seen that, although the process of transforming a sulfonium compound to a thioether is thermodynamically favored, large activation parameters prevent the reaction from going to completion in water, except under forcing conditions.

The reaction of **2b** with several inorganic nucleophiles gives the kinetic data of Table VI, which is shown graphically in Figure 3. The linear free-energy relationship of Swain and Scott[24]

$$\log k_n = \log k_0 + sn$$

where n is the nucleophilicity constant for the particular nucleophile employed and s is the susceptibility of the substrate undergoing nucleophilic attack. The value of s obtained from Figure 3 (1.14 ± 0.06) is close to that arbitrarily assigned for the reaction of methyl bromide with various nucleophiles.[24] Since the reaction of methyl bromide with added nucleophiles is

Figure 5.—Hammett plot for the reaction of **2** with pyrrolidine (O) and *n*-butylamine (●) in acetonitrile at 25°.

known to be a simple S_N2 displacement reaction,[38] the similar magnitude of the s values (*ca.* 1.0) for both methyl bromide and **2b** would suggest that in both cases bond-breaking is not far advanced in the transition state; *i.e.*, little development of positive charge has occurred on the carbon undergoing attack. By contrast, recent studies on several types of methylsulfonium compounds provide information on the mechanism of transalkylation for alkyl groups capable of forming more stable incipient carbonium ions. The generalized structures studied are shown in **7–9**, and the alkyl residue attacked

7

8

9

in each case is indicated by the arrow. In no case is the methyl group "transferred" to the attacking nucleophile at elevated temperatures (60–70°). The decomposition of **7** in aqueous ethanol or other mixed solvents was studied by Hyne and Jensen[39] and, in a related case, Jendrek[40] studied the decomposition of **8**, where R is allyl, cinnamyl, and substituted benzyl. These reactions obey the Swain–Scott relationship,[24] and, although neither group of workers discussed the significance of the s values derived from their data, both plots clearly

(34) A. W. Johnson and R. B. LaCount, *Tetrahedron*, **9**, 130 (1960).

(35) V. Franzen and H. E. Driessen, *Chem. Ber.*, **96**, 1881 (1963).

(36) (a) W. von E. Doering and A. K. Hoggman, *J. Amer. Chem. Soc.*, **77**, 521 (1955); (b) ref 3, p 61; (c) ref 9, p 70.

(37) (a) S. H. Mudd, W. A. Klee, and P. D. Ross, *Biochemistry*, **5**, 1653 (1966); (b) J. Durell, M. Rawitscher, and J. M. Sturtevant, *Biochem. Biophys. Acta*, **56**, 552 (1962); (c) J. Durell and J. M. Sturtevant, *ibid.*, **26**, 282 (1957).

(38) C. A. Bunton, "Nucleophilic Substitution at Saturated Carbon," Elsevier, Amsterdam, 1963.

(39) (a) J. B. Hyne and J. H. Jensen, *Can. J. Chem.*, **43**, 57 (1965), and references therein; (b) J. H. Jensen, Ph.D. Thesis, University of Alberta, Calgary, Alberta, 1964.

(40) J. F. Jendrek, Ph.D. Thesis, Tulane University, New Orleans, La., 1967; *Diss. Abstr.*, *B*, **28**, 4031 (1968).

show a very low sensitivity of rate to the added nucleophilic species, and a value of $s = 0.16 \pm 0.02$ is obtained. It is apparent that in molecules such as **7** and **8**, which contain groups capable of forming stable carbonium ions, low s values are obtained, indicative of considerable development of carbonium ion character in the transition state; *i.e.*, bond-breaking of the C–S bond is far advanced in the transition state. Similarly, the decomposition of **9** studied by Schowen[41] proceeds with exclusive attack of OH$^-$ on the benzylic carbon to the complete exclusion of the transmethylation reaction. This would suggest the development of considerable bond-breaking in the transition state, but a more rigorous proof is not immediately discernible from the available data.

In order to explain the observed rate-enhancing effect of the *o*-methyl substituent (**2i**, Table IV), steric factors must be considered. The fact that the ortho-substituted compound (**2i**) is hydrolyzed *ca.* twice as fast as the corresponding para isomer (**2g**) must be due to the steric bulk of the *o*-methyl group. This substituent presumably forces the dimethylsulfonio group out of the plane of the aromatic ring, thus decreasing orbital overlap and making delocalization of the positive charge less likely. Of interest in this regard are the recent data of Dunn and Bruice,[42] which demonstrate a similar rate enchancement by ortho substituents for the reaction shown in eq 4. The similarity between the oxonium ion transition state of eq 4 and the sulfonium

ions of the present work is obvious, and it is not surprising that similar rate effects on hydrolytic reactions should be observed with bulky ortho substituents. In the course of investigating possible intramolecular transmethylation reactions, the reactions of **2j** (*o*-COO$^-$) and **21** (*o*-CH$_2$NH$_2$) with hydroxide ion were studied. The data of Table IV show a 50% rate enhancement for the more bulky *o*-CH$_2$NH$_2$ substituent (**21**) in comparison to the *o*-CH$_3$ group (**2i**). This is to be expected based on the steric considerations discussed above. However, the decreased rate of hydrolysis observed for **2j** (*o*-COO$^-$) *vs.* **2i** is not predicted on steric grounds.[42] The *o*-carboxylate anion seems to stabilize the sulfonium compound against hydrolytic decomposition, presumably by an electrostatic interaction between the adjacent formally charged groups. This type of interaction has been suggested by Casanova and

coworkers[43] to explain the large decrease in pK_a for *o*-(dimethylsulfonio)phenylacetic acid in comparison with the para isomer. In contrast, the data of Dunn and Bruice for the reaction shown in eq 4 indicate a large rate enhancement when R = COO$^-$. The important difference between the two cases is that in eq 4 steric acceleration by the bulky *o*-carboxylate group results in a more facile reaction, while in the present work stabilization of the formally charged sulfonium ion by the *o*-carboxylate in the ground state results in an increase in the activation energy, and therefore a slower rate of reaction.

The reaction of sulfonium compounds with amines in acetonitrile was studied in the same way as described above for the hydroxide-catalyzed reactions in water, and the derived data are shown in Tables VII and VIII. The relative insensitivity of k_2 to changes in pK_a of the attacking nucleophile (Figure 4), as indicated by the low β value of 0.35, shows that the transfer of the electrophilic methyl group of **2b** is not far advanced in the transition state, in accord with the conclusion deduced from data obtained for hydroxide ion and compounds of type **2** in water. The fact that the data of Figure 4 clearly separates into two lines, one for primary amines and the other for secondary amines, is of interest since this type of behavior is generally attributed to solvation effects in aqueous media.[44] However, as has been pointed out by Gregory and Bruice,[44a] these examples involve substrates in which bond formation between nucleophile and the substrate is not very complete in the transition state. By contrast, a substrate in which bond formation is much more complete in the transition state (*e.g.*, phenyl acetate[45]) does not distinguish between primary and secondary amines. The fact that sulfonium ions such as **2** exhibit this type of discrimination is further evidence that bond-making between the nucleophile and sulfonium methyl group is not far advanced in the transition state. The deviation of di(*n*-butyl)amine from the line for secondary amines is presumably due to steric hindrance to nucleophilic attack by an acyclic secondary amine in comparison to a more facile attack by the exposed nitrogen lone pair of cyclic secondary amines. This type of steric inhibition to nucleophilic attack should be even more pronounced in the case of tri(*n*-butyl)amine, which is considerably slower than di(*n*-butyl)amine in this reaction. However, one of the products formed in the reaction of tri-(*n*-butyl)amine with **2b** is tri(*n*-butyl)methylammonium perchlorate. The formation of this formally charged ammonium compound could be retarded in an aprotic solvent such as acetonitrile, thus leading to a depressed rate of reaction in comparison to other amines of similar pK_a. An explanation for the slight negative deviation of ethanolamine from the line for primary amines is not readily apparent at this time. Considering the uncertainties in the estimated pK_a values for β-phenylethylamine and β-phenylethanolamine, the rate data show that these amines react at a rate consistent with their base strength. Unfortunately, it was not possible

(41) (a) C. G. Swain, W. D. Burrows, and B. J. Schowen, *J. Org. Chem.*, **33**, 2534 (1968). (b) B. J. Schowen, Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, Mass., 1964; Abstracts of Theses, 1964–1965, MIT Press, Cambridge, Mass., 1969, p 240.

(42) B. M. Dunn and T. C. Bruice, *J. Amer. Chem. Soc.*, **92**, 2410, 6589 (1970).

(43) J. Casanova, Jr., N. D. Werner, and H. R. Kiefer, *ibid.*, **89**, 2411 (1967).

(44) (a) M. J. Gregory and T. C. Bruice, *ibid.*, **89**, 2327 (1967); (b) S. J. Benkovic and P. A. Benkovic, *ibid.*, **88**, 5504 (1966); (c) A. J. Kirby and W. P. Jencks, *ibid.*, **87**, 3209 (1965); (d) R. G. Pearson and F. V. Williams, *ibid.*, **76**, 258 (1954).

(45) T. C. Bruice, A. R. Donzel, R. W. Huffman, and A. R. Butler, *ibid.*, **89**, 2106 (1957).

TABLE IX

COMPARISON OF KINETIC DATA FOR **2** AND METHYL IODIDE[a]

Nucleophile Substrate	OH⁻				R₃N			Inorganic anions			
	k_{OH}^{298}	E_a	$\Delta F_{298}^{\ddagger}$	$\Delta S_{298}^{\ddagger}$	k_{R_3N}	β	s	k_{SCN}^{298}	E_a	$\Delta F_{298}^{\ddagger}$	$\Delta S_{298}^{\ddagger}$
$CH_3S^+ <^{CH_3}_{C_6H_4R(p)}\ ClO_4^-$	3.05×10^{-7} [b]	25.6	26.3	−5.0	1.61×10^{-3} [c]	0.35	1.14	5.01×10^{-6} [d]	23.8	24.6	−4.7
CH_3I	6.52×10^{-6} [e]	22.2 [e]	23.1	−5.0	3.1×10^{-3} [f]	0.22 [f]	1.15 [e]	4.68×10^{-4} [g]	21.9		

[a] Reactions carried out in water, except when noted otherwise. All rate data are in units of M^{-1} sec^{-1}; E_a and ΔF are in units of kcal/mol, and ΔS values are in entropy units (gibbs). [b] R = Cl; extrapolated from Figure 2. [c] R = Cl; data for n-butylamine from Table VIII; reaction carried out in 100% acetonitrile. [d] R = NO₂; extrapolated from data of ref 22 and this research. [e] Data from a compilation of earlier work cited in ref 49. [f] Derived from data of ref 48; k_{R_3N} is for methylamine at 30°. [g] Value obtained from data of footnote e for other inorganic nucleophiles and assuming that k_{SCN} lies on the Swain–Scott[24] line of slope, $s = 1.15$.

to study the reaction of norepinephrine in this system because of the low solubility of the amine in acetonitrile.

In Figure 5, the rate data of Table VIII for reaction of **2** with pyrrolidine and n-butylamine are plotted by the method of Hammett.[18] The similarity in the slopes of the lines obtained with two different amine nucleophiles, in addition to the similar slope using hydroxide ion as the nucleophile (Figure 1), serves to indicate that the substituent effect on the rate of attack at the methyl group of **2** are not sensitive to the nature of the attacking nucleophile. The effect of a change in substituent directly attached to the trivalent sulfur is shown by comparing the data in Table VIII for **2a** and **3a**. Using either pyrrolidine or n-butylamine as the added nucleophile, k_2 for **3a** is ca. 20 times that for **2a**, indicating the large rate-enhancing effect of placing a more electron-withdrawing group directly on the already electron-deficient sulfur atom. This substituent effect could not be investigated more completely because of the inability to synthesize **3** containing R groups more electron deficient than phenyl. No reaction could be detected between **3b** and n-butylamine in acetonitrile at ambient temperature by repetitive scanning in the ultraviolet and visible region of the spectrum. This is in contrast to the observation of a facile reaction between p-toluenethiolate anion and ethoxydiphenylsulfonium tetrafluoroborate in ethanol at −10 to −5°.[46] The mechanism proposed for this reaction involves the initial attack by thiolate anion on the trivalent sulfur atom, displacing ethoxide ion as shown in eq 5. The lack of

$$(5)$$

reactivity of **3b** toward an amine nucleophile presumably is due to the inability of the amine to displace ethoxide ion in acetonitrile.

Of primary interest in the present study is the delineation of the kinetic parameters for methylations involving methylsulfonium compounds vis-à-vis those reactions utilizing other methylating agents such as methyl iodide. A summary of some comparative data is given in Table IX. It can be seen that in all cases the reaction of a given nucleophile with methyl iodide is ca. 10 to 100 times faster than with **2**. In the case of the hydroxide-catalyzed hydrolyses, similar entropies of activation are calculated for the two reactions, and the

rate differences therefore must arise from the more positive energy of activation for **2** vs. methyl iodide. These data provide additional evidence for the bimolecular nature of the reaction of **2** with nucleophiles, since negative entropies of activation of this magnitude are associated with many bimolecular processes.[47] The value of β for the reaction of amines with **2** is similar to that observed in the aminolysis of methyl iodide in water, where the low β value of 0.2 has been taken as evidence indicating little bond formation between amine and methyl iodide in the transition state.[48] The reaction of methyl iodide with mercaptoethylamine has been shown to occur very readily at 25° in aqueous media,[49] and recent observations in this laboratory have demonstrated a similar facile reaction between thiols and **2**.[50] These qualitative and quantitative similarities in the kinetic properties of **2** and methyl iodide indicate that the mechanism of transmethylation from simple sulfonium compounds to a variety of added nucleophiles is very similar to that involved in nucleophilic attack on methyl iodide i.e., a classic SN2 displacement mechanism. Of interest in terms of enzyme-catalyzed transmethylation is the relative reactivity of added nucleophiles (O < N < S) observed in the system described in eq 1. Schlenk and coworkers[51] have recently delineated the requirements for the sulfonium methyl donor in three enzyme-catalyzed reactions, involving methyl transfer to oxygen, nitrogen, and sulfur nucleophiles. The data for the enzymic processes clearly show a strict requirement for the usual methyl donor, SAM, in the O-methylase reaction (acetylserotonin methyltransferase), whereas the N-methylase (histamine N-methyltransferase) will carry out the reaction, albeit quite inefficiently, using the inosine analog of SAM as the methyl donor. These findings are in accord with the present work in that the more reactive amine nucleophile involved in an N-methylase can be expected to be less discriminating in its reactions than the much less reactive oxygen nucleophiles. Similarly the highly reactive thiol group should be even less discriminating toward methylsulfonium compounds, and the S-methylases use a number of derivatives of SAM in vitro.[51] In vivo, even simple thetins and S-methylmethionine are effective with the S-methylase.[9]

From the current work, it is concluded that the transition state for nucleophilic attack on **2** by a variety of nucleophiles is as shown in **10**. It seems reasonable to

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$$R_1 \diagdown \overset{\delta+}{S} \cdots CH_3 \cdots \cdots \overset{\delta-}{Nuc}$$
$$R_2 \diagup$$

10

assume that a similar transition state is involved in methyl transfer from any methylsulfonium compound. In order to test this hypothesis, we are continuing the study of nonenzymic transmethylation on molecules which are more closely related to SAM in structure, but which are not so readily decomposed in basic media.

Catalysis of Nucleophilic Substitutions by Micelles of Dicationic Detergents[1]

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Dicationic detergents (I), $RN^+Me_2(CH_2)_nN^+Me_2R\ 2Br^-$ (where R = cetyl and n = 4 and 6), readily micellize, and the micelles are effective catalysts of the reactions of hydroxide ions with chloro- and fluoro-2,4-dinitrobenzene and hydroxide and fluoride ions with p-nitrophenyl diphenyl phosphate. With n = 4 and 6, those detergents are two- to fivefold better catalysts than cetyltrimethylammonium bromide, CTABr. The dicationic detergent $RN^+Me_2CH_2C\equiv CCH_2N^+Me_2RBr_2^-$ also micellizes, but it and I (n = 2) are not markedly better catalysts than CTABr.

Catalysis by ionic micelles and polyelectrolytes is well established and has been extensively reviewed.[3-6] The catalysis can be explained qualitatively in terms of the ionic and hydrophobic interactions of the reactants and transition state with the micelle, and, although strong binding is observed between substrate and many micelles,[7,8] micellar catalysis is generally relatively small *e.g.*, in the 10–100 range. Micellar catalysis can be increased by introducing the reagent into the micelle,[9] either by chemical binding or by comicellization,[10] and modification of the micellar structure is another approach.[8c] Polyelectrolyte catalysis is often much larger than micellar catalysis.[3] Micelles have very mobile structures,[11] whereas the charged groups in a polyelectrolyte are linked by alkyl or other chains, and we have therefore prepared a series of dicationic detergents (I and II), which combine some features of polyelectrolytes and detergents and compared their effectiveness

$$\overset{+}{RMe_2N}(CH_2)_n\overset{+}{N}Me_2R\ 2Br^- \qquad \overset{+}{RMe_2N}CH_2C\equiv CCH_2\overset{+}{N}Me_2R\ 2Br^-$$
$$\text{I} \qquad\qquad\qquad\qquad \text{II}$$

R = cetyl; n = 2, 4, 6 for Ia, b, c, respectively

as catalysts with that of cetyltrimethylammonium bromide (CTABr) for anionic nucleophilic attack upon uncharged substrates in the hope of increasing the effectiveness of micellar catalysis and the ease of micellization. The reactions used were those of hydroxide ion with chloro- and fluoro-2,4-dinitrobenzene (2,4-DNCB and DNFB),[8a,12] and hydroxide and fluoride ion with p-nitrophenyl diphenyl phosphate.[8b,c] There was also a possibility that some of these dicationic detergents might not form micelles because of constraints imposed by the bridging methylene chains, or the butyne group, and therefore the critical micelle concentrations (cmc) were also measured. We found that these dicationic detergents were sometimes catalytically active at very low concentrations and more effective than CTABr.

Experimental Section

Materials.—The N,N'-tetramethyldiamines were commercial products (Aldrich) and were redistilled before use. They were quaternized with a 10% excess of cetyl bromide in refluxing ethanol under nitrogen for 2–3 days (12 days for the ethane derivative, Ia). The detergents were precipitated with ether after evaporation of the bulk of ethanol, washed well with ether, and recrystallized from aqueous ethanol. The values of the cmc and the elemental analyses are given in Table I.

In order to make certain that both amino groups were quaternized, we showed spectrophotometrically that the reaction of hydroxide ion with the fluoro- or chloro-2,4-dinitrobenzene gave 2,4-dinitrophenol rather than the dinitroaniline which would have been formed had the solution contained free amine.

Kinetics.—The reactions were followed spectrophotometrically using a Gilford spectrophotometer with a water-jacketed cell compartment at 25.0° following methods already described.[8,12] p-Nitrophenyl diphenyl phosphate was added as a solution in purified dioxane, so that the final solution contained 0.5%

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(2) Recipient of an award under Project Catalyst of the American Chemical Society.

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Bridging group	10^5 cmc, M^a	Formula	Calcd, % C	H	N	Br	Found, % C	H	N	Br
Ia ethane	1	$C_{38}H_{82}N_2Br_2H_2O$	61.3	11.4	3.8	21.4	61.5	11.5	3.8	21.9
	1.4^b									
	1.0^c									
Ib butane	3	$C_{40}H_{86}N_2Br_2H_2O$	62.2	11.5	3.6	20.7	61.9	11.7	3.5	20.9
	3.2^b									
	3.5^c									
Ic hexane	7	$C_{42}H_{90}N_2Br_2$	64.4	11.5	3.6	20.3	64.5	11.8	3.7	20.7
	6.5^b									
	7.0^c									
	6.5^d									
II butyne	1	$C_{40}H_{82}N_2Br_2$	64.0	11.1	3.7	21.3	63.9	11.1	3.7	21.0

^{a} Measured using the dye method unless specified; addition of 10^{-5} M p-nitrophenyl diphenyl phosphate and 0.5 vol % dioxane did not change the cmc of Ia. ^{b} Measured by surface tension. ^{c} In the presence of 0.01 M NaOH. ^{d} In the presence of 0.01 M NaF.

dioxane, and for the reaction in which fluoride ion was the nucleophile the solution was maintained at pH 9.0 using 0.01 M sodium borate. The concentrations of the substrates were $<10^{-5}$ M. The first-order rate constants, k_ψ, sec^{-1}, were calculated graphically, and the second-order rate constants, k_2, are in l. mol^{-1} sec^{-1}.

Critical Micelle Concentrations.—The values of the cmc were determined by the dye method,[11,13,14] using bromophenol blue (Table I). We also attempted to determine the cmc conductometrically[11,15] but were unable to observe breaks in plots of equivalent conductance against concentration characteristic of micellization, probably because the free detergent is a weak electrolyte. Because of the low cmc's we were unable to use viscosity measurements for determining them, but in favorable cases the cmc can be determined by surface tension measurements.[11] Plots of the surface tension against log C_D (where C_D is the detergent concentration) decreased with increasing C_D to a sharp break at the cmc, and then remained constant up to concentrations several fold greater than the cmc. The surface tension was measured conventionally by De Ncuy's method.

Results

The rate constants are shown as a function of detergent concentration in Figures 1 and 2 and Tables II-VI.

TABLE II

REACTION OF HYDROXIDE ION WITH
p-NITROPHENYL DIPHENYL PHOSPHATE^a

$10^4 C_D$, M	Detergent Ib	Ic
5.00	9.58	13.2
7.50		10.5
8.00	7.67	
10.0	7.39	9.16
20.0	5.84	6.86

^{a} Values of k_2, l. mol^{-1} sec^{-1}, at 25.0° with 0.01 M NaOH and high concentrations of Ib,c.

(Note the break in the scale of Figure 2 which allows the plot to cover a wide range of detergent concentration.) The results for reactions of p-nitrophenyl diphenyl phosphate are given in Figures 1 and 2, Table II includes rate constants at higher concentrations of Ib,c, and Table III gives rate constants in the presence of II. These results show that very low concentrations of detergent have little kinetic effect. Tables IV-VI give rate constants for reactions of the halobenzenes. Neither of the detergents Ia or II derived from the

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Figure 1.—Catalysis by dicationic detergents of the reaction of 0.01 M sodium hydroxide with p-nitrophenyl diphenyl phosphate at 25.0°: ◇, Ia; □, Ib; ○, Ic.

Figure 2.—Catalysis by cationic detergents of the reaction of 0.01 M sodium fluoride with p-nitrophenyl diphenyl phosphate at 25.0° and pH 9.0: ◆, Ia; ■, Ib; ●, Ic.

ethane- and butyneamines were effective catalysts of the reaction of hydroxide ion with chloro- and fluoro-2,4-dinitrobenzene (Tables IV and VI). Both of these detergents are less soluble than CTABr and the detergents (Ib,c) derived from the butane- and hexanediamines, and little catalysis was observed within the concentration limits imposed by solubility; this factor pre-

TABLE III

REACTIONS OF *p*-NITROPHENYL DIPHENYL PHOSPHATE
WITH HYDROXIDE AND FLUORIDE IONS[a]

	Reagent			Reagent	
10^4C_D, M	OH⁻	F⁻	10^4C_D, M	OH⁻	F⁻
0	4.83	1.05	1.50	31.6	64.9, 68.1
0.01		0.99	2.00	47.8	70.9
0.02		1.00	2.50		89.1
0.05		1.40	3.00	56.8	94.8
0.25		32.0	3.50	45.5	97.2
0.50	5.60	40.6	4.00	61.5	92.4
1.00	13.2	60.9	4.50	53.0, 61.7	88.1

[a] Values of $10k_2$ l. mol⁻¹ sec⁻¹, with 0.01 M nucelophile at 25.0°, with II.

TABLE IV

REACTION OF HYDROXIDE ION WITH
FLUORO-2,4-DINITROBENZENE[a]

	Detergent		
10^4C_D, M	Ia	Ib	Ic
	0.12	0.12	0.12
0.20	0.21	0.47	
0.30	0.24		0.52
0.40	0.37		
0.50	0.41	1.17	0.87
0.60	0.41		
0.75	0.39		1.43
0.90	0.34		
1.00	0.34	2.03	2.09
1.40	0.27		
1.60	0.24		
2.00		2.84	
3.00			4.78
3.00		3.84	
5.00		7.28	6.87
7.50			9.24
10.0		9.98	12.0
20.0		13.3	
30.0		16.0	14.3
36.0		16.9	14.2
50.0		17.2	
70.0		17.9	14.2

[a] Values of k_2, l. mol⁻¹ sec⁻¹ at 25.0° and 0.01 M NaOH.

TABLE V

REACTION OF HYDROXIDE ION WITH
CHLORO-2,4-DINITROBENZENE[c]

	Detergent		
10^4C_D, M	Ia	Ib	Ic
0	1.4	1.4	1.4
0.10	1.6	6.36	
0.25	3.4	13.8	7.4
0.40	4.0[b]		
0.50		28.4	14.9
0.75		40.0	24.0
1.00		70.6	34.6
1.50			54.4
2.50		152	76.4
5.00		169	137
7.50		198	168
10.0		212	207
20.0		255	220
36.0		244	
50.0		238	208
60.0		205	206

[a] Values of 10^4k_2, l. mol⁻¹ sec⁻¹, at 25.0° and 0.05 M NaOH; with 1×10^{-5} M II, $10^4k_2 = 1.5$ l. mol⁻¹ sec⁻¹. Higher detergent concentrations could not be used because of the low solubility of II in 0.05 M NaOH. [b] Precipitation occurred at higher concentrations of Ia.

TABLE VI

REACTION OF FLUORO-2,4-DINITROFLUOROBENZENE
WITH HYDROXIDE ION[a]

10^4C_D, M	$10k_2$, l. mol⁻¹ sec⁻¹
0	1.20
0.05	0.90
0.10	1.20
0.15	1.00
0.20[b]	1.14

[a] With II and 0.01 M NaOH at 25.0°. [b] Precipitation occurred at this and higher concentrations.

vented our studying some of these reactions in detail over a range of detergent concentrations.

Critical Micelle Concentrations.—For all these dicationic detergents the values of the cmc are much lower (Table I) than those found for a cationic detergent such as CTABr for which cmc $\approx 10^{-3}$ M[11] (the actual value depends upon the medium and the method of measurement).

The cmc values were first obtained using a dye which could affect micellization,[11,14] particularly because the cmc is sometimes not much larger than the dye concentration of $1-10 \times 10^{-5}$ M. (Lower dye concentrations were used with those detergents which had the lowest cmc.) Although the dye method is not particularly reliable, the cmc values using this method and that of surface tension are in reasonable agreement.

We generally observed catalysis at detergent concentrations considerably below the cmc. We therefore measured the cmc under conditions corresponding more closely to those used in the kinetic runs and found little change in the cmc (Table I).

Quantitative Treatment of the Rate Data.—It is generally assumed that micellar catalysis and in-

hibition of the substrate, S, with X⁻ can be interpreted in terms of the following scheme[5,7a,8]

$$D_n + S \underset{}{\overset{K}{\rightleftharpoons}} SD_n$$

$$X^- \downarrow k_2^w \quad X^- \downarrow k_2^m$$

products

leading to the rate equation

$$k_2 = \frac{k_2^w + k_2^m(K/N)(C_D - \text{cmc})}{1 + (K/N)(C_D - \text{cmc})} \quad (1)$$

where C_D is the detergent concentration and N the aggregation number. Equation 1 can be written as[7a]

$$\frac{1}{k_2 - k_2^w} = \frac{1}{k_2^m - k_2^w} + \frac{N}{(k_2^m - k_2^w)K(C_D - \text{cmc})} \quad (1a)$$

This treatment assumes that only one substrate molecule is incorporated into each micelle, D_n, an assumption which is reasonable when the micelles are in a large excess over the substrate. It has been used successfully for a number of spontaneous reactions but cannot be applied in any simple way for many reactions which involve an external ionic reagent, because these reactions generally lead to rate maxima in plots of rate constant against detergent concentration,[4,5,8,16] whereas eq 1 predicts a rate plateau. These rate maxima have

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	Detergent									
	CTABr		Ia		Ib		Ic		II	
Reaction[b]	k_r	C_D (max)	k_r	C_D (max)	k_r	C_D (max)	k_r	C_D (max)	k_r	C_D (max)
$ArOPO(OPh)_2 + OH^-$	11	4×10^{-3}	15	5×10^{-5}	30	2×10^{-4}	28	3×10^{-4}	12	4×0^{-4}
$ArOPO(OPh)_2 + F^-$	33	2×10^{-3}	72	7×10^{-5}	155	1×10^{-4}	182	1.5×10^{-4}	93	3.5×10^{-4}
2,4-DNFB + OH^- [c]	60	2×10^{-2}	36	6×10^{-5}	150	7×10^{-3}	120	4×10^{-3}		
2,4-DNCB + OH^- [c]	61	1.4×10^{-2}			182	2×10^{-3}	157	2×10^{-3}		

[a] In water at 25.0° k_r is the maximum relative to that in water. [b] Ar = p-nitrophenyl. [c] The rate maxima could not be reached for these reactions with some of the detergents.

been explained in terms of ionic deactivation by the micelle[8,17] (for an alternative explanation, see ref 4 and 16).

In favorable cases the binding constant, K, can be determined directly,[4,5,7b,8] but this procudure is not feasible for a number of substrates such as fluoro-2,4-dinitrobenzene where there is a slow reaction even at low pH in the presence of cationic detergents.[12]

For the reaction of hydroxide ion with fluoro-2,4-dinitrobenzene in the presence of the detergents derived from the butane- and hexanediamines (Ib,c), we unexpectedly observed plateaus rather than rate maxima in plots of rate constant against detergent concentration (Table IV). We therefore attempted to apply eq 1a to these two reactions. A major problem is that, in using eq 1a, it is necessary to assume that the cmc in the kinetic solution is that determined in the absence of substrate. This assumption is clearly unsatisfactory because in all these reactions there is extensive catalysis at detergent concentrations below the cmc (Table I). This behavior appears to be general with substrates which are strongly incorporated into the micelle, suggesting that submicellar aggregates are catalytically active or that the substrate promotes micellization.[8b,9b,15] (There is considerable evidence for promotion of micellization by added solutes.[11])

Because eq 1a cannot be used, we rewrite it as[8b]

$$\frac{k_2 - k_2^w}{k_2^m - k_2} = \frac{K}{N}(C_D - cmc) \qquad (2)$$

which can be used without making any assumptions about the cmc, except that it is constant under the reaction conditions, although it is necessary to assume that k_2^m is given by the values of k_2 in the plateau region at the high detergent concentrations, and use of eq 2 places a great deal of weight on the values of k_2 at intermediate detergent concentrations. Figure 3 illustrates the treatment for the reaction of fluoro-2,4-dinitrobenzene with 0.01 M sodium hydroxide in solutions of the dicationic detergents (Ib,c) derived from the butane and hexane diamines and gives values of $K/N \approx 1300$ and 2000, respectively.

We could not calculate K/N for fluoro-2,4-dinitrobenzene in CTABr using either kinetic or distribution methods,[12] but for chloro-2,4-dinitrobenzene in CTABr $K/N \approx 75$.[8a] (For the anionic detergent sodium lauryl sulfate, K/N is approximately the same for chloro- and fluoro-2,4-dinitrobenzene,[8a,12] and this is therefore probably true also for CTABr.) Also we do not know the value of the aggregation number, N, for micelles of these dicationic detergents, although because of methylene bridging they could well be smaller than for CTABr,

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Figure 3.—Quantitative treatment of the micellar catalyzed reaction of 0.01 M sodium hydroxide with 2,4-dinitrofluorobenzene at 25.0°: ■, Ib; ●, Ic.

but our kinetic results suggest that these micellized dicationic detergents (Ib,c) derived from the butane- and hexanediamines are much better than CTABr at binding nonpolar solutes. Even though the treatments based on eq 1 depend on a variety of assumptions and approximation, the indications of strong substrate-micelle binding are supported by the steepness of plots of rate constant against detergent concentration for all these dicationic detergents.

Discussion

In Table VII we compare the maximum rate enhancements (relative to rates in the absence of detergent) and the corresponding detergent concentrations for these dicationic detergents with those observed earlier using CTABr.[8,12] These results illustrate the greater catalytic efficiency of most of these detergents over CTABr. For most of these reactions the rate maxima are observed at lower detergent concentrations with these dicationic detergents than with CTABr.[8,12]

The critical micelle concentrations are also considerably lower with micelles derived from these dicationic detergents as compared with CTABr. Micellization occurs when hydrophobic binding overcomes the electrostatic repulsions, and bridging the quaternary ammonium residues should therefore stabilize the micelles provided that the bridging group is not so rigid as to

make it difficult for the long alkyl chains to bind together. Ethane and butyne bridging groups should impose a considerable degree of rigidity upon the detergents and make it difficult for them to form approximately spherical micelles, but even here micellization is observed and the cmc's are low. Micelles of monocationic detergents are approximately spherical,[5,11] but this may not be true with micelles of Ia and II, and evidence on the size and shape of these micelles is needed.

The fact that rate maxima or plateaus are observed at low concentrations of these dicationic detergents, relative to CTABr, indicates strong interactions between substrate and micelle. (The low cmc is also a factor, because micelles then form at low detergent concentration.) The concentrations for rate maxima are smaller by a factor of 10–100 for these dicationic detergents than for CTABr[8,12] (Table VII). This rate enhancement at low catalyst concentration is one measure of effectiveness; another is the extent of the rate enhancement. On this score also, these dicationic detergents are better micellar catalysts for some reactions than CTABr, although the relative effectiveness depends very much upon the reaction under consideration (Table VII). The dicationic detergents (Ib,c) derived from the butane- and hexanediamines are better catalysts than CTABr for all the reactions considered, but their superiority is most marked for the reaction of fluoride ion with *p*-nitrophenyl diphenyl phosphate. The bridging methylene chain which increases micellar stability could also sterically hinder approach of the anionic nucleophile to a phosphate ester at or near the micellar surface, and this hindrance could be less for an attacking fluoride than for the more strongly hydrated hydroxide ion.

The detergents Ia and II derived from the ethane- and butynediamines are no better catalysts than CTABr for the attack of hydroxide ion upon the substrates (Table VII). They are, however, very effective catalysts when fluoride is the attacking anion, as appears to be general for micelles of these dicationic detergents.

Some studies on the bipyridylium ions (III) have

R—N⁺⟨═⟩—⟨═⟩N⁺—R

III

some bearing on the properties of our dicationic detergents I and II. The dications III are very readily re-

duced to radical cations,[18] whose stabilization requires coplanarity of the rings, but, if R = cetyl, the radical cation does not form,[19] probably because bonding of the alkyl groups in a micelle forces the rings into a nonplanar skew conformation.

Catalysis by Submicellar Aggregates.—In some reactions, *e.g.*, those catalyzed by Ia, the maximum rate is observed at detergent concentrations below the cmc, *i.e.*, in a region where the detergent is apparently not micellized, and where it is not in a large excess over the substrate.

The simple treatment of micellar catalysis, eq 1, assumes that only a fully formed micelle is catalytically active, and that incorporation of the substrate does not markedly perturb the structure of the micelle.[5,7a] This treatment is rarely completely satisfactory because catalysis is often observed at detergent concentrations below the cmc, and there is evidence for the promotion of micellization by added solutes.[11,14] It seems that these effects are more than usually important for reactions catalyzed by these dicationic detergents, especially Ia.

One additional aspect of micellar catalysis by Ia is the very sharp decrease of the rate constant with increasing detergent concentration past that for the rate maximum. Although we cannot interpret the rate profiles quantitatively, this steep fall suggests that this detergent (relative to the others) interacts very strongly with the nucleophilic anion so that there is considerable deactivation of it at high detergent concentrations.

Comparison between the catalytic effectiveness of these dicationic detergents with that of CTABr brings out the way in which structural changes can affect micellar catalysis, and at present we have no explanation for the large differences in the rate enhancements of reactions which are at first sight very similar (Table VII).

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Fluoro Olefins. IV. The Stereochemistry of Nucleophilic Displacement of Chloride Ion on β-Substituted 1-Chloroperfluoro Olefins[1]

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A series of cis- and trans-β-substituted 1-chloroperfluoro olefins were treated with methoxide ion (from methanol and potassium hydroxide) in methanol at room temperature. Retention of the original cis or trans configuration was observed in all cases. The type of β substituent (aromatic or alkyl), the type of para substituent in aromatic group (electron releasing or electron withdrawing), and the size of the perfluoro alkyl group had no effect on the stereochemical results. The results of these reactions can best be rationalized by an irreversible trans addition of methoxide to the olefin to give a short-lived carbanionic intermediate followed by a rapid cis elimination of halide ion.

Vinylic halogen is normally inert toward displacement by nucleophiles, but reaction will occur if the olefin is activated by an electron-withdrawing group. A number of workers have investigated the stereochemistry of nucleophilic displacement reactions on cis–trans pairs of such olefins. Vinyl halides activated by such diverse groups as sulfone,[3-7] carbonyl,[8-10] aromatic,[11-16] and cyano[17] have been investigated. A wide variety of nucleophilic reagents have been employed in these studies, including alkoxide,[4,8,10,15-17] azide,[5] iodide,[1] thiophenoxide,[3,5,9,10,12,13,17] diphenylarsine,[14] and diphenyl phosphide[18-20] ion and amines.[6,7,17]

Displacement reactions using pure cis or trans vinyl halide usually proceeded quite stereospecifically, with retention of the original cis or trans configuration (eq 1).

$$A = \text{activating group; } Nu = \text{nucleophile; } X = \text{Cl, Br}$$

Nonstereospecific displacement of halide ion occurs when amines[6,7,17] are used as nucleophiles. This was also encountered when iodide ion[11] was used as the nucleophile, due to reversible reaction of the vinyl iodide product with other halide ion.

These reactions are usually postulated to take place *via* the addition–elimination mechanism shown in eq 2.

$$A = \text{activating group; } Nu = \text{nucleophile; } X = \text{halogen}$$

A number of workers[8,10,12,16,17] have observed clean second-order kinetics in these reactions, first order each in vinyl halide and nucleophile. In the first step of the reaction, the nucleophile adds to vinyl halide to form a carbanionic species. The addition is postulated to be irreversible,[16] with the incoming nucleophile and electron pair entering trans to the plane of the original π orbital.[8,9,11] The carbanion carbon of this intermediate species has been proposed to be either tetrahedral[8,9,11] or planar.[21] In the second step, halide ion is eliminated either in a trans fashion *via* inversion of the carbanion center and rotation through 30°,[8,9,11] or by cis elimination *via* rotation through 30°.[8,9] The stereospecificity of the reaction indicates that the carbanionic intermediate has a very short lifetime.[17] Modena[15] has found that reaction of β-fluoro-4-methoxybenzoyl-styrene with ethoxide ion is nonstereospecific due to slow breaking of the carbon–fluorine bond, yielding a relatively long-lived carbanionic species, which forms the most thermodynamically stable olefinic product. The possibility that the intermediate carbanionic species is protonated before going to product was eliminated by reaction of nucleophiles and β-halostyrenes labeled with deuterium in the α position[10] or with unlabeled β-halostyrene in deuterated ethanol.[8] No loss or incorporation of deuterium, respectively, was found to occur.

In the reaction of certain activated β-halostyrenes with an α hydrogen, an elimination–addition mechanism may be operative. Modena[10,22] observed that the very basic nucleophile, methoxide ion, reacted with cis-4-methoxybenzoyl-β-bromo- (or chloro-) styrene to substitute halide ion as shown in eq 3. In the corresponding trans isomer, the reaction proceeds *via* the normal addition–elimination sequence, due to the unfavorable cis elimination of hydrogen halide that would have to occur for the elimination–addition mechanism to operate. A whole spectrum of other mechanisms have also been proposed, including direct sub-

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(2) National Institutes of Health Predoctoral Fellow, 1965–1968.
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$$p\text{-}CH_3OC_6H_4CO \diagdown C = C \diagup Br(Cl) \quad + CH_3O^- \xrightarrow{-HBr}$$
$$H \diagup \quad \diagdown H \qquad\qquad p\text{-}CH_3OC_6H_4COC\equiv CH \quad (3)$$

$$p\text{-}CH_3OC_6H_4COC\equiv CH + CH_3O^- \longrightarrow \longrightarrow$$
$$p\text{-}CH_3OC_6H_4COCH=CHOCH_3$$

stitution and a concerted mechanism. These are summarized by Miller[11] and Jones[8] among others.

Vinyl halides activated by polyfluorinated alkyl groups are also useful for this type of study. However, only a few reports have appeared describing the stereochemistry of nucleophilic displacement on such olefins. Park[23] has examined the reaction of alkoxide ion with *cis*- and *trans*-2,3-dichlorohexafluoro-2-butene. Displacement of chloride ion on the cis isomer occurred with greater than 90% stereospecificity; displacement of chloride ion on the trans isomer was approximately 70% stereospecific. Displacement proceeded with retention of the original cis or trans configuration (eq 4).

$$F_3C \diagdown C=C \diagup CF_3 \quad + RO^- \longrightarrow$$
$$Cl \diagup \quad \diagdown Cl$$

$$F_3C \diagdown C=C \diagup CF_3 \quad + Cl^- \text{ (90\% plus)}$$
$$Cl \diagup \quad \diagdown OR$$

$$F_3C \diagdown C=C \diagup Cl \quad + RO^- \longrightarrow$$
$$Cl \diagup \quad \diagdown CF_3$$

$$F_3C \diagdown C=C \diagup OR \quad + Cl^- \text{ (approx 70\%)}$$
$$Cl \diagup \quad \diagdown CF_3$$

$$R = CH_3-, C_2H_5-, i\text{-}C_3H_7-$$

(4)

The authors concluded that alkoxide substitution on these olefins is governed by kinetic control. They postulated the formation of a planar carbanion as the reaction intermediate, which eliminated chloride ion stereospecifically, since rotation was prevented by the bulky trifluoromethyl groups. A similar investigation was carried out on these compounds using sodium borohydride in diglyme and lithium aluminum hydride in ether as nucleophiles.[24] Sodium borohydride reacted much more stereospecifically with the cis isomer than the trans isomer; displacement of chloride ion by hydride (as borohydride) ion took place 99% stereospecifically with the cis isomer with retention of configuration, but only 55% stereospecifically, with retention of configuration, with the trans isomer. Lithium aluminum hydride reacted less stereospecifically with cis starting material than did sodium borohydride, but more stereospecifically with the trans isomer. Fontanelli and coworkers[25] have investigated the reaction of 1-hydroperfluoropropene with alkoxide ion. They concluded that the stereochemical course of the reaction was "cis stereospecific."

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(24) R. T. Bogan and D. J. Burton, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, p K 29.
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Results and Discussion

Because of this rather small number of reports on the stereochemical course of nucleophilic displacement reactions on polyfluorinated olefins, and because we had model compounds available,[26,27] it became desirable to us to make such an investigation. Several cis and trans β-substituted 1-chloroperfluoro olefins were used as model polyfluorinated olefins; methoxide ion, generated *in situ* from the dissolution of potassium hydroxide in methanol, was used as the nucleophilic reagent. The β substituent and the size of the perfluoroalkyl group were both varied to determine what effect, if any, these would have on the overall stereochemistry of the displacement reaction. The general procedure used in these displacement reactions involved adding a solution of potassium hydroxide in methanol to a stirred solution of an equimolar amount of olefin (*vs.* potassium hydroxide) in methanol. The reaction was normally carried out at room temperature.

When methoxide ion was allowed to react with pure cis or trans olefin, chloride ion was displaced 90–96% stereospecifically. Retention of the original cis or trans configuration was always observed (eq 5). The

$$AR(R) \diagdown C=C \diagup Cl \quad + CH_3O^- \longrightarrow$$
$$R_f \diagup \quad \diagdown F$$
$$\text{A}$$

$$AR(R) \diagdown C=C \diagup OCH_3 \quad + Cl^-$$
$$R_f \diagup \quad \diagdown F$$
$$\text{I}$$

$$AR(R) \diagdown C=C \diagup F \quad + CH_3O^- \longrightarrow$$
$$R_f \diagup \quad \diagdown Cl$$
$$\text{B}$$

$$AR(R) \diagdown C=C \diagup F \quad + Cl^-$$
$$R_f \diagup \quad \diagdown OCH_3$$
$$\text{II}$$

(5)

reaction was quite clean; yields of methoxy product from chloride ion displacement ranged as high as 77%; only 3–4% yield each of products arising from displacement of fluoride ion or both fluoride and chloride ion were observed. The stereochemical results of these reactions is summarized in Table I. Cis–trans isomer

TABLE I

RESULTS OF REACTION OF METHOXIDE ION WITH
VARIOUS β-SUBSTITUTED 1-CHLOROPERFLUORO OLEFINS

AR(R)	Registry no.	Rf	Isomer	% I	% II
C_6H_5	19302-03-5	CF_3	A	96	4
	19302-02-4		B	4	96
C_6H_5	24165-18-2	C_2F_5	A	90	10
	24165-19-3		B	9	91
$p\text{-}ClC_6H_4$	19302-07-9	CF_3	A	94	6
	19302-06-8		B	8	92
$p\text{-}CH_3OC_6H_4$	19302-11-5	CF_3	A	92	8
	19302-10-4		B	6	94
$c\text{-}C_6H_{11}$	24164-52-1	CF_3	A	96	4
	24277-52-9		B	4	96

ratios (and yields) were determined by glpc analysis of the reaction mixture, and the absolute configuration of the methoxy product was determined by ^{19}F nmr spectroscopy (Table II). *cis*-Vinylfluorine–$CF_3(CF_2X)$ coupling constants were in the range of 24–27 cps, and the corresponding trans coupling constants were in the

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Table II
¹⁹F and ¹H Nmr[a] Data on β-Substituted 1-Methoxyperfluoro Olefins

$$AR(R)C(CF_2X)=CFOCH_3$$

AR(R)	X	Registry no.	(1) Isomer	J (1),(2)	(2) (3) φ (1)	φ (2)	J (2),(3)	δ (3)
C_6H_5	F	29799-98-2	A	24	81.7	57.2	1.0	3.57
		29799-99-3	B	13	80.0	57.2	0.9	3.71
C_6H_5	CF_3	29800-00-8	A	26	79.8	108.3	1.0	3.57
		29800-01-9	B	10	75.3	108.0	1.0	3.78
p-ClC_6H_4	F	29800-02-0	A	24	81.4	57.1	1.1	3.63
		29800-03-1	B	13	80.8	57.7	1.0	3.79
p-$MeOC_6H_4$	F	29800-04-2	A	24	80.7	56.8	1.0	3.68
		29800-05-3	B	13	79.4	57.3	0.9	3.83
c-C_6H_{11}	F	29800-06-4	A	27	82.8	57.4	1.0	3.75
		29800-07-5	B	13	81.9	58.0	1.0	3.76

[a] The chemical shift values are expressed in ϕ values in parts per million upfield from CCl_3F or in δ values in parts per million downfield from tetramethylsilane, and the coupling constant values are in cycles per second.

range of 10–13 cps. This is in agreement with data on similar compounds published by Swalen[28] and Stone.[29] Both infrared and elemental analysis are also in agreement with the assigned structures.

The method used for methoxide ion generation did not affect the stereochemical course of the reaction. Potassium methoxide generated from potassium metal and dry methanol displaced chloride ion with exactly the same stereochemistry and stereospecificity as did potassium methoxide generated from potassium hydroxide and methanol (eq 6).

(6)

As Table I illustrates, the overall stereochemical course and stereospecificity of the displacement reaction is largely unaffected by changing either of the substituents attached to the β-olefinic carbon. Thus, the reaction is not affected by electron-releasing or -withdrawing groups on the phenyl ring or by substitution of an aliphatic group in place of the phenyl ring. Furthermore, it is also largely unaffected by increasing the size of the perfluoroalkyl group from perfluoromethyl to perfluoroethyl. The only difference observed was a lower reactivity of the cyclohexyl substituted olefin toward the methoxide ion. Reaction required refluxing overnight, whereas the corresponding aryl-substituted olefins required only stirring for several hours at room temperature to effect reaction.

The stereochemical course of these reactions can be best rationalized by postulating an irreversible trans addition of the incoming nucleophile and electron pair across the double bond to form an unstable (short-lived) carbanionic species in the first step. Rapid cis elimination of chloride ion in the second step then forms the product methoxy olefin (eq 7).

The fact that no evidence of cis–trans isomerization was observed in recovered starting olefin demonstrated irreversible addition of nucleophile. Cis elimination of halide ion, although not common, has been documented;[30,31] a carbanionic intermediate is proposed for such cis eliminations. The possibility of protonation of the carbanionic intermediate, followed by elimination of hydrogen chloride to form product olefin, is unlikely because of the high stereospecificity observed for both isomers. Protonation would allow rotation to take place, yielding the most thermodynamically favorable isomer or isomer ratio (eq 8). The alternative possibility of cis addition of nucleophile followed by trans elimination of chloride ion does not appear likely, since both the initial addition and the following elimination would cause eclipsing of the attached groups (eq 9).

Further, if rotation occurred, the overall reaction would not be so stereospecific as the data indicate, since rotation would allow time for the carbanion to equilibrate (invert); rotation in addition requires the carbanion to be reasonably stable (long-lived), which also does not seem very likely. Indirect proof for this assumption

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(29) J. D. Swalen and C. A. Reily, *J. Chem. Phys.*, **34**, 2122 (1961).

(30) S. J. Cristol and N. L. House, *J. Amer. Chem. Soc.*, **74**, 2193 (1952).
(31) S. J. Cristol and R. P. Argan Bright, *ibid.*, **79**, 3441 (1957).

was provided by reaction of 2-phenylperfluoro-1-butene with methoxide ion (eq 10). If the intermediate car-

$$C_6H_5C(C_2F_5){=}CF_2 + CH_3O^- \longrightarrow C_6H_5C \underset{\diagdown}{\overset{\diagup}{}} \begin{matrix} CF_2OCH_3 \\ \\ CF_2CF_3 \end{matrix} \quad (10)$$
$$\underset{V}{}$$

$$V \longrightarrow \underset{VI}{C_6H_5C(C_2F_5){=}CFOCH_3} + \underset{VII}{C_6H_5C(CF_2OCH_3){=}CFCF_3}$$

banion V is reasonably long-lived (stable), the more thermodynamically stable compound VII should be the predominant product; experimentally, the product consisted of 50% VI and 50% VII. This ratio would occur if the intermediate carbanion V was unstable (short-lived) and eliminated fluoride ion in a statistical fashion from the $-CF_2OCH_3$ or $-CF_2CF_3$ group. Product ratios were determined by glpc analysis of the reaction mixture; structures were determined by ^{19}F nmr spectroscopy. The observed stereochemistry of the displacement reaction rules out trans addition–trans elimination or cis addition–cis elimination mechanisms.

Experimental Section

A. Reaction of β-Substituted 1-Chloroperfluoro Olefins with Methoxide Ion.—Into a 100-ml three-necked round-bottom flask equipped with a magnetic stirrer, reflux condenser, and pressure-equalized dropping funnel was placed 0.009 mol (*ca.* 2 g) of pure cis or trans olefin and 10 ml of methanol. Stirring was started and a solution of 0.6 g (85% pure) of potassium hydroxide (0.009 mol) in 8 ml of methanol was added dropwise. The resulting mixture was allowed to stir an additional 3 hr at room temperature and then poured into 100 ml of water. The resulting mixture was extracted twice with 30-ml portions of ether, which were combined, washed three times with 25-ml portions of water, and dried over anhydrous magnesium sulfate. Product yields

were determined using an external standard of the corresponding methoxy compound employing a 6-ft 10% silicone rubber on Gas-Chrom P analytical column, and cis–trans isomer ratios were determined using a 6-ft 10% Carbowax 20M or Chromosorb P analytical column. Fluorine nmr spectroscopy was used to assign the absolute configuration of products.

B. Reaction of $C_6H_5C(CF_3){=}CFCl$ (Phenyl and Chlorine Trans) with Potassium Methoxide Generated from Potassium Metal and Methanol.—In a 50-ml three-necked round-bottom flask equipped with a magnetic stirrer, reflux condenser, and dropping funnel was placed 3 ml of methanol (dried by distillation from CaO), and 0.5 g (0.0022 mol) of pure $C_6H_5C(CF_3){=}CFCl$ (phenyl and chlorine trans). Into this solution was added dropwise 2 ml of methanol (dried by distillation from CaO), in which 0.087 g (0.0022 g-atom) of potassium metal had been dissolved. The resulting mixture was allowed to stir an additional 3 hr at room temperature and then worked up as in part A. Glpc analysis on the Carbowax 20M column (see part A) demonstrated that 96% of the $C_6H_5C(CF_3)C{=}CFOMe$ formed existed as the isomer bearing the phenyl and methoxy groups trans, while the remaining 4% existed as the corresponding cis isomer. Recovered starting material was unisomerized.

C. Reaction of $C_6F_5C(C_2F_5){=}CF_2$ with Methoxide Ion.—Into a 50-ml one-necked flask was placed 10 ml of methanol and 1.2 g (0.005 mol) of $C_6F_5C(C_2F_5){=}CF_2$.[32] To the resulting mixture was added 0.3 g (85% pure, 0.005 mol) of potassium hydroxide. The resulting mixture was stirred an additional 1 hr and then subjected to work-up (see part A). Glpc analysis of the dried ether extract on the silicone rubber column (see part A) showed that the product consisted of a 50:50 mixture of $C_6H_5C(C_2F_5){=}CFOCH_3$ and $C_6H_5C(CF_2OCH_3){=}CFCF_3$. Structural assignments were obtained *via* fluorine nmr spectroscopy. When a similar mixture was allowed to reflux for 6 hr, the corresponding product ratio was 52:48.

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Stable Carbocations. CXX.[1] Preparation of Alkyl (Aryl) Carbenium Ions from Olefins

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Experimental conditions have been found for protonation of olefins in superacids to form stable carbenium ions without concomitant polymerization.

Cationic polymerization generally occurs when treating reactive olefins with strong acids.[2] The first step in cationic polymerization of olefins is assumed to be protonation of the double bond to form a carbenium ion. Intermediate carbenium ions, however, have never been observed in cationic polymerizations. Carbenium ions formed react immediately with excess of

monomer olefin in the fast chain propagation reaction. Termination of the polymer chain generally takes place by transfer reaction or elimination. Stable alkyl (aryl) carbenium ions can be generated by ionization of different precursors in strong acids,[3] but protonation of olefins, although proceeding with ease, generally yields complex mixtures. There are qualitative claims in the literature concerning generation of stable carbenium ions by protonation of phenyl- and methyl-substituted olefins.[4-7] However, it has never been shown that these reactions can lead to the clean formation of the

(1) (a) Part CXIX: G. A. Olah, P. R. Clifford, and Y. Halpern, *J. Amer. Chem. Soc.*, in press. Note change in title of series of publications to "Stable Carbocations," instead of previously used "Stable Carbonium Ions." Carbonium ions, as outlined in part CXVIII, are pentacoordinated ions as contrasted with trivalent carbenium ions. The general naming of carbocations (in accordance with the naming of carbanions) seems to be appropriate. (b) Concerning the definition and naming of carbocations (the generic name for all cations of carbon compounds, as carbanion are the anions), we recently suggested a clear differentiation between trivalent carbenium (and/or carbynium) and penta- and tetracoordinated carbonium ions: G. A. Olah, *ibid.*, in press.

(2) S. Bywater, in "Chemistry of Cationic Polymerization," P. H. Plesch, Ed., Pergamon Press, New York, N. Y. 1963, p. 311.

(3) G. A. Olah and J. A. Olah in "Carbonium Ions," Vol. II, G. A. Olah and P. v. R Schleyer, Ed., Interscience, New York, N. Y., 1970, Chapter 17.

(4) V. Gold and F. L. Tye, *J. Chem. Soc.*, 2172 (1952).

(5) D. G. Farnum, *J. Amer. Chem. Soc.*, **89**, 2970 (1967).

(6) H. C. Den., C. U. Pittman, Jr., and J. O. Turner, *ibid.*, **87**, 2154 (1965).

(7) (a) D. M. Brouwer, *Recl. Trav. Chim. Pay-Bas* **87**, (3), 210 (1968); (b) D. M. Brouwer and E. L. Mackor, *Proc. Chem. Soc., London*, 147 (1964).

expected cations, without concurrent formation of complex mixtures of cyclized or polymeric cations and other polymeric materials. For years in our laboratory attempts were made to clearly generate stable monomeric carbenium ions by protonation of olefins. It became obvious that one must find proper conditions to minimize the possibility of reaction between the carbenium ion and excess olefin.

We have now succeeded in finding the conditions which allow the formation of stable monomeric carbenium ions as the only or predominant product in high yields of the protonation of olefins in superacids. We should emphasize that there is not a single general procedure which can be applied to any olefin, but specific conditions have to be used in each case. The purpose of this paper is to describe characteristic procedures for the preparation of different types of carbenium ions by protonation of olefins.

Results and Discussion

A. Diphenylbenzylcarbenium Ion (1).—Attempts to generate ion 1 by protonation of triphenylethylene with HSO_3F–SbF_5 (either in SO_2 or SO_2ClF solution) at low temperatures were unsuccessful. On the other hand, slow addition of an SO_2 (or SO_2ClF) solution of triphenylethylene to tenfold molar excess of HSO_3F in the same solvent results in the formation of a pale red solution whose pmr spectrum is identical with that previously reported for ion 1.[8] By quenching cation 1 with H_2O–KOH, 1,1,2-triphenylethanol is obtained in about 80% yield.

$$(C_6H_5)C{=}CHC_6H_5 \xrightarrow[-80°]{HSO_3F-SO_2(SO_2ClF)}$$

$$(C_6H_5)_2\overset{+}{C}CH_2C_6H_5 \xrightarrow[-80°]{KOH-H_2O} (C_6H_5)_2\overset{OH}{\underset{|}{C}}CH_2C_6H_5$$

B. Diphenylmethylcarbenium Ion (2).—Attempted protonation of 1,1-diphenylethylene by HSO_3F–SbF_5 (1:1) or HF–SbF_6 (1:1) in SO_2 or SO_2ClF solution results in dark red somewhat viscose solutions whose pmr spectra show only very broad absorption peaks due to polymeric materials. However, addition of 1,1-diphenylethylene to HSO_3F (in SO_2 or SO_2ClF), using the same technique as above, gives a clear red solution whose pmr spectrum is identical with that reported previously for ion 2.[9]

C. Phenyldimethylcarbenium Ion (3).—Difficulties arise in producing ion 3 by protonation of α-methylstyrene, not because of the instability of the ion but because of the highly nuceophilic character of the olefin[2] causing polymerization. This difficulty is not overcome by the very slow addition of dilute solution of the olefin to the acid at low temperature. On the other hand, by dissolving the olefin in a solvent (CS_2) which is immiscible with the acid solution and adding the solution of the olefin to the acid at low temperature reaction occurs only in the contact layer. The protonated olefin so formed is immediately extracted into the acid layer and its chance to react with additional olefin is minimized. By applying this procedure to the

protonation of α-methylstyrene, using HF–SbF_5 (5:1) as the acid, phenyldimethylcarbenium ion 3 is formed and shows an identical spectrum as reported previously.[5,6,9,10]

$$C_6H_5\underset{\underset{CH_3}{|}}{C}{=}CH_2 \text{ (in } CS_2) \xrightarrow[-80°]{HF-SbF_5\ (5:1)-SO_2ClF} C_6H_5\overset{+}{\underset{\underset{CH_3}{|}}{C}}CH_3$$

D. Dimethylethylcarbenium Ion (4).—By slow, careful addition of dilute solutions of 2-methyl-2-butene in SO_2 or SO_2ClF to various ratios of HSO_3F–SbF_5 or HF–SbF_6 in either SO_2 or SO_2ClF at low temperature, almost no polymeric product is formed. The clear solutions obtained exhibit pmr spectra which indicate the presence of three cations: the expected dimethylethylcarbenium ion (4) as well as dimethylisopropylcarbenium ion (5) and trimethylcarbenium ion (6). By varying the relative molar ratio of HSO_3F–SbF_5 and HF–SbF_6, different ratios of the cations are obtained. The highest ratio of *tert*-amyl$^+$–*tert*-hexyl$^+$ (12:1) is obtained by using HF–SbF_6 (5:1). The presence of *tert*-hexyl and *tert*-butyl cations in this reaction mixture indicates that some of the *tert*-amyl$^+$ cation reacts with excess isopentene to form a dimeric ion (C_{10} species) which is then cleaved by the strong acid to form *tert*-butyl and *tert*-hexyl cations, or two *tert*-amyl cations.

$$\underset{CH_3}{\overset{CH_3}{>}}C{=}C\underset{CH_3}{\overset{H}{<}} + HF{-}SbF_5 \xrightarrow[-80°]{SO_2ClF} CH_3\overset{+}{\underset{\underset{CH_3}{|}}{C}}CH_2CH_3$$

$$(CH_3)_2\overset{+}{C}CH_2CH_3 + (CH_3)_2C{=}CHCH_3 \longrightarrow [C_{10}H_{21}]^+$$

$$\downarrow HF{-}SbF_5$$

$$tert\text{-butyl}^+ + tert\text{-hexyl}^+ \quad 2\ tert\text{-amyl}^+$$

E. Dimethylisopropylcarbenium Ion (5).—A mixture of *tert*-hexyl cations is formed by ionizing hexyl halides or alcohols, or hexane itself with superacids.[7,11,12] The distribution of the three tertiary isomers is temperature dependent. Below −60° the unrearranged *tert*-hexyl cations are formed from the appropriate tertiary isohexane precursors. Raising the temperature results in increasingly converting the slightly less stable isomers (methyldiethyl and dimethyl-*n*-propylcarbenium ions) into the more stable dimethylisopropylcarbenium ion.[12] The expected unrearranged dimethylisopropylcarbenium ion (5) is formed only in minor amounts together with a higher yield of *tert*-butyl and *tert*-amyl cations when treating a dilute SO_2 (or SO_2ClF) solution of 2,3-dimethyl-2-butene with various superacid systems (varying ratios of HSO_3F–SbF_5 or HF–SbF_6 in SO_2 or SO_2ClF) at −80°. Results show that under these reaction conditions a large portion of the initially formed *tert*-hexyl cation reacts further with excess unprotonated olefin to produce polymeric ions which are cleaved subsequently by the superacid to form the more stable *tert*-butyl and *tert*-amyl cations. On the other hand, addition of a solution of 2,3-dimethyl-2-butene in SO_2ClF to a fivefold molar excess of HF–SbF_6 (5:1)–SO_2ClF at −120° results in

(8) G. A. Olah, C. U. Pittman, Jr., E. Namanworth, and M. B. Comisarow, *J. Amer. Chem. Soc.*, **88**, 5571 (1966).

(9) G. A. Olah, *ibid.*, **86**, 932 (1964).

(10) D. G. Farnum, *ibid.*, **86**, 934 (1964).

(11) G. A. Olah, J. Sommer, and E. Namanworth, *ibid.*, **89**, 3576 (1967).

(12) G. A. Olah and J. Lukas, *ibid.*, **89**, 4739 (1967).

the almost exclusive formation of the dimethylisopropylcarbenium ion. The pmr spectrum of this reaction mixture shows the only impurity to be the *tert*-butyl cation. By adding a dilute SO_2ClF solution of 2,3-dimethyl-2-butene to a fivefold excess of HF in the same solvent at $-80°$, 2,3-dimethyl-2-fluorobutane is obtained. Addition of excess SbF_5 in the same solvent leads to the almost exclusive formation of dimethylisopropylcarbenium ion. Based on these results an addition–elimination mechanism is probable in the reaction at $-120°$.

$$(CH_3)_2C = C(CH_3)_2 + HF \xrightarrow[-80°]{SO_2ClF}$$

$$(CH_3)_2CHCF(CH_3)_2 \xrightarrow[-80°]{SbF_5-SO_2ClF}$$

$$(CH_3)_2CH\overset{+}{C}(CH_3)_2 \rightleftharpoons (CH_3)_2\overset{+}{C}CH(CH_3)_2$$

F. Trimethylcarbenium Ion (6).—By adding an SO_2ClF solution of isobutylene into a fivefold molar excess of $HF-SbF_5$ (5:1)–SO_2ClF at $-80°$, a clear, pale yellow solution is obtained whose pmr spectrum shows it to be almost exclusively the trimethylcarbenium ion.

$$\overset{\overset{\displaystyle CH_3}{|}}{CH_3C} = CH_2 + HF-SbF_6 \ (5:1) \xrightarrow[-80°]{SO_2ClF} (CH_3)_3C^+$$

G. Dimethyl-*tert*-butylcarbenium Ion (7).—Protonation of 2,3,3-trimethyl-1-butene by $HF-SbF_5$ (5:1) in SO_2ClF leads to the formation of the expected dimethyl-*tert*-butylcarbenium ion, together with some *tert*-butyl cation as the only impurity. The fact that raising the temperature of the solution of the cations decreases the concentration of the *tert*-heptyl cation while increasing the concentration of the *tert*-butyl cation indicates that the *tert*-heptyl cation is cleaved by the strong acid to the more stable *tert*-butyl cation.

H.—In the protonation of 2,4,4-trimethyl-2-pentene and 2,4,4-trimethyl-1-pentene, the expected product is the **dimethylneopentylcarbenium ion (8)**. In both cases protonation with $HF-SbF_5$ (5:1) in SO_2ClF results, however, only in the formation of the *tert*-butyl cation. This indicates that either both protonation of the double bond of the olefin and protolysis of the C_3–C_4 bond in cation 8 occurs[13] or that β cleavage of the dimethylneopentylcarbenium ion is fast.

$$\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3 \quad CH_3}{| \quad |}}{CH_3C}} = CHCCH_3$$

or

$$\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3 \quad CH_3}{| \quad |}}{CH_2}} = CCH_2CCH_3$$

$$\xrightarrow[SO_2ClF]{HF-SbF_5 \ (5:1)} \underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3 \quad CH_3}{| \quad |}}{CH_3CCH_2CCH_3}} \xrightarrow{H^+} 2CH_3\overset{+}{C} \overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{|}}$$
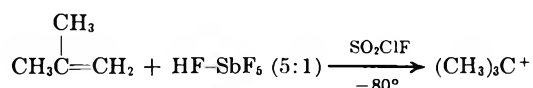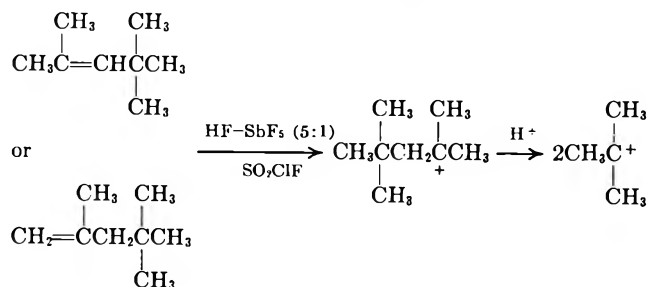
(13) G. A. Olah, Y. Halpern, J. Shen, and Y. K. Mo., *J. Amer. Chem. Soc.*, **93**, 1251 (1971).

I. Methylcarbenium Ion, Ethyl Cation (9).—Ethyl cation 9 has only recently been indicated to exist in the equilibrating $CH_3CH_2F \rightarrow SbF_5$ system in SO_2 solution.[14] When ethylene is treated with HSO_3F-SO_2ClF at $-80°$, a clear solution is obtained which exhibits the pmr spectrum of ethylfluorosulfonate, $CH_3CH_2OSO_2F$, consisting of a quartet at 5.1 ppm ($J = 7.5$ Hz) and a triplet at 1.7ppm ($J = 7.5$ Hz) for the methylene and methyl groups, respectively. Performing the reaction in $HF-SbF_5$ (1:1) instead of HSO_3F results in formation of the ethyl fluoride–antimony pentafluoride complex[14] which exhibits a pmr spectrum consisting of a quartet at 5.53 ppm ($J = 8$ Hz) and a triplet at 2.3 ppm ($J = 8$ Hz) for the methylene and methyl groups, respectively. This complex is formed together with some *tert*-butyl, *tert*-amyl, and *tert*-hexyl cations. These products may be formed either by reaction of the intermediate ethyl cation 9 (produced either on protonation of ethylene or present in equilibrium in the ethyl fluoride–antimony pentafluoride complex) with ethylene or by polycondensation of the ethyl fluoride complex.[14]

Whereas our previous studies in this field were primarly directed toward the structural study of intermediate, long-lived carbenium ions, present investigations we feel would open up the possibility of preparative work with carbenium ion salts. Olefins are the most convenient precursors to carbenium ions, and, consequently, it was felt that it would be useful to develop practical methods to generate carbenium ions directly from olefins. Having achieved this goal we are carrying out studies in the application of stable carbenium ion complexes in synthetic reactions and will report our results.

Experimental Section

All the olefins used were commercially available.

Pmr spectra were taken using a Varian Model A-56/60A spectrometer, equipped with variable low-temperature probe, operating geneally at $-75°$.

Preparation of Cations.—Dilute solutions (between 5–10% w/w) of olefin in the solvents discussed were added dropwise into the previously prepared acid solution (in SO_2 or SO_2ClF) at low temperature, $-85°$ (Dry Ice–acetone bath) or $-120°$ (ethanol-liquid N_2 bath), according to the specific olefin in question (see Discussion). The reaction mixtures were vigorously stirred during the slow addition of the solutions of olefins to avoid local overheating. The rate of addition is determined by the ability to keep temperatures close to constant during additions.

Quenching procedures were identical with those described previously.[8]

(14) G. A. Olah, J. R. DeMember, R. H. Schlosberg, and Y. Halpern, *ibid.*, in press.

A Search for General Acid Catalysis of Acetal and Ketal Hydrolysis Reactions Based on Stability of the Intermediate Carbonium Ion

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A search has been made for general acid catalysis by weak buffer acids in the hydrolysis reactions of (1) benzophenone diethyl ketal, (2) 2,2-(p-methoxyphenyl)-1,3-dioxolane, (3) 2,3-diphenylcyclopropenone diethyl ketal, (4) ferrocene carboxaldehyde dimethyl acetal, and (5) tropone ethylene ketal. General acid catalysis could not be detected in any of the reactions except with tropone ethylene ketal in which case the weak acids Tris $(H)^+$ and $H_2PO_4^-$ are good catalysts. Thus, for general acid catalysis to be observed, the intermediate carbonium ion must be exceedingly stable when the leaving group is poor. For a series of acetals and ketals of aliphatic alcohols, the boundary between the normal A1 mechanism for acetal hydrolysis and the mechanism involving catalysis by general acids lies somewhere between the intermediate carbonium ion stability exemplified by the alkoxy tropylium ion and that of the alkoxy 2,3-diphenylcyclopropenyl ion.

The generally accepted mechanism for the acid-catalyzed hydrolysis of simple acetals and ketals involves preequilibrium protonation by hydronium ion followed by rate-determining unimolecular decomposition to an alcohol and a resonance-stabilized carbonium ion.[2] In order to observe protonation by hydronium ion as part of the rate-limiting step, along with general acid catalysis by buffer acids, either protonation must be made more difficult by reducing basicity or the bond-breaking process must be made relatively easy. In the case of 2-(p-nitrophenoxy)tetrahydropyran, with which a pronounced general acid catalysis is observed,[3,4] the strong electron withdrawal in the leaving group will both lower basicity and facilitate C–O bond breaking. General acid catalysis has also been detected in the hydrolysis of benzaldehyde methyl phenyl acetals[5] where the structural features promoting general acid catalysis are undoubtedly the same as with the phenoxytetrahydropyrans.

Buffer acid catalysis is seen with tropone diethyl ketal,[6] a ketal having a poor leaving group but one in which C–O bond breaking is relatively easy, because of the exceedingly great stability of the intermediate carbonium ion. An important question then concerns the degree of carbonium ion stability necessary for general acid catalysis to be detectable with acetals having poor leaving groups. We have therefore studied the hydrolysis of a series of acetals and ketals of aliphatic alcohols with which progressively more stable carbonium ions are formed (compounds I–V).

I   II   III   IV   V

Experimental Section

Materials. 2,2-(p-Methoxyphenyl)-1,3-dioxolane was prepared by treating p,p'-dimethoxybenzophenone, from K and K Laboratories, with ethylene glycol in refluxing benzene. A trace of p-toluenesulfonic acid was added as a catalyst. Water was continuously removed from the reaction by azeotropic distillation with the benzene. Refluxing was continued until a theoretical amount of H_2O had been removed. The mixture was cooled and allowed to stand over NaOH pellets. Removal of the benzene left a solid residue which, after recrystallization from an ether–petroleum ether mixture, melted at 48–50°.

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.03; H, 6.11.

Benzophenone diethyl ketal was prepared by adding dichlorodiphenylmethane (17.8 g, 0.075 mol) to a solution of sodium (3.45 g, 0.15 mol) in absolute ethanol. The mixture was stirred overnight and filtered. The ethanol was removed on a rotary evaporator, and the liquid residue was distilled. The product boiled at 128° (2.7 mm), n^{23}D 1.5944, and solidified, mp 50–51° (lit.[7] mp 51–52°).

2,3-Diphenylcyclopropenone was prepared by elimination of HBr from α,α'-dibromodibenzyl ketone by the method of Breslow, *et al.*[8] Chromatography on silica gel (Baker) gave the ketone, mp 120–121° (lit.[9] mp 121–121.5°).

1-Ethoxy-2,3-diphenylcyclopropenyl fluoroborate was prepared by adding a solution of diphenylcyclopropenone (0.06 mol) in methylene dichloride (10 ml) dropwise to a stirring solution of triethyloxonium fluoroborate (0.06 mol) in methylene dichloride (25 ml). The product separated as white needles in 95% yield, mp 153–154° (lit.[10] mp 152° dec).

2,3-Diphenylcyclopropenone diethyl ketal was prepared by adding 1-ethoxy-2,3-diphenylcyclopropenyl fluoroborate (0.05 mol) to a solution of sodium ethoxide (0.07 mol) in 25 ml of absolute ethanol. After the vigorous reaction subsided, the resultant solution was poured into 100 ml of 2% aqueous Na_2CO_3 solution, and the suspension was extracted with ether. Evaporation of the ether left a pale yellow liquid still containing ethanol. After being allowed to stand for 2 hr the solution deposited white crystals. After recrystallization from ethanol the material melted at 67–68°.

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.43; H, 7.14. Found: C, 81.67; H, 7.14.

Ferrocene carboxaldehyde dimethyl acetal was prepared by treatment of ferrocene carboxaldehyde (Aldrich) with trimethyl-

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TABLE I

RATE CONSTANTS FOR HYDROLYSIS OF BENZOPHENONE KETALS IN 20% OR 50% DIOXANE–WATER (v/v) AT 30°

Compd	Buffer	HA, M	A$^-$, M	pH	$k_{obsd} \times 10^4$ sec^{-1}
Benzophenone diethyl ketal	Chloroacetate[a]	0.6	0.2	3.50	1.88
		0.3	0.1	3.50	1.88
		0.06	0.02	3.50	1.87
	Chloroacetate[b]	0.24	0.24	3.17	93.7
		0.03	0.03	3.16	96.2
2,2-(p-Methoxyphenyl)-1,3-dioxolane	Dichloroacetate[a]	0.60	0.20	2.54	5.46
		0.33	0.11	2.56	5.21
		0.06	0.02	2.58	3.92
	Chloroacetate[b]	0.24	0.24	3.17	6.24
		0.17	0.17	3.17	6.47
		0.132	0.132	3.16	6.30
		0.024	0.024	3.15	6.28
	Formate[c]	1.0	0.2	3.78	1.23
		0.5	0.1	3.79	1.21
		0.25	0.05	3.79	1.21
		0.04	0.008	3.80	1.22

[a] 50% dioxane-H_2O, $\mu = 0.20$ maintained with KCl. [b] 20% dioxane-H_2O, $\mu = 0.24$ maintained with KCl. [c] 50% dioxane-H_2O, $\mu = 0.50$ maintained with KCl, at 50°.

orthoformate in acidic methanol. The product was obtained as a red liquid boiling at 106° (0.6 mm).

Anal. Calcd for $C_{13}H_{16}FeO_2$: C, 60.04; H, 6.16; Fe, 21.49. Found: C, 60.24; H, 6.20; Fe, 21.22.

Tropone ethylene ketal was prepared by the method of Simmons and Fukunaga.[11] Acetonitrile was Eastman Kodak Spectrograde which was further purified by twice distilling from P_2O_5 and once from K_2CO_3. Dioxane was purified by the method of Fieser[12] and stored frozen in brown bottles.

Kinetic Measurements.—The rates of hydrolysis were measured on a Cary 15 spectrophotometer by following the appearance of the aldehyde or ketone product. Temperature was maintained constant ($\pm 0.05°$) by circulating water from a Precision Scientific Temptrol 154 water bath through a Thelma thermostated cell. Temperature was measured inside the cuvette. Buffers were maintained at constant ionic strength with KCl. The reactions were followed to completion and pseudo-first-order rate constants (k_{obsd}) were calculated by a rigorous least-squares procedure with an IBM 360-40 computer. The spectra of solutions upon completion of the reaction were identical in each case with that of the parent ketone or aldehyde. pH values were determined at the temperature of the experiments with a Radiometer pHM-22 meter. The glass electrode gives the correct pH reading in dioxane-H_2O mixtures.[13]

Results

In Table I rate constants are given for hydrolysis of benzophenone diethyl ketal and 2,2-(p-methoxyphenyl)-1,3-dioxolane in dioxane–water mixtures (20 and 50%) in the presence of various buffers. It is apparent that buffer catalysis is not observed for these ketals in chloroacetate or formate buffers. A small rate enhancement is seen in dichloroacetate buffer with 2,2-(p-methoxyphenyl)-1,3-dioxolane as the buffer concentration is increased. Since general acid catalysis will be easier to detect with weaker acids in cases where spontaneous hydrolysis is hydronium ion catalyzed (see Discussion), which is the case with this dioxolane, the enhancement in rate in the dichloroacetate buffer must not be caused by genuine, general acid catalysis. It is possible that a medium effect is important at high dichloroacetic acid concentrations. That this is at least a partial explanation is indicated by the fact that k_{obsd} in the presence of

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0.1 M HCl in 50% dioxane-H_2O is increased from 1.11 $\times 10^{-2}$ sec^{-1} to 1.17 $\times 10^{-2}$ sec^{-1} by the addition of 0.3 M dichloroacetic acid. At such high hydronium ion concentration, general acid catalysis would not be seen. Thus, the 6% increase in the rate constant is most likely a medium effect.

Rate constants for hydrolysis of 2,3-diphenylcyclopropenone diethyl ketal in 20% dioxane–water in phosphate buffers ($H_2PO_4^-/HPO_4^{2-} = 1.0$) are presented in Table II. Buffer catalysis cannot be detected. The

TABLE II

RATE CONSTANTS FOR HYDROLYSIS OF 2,3-DIPHENYLCYCLO-PROPENONE DIETHYL KETAL IN 20% DIOXANE–WATER (v/v) AT 30° AND $\mu = 0.48$ (MAINTAINED WITH KCl)[a]

Buffer	HA, M	A$^-$, M	pH	$k_{obsd} \times 10^3$ sec^{-1}
Phosphate	0.125	0.125	6.75	3.27
	0.0625	0.0625	6.75	3.06
	0.025	0.025	6.75	2.95
	0.0125	0.0125	6.75	3.13

[a] Reactions were followed at 288 mμ.

reactions in phosphate buffers followed excellent pseudo-first-order kinetics, but, with imidazole and ethanolamine buffers, deviations from pseudo-first-order kinetics were observed. This was also the case with ferrocene carboxaldehyde dimethyl acetal and tropone ethylene ketal.

Buffer catalysis is not observed in the hydrolysis of ferrocene carboxaldehyde dimethyl acetal in acetate or phosphate buffers in water at 15°. These rate constants are presented in Table III. It will be noted that a small decrease in k_{obsd} is seen as the buffer is diluted at a ratio, CH_3COO^-/CH_3COOH, of 3. This decrease is accounted for primarily by a small increase in the pH of the solutions. Second-order rate constants (k_{obsd}/a_H) are reasonably constant in these acetate buffers (5000 ± 200 M^{-1} sec^{-1}). The pseudo-first-order rate constants in phosphate buffers are much less than those in acetate buffer indicating that the reaction is predominantly hydronium ion catalyzed in that pH range, but the calculated second-order rate constants were slightly greater (7500 ± 300 M^{-1} sec^{-1}) than calculated from the acetate buffer data.

Table III

Rate Constants for Hydrolysis of Ferrocene Carboxaldehyde Dimethyl Acetal in H$_2$O at 15° and μ = 1.0 M (Maintained with KCl)[a]

Buffer	HA, M	A$^-$, M	pH	$k_{obsd} \times 10^2$ sec^{-1}
Acetate	0.33	1.0	5.11	3.80
	0.165	0.495	5.14	3.48
	0.11	0.33	5.16	3.25
	0.033	0.10	5.17	3.11
Acetate	0.167	1.0	5.42	1.95
	0.1167	0.70	5.38	2.11
	0.087	0.536	5.41	2.08
	0.0557	0.334	5.39	2.06
	0.0167	0.10	5.41	2.06
Phosphate	0.25	0.25	6.51	0.251
	0.125	0.125	6.46	0.249
	0.095	0.095	6.46	0.257
	0.0625	0.0625	6.46	0.265

[a] Appearance of aldehyde was measured at 470 mμ.

As was the case with tropone diethyl ketal,[6] significant buffer catalysis can be observed in the hydrolysis of tropone ethylene ketal in phosphate and Tris buffers [tris(hydroxymethyl)aminomethane]. Rate constants for these reactions are given in Table IV. The values

Table IV

Rate Constants for Hydrolysis of Tropone Ethylene Ketal in H$_2$O at 25°

Buffer	HA, M	A$^-$, M	pH	$k_{obsd} \times 10^3$ sec^{-1}
Phosphate[a]	0.15	0.15	6.75	2.79
	0.075	0.075	6.75	2.45
	0.015	0.015	6.75	2.16
Tris[b]	0.30	0.30	8.25	0.415
	0.15	0.15	8.25	0.345
	0.03	0.03	8.25	0.290

[a] μ = 0.6 maintained with KCl. Appearance of ketone was measured at 311 mμ. [b] μ = 0.3 maintained with KCl.

of k_{HA} are 4.48 $\times$ 10^{-3} M^{-1} sec^{-1} for H$_2$PO$_4^-$ and 4.64 $\times$ 10^{-4} M^{-1} sec^{-1} in the case of Tris (H)$^+$. A rate constant for hydronium ion catalysis, k_{H^+}, was calculated from the values of k_{obsd} at zero phosphate buffer concentration and has the value 1.19 $\times$ 10^4 M^{-1} sec^{-1}. Thus the rate constants for both general acid and hydronium ion catalysis are considerably smaller with tropone ethylene ketal at 25° than in the case of tropone diethyl ketal at 15°.[6]

Discussion

A fundamental question that must be asked in any search for general acid catalysis concerns the buffer concentration that will be necessary in order to observe catalysis if indeed it is present. The weaker the catalyst general acid, the easier it will be to detect general acid catalysis if spontaneous hydrolysis is a hydronium ion catalyzed reaction. This is because the observed pseudo-first-order rate constant for hydronium ion catalysis will decrease by a factor of 10 per pH unit with increasing pH, whereas the second-order rate constant for general acid catalysis will decrease by a factor of less than 10 per pK_a unit of the catalyst, the magnitude of the Brønsted coefficient α being less than one. An exception to this general rule obtains if the spon-

taneous reaction is pH independent, since as the pK_a of the general acid is increased a progressively larger portion of the reaction will then be due to spontaneous hydrolysis. Thus, in the hydrolysis of tropone ketals, general acid catalysis is observed over a rather narrow range of pK_a values, only data from H$_2$PO$_4^-$ and Tris (H$^+$) buffers being reported, since at pH values below approximately 6 the hydronium ion catalysis is too great to allow easy detection of general acid catalysis, while at high pH the relatively rapid pH-independent spontaneous reaction makes detection of general acid catalysis difficult; indeed, catalysis by HCO$_3^-$ was not observed.[6]

In Table V the fractional increase in the rate constant produced by general acids of various pK_a values at a concentration of 1.0 M (half-neutralized buffer, total concentration 2.0 M) in comparison to the intercept rate constants [($k_{obsd} - k_o)/k_o$] is given for a series of pK_a and α values,[14] assuming that the point for hydronium ion lies on the Brønsted line. This may not always be the case, but in ortho ester hydrolysis reactions this point does not deviate greatly,[15-17] and in general acid catalyzed acetal hydrolysis reactions investigated to date the fit of the point for hydronium ion on Brønsted plots is actually quite good.[4,5,18] If the above assumption is not valid for a given reaction, the numbers in Table V will still indicate relative changes in the fractional increase. For a given value of α, the fractional increase becomes greater as the acid becomes weaker with the exception noted previously for low values of α and at high pK_a. With reactions in which α is greater than approximately 0.70, the necessity of employing either very high concentrations of general acids or relatively weak acids is clear. For example, assuming an α of 0.75, a 1.0 M concentration of an acid of pK_a 2.0 (HA = A$^-$) would increase the rate of hydrolysis by only a factor of 16%.

Compounds such as benzophenone ketals would be expected to have α values close to unity if general acid catalysis could in fact be detected. Very high concentrations of buffer acids were employed in the present study of these compounds, and it is concluded that the reaction is not general acid catalyzed. The enhancements in the rate of hydrolysis of 2,2-(p-methoxyphenyl)-1,3-dioxolane produced by increasing dichloroacetic acid buffer concentration must be due to causes such as medium effects or specific salt effects since weaker acids are not catalysts. De Wolfe, *et al.*,[19] have recently claimed that hydrolysis of that ketal is general acid catalyzed because of studies in dichloroacetic acid, although they did not observe catalysis in formic acid buffers. Buffer acid catalysis of the hydrolysis of benzophenone diethyl ketal was also claimed in dichloroacetate and chloroacetate buffers.[19] We can find no evidence for catalysis of the hydrolysis of either ketal in chloroacetate buffer. Capon and Smith[20] could not detect catalysis of benzophenone diethyl ketal hydroly-

(14) These values were calculated on an IBM-360-40 computer from a program written by E. Anderson.

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(16) J. N. Bronsted and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **25**, 59 (1929).

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(18) E. Anderson and T. H. Fife, *ibid.*, **93**, 1701 (1971).

(19) R. H. De Wolfe, K. M. Ivanetich, and N. F. Perry, *J. Org. Chem.*, **34**, 848 (1968).

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TABLE V

FRACTIONAL INCREASE IN THE OBSERVED RATE CONSTANT $[(k_{obsd}^{HA} - k_0)/k_0]$ PRODUCED BY A 1.0 M CONCENTRATION OF A GENERAL ACID CATALYST[a] AT DIFFERENT α VALUES AND AT DIFFERENT VALUES OF pK_a OF THE CATALYST

α	$pK_a = 1$	$pK_a = 2$	$pK_a = 3$	$pK_a = 4$	$pK_a = 5$	$pK_a = 6$	$pK_a = 7$	$pK_a = 8$
0.20	2.27	5.15	4.39	2.87	1.82	1.15	0.72	0.46
0.25	1.99	3.54	14.22	9.95	5.73	3.23	1.82	1.02
0.30	1.50	7.17	24.85	30.45	17.84	9.10	4.57	2.29
0.35	1.10	4.87	20.37	55.61	50.82	25.35	11.46	5.12
0.40	0.80	3.19	12.56	45.53	95.53	66.39	28.56	11.46
0.45	0.58	2.07	7.35	25.70	79.79	125.88	68.15	25.52
0.50	0.43	1.35	4.26	13.45	41.66	109.22	127.47	55.14
0.55	0.31	0.88	2.47	6.96	19.56	53.48	116.22	99.55
0.60	0.23	0.57	1.43	3.60	9.03	22.58	54.29	95.64
0.65	0.17	0.37	0.83	1.86	4.16	9.30	20.68	43.50
0.70	0.12	0.24	0.48	0.96	1.91	3.82	7.61	15.04
0.75	0.09	0.16	0.28	0.50	0.88	1.57	2.78	4.94
0.80	0.06	0.10	0.16	0.26	0.41	0.64	1.02	1.61
0.85	0.05	0.07	0.09	0.13	0.19	0.26	0.37	0.53
0.90	0.03	0.04	0.05	0.07	0.09	0.11	0.14	0.17

[a] Half-neutralized buffers.

sis in acetate buffers. The highest concentration of chloroacetic acid employed by De Wolfe, et al.,[19] in any buffer was only 0.131 M. On the other hand, the maximum concentration of formic acid employed in 20% dioxane (0.207 M) might have been sufficient to detect catalysis but none was seen.

When the rates of hydrolysis are too slow to measure accurately with buffers of weak acids at relatively high pH, it may not be possible to determine clearly whether compounds with which α must be close to 1.0 are subject to general catalysis. In such cases it is generally preferable to consider that the compounds hydrolyze by the well established A1 mechanism rather than by a borderline ASE2 mechanism. The only convincing evidence for a mechanism change in these acid-catalyzed reactions at the present time is the observation of general acid catalysis.[21]

It would appear that the boundary between the A1 and ASE2 mechanism may in fact be rather sharp. In eq 1 is the scheme followed by a typical acid-cata-

$$S + H_3O^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SH^+ + H_2O$$
$$SH^+ \overset{k_2}{\longrightarrow} products \qquad (1)$$
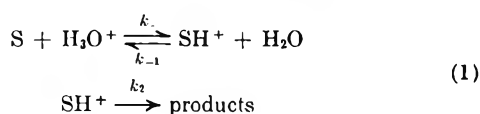
lyzed reaction. If k_2 is small relative to k_{-1} (H₂O), then the reaction will be an example of an A1 mechanism. If, however, k_2 is much greater than k_{-1} (H₂O), then k_1 will be rate determining. Taking the borderline case to be $k_2 \cong k_{-1}$ (H₂O)

$$k_{obsd} = \frac{k_1 k_2}{k_{-1} (H_2O) + k_2} (a_H) \qquad (2)$$

A structural change for a true borderline case that changed the magnitude of k_2 relative to k_{-1} (H₂O) by a factor of only 10 could therefore produce a situation in which the mechanism of the reaction would be for all practical purposes an example of one of the extreme cases. If the conjugate acid is not a discrete intermediate in acetal and ketal hydrolysis, the mechanism

must involve protonation and C–O bond breaking occurring in a concerted manner.[22] Bond breaking would then necessarily be facile enough so that the transition state could be attained without complete proton transfer. Increasing the stability of the carbonium ion intermediate would then give rise to a transition state in which less bond breaking was occurring and in which proton transfer would be less complete, thereby lowering the Brønsted α. Once the mechanism had changed from A1 to concerted, it would be expected that only a small further increase in carbonium ion stability would allow general acid catalysis to be observable. Thus, when the borderline area between these classes of mechanism is approached, a fairly small change in structure will be sufficient to produce a clear mechanism change.

General acid catalysis was also not observable in the hydrolysis of 2,3-diphenylcyclopropenone diethyl ketal and ferrocene carboxaldehyde dimethyl acetal. These data are subject to the reservations expressed above; however, it would be expected that general acid catalysis would be detectable with the buffers employed if it were indeed present. It can be seen in Table II that in phosphate buffer, where catalysis of tropone ketals is easily detected, catalysis is absent in the case of 2,3-diphenylcyclopropenone diethyl ketal.

These compounds will give rise to carbonium ion intermediates that are quite stable. In Table VI values of pK_{R^+} are given for some carbonium ions related to the compounds studied. The pK_{R^+} is the pH value at which a solution of an alcohol will give rise to a 50% concentration of carbonium ion. Thus, these pK_{R^+} values can be considered an indication of the relative stability of the alkoxy carbonium ion intermediate produced in the hydrolysis of the corresponding ketal. The values become more positive upon going from diphenylmethyl to 2,3-diphenylcyclopropenyl to tropylium. The pK_{R^+} of the ferrocenyl carbonium ion is not known, but the second-order rate constant for hydronium ion catalyzed hydrolysis of ferrocene carboxaldehyde dimethyl acetal is comparable to that for

(21) As an example, we prefer to regard the mechanism of acid-catalyzed hydrolysis of 2-phenyl-1,3-oxathiolanes and benzaldehyde methyl S-(substituted phenyl) thioacetals as A1 even though the solvent isotope effect is lower than normal and ΔS^* is more negative, since these changes can be explained in ways other than by postulating a mechanism change and since general acid catalysis cannot be observed even in cases which should be very favorable: T. H. Fife and E. Anderson, *J. Amer. Chem. Soc.*, **92**, 5464 (1970).

(22) The positive ρ values for general acid catalyzed hydrolysis of 2-(substituted phenoxy)tetrahydropyrans[4] and benzaldehyde methyl (substituted phenyl)acetals[5] provide evidence against protonation being strictly rate determining in cases where buffer catalysis has been observed in acetal hydrolysis.

TABLE VI

pK_{R^+} VALUES FOR VARIOUS CARBONIUM IONS

Carbonium ion	pK_{R^+}	General acid catalysis[a]
Diphenylmethyl[b]	−13.3	−
Di-p,p'-methoxyphenylmethyl[b]	−5.71	−
2,3-Diphenylcyclopropenyl[c]	−0.67	−
Tropylium[d]	+4.7	+

[a] Catalysis of the hydrolysis of the respective ketal. [b] N. C. Deno and A. Schriesheim, *J. Amer. Chem. Soc.*, **77**, 3051 (1955); N. C. Deno, J. J. Jaruzelski, and A. Schriesheim, *ibid.*, **77**, 3044 (1955). [c] R. Breslow, H. Hover, and H. W. Chang, *ibid.*, **84**, 3168 (1962). [d] G. Naville, H. Strauss, and E. Heilbronner, *Helv. Chim. Acta*, **43**, 1221, 1243 (1960); W. von E. Doering and L. H. Knox, *J. Amer. Chem. Soc.*, **76**, 3203 (1954).

2,3-diphenylcyclopropenone diethyl ketal, making a reasonable allowance for the difference in temperature at which the rate measurements were made. Tropone ethylene ketal was the only compound in the series for which general acid catalysis was observed. Therefore, the boundary line between the A1 mechanism and one involving general acid catalysis, in terms of carbonium ion stability, lies somewhere between pK_{R^+} values of −0.67 and +4.7, with probability that it lies closest to the more positive figure. Thus, for general acid catalysis of acetal hydrolysis to occur in cases where the leaving group is poor, the intermediate carbonium ion must be exceedingly stable, *i.e.*, the bond-breaking step must be quite easy.

The Chemistry of Carbanions. XIX. The Alkylation of Enolates from Unsymmetrical Ketones[1a]

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The alkylation of specific structural isomers of lithium enolates derived from 1-decalone (1), 2-methylcyclohexanone (2), 2-benzylcyclohexanone (3), cyclohexanone, and 2-heptanone (23) has been studied. The more highly substituted enolate isomers are best obtained by reaction of the corresponding enol acetates or enol trimethylsilyl ethers with methyllithium. The advantage gained with the silyl enol ethers in avoiding dialkylation is offset by the frequent difficulty in obtaining a single structural isomer of the silyl ether. The less highly substituted lithium enolates of unsymmetrical ketones are best obtained by a kinetically controlled deprotonation of the ketone with the hindered base, lithium diisopropylamide. Although the less hindered lithium enolates from cyclic ketones can be alkylated with good structural specificity, this procedure was not satisfactory for alkylation at the methyl group of 2-heptanone because of a combination of an unfavorable position of enolate equilibria and, especially, an unfavorable ratio of alkylation rates for the structurally isomeric enolates.

Often in the course of a synthesis, the need arises to introduce an alkyl group selectively at one of the two α positions of an unsymmetrical ketone. Among the useful methods for accomplishing this synthetic objective,[2] the reaction of an alkylating agent with a particular structural isomer of an enolate anion is very common. The formation of the desired enolate isomer may be accomplished either by modifying the structure of the starting ketone with a blocking group or an activating group or by generating the enolate from a suitable precursor under conditions where equilibration among the possible enolate structural isomers does not occur.[2] The most useful methods in this latter category have been the reduction with metals of α,β-unsaturated ketones[3] or α-halo ketones[4] and

the reaction of enol esters[5] or enol silyl ethers[6,7] with organometallic reagents, especially alkyllithium reagents. Among these possibilities, the use of enol esters or ethers offers the most versatility since the starting material for the alkylation sequence is the saturated ketone. The methods now available for the formation of enol acetates or trimethylsilyl enol ethers sometimes allow a particular structural isomer to be isolated in high yield; furthermore, any of the undesired isomers of these enol derivatives may be easily reconverted to the starting ketone.

By use of equilibrating reaction conditions accompanied, if necessary, by selective hydrolysis, it is usually possible to convert an unsymmetrical ketone to the corresponding more highly substituted enol acetate isomer in 95% purity on a preparatively useful scale.[2,5] The use of equilibrating reaction conditions permits preparation of mixtures of trimethylsilyl enol ethers in which the more highly substituted enol derivative predominates (typically 70–90% of the mixture).[7] However, it is often very difficult to obtain a pure

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(1) (a) This research has been supported by Public Health Service Grant RO1-CA-10933 from the National Cancer Institute. (b) National Institutes of Health Predoctoral Fellow, 1968–1970. (c) National Institutes of Health Predoctoral Fellow, 1966–1968.

(2) For a recent review, see H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., Chapter 9, in press.

(3) (a) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, **87**, 275 (1965); (b) H. A. Smith, B. J. L. Huff, W. J. Powers, III, and D. Caine, *J. Org. Chem.*, **32**, 2851 (1967); (c) L. E. Hightower, L. R. Glasgow, K. M. Stone, D. A. Albertson, and H. A. Smith *ibid.*, **35**, 1881 (1970).

(4) (a) M. J. Weiss and coworkers, *Tetrahedron*, **20**, 357 (1964); (b) T. A. Spencer R. W. Britton, and D. S. Watt, *J. Amer. Chem. Soc.*, **89**, 5727 (1967).

(5) (a) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341, 2502 (1965); (b) H. O. House, *Rec. Chem. Progr.*, **28**, 99 (1967); (c) H. O. House and C. J. Blankley, *J. Org. Chem.*, **32**, 1741 (1967); (d) H. O. House and T. M. Bare, *ibid.*, **33**, 943 (1968).

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

(7) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

sample of a more highly substituted trimethylsilyl enol ether isomer from an unsymmetrical ketone without recourse to either an efficient fractional distillation or preparative gas chromatography. Acetates and trimethylsilyl ethers of the less highly substituted enol derived from an unsymmetrical ketone are most easily obtained by reaction of the ketone with a very hindered base under nonequilibrating conditions. The mixture of enolates formed by this kinetically controlled proton abstraction is then quenched in excess acetic anhydride or trimethylsilyl chloride. Although bases such as lithium, sodium, or potassium triphenylmethide,[5,6] or the lithium or sodium derivative of bis(trimethylsilyl) amine[8,9] have been used to form mixtures of enolate anions under conditions of kinetic control, we have found the hindered base lithium diisopropylamide to be especially effective in forming mixtures of enolate anions containing mainly the less highly substituted lithium enolate isomer.[7] This strong base offers a number of additional advantages including the fact that it is easily prepared from available materials, it is soluble in common solvents such as ether, tetrahydrofuran (THF), and 1,2-dimethoxyethane (DME), and its presence in these solvents is readily detected by means of the red to purple colored charge-transfer complex it forms with small amounts of 2,2-bipyridyl added to the reaction mixture as an indicator.[10,11] Diisopropylamine, the conjugate acid formed from this base, is a very weak acid and is sufficiently volatile (bp 84°) to be readily separated from the reaction products; this amine is a very poor nucleophile, being so hindered that its reaction with reactive alkylating agents such as methyl iodide, benzyl bromide, and trimethylsilyl chloride is negligible under the conditions required to alkylate enolate anions. Although the mixtures of lithium enolates obtained by the kinetically controlled reaction of this hindered base with unsymmetrical ketones can be quenched with acetic anhydride or, preferably, trimethylsilyl chloride to form primarily derivatives of the less highly substituted enol,[7] it appeared more profitable to use this mixture of lithium enolates directly for alkylation reactions. This paper reports a study of the alkylation of several lithium enolates generated by these various methods.

Results and Discussion

Equations A–C summarize our results from alkylating the mixtures of lithium enolates obtained from reaction of the cyclic ketones **1**, **2**, and **3** with lithium diisopropylamide under conditions of kinetic control. In these cases the predominant monoalkylated product does not correspond to the enolate isomer expected to predominate at equilibrium; the position of equilibrium for the lithium enolate isomers from ketones **1** and **2** is 34% **4a** $\rightleftharpoons$ 66% **4b**[5a] and 10–11% **7a** $\rightleftharpoons$ 89–

(8) C. R. Krüger and E. G. Rochow *J. Organometal. Chem.*, **1**, 476 (1964).

(9) (a) D. H. R. Barton, R. H. Hesse, G. Tarzia, and M. M. Pechet, *Chem. Commun.*, 1497 (1969); (b) M. Tanabe and D. F. Crowe, *ibid.*, 1498 (1969).

(10) For the use of this indicator with organomagnesium and organolithium compounds, see S. C. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967).

(11) Triphenylmethane may also be used as an indicator for organolithium reagents in DME or THF solution where the red triphenylmethyl anion is formed.

90% **7b**.[12] It will be seen in these cases that the monoalkylated product will contain at least 90% of material resulting from alkylation at the less highly substituted
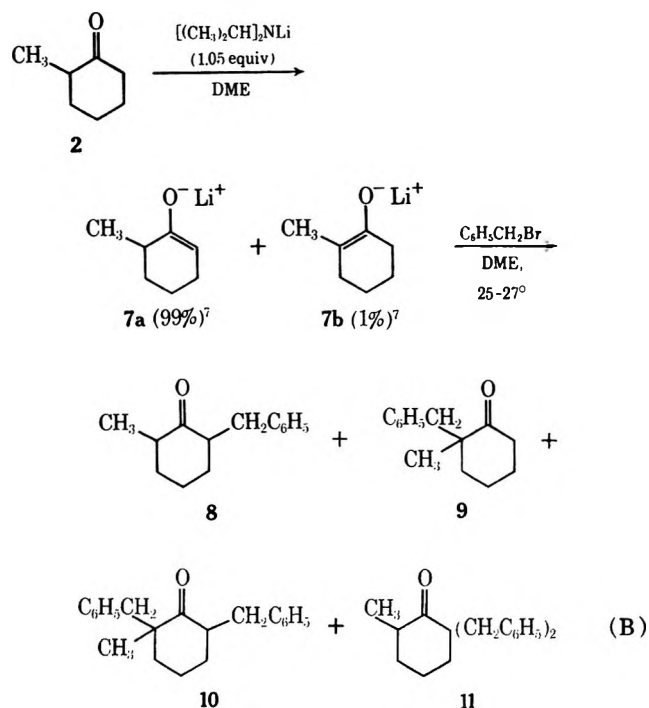
—Concentration, M—		Reaction time, min	—————Product yields, %—————			
7	C_6H_5-CH_2Br		**8**	**9**	**10**	**11**
0.19	0.20	1	9	2		
		5	27	6		
		30	33	19	8	6
0.19	1.00	1	59	3		
		5	68	4	4	4
		10	65	6	5	4
0.38	0.80	1	27	2		
		5	63	6	5	4
		10	58	6	5	5
0.38 (30–50°, preparative scale)	0.80	6	49–55	7–9	Not determined	

(12) (a) D. Caine and B. J. L. Huff, *Tetrahedron Lett.*, 4695 (1966); 3399 (1967). (b) B. J. L. Huff, F. N. Tuller, and D. Caine, *J. Org. Chem.*, **34**, 3070 (1969).

position when suitable precautions are taken to form the mixture of enolates under conditions of kinetic control and to complete the alkylation more rapidly than the alkylated product can equilibrate with the starting enolate. Rapid reaction (total reaction time 10 min. or less) of the enolates with the alkylating agent has been achieved in the cases studied here by the use of reactive alkylating agents and by the use of

3

12a   **12b**

8   **9**   dialkylated products   (C)
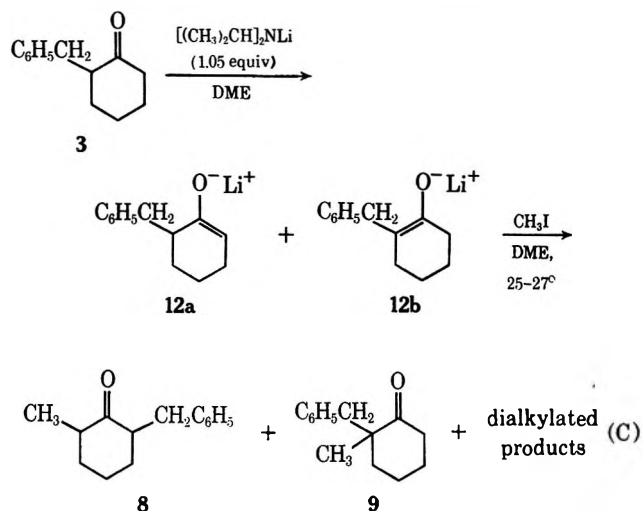
—Concentrations, M—		Reaction time,	—Product yields. %—		
12	CH₃I	min	8	9	Dialkylated
0.19	0.20	1	49	5	3
		5	64	5	6
0.19	1.00	1	76	6	5
		5	73	6	4

relatively high concentrations of reactants, especially the alkyl halide, for this bimolecular reaction. The effect on both the rate of reaction and the composition of the alkylated product is illustrated by the data in eq B. The necessity to prepare the enolates by adding the ketone to a slight excess of the strong base so that no un-ionized ketone is present is best illustrated by comparison of the data summarized in eq B and D. In the latter experiment, the mixture of enolates was formed by adding an excess of the ketone to the solution of strong base so that no excess lithium diisopropylamide was present (*i.e.*, the indicator was colorless) before the alkylating agent was added. However, with suitable precautions the selective alkyla-

2   mixture of lithium enolates $\xrightarrow[\text{DME, 25-27°} \atop \text{6 min}]{C_6H_5CH_2Br \atop (2.1\,equiv)}$

8 (9% yield)   **(9 31% yield)**   dialkylated products   (D)
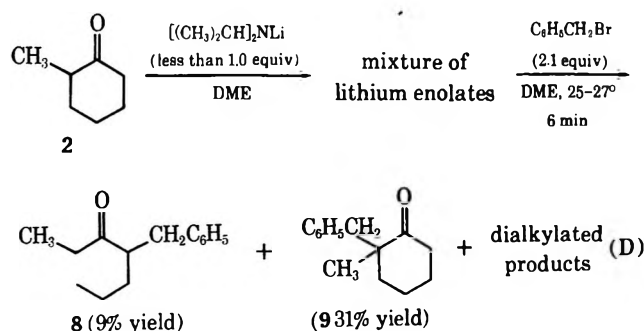
tion of the ketone **2** to form **8** is a practical preparative procedure; the result is particularly striking when one considers that not only is the "wrong" lithium enolate isomer **7b** favored at equilibrium but also the enolate **7b** is 1.7–2.3 times more reactive toward alkyl halides than is its isomer **7a**.[12]

As the foregoing comments imply, the selective alkylation of a cyclic ketone at the more highly substituted α position can be accomplished fairly easily since both the position of enolate equilibrium and the rate of reaction with the alkylating agent favor this site. The principal difficulty is encountered in preparing, easily, a pure sample of a suitable precursor for lithium enolate which will not result in competing formation of dialkylated products. As noted earlier, it is relatively easy to obtain pure samples of a more highly substituted enol acetate isomer such as **13** (eq E); however, the corresponding trimethylsilyl enol ethers, *e.g.*, **14** (eq F), are usually obtained as the predominant

(E)

2   **13 (87–92% yield)**

2 + (CH₃)₃SiCl $\xrightarrow[\text{(CH₃)₂NCHO,} \atop \text{reflux}]{Et₃N}$

(F)

14 (78% of product)   **15 (22% of product)**

$\underbrace{\qquad\qquad\qquad\qquad}_{\text{80% yield}}$

13, R = COCH₃
14, R = Si(CH₃)₃

7b (0.19 M)   + (CH₃)₄Si or (CH₃)₃CO⁻ Li⁺ $\xrightarrow[\text{DME, 25-27°}]{C_6H_5CH_2Br \atop (1.0\,M)}$

9   **10**   (G)
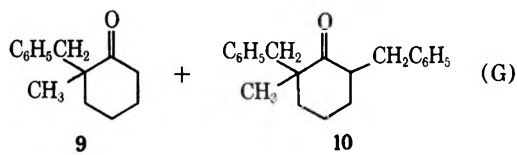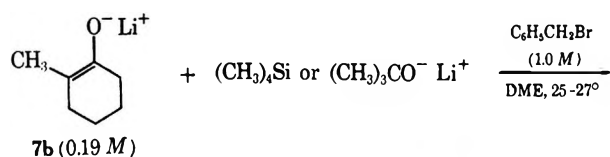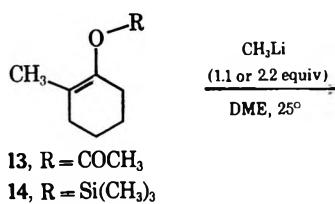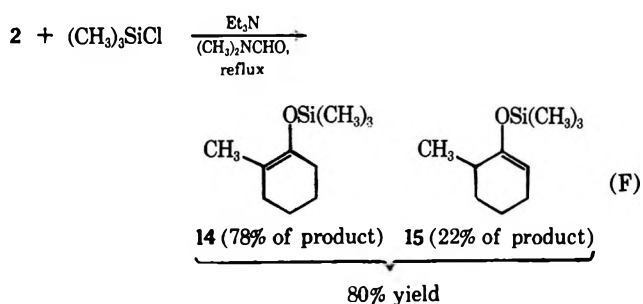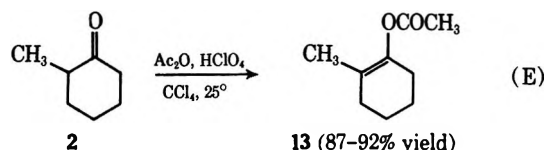
R	Reaction time, min	Product yields. %	
		9	10
Si(CH₃)₃	1	80	3
	5	84	7
COCH₃	1	59	22
	5	48	41
COCH₃ (preparative scale)	2.5	53–58%	Not determined

components in a difficultly separable mixture. Although each of these pure enol derivatives **13** and **14** is readily converted to a single enolate anion, **7b**, the by-product of these preparations is either the inert

16 (contains 11% of the $\Delta^{1,2}$ isomer)

$\xrightarrow[\text{DME, 25°}]{\text{CH}_3\text{Li} \ (1.2 \text{ equiv})}$

4b (contains *ca.* 10% of the $\Delta^{1,2}$ isomer)

$\xrightarrow[\text{DME, 0°, 40 sec}]{\text{CH}_3\text{I} \ (1.8 \text{ equiv})}$

6 (43% yield) + 17 (12% yield) + 5 (10% yield) (H)

+

dialkylated products (9% yield)

18

$\xrightarrow[\text{Et}_2\text{O, 25°}]{\text{CH}_3\text{Li} \ (1.0 \text{ equiv})}$

19 (insoluble in Et$_2$O)

$\xrightarrow[\text{DME, 0°, 15 sec}]{\text{CH}_3\text{I} \ (7.8 \text{ equiv})}$

2 (56% yield) + dialkylated products (*ca.* 13% yield) (I)

18

$\xrightarrow[\text{Et}_2\text{O, 25°}]{\text{CH}_3\text{Li} \ (1.0 \text{ equiv})}$

19

$\xrightarrow[\text{solvent, 25–27°}]{\text{C}_6\text{H}_5\text{CH}_2\text{Br} \ (1.1 \text{ equiv})}$

3 + 20 + 21 +

22 (CH$_2$C$_6$H$_5$) (J)
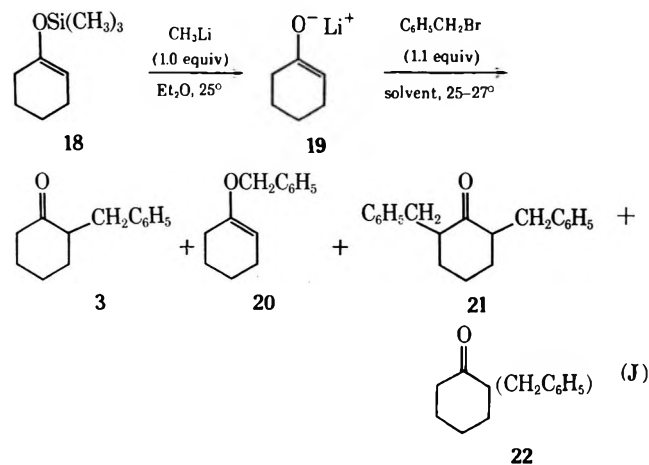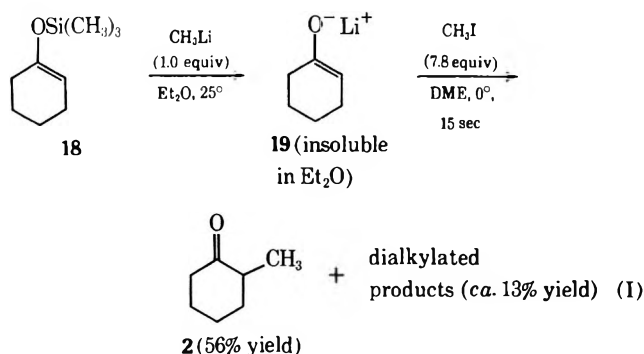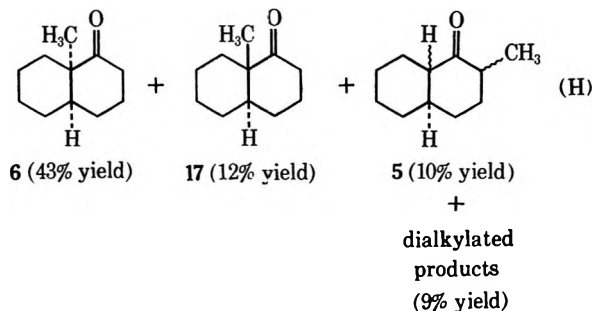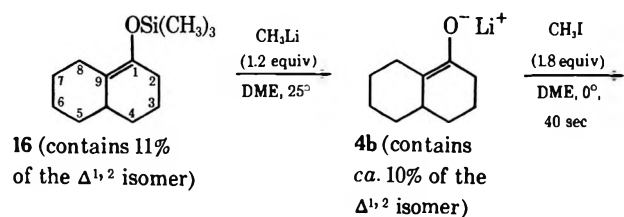
Solvent	Reaction time, min	Product yields, %			
		3	20	21	22
Et$_2$O (heterogeneous)	60	45		5	5
DME (homogeneous)	60	51		4	9
DME (preparative scale)	15	58		Not determined	
HMP (homogeneous)	15	27	3	5	20

tetramethylsilane or the base, lithium *tert*-butoxide. Since the alkoxide reacts very slowly with alkylating agents under the conditions of enolate alkylation, it remains in the reaction mixture and can react with

the initial monoalkylated product 9 to form a new enolate which yields a dialkylated ketone 10. As eq G illustrates, this problem can be lessened by use of excess alkylating agent with short reaction times. However, if the silyl ether 14 were readily available in pure form, it would clearly be the more satisfactory precursor for the enolate 7b.

Other examples of alkylations of lithium enolates derived from trimethylsilyl enol ethers are summarized in eq H–J. It will be noted that dialkylation is still a serious side reaction unless precautions (high concentrations of reactants and excess alkylating agent) are taken to make the initial alkylation reaction rapid. Thus, even in the absence of lithium *tert*-butoxide (formed from an enol acetate precursor), the starting enolate anion (*e.g.*, 19) can serve as a base to convert the initial alkylated product (*e.g.*, 3) to a new enolate anion. This enolate equilibration becomes particularly troublesome (see eq J) when the reaction is conducted in a polar, aprotic solvent such as hexamethylphosphoramide (HMP). Use of this solvent also leads to the formation of some O-alkylated product (*e.g.*, 20) as has been noted elsewhere.[2,13] However, the benzylations of the various lithium enolates (*e.g.*, 19) in 1,2-dimethoxyethane were not complicated by O-alkylation; appropriate control experiments demonstrated that the enolate 19 did not react with the O-benzyl ether 20 to form the C-benzylated product 3.

The foregoing method could also be used successfully to alkylate the more highly substituted α position of the methyl alkyl ketone 23 (eq 11);[14] other examples

$n\text{-C}_4\text{H}_9\text{CH}_2\text{COCH}_3$ $\xrightarrow[\text{HClO}_4 \text{ (cat. amt), CCl}_4]{\text{Ac}_2\text{O}}$
23

$n\text{-C}_4\text{H}_9\text{CH}=\overset{\text{OCOCH}_3}{\text{C}}\text{CH}_3$ $\xrightarrow[\text{DME, 25–27°}]{\text{CH}_3\text{Li} \ (2.06 \text{ equiv})}$
24

$n\text{-C}_4\text{H}_9\text{CH}=\overset{\text{O}^- \text{Li}^+}{\text{C}}\text{CH}_3$ $\xrightarrow[\text{DME, 25–27°}]{\text{C}_6\text{H}_5\text{CH}_2\text{Br} \ (1.0 \ M)}$
25a (0.19 M)

$n\text{-C}_4\text{H}_9\overset{\text{CH}_2\text{C}_6\text{H}_5}{\text{CH}}\text{COCH}_3$ +
26

$n\text{-C}_4\text{H}_9\text{CH}_2\text{COCH}_2\text{CH}_2\text{C}_6\text{H}_5$ + $n\text{-C}_4\text{H}_9\overset{\text{CH}_2\text{C}_6\text{H}_5}{\text{CH}}\text{COCH}_2\text{CH}_2\text{C}_6\text{H}_5$ +
27 28

$n\text{-C}_4\text{H}_9\overset{\text{COCH}_3}{\text{C}}(\text{CH}_2\text{C}_6\text{H}_5)_2$ + $n\text{-C}_4\text{H}_9\text{CH}_2\text{COCH}(\text{CH}_2\text{C}_6\text{H}_5)_2$ (K)
29a 29b
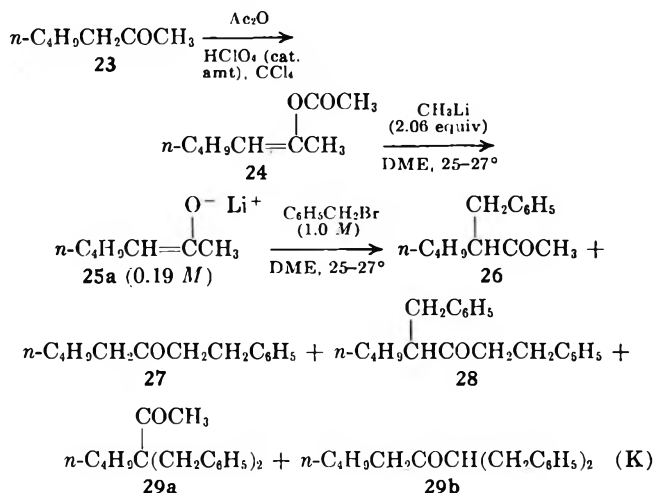
Reaction time, min	Product yields, %			
	26	27	28	29
1	57	1	4	1
5	70		11	6
45	61		9	27

of this type have been reported elsewhere.[5a,d] As was true for the benzylation of the cyclic ketones, the monoalkylated product 26 was obtained in good purity and the formation of dialkylated products became a serious problem only when relatively long reaction

(13) (a) H. D. Zook, T. J. Russo, E. F. Ferrand, and D. S. Stotz, *J. Org. Chem.*, **33**, 2222 (1968); (b) W. J. leNoble and H. F. Morris, *ibid.* **34**, 1969 (1969); (c) R. M. Coates and J. E. Shaw, *ibid.*, **35**, 2597, 2601 (1970); (d) A. L. Kurz, I. P. Beletskaya, A. Macias, and O. A. Reutov, *Tetrahedron Lett.*, 3679 (1968); (e) S. J. Rhoads and R. W. Holder, *Tetrahedron*, **25**, 5443 (1969); (f) H. Normant, *Angew. Chem., Int. Ed. Engl.*, **6**, 1046 (1967).

(14) Mixtures of the cis and trans isomers of the enolate 25a were employed in the present studies. The composition of these mixtures of geometrical isomers are described in ref 5 and 7.

$$n\text{-C}_4\text{H}_9\text{CH}{=\!\!=}\text{C}{=\!\!=}\text{CH}_2 \quad \overset{\text{CH}_3\text{Li (1.08 equiv)}}{\underset{\text{DME, 25}^\circ}{\longrightarrow}}$$

with $\overset{\text{OSi(CH}_3)_3}{|}$ above the central carbon and H below

30 (84% $\Delta^{1,2}$ and 16% $\Delta^{2,3}$ isomer)

$$n\text{-C}_4\text{H}_9\text{CH}_2\text{COCH}_3 \quad \overset{[(\text{CH}_3)_2\text{CH}]_2\text{NLi}}{\underset{\substack{\text{DME,}\\ -78 \text{ to } 25^\circ}}{\xrightarrow{\text{(1.4 equiv)}}}} \quad n\text{-C}_4\text{H}_9\text{CH}{=}\overset{\text{O}^-\text{Li}^+}{\overset{|}{\text{C}}}\text{CH}_3 \; + \; n\text{-C}_4\text{H}_9\text{CH}_2{-}\overset{\text{O}^-\text{Li}^+}{\overset{|}{\text{C}}}{=}\text{CH}_2 \quad \overset{\text{C}_6\text{H}_5\text{CH}_2\text{Br}}{\underset{\text{DME, 25}^\circ}{\longrightarrow}}$$

23 **25a** (16% of the mixture) **25b** (84% of the mixture)

$$n\text{-C}_4\text{H}_9\text{CH}_2\text{COCH}_2\text{CH}_2\text{C}_6\text{H}_5 \; + \; n\text{-C}_4\text{H}_9\overset{\text{CH}_2\text{C}_6\text{H}_5}{\overset{|}{\text{CH}}}\text{COCH}_3 \; + \; n\text{-C}_4\text{H}_9\text{CH}_2\text{COCH}(\text{CH}_2\text{C}_6\text{H}_5)_2 \; + \; n\text{-C}_4\text{H}_9\overset{\text{CH}_2\text{C}_6\text{H}_5}{\overset{|}{\text{CH}}}\text{COCH}_2\text{CH}_2\text{C}_6\text{H}_5 \quad \text{(L)}$$
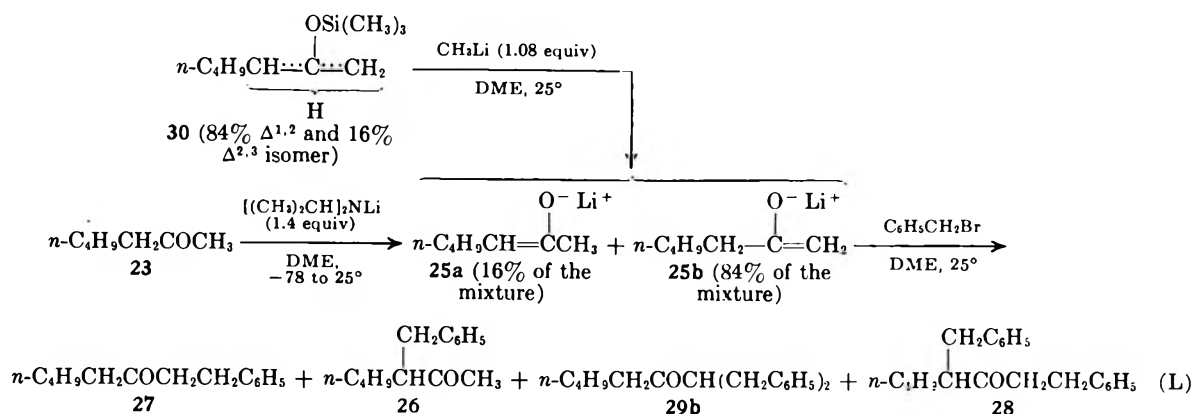
27 **26** **29b** **28**

Reactant concentrations, M		Reaction time, min	Product yields %			
25	PhCH₂Br		27	26	29b	28
0.19	1.00	1	27	19	3	2
		5	16	31	13	9
		45	15	33	14	10
0.17	0.20	10	4	23	Ca. 3	Ca. 3
		120	1	41	6	6
0.07	0.70	60	13	28	16	12

periods were employed. However, attempts to alkylate this same ketone **23** selectively at the methyl group (the less hindered α position) revealed a clear limitation of these alkylation procedures. Equation L illustrates the fact that addition of this ketone **23** to lithium diisopropylamide offers a reasonably selective procedure for forming the terminal lithium enolate **25b** (84% of the enolate mixture); the same mixture of enolates could also be obtained by reaction of the corresponding mixture of trimethylsilyl enol ethers with methyllithium. In 1,2-dimethoxyethane solution the equilibrium composition of this enolate mixture is *ca.* 13% **25b** ⇌ *ca.* 87% **25a**.[5a] Irrespective of the method used to obtain this enolate mixture, subsequent reaction with benzyl bromide produced a substantial amount of the product **26** from monoalkylation at the more highly substituted α position and the expected monobenzylated ketone **27** was the major monoalkylated product only when the reaction was run for a short period of time (1 min) with relatively high concentrations of reactants.

Consideration of the data summarized in eq K and L requires that the internal enolate isomer **25a** must react some 5–10 times as rapidly as the terminal enolate **25b** with benzyl bromide. Furthermore, the enolates derived from the monoalkylated product **27** must also react more rapidly than the starting terminal enolate **25b**. The net result of this slow rate of alkylation of the terminal enolate **25b** is to allow time for equilibration between the starting enolates and the alkylated product; this equilibration favors both the consumption of the desired monoalkylated product **27** and the formation of the isomeric monoalkylated ketone **26** from the enolate **25a**, which is both more reactive and is also favored at equilibrium.[15] As a result of these factors, it appears that selective alkylation at the methyl group of ketone RCH₂COCH₃ by any

method which involves the generation of the enolate RCH₂C(O⁻)=CH₂ Li⁺ in an ethereal solvent will not be a good synthetic procedure and other synthetic methods (*e.g.*, introduction of an activating substituent)[2] will be preferable.

The fact that less highly substituted alkali metal enolates may sometimes react more slowly with alkyl halides than their analogs having additional α substituents has been noted in several studies.[12,13a,16] These observations initially seem curious since adding α substituents would be expected to increase the steric interference to forming a new bond at the α-carbon atom. However, there is considerable evidence that many of the metal enolates (and the related metal alkoxides) exist in ethereal solvents either as tightly associated ion pairs or as aggregates (dimers, trimers, tetramers) of these ion pairs;[13a,17–19] structures such as **31–34** (M = metal; n = 1, 2, or 3; R = alkyl or the substituted vinyl portion of an enolate) have been suggested for such materials with the smaller aggregates being favored as the steric bulk of the group R increases. Thus, the bromomagnesium enolate of isopropyl mesityl ketone is suggested to have structure **31** (M = MgBr), whereas the enolate of the analogous methyl ketone is believed to have structure **32** (M = MgBr).[18] The sodium enolates of several ketones are suggested to have the trimeric structures **33** in various ethereal solvents.[13a,17] Since the reactivities of metal enolates toward alkyl halides are very dependent on the degree of association and/or aggregation,[2,13,17] we suggest that the decreased reactivity observed for less highly substituted metal enolates both in this study

(15) Although data concerning rates of proton transfer from an unionized ketone to each of the enolate anions **25** are not available, it is possible that proton transfer to the terminal enolate isomer **25b** is faster than transfer to the internal isomer **25a**. This circumstance would further complicate attempts to alkylate the terminal enolate **25b** without competing isomerization.

(16) K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **31**, 1035 (1966).

(17) (a) H. D. Zook and T. J. Russo, *J. Amer. Chem. Soc.*, **82**, 1258 (1960); (b) H. D. Zook and W. L. Gumby, *ibid.*, **82**, 1386 (1960); (c) W. L. Rellahan, W. L. Gumby, and H. D. Zook, *J. Org. Chem.*, **24**, 709 (1959); (d) H. D. Zook, W. L. Kelly, and I. Y. Posey, *ibid.*, **33**, 3477 (1968).

(18) A. G. Pinkus, J. G. Lindberg, and A. B. Wu, *Chem. Commun.*, 1350 (1969); 859 (1970).

(19) For related studies of the structures of metal alkoxides, see (a) G. E. Coates, J. A. Heslop, M. E. Redwood, and D. Ridley, *J. Chem. Soc. A*, 1118 (1968); (b) E. Weiss, H. Alsdorf, and H. Kühr, *Angew. Chem., Int. Ed. Engl.*, **6**, 801 (1967).

and elsewhere[12,13a,16] may be attributable to a greater degree of aggregation of these enolates.

Experimental Section[20]

Reagents and Starting Materials.—The preparation and characterization of trimethylsilyl enol ethers 14, 16, 18, and 30 and the enol acetates 13 and 24 have been described previously.[5a,7,21] Although the pure silyl ether 14 [bp 100–101° (45 mm), n^{24}D 1.4476, glpc analysis, Apiezon L on Chromosorb P] could be separated from its isomer 15 by fractional distillation, this separation technique was not useful for obtaining single structural isomers from the enol derivatives 16 and 30. Consequently, the decalone derivative 16 used contained [glpc analysis, 1,2,3-tris-(β-cyanoethoxy)propane on Chromosorb P] 89% of the Δ¹,⁹ isomer and 11% of the stereoisomeric Δ¹,² isomers, and the 2-heptanone derivative 30 used contained (glpc analysis, Carbowax 20M on Chromosorb P) 84% of the Δ¹,² isomer and 16% of the stereoisomeric Δ²,³ isomers. All of these trimethylsilyl enol ether isomers have been separated and characterized in earlier studies.[7] The following paragraphs summarize improved preparative procedures for the previously characterized[21] enol acetates 13 and 24.

A solution of 230 g (2.25 mol) of Ac₂O, 56 g (0.50 mol) of 2-methylcyclohexanone, and 0.34 ml (2 mmol) of aqueous 70% HClO₄ (added last) in 600 ml of CCl₄ was stirred at 25° for 3 hr and then poured into a cold (0–5°) mixture of 400 ml of pentane and 400 ml of saturated aqueous NaHCO₃. After excess solid NaHCO₃ had been added to neutralize all the HOAc formed, the pentane layer was separated and the aqueous phase was extracted with pentane. The combined pentane solutions were dried, concentrated, and distilled to separate 66.6–70.9 g (87–92%) of the enol acetate 13 [bp 81–86° (18 mm), n^{25}D 1.4562–1.4572] which contained (nmr analysis[21]) >95% of the more highly substituted isomer.

A mixture of 114.2 g (1.00 mol) of 2-heptanone, 209 g (2.07 mol) of isopropenyl acetate, and 6.0 g (35 mmol) of p-toluenesulfonic acid was refluxed with stirring in an apparatus fitted with a condenser partially filled with refluxing acetone.[22] In this way acetone which formed as the reaction progressed was allowed continuously to distil from the reaction mixture. After 12 hr, when the conversion of 2-heptanone was nearly complete (glpc analysis), the mixture was partitioned between 500 ml of pentane and 600 ml of cold (0–5°) saturated, aqueous NaHCO₃. The

organic layer was separated, dried, and distilled to separate 146 g (94%) of the crude product [bp 168–176° (760 mm)] which contained (glpc analysis, Carbowax 20M on Chromosorb P) 4% 2-heptanone (retention time 6.5 min), 57% 2-acetoxy-trans-2-heptene (11.6 min), 15% 2-acetoxy-1-heptene (12.4 min), and 24% 2-acetoxy-cis-2-heptene (14.1 min). Fractional distillation through a 90-cm spinning-band column separated 121 g (76.9%) of product, bp 85–90° (30 mm), n^{23}D 1.4245, which contained >95% of the Δ²,³ enol acetate stereoisomers 24.

Ethereal solutions of halide-free methyllithium were obtained from Alpha Inorganics; these solutions were standardized by the titration procedure of Watson and Eastham.[10] Diisopropylamine was distilled from CaH₂, benzyl bromide was freshly distilled [bp 78–79° (12 mm)], and 1,2-dimethoxyethane was distilled from LiAlH₄ immediately before use. In all reactions involving methyllithium, a few milligrams of either 2,2-bipyridyl or triphenylmethane was added as an indicator to establish when excess methyllithium was present;[10,11] similarly, small amounts of 2,2-bipyridyl were added as an indicator for solutions of lithium diisopropylamide. This amide is a sufficiently strong base that it attacks 1,2-dimethoxyethane at a significant rate; in a 0.5 M solution at 0–10°, approximately 25% of this base was consumed after 45 min by reaction with the solvent. For a comparable solution at −20°, less than 10% of the lithium diisopropylamide was consumed after 30 min.

Authentic Samples of the Alkylated Cyclohexanones. A. 2-**Benzylcyclohexanone (3).**—2-Benzalcyclohexanone, prepared in 62% yield as previously described,[23] was obtained as yellow prisms: mp 54–54.5°; ir (CCl₄) 1690 (conj C=O) and 1610 cm⁻¹ (conj C=C); uv maxima (95% EtOH) 223 mμ (ε 7100) and 290 (16,500); nmr (CCl₄) δ 7.0–7.5 (6 H, m, aryl and vinyl CH) and 1.4–3.0 (6 H, m, aliphatic CH). An ethanol solution of this material was hydrogenated[24] over a Pt catalyst (from PtO₂) to yield 56% 2-benzylcyclohexanone (3) as a colorless liquid: bp 112–114° (0.6 mm); n^{24}D 1.5347–1.5362 [lit.[24] bp 142° (1.0 mm); n^{18}D 1.5356]; ir (CCl₄) 1710 cm⁻¹ (C=O); uv (95% EtOH) series of weak maxima (ε 134–331) in the region 240–284 mμ; nmr (C₆D₆) δ 7.0–7.3 (5 H, m, aryl CH), 3.0–3.5 (2 H, AB part of ABX pattern centered at δ 3.28, benzylic CH₂), and 1.0–2.6 (9 H, m, aliphatic CH); mass spectrum m/e (rel intensity) 188 (13, M⁺), 97 (26), 91 (100), 65 (21), 55 (26), 51 (23), 44 (99), 41 (51), 40 (45), and 39 (51).

B. 1-**Benzyloxycyclohexene (20).**—A mixture of 24.5 g (0.25 mol) of cyclohexanone, 39.0 g (0.375 mol) of 2,2-dimethoxypropane, 216 g of benzyl alcohol, 75 ml of hexane, and 0.1 g of p-toluenesulfonic acid was refluxed with stirring over a period of 30 hr, while the low-boiling products (MeOH and acetone) were fractionally distilled from the reaction vessel and portions of hexane were added periodically to the reaction flask.[25] The hexane was then distilled from the reaction mixture and the residual liquid was neutralized (0.1 g of NaOMe in 5 ml of MeOH) and distilled under reduced pressure to separate various lower boiling components [bp 70° (0.35 mm) to 138° (0.05 mm)] followed by 57.01 g (77%) of crude 1,1-dibenzyloxycyclohexane, bp 138–157° (0.06 mm), n^{25}D 1.5481. On thin layer chromatography (silica gel coating and PhH eluent) the Rf values of the materials formed in this reaction were benzyl alcohol, 0.13; the ketal, 0.50; dibenzyl ether, 0.63; and the enol ether 20, 0.74. Redistillation in apparatus, previously washed with base, separated the pure ketal as a pale yellow liquid: bp 151–153° (0.03 mm); n^{26}D 1.5479; ir (CCl₄) 1040 and 1090 cm⁻¹ (ketal CO); uv (95% EtOH) series of weak (ε 170–392) maxima in the region 240–270 mμ; nmr (CCl₄) δ 6.9–7.6 (10 H, m, aryl CH), 4.45 (4 H, s, benzylic CH₂O), and 1.2–2.1 (10 H, m, aliphatic CH).

Anal. Calcd for C₂₀H₂₄O₂: C, 81.04; H, 8.16. Found: C, 81.12; H, 8.28.

A mixture of 9.86 g (33 mmol) of this ketal and 0.5 g of powdered NH₄H₂PO₄ was heated to 190–198° for 10 min and then cooled and distilled under reduced pressure. The higher boiling fractions obtained [7.8 g, bp 44–121° (1.0 mm), n^{25}D 1.5388–1.5410] were fractionally distilled to separate 3.30 g (53%) of the pure enol ether 20, as a colorless liquid: bp 74–76° (0.08 mm); n^{30}D 1.5356; ir (CCl₄) 1660 cm⁻¹ (C=C); uv (95%

(20) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer Model 237 infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The nmr spectra were determined at 60 Mc with a Varian Model A-60 or Model T-60 nmr spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to a tetramethylsilane internal standard. The mass spectra were obtained with a Hitachi Perkin-Elmer mass spectrometer. All reactions involving strong bases or organometallic intermediates were performed under a nitrogen atmosphere.

(21) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963).

(22) This procedure was developed in our laboratories by Mr. Allan Y. Teranishi and Dr. Thomas M. Bare.

(23) H. O. House and R. L. Wasson, *J. Amer. Chem. Soc.*, **78**, 4394 (1956), and references therein.

(24) J. D. Billimoria, *J. Chem. Soc.*, 1126 (1955).

(25) This method for preparing ketals was described by N. B. Lorette and W. L. Howard, *J. Org. Chem.*, **25**, 521 (1960).

EtOH) intense end absorption with a series of weak (ϵ 181–222) maxima in the region 245–270 mμ; nmr (CCl$_4$) δ 7.2–7.6 (5 H, m, aryl CH), 4.74 (2 H, s, benzylic CH$_2$O), 4.6 (1 H, m, vinyl CH), and 1.3–2.5 (8 H, m, aliphatic CH); mass spectra M$^+$ at *m/e* 188 with abundant fragment peaks at *m/e* 92, 91, 65, 55, 51, 41, and 39.

Anal. Calcd for C$_{13}$H$_{16}$O: C, 82.93; H, 8.57. Found: C, 82.79; H, 8.58.

C. 2,6-Dibenzylcyclohexanone (21).—An ethyl acetate solution of 2,6-dibenzalcyclohexanone[26] was hydrogenated at 26° and atmospheric pressure over the catalyst from PtO$_2$. The crude crystalline product, separated in the usual way, was recrystallized from methanol to separate the pure cis-2,6-dibenzylcyclohexanone (21, 28% yield) as colorless crystals: mp 121–122° (lit. mp 122°,[27] 124–125°[28]); ir (CCl$_4$) 1715 cm^{-1} (C=O); uv (95% EtOH) series of weak maxima (ϵ 438–728) in the region 240–270 mμ with a maximum at 287 mμ (ϵ 48); nmr (CCl$_4$) δ 6.9–7.3 (10 H, m, aryl CH), 2.9–3.5 (4 H, m, AB part of ABX pattern centered at 3.21, benzylic CH$_2$), and 1.2–2.6 (8 H, m, aliphatic CH); in C$_6$D$_6$ solution the AB part of the ABX pattern is centered at δ 3.32; mass spectrum *m/e* (rel intensity) 278 (47, M$^+$), 187 (58), 167 (21), 146 (24), 131 (22), 130 (33), and 91 (100).

D. 2,2-Dibenzylcyclohexanone (22).—Cyclohexanone (24.5 g or 0.25 mol) was alkylated with 0.50 mol of benzyl bromide and 0.53 mol of sodium *tert*-amylate in 567 ml of benzene according to the procedure of Conia.[29] The crude product was fractionally distilled to separate the unchanged benzyl bromide and the monobenzylated ketone as fractions, bp 35–111° (0.10–0.15 mm). The residual viscous liquid was crystallized from a PhH–EtOH mixture to separate 19.9 g (29%) of the 2,2-dibenzyl ketone 22: mp 64.5–65° (lit.[30] 69–70°); ir (CHCl$_3$) 1705 cm^{-1} (C=O); uv (95% EtOH) series of weak (ϵ 229–430) maxima in the region 240–270 mμ as well as a maximum at 296 mμ (ϵ 117); nmr (CCl$_4$) δ 6.8–7.3 (10 H, m, aryl CH) with an AB pattern at 3.08 (2 H, d, *J* = 13.6 Hz) and 2.55 (2 H, d, *J* = 13.6 Hz), attributable to the benzylic CH$_2$ groups, and 1.4–2.5 (8 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 278 (2, M$^+$), 187 (100), 91 (60), and 78 (32).

E. 2-Methyl-6-benzylcyclohexanone (8).—A mixture of 84 g (0.79 mol) of benzaldehyde, 60 g (0.54 mol) of 2-methylcyclohexanone, 35.2 g (0.88 mol) of sodium hydroxide, 50 ml of 1,2-dimethoxyethane, 270 ml of H$_2$O, and 192 ml of EtOH was refluxed for 3 hr and diluted with pentane. The organic layer was separated, dried, and distilled to separate 76.7 g (71.7%) of crude 2-methyl-6-benzalcyclohexanone as a yellow liquid, bp 127–130° (0.05 mm). The pure benzal ketone crystallized from hexane as white needles: mp 58–60° (lit.[31] mp 62°); ir (CCl$_4$) 1685 cm^{-1} (conj C=O); uv maxima (95% EtOH) 221 mμ (ϵ 6800) and 287 (15,300); nmr (CCl$_4$) δ 7.1–7.4 (6 H, m, aryl and vinyl CH), 1.3–3.3 (7 H, m, aliphatic CH), and 1.19 (3 H, d, *J* = 6.3 Hz, CH$_3$); mass spectrum *m/e* (rel intensity) 200 (100, M$^+$), 199 (45), 172 (38), 157 (52), 130 (37), 129 (81), 128 (40), 117 (69), 115 (94), 91 (55), and 81 (89).

A solution of 20.0 g (0.100 mol) of 2-methyl-6-benzalcyclohexanone in 200 ml of EtOH was hydrogenated over 0.5 g of Raney nickel catalyst at 22° and 38 psi. The reaction was stopped after 135 min and the crude product was distilled to separate 18.0 g (89.1%) of the ketone 8 as a colorless liquid: bp 110–112° (0.7 mm); n^{25}D 1.5262–1.5280 [lit.[32] bp 167° (20 mm), $n^{10.5}$D 1.5309]; ir (CCl$_4$) 1710 cm^{-1} (C=O); uv (95% EtOH) series of weak (ϵ 245–335) maxima in the region 240–270 mμ as well as a maximum at 285 mμ (ϵ 202); mass spectrum *m/e* (rel intensity), 202 (78, M$^+$), 159 (42), 145 (33), 131 (28), 117 (45), 111 (39), and 91 (100). The nmr spectrum indicates that the product is a mixture of cis (major) and trans (minor) isomers;

the spectrum (CCl$_4$) has absorption at δ 6.9–7.3 (5 H, m, aryl CH), 2.8–3.4 (1 H, m, one benzylic CH), 1.2–2.7 (9 H, m, aliphatic CH and one benzylic CH), and two doublets together corresponding to 3 H at δ 1.04 (*J* = 6.5 Hz) and 0.97 (*J* = 6.0 Hz). The more intense (*ca.* 80%) methyl signal (at δ 0.97), attributable to an equatorial methyl group in the cis isomer, was not changed when the solvent was changed from CCl$_4$ to C$_6$D$_6$, whereas the weaker (*ca.* 20%) methyl signal (at δ 1.04 in CCl$_4$) was shifted upfield (to about δ 0.97) when the solvent was C$_6$D$_6$. This is the behavior expected of an axial methyl group[33] and corresponds to *trans*-2-methyl-6-benzylcyclohexanone in which one of the favorable conformers will have an axial methyl group. The presence of these two isomers did not interfere with the subsequently described glpc analyses because the two isomers were equilibrated under the conditions required to elute them from various glpc columns.

F. 2,2-Dibenzyl-6-methylcyclohexanone (11).—An ethereal solution containing 37.8 mmol of methyllithium was concentrated under reduced pressure and the organolithium reagent was redissolved in 145 ml of 1,2-dimethoxyethane containing several milligrams of 2,2-bipyridyl. After the solution had been cooled to 0° and treated with 3.82 g (37.8 mmol) of diisopropylamine, 25 ml of a solution containing 10.0 g (35.9 mmol) of 2,2-dibenzylcyclohexanone (22) in 1,2-dimethoxyethane was added dropwise and with stirring over 20 min. The resulting solution of the lithium enolate was warmed to about 35° and then 20.2 g (143 mmol) of methyl iodide was added rapidly and with vigorous stirring. After the mixture had been stirred for 5 min, it was partitioned between pentane and saturated aqueous NaHCO$_3$. The organic layer was separated, washed successively with aqueous 5% HCl and aqueous NaHCO$_3$, dried, and distilled. The crude product, 7.94 g (76%) of a colorless liquid collected at 159–170° (0.1 mm) [lit.[34] bp 230–232° (15 mm)], contained (tlc analysis with a silica gel coating and PhH as an eluent) a mixture of the desired ketone 11 (R_f 0.53) and the starting ketone 22 (R_f 0.39). A 1.914-g sample of this product was chromatographed on silica gel to separate 0.435 g of the starting material 22 (eluted with PhH) and 1.426 g (corresponding to a 57% yield) of the methylated ketone 11 as a colorless liquid which failed to crystallize: ir (CCl$_4$) 1706 cm^{-1} (C=O); uv (95% EtOH) series of weak (ϵ 218–418) maxima in the region 240–270 mμ as well as a maximum at 300 mμ (ϵ 97); nmr (CCl$_4$) δ 6.9–7.3 (10 H, m, aryl CH), 3.16 (1 H, d, *J* = 13.5 Hz, one benzylic CH), 2.86 (2 H, s, benzylic CH$_2$), 2.36 (1 Hd, *J* = 13.5 Hz, one benzylic CH), 1.6–2.5 (7 H, m, aliphatic CH), and 0.97 (3 H, d, *J* = 6.0 Hz, CH$_3$); mass spectrum *m/e* (rel intensity) 292 (1, M$^+$), 201 (90), 117 (19), 115 (15), and 91 (100).

Anal. Calcd for C$_{21}$H$_{24}$O: C, 86.25; H, 8.27. Found: C, 86.51; H, 8.35.

2-Benzyl-2-methylcyclohexanone (9). General Procedure for the Formation and Alkylation of an Enolate from an Enol Acetate.—Methyllithium (400 mmol, obtained by concentrating an Et$_2$O solution under reduced pressure) and 20 mg of 2,2-bipyridyl were dissolved in 400 ml of 1,2-dimethoxyethane and the resulting purple solution was cooled to 0°. While the temperature of the solution was kept at 0–10°, 29.3 g (190 mmol) of the enol acetate 13 was added dropwise and with stirring over 35–45 min. To the resulting cold (10°) red-orange (indicating excess methyllithium) solution was added rapidly (15 sec) 68.4 g (400 mmol) of benzyl bromide. The reaction mixture was stirred for 2–2.5 min (during which time the temperature rose to 30°) and then poured into 500 ml of cold (0–10°) saturated, aqueous NaHCO$_3$ and extracted with pentane. The pentane extract was dried, concentrated, and fractionally distillated to separate 31.4–40.8 g of forerun fractions [bp 71° (20 mm) to 87° (0.03 mm), n^{25}D 1.5045–1.5629] containing (glpc analysis, silicone gum, no. XE-60, on Chromosorb P) varying amounts of 2-methylcyclohexanone (retention time, 5.3 min), benzyl bromide (9.0 min), and bibenzyl (22.6 min).[35] Continued distillation afforded 20.7–22.2 g (53–58%) of 2-benzyl-2-methylcyclohexanone (9) as a colorless

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(27) R. Cornubert, M. Andre, M. de Demo, R. Joly, and A. Strebel, *Bull. Soc. Chim. Fr.*, **6**, 103 (1939).

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(29) J. M. Conia, C. Nevot, and P. Gosselin, *Bull. Soc. Chim. Fr.*, 1511 (1959); also see J. M. Conia, *Rec. Chem. Progr.*, **24**, 43 (1963).

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(31) W. S. Johnson, *J. Amer. Chem. Soc.*, **65**, 1317 (1943).

(32) R. Cornubert and C. Borrel, *C. R. Acad. Sci.*, **183**, 294 (1926); *Bull. Soc. Chim. Fr.*, **45**, 1148 (1929).

(33) (a) N. S. Bhacca and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 159–182; (b) J. Ronayne and D. H. Williams, *Ann. Rev. Nmr Spectrosc.*, **2**, 83 (1969).

(34) R. Cornubert and H. LeBihan, *C. R. Acad. Sci.*, **186**, 1126 (1928).

(35) The bibenzyl is formed from reaction of benzyl bromide with any excess methyllithium: see H. Gilman and F. K. Cartledge, *J. Organometal. Chem.*, **2**, 447 (1964); H. Gilman and A. H. Haubein, *J. Amer. Chem. Soc.*, **66**, 1515 (1944).

to pale yellow liquid, bp 87-93° (0.03 mm), n^{25}D 1.5322-1.5335 [lit. 178° (27 mm),[34] 147° (1.8 mm),[36] n^{15}D 1.5385[34]]. Glpc analysis (silicone gum, no. XE-60, on Chromosorb P) indicated that this ketone 9 (retention time 46.2 min.) contained less than 5% of the isomeric ketone 8 (43.0 min): ir (CCl₄) 1710 cm⁻¹ (C=O); uv (95% EtOH) series of weak (ε 134-253) maxima in the region 240-270 mμ with a maximum at 293 mμ (ε 70); nmr (CCl₄) δ 6.9-7.3 (5 H, m, aryl CH), 2.78 (2 H, s, benzylic CH₂), 2.2-2.6 (2 H, m, CH₂CO), 1.4-2.0 (6 H, m, aliphatic CH), and 0.95 (3 H, s, CH₃). The most reliable method we found for analyzing mixtures of ketones 8 and 9 consisted of measuring the nmr spectrum of mixtures in C₆D₆; in this solvent the ketone 9 has a characteristic 2 H singlet at δ 2.78 while the isomer 8 has a 1 H multiplet in the region 2.9-3.5 attributable to one of the two benzylic hydrogen atoms in the molecule. This analytical technique indicated that the product of this reaction, 9, contained less than 2% of its isomer 8. The mass spectrum of this product has the following relatively abundant peaks: m/e (rel intensity) 202 [32, M⁺], 91 (100), 55 (22), 44 (35), and 43 (23).

The brown residue (10 g) from the above distillation was triturated with pentane to separate the crude dibenzylated ketone 10 as white needles. A portion of this product was recrystallized from pentane to separate the pure 2,6-dibenzyl-2-methylcyclohexanone (10) as white needles: mp 106-107° (lit.[34] mp 105°); ir (CCl₄) 1710 cm⁻¹ (C=O); uv (95% EtOH) series of weak maxima (ε 265-436) in the region 240-270 mμ as well as a maximum at 296 mμ (ε 56); nmr (CCl₄) δ 7.0-7.3 (10 H, m, aryl CH), 3.22 (1 H, d of d, J = 12.0 and 3.5 Hz, one benzylic CH), 2.80 (2 H, s, benzylic CH₂), 2.0-2.7 (2 H, m, CHCO and one benzylic CH), 1.3-2.1 (6 H, m, aliphatic CH), and 1.12 (3 H, s, CH₃); mass spectrum m/e (rel intensity) 292 (17, M⁺), 201 (14), 117 (20), and 91 (100). In C₆D₆ solution, the nmr spectrum differs in that the benzylic CH₂ singlet is shifted downfield to δ 2.94 and the CH₃ singlet is shifted upfield to δ 0.86. These data indicate that the principle conformer present in the crystalline stereoisomer, mp 106-107°, which we have isolated has the methyl group axis.[33] Accordingly, we assign the crystalline product the configuration in which the benzyl groups at C-2 and C-6 are cis. The subsequently described glpc data indicate that the other stereoisomer, 2-methyl-*trans*-2,6-dibenzylcyclohexanone, was also present in the reaction mixture and that the two isomers were being interconverted under the conditions used for glpc analysis.

The results of other small-scale benzylations of the enolate anion 7b are summarized in eq 6. In these experiments, weighed amounts of an internal standard (hexadecane) were added to the crude alkylated product and it was subjected to glpc analysis employing equipment calibrated with known mixtures of authentic samples. For one of the glpc columns (silicone gum, no. SE-52, on Chromosorb P) employed, the following retention times were observed: 2, 4.2 min; benzyl bromide, 8.0 min; hexadecane, 23.5 min; monobenzyl products 8 and 9 (not resolved), 25.8 min; *trans*-stilbene, 27.7 min; dibenzyl product 11, 41.6 min; two stereoisomers of dibenzyl product 10 (partially resolved), 43.0 min. Since the monobenzylated products 8 and 9 were not resolved on this column, the proportions of these two isomers present were determined both by the previously described nmr analysis and by glpc analysis (silicone gum no. XE-60, on Chromosorb P). Retention times were as follows: 2,6 isomers 8, 34.0 min; 2,2 isomer 9, 36.0 min; and *trans*-stilbene, 39.9 min. The *trans*-stilbene was produced in small amounts in experiments where benzyl bromide was added to reaction mixtures which contained a substantial excess of lithium diisopropylamide.[37] Collected samples from typical reaction mixtures were identified with the previously described authentic samples by comparison of ir spectra and glpc retention times.

2-Methyl-6-benzylcyclohexanone (8). General Procedure for the Formation and Alkylation of an Enolate from a Kinetically Controlled Deprotonation of a Ketone with Lithium Diisopropylamide.—A solution of 200 mmol of methyllithium and 45 mg of 2,2-bipyridyl in 400 ml of 1,2-dimethoxyethane was prepared as previously described and then cooled to −50°. Diisopropylamine (21.0 g or 200 mmol) was added dropwise and with stirring over 2-3 min; during this addition external cooling was used to prevent the temperature of the solution from rising

above −20°. The resulting reddish-purple solution was stirred at −20° for 2-3 min and then 50 ml of a solution containing 21.3 g (190 mmol) of 2-methylcyclohexanone (2) in 1,2-dimethoxyethane was added, dropwise and with stirring over 25 min, during which time the temperature of the solution was kept between −20 and 0°. The resulting reddish-purple (indicating the presence of excess lithium diisopropylamide) solution was rapidly warmed to 30° with stirring and then 68.4 g (400 mmol) of benzyl bromide was added rapidly (15 sec). The resulting mixture was stirred for 6 min (during which time the temperature rose to 50° and then began to fall) and then poured into 500 ml of cold (0-10°) saturated, aqueous NaHCO₃ and extracted with pentane. The pentane extract was washed successively with aqueous 5% HCl and with aqueous NaHCO₃ and then dried, concentrated, and fractionally distilled. After separation of the forerun [31-34 g, bp 67° (20 mm) to 91° (0.03 mm)] containing 2-methylcyclohexanone and benzyl bromide, the monoalkylated product was collected as 21.3-23.3 g (54-61%) of colorless liquid, bp 91-97° (0.03 mm), n^{25}D 1.5282-1.5360. The monoalkylated product contained (previously described nmr and glpc analyses) 86-90% of the 2,6 isomers 8 and 10-14% of the 2,2 isomer 9. In some runs a few per cent of *trans*-stilbene was also present.[37] The pure 2,6 isomer 8 was separated from this mixture by selective formylation of the unwanted 2,2 product 9.[38,39] A mixture of the monoalkylated product (21-23 g or 104-114 mmol) and 3.74 g (50.5 mmol) of freshly distilled ethyl formate was added to a cold (0°) suspension of 2.59 g (47.8 mmol) sodium methoxide in 90 ml of anhydrous diethyl ether which was cooled in an ice bath. After the resulting suspension had been stirred for 10 min, the ice bath was removed and stirring was continued for an additional 50 min. Then the mixture was diluted with 300 ml of H₂O and extracted with ether. The ethereal extract was washed with aqueous 1 M NaOH and then dried, concentrated, and distilled. The pure 2-methyl-6-benzylcyclohexanone (8) was collected as 16.2-17.3 g of colorless liquid, bp 95-100° (0.3 mm), n^{25}D 1.5299-1.5328, which was identified with the previously described sample by comparison of glpc retention times and ir and nmr spectra.

This same alkylation reaction was performed on a small scale utilizing the various conditions summarized in eq B-D. An internal standard (hexadecane) was added to the crude alkylated product and it was subjected to analysis by the glpc and nmr methods previously described. On the glpc column (silicone gum, SE-52, on Chromosorb P) used to determine yields in the alkylation of 2-benzylcyclohexanone (3), the following retention times were observed: hexadecane, 24.6 min; ketone 3, 25.7 min; ketone 8 and 9 (not resolved), 27.0 min; dimethylated products from 2-benzylcyclohexanone, 27.5 min.

2-Benzylcyclohexanone (3). General Procedure for the Formation and Alkylation of an Enolate from a Trimethylsilyl Enol Ether.—A mixture of 15.31 g (90 mmol) of the silyl enol ether 18 and 65 ml of an ether solution containing 91 mmol of methyllithium was stirred at 25° for 30 min and then the ether was removed from the suspension of the lithium enolate. The residue was dissolved in 55 ml of 1,2-dimethoxyethane at 25° and then 16.20 g (94.9 mmol) of benzyl bromide was added. The solution, which was heated to boiling by the exothermic reaction, was stirred for 5 min and then partitioned between pentane and 100 ml of saturated aqueous NaHCO₃. Concentration and subsequent distillation of the pentane extract separated 0.36 g of forerun [bp 29-119° (1.1 mm), containing cyclohexanone, benzyl bromide, and the products from self-condensation of cyclohexanone] and 9.76 g (58%) of 2-benzylcyclohexanone (3) [bp 110-158° (1.1 mm), containing about 10% of the products from the the self-condensation of cyclohexanone]. The residue (3.97 g of yellow liquid) from the distillation was composed of the 2,2-dibenzyl ketone 22 (ca. 65%) and the 2,6-dibenzyl ketone 21 (ca. 35%). In a comparable reaction, the lithium enolate 19, prepared from 17.59 g (103.3 mmol) of the silyl enol ether 18 and 105.5 mmol of methyllithium in 75 ml of ether, was separated by centrifugation, washed with ether and dried under reduced pressure. The resulting solid enolate (9.52 g or 89% yield) was dissolved in 50 ml of 1,2-dimethoxyethane and then treated with 18.51 g (108.1 mmol) of benzyl bromide to yield

(36) S. Boatman, T. M. Harris, and C. R. Hauser, *J. Amer. Chem. Soc.*, **87**, 82 (1965).

(37) For examples of this transformation, see C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *ibid.*, **78**, 1653 (1956); D. R. Bryant, S. D. Work, and C. R. Hauser, *J. Org. Chem.*, **29**, 235 (1964).

(38) This experiment was performed in our laboratories by Mr. Michael J. Umen.

(39) This procedure was developed by W. J. Bailey and M. Madoff, *J. Amer. Chem. Soc.*, **76**, 2707 (1954); F. E. King, T. J. King, and J. G. Topliss, *J. Chem. Soc.*, 919 (1957).

10.58 g (62%) of the monoalkylated ketone **3**, bp 100–160° (1 mm). The distillation residue (2.00 g) contained the dialkylated products **21** and **22**.

The results of a number of small scale alkylations are summarized in eq J. In these reactions known amounts of an internal standard (tetralin) were added to the crude alkylation product before analysis. On the glpc column (Apiezon M on Chromosorb P) used for these analyses, the following retention times were observed: cyclohexanone, 4.0 min; the silyl enol ether **18**, 9.1 min; benzyl bromide, 14.0 min; tetralin, 19.8 min; 2-(1-cyclohexenyl)cyclohexanone and its double bond isomer, 41.0 and 42.4 min; benzyl enol ether **20**, 45.5 min; benzyl ketone **3**, 47.5 min; the 2,2-dibenzyl ketone **22**, 87.0 min; and the 2,6-dibenzyl ketone **21** 93.0 min. The apparatus used for analysis was calibrated with known mixtures of authentic samples and collected samples of the products from representative runs were identified with authentic samples by comparison of the glpc retention times and ir spectra. A collected sample of the selfcondensation product had spectroscopic properties consistent[40] with its formulation as the β,γ-unsaturated ketone, 2-(1-cyclohexenyl)cyclohexanone, accompanied by small amounts of the corresponding α,β-unsaturated isomer: ir (CCl₄) 1710 (strong, unconj C=O), 1685 (weak, conj C=O), and 1620 cm⁻¹ (C=C); nmr (CCl₄) δ 5.35 (*ca.* 0.7 H, broad, vinyl CH) and 1.2–3.1 (*ca.* 17 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 178 (72, M⁺) 149 (100), 135 (27), 81 (33), 79 (31) 67 (30), and 41 (24).

To demonstrate that the *O*-benzyl enol ether **20** does not react with the enolate anion 19 to form the benzyl ketone **3** under the conditions of the alkylation reaction, solutions containing approximately equimolar concentrations of the enolate anion 19 (from the silyl enol ether **18**) and either the benzyl enol ether **20** or the ketone **3** were stirred for 1 hr at 25°. The crude products, isolated as previously described, were mixed with weighed amounts of an internal standard (tetralin) and subjected to the glpc analysis. In one experiment, the recoveries of enol ether **20** and cyclohexanone were 97 and 100%, respectively. In the other experiment, the recovered 2-benzylcyclohexanone (**3**) and cyclohexanone amounted to 98 and 91%; the only other material detected was the previously described 2-(1-cyclohexenyl)cyclohexanone.

2-Methylcyclohexanone (2).—The lithium enolate 19, prepared from 17.0 g (100 mmol) of the silyl enol ether **18**, was separated from ether, dissolved in 120 ml of 1,2-dimethoxyethane, and methylated with methyl iodide to give the results summarized in eq I. The distilled product [8.41 g, bp 153–155° (760 mm)] contained (glpc analysis, Apiezon M suspended on Chromosorb P) *ca.* 8% cyclohexanone (retention time 6.8 min.), *ca.* 75% 2-methylcyclohexanone (**2**, 11.1 min), and *ca.* 17% of dialkylated products (14.8 and 17.2 min). A collected sample of the 2-methyl ketone **2** was identified with an authentic sample by comparison of glpc retention times and ir spectra.

Methylation of 1-Decalone (1). A. Formation of the Enolate Anion by Kinetically Controlled Deprotonation.—Following previously described procedures, the solution of enolate 4 in 25 ml of cold (−20°) 1,2-dimethoxyethane was prepared from 36 mmol of lithium diisopropylamide and 5.33 g (35.1 mmol) of 1-decalone (1). The pink (Ph₃CH indicator) solution was warmed to 26° and then allowed to react with 255 mmol of methyl iodide for 10 min. The crude product, 7.31 g of yellow liquid, contained (glpc analysis) *ca.* 17% of unchanged 1-decalone (1), *ca.* 80% of the 2-methyl isomers 5, and *ca.* 3% of the cis 9-methyl isomer **6**. The 2-methyl-1-decalone mixture was composed of *ca.* 40% of the most stable stereoisomer **5a** and *ca.* 60% of a second stereoisomer believed to have the stereochemistry indicated in structure **5b**. Three different glpc columns were used to analyze the mixtures of decalone derivatives. The retention times observed with the various glpc columns follow. (1) Apiezon M on Chromosorb P: 1-decalone (1), 12.3 min; cis 9-methyl isomer **6** accompanied by one or more of the 2-methyl isomers **5**, 16.7 min; *trans*-9-methyl isomer **17** and one or more of the 2-methyl isomers **5**, 19.2 min; dimethylated 1-decalones (isomers not identified), 24.2 min. (2) Carbowax 20M on Chromosorb P: 1-decalone (1) and the 2-methyl isomers **5** (not resolved), 31.4 min; cis 9-methyl isomer **6**, 36.3 min; *trans*-9-methyl isomer **17**, 43.8 min. (3) 1,2,3-Tris-(β-cyanoethoxy)propane on Chromosorb P: 2-methyl isomer **5a**, 21.2 min; 2-

5a   **5b**
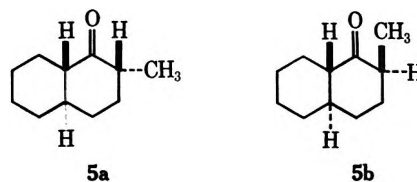
methyl isomer tentatively assigned stereochemistry **5b** and cis 9-methyl isomer 5 (not resolved), 24.5 min; trans 9-methyl isomer **17**, 31.0 min.

A solution of the crude alkylation product and 0.25 g of NaOCH₃ in 50 ml of methanol was refluxed for 1 hr and then concentrated and partitioned between aqueous NaCl and pentane. The mixture of 2-methyl isomers in the recovered product (5.14 g) was composed (glpc analysis) of *ca.* 87% of the most stable isomer **5a** accompanied by *ca.* 9% of the isomer thought to be **5b** and 4% of two minor unidentified components. To remove any remaining 1-decalone, a solution of the crude product, 1.00 g (10.4 mmol) of furfural,[41] 0.60 g (15 mmol) of NaOH, and 4 ml of H₂O in 200 ml of methanol was stirred at 25° for 2 hr, concentrated, acidified (aqueous HCl), and extracted with pentane. The pentane solution was dried, concentrated, and distilled to separate 3.86 g (66%) of 2-methyl-1-decalone, bp 78–80° (1.5 mm), n^{23}D 1.4811. This product contained (glpc analysis) 87% of the most stable isomer **5a** accompanied by 7% of the epimer believed to be **5b**, 3% of the *cis*-9-methyl isomer **6**, and 3% of two minor, unidentified components. This product was identified with the previously described[5a] sample of 2-methyl-1-decalone by comparison of glpc retention times and ir and mass spectra.

B. Formation of the Enolate Anions from the Trimethylsilyl Enol Ethers.—A solution of the enolates 4 in 30 ml of 1,2-dimethoxyethane, prepared from 40 mmol of methyllithium and 7.46 g (33.9 mmol) of the silyl ethers 16 (89% $\Delta^{1,9}$ and 11% $\Delta^{1,2}$ isomer), was cooled to 0° and treated with 8.42 g (59 mmol) of CH₃I. After the mixture had been stirred 40 sec, it was quenched with 50 ml of aqueous 5% HCl and then partitioned between pentane and aqueous NaCl. Distillation of the crude product afforded 4.46 g (79%) of 9-methyl-1-decalone, bp 69–71° (0.6 mm), n^{23}D 1.4874. This product contained (glpc analysis) *ca.* 8% of 1-decalone (1), *ca.* 12% of the 2-methyl isomers 5, *ca.* 54% of the *cis*-9-methyl ketone 6, *ca.* 15% of the *trans*-9-methyl ketone 17, and *ca.* 11% of dialkylated products. Collected samples of the 9-methyl ketones 6 and 17 were identified with previously described[5a] samples by comparison of glpc retention times and ir and mass spectra.

Preparation of Authentic Samples of the 2-Heptanone Derivatives. A. 1-Phenyl-3-octanone (27).—Condensation of 100 g (0.878 mol) of 2-heptanone with 100 g (0.944 mol) of benzaldehyde in the presence of 6.0 g (0.15 mol) of NaOH and 10 ml of H₂O yielded 58% of crude *trans*-1-phenyl-1-octen-3-one as a yellow liquid, bp 106–110° (0.1 mm). The product crystallized from pentane as white needles: mp 44.5–45.5° (lit.[42] mp 47°); ir (CCl₄), 1690, 1675 (conj C=O), and 1615 cm⁻¹ (conj C=C); uv maxima (95% EtOH) 222 mμ (ε 11,200) and 288 (21,800); nmr (CCl₄) δ 7.1–7.7 (6 H, m, aryl and vinyl CH), 6.62 (1 H, d, *J* = 16.6 Hz, vinyl CH), 2.54 (2 H, t, *J* = 6.7 Hz, CH₂CO), and 0.7–1.9 (9 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 202 (7, M⁺), 146 (48), 131 (100), 103 (34), and 77 (20).

The high boiling residue (35 g) also formed in this aldol condensation solidified on standing. Recrystallization from pentane and from hexane separated a white solid, mp 86–92°, believed to be a mixture of the stereoisomers of structure **35**: ir (CCl₄) 1715 (C=O), 1690, 1660 (conj C=O), 1615 (conj C=C), and 980 cm⁻¹ (trans CH=CH); uv maximum (95% EtOH), 295 mμ (ε 22,200); nmr (CCl₄) δ 6.7–7.4 (11 H, m, aryl and vinyl CH), 6.34 (1 H, d, *J* = 16.0 Hz, vinyl CH), 3.45 (1 H, q, *J* =

n-C₄H₉CHCOCH=CHC₆H₅
   |
C₆H₅CHCH₂COC₅H₁₁-*n*

35   **36**
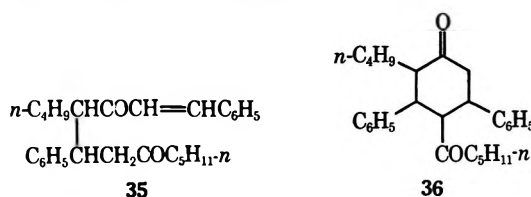
(40) E. Wenkert, S. K. Bhattacharya, and E. M. Wilson, *J. Chem. Soc.*, 5617 (1964), and references therein.

(41) W. S. Johnson, B. Bannister, and R. Pappo, *J. Amer. Chem. Soc.*, **78**, 6331 (1956).

(42) M. Metayer, *Recl. Trav. Chim. Pays-Bas*, **71**, 153 (1952).

7.0 Hz, CHCO), 2.8–3.2 (1 H, m, CH), 2.71 (2 H, d, J = 7.0 Hz, CH$_2$CO), 1.9–2.3 (2 H, m, CH$_2$CO), and 0.3–1.8 (18 H, m, aliphatic CH); mass spectrum m/e (rel intensity) 404 (3, M$^+$), 202 (13), 131 (100), 103 (30), 99 (18), 77 (16), and 43 (41).

Anal. Calcd for C$_{28}$H$_{36}$O$_2$: C, 83.12; H, 8.97. Found C, 83.06; H, 8.93.

The formation of dimers from a Michael reaction also occurred in attempts to generate the enolate from *trans*-1-phenyl-1-octen-3-one. A suspension of NaH (obtained by washing 1.2 g of a 50% dispersion with pentane) in 50 ml of 1,2-dimethoxyethane containing 10.1 g (50 mmol) of *trans*-1-phenyl-1-octen-3-one was stirred at ambient temperature for 6 hr and then partitioned between ether and aqueous NaHCO$_3$. After the ethereal extract had been dried and concentrated, recrystallization of the residual yellow solid from hexane separated 1.2 g of one stereoisomer of the crude diketone 36 as white needles, mp 135–160°. Recrystallization gave a pure stereoisomer of 36: mp 166–167°; ir (CCl$_4$), 1720 cm^{-1} (C=O); uv (95% EtOH) a series of weak (ϵ 173–536) maxima in the region 240–275 mμ; nmr (CDCl$_3$) δ 7.0–7.4 (10 H, m, aryl CH), 2.5–3.5 (6 H, m, CH α to CO and phenyl), 0.4–1.6 (20 H, m, aliphatic CH); mass spectrum m/e (rel intensity), 404 (25, M$^+$), 333 (17), 299 (22), 244 (24), 243 (100), 193 (25), 149 (73), 131 (25), 91 (38), and 43 (50).

Anal. Calcd for C$_{28}$H$_{36}$O$_2$: C, 83.12; H, 8.97. Found: C, 83.06; H, 9.12.

A methanol solution of the mother liquors from this separation deposited a second stereoisomer of diketone 36 as white needles: mp 87–88.5°; ir (CCl$_4$) 1715 cm^{-1} (C=O); uv (95% EtOH) series of weak (ϵ 179–549) maxima in the region 240–270 mμ; nmr (CCl$_4$) δ 6.8–7.3 (10 H, m, aryl CH), 2.5–3.9 (6 H, m, CH α to CO and phenyl), and 0.4–1.8 (20 H, m, aliphatic CH); mass spectrum m/e (rel intensity), 404 (12, M$^+$), 348 (16), 299 (22), 277 (25), 243 (48), 193 (45), 160 (100), 131 (41), 117 (53), 115 (32), 104 (36), 99 (31), 91 (48), 71 (26), and 43 (61).

Anal. Calcd for C$_{28}$H$_{36}$O$_2$: C, 83.12; H, 8.97. Found: C, 83.02; H, 9.06.

A solution of 20.2 g (0.100 mol) of *trans*-1-phenyl-1-octen-3-one in 150 ml of EtOH was hydrogenated at 25° and 14 psi over the catalyst from 300 mg of PtO$_2$. After 40 min the H$_2$ uptake (0.12 mol) ceased and the crude product was isolated and distilled. The 1-phenyl-3-octanone (27, 16.9 g or 83%) was collected as a pale yellow liquid: bp 85–88° (0.14 mm); n^{25}D 1.4941 [lit.[42] bp 165–167° (20 mm), n^{16}D 1.5056]; ir (CCl$_4$) 1720 cm^{-1} (C=O); uv (95% EtOH) series of weak (ϵ 174–220) maxima in the region 240–270 mμ as well as a maximum at 279 mμ (ϵ 49); nmr (CCl$_4$) δ 6.9–7.2 (5 H, m, aryl CH), 2.0–3.0 (6 H, m, COCH$_2$ and PhCH$_2$), and 0.6–1.8 (9 H, m, aliphatic CH); mass spectrum m/e (rel intensity) 204 (29, M$^+$), 148 (26), 132 (37), 130 (24), 105 (67), 99 (41), 91 (100), 71 (26), and 43 (47).

B. 3-Benzyl-2-heptanone (26).—A mixture of 53 g (0.47 mol) of 2-heptanone, 58 g (0.55 mol) of benzaldehyde, 125 ml of concentrated aqueous HCl, and 75 ml of 1,2-dimethoxyethane was refluxed for 3.5 hr and then partitioned between pentane and aqueous NaHCO$_3$. The organic layer was dried, concentrated, and distilled to separate 37 g (39%) of 3-benzal-2-heptanone as a yellow liquid: bp 97–98° (0.5 mm); n^{28}D 1.5452 [lit.[42] 154–158° (10 mm); n^{17}D 1.5512]; ir (CCl$_4$) 1675 (conj C=O) and 1625 cm^{-1} (conj C=C); uv maxima (95% EtOH) 220 mμ (ϵ 8850) and 280 (15,800); nmr (CCl$_4$) δ 6.9–7.2 (6 H, m, vinyl and aryl CH), 2.26 (3 H, s, CH$_3$CO), 2.1–2.5 (2 H, m, allylic CH$_2$), and 0.7–1.6 (7 H, m, aliphatic CH); mass spectrum m/e (rel intensity), 202 (75, M$^+$), 201 (47), 187 (33), 145 (23), 131 (22), 129 (24), 117 (100), 91 (85), and 43 (54).

A solution of 20.2 g (0.100 mol) of this unsaturated ketone in 150 ml of ethanol was hydrogenated at 25° and 31 psi over 0.5 g of Raney nickel catalyst. The crude product was distilled to separate 16.6 g (81%) of the ketone 26 as a colorless liquid: bp 87–98° (0.25 mm); n^{25}D 1.4968–1.4972 [lit.[42] bp 150° (14 mm.); n^{16}D 1.5040]; ir (CCl$_4$) 1715 cm^{-1} (C=O); uv (95% EtOH) series of weak (ϵ 180–264) maxima in the region 240–270 mμ; nmr (CCl$_4$) δ 6.9–7.2 (5 H, m, aryl CH), 2.4–2.9 (3 H, m, CHCO and benzylic CH$_2$), 1.85 (3 H, s, CH$_3$CO), and 0.7–1.7 (9 H, m, aliphatic CH); mass spectrum m/e (rel intensity), 204 (7, M$^+$), 148 (32), 147 (77), 91 (100), 44 (22), and 43 (63).

C. 1-Phenyl-4-benzyl-3-octanone (28).—Dibenzalacetone, mp 110–111° (lit.[43] 111°), was prepared as previously described: ir (CHCl$_3$) 1650 (conj C=O) and 1620 cm^{-1} (conj C=C); uv

maxima (95% EtOH) 231 mμ (ϵ 14,300) and 335 (34,100); nmr (CDCl$_3$) δ 7.70 (2 H, d, J = 15.8 Hz, vinyl CH), 7.2–7.6 (10 H, m, aryl CH), and 7.00 (2 H, d, J = 15.8 Hz, vinyl CH); mass spectrum m/e (rel intensity), 234 (100, M$^+$), 233 (82), 131 (54), 128 (25), 103 (89), 91 (34), 77 (71), and 51 (26). A solution of 20.0 g (85.5 mmol) of this unsaturated ketone in 200 ml of EtOAc was hydrogenated at 23° and 24 psi over 0.5 g of Raney nickel catalyst. After 80 min the H$_2$ uptake (0.16 mol) ceased and the crude product was separated and distilled. 1,5-diphenyl-3-pentanone was collected as 18.82 g (83%) of colorless liquid: bp 139–145° (0.09 mm); n^{24}D 1.5555–1.5570 [lit.[44] bp 223–227° (15 mm)]; ir (CCl$_4$) 1720 cm^{-1} (C=O); uv (95% EtOH) series of weak (ϵ 254–426) maxima in the region 240–270 mμ as well as a maximum at 280 mμ (ϵ 81); nmr (CCl$_4$) δ 6.8–7.3 (10 H, m, aryl CH) and 2.2–3.0 (8 H, m, aliphatic CH$_2$); mass spectrum m/e (rel intensity), 238 (42, M$^+$), 134 (26), 133 (61), 106 (26), 105 (23), and 91 (100).

A solution of the lithium enolate in 200 ml of cold (−60°) 1,2-dimethoxyethane was prepared as previously described by reaction of 11.21 g (47.2 mmol) of 1,5-diphenyl-3-pentanone with 60 mmol of lithium diisopropylamide. The purple (2,2-bipyridyl indicator) solution was warmed to 25°, mixed with 8.21 g (50 mmol) of *n*-butyl iodide, stirred for 14 hr, and then partitioned between pentane and aqueous NaHCO$_3$. The organic solution was washed successively with aqueous 10% HCl and aqueous NaHCO$_3$ and then dried and concentrated. Distillation afforded 10.93 g of colorless liquid as fractions, bp 135–146° (0.1 mm), $n^{23.5}$D 1.5359–1.5431, which contained (glpc analysis, silicone fluid, no. 710, on Chromosorb P) varying proportions of 1,5-diphenyl-3-pentanone (retention time 30.0 min, ca. 27% recovery), 1-phenyl-4-benzyl-3-octanone (28, 47.6 min, ca. 40% yield), and one or both of the dialkylated products 37, (73.6 min, ca. 9% yield). A collected (glpc) sample of the dialkylated material 37 had ir absorption (CCl$_4$) at 1715 cm^{-1} (C=O); mass

$$n\text{-C}_4\text{H}_9\text{CHCOCHC}_4\text{H}_9\text{-}n \qquad (n\text{-C}_4\text{H}_9)_2\text{CCOCH}_2\text{CH}_2\text{C}_6\text{H}_5$$
$$\underset{\text{C}_6\text{H}_5\text{CH}_2}{|} \quad \underset{\text{CH}_2\text{C}_6\text{H}_5}{|} \qquad\qquad \underset{\text{CH}_2\text{C}_6\text{H}_5}{|}$$
$$\textbf{37a} \qquad\qquad\qquad \textbf{37b}$$
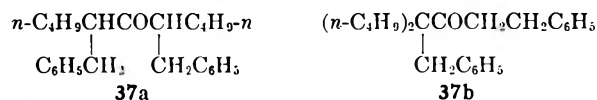
spectrum m/e (rel intensity) 350 (1, M$^+$), 161 (15) and 91 (100). A collected (glpc) sample of the ketone 28 was obtained as a colorless liquid: bp 146–147° (0.08 mm); $n^{23.5}$D 1.5331; ir (CCl$_4$) 1715 cm^{-1} (C=O); uv (95% EtOH) series of weak (ϵ 268–444) maxima in the region 240–270 mμ as well as a maximum at 290 mμ (ϵ 163); nmr (CCl$_4$) δ 6.7–7.2 (10 H, m, aryl CH), 2.1–3.0 (7 H, m, benzylic CH and CHCO), and 0.6–1.6 (9 H, m, aliphatic CH); mass spectrum m/e (rel intensity) 294 (13, M$^+$), 238 (22), 237 (32), 133 (27), 105 (40), and 91 (100).

Anal. Calcd for C$_{21}$H$_{26}$O: C, 85.66; H, 8.90. Found: C, 85.77; H, 8.91.

D. 1-Phenyl-2-benzyl-3-octanone (29b).—The usual procedure was employed to form the lithium enolate from 10.6 g (51.8 mmol) of 1-phenyl-3-octanone (27) and 60 mmol of lithium diisopropylamide in 235 ml of 1,2-dimethoxyethane. After 8.97 g (52.5 mmol) of benzyl bromide had been added, the mixture was stirred at ambient temperature and aliquots were removed periodically, hydrolyzed, and mixed with an internal standard (hexadecane) for glpc analysis. After 25 min the calculated yields were 49% of unchanged ketone 27, 35% of ketone 29b, and 15% of ketone 28. Two glpc columns were employed for this analysis; on a column packed with silicone gum SE-52 on Chromosorb P retention times were for benzyl bromide, 6.0 min; hexadecane, 20.2 min; ketone 27, 21.6 min; ketone 29b, 36.0 min; and ketone 28, 37.2 min. The retention times for a glpc column packed with silicone fluid no. 710 on Chromosorb P follow: ketone 29b, 13.8 min, and ketone 28, 15.6 min. The reaction mixture was stirred for 12 hr and then partitioned between pentane and aqueous NaHCO$_3$. Distillation of the organic phase separated 3.24 g (32%) of the starting ketone 27, bp 90–115° (0.1 mm), $n^{23.5}$D 1.5056, and 4.46 g (30%) of a mixture of monoalkylated products, bp 142–144° (0.1 mm), $n^{23.5}$D 1.5301–1.5320, containing 61% of ketone 29b and 39% of ketone 28. A pure sample of ketone 29b was collected (glpc): ir (CCl$_4$) 1715 cm^{-1} (C=O); uv (95% EtOH) series of weak (ϵ 303–476) maxima in the region 240–270 mμ and a maximum at 287 mμ (ϵ 129); nmr (CCl$_4$) δ 6.9–7.3 (10 H, m, aryl CH), 2.4–3.1 (5 H, m, benzylic CH and CHCO), and 0.5–2.0 (11 H, m, aliphatic CH); mass

(43) C. R. Conrad and M. A. Dolliver, "Organic Syntheses," Collect. Vol. 2, Wiley, New York, N. Y., 1943, p 167.

(44) J. M. Conia and P. Gosselin, *Bull. Soc. Chim. Fr.*, 836 (1961).

spectrum *m/e* (rel intensity) 203 (29), 91 (100), 71 (20), and 43 (44).

Anal. Calcd for $C_{21}H_{26}O$: C, 85.66; H, 8.90. Found: C, 85.40; H, 8.91.

The Benzylation of 2-Heptanone (23).—Solutions of lithium enolates were prepared from the ketone **23**, the enol acetate **24**, or the silyl enol ether **30** (contains 84% $\Delta^{1,2}$ and 16% $\Delta^{2,3}$ isomers) by the methods previously described. The results of the benzylation reactions are summarized in eq K and L. For small scale reactions the crude alkylated products were mixed with a weighed amount of internal standard (hexadecane) and analyzed by glpc (silicone gum SE-52 on Chromosorb P). The retention times of the various components follow: ketone **23**, 3.4 min; benzyl bromide, 8.4 min; ketone **26**, 19.6 min; hexadecane, 20.6 min; ketone **27**, 22.2 min; ketone **29b**, 34.0 min; and ketone **28**, 37.6 min. The glpc apparatus was calibrated with known mixtures of authentic samples and collected (glpc) samples of products from representative reactions were identified with authentic samples by comparison of glpc retention times and ir spectra. In certain of the alkylation experiments a third dialkylated product, thought to be **29a**, was also detected (retention time, 37.0 min on a glpc column packed with silicone gum SE-52 Chromosorb P). On a glpc column packed with silicone fluid no. 710 on Chromosorb P, retention times were for **29b**, 34.0 min; **29a**, 36.4 min; and **28**, 38.8 min. The nmr spectra (CCl_4) of collected samples containing this component **29a** had an additional singlet at δ 1.75 ($COCH_3$). Although we did not obtain a sufficient amount of this ketone **29a** for complete characterization, the spectra of a collected sample are consistent

with the structure assigned: ir (CCl_4) 1705 (C=O) and 1355 cm^{-1} (CH_3CO); mass spectrum *m/e* (rel intensity), 203 (28), 147 (46), 91 (65), and 43 (100).

In a preparative reaction performed in dilute solution where alkylation was relatively slow, the enolate from 11.06 g (87 mmol) of 2-heptanone (**23**) and 116 mmol of lithium diisopropylamide was allowed to react for 2.5 hr at 25° with 17.5 g (102 mmol) of benzyl bromide in 500 ml of 1,2-dimethoxyethane. Distillation of the crude product separated 5.6 g of forerun [bp 32° (60 mm) to 95° (8 mm), mainly 2-heptanone], 8.0 g (41%) of monobenzylated products [bp 70–80° (0.08 mm), n^{25}D 1.4912–1.5071, primarily ketone **26**], and 3.3 g (12%) of a mixture of dibenzylated ketones **28** and **29b** [bp 131–138° (0.08 mm), n^{25}D 1.5203–1.5281].

Registry No.—1, 583-60-8; 3, 946-33-8; 5a, 29478-32-8; 5b, 29478-33-9; *cis*-8, 29478-34-0; *trans*-8, 29478-35-1; 9, 1206-21-9; 10, 29478-36-2; 11, 29494-41-5; 20, 29494-42-6; 21, 7382-10-7; 22, 7382-11-8; 26, 29494-51-7; 27, 6047-99-0; 28, 29494-45-9; 29a, 29494-46-0; 29b, 29494-47-1; 35, 29478-38-4; 36, 29494-48-2; 1,1-dibenzyloxycyclohexane, 29494-49-3; 2-methyl-6-benzalcyclohexanone, 29494-50-6; *trans*-1-phenyl-1-octen-3-one, 29478-39-5; 3-benzal-2-heptanone, 10225-39-5; 1,5-diphenyl-3-pentanone, 5396-91-8.

Notes

A Comparison of Various Tetraalkylammonium Salts as Supporting Electrolytes in Organic Electrochemical Reactions[1]

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In both polarographic measurements[2a,b] and preparative electrochemical reactions[2a,c–e] with organic substrates, it has become common to use certain tetraalkylammonium salts as supporting electrolytes, especially with aprotic organic solvents such as acetonitrile, dimethylformamide (DMF), hexamethylphosphoramide (HMP), tetrahydrofuran (THF), or 1,2-dimethoxyethane.[3] In such aprotic solvents, electrochemical reductions at a mercury cathode may be performed at

highly negative potentials (−2.5 to −2.9 V *vs.* sce), the reduction potential ultimately being limited by the reduction of the quarternary ammonium cation **1** to form an amalgam **2**.[4] Although a variety of tetraalkyl-

$$R_4N^+ \xrightarrow[\text{Hg cathode}]{e^-} (R_4N)Hg_n$$

$$\mathbf{1} \qquad \qquad \mathbf{2},\ n = 12{-}13$$

ammonium salts have been prepared and studied,[3,4a,b,5] the salts most commonly used in electrochemical studies have been the readily available tetraethylammonium, tetra-*n*-propylammonium, and tetra-*n*-butylammonium salts, the counterions being iodide, bromide, chloride, perchlorate, and tetrafluoroborate. For polarographic measurements, the selection of a particular supporting electrolyte from among this group of salts is often not critical[6] since these measurements involve very small cell currents and low concentrations of electrolytes. However, the choice becomes more demanding for preparative electrochemical cells. Since relatively high cell currents are involved, it is important to keep the electrical resistance of the cell as low as practical to

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(2) (a) L. Meites, "Polarographic Techniques," 2nd ed, Interscience, New York, N. Y., 1965; (b) O. H. Müller, "Technique of Organic Chemistry," A. Weissberger, Ed., Vol. 1, Part 4, 3rd ed, Interscience, New York, N. Y., 1960, pp 3155–3279; (c) L. Meites, ref 2b, pp 3281–3333; (d) S. Swann, Jr., "Technique of Organic Chemistry," A. Weissberger, Ed., Vol. 2, 2nd ed, Interscience, New York, N. Y., 1956, pp 385–523; (e) M. J. Allen, "Organic Electrode Processes," Reinhold, New York, N. Y., 1958.

(3) For a review of the properties of these solvents and a brief survey of supporting electrolytes, see C. K. Mann, "Electroanalytical Chemistry," A. J. Bard, Ed., Vol. 3, Marcel Dekker, New York, N. Y., 1969, pp 57–134.

(4) (a) B. C. Southworth, R. Osteryoung, K. D. Fleischer, and F. C. Nachod, *Anal. Chem.,* **33**, 208 (1961); (b) J. D. Littlehailes and B. J. Woodhall, *Discuss. Faraday Soc.,* 187 (1968); (c) J. Myatt and P. F. Todd, *Chem. Commun.,* 1033 (1967); (d) analogous amalgams are formed by the reduction of phosphonium and sulfonium salts [W. R. T. Cottrell and R. A. N. Morris, *ibid.,* 409 (1968)].

(5) For examples, see (a) J. E. Gordon, *J. Amer. Chem. Soc.,* **87**, 4347 (1965); (b) T. G. Coker, J. Ambrose, and G. J. Janz, *ibid.,* **92**, 5293 (1970).

(6) J. P. Petrovich [*Electrochim. Acta,* **12**, 1429 (1967)] has reported changes in the values for polarographic half-wave potentials which appear to depend on the size of the quaternary ammonium cation.

TABLE I

SOLUBILITIES OF TETRAALKYLAMMONIUM SALT ELECTROLYTES AND SPECIFIC RESISTANCES OF THE SOLUTIONS

	Solvent							
	CH₃CN		CH₃OCH₂CH₂OCH₃		Tetrahydrofuran		(CH₃)₂NCHO	
Electrolyte (mp, °C)	Solubility, g/100 ml of solution (concn, M)	Specific resistance, ohm cm (concn, M)	Solubility, g/100 ml of solution (concn, M)	Specific resistance, ohm cm (concn, M)	Solubility, g/100 ml of solution (concn, M)	Specific resistance, ohm cm (concn, M)	Solubility, g/100 ml of solution (concn, M)	Specific resistance, ohm cm (concn M)
Et_4NClO_4 (351–352.5 dec)	26 (1.13)	26 (0.60)	(<0.01)		(<0.01)		23 (1.00)	52 (0.60)
$(n\text{-}Pr)_4NClO_4$ (239–240.5)	21 (0.74)	31 (0.60)	(<0.01)		(<0.01)		21 (0.74)	64 (0.60)
$(n\text{-}Bu)_4NClO_4$ (212.5–213.5)	70 (2.05)	37 (0.60)	31 (1.10)	312 (1.0)	50 (1.48)	368 (1.0)	79 (2.29)	77 (0.60)
Et_4NBF_4 (377–378 dec)	37 (1.69)	18 (1.0)	(<0.01)		(<0.01)		27 (1.24)	38 (1.0)
$(n\text{-}Pr)_4NBF_4$ (248–249)	36 (1.32)	23 (1.0)	(<0.01)		(<0.01)		32 (1.17)	51 (1.0)
$(n\text{-}Bu)_4NBF_4$ (162–162.5)	71 (2.21)	31 (1.0)	53 (1.70)	228 (1.0)	65 (2.02)	373 (1.0)	75 (2.34)	69 (1.0)
Et_4NBr (282–287 dec)	7.8 (0.37)		(<0.01)		(<0.01)		4.1 (0.19)	
$(n\text{-}Pr)_4NBr$ (274–281 dec)	29 (1.09)	39 (0.60)	(<0.01)		(<0.01)		18 (0.70)	88 (0.60)
$(n\text{-}Bu)_4NBr$ (119–119.5)	66 (1.99)	48 (0.60)	(<0.1)		4.8 (0.14)		52 (1.57)	106 (0.60)

TABLE II

SPECIFIC RESISTANCES AND LIMITING REDUCTION POTENTIALS FOR TETRAALKYLAMMONIUM SALT SOLUTIONS

	Salt							
	Et_4NBF_4		$(n\text{-}Bu)_4NBF_4$		$(n\text{-}Bu)_4NClO_4$		$(n\text{-}Bu)_4NBr$	
Solvent	Specific resistance, ohm cm (concn, M)	Limiting reduction potential, V (vs. sce)[a]	Specific resistance, ohm cm (concn, M)	Limiting reduction potential, V (vs. sce)[a]	Specific resistance, ohm cm (concn, M)	Limiting reduction potential, V (vs. sce)[a]	Specific resistance, ohm cm (concn, M)	Limiting reduction potential, V (vs. sce)[a]
Tetrahydrofuran			373 (1.0), 587 (0.50)	−2.75	369 (1.0), 583 (0.50)	−2.90		
1,2-Dimethoxy-ethane			228 (1.0), 339 (0.50)	−2.75	312 (1.0), 495 (0.50)	−2.85		
Acetonitrile	18 (1.0), 27 (0.50)	−2.70	31 (1.0), 33 (0.50)	−2.74	37 (0.60), 39 (0.50)	−2.77	48 (0.60), 48 (0.50)	−2.76
Dimethyl-formamide	38 (1.0), 54 (0.50)	−2.72	69 (1.0), 72 (0.50)	−2.80	77 (0.60), 82 (0.50)	−2.85	106 (0.60), 110 (0.50)	−2.80
Hexamethyl-phosphoramide	538 (0.30)	−2.70[b]	555 (0.50)	−2.90	1125 (0.50)	−2.85	1135 (0.30)	−2.85[b]

[a] The voltage at which the actual residual current exceeds by a factor of three the value obtained by extrapolating the line defined by the residual current readings in the region −0.5 to −1.5 V. Unless otherwise noted all solutions used for polarographic measurement were 0.50 M in the ammonium salt. [b] The concentration of the ammonium salt was 0.30 M.

avoid a large voltage drop across the cell and the associated liberation of excessive heat as the electrolysis proceeds. Furthermore, the substantial amounts of these electrolytes required in preparative electrolyses make it prudent to select salts which both are easily prepared and/or purified and are relatively economical.

To provide a basis for selecting supporting electrolytes from among the easily accessible ammonium salts, we have prepared and/or purified the commonly used salts and have determined the solubilities of these salts in the aprotic solvents frequently used in electrochemical reactions. In those cases where the salts were soluble in useful concentrations, the specific resistances of the solutions were also determined. For those solvent–electrolyte solutions which appeared most useful for electrochemical preparations, the specific resistances were measured at two different concentrations and the background reduction potentials for the solutions were measured. These data are summarized in Tables I and II.

Experimental Section[7]

Preparation of the Tetrafluoroborates. A. Tetra-n-butylammonium Tetrafluoroborate.—A solution of 8.4 g (25 mmol) of (n-Bu)₄NBr (Eastman) in a minimum volume of H_2O (ca. 18 ml) was treated with 3.6 ml (ca. 26 mmol) of aqueous 48–50% HBF₄ (Allied Chemical). The resulting mixture was stirred at 25° for 1 min and then the crystalline salt was collected on a filter, washed with H_2O until the washings were neutral, and dried. The crude salt (6.3 g or 79%, mp 155–157°) was recrystallized three times from EtOAc–pentane mixtures to separate 6.0 g (75%) of (n-Bu)₄NBF₄ as white needles: mp (after drying) 162–162.5° (lit. mp 153–155°,[8a] 161.8°,[8b] 166⁵ᵇ); ir (CHCl₃) no OH, NH, or C=O absorption in 3- and 6-μ regions; uv (95%

(7) All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined with a Perkin-Elmer Model 237 or Model 257 infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The nmr spectra were determined at 60 Mc with a Varian Model A-60 or Model T-60 nmr spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to a tetramethylsilane internal standard.

(8) (a) C. M. Wheeler, Jr., and R. A. Sandstedt, *J. Amer. Chem. Soc.*, **77**, 2025 (1955); (b) C. R. Witschonke and C. A. Kraus, *ibid.*, **69**, 2472 (1947).

EtOH) weak end absorption (ϵ 1.6 at 205 mμ); nmr (CDCl$_3$) δ 3.0–3.5 (8 H, m, CH$_2$N), 1.2–2.0 (16 H, m, CH$_2$), and 0.8–1.2 (12 H. m, CH$_3$).

B. Tetra-*n*-propylammonium Tetrafluoroborate.—Use of the same procedure with 6.7 g (25 mmol) of (*n*-Pr)$_4$NBr (Eastman) in *ca.* 13 ml of H$_2$O yielded 5.1 g (75%) of the crude tetrafluoroborate salt, mp 243–245°. Recrystallization from a MeOH–petroleum ether (bp 30–60°) mixture afforded 4.6 g (65%) of the pure (*n*-Pr)$_4$NBF$_4$ as white needles: mp (after drying) 248–249° (lit. mp 239°,[5b] 244–244.5°,[9] 249–250[8a]); ir (CHCl$_3$) no OH, NH, or C=O absorption in 3- and 6-μ regions; nmr (CDCl$_3$) δ 3.0–3.4 (8 H, m, CH$_2$N), 1.3–2.1 (8 H, m, CH$_2$), and 1.03 (12 H, t, J = 7 Hz, CH$_3$).

C. Tetraethyl Tetrafluoroborate.—Reaction of 5.3 g (25 mmol) of Et$_4$NBr (Eastman) in *ca.* 8 ml of H$_2$O with HBF$_4$ followed by concentration, dilution with Et$_2$O, and filtration afforded 4.6 g (85%) of the crude tetrafluoroborate salt, mp 375–378° dec. Two recrystallizations from a MeOH–petroleum ether (bp 30–60°) mixture separated 3.7 g (69%) of pure Et$_4$NBF$_4$ as white needles: mp (after drying) 377–378° dec (lit. mp 365–367°,[8a] 377–378°[10]); ir (KBr pellet) no OH, NH, or C=O absorption in the 3- and 6-μ regions; nmr (D$_2$O) δ 3.23 (8 H, q, J = 8 Hz, CH$_2$N) and 1.28 [12 H, triplet of triplets, J = 8 Hz (H–H) and 2 Hz (N–H)].

Before use in various measurements, each of these tetrafluoroborate salts was pulverized and dried at 80–100° under reduced pressure (0.2–0.3 mm) for 48–96 hr.

Preparation of the Perchlorates. A. Tetra-*n*-butylammonium Perchlorate.—A saturated aqueous solution of 8.4 g (25 mmol) of (*n*-Bu)$_4$NBr in 18 ml of H$_2$O was treated with 2.1 ml (*ca.* 26 mmol) of aqueous 70–72% HClO$_4$ (Baker). After the resulting insoluble perchlorate salt had been collected, washed with cold H$_2$O, and dried, the yield was 8.0 g (94%), mp 197–199°. Two recrystallizations from an EtOAc–pentane mixture separated 7.6 g (90%) of pure (*n*-Bu)$_4$NClO$_4$ as white needles which were dried at 100° under reduced pressure: mp 212.5–213.5° (lit. mp 207–209°,[11a] 212–212.5°,[11b] 213.3–213.6°[11c]); ir (CHCl$_3$) no OH, NH, or C=O absorption in the 3- and 6-μ regions; nmr (pyridine-*d$_5$*) δ 3.2–3.7 (8 H, m, CH$_2$N), 1.2–2.2 (16 H, m, CH$_2$), and 0.8–1.2 (12 H, m, CH$_3$).

B. Tetra-*n*-propylammonium Perchlorate.—By the same procedure 6.7 g (25 mmol) of (*n*-Pr)$_4$NBr (in *ca.* 13 ml of H$_2$O) was converted to 6.8 g (94%) of the crude perchlorate salt, mp 232–235°. Recrystallization from aqueous acetone afforded 5.9 g (82%) of the pure (*n*-Pr)$_4$NClO$_4$ as white needles which were dried at 100° under reduced pressure: mp 239–240.5° (lit. mp 237–239°[11a]); ir (KBr pellet) no OH, NH, or C=O absorption in the 3- and 6-μ regions; nmr (pyridine-*d$_5$*) δ 3.1–3.6 (8 H, m, CH$_2$N), 1.3–2.2 (8 H, m, CH$_2$), and 0.95 (12 H, t, J = 7 Hz, CH$_3$).

C. Tetraethylammonium Perchlorate.—The same procedure was used to convert 5.3 g (25 mmol) of Et$_4$NBr (in *ca.* 8 ml of H$_2$O) to 4.7 g (81%) of the crude perchlorate salt, mp 343–344° dec (solution cooled before filtration). Recrystallization from water separated 4.3 g (75%) of the pure Et$_4$NClO$_4$ as white needles which were dried at 100° under reduced pressure: mp 351–352.5° dec;[12] ir (KBr pellet) no OH, NH, or C=O absorption in the 3- and 6-μ regions; nmr (pyridine-*d$_5$*) δ 3.39 (8 H, q, J = 7.5 Hz, CH$_2$N) and 1.28 [12 H, triplet of triplets, J = 7.5 Hz (H–H) and 1.9 Hz (N–H)].

Each of the perchlorate salts was pulverized and dried at 80–100° under reduced pressure (0.2–0.3 mm) for 48–96 hr before being used to obtain the measurements summarized in Tables I and II.

Purification of the Tetraalkylammonium Bromides.—Commercial samples of each of the three bromides were dissolved in boiling CHCl$_3$ and then the hot solution was filtered, diluted with petroleum ether (bp 30–60°), and cooled. Each of the crystalline bromides was collected, pulverized, and dried at 100° under reduced pressure (0.2–0.3 mm) for 10 hr. Tetra-*n*-butylammonium bromide was obtained as white prisms: mp 119–119.5°

(lit. mp 118°,[8b,13] 122°[5b]); ir (CCl$_4$) weak, broad absorption at 3380 cm^{-1} (associated OH of H$_2$O impurity) with no other OH, NH, or C=O absorption in the 3- and 6-μ regions; nmr (CCl$_4$) δ 3.3–3.8 (8 H, m, CH$_2$N), 1.3–2.2 (16 H, m, CH$_2$), and 0.8–1.3 (12 H, m, CH$_3$); uv (95% EtOH) end absorption (ϵ 400 at 210 mμ).

Tetra-*n*-propylammonium bromide was obtained as white prisms: mp 274–281° dec (dependent on rate of heating; lit.[14] mp 252°); ir (CHCl$_3$) broad, weak absorption at 3360 cm^{-1} (assoc OH of H$_2$O impurity) with no other OH, NH, or C=O absorption in the 3- or 6-μ regions; nmr (CDCl$_3$) δ 3.2–3.7 (8 H, m, CH$_2$N), 1.4–2.2 (8 H, m, CH$_2$), and 1.06 (12 H, t, J = 7 Hz, CH$_3$); uv (95% EtOH) end absorption (ϵ 360 at 210 mμ).

Tetraethylammonium bromide was obtained as white prisms: mp 282–287° dec (dependent on rate of heating; lit.[15] 305° dec); ir (CHCl$_3$) 3370 cm^{-1} (broad, assoc OH of H$_2$O impurity), no C=O absorption in the 6-μ region; nmr (CDCl$_3$) δ 3.51 (8 H, q, J = 7 Hz, CH$_2$N) and 1.43 (12 H, triplet of multiplets, J = 7 Hz, CH$_3$); uv (95% EtOH) end absorption (ϵ 400 at 210 mμ).

Tetra-*n*-butylammonium Acetate.—To 29 ml of a MeOH solution containing 28 mmol of (*n*-Bu)$_4$NOH was added 1.65 g (28 mmol) of HOAc. The solution was concentrated under reduced pressure at 25°. The yellow solid which separated upon cooling was collected and recrystallized from 1,2-dimethoxyethane at Dry Ice temperature. The crude (*n*-Bu)$_4$NOAc separated as 2.89 g (67%) of fine yellow crystals: mp 75–83°; ir (KBr pellet) 1420 and 1570 cm^{-1} (carboxylate C=O); nmr (CDCl$_3$) δ 3.2–3.6 (8 H, m, CH$_2$N), 1.96 (3 H, s, CH$_3$CO), 1.3–2.0 (16 H, m, CH$_2$), and 0.9–1.2 (12 H, m, CH$_3$).

All of our attempts to further purify this salt resulted in sufficient decomposition to yield the less soluble acetic acid solvate (*n*-Bu)$_4$NOAc·HOAc. This material crystallized from benzene as white needles: mp 112.5–114° (lit. mp 113–117°,[16] 116.5–117.5°,[11b] 118°[8b]); ir (KBr pellet) 1675 (broad) and 1390 cm^{-1} (broad, carboxyl and carboxylate C=O); nmr (CDCl$_3$) δ 12.85 (1 H, s, OH), 3.1–3.5 (8 H, m, CH$_2$N), 1.91 (6, H, s, CH$_3$CO), 1.2–2.0 (16 H, m, CH$_2$), and 0.8–1.2 (12 H, m, CH$_3$).

Purification of Solvents.—Tetrahydrofuran and 1,2-dimethoxyethane were distilled from LiAlH$_4$ immediately before use. Commercial acetonitrile was first distilled from NaH[17] and then redistilled from P$_2$O$_5$ to give pure material, bp 80–80.5°, n^5D 1.3440. Sodium (4 g/l.) was dissolved in freshly distilled hexamethylphosphoramide and the pure solvent was distilled from this blue solution under reduced pressure, bp 76.5° (1.4 mm). Because of the continual difficulty we encountered from the presence of dimethylamine when dimethylformamide was distilled at atmospheric pressure,[3] we followed the purification procedure of Brummer[18] in which the DMF was allowed to stand over molecular sieves, type 4A, for several hours and the solvent was then decanted and distilled under reduced pressure, bp 43° (6 mm). The specific resistances of these purified solvents, determined as described subsequently, follow: THF, 2.7 × 10^5 ohm cm; 1,2-dimethoxyethane, 3.5 × 10^6 ohm cm; DMF, 8.0 × 10^6 ohm cm; acetonitrile, 1.5 × 10^6 ohm cm; and HMP, 1.6 × 10^5 ohm cm.

Measurement of Solubilities.—Mixtures of the purified solvents and an excess of each dried, purified salt were stirred in a bath at 25° and 3.00-ml aliquots of the supernatant liquid were removed after periods of 2 and 3 hr. The aliquots were concentrated to dryness under reduced pressure, and the weights of the residual solutes were determined when these weights became constant. The results are summarized in Table I. Since several of the very concentrated solutions were extremely viscous, complete saturation of the solvent may not have been achieved. Because of the difficulty of removing HMP from solutions, the maximum solubility of salts in this solvent were not determined.

Specific Resistance Measurements.—A conductivity cell, fitted with platinized Pt electrodes and immersed in a 25° bath, was used for all measurements. The cell constant, 1.06 cm^{-1}, for this cell was determined with aqueous 0.100 M KCl.[19] The

(9) P. H. Reichenbacher, M. D. Morris, and P. S. Skell, *J. Amer. Chem. Soc.*, **90**, 3432 (1968).

(10) N. S. Moe, *Acta Chem. Scand.*, **19**, 1023 (1965).

(11) (a) N. C. Deno and H. E. Berkheimer, *J. Org. Chem.*, **28**, 2143 (1963); (b) S. Winstein, P. E. Klinedinst, and G. C. Robinson, *J. Amer. Chem. Soc.*, **83**, 885 (1961); (c) Y. H. Inami and J. B. Ramsey, *J. Chem. Phys.*, **31**, 1297 (1959).

(12) For previous descriptions of this salt, see I. M. Kolthoff and J. F. Coetzee, *J. Amer. Chem. Soc.*, **79**, 870 (1957); M. Sakuma and P. J. Elving, *Electrochim. Acta*, **10**, 309 (1965).

(13) M. B. Reynolds and C. A. Kraus, *J. Amer. Chem. Soc.*, **70**, 1709 (1948).

(14) S. Sugden and H. Wilkins, *J. Chem. Soc.*, 1291 (1929).

(15) K. R. Brower and J. S. Chen, *J. Amer. Chem. Soc.*, **87**, 3396 (1965).

(16) C. D. Russell and F. C. Anson, *Anal. Chem.*, **33**, 1282 (1961).

(17) G. A. Forcier and J. W. Olver, *ibid.*, **37**, 1447 (1965).

(18) S. B. Brummer, *J. Chem. Phys.*, **42**, 1636 (1965).

(19) The specific conductance of this solution at 25° was taken as 0.012856 ohm^{-1} cm^{-1}; G. Jones and B. C. Bradshaw, *J. Amer. Chem. Soc.*, **55**, 1780 (1933).

resistances were measured with a 1-kHz sine wave signal employing either a General Radio Co. Impedance Comparator, Type 1605-A, or a Serfass Conductivity Bridge, Model RCM15. The specific resistance values for the various electrolyte solutions are summarized in Table I and II.

Polarographic Reduction Potentials.—The background reduction potentials listed in Table II were obtained with a Heath dropping mercury electrode apparatus (Model EUA-19-6) connected to a Heath polarograph module (EUA-19-2), operational amplified (EUA-19-B), amplifier stabilizer (EUA-19-4), and recorder (EU-20V). A Pt wire was employed as an anode and the reference electrode, a Coleman Model 3-512 saturated calomel electrode, was connected to the solution through salt bridges of aqueous 1.0 M NaNO$_3$ and 0.5 M Et$_4$NBF$_4$ in DMF. The limiting background reduction potential for the various solutions was arbitrarily selected to be that voltage at which the actual residual current exceeded by a factor of three, the value obtained by extrapolating the line determined by the residual current readings in the region -0.5 to -1.5 V. To determine the effect of H$_2$O on these background readings, a portion of each solution was diluted with 5% (by volume) of H$_2$O (concentration 2.8 M) and the readings were repeated. These solutions exhibited an additional polargraphic wave with $E_{1/2}$ values in the range -1.7 to -2.0 V vs. sce.
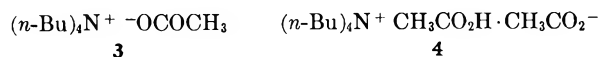
Discussion

Of the various methods[3] which have been employed to prepare the tetraalkylammonium perchlorates and tetrafluoroborates in the laboratory, we consider the reaction of concentrated aqueous solutions of the commercially available tetraalkylammonium bromides with either perchloric acid or tetrafluoroboric acid to be both the most convenient and the most economical. The resulting perchlorates and tetrafluoroborates, which are sparingly soluble in water, were readily collected and then recrystallized from organic solvents and dried to afford the pure salts in good yield. It is often desirable in preparative electrolytic reductions to select a supporting electrolyte whose anion will be oxidized at the anode to produce materials which will not interact with the reduction products formed at the cathode.[20] For this reason the use of tetraalkylammonium bromides as supporting electrolytes is often objectionable because bromine is produced at inert anodes (e.g., Pt or C) and the use of a silver anode (to form AgBr) becomes prohibitively expensive for large-scale preparations. The perchlorate and tetrafluoroborate salts also do not provide the necessary reactants for a discrete anode reaction to form inert products; instead, oxidation of the perchlorate anion or oxidative degradation of the solvent is often observed.[21] Because of these problems, we were led to explore the possibility of preparing a tetraalkylammonium acetate salt as a supporting electrolyte. The acetate anion moiety in such salts would provide the reactant for a Kolbe reaction[22] at the anode to form ethane and carbon dioxide. Although our attempts to obtain crystalline acetates with the tetraethylammonium and tetra-n-propylammonium cation were not successful, we were able to obtain a crude sample of tetra-n-butylammonium acetate (3), mp 75–83°. However, all our efforts to purify this salt 3 resulted in

(20) This consideration is true even with divided cells since any inert cell divider which offers a reasonably low electrical resistance will also allow material to diffuse from the anode compartment to the cathode compartment.

(21) (a) For examples, see N. L. Weinberg and H. R. Weinberg, *Chem. Rev.*, **68**, 449 (1968); (b) R. Brettle and D. Seddon, *J. Chem. Soc. C*, 1153 (1970); (c) K. Koyama, T. Susuki, and S. Tsutsumi, *Tetrahedron*, **23**, 2665 (1967); (d) M. Fleischmann and D. Pletcher, *Tetrahedron Lett.*, 6255 (1968); (e) K. Nyberg, *Chem. Commun.*, 774 (1969).

(22) For a recent review and leading references, see A. K. Vijh and B. E. Conway, *Chem. Rev.*, **67**, 623 (1967).

$$(n\text{-Bu})_4\text{N}^+ \ ^-\text{OCOCH}_3 \qquad (n\text{-Bu})_4\text{N}^+ \ \text{CH}_3\text{CO}_2\text{H}\cdot\text{CH}_3\text{CO}_2^-$$
$$\mathbf{3} \qquad\qquad\qquad\qquad\qquad \mathbf{4}$$

its partial decomposition (presumably in a Hofmann degradation) to form the less soluble complex 4, mp 112.5–114°, which contained 1 mol of acetic acid per mol of salt. The acetic acid–salt complex 4 has been reported previously[8b,11b,16] but some workers have erroneously referred to it as pure tetra-n-butylammonium acetate. We are continuing our search for quaternary ammonium carboxylate salts which will be both readily accessible and easily obtainable in pure form.

Among the bromide, perchlorate, and tetrafluoroborate salts which we have examined (Table I), the bromides are distinctly less soluble than the other salts in aprotic solvents, tetra-n-butylammonium bromide being the least objectionable in this respect. The solubility properties of the tetrafluoroborates and the corresponding perchlorates are very similar with the tetra-n-butylammonium derivatives being more soluble than the lower homologs in both series. At equivalent molar concentrations the specific resistances (Table II) of solutions containing the tetrafluoroborates and the corresponding perchlorates are also very similar. As might be expected with a series of homologous salts, the specific resistance of the solutions increases slightly with an increase in the steric bulk of the quaternary ammonium cation. A much more important factor in determining the specific resistance of these concentrated electrolytic solutions is the solvent used. With the relatively nonpolar solvents, tetrahydrofuran and 1,2-dimethoxyethane [dielectric constants[3] 7.39 (25°) and 3.49 (20°)], the specific resistances of concentrated electrolyte solutions are about ten times the values obtained with solutions in the polar solvents, acetonitrile and dimethylformamide [dielectric constants[3] 37.45 (20°) and 36.7 (25°)]. This is presumably attributable to the higher average degree of aggregation of the concentrated (0.5–1.0 M) salt solutions in the nonpolar ethereal solvents. Although hexamethylphosphoramide is a relatively polar solvent [dielectric constant 30 (20°)],[23] concentrated solutions of the quaternary ammonium salts in this solvent are very viscous and the high specific resistance of these solutions is presumably attributable to this fact. Table III illustrates that with less-concentrated solutions of n-Bu$_4$NBF$_4$ the specific resistances become more nearly the same in hexamethylphosphoramide and in dimethylformamide. For the more dilute solutions in hexamethylphosphoramide, the resistance values obtained correspond to values obtained in conductance measurements with similar salts.[24]

As indicated in Table II, the reduction potentials at a mercury cathode with these supporting electrolytes are limited to about -2.7 V (vs. sce) for the tetraethylammonium salts and about -2.8 to -2.9 V (vs. sce) for the tetra-n-butylammonium salts. At these potentials reduction of the quaternary ammonium cation 1 to the amalgams begins to occur at a significant rate [$E_{1/2}$ values (vs. sce),[4b] -2.8 V for Et$_4$N$^+$, and -3.0 V for (n-Bu)$_4$N$^+$]. The values of these limiting potentials are approximately constant for the various aprotic solvents examined. The deliberate addition of water

(23) H. Normant, *Bull. Soc. Chim. Fr.*, 791 (1968).

(24) A. Cserhegyi, J. Jagur-Grodzinski, and M. Szwarc, *J. Amer. Chem. Soc.*, **91**, 1892 (1969).

Electrolyte concn, M	Specific resistance at 25°, ohm cm	
	DMF	HMP
0.5	73	555
0.25	110	608
0.05	382	1780
0.01	1450	5250

(2.8 M) to these solutions resulted in the appearance of a new reduction wave in the potential range -1.7 to -2.0 V ($vs.$ sce) which we presume corresponds to the reduction of protons to hydrogen. However, the presence of small amounts of water in these solutions does not significantly change the limiting reduction potentials attainable.[25]

From the foregoing information we concluded that the optimum salts to use as supporting electrolytes in aprotic solvents are the tetra-n-butylammonium salts. Only in instances where obtaining the minimum resistance in an electrolyte solution is essential (as in salt bridges to reference electrodes) does there appear to be any advantage offered by the tetraethylammonium salt.

Either the tetrafluoroborate or the perchlorate salt of a particular quaternary ammonium cation offer about the same advantages in terms of solubility and solution resistance. However, except in certain oxidations where the choice of the anion may control the nature of the reaction product,[21e] there are at least two reasons why we believe use of the tetrafluoroborate salts is preferable. In the preparation and purification of these electrolytes we consistently found the tetrafluoroborates to be easier to purify and, especially, to dry than the corresponding perchlorates. Also, we have consistently felt concern about the potential explosive nature of perchlorate salts or of the mixtures of organic materials and perchloric acid which could be formed when these salts are stored or are used as supporting electrolytes. Thus, at least for preparative electrolytic reductions in aprotic solvents, we concluded that the properties and ready availability of tetra-n-butylammonium tetrafluoroborate make this salt the supporting electrolyte of choice.

Registry No.—Et₄NClO₄, 2567-83-1; $(n\text{-Pr})_4$NClO₄, 15780-02-6; $(n\text{-Bu})_4$NClO₄, 1923-70-2; Et₄NBF₄, 429-06-1; $(n\text{-Pr})_4$NBF₄, 15553-52-3; $(n\text{-Bu})_4$NBF₄, 429-42-5; Et₄NBr, 71-91-0; $(n\text{-Pr})_4$NBr, 1941-30-6; $(n\text{-Bu})_4$-NBr, 1643-19-2; tetra-n-butylammonium acetate, 10534-59-5.

(25) However, small amounts of water may strikingly alter the lifetimes of anions or anion radicals formed as intermediates in electrochemical reductions. See K. W. Bowers, R. W. Giese, J. Grimshaw, H. O. House, N. H. Kolodny, K. Kronberger, and D. K. Roe, *J. Amer. Chem. Soc.*, **92**, 2783 (1970).

The Reaction of Dimethylsulfoxonium Methylide and Griseofulvin

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Our finding that the behavior of the β-methoxy-substituted enone system in griseofulvin (1) toward per-

oxide in base parallels that of enone systems generally in undergoing ready epoxidation[1] prompted us to attempt to introduce the cyclopropyl moiety at position

1
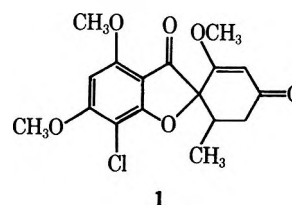
$2'-3'$ by allowing 1 to react with dimethylsulfoxonium methylide (2). The latter reagent was first shown by Corey[2] and then by others[3] to react readily with α,β-unsaturated ketones to give the corresponding cyclopropyl ketones.

We have found that allowing griseofulvin (1) to react with approximately 1 molar equiv of 2 in dimethyl sulfoxide (DMSO) at room temperature for 20 hr gave a product mixture which could be resolved by partition chromatography into a fraction containing considerable amounts of starting griseofulvin and a new crystalline product. This product melted at 165–175°, showed a band at 5.9 μ in the carbonyl region of the infrared, and an nmr spectrum in chloroform which had as its outstanding feature a new sharp 3-proton singlet at δ 3.13 shifted ε 0.5 upfield from the vinyl OCH₃ signal in griseofulvin. This latter result we attributed to a new OCH₃ group located on a saturated carbon. (The remainder of the chloroform spectrum is given in the Experimental Section. The saturated OCH₃ region in the griseofulvin-containing fraction isolated from the partition chromatogram showed only weak absorption.) The mass spectrum of the product immediately eliminated the cyclopropyl ketone 3 as a possible structure, since it showed a parent ion at m/e 380 corresponding to the introduction of two CH₂ units into the griseofulvin substrate. This was also indicated by its elemental analysis.

The nmr spectrum (60 MHz) of the product in pyridine-d_5 with spin decoupling (done in part at 60 and in part at 100 MHz) permitted its unequivocal formulation as the cyclopropyl epoxide 4. (Decoupling could

3

2

4
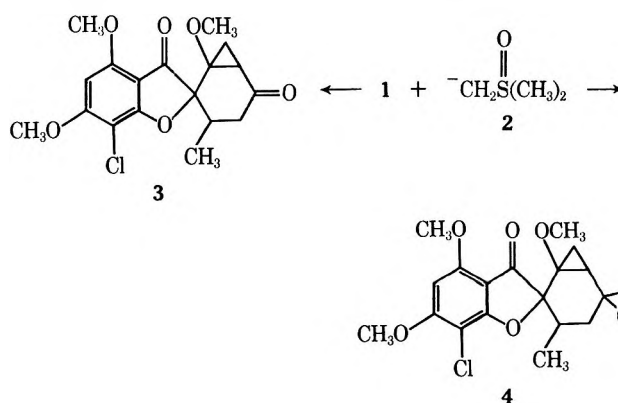
not be done in deuterated chloroform because the sample was further transformed during the time required

(1) H. Newman, *J. Org. Chem.*, **35**, 3990 (1970).

(2) (a) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 867 (1962); (b) *ibid.*, **87**, 1353 (1965).

(3) (a) H. R. Lehmann, H. Muller, and R. Wiechert, *Chem. Ber.*, **98**, 1470 (1965); (b) G. W. Krakower and H. A. VanDine, *J. Org. Chem.*, **31**, 3467 (1966); (c) N. H. Dyson, J. A. Edwards, and J. H. Fried, *Tetrahedron Lett.*, 1841 (1966).
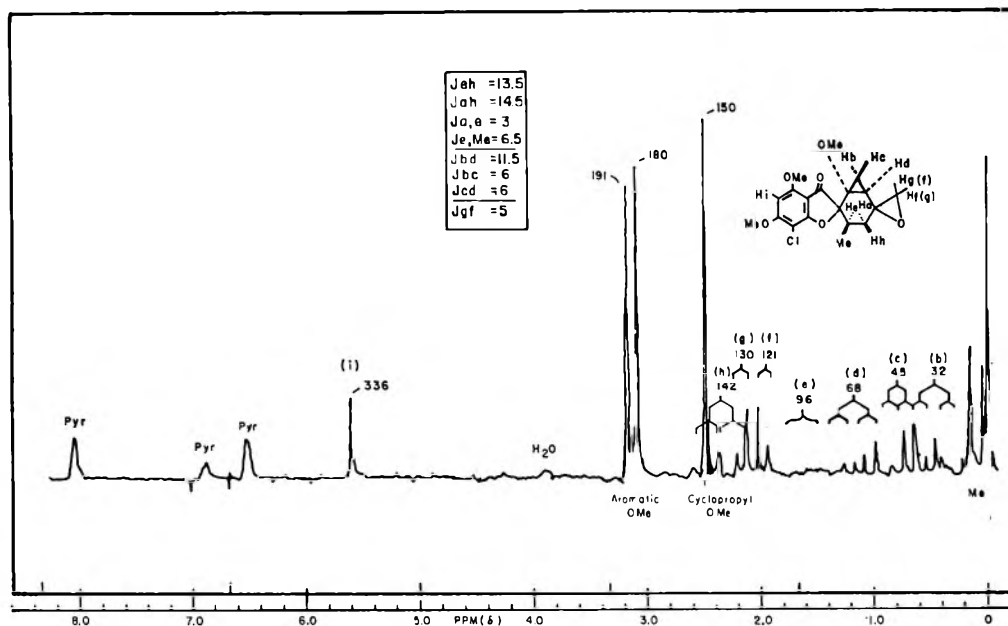
Figure 1.—Nmr spectrum of **4** in pyridine-d_5. The various chemical shift and coupling constant assignments are derived from spin decoupling experiments. Since the data does not permit a delineation of the stereochemical relationship of any of the protons on C-5' or C-6' with that at C-2' or those on the cyclopropyl group, the heavy and dotted lines are meant to show stereochemistry *only within* each of the two groups.

for the experiment, presumably owing to the sensitivity of **4** to traces of acid present in this solvent.)

Thus, in the spectrum of **4** shown in Figure 1, which incidentally indicates a single isomer, the H_b and H_d signals were considerably simplified on irradiation of H_c, the H_b multiplet went to an approximate doublet on irradiating H_d, irradiating H_g and H_f, sequentially, collapsed first one then the other to approximately a singlet, irradiating H_a collapsed H_b to a doublet, and irradiation of the C-6' CH_3 collapsed H_e to a double doublet. A rather interesting feature of the spectrum is the relatively low-field signal of the cyclopropyl protons H_b and H_c. The signal for this proton type usually appears considerably further upfield in the $\delta \leq 0.5$ region.[4a] The magnitude of the gem coupling constant of these protons is, on the other hand, on the order expected for this proton type[4b] which is considerably less (*ca.* 5 Hz) than that observed for gem protons on a carbon with tetrahedral geometry (*ca.* 15 Hz).

With regard to the stereochemistry of the epoxy and cyclopropyl groups in **4**, the CH_2 of the former is tentatively assumed to be cis (equatorial) to the C-6' CH_3 by analogy with the results of Corey[2b] with substituted cyclohexanones, while the orientation of the latter is at present unknown.

In agreement with structure **4**, the product reacted with methoxide ion in refluxing methanol to give the ether–alcohol **5** and with methanolic dimethylamine to give the amino alcohol **6**.

Our failure to isolate any of the cyclopropyl ketone **3** indicates that any **3** initially formed reacts competitively with griseofulvin toward dimethylsulfoxonium methylide. This contrasts with the observations of Corey[2] and others[3] for α,β-unsaturated ketones which, they found, are readily converted to the corresponding cyclopropyl ketones indicating a considerably faster reaction rate for the former compared to the latter.

(4) (a) N. S. Bhacca and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 190; (b) p 56.

5, X = —OCH_3
6, X = —$N(CH_3)_2$
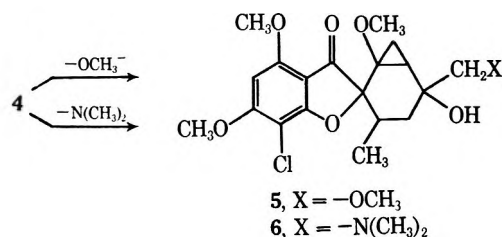
Our results and theirs are not inconsistent, since one would expect our enone system to be rendered less reactive toward nucleophilic attack by the electron-releasing β-methoxy substituent present, thus allowing the initially formed cyclopropyl ketone **3** to compete effectively for the methylide. The fact that no **3** was isolated would seem to indicate that **3** is actually more reactive than griseofulvin since it effectively competes with the latter even at initially low concentrations. This observation would appear to be in conflict with that of Krakower, *et al.*[3b] who report that, even in the presence of a 5 molar excess of methylide, the steroidal α,β-unsaturated ketone **7** was converted to the corresponding cyclopropyl ketone **8** in 40% yield, with ostensibly no further reaction of the latter.

7   **8**
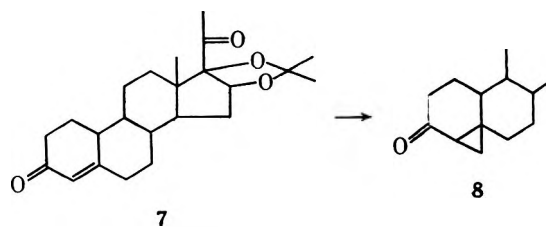
By doubling the amount of methylide **2** used in the reaction, we found we could significantly increase the yield of **4**. We were also able to isolate **4** by a fractional crystallization from ethyl acetate thereby avoiding the partition chromatography. The recovery, however, was not so good.

Experimental Section[5]

Reaction of Dimethylsulfoxonium Methylide (2) with Griseofulvin. Formation of 7-Chloro-1',4,6-trimethoxy-3'-methyldispirobenzofuran-2(3H)-2'-norcarane-5'-2''-oxirane. (4).—A solution of 0.005 mol of dimethylsulfoxonium methylide in 10 ml of dry dimethyl sulfoxide (DMSO) (the solvent was stored over molecular sieves and used directly) was prepared by adding 225 mg (0.005 mol) of a 54% NaH dispersion in mineral oil (Foote Mineral Co., Exton, Pa.) to 1.1 g (0.005 mol) of trimethylsulfoxonium iodide (Aldrich) in the solvent at room temperature under nitrogen with stirring. The vigorous gas evolution which accompanied the addition of the sodium hydride ceased after *ca.* 15 min. After *ca.* an additional 30 min another 10 ml of DMSO was added followed by 1.4 g (0.004 mol) of griseofulvin and the resulting light yellow solution was stirred at room temperature under nitrogen for 20 hr and then poured into ice-water. The solid which separated was collected, washed well with water, and air-dried to give a 1.2-g yield of crude product (contaminated with mineral oil), 0.5 g of which was further purified by partition chromatography on Celite 545 using heptane–chloroform–methanol–water 50:8:16:1. One major peak appeared in the chromatogram at *ca.* 8 holdback volumes. Evaporation of the corresponding eluate left 72 mg (5%) of an ivory colored solid: mp 165–175°; λ_{max}^{KBr} 5.90 μ; λ_{max}^{MeOH} 324 nm (ϵ 5200), 290 (23,000), 233 (infl) (14,500), and 212 (27,000); $\delta_{TMS}^{CDCl_3}$ 6.15 (1-proton singlet, aromatic H), 4.03 and 4.00 (two 3-proton singlets, aromatic OCH₃'s), 3.13 (3-proton singlet, OCH₃ on C-2' in 4, 2.83 (represents the center of a 3-proton multiplet due to the epoxy CH₂ protons and H₆ at C-5'), 2.00–1.55 (1-proton multiplet due to H₄), 1.33–1.10 (2-proton multiplet due to H₆ and H₆), and 0.75 (3-proton doublet, *J* = 6 Hz, C-6' CH₃). H₆ and H₆ in 4 appear as multiplets in the δ 2.7–2.08 and 1.0 region, respectively. The major high mass peak in the mass spectrum of the compound was at *m/e* 380 with the expected *m/e* 382 peak ⅓ as intense due to the chlorine isotope, mol wt 37. (Very minor contamination by a still higher molecular weight product was indicated by a weak *m/e* 394 peak.)

The compound showed essentially a single spot on tlc (C₆H₆–EtOAc 1:1), *R*ₜ *ca.* 0.38 (*R*ₜ griseofulvin under these conditions is 0.42).

Anal. Calcd for C₁₉H₂₁O₆Cl (380.82): C, 59.90; H, 5.56; Cl, 9.31. Found: C, 59.34; H, 5.60; Cl, 9.08.

The remainder of the chromatographed product was isolated from the methanol wash of the column (yield 318 mg) and was shown by nmr to be a mixture containing 50% or more of griseofulvin. The saturated OCH₃ region (3.5–3.08) in the nmr spectrum of this mixture did not show any significant absorptions.

A significantly improved yield of 4 was obtained by running the reaction in the presence of a 2 molar equiv of the dimethylsulfoxonium methylide and reducing the reaction time to 1 hr and 5 min. Work-up essentially as above except that the mineral oil contaminant was removed before partition chromatography by washing the crude solid with petroleum ether (bp 30–60°) gave 0.91 g (16%) of 4 [from 4.2 g (0.015 mol) of griseofulvin], melting at 170–180° after triturating with methanol.

Anal. Found: C, 59.60; H, 5.62; Cl, 9.65.

The product showed ir, nmr, and mass spectra identical with those of the product above. The pyridine-*d*₅ spectrum and the decoupling experiments were run on a sample of this product.

The reaction was also run using 3 molar equiv of the methylide and the reduced reaction time (1.25 hr) (2.4 g of griseofulvin was used). A comparison of the yield from this experiment with the other two is, however, precluded because of a change in the work-up in an attempt to eliminate the chromatography step. Thus, after removing the mineral oil with petroleum ether (bp 30–60°), the product was triturated with methanol then recrystallized from EtOAc to give the desired 4 in analytically pure form (yield *ca.* 200 mg, mp 173–179°).

[The rather broad melting point observed for the various preparations of "analytically pure" 4 is more probably due to minor contamination by trace amounts of higher molecular weight material as indicated by the various mass spectra than to its being an isomeric mixture. The latter possibility appears to be precluded by its nmr spectra (see Discussion)].

Reaction of 4 with Methanolic Sodium Methoxide. Formation of 7-Chloro-5'-hydroxy-1',4,6-trimethoxy-5'-(methoxymethyl)-3'-methylspiro[benzofuran-2(3H)-2'-norcaran]-3-one (5).—A suspension of 240 mg (0.63 mmol) of 4 in 4 ml of *ca.* 1 *M* methanolic sodium methoxide (4 mmol) was stirred and heated under reflux for 1 hr. The reaction mixture became homogeneous during this time (orange solution). The mixture was poured into ice-water and the organic product extracted with CH₂Cl₂–ether. Drying and evaporating the organic extract left a 210-mg solid residue which showed a major new spot on tlc (C₆H₆–EtOAc 1:1), *R*ₜ *ca.* 0.3 along with a somewhat faster running minor spot corresponding in *R*ₜ to starting 4. The minor contaminant was removed by partition chromatography on Celite 545 using heptane–ethylene chloride–methanol–water 50:8:16:1 giving 137 mg of essentially pure 5 which melted at 217–220° after heating suspended in boiling ethyl acetate (partial solution): λ_{max}^{KBr} 2.9 (m) (OH) and 5.89 (s) (ring B C=O); λ_{max}^{MeOH} 324 nm (ϵ 5100), 290 (24,000), 232 (infl) (16,000), and 212 (29,000); $\delta_{TMS}^{CDCl_3}$ 6.15 (aromatic H), 4.05 and 4.02 (aromatic OCH₃'s), 3.58 (singlet, CH₂OCH₃), 3.50 (singlet, CH₂OCH₃), 3.14 (singlet, cyclopropyl OCH₃), and 0.8 (doublet, *J* = 6 Hz, C-6' CH₃). The signals for the remaining protons appeared between δ 2.4 and 1.0. (Unlike 4, 5 was stable in CDCl₃.) The mass spectrum of 5 showed a parent ion at *m/e* 412 and a very strong M − 45 peak (base peak) corresponding to the loss of –CH₂OCH₃.

Anal. Calcd for C₂₀H₂₅O₇Cl (412.86): C, 58.18; H, 6.10; Cl, 8.59. Found: C, 58.01; H, 6.15; Cl, 8.55.

Reaction of 4 with Dimethylamine. Formation of the Dimethylamino Adduct 6.—A suspension of 10 mg of 1 in *ca.* 0.5 ml of saturated methanolic dimethylamine was stirred at room temperature for 1 hr, the excess solvent removed in a stream of nitrogen, and the residue triturated with ether to give a colorless solid which melted partially at 180–184° and gave a completely clear melt at 211°: λ_{max}^{KBr} 2.9 μ (m) (OH), 5.90 (s) (ring B >C=O). The mass spectrum of the product showed a parent ion at *m/e* 425 and a major fragment at M − 58 and at *m/e* 58 (base peak) corresponding to the loss of –CH₂N(Me)₂ from 6 and the fragment –CH₂N(Me)₂, respectively.

Anal. Calcd for C₂₁H₂₈ClO₆N·H₂O (443.9): C, 56.81; H, 6.81; N, 3.16. Found: C, 57.23; H, 6.50; N, 2.90.

Registry No.—1, 126-07-8; 2, 5367-24-8; 4, 30256-33-8; 5, 30256-34-9; 6, 30256-35-0; methanolic sodium methoxide, 124-41-4.

The Debromination of Stilbene Dibromides and Other Vicinal Dibromides by Tricovalent Phosphorus[1]

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Recent reports on the debromination of stilbene dibromide 1 by triethyl phosphite (TEP)[3] and by various

TABLE I

DEBROMINATION OF VICINAL DIBROMIDES BY TRIVALENT PHOSPHORUS

Run	Substrate	Trivalent phosphorus reagent	Reaction conditions[a]	Yields, %			
				1	trans-2	cis-2	Other products
1	meso-Stilbene dibromide (1)	TPP	In benzene, 24 hr		99[b]	0	TPP oxide,[b] 95
2		TEP	In benzene, 25 hr	84[b,d]	0	0	TPP[b]
3	dl-1	TPP	In benzene, 24 hr		7[c]	1[c]	11
4		TPP	In toluene, 24 hr	48[d]	40[c]	16[c]	31
5		TPP	In toluene, 77 hr	39[d]	44[c]	15[c]	52
6		TPP	Toluene 24 hr, ROH[f]	47[e]	24[c]	28[c]	43
7		Tributyl-phosphine	Toluene, 24 hr, ROH[f]	10[e]	65[c]	25[c]	
8	trans-1,2-Dibromoindan	TPP	In toluene, 21 hr				Indene, 19[b]
9	trans-1,2-Dibromocyclohexane	TPP	In toluene, 24 hr				Cyclohexene,[g] 11
10		TEP	In toluene, 24 hr				Cyclohexene,[g] 0
11		Tributyl-phosphine	In toluene, 24 hr				Cyclohexene,[g] 40

[a] All reactions under reflux conditions. [b] Isolated yield. [c] By vpc on reaction mixture. [d] By bromine analysis (see Experimental Section). [e] By nmr ratio of 1 and cis-2, related to yields of cis-2 and trans-2 (vpc). [f] 2-Propanol (6.5 equiv) added. [g] By vpc on distillate. All vpc analyses are ±2%.

other reductants[4] prompt us to report our results on the debromination of 1 with triphenylphosphine (TPP) and on related reactions.[5]

As indicated in Table I, reaction of meso-1 with TPP in benzene at reflux gives only trans-stilbene (2). Thus TPP, along with many other two-electron reducing agents, probably debrominates meso-1 stereospecifically in an antielimination.[4a] Under the same conditions, TEP gives no reaction with meso-1. The reported conversion of 1 (unspecified as to meso or dl) to 2 (unspecified as to cis or trans) occurs with neat TEP at 185°.[3] These results suggest that TPP is more "halophilic" (nucleophilic toward halogen) than is TEP. TPP should be "softer," and therefore more reactive toward "soft" halogen such as bromine, than is TEP by virtue of the greater electron density at phosphorus in the phosphine than in the phosphite.[6-8] This order of reactivity toward bromine has been found in the reactions of tricovalent phosphorus with α-bromo ketones wherein attack on bromine occurs with TPP[9] but not with TEP.[8]

The reaction of dl-1 with TPP is much slower than the corresponding reaction with meso-1, in keeping with rate data found for the reactions of these bromides with metal halides.[4b,c] This system gives mixtures of trans- and cis-2. Formation of a mixture, rather than just cis-2, is due, mainly and perhaps exclusively,[10] to the isomerization of cis-2 to trans-2 by the other product, triphenylphosphine dibromide, and by small amounts of hydrogen bromide.[11] Thus cis-2 is converted to 99:1 trans-2–cis-2 by triphenylphosphine dibromide (3) in toluene. Similar reaction of cis-2 with 3 in the presence of 2-propanol (6.5 equiv), which rapidly destroys 3,[12] causes less but significant isomerization to 54:46 trans-2–cis-2, probably due to hydrogen bromide. A comparison of runs 4 and 6 (Table I) shows the effect of 2-propanol in decreasing the ratio of trans-2–cis-2 from dl-1 and TPP.

A comparison of the ease of TPP debromination of trans-1,2-dibromoindane (4) and trans-1,2-dibromocyclohexane (5) with that of meso-1 illustrates the enhancing effect of aromatic rings as electron-withdrawing groups. Finally, the reactivity order observed in the conversions of dl-1 to 2 and 5 to cyclohexene (7) (tributylphosphine > TPP >> TEP) are in parallel with the known nucleophilicities toward carbon of these reagents,[13] suggesting that there is at least some correlation between "halophilicity" and "carbophilicity."[14]

(4) (a) I. M. Mathai, K. Schug, and S. I. Miller, *J. Org. Chem.*, **35**, 1733 (1970); (b) I. M. Mathai and S. I. Miller, *ibid.*, **35**, 3416 (1970); (c) W. K. Kwok, I. M. Mathai, and S. I. Miller, *ibid.*, **35**, 3420 (1970).

(5) The use of phosphites and phosphines in vicinal debrominations is well known: (a) S. Dershowitz and S. Proskauer, *ibid.*, **26**, 3595 (1961); (b) R. D. Partos and A. J. Speziale, *J. Amer. Chem. Soc.*, **87**, 5068 (1965); (c) other references cited in ref 3.

(6) R. Pearson, *Surv. Prog. Chem.*, **5**, 1 (1969).

(7) (a) There is little kinetic but much qualitative data available to support this point;[7b,8,9] (b) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press, New York, N. Y., 1965, Chapter 5.

(8) I. J. Borowitz, M. Anschel, and S. Firstenberg, *J. Org. Chem.*, **32**, 1723 (1967).

(9) (a) I. J. Borowitz, P. E. Rusek, and R. Virkhaus, *ibid.*, **34**, 1595 (1969); (b) I. J. Borowitz, K. C. Kirby, Jr., P. E. Rusek, and E. W. R. Casper, *ibid.*, **36**, 88 (1971).

(10) The reactions of dl-1 with some nucleophiles are not stereospecific, giving both trans-2 and cis-2.[4b,c] We feel that TPP, in common with other "soft" two-electron nucleophiles, probably gives only antielimination.[4a]

(11) For the isomerization of stilbenes with TsOH, see I. Ho and J. G. Smith, *Tetrahedron*, **26**, 4277 (1970).

(12) For the (rapid) reaction of triphenylphosphine dibromide with related alcohols, see G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Amer. Chem. Soc.*, **86**, 964 (1964).

(13) (a) G. Aksnes and D. Aksnes, *Acta Chem. Scand.*, **18**, 38 (1964); (b) W. A. Henderson, Jr., and S. A. Buckler, *J. Amer. Chem. Soc.*, **82**, 5794 (1960).

(14) This correlation breaks down for some phosphorus nucleophiles. Thus diphenylphosphine is less carbophilic than is TPP but it is more halophilic: I. J. Borowitz, K. C. Kirby, Jr., P. E. Rusek, and E. Lord, *J. Org. Chem.*, **34**, 2687 (1969).

(14a) NOTE ADDED IN PROOF.—Also, TPP > Ph₂POC₂H₅ (8) > PhP-(OC₄H₉)₂ (9) > P(OC₂H₅)₃. Thus 8 + dl-1 gives dl-1, trans-2, and cis-2 (55:33:12) and 9 + dl-1 gives a 72:18:10 ratio.

Experimental Section[15]

All reactions were run under dry nitrogen. Vpc analyses were performed on a Varian Aerograph A-700 gas chromatograph employing a 5% SE-30 on a Chromosorb W-DMCS Pyrex column unless otherwise noted.

Materials.—*meso*-Stilbene dibromide, mp 239–240.3° (lit.[4a] mp 237–238°), *dl*-stilbene dibromide, mp 109–110° (lit.[4a] mp 112–113°), and *trans*-1,2-dibromocyclohexane, bp 108–112° (25 mm),[16] were prepared by known procedures.

trans-1,2-Dibromoindan (4) from indene had mp *ca.* 25° (lit.[17] mp 30–32°); tlc (20% CH_3OH–C_6H_6 on silica gel HF_{254}) one spot with R_f 0.81 (as for indene); nmr ($CDCl_3$) τ 2.65–2.90 (m, 5, aryl H), 4.44 (s, 1, C_1 H), 5.35 (2 t, 1, C_2 H, $J_{3A2} \cong 1.5$ Hz, $J_{3B2} \cong 5.0$ Hz), and 6.67 (q, 2, C_3 H, $J_{3AB} = 18$ Hz, $J_{3A2} \cong 1.5$ Hz, $J_{3B2} \cong 5.0$ Hz).[18]

Anal. Calcd for $C_9H_8Br_2$: Br, 57.91. Found: Br, 58.07.

Debromination Reactions.—For the dibromostilbene reactions, *meso*- or *dl*-1 was added to TPP or TEP (1.1 equiv) in the appropriate solvent as in Table I. In the TPP reactions, triphenylphosphine dibromide (3) was filtered from the reaction mixture after the indicated reaction time and was decomposed by (moist) air or the addition of methanol to give triphenylphosphine oxide. In the *meso*-1 run, the resultant filtrate was evaporated *in vacuo* to give a mixture of *trans*-2 and triphenylphosphine oxide (identified by the R_f values and uv maxima of tlc spots and by mixture melting point in comparison with genuine samples). In the *dl*-1 runs, the filtrate was analyzed by tlc as above and by vpc. Unreacted *dl*-1 was also estimated by per cent bromine analysis. The ratio of *dl*-1 to *cis*-2 was also determined from an nmr spectrum of the mixture (in $CDCl_3$), in some cases, utilizing peaks at τ 5.37 (s, benzylic H of *dl*-1) and 4.38 (s, vinyl H of *cis*-2). The vinyl proton of *trans*-2 overlapped with the aromatic protons so that *trans*-2 could not be so determined. Unreacted TPP was removed by its reaction with methyl iodide or with mercuric chloride.[19] The ratio and yield of *cis*- and *trans*-2 were determined by vpc at an optimal column temperature of 170°. Since unreacted *dl*-1 was found to partially decompose to *trans*-2 (24–28%) and *cis*-2 (1–4%) at column temperatures above 175°, the *trans*-/*cis*-2 ratios in early runs (3–5) at 177° had to be corrected.

The reaction of *trans*-1,2-dibromoindan (4) with TPP gave a brown mixture which was analyzed by vpc at 111° after decomposition of triphenylphosphine dibromide as above.

Treatment of *trans*-1,2-dibromocyclohexane (5) in toluene with tricovalent phosphorus species (Table I), followed by addition of 1-butanol (to decompose any triphenylphosphine debromide which formed), and distillation at 760 mm gave a solution of cyclohexene in toluene. It was analyzed by vpc (20% DEGS) with a calibration curve based upon known amounts of cyclohexene in toluene.

Control Experiments.—A solution of *dl*-1 in toluene, kept at reflux for 24 hr, gave recovered *dl*-1 (95%), mp 108–111.5°, and no *meso*-1. Similar treatment of 5 for 10 hr gave a 92% recovery and no cyclohexene. No isomerization of *cis*-2 to *trans*-2 occurred after treatment with TPP in benzene at reflux for 67 hr or under the vpc conditions used.

Reaction of Triphenylphosphine Dibromide with *cis*-Stilbene. —To TPP (0.524 g, 0.00200 mol) in dry toluene (50 ml) was added bromine (0.32 g, 0.00200 mol) in benzene (5 ml) dropwise at 25°. After 20 min the apparatus was evacuated to remove any unreacted bromine, nitrogen was reintroduced, the mixture was brought to reflux, and *cis*-stilbene (0.36 g, 0.00200 mol) in toluene (10 ml) was added with stirring. The resultant mixture was stirred at reflux for 24 hr and cooled and the solvent distilled at 760 mm through a 120-mm nichrome helix packed column to give a reduced volume (5 ml) which precipitated triphenylphosphine oxide (0.51 g, 0.00183 mol, 92%): mp 150–155°. The filtrate was analyzed by vpc to contain *trans*-2–*cis*-2 in a 99:1 ratio. A similar reaction in cyclohexane gave *trans*-2 (64%) and *cis*-2 (19%) in 3.4:1 ratio. When 2-propanol (6.5 equiv) was added to the *cis*-2, the above conditions in toluene gave a vpc ratio of

54:46 *trans*-2–*cis*-2 and an actual recovery of *cis*-2 of 45% by vpc calibration curve.

Reactions of Phosphorus Compounds. XXV. Preparation of Cyclopropyl Ketones from Esters of 3-Hydroxypropylphosphonium Salts[1]

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Phosphoranes have been employed as intermediates in the synthesis of cyclopropanes by two general pathways: (a) the Michael addition of the ylide carbanion to activated double bonds with subsequent Sni expulsion of the tertiary phosphine;[2-4] (b) attack of the ylide
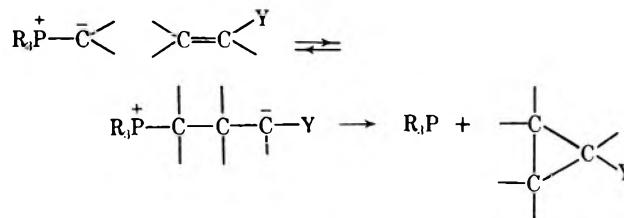
Y = electron withdrawing moiety

carbanion on epoxides followed by thermal decomposition of the oxaphospholane formed.[5-11] The mechanism postulated[11] involves fission of the oxaphospholane carbon–phosphorus bond to give a carbanion which cyclizes with the concommittant expulsion of phosphine oxide. Reasonable yields of cyclopropanes have only been obtained when the phosphorane employed is of such a nature as to produce an oxaphospholane with a carbanion stabilizing group (R′) in the C_3 position (Scheme I). However, ketophosphoranes have been found to be too stable to be useful for the synthesis of

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(11) S. Trippett, *Quart. Rev., Chem. Soc.*, **17**, 406 (1964).

(15) The instrumental and other techniques used have been recorded previously.[8]

(16) H. R. Snyder and L. A. Brooks, "Organic Syntheses," Collect. Vol. 2, A. H. Blatt, Ed., Wiley, New York, N. Y., 1961, p 1.

(17) S. Winstein and R. M. Roberts, *J. Amer. Chem. Soc.*, **75**, 2297 (1953).

(18) An approximate first-order analysis wherein C_1 H is "down," C_2 H is "up" and on C_3 (allylic CH_2) H_A is "up" and H_B is "down."

(19) I. J. Borowitz, K. C. Kirby, Jr., and R. Virkhaus, *J. Org. Chem.*, **31**, 4031 (1966).

SCHEME I

$$R_3P=CHR' + R''CH\!-\!CH_2 \longrightarrow$$

$$\begin{array}{c} R_3\overset{+}{P}\!-\!\overset{-O}{\underset{}{\ }}CHR'' \\ CH\!-\!CH_2 \\ R' \end{array}$$

$$\begin{array}{c} R_3\overset{+}{P}\!-\!O \\ \overset{-}{C}H\!-\!CH_2 \\ R' \end{array} \longleftarrow \begin{array}{c} R_3P\!-\!O \\ CH\!-\!CH_2 \\ R' \end{array}$$

$$R_3PO + R'\!-\!CH\!-\!CH_2$$

cyclopropyl ketones due to the low nucleophilicity of the ylide carbanion toward epoxides.[6]

We wish to report a procedure which enhances the utility of phosphonium salts as precursors for cyclopropyl ketones and thus supplements the above-mentioned techniques.

Esters of 3-hydroxypropylphosphonium salts 1 on treatment with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol gave the corresponding cyclopropyl ketones 5 in 42–59% yields, respectively. The mechanism, as shown in Scheme II, may be postulated as

SCHEME II

$$\begin{array}{c} O \; R' \\ RCOCCH_2CH_2\overset{+}{P}(C_6H_5)_3Br^- \\ R'' \end{array} \xrightarrow[\text{HOC(CH}_3)_3, \; \Delta]{\text{KOC(CH}_3)_3}} \begin{array}{c} O \; R' \\ RCOCCH_2CHP^-{}^+C_6H_5)_3 \\ R'' \end{array}$$

1a–d   **2a–d**

2a–d ——

$$\left[\begin{array}{c} (C_6H_5)_3\overset{+}{P}\overset{-O}{\underset{}{\ }}CR'R'' \\ CH\!-\!CH_2 \\ RC\!=\!O \end{array} \rightleftharpoons (C_6H_5)_3\overset{+}{P}\overset{O}{\underset{}{\ }}CR'R'' \\ CH\!-\!CH_2 \\ RC\!=\!O \right]$$

3a–d

$$\textbf{3a–d} \longrightarrow \left[\begin{array}{c} (C_6H_5)_3\overset{+}{P}\overset{O}{\underset{}{\ }}CR'R'' \\ RC\!-\!CH\!-\!CH_2 \\ \underset{O}{\parallel} \end{array}\right] \longrightarrow$$

4

$$\begin{array}{c} O \quad CH_2 \\ RCCH\!-\!\!-\!CR'R'' + (C_6H_5)_3PO \end{array}$$

5a–d

5a, R = CH₃; R' = R'' = H (49%)
 b, R = -C₆H₅; R' = R'' = H (59%)

c, R = -CH₃; R' = -C₆H₅; R'' = -CC₆H₅ (42%)

d, R = -C₆H₅; R' = -C₆H₅; R'' = -CC₆H₅ (51%)

initial formation of the ylide 2. An intramolecular acylation of the ylide 2 in the manner described by

House and Babad[12] yields the alkoxyphosphonium zwitterion ↔ oxaphospholane intermediate 3, which rapidly cleaves to the enolate phosphonium zwitterion 4, followed by loss of triphenylphosphine oxide and formation of the cyclopropyl ketone 5.

The ease of the reaction is attested to by the fact that 1b gives 5b in 55% yield when the reaction is run at room temperature instead of at the temperature of refluxing *tert*-butyl alcohol.

There are, unfortunately, other reactions possible as attested to by isolation of the following side products. (a) The reaction of 1b always gave small amounts of the stable phosphorane 6 which could arise from either the intermolecular acylation of 2b or the alkoxide moiety of 3b (we favor the former). The hydroxyphosphonium salt 7 or the corresponding alkoxyphosphonium zwit-

$$\textbf{1b} + \textbf{2b} \; (\text{or } \textbf{3b}) \longrightarrow (C_6H_5)_3P\!=\!C \overset{\overset{O}{\underset{}{\parallel}}CC_6H_5}{\underset{CH_2CH_2OCC_6H_5}{\underset{\underset{O}{\parallel}}{}}} \quad +$$

6

$$[HOCH_2CH_2CH_2\overset{+}{P}(C_6H_5)_3Br^-]$$
7

terion–oxaphospholane was not isolated. (b) From the reaction of 1c and 1d the deesterified products 8 and 9 were isolated and identified as previously described.[13]

$$\begin{array}{c} (C_6H_5)_3P\overset{-O}{\underset{}{\ }}C(C_6H_5)\overset{O}{\underset{}{\parallel}}CC_6H_5 \\ CH_2\!-\!CH_2 \end{array}$$
8

$$\begin{array}{c} OH \quad O \\ Br^-(C_6H_5)_3\overset{+}{P}CH_2CH_2C(C_6H_5)CC_6H_5 \end{array}$$
9

The deesterification may occur due to the reaction on 1 of the *tert*-butylate anion or the phosphorane 2c,d; however, no stabilized phosphorane corresponding to 6 was observed.

Thus, it has been shown that esters of 3-hydroxyphosphonium salts on treatment with alcoholic base give good yields of acylcyclopropanes.

Experimental Section

Infared spectra were obtained on a Perkin-Elmer Infracord 137, ultraviolet spectra on a Perkin-Elmer 202, and nmr spectra on a Varian A-60A analytical nmr spectrometer using tetramethylsilane as standard. Melting points are uncorrected and were obtained with a Thomas-Hoover capillary melting point apparatus. Analyses are by M-H-W Laboratories, Garden City, Mich. Unless otherwise indicated, all reactions were undertaken in anhydrous conditions under a blanket of dry nitrogen. Potassium *tert*-butylate used was obtained from Alpha Inorganics, Beverly, Mass.

3-Acetoxypropyltriphenylphosphonium Bromide (1a).—3-Bromopropyltriphenylphosphonium bromide (Aldrich), 32.5 g (0.07 mol), was dissolved in 200 ml of 4:1 acetone–water, and sodium acetate, 12.3 g (0.15 mol), was added. After 12 hr of reflux, acetone was distilled off, and the solution diluted with 200 ml of water, extracted with 250 ml of chloroform, dried (MgSO₄), and concentrated to about 150 ml. Slow addition of ethyl acetate then precipitated crystals of a white salt 1a: 30 g (97%); mp 180–182°; ir (CHCl₃) ν 1040 (m), 1060 (m), 1110 (s, CP), 1230 (s), 1730 cm⁻¹ (s, ester C=O); nmr (CDCl₃)

(12) H. O. House and H. Babad, *J. Org. Chem.*, **28**, 90 (1963).

(13) E. E. Schweizer, W. S. Creasy, J. G. Liehr, M. E. Jenkins, and D. L. Dalrymple, *ibid.*, **35**, 601 (1970).

δ 1.8–2.3 (m, 2, CH_2), 2.0 (s, 3, CH_3), 3.4–4.5 (m, 4, CH_2 CH_2P, 7.5–8.1 ppm (m, 15, C_6H_5).

Anal. Calcd for $C_{23}H_{24}O_2PBr$: C, 67.10; H, 5.88; Br, 19.42. Found: C, 66.92; H, 5.84; Br, 19.09.

3-Benzoyloxypropyltriphenylphosphonium Bromide (1b).— Compound **1b** was prepared in a manner similar to that reported in the previous experiment: 76% yield; mp 182–184°; ir (CHCl₃) ν 1030 (m), 1070 (m), 1115 (s, CP), 1250 (s), 1170 cm⁻¹ (s, ester C=O); nmr (CDCl₃) δ 1.9–2.4 (m, 2, CH_2), 3.4–4.3 (m, 2, CH_2P), 4.6 (t, 2, OCH_2), 7.2–8.1 ppm (m, 20, C_6H_5).

Anal. Calcd for $C_{28}H_{26}O_2PBr$: C, 70.99; H, 5.53; Br, 16.87. Found: C, 70.81; H, 5.62; Br, 16.69.

Methyl Cyclopropyl Ketone (5a).—Salt **1a**, 13.4 g (0.03 mol), and potassium *tert*-butylate, 3.4 g (0.03 mol), were allowed to reflux 24 hr in 150 ml of dry *tert*-butyl alcohol. The solution was then cooled and filtered. Methyl cyclopropyl ketone **5a** was identified in this solution by vpc and by treating with 160 ml of 2,4-dinitrophenylhydrazine reagent, which gave orange crystals of the 2,4-dinitrophenylhydrazone, 2.8 g (49%). After recrystallization from ethanol, the crystals had mp 146–148° (lit.[14] 149–150°). Mixture melting point with the authentic sample showed no depression.

Phenyl Cyclopropyl Ketone (5b).—Salt **1b**, 10.1 g (0.02 mol), and potassium *tert*-butylate, 2.2 g (0.02 mol), were treated as described in the previous experiment. The gum obtained was washed well with hexane and the washings were concentrated to give 1.7 g of **5b** (59%) identified by vpc, ir, and nmr comparison with an authentic sample. Washing the hexane-insoluble residue with ether and filtering left a white powder, triphenylphosphine oxide (77%). Cooling the ether filtrate at 0° gave 0.9 g of 1-benzoyl-3-benzoyloxypropyltriphenylphosphorane (6), mp 142–146° (17%), one spot by tlc. Repeating this experiment at 20–25° for 36 hr gave 1.55 g of **5b** (53%), identified as described above.

3-Benzoyl-3-benzoyloxypropyltriphenylphosphorane (6): ir (CHCl₃) ν 1105 (s, CPO), 1480 (s, O=CC=P), 1720 cm⁻¹ (s, ester C=O); nmr (CDCl₃) δ 2.1–2.9 (m, 2, CH_2), 3.95 (t, 2, OCH_2), 7.1–7.9 ppm (m, 25, C_6H_5).

Anal. Calcd for $C_{35}H_{29}O_3P$: C, 79.53; H, 5.53. Found: C, 79.62; H, 5.55.

3-Acetoxy-3,4-diphenyl-4-oxobutyltriphenylphosphonium Bromide (1c).—A mixture of 3,4-diphenyl-3-hydroxy-4-oxobutyltriphenylphosphonium bromide[13] (23.2 g, 0.04 mol), NaOAc (0.5 g) and acetic anhydride (12.2 g, 0.12 mol) in 100 ml of dry pyridine was allowed to reflux for 2 hr and stirred at 25° for 8 hr. The mixture was cooled, filtered, and dropped into 1 l. of ether (anhydrous). After decanting the ether, the oily precipitate was boiled briefly in 300 ml of ethyl acetate, which was decanted and recrystallized from chloroform–ether. The yield of **1c** was 18.1 g (73%): mp 221–224°; ir (CHCl₃) ν 1115 (s, CP), 1680 (s, ketone C=O), 1745 cm⁻¹ (s, ester C=O); nmr (CDCl₃) δ 2.3 (s, 3, CH_3), 2.4–4.5 (m, 4, CH_2CH_2P), 7.2–7.9 ppm (m, 25, C_6H_5).

Anal. Calcd for $C_{36}H_{32}O_3PBr$: C, 69.34; H, 5.18; Br, 12.82. Found: C, 69.37; H, 5.28; Br, 12.59.

1-Acetyl-2-benzoyl-2-phenylcyclopropane (5c).—Salt **1c**, 12.5 g (0.02 mol), was suspended in *tert*-butyl alcohol freshly distilled from CaH_2, potassium *tert*-butylate was added (2.8 g, 0.025 mol), and the light yellow solution was allowed to reflux 48 hr. The cooled solution was dropped in 1 l. of hexane and the clear solution decanted. The residual oil was washed with acetonitrile, leaving 8, 3.2 g (32%), melting point and mixture melting point and spectral data were identical with that of the authentic sample.[13] Concentration of the washings followed by trituration with ether yielded 1.1 g of triphenylphosphine oxide.[3]

Concentration of the original hexane solution and chromatography on florisil gave the cyclopropane **5c**: 2.2 g (42%); only one isomer; mp 100–101.5°; ir (CHCl₃) ν 1005 (m), 1180 (s), 1270 (s), 1680 (s, PhC=O), 1700 cm⁻¹ (s, CH₃C=O); uv (CH₃OH) λ_{max} 230 mμ (sh, ϵ 12,400), 258 (17,000); nmr (CDCl₃) δ 1.2 (d d, 1, CH_2), 1.8 (s, 3, CH_3), 2.3 (d d, 1, CH_2), 3.2 (d d, 1, CH), 6.7–7.4 and 7.4–7.9 ppm (m, 10, C_6H_5).

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.08. Found: C, 81.84; H, 6.01.

cis- and trans-1,2-Dibenzoyl-1-phenylcyclopropane (5d).—A suspension of 3-benzoyloxy-3,4-diphenyl-4-oxobutyltriphenylphosphonium chloride (1d)[13] (25.6 g, 0.04 mol) was treated with

an equimolar quantity of potassium *tert*-butylate as described in the previous experiment and afforded 5-benzoyl-2,2,2,5-tetraphenyloxa-2-phospholane (8),[13] 4.2 g (21%), salt 9, 2.7 g (11%),[13] triphenylphosphine oxide, 5.0 g (45%), and the cyclopropanes **5d**, cis and trans, 6.6 g (51%), in a 23/77 ratio, respectively.

cis-1,2-Dibenzoyl-1-phenylcyclopropane (23%): mp 133–135° (lit.[15] 126°); ir (CHCl₃) ν 1100 (s), 1130 (s), 1680 cm⁻¹ (s, C=O); uv (CH₃OH) λ_{max} 205 mμ (ϵ 35,000), 250 (31,500); nmr (CDCl₃) δ 2.0 (d d, 1) and 2.5 (d d, 1, CH_2), 3.3 (d d, 1 CH), 7.1–7.6 and 8.2–7.7 ppm (m, 15, C_6H_5).

Anal. Calcd for $C_{23}H_{18}O_2$: C, 84.66; H, 5.52. Found: C, 84.64; H, 5.68.

trans-1,2-Dibenzoyl-1-phenylcyclopropane (77%): mp 121–122° (lit.[15] 123°); ir (CHCl₃) ν 1025 (s), 1230 (s), 1270 (s), 1680 cm⁻¹ (s, PhC=O); uv (CH₃OH) λ_{max} 295 mμ (ϵ 24,000), 320 (sh, 8900); nmr (CDCl₃) δ 1.6 (d d, 1) and 2.8 (d d, 1, CH_2) 4.1 (d d, 1, CH), 6.9–7.5 and 8.2–7.7 ppm (m, 15, C_6H_5). This compound was found to be identical with an authentic sample prepared by the method of Allen and Barker.[15]

Anal. Calcd for $C_{23}H_{18}O_2$: C, 84.66; H, 5.52. Found: C, 84.86; H, 5.48.

Registry No.—**1a**, 30698-17-0; **1b**, 30698-18-1; **1c**, 30698-19-2; **5c**, 30698-20-5; *cis*-**5d**, 30698-21-6; *trans*-**5d**, 30698-22-7; **6**, 30698-23-8.

(15) C. F. H. Allen and W. E. Barker, *J. Amer. Chem. Soc.*, **54**, 736 (1932).

Photochemical Cycloadducts. VI.[1]
The Structure of Tetrafluoroethylene and
Dichloroethylene Photoadducts of
3β-Acetoxypregna-5,16-dien-20-one

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In connection with our investigation of the photochemical cycloadditions to conjugated double bonds, we have previously reported the reactions of 3β-acetoxypregna-5,16-dien-20-one (1, R = COCH₃) with tetrafluoroethylene and *cis*- and *trans*-dichloroethylene.[3] We now wish to report the structures of the products which were not fully characterized.

The photoaddition of tetrafluoroethylene to **1** (R = COCH₃) gave three products, two of which have been identified as the α- and β-face adducts **2** and **3**.[3] The structure of the third adduct (mp 180–182°) is now established as **4** by X-ray crystallographic analysis of its 3β-(*p*-bromobenzoate) derivative ($C_{30}H_{33}F_4O_3Br$, space group $P2_12_12_1$ with four molecules per unit cells, a = 22.891, b = 10.692, and c = 11.313 Å⁴).

The photoadditions of certain unsymmetrical olefins to cyclic α,β-unsaturated ketones are generally explained by stepwise mechanisms involving initial car-

(1) For part V, see P. Boyle, J. A. Edwards, and J. H. Fried, *J. Org. Chem.*, **35**, 2560 (1970).

(2) Syntex, S. A., Apartado Postal 2679, Mexico, D. F., Mexico.

(3) P. Sunder-Plassman, P. H. Nelson, P. H. Boyle, A. Cruz, J. Iriarte, P. Crabbé, J. A. Zderic, J. A. Edwards, and J. H. Fried, *J. Org. Chem.*, **34**, 3779 (1969).

(4) For further details of the X-ray diffraction results, see E. Thom and A. T. Christensen, *Acta Crystallogr.*, in press.

(14) E. H. Rodd, "The Chemistry of Carbon Compounds," Vol. IIA, Elsevier, New York, N. Y., 1953, p 34.
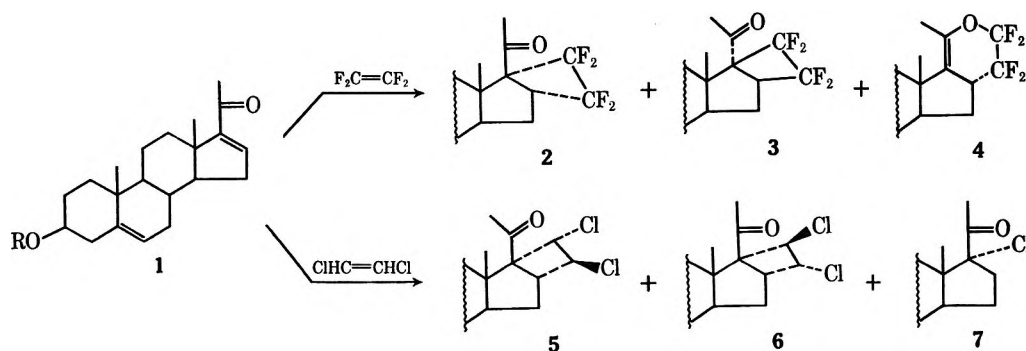
bon–carbon bond formation at either the α[5] or the β position[6] to the carbonyl group. In our case the formation of the β-face adduct 3 and the pyran derivative 4 suggest that the initial bond formation occurs at C-16, *i.e.*, at the β position to the carbonyl function. The resulting diradical intermediate[7] can then lead to products 3 or 4 by ring closure at either C-17 or on the carbonyl oxygen, respectively.

Photochemical cycloaddition of *cis*- or *trans*-dichloroethylene to 1 (R = COCH₃) gave a small amount of 17α-chloro-3β-acetoxypregn-5-en-20-one (7) and two α-face adducts (mp 172–173° and 214–215°) which differ only in the stereochemistry of the chlorine atoms.[3]

The stereochemistry of the 17′ chlorines have been assigned[3] as being endo in the higher melting isomer 5 and exo in the other (6) on the basis of the observed long-range coupling ($J = 1.5$ Hz, see Table I) between

TABLE I
SUMMARY OF NMR DATA OF DICHLOROETHYLENE ADDUCTS 5 AND 6

Compd	—Resonances (CDCl₃, δ, ppm)— 18-H	21-H	16′-H	17′-H	H–H spin couplings,[a] Hz
5, R = COCH₃	0.61	2.18	3.80	4.34	$J_{16\beta,16'\alpha} = 4.5$
					$J_{16\beta,17'\beta} = 1.5$
					$J_{16'\alpha,17'\beta} = 6.0$
6, R = COCH₃	0.71	2.26	4.42	4.26	$J_{16\beta,16'\beta} = 9.5$
					$J_{16\beta,17'\alpha} = 0$
					$J_{16'\beta,17'\alpha} = 7.5$

[a] Confirmed by double resonance experiments.

the 16β and 17′β protons in 5 which are in a "W" spatial relationship to each other. This long-range coupling is absent in 6. Since the configuration at the 16′ position could not be assigned with confidence on the basis of the $J_{16\beta,16'}$ and $J_{16',17'}$ values alone, the 3β-bromoacetate derivative of isomer 5 was subjected to X-ray analysis (C₂₅H₃₃O₃Cl₂Br; orthorhombic crystals with $a = 32.37$, $b = 9.77$, and $c = 7.89$ Å; space group $P2_12_12_1$ from systematic absences[8]), establishing the presence of a 16′ exo chlorine in 5. The cyclobutyl ring in 5 is planar to within 0.015 Å with 110 and 119° dihedral angles between the 16β,16′α and 16′α,17′β protons.

The stereochemistry of the 16′ chlorine in 6 can now be inferred by comparison of the $J_{16\beta H,16'H}$ (9.5

(5) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, New York, N. Y., 1965, p 207; P. J. Wagner and G. S. Hammond, *Advan. Photochem.*, **5**, 118 (1968); J. W. Hanifin and E. Cohen, *J. Amer. Chem. Soc.*, **61**, 4494 (1969); T. S. Cantrell, W. S. Haller, and J. C. Williams, *J. Org. Chem.*, **34**, 509 (1969).

(6) W. L. Dilling, T. E. Tabor, F. P. Boer, and P. P. North, *J. Amer. Chem. Soc.*, **92**, 1399 (1970).

(7) The possibility of this intermediate being a zwitterion is not excluded.

(8) Full details of the X-ray work will be published in *Acta Crystallogr.*

vs. 4.5 Hz) and $J_{16'H,17'H}$ values (7.5 *vs.* 6.0 Hz) in the two isomers (see Table I). These values indicate a difference in the relative configuration of the 16β,16′ protons which is trans in compound 5 and therefore has to be cis with a very small dihedral angle in 6. Consequently, the configuration of the 16′ chlorine is endo in 6 which is consistent with the observed trans relationship of the 16′,17′ protons in both isomers.

The fact that both *cis*- and *trans*-dichloroethylene gave the same product composition[3] is in good agreement with a stepwise addition mechanism forming a diradical intermediate[7] which can undergo free rotation at the 16′–17′ bond before ring closure.

Experimental Section[9]

3β-(*p*-Bromobenzoyloxy)androst-5-eno[16α,17-*d*]-2′,2′,3′,3′-tetrafluoro-2′,3′-dihydro-6-methylpyran (4, R = COC₆H₄Br).— A solution of the 3β-acetoxy compound[3] 4 (R = COCH₃, 450 mg) in methanol (30 ml) containing potassium bicarbonate (450 mg) and water (0.6 ml) was heated under reflux for 1.75 hr. After cooling, the methanol was removed under reduced pressure and the residue extracted with ethyl acetate. Drying (Na₂SO₄) and evaporation of the solvent gave the crude crystalline 3β-hydroxy compound 4 (R = H, 380 mg) which was dissolved in pyridine (5 ml) and heated for 2 hr on a steam bath with *p*-bromobenzoyl chloride (420 mg). The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid and with aqueous sodium carbonate. Drying and evaporation of the solvent yielded the crude *p*-bromobenzoate 4 (R = *p*-COC₆H₄Br, 510 mg). Recrystallization from chloroform–methanol gave the analytical sample: mp 254–256°; ν_{max} (Nujol) 1720 cm⁻¹; nmr (CDCl₃) 0.96 (18-H), 1.07 (19-H), 1.89 (d, $J_{16\beta H,21H} = 2$ Hz, 21-H), 3.26 (b m, 16β-H), 4.6–5.0 (3α-H), 5.42 (m, $W_{1/2} = 9$ Hz, 6-H), 7.56 (d, $J = 8.5$ Hz, aromatic H), and 7.89 ppm (d, $J = 8.5$ Hz, aromatic H); mass spectrum 596 and 598 (M⁺ with ⁷⁹Br and ⁸¹Br), 396 (M⁺ − BrC₄H₆COOH). *Anal.* Calcd for C₃₀H₃₃O₃F₄Br: C, 60.31; H, 5.52. Found: C, 60.44; H, 5.77.

3β-Hydroxy-16α,17α-(16′-*exo*,17′-*endo*-dichloro)ethylenepregn-5-en-20-one (5, R = H).—A solution of 3β-acetoxy-16α,17α-(16′-*exo*,17′-*endo*-dichloro)ethylenepregn-5-en-20-one (5, R = COCH₃, 2.5 g) in tetrahydrofuran (80 ml) was treated with 1.5% methanolic potassium hydroxide (250 ml) at room temperature for 1.5 hr. The reaction mixture was diluted with water and extracted with methylene chloride, and the organic extracts were washed with water and then dried (Na₂SO₄). Evaporation of the solvent and recrystallization of the residue from acetone gave the 3β-alcohol (5, R = H, 2.0 g): mp 224–226°; [α]D −81°; $\lambda_{max}^{dioxane}$ 286–290 nm (ϵ 81); ν_{max} 3550, 3400, 1706, 1670, 796,

775, 681, 658 cm^{-1}. *Anal.* Calcd for $C_{23}H_{32}O_2Cl_2$: C, 67.14; H, 7.84; Cl, 17.24. Found: C, 67.09; H, 7.79; Cl, 17.84.

3β-Bromoacetoxy-16α,17α-(16'-*exo*,17'-*endo*-dichloro)ethylene-pregn-5-en-20-one (5, R = COCH$_2$Br).—3β-Hydroxy-16α,17α-(16'-*exo*,17'-*endo*-dichloro)ethylenepregn-5-en-20-one (5, R = H, 1.8 g) dissolved in dry pyridine (2 ml) and anhydrous benzene (500 ml) was treated with 6 ml of a bromoacetyl bromide-benzene mixture (1:2) at room temperature for 7 hr. The reaction mixture was poured into ice–water and the organic layer was washed with dilute hydrochloric acid, aqueous sodium bicarbonate, and water, and then dried (Na$_2$SO$_4$). Evaporation of the benzene gave the 3β-bromoacetoxy derivative (5, R = COCH$_2$Br), which was recrystallized from methylene chloride-methanol (2.0 g): mp 202–203.5°; [α]D −53°; ν_{max} 1735, 1705, 1225 cm^{-1}; nmr (CDCl$_3$) 0.62 (18-H), 1.02 (19-H), 2.19 (21-H), 3.17 (m, 16-H), 3.80 (s, BrCH$_2$CO), 3.88 (d d, $J_{16,16'}$ = 4.5, $J_{16',17'}$ = 6 Hz, 16'-H), 4.35 (d d, $J_{16,17}$ = 1.5, $J_{16',17'}$ = 6 Hz, 17'-H), 4.50–4.80 (3α-H), 5.43 ppm (m, 6-H).

Anal. Calcd for $C_{25}H_{33}O_3Cl_2Br$: C, 56.38; H, 6.25; Cl, 13.32; Br, 15.03. Found: C, 56.37; H, 6.35; Cl, 13.55; Br, 15.10.

Registry No.—4 *p*-bromobenzoate, 29765-32-0; **5** (R = H), 29913-50-6; **5** (R = COCH$_2$Br), 29765-33-1; **5** (R = COCH$_3$), 29765-34-2; **6** (R = COCH$_3$), 29765-35-3.

## Acetalation and Acetylation of Pyrimidine Nucleosides in Dioxane–Acetonitrile–Hydrogen Chloride

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The use of hydrogen chloride in anhydrous dioxane as a catalyst for the conversion of ribonucleosides to corresponding 2',3'-*O*-alkylidene derivatives has been described by Chládek.[2-4] It has now been found that this catalyst–solvent system, when employed in combination with acetonitrile,[5] effects a smooth transformation of uridine (1) to 2',3'-*O*-ethylideneuridine (2). The latter was obtained in 74% yield and was characterized by elemental analysis and spectral (ir and nmr) data. The key step in this conversion is probably the acid-catalyzed cleavage of dioxane to acetaldehyde which in turn reacts with 1 in the usual manner to give the corresponding alkylidene derivative 2. A possible mechanism of dioxane cleavage in the

presence of acid is indicated in Scheme I. In support of the proposed pathway, it has been known for many

SCHEME I
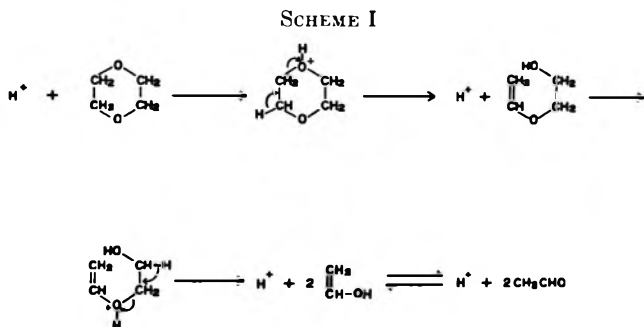
years that the action of sulfuric acid or zinc chloride on dioxane leads to acetaldehyde.[6]

By contrast, thymidine (3), which lacks the cis-vicinal diol grouping, reacts with dioxane–acetonitrile–HCl to give 3',5'-di-*O*-acetylthymidine[7] (5) in 56% yield after treatment of the reaction mixture with sodium acetate in water (Scheme II). In this case the formation of a stable cyclic alkylidene derivative is precluded and the acylation of both hydroxy groups most likely takes place through a bis acetimido ether intermediate 4. The latter is then hydrolyzed during the work-up to 5. The reaction represents an alternative synthesis of 3',5'-di-*O*-acetyl-2'-deoxyribonucleosides, employing nonbasic conditions instead of the more usual acetic anhydride–pyridine method.

Uridine (1), on treatment with anhydrous hydrogen chloride in acetonitrile and in the absence of dioxane, gave 5'-*O*-acetyluridine (46%) and 2',3',5'-tri-*O*-acetyluridine (23%) in addition to other minor products after hydrolysis of the reaction mixture in acetate buffer.

Experimental Section[8]

2',3'-*O*-Ethylideneuridine (2).—Uridine (1, 0.24 g, 1 mmol) dried at 100° (0.1 mm) was shaken with acetonitrile (0.52 ml, 10 mmol) and a 6.5 *M* solution of anhydrous hydrogen chloride in dioxane (2 ml) for 43 hr at room temperature. After standing for an additional 3 days at room temperature, the solution was added dropwise with stirring to 7 *M* ammonium hydroxide (40 ml). The solvents were evaporated to dryness *in vacuo* and the residue was dissolved in acetonitrile (40 ml). The insoluble portion was removed by filtration, the filtrate was evaporated to dryness, and the residue was dried at 50° (0.1 mm) to give a glassy material (2) which gradually crystallized. The latter was judged to contain 8% uridine according to paper chromatography (S$_1$). Substance 2 in water was put on a column of Amberlite resin (OH$^-$ form, 6 × 4 cm) which was eluted with water. The eluate was evaporated to a solid which crystallized from 90% ethanol, affording 0.2 g (74%) of 2: mp 192–195°; ir (CHCl$_3$) similar to those of 2',3'-*O*-alkylideneuridines;[9] R_f (S$_1$) 0.55,

(1) Address correspondence to Rollin H. Stevens Memorial Laboratory, Detroit Institute of Cancer Research Division of Michigan Cancer Foundation, 4811 John R Street, Detroit, Mich. 48201.

(2) S. Chládek and J. Smrt, *Collect. Czech. Chem. Commun.*, **28**, 1301 (1963).

(3) S. Chládek in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. I, W. W. Zorbach and R. S. Tipson, Ed., Wiley, New York, N. Y., 1968, p 230.

(4) S. Chládek, ref 3, p 292.

(5) Although the role of acetonitrile in this transformation remains to be clarified, it is possible that the latter serves as an effective scavenger of water under the imposed conditions and thus favorably influences the acetalation equilibrium.

(6) A. Faworski, *J. Russ. Phys. Chem. Soc.*, **38**, 741 (1906).

(7) R. E. Belz and D. M. Visser, *J. Amer. Chem. Soc.*, **77**, 736 (1955).

(8) Analyses were performed in the Analytical Department of the Institute of Organic Chemistry and Biochemistry under the direction of Dr. J. Horáček. Melting points were determined on a Kofler block and are uncorrected. All evaporations were carried out *in vacuo*; nmr spectrum was measured on a Varian A-60A spectrometer, using sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard. Paper chromatography in a descending arrangement was performed on a Whatman No. 1 paper using the following solvent systems: 1-butanol saturated with water (S$_1$); 1-butanol–acetic acid–water, 5:2:3 (S$_2$); 2-propanol–concentrated ammonium hydroxide–water, 7:1:2 (S$_3$); and on Whatman No. 4 paper impregnated with formamide in chloroform as the solvent (S$_4$). The spots were viewed under the ultraviolet ("Chromatolite").

(9) J. Piťha, S. Chládek, and J. Smrt, *Collect. Czech. Chem. Commun.*, **28**, 1622 (1963).

SCHEME II

I

U = URACIL

3   4   5
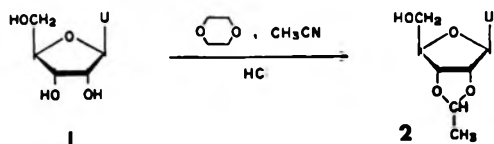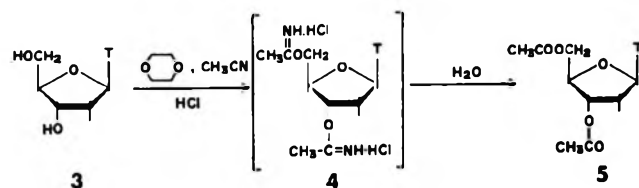
T = THYMINE

(S₂) 0.7, (S₃) 0.59; nmr (CD₃SOCD₃ + D₂O) δ 7.74 (d, 1 H, H₆), 5.69 (two overlapping doublets, 2 H, H₁′ + H₅), 5.18 (d, 1 H, CH, acetal), 4.74 (m, 2 H, H₂′ + H₃′), 4.10 (poorly resolved, overlapped with HDO signal, 1 H, H₄′), 3.62 (d, 2 H, H₅′) 1.40 (d, 3 H, CH₃).

Anal. Calcd for C₁₁H₁₄N₂O₆: C, 48.89; H, 5.22; N, 10.37. Found: C, 48.75; H, 5.37; N, 10.58.

3′,5′-Di-O-acetylthymidine (5).—Thymidine (3, 0.12 g, 0.5 mmol) was shaken with acetonitrile (5 ml) and a 6.5 *M* solution of anhydrous hydrogen chloride in dioxane (0.5 ml) for 48 hr at room temperature. Only after 3 hr did the reaction mixture become homogeneous. The solution was added dropwise to an excess of sodium acetate in water and the mixture was extracted with chloroform. The dried organic layer was evaporated to dryness. The syrupy residue solidified after drying at 0.1 mm to give 90 mg (56%) of chromatographically pure solid 5: mp 123–125° (crystallized from benzene–carbon tetrachloride 2:1 mixture) (lit.[7] mp 123–125°); R_f (S₁) 0.76, (S₄) 0.81. Ammonolysis of 5 gave thymidine as found by paper chromatography (S₁).

Anal. Calcd for C₁₄H₁₈N₂O₇: C, 51.53; H, 5.56; N, 8.59. Found: C, 51.52; H, 5.56; N, 8.38.

Reaction of Uridine with Acetonitrile and Anhydrous Hydrogen Chloride.—A suspension of uridine (1, 0.12 g, 0.5 mmol) in acetonitrile (10 ml) was saturated with hydrogen chloride, and the solution, which contained a small amount of undissolved solid, was held overnight at room temperature. The reaction mixture was evaporated to dryness; a portion of the crude product was dissolved in 1 *M* triethylammonium acetate (pH 6), and chromatographed in S₁. Authentic samples of 1, 5′-O-acetyluridine, and 2′,3′,5′-tri-O-acetyluridine were run simultaneously. Five spots were detected, which were eluted with water and the amount of uv-absorbing material was determined spectrophotometrically at 260 nm (Table I).

TABLE I

Compound	R_f	%[a]
Uridine (1)	0.15	1
5′-O-Acetyluridine	0.26	46
Unidentified	0.37	14
Unidentified	0.51	16
2′,3′,5′-Tri-O-acetyluridine	0.74	23

[a] Based on sum of the uv absorbances of the five eluted spots.

A Novel Photochemical Rearrangement–Elimination of an Allylic Alcohol Having a Di-π-methane Structure[1]

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In the course of a study of the di-π-methane rearrangement, the photochemistry of a variety of compounds having a geminal phenyl group allylic to two double bonds has been examined. Generally, compounds having this chromophoric structural feature rearrange to give cyclopropyl products either by 1,3-vinyl–vinyl interaction such as in 1 to 2,[3] and ultimately 3, or by 1,3-vinyl–aryl interaction such as in 4 to 5.[4]
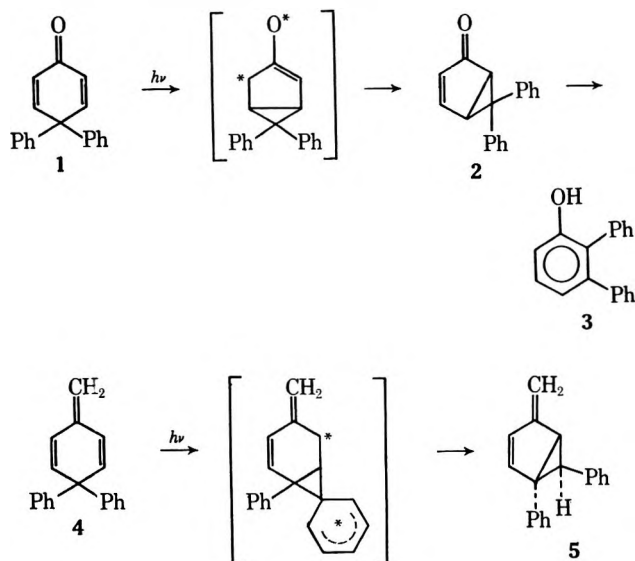
In contrast, when 1-hydroxy-4,4-diphenyl-2,5-cyclohexadiene (6) was irradiated in an ethanolic solution with a Vycor filter (λ >210 nm), the only low molecular weight photoproduct was an aromatic hydrocarbon. The product was identified as *o*-terphenyl (7) by comparison of its spectra with those of the known compound. A dark control, run parallel with the irradiation, showed no reaction. When the reaction was followed using thin layer chromatography, no buildup of an intermediate could be detected.

The 1,2-phenyl migration in such a system is a common process, but the elimination of water is quite distinctive. Of two possible mechanisms involving intermediates related to structures 2 and 5, only the alcohol 8 related to the former type has been evaluated owing to synthetic difficulties leading to an alcohol related to 5, *i.e.*, 1,6-diphenylbicyclo[3.1.0]hex-2-en-4-ol. An intermediate such as 8 could photochemically rearrange

(1) This work was supported, in part, by Grant No. AM-00709, National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service, and the Hoffmann-La Roche Foundation.

(2) National Institute of Health Predoctoral Fellow, 1967–1970.

(3) H. E. Zimmerman and D. I. Schuster, *J. Amer. Chem. Soc.*, **84**, 4527 (1962).

(4) H. E. Zimmerman, P. Hackett, D. F. Juers, and B. Schroder, *ibid.*, **89**, 5973 (1967).
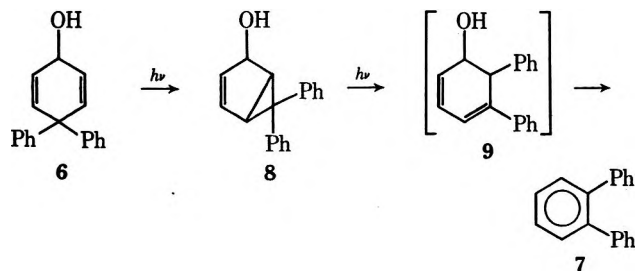
to a second intermediate **9** which, in turn, could dehydrate to the observed product. The alcohol **8** was prepared from the ketone **2** by lithium aluminum hydride reaction. The alcohol was unstable upon silica gel and alumina and so was characterized by spectral properties; oxidation of it gave back the starting ketone.

Direct irradiation of **8** in ethanol with a Vycor filter yielded the expected *o*-terphenyl. A dark control reaction yielded no *o*-terphenyl. The rate of photoinduced disappearance was three times as rapid as that of **6**; such a result is required since no buildup of an intermediate had been detected. Thus, the involvement of the cyclopropane alcohol **8** is not only feasible but possible. As with other related compounds with the 4,4-diphenyl-2-cyclohexenyl chromophore,[5] the reaction of **8** proceeds *via* the triplet state, the reaction being sensitized by acetophenone.

Experimental Section

Preparation of 4,4-Diphenyl-2,5-cyclohexadienone (1).—2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 5.8 g, 0.026 mol) and 4,4-diphenyl-2-cyclohexanone[3] (5.8 g, 0.024 mol) were dissolved in 50 ml of dioxane and refluxed for 15 hr. After work-up, the product was recrystallized from a methylene chloride–hexane solution to give 3.1 g (48%) of **1**, mp 122–123° (lit.[3] mp 121–123°).

Preparation of 1-Hydroxy-4,4-diphenyl-2,5-cyclohexadiene (6).—4,4-Diphenyl-2,5-cyclohexadienone (1.35 g) and sodium borohydride (0.2 g) were dissolved in 50 ml of ethanol and stirred overnight at room temperature. Upon work-up, the residue (1.05 g, 78%) crystallized on standing. Compound **6** has the following properties: mp 82–84°; uv max (95% EtOH) 260 nm (ε 420); ir (CCl₄) 3430 and 695 cm⁻¹; nmr (CCl₄) δ 6.97 (s, 10, phenyl), 5.6–6.0 (m, 4, CH=CH), 4.23 (s, 1, CHOH), 2.92 (s, 1, CHOH); mass spectrum *m/e* 248, 231, 230, 229, 228, 215, and 202.

Anal. Calcd for C₁₈H₁₆O: C, 87.06; H, 6.49. Found: C, 86.85; H, 6.53.

Irradiation of 1-Hydroxy-4,4-diphenyl-2,5-cyclohexadiene (6). —A solution of 235 mg of 1-hydroxy-4,4-diphenyl-2,5-cyclohexadiene (1) in 235 ml of absolute ethanol was irradiated under a nitrogen atmosphere using a 450-W Hanovia lamp and a Vycor filter (λ >210 nm). The progress of the irradiation was followed by thin layer chromatography. After 30 min the irradiation was halted, the solvent was removed by rotary evaporation, and the photomixture was separated by silica gel column chromatography. Two fractions were isolated, 31 mg of starting alcohol and 81 mg (43% based on reacted alcohol) of an aromatic hydrocarbon. The remainder of the photomixture was high molecular weight. The photoproduct was identified as o-terphenyl by comparison of spectra with those of the known compound. A dark control run parallel with the photoreaction showed no reaction.

Preparation of 6,6-Diphenylbicyclo[3.1.0]hex-3-en-2-ol (8).—A solution of 100 mg of 6,6-diphenylbicyclo[3.1.0]hex-3-en-2-one (2)[3] in 100 ml of anhydrous ether was added, dropwise, to a suspension of 128 mg of lithium aluminum hydride in 150 ml of anhydrous ether. The reaction mixture was stirred for 1 hr, water was carefully added, and the ethereal layer was separated and dried. The solvent was rotary evaporated. The crude **8** had the following properties: ir (CCl₄) 3420 and 1120 cm⁻¹; nmr (CCl₄) δ 7.12–7.17 (m, 10, phenyl), 6.02 (m, 2, CH=CH),

4.7 (m, 1, CHOH), 3.68 (s, 1, CHOH), 2.0–2.6 (m, 2, cyclopropyl); mass spectrum *m/e* 248, 230, 215, 202. Oxidation of the alcohol with chromic acid in pyridine[6] yielded the starting ketone.

Irradiation of 6,6-Diphenylbicyclo[3.1.0]hex-3-en-2-ol (8).—A solution of 100 mg of **8** in 235 ml of absolute ethanol was irradiated under a nitrogen atmosphere using a 450-W Hanovia lamp and a Vycor filter. After 30 min, the irradiation was stopped, the solvent was rotary evaporated, and the photomixture was separated by silica gel column chromatography. o-Terphenyl (79 mg) was isolated and identified by comparison with an authentic sample.

Sensitized Irradiation of 6,6-Diphenylbicyclo[3.1.0]hex-3-en-2-ol (8).—A solution of 370 mg of **8** in 230 ml of benzene, 15 ml of methanol, and 7 ml of acetophenone was irradiated under a nitrogen atmosphere using a 450-W Hanovia lamp and a Nonex filter (λ >310 nm). After 20 min, the irradiation was stopped, the benzene and methanol were rotary evaporated, and the acetophenone was distilled at reduced pressure. The residue was chromatogaphed on 70 g of basic Woelm alumina (activity III) and 84 mg of o-terphenyl eluted with 5% ethyl acetate-hexane. A dark control reaction showed no reaction.

Registry No.—**6**, 29765-37-5; **8**, 29765-38-6.

(6) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).

Synthesis of 5,6-Dihydropyrido[2,3-*d*]pyrimidine Derivatives Directly from Acyclic Precursors

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Existing methods for the synthesis of 5,6-dihydropyrido[2,3-*d*]pyrimidines involve several steps including production and isolation of one or more pyrimidine[1] or piperidine[1a,2] derivatives and subsequent ring closure. We wish to report a method by which several members of this class of compounds may be prepared in a single synthetic step starting with acyclic precursors.

Ethyl cyanoacetate sodium salt was caused to react with methyl acrylate or methyl methacrylate forming diethyl 2-cyanoglutarate[3] (**1a**) or diethyl 2-cyano-4-methylglutarate (**1b**). The reaction of gunaiidne with

1a, R = H
b, R = CH₃
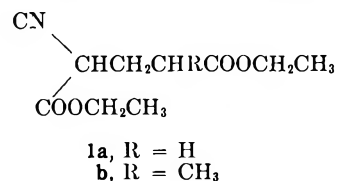
1a and **1b** in ethanol afforded 2-amino-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (**2a**) and its 6-methyl analog **2b**, respectively. A similar reaction of **1a** with benzamidine afforded **3**. The pmr spectrum of

(1) (a) W. J. Irwin and D. G. Wibberley, *Advan. Heterocycl. Chem.*, **10**, 149 (1969); (b) J. Biggs and P. Sykes, *J. Chem. Soc.*, 1849 (1959); (c) L. Suranyi and L. Schuler, German Patent 1,100,030 (1961); *Chem. Abstr.*, **57**, 2231 (1962); (d) B. R. Baker and P. I. Almaula, *J. Heterocycl. Chem.*, **1**, 263 (1964); (e) V. Papesch, U. S. Patents 3,235,554 and 3,235,555 (1966); *Chem. Abstr.*, **64**, 14198 (1966); (f) B. Blank and W. T. Caldwell, *J. Org. Chem.*, **24**, 1137 (1959).

(2) J. DeGraw and L. Goodman, *Can. J. Chem.*, **41**, 3137 (1963).

(3) (a) C. F. Koelsch, *J. Amer. Chem. Soc.*, **65**, 2458 (1943); (b) L. Ruzicka, A. Borgesde Almeida, and A. Brack, *Helv. Chim. Acta*, **17**, 183 (1934); (c) P. C. Guha and D. D. Gupta, *J. Indian Inst. Sci.*, Sect. A, **22**, 255 (1939); (d) L. Barthe, *C. R. Acad. Sci.*, **118**, 1268 (1894).

(4) C. K. Ingold, *J. Chem. Soc.*, **119**, 329 (1921).

(5) W. G. Dauben and W. A. Spitzer, *J. Amer. Chem. Soc.*, **92**, 5817 (1970).

2a, R = H
b, R = CH₃

3
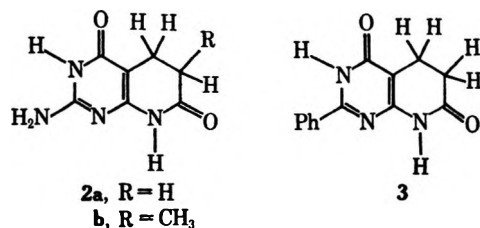
2b run in basic D_2O showed its C_6-methyl protons at τ 8.88 as a singlet and C_5 protons at τ 7.52 ($J = 15$ Hz) as an AB quartet. Mass spectral analysis of **2a** showed a molecular ion peak at m/e 180.

These results are in contrast to the reported isolation of 4-amino-5-ethoxycarbonylmethyl-6-hydroxy-2-methylpyrimidine and its 2-phenyl analog,[5] but in agreement with the more recent observation that methyl β-(4-hydroxy-2-methyl-5-pyrimidyl)propionate, when treated with methanolic ammonia at 110°, gave 2-methyl-5,6-dihydropyrido[2,3-*d*]pyrimidine-7(8*H*)-one.[1b]

Ethyl 4,4-dicyanobutyrate (**4**), prepared from the sodium salt of malononitrile[6] and ethyl 3-bromopropionate, undergoes an analogous condensation with guanidine forming 2,4-diamino-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**5**).

5
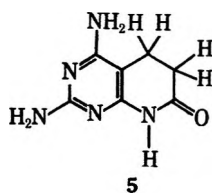
Experimental Section

Uv spectra were determined using a recording Beckman DB-G spectrophotometer. Pmr spectra were obtained with a Varian A-60 spectrometer using tetramethylsilane or 3-trimethylsilylpropane sulfonic acid sodium salt as internal references. Analyses were performed by Galbraith Analytical Laboratories, Knoxville, Tenn. Melting points are uncorrected.

Diethyl 2-Cyano-4-methylglutarate (1b).—This material was prepared by the method of Koelsch,[3a] using ethyl cyanoacetate (18.8 g, 0.167 mol) and methyl methacrylate (16.7 g 0.167 mol). The oil obtained after work-up was distilled giving 15 g (39%) of **1b**, bp 105–120° (0.20 mm) [lit.[4] bp 160–162° (24 mm)].

2-Amino-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (2a).—Guanidine carbonate (0.89 g, 5.0 mmol) was added to a solution prepared by addition of 40 ml of ethanol to sodium (0.23 g, 0.010 g-atom) and stirred for 2 days at room temperature. The precipitate was collected by filtration and washed thoroughly with water, ethanol, and ether giving 0.33 g of **2a** as an off-white powder. An additional 0.10 g was obtained from the concentrated filtrate. The total yield was 0.43 g (24%). Recrystallization from boiling acetic acid gave a white powder: mp >400°; uv max (H₂O) 299 mμ ($\epsilon \times 10^{-3}$ 7.8), uv min 258 (1.1); uv max (pH 1) 292 (8.2), uv min 258 (2.4); uv max (pH 13) 290 (5.4), uv min 261 (2.1); pmr (D₂O containing NaOH) τ 7.45 (m).

Anal. Calcd for C₇H₈N₄O₂: C, 46.64; H, 4.48; N, 31.11. Found: C, 46.77; H, 4.43; N, 31.04.

Compound **2a** was converted to a derivative, **2-benzamido-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione.** A mixture of benzoic anhydride (4.5 g, 0.020 mol) and **2a** (1.0 g, 5.5 mmol) was heated gradually to 180–190°. After 15 min of heating, 50 ml of ethanol was added and the mixture refluxed for 10 min, cooled to room temperature, filtered, and washed with ethanol giving 0.90

g (58%) of tan solid. Recrystallization from 500 ml of boiling DMF gave a white powder, mp 376–378°.

Anal. Calcd for C₁₄H₁₂N₄O₃: C, 59.15; H, 4.25; N, 19.71. Found: C, 59.05; H, 4.41; N, 19.79.

2-Amino-6-methyl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7-(3*H*,8*H*)-dione (2b).—This material was prepared from **1b** using the same procedure and the same scale of reactants as used for **2a** giving 0.72 g (36%) of tan solid. Recrystallization from 600 ml of acetic acid gave a white powder: mp >400°; uv max (H₂O) 299 mμ ($\epsilon \times 10^{-3}$ 8.3), uv min 258 (0.9); uv max (pH 1) 293 (8.5), uv min 258 (2.4); uv max (pH 13) 291 (5.7), uv min 262 (1.9).

Anal. Calcd for C₈H₁₀N₄O₂: C, 49.48; H, 5.19; N, 29.25. Found: C, 49.62; H, 5.19; N, 29.02.

2-Phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (3).—Benzamidine hydrochloride hydrate (7.2 g, 0.046 mol) was added to a solution prepared by adding 50 ml of ethanol to sodium (1.0 g, 0.046 g-atom). Sodium sulfate (2.0 g) was added and the mixture was filtered. The filtrate was treated with **1a** (9.74 g, 0.046 mol) and the solution was refluxed 12 hr. Work-up was handled as for **2a** giving 1.3 g (11%) of **3** as a light tan powder: mp >400°; uv max (95% EtOH) (pH 8) 313 and 244 mμ, uv min 279 and 223; uv max (pH 1) 312 and 247 mμ, uv min 278 and 212; uv max (pH 13) 294 mμ (sh, $\epsilon \times 10^{-3}$ 6.5), 288 (sh, 7.2), and 260 (sh, 14.4); pmr (D₂O containing NaOH) τ 7.32 (m, 2, CH₂CD₂CO), 2.48 (m, 3, C₆H₅).

Anal. Calcd for C₁₃H₁₁N₃O₂: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.72; H, 4.54; N, 17.37.

Ethyl 4,4-Dicyanobutyrate[7,3] (4).—The sodium salt of malononitrile was prepared by the method of Krapcho and Huyffer.[6] A solution of malononitrile (66.06 g, 1 mol) in 500 ml of dimethoxyethane was added dropwise during 1 hr to a stirred mixture of 55.9% sodium hydride (22.00 g, 0.52 mol) in mineral oil in 200 ml of dimethoxyethane. After 15 min, a solution of ethyl 3-bromopropionate (90.52 g, 0.50 mol) in 100 ml of dimethoxyethane was added dropwise during 30 min to the stirred mixture. After 12 hr of stirring at room temperature, the mixture was poured into a mixture of 1 l. of benzene and 1 l. of acidified saturated aqueous NaCl solution. The organic layer was washed with two 500-ml portions of saturated aqueous NaCl solution, dried (Na₂SO₄), filtered, and concentrated to give the product layer covered with mineral oil. The mineral oil was removed using a separatory funnel. Failure to remove the oil resulted in its codistillation with the product fractions. The crude product mixture was fractionally distilled giving 33.6 g of **4** (57%): bp 118–120° (0.10 mm); pmr (CCl₄) τ 8.73 (t, 3, OCH₂CH₃), 7.57 (m, 4, CHCH₂CH₂CO), 5.82 (quartet, 2, OCH₂CH₃), and 5.80 (t, 1, CHCH₂), with the latter two signals overlapping but discernible; ν_{max}^{film} 2250 cm⁻¹ (CN).

Anal. Calcd for C₈H₁₀N₂O₂: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.61; H, 6.02; N, 16.71.

The higher boiling fraction consisted of 18 g of diethyl 4,4-dicyanopimelate: bp 140–144° (0.08 mm); pmr (CCl₄) τ 8.71 (t, 6, OCH₂CH₃), 6.53 (m, 8, CHCH₂CH₂CO), and 5.85 (quartet, 4, OCH₂CH₃).

Anal. Calcd for C₁₃H₁₈N₂O₄: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.44; H, 6.58; N, 10.43.

2,4-Diamino-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one (5).—This material was prepared in 50% yield from guanidine carbonate and **4** using the method for **2a** above. Recrystallization from boiling acetic acid gave **5** as a white powder: mp 373–375°; uv max (95% EtOH) 292 mμ, uv min 261; uv max (pH 1) 305 mμ, uv min 261; uv max (pH 13) 298 mμ ($\epsilon \times 10^{-3}$ 8.2), uv min 264 (2.4); pmr[9] (D₂O containing NaOH) τ 7.75 (m, CH₂CD₂CO).

Anal. Calcd for C₇H₉N₅O: C, 46.90; H, 5.06; N, 39.10. Found: C, 47.14; H, 4.96; N, 38.94.

Registry No.—**2a**, 29668-91-5; **2b**, 29668-92-6; **3**, 29784-74-5; **4**, 29668-93-7; **5**, 29668-94-8; 2-benzamido-

(5) (a) I. G. Farbenindustrie, German Patent 671,787 (1939); (b) Z. Foldi, G. v. Foder, I. Demjen, H. Szekens, and I. Holmes, *Ber.,* **75,** 755 (1942).

(6) A. P. Krapcho and P. S. Huyffer, *J. Org. Chem.,* **28,** 2461 (1963).

(7) E. M. Gal, F. Fung, and D. M. Greenberg, *Cancer Res.,* **12,** 565 (1952), reported the preparation of **4** without accompanying spectral or analytical data.

(8) Pure samples of **4** were obtained by reacting malononitrile and ethyl 3-bromopropionate with NaH in dimethoxyethane.[6] The procedure using sodium ethoxide and ethanol also gave **4** along with imino ether contaminants. Malononitrile and its derivatives form imino ethers in the presence of alcohols and acidic or basic catalysts. See B. C. Hesse, *Amer. Chem. J.,* **18,** 723 (1896).

(9) Compound **5** is unstable in aqueous base.

5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7-(3*H*,8*H*)-dione, 29668-95-9; diethyl 4,4-dicyanopimelate, 29668-96-0.

The Direct Preparation of *tert*-Butyl Azidoformate

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The carbo-*tert*-butoxy (BOC) function has achieved a role of major importance as a blocking group, particularly in peptide chemistry.[2] The "carbo-*tert*-butoxylating" agent of choice is *tert*-butyl azidoformate (**3**).[3] The value of the carbo-*tert*-butoxy group and the rather high cost of the reagent created a demand for a better and more convenient synthesis of **3**.

The instability of *tert*-butyl chloroformate (**1**) prevented its use as a direct precursor of **3** by displacement *via* the usual "azide method" and the azido group had to be built by the hydrazide–nitrosation route (eq 1).

$$\text{H}_2\text{NNHCO}_2\text{C(CH}_3)_3 \xrightarrow{\text{HONO}} \text{N}_3\text{CO}_2\text{C(CH}_3)_3 \xleftarrow{\;\;\;/\!/\;\;\;} \begin{array}{c}\text{N}_3^- \text{ (aqueous)}\\ +\\ \text{ClCO}_2\text{C(CH}_3)_3\end{array} \quad (1)$$
$$\quad\;\; \mathbf{2} \qquad\qquad\qquad \mathbf{3} \qquad\qquad\qquad\qquad \mathbf{1}$$

Thus, most attempts at improving Carpino's method centered on the precursor of **3**, *tert*-butyl carbazate (**2**).[4] The several routes to **2** which have been published differ from Carpino's original procedure and each other only in the nature of the group being displaced by hydrazine (X in **4**).[5]

$$\text{XCO}_2\text{C(CH}_3)_3 + \text{H}_2\text{NNH}_2 \longrightarrow \text{H}_2\text{NNHCO}_2\text{C(CH}_3)_3 \quad (2)$$
$$\qquad\quad \mathbf{4} \qquad\qquad\qquad\qquad\qquad \mathbf{2}$$

Our general interest in azides[6] and in selective protective groups[7] provided a strong impetus to the search for an improved synthesis of *tert*-butyl azidoformate. In 1966, Papa[8] reported the synthesis of guanidinium azides which are ionic and *soluble* in organic solvents. Since *tert*-butyl chloroformate (**1**) is easily prepared in

high yield from the reaction of *tert*-butyl alcohol and phosgene at −78°,[9] it was felt that the reaction of tetramethylguanidinium azide (TMGA) (**5**) with **1** might provide a more convenient and direct synthesis of *tert*-butyl azidoformate.

$$\text{ClCO}_2\text{C(CH}_3)_3 + \text{N}_3^-\text{H}_2\overset{+}{\text{N}}{=}\text{C(NMe}_2)_2 \longrightarrow$$
$$\qquad \mathbf{1} \qquad\qquad\qquad \mathbf{5}$$

$$\text{N}_3\text{CO}_2\text{C(CH}_3)_3 + \text{Cl}^-\text{H}_2\overset{+}{\text{N}}{=}\text{C(NMe}_2)_2$$
$$\qquad\qquad \mathbf{3}$$

The results of the experiment exceeded our expectations. The reaction of *tert*-butyl chloroformate with TMGA gave a near-quantitative yield of *tert*-butyl azidoformate, isolated as an amber liquid, *without distillation*. Its purity as judged from comparison of its infrared spectrum with that of a commercial sample appeared to be better than 98%. Phenyl and *tert*-amyl azidoformates[10] were obtained in 97 and 84% yields, respectively.

Tetramethylguanidinium azide is prepared very simply in high yields (86%)[8,11] by the addition of an ethereal solution of hydrazoic acid to tetramethylguanidine.[12] Although it is hygroscopic and thus immediate use is recommended, TMGA can be kept in a desiccator in the cold for long periods of time. *tert*-Butyl chloroformate was prepared by the addition of phosgene to *tert*-butyl alcohol at −78° in the presence of pyridine. The reaction of **1** with TMGA was carried out at 0° in ether with pyridine as the base. The ease and high yields of this procedure coupled with the ready availability of the required starting materials recommend it as a convenient and direct source of *tert*-butyl azidoformate and related azides.

Experimental Section

tert-**Butyl Azidoformate.**—*tert*-Butyl chloroformate was prepared in solution as follows. Dry phosgene was introduced into a solution of 18 g (0.24 mol) of *tert*-butyl alcohol in 500 ml of anhydrous ether until about 52 g (0.5 mol) had been absorbed and the mixture was cooled in a Dry Ice–acetone bath. Then a solution of 20 g (0.25 mol) of pyridine in 200 ml of anhydrous ether was added dropwise with vigorous stirring. The reaction mixture was stored overnight in a Dry Ice box. The precipitated pyridine hydrochloride was filtered and the volume of the filtrate was reduced to ∼70 ml at reduced pressure with cooling in an ice-water bath.[13] This cold solution of *tert*-butyl chloroformate was added over 30 min to a vigorously stirred solution of 31.6 g (0.2 mol) of tetramethylguanidinium azide in 200 ml of chloroform;[8,14] the temperature was kept at 0° throughout the addition. The bath was removed and the reaction mixture stirred for an additional hour and then poured into 500 ml of ice water containing ∼2 ml of acetic acid. Extraction with two 60-ml portions of ether followed by careful evaporation of the dried (magnesium

(1) Alfred P. Sloan Fellow.

(2) M. Bodansky and M. A. Ondetti, "Peptide Synthesis," Interscience, New York, N. Y., 1966, p 29 ff.

(3) L. A. Carpino, *et al.*, *Org. Syn.*, **44**, 20 (1964).

(4) See, however, M. A. Insalaco and D. S. Tarbell, *ibid.*, **50**, 9 (1970); and H. Yajima and H. Kawatani, *Chem. Pharm. Bull.*, **16**, 183 (1968); **18**, 850 (1970).

(5) (a) L. A. Carpino, *J. Amer. Chem. Soc.*, **79**, 98 (1957); (b) G. W. Anderson and A. C. McGregor, *ibid.*, **79**, 6180 (1957); (c) F. Eloy and C. Moussebois, *Bull. Soc. Chim. Belg.*, **68**, 409 (1959); (d) W. Klee and M. Brenner, *Helv. Chim. Acta*, **44**, 2151 (1961); (e) M. Muraki and T. Misoguchi, *Chem. Pharm. Bull.*, **18**, 217 (1970).

(6) For the latest paper in this general area, see K. Sakai, N. Koga, and J.-P. Anselme, *Tetrahedron Lett.*, 4553 (1970).

(7) N. Koga and J.-P. Anselme, *Org. Prep. Proced.*, **2**, 125 (1970).

(8) A. J. Papa, *J. Org. Chem.*, **31**, 1426 (1966).

(9) (a) S. Sakakibara, *et al.*, *Bull. Chem. Soc. Jap.*, **38**, 1522 (1965); **40**, 2415 (1967); (b) R. B. Woodward, *et al.*, *J. Amer. Chem. Soc.*, **88**, 852 (1966).

(10) TMGA was *not* isolated and weighed in this case and thus the actual yield of this reaction is probably nearly quantitative also.

(11) Dr. Papa has informed us that he has prepared TMGA on a molar scale about a dozen times without incident although he *strongly* urges the usual *extreme* caution that must be observed with *any* azide. Of course, the toxic and explosive properties of hydrazoic acid are well known and should be respected.

(12) Tetramethylguanidine is available from American Cyanamid Co. whom we thank for a sample.

(13) It is advisable as a cautionary measure to purge the reaction mixture of any excess phosgene by bubbling nitrogen through the *cold*, stirred reaction mixture. Carbonyl azide which would be formed during the reaction with TMGA is an extremely potent explosive.

(14) Concentrated hydrochloric acid was used instead of concentrated sulfuric acid to generate hydrazoic acid. The product obtained was used without purification.

sulfate) organic phase gave *tert*-butyl azidoformate as a pale amber liquid in quantitative yield.[15]

tert-Amyl azidoformate[9a] was prepared in 84% yield[10] from *tert*-amyl chloroformate. Similarly phenyl azidoformate was prepared in better than 97% yield using chloroform as the sole solvent; in this case, tetramethylguanidinium chloride (87% yield) crystallized out of solution.

Registry No.—3, 1070-19-5.

(15) Neutralization of the aqueous layer followed by extraction with ether allows recovery of tetramethylguanidine.

Dimethyl Sulfide–Borane.
A Convenient Hydroborating Agent

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The utility of hydroboration as a tool in reducing and synthetic reactions has received extensive study since the extent of the reaction was first indicated by Brown and Subba Rao.[1,2] However, the application of this tool has been limited by certain properties of the reagent diborane and its solutions. These properties follow: (1) diborane itself is not stable at room temperature and hence it must normally be generated *in situ* in the glycol ethers, (2) it may be purchased as a quite dilute (1.5 wt %) solution in tetrahydrofuran,[3] but this solvent and the glycol ethers are slowly cleaved by borane at room temperature, (3) both these solvents are relatively expensive and hazardous to store and purify. They are also miscible with both polar and nonpolar solvents and hence difficult to separate from desired products.

It seemed to us that dimethyl sulfide–borane (I), which was first reported by Burg and Wagner[4] and studied by Stone, *et al.*,[5,6] might have certain advantages as a storable hydroboration agent. Chief among these is that I is a stable liquid at room temperature. Samples stored in a nitrogen atmosphere have retained their hydridic activity after several months at room temperature. The density was found to be 0.80 g/ml at room temperature (23°). Since the formula weight is 76 g/mol, 1.0 mmol is conveniently 0.10 ml. Tetrahydrofuran–borane solution has a millimolar volume tenfold greater and gaseous diborane in the dilutions which can be shipped at ambient temperatures has a millimolar volume 10[5] greater. I is also miscible with inexpensive, unreactive volatile solvents such as petroleum ether, benzene, diethyl ether, and methylene chloride.

(1) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1135 (1957).

(2) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962.

(3) Alfa Inorganics, Beverly, Mass.

(4) A. B. Burg and R. I. Wagner, *J. Amer. Chem. Soc.*, **76**, 3307 (1954).

(5) W. A. G. Graham and F. G. A. Stone, *J. Inorg. Nucl. Chem.*, **3**, 1964 (1956).

(6) T. D. Coyle, H. D. Kaesz, and F. G. A. Stone, *J. Amer. Chem. Soc.*, **81**, 2989 (1959).

Chart I

aldehydes	$\longrightarrow$ alcohol
ketones	$\longrightarrow$ alcohol
acid chloride	$\longrightarrow$ no reaction
lactone	$\longrightarrow$ glycol
epoxide	$\longrightarrow$ alcohol
ester	$\longrightarrow$ alcohol (slow)
carboxylic acid	$\longrightarrow$ alcohol (fast)
nitrile	$\longrightarrow$ amine
nitro	$\longrightarrow$ no reaction
olefin	$\longrightarrow$ organoborane (fast)

Brown and Subba Rao[1,2] listed reduction products (Chart I) from hydroboration (after hydrolysis) for some of the common functional groups. They initially studied the reactivity of borane in ethers toward these groups on a millimolar scale. The results were evaluated by measuring the residual hydridic hydrogen after reaction between stoichiometric quantities of the borane and the reducible moiety. Hence we studied the reactivity of I as a hydroborating agent on a millimolar scale by a procedure parallel to that of Brown and Subba Rao. I (2.0 mmol, measured in a glove bag as 0.20 ml with a hypodermic syringe) was injected into 5 ml of benzene in a 25-ml two-necked flask, one neck of which was fitted with a serum cap and the other with a gas delivery tube leading through a mercury bubbler to a gas measuring tube over water. The reducible organic compound (6 mmol) was then added. The benzene was generally necessary as a heat diluent to avoid uncontrolled reactions. After the mixture was stirred for 30 to 45 min, 5 ml of methanol was added to consume any unreacted borane. The gas evolved was measured over water and assumed to be hydrogen. Results with

$$(CH_3)_2SBH_3 + 3CH_3OH \longrightarrow B(OCH_3)_3 + 3H_2 + (CH_3)_2S$$
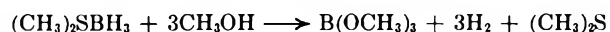
typical organic functional groups are presented in Table I. The data represents averages of at least three determinations. In the last column comparable results by Brown and Subba Rao[1] with diborane in ethers are tabulated.

Coyle, Kaesz, and Stone[6] reported that tetrahydrothiophene, another readily available sulfide, is a weaker base toward borane than dimethyl sulfide. This should make tetrahydrothiophene–borane (II) a better hydroborating agent. We found that tetrahydrothiophene absorbed diborane quite slowly at room temperature and required very vigorous stirring to completely absorb 1 equiv of borane. II also proved to dissolve slowly in benzene, requiring about 15 min to form a homogeneous solution with moderate magnetic stirring. The density was measured to be 0.94 g/ml. Its reaction with several substrates was tested. These are summarized in Table II and again compared with the results of Brown and coworkers.

Discussion

In general the reactivity of dimethyl sulfide–borane parallels that of the ether–boranes. Table I indicates significantly less reaction with acids, nitriles, epoxides, and lactones. With epoxides the ether–boranes have been reported to react very slowly except in the presence of traces of borohydride.[7] Traces of boron trifluoride catalyze the reduction of lactones.[8] These substances are generally present in diborane generated *in situ* by the following reaction in the dimethyl ether of dieth-

(7) H. C. Brown and N. M. Yoon, *ibid.*, **90**, 2686 (1968).

(8) K. M. Biswas and A. H. Jackson, *J. Chem. Soc. C*, 1667 (1970).

Table I

RESULTS OF REACTION OF DIMETHYL SULFIDE–BORANE[a] WITH ORGANIC COMPOUNDS

Compd	Compound used, mmol	H2 after addition of compound, mmol	H2 evolved after MeOH addition, mmol	H− involved in reduction of organic compd, mmol	mmol of H− from I consumed/mmol of organic function	Brown[b] results with ether boranes for same functional group
Blank		0	6.0	0	0	0
Pentene	6.0	0	0	6.0	1.0	1.0
Propargyl bromide	3.0	0	0.4	5.6	1.87	1.57 to 1.85
3-Hexyne	3.0	0	0.55	5.45	1.78	1.57 to 1.85
Benzaldehyde	6.0	0	0	6.0	1.0	1.0
Acetone	6.0	0	0	6.0	1.0	1.0
Acetic acid	2.0	2.7	0.41	2.9	1.45	2.8
Formic acid	2.0	0.0 to 5.0[c,d]	0	6.0 to 1.0	3.0 to 0.5	2.8
Benzoyl chloride	3.0	0	4.59	1.41	0.47	0.4
N,N-Dimethylacetamide	6.0	0	0.39	5.61	0.94	
Ethyl acetate	6.0	0	0 to 4.0[d]	6.0 to 2.0	1.0 to 0.3	0.4
Ethyl formate	6.0	0.82	1.0	4.18	0.7	0.4
Acetonitrile	3.0	0	3.6	2.4	0.8	2.0
Benzonitrile	3.0	0	0 to 4.0[d]	6.0 to 2.0	2.0 to 0.7	2.0
Butyrolactone	6.0	0	4.06	1.94	0.32	2.0
1,2-Butylene oxide	6.0	0	2.59	3.41	0.57	1.2
Nitroethane	2.0	0	5.47	0.53	0.26	0.1
Sulfolane	3.0	0	3.62	2.38	0.79	

[a] Two millimoles. [b] References 1 and 2. [c] Solid insoluble in benzene formed. [d] Unexplained erratic behavior.

Table II

Organic compd	II, mmol	Organic compd, mmol	H2 released on addition of organic compd, mmol	H2 released after addition of methanol, mmol	mmol of H− involved in reduction/mol of organic compd	Brown[a] results with ether boranes for same functional group
Benzaldehyde	2.0	6.0	2.0	0.4	0.6	1.0
Acetophenone	4.0	4.0	0	9	0.75	1.0
	4.0	12.0	2.4	3.7	0.56	1.0
Cyclohexene	4.0	12.0	1.0	0	1.0	1.0
Acetyl chloride	2.0	6.0	0	6.0	0	0.4
Formic acid	2.0	6.0	2.9[b]	0.0	1.0	2.8

[a] References 1 and 2. [b] White solid formed and gas evolution ceased after addition of 2.7 mmol of formic acid.

ylene glycol (diglyme). We have studied the effect of

$$3NaBH_4 + 4BF_3 \cdot OEt_2 \xrightarrow{\text{diglyme}} 2B_2H_6 + 3NaBF_4 + 4Et_2O$$
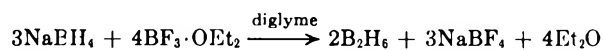
adding 1 drop of boron trifluoride–ethyl etherate (III) to the reductions of lactones and epoxides with I and found that it does indeed give results equivalent to those with ether–boranes.

The mechanism and products of hydroboration of nitriles have been shown to be quite complex;[9] nevertheless we corroborated Brown and Subba Rao's data with tetrahydrofuran–borane. Addition of III did not appreciably catalyze their reduction by I. We attribute the difference in reactivity of I to the fact that nitriles are weaker donors than alkyl sulfides, but stronger than ethers toward soft Lewis acids.[10]

We have no explanation for the erratic results with formic acid. Brown has postulated the formation of triacylboranes as intermediates in the reduction of acids by borane. These should also be soft acids which would

$$3RCOOH + BH_3 \longrightarrow (RCOO)_3B + 3H_2$$
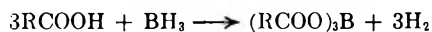
coordinate dimethyl sulfide more strongly than ethers. This may hinder further reduction. Brown and co-

workers[11] have recently reported that disiamylborane $\{[(CH_3)_2CHCHCH_3]_2BH\}$ also does not reduce acids and reacts very sluggishly with nitriles. They attribute these differences to steric hindrance.

Conclusions

Dimethyl sulfide–borane (I) provides a means of handling diborane as a storable liquid with most of its hazardous nature tamed, yet retaining sufficient reactivity for most hydroboration and reduction applications. Contrary to expectations tetrahydrothiophene–borane is less reactive than dimethyl sulfide–borane and hence less useful for general hydroborations and reductions.

(9) J. R. Jennings and K. Wade, *J. Chem. Soc. A*, 1946 (1968).
(10) R. G. Pearson, *J. Amer. Chem. Soc.*, **85**, 3533 (1963).
(11) H. C. Brown, D. B. Bigley, S. K. Arora, and N. M. Yoon, *ibid.*, **92**, 7161 (1970).

A Synthesis of Frontalin and Brevicomin

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Frontalin, 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane is an aggregating pheromone of the southern pine beetle, *Dendroctonus frontalis*.[2] A Diels–Alder reaction of methyl vinyl ketone and methacrolein (**1a**) does not afford the correct adduct (**2a**) for further elaboration to frontalin (**4**). However, use of methyl methacrylate (**1b**) affords a mixture containing only the dimer of methyl vinyl ketone and **2b**. Lithium aluminum hydride reduction of **2b** gives **3** which is immediately cyclized to **4**. The yield of **4** from **2b** is 40%, and it seems reasonable that the overall conversion could be improved.[3]
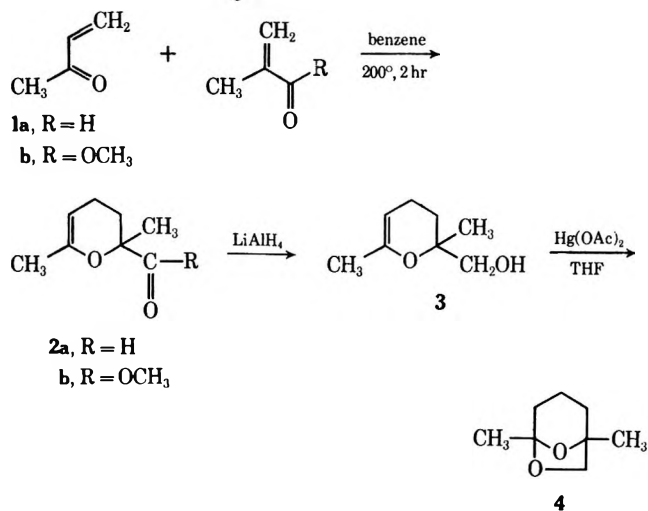
Similarly, we have obtained brevicomin (**7**), a pheromone of *Dendroctonus brevicomis*, the western pine beetle. Treatment of the Diels–Alder adduct **5** with the ethyl Grignard reagent affords **6**.[4] This is converted, without purification, to a mixture containing 9% brevicomin. Although this process does not afford a high yield of the pheromone, the simplicity makes it considerably more attractive than the previously reported syntheses.[5]

(1) NDEA Predoctoral Fellow, 1968–1971.

(2) (a) G. W. Kinzer, A. F. Fentman, T. F. Page, R. L. Foltz, J. P. Vite, and G. B. Pitman [*Nature*, **221**, 477 (1969)] reported the isolation, identification, and synthesis of this pheromone; (b) W. D. Bedard, R. M. Silverstein, and D. L. Wood (*Science*, **167**, 1638 (1970)] discussed nomenclature problems associated with frontalin and questioned the importance of this compound as an active pheromone.

(3) The previously reported synthesis of frontalin[2a] gave no Experimental Section and was based on a Diels–Alder reaction of methallyl alcohol and acrolein which resulted in a direct 21% yield of 1-methyl-6,8-dioxabicyclo-[3.2.1]octane [C. W. Smith, D. G. Morton, and S. A. Ballard, *J. Amer. Chem. Soc.*, **73**, 5270 (1951)]. We repeated the work of Kinzer, *et al.*,[2a] and have obtained a 6.7% yield of frontalin. Our reported synthesis with no attempt to maximize yields gave an equivalent overall yield and has the potential to be improved. For example, the separation of the methyl vinyl ketone dimer and **2b** via the bisulfite addition product was only attempted once giving a 37% recovery of **2b**.

(4) The synthesis of brevicomin was carried out without isolation of intermediate products.

(5) (a) T. E. Bellas, R. G. Brownlee, and R. M. Silverstein, *Tetrahedron*, **25**, 5149 (1969); (b) H. H. Wasserman and E. H. Barker, *J. Amer. Chem. Soc.*, **91**, 3674 (1969).
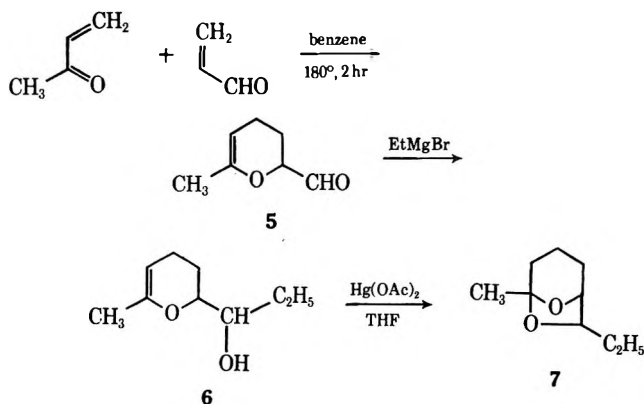
Experimental Section[6]

Methyl 2,3,4-Trihydro-2,6-dimethylpyran-2-carboxylate (2b).—A mixture of 14.0 g of methyl vinyl ketone, 20.0 g of methyl methacrylate, and 25 ml of benzene was heated for 2 hr at 200° in an autoclave. Distillation gave 13.0 g of a mixture composed of 67% **2b** and 33% methyl vinyl ketone dimer. Separation of the dimer from **2b** was achieved by way of a bisulfite addition complex. The ir spectrum of **2b** had major absorptions at 3020, 2910, 2830, 1750, 1730, 1680, 1455, 1435, 1380, 1315, 1295, 1220, 1190, 1168, 1113, 1105, 1070, 985, and 760 cm⁻¹. The nmr spectrum of **2b** exhibited a singlet at δ 1.49 (3 H), a singlet at 1.8 (3 H), a methylene envelope from 1.85 to 2.4 (4 H), a singlet at 3.72 (3 H), and a triplet at 4.50 (1 H).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.49; H, 8.31. Found: C, 63.70; H, 8.61.

Preparation of Frontalin (4).—The 3.5 g of **2b** was reduced by 0.4 g of lithium aluminum hydride in anhydrous THF under dry nitrogen to give 2.4 g of a colorless liquid (**3**). This was treated with 6.0 g of mercuric acetate in 20 ml of dry THF. After it stirred at room temperature for 20 hr, 20 ml each of solutions containing 3 M potassium hydroxide, 0.5 M sodium borohydride in 3 M potassium hydroxide, saturated sodium chloride, and water were added in turn. Extraction with methylene chloride gave 1.8 g of colorless liquid which was 65% frontalin (**4**) by glc (20 ft × ³/₈ in. column packed with 30% SE-30 on Chromosorb W at 150° with a 150–200-ml/min flow rate). Ir and nmr[2a] spectra of a sample collected from preparative glc were identical with those of an authentic sample of frontalin obtained from the U. S. Forest Service.

Synthesis of Brevicomin (7).—In a process similar to that for frontalin, 15 g of methyl vinyl ketone, 30 g of acrolein, and 80 ml of benzene were heated in an autoclave at 180° for 2 hr. The crude product was partially purified by short-path distillation, yielding 18 g of a product mixture, bp 35–40° (2 mm). This product (4 g) was added to a Grignard solution prepared from 1.2 g of magnesium and 5.4 g of ethyl bromide in 80 ml of anhydrous ether. After work-up, the mixture containing **1b** (4.0 g) was stirred with 9.6 g of mercuric acetate in 75 ml of dry THF. The product mixture, isolated as previously discussed, was subjected to glc analysis and was shown to contain 9% brevicomin. The ir and nmr spectra were identical with those of an authentic sample. The nmr and mass spectra were identical with those reported by Silverstein.[7]

Registry No.—2b, 29765-30-8; 4, 22625-04-3; 7, 20290-99-7.

(6) Melting points and boiling points are uncorrected. Nmr spectra were recorded on a Varian A-60 spectrometer using TMS as an internal standard. Infrared spectra were recorded on a Beckman IR-5 instrument. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz.

(7) R. M. Silverstein, *J. Chem. Educ.*, **45**, 794 (1968). We also obtained some of the endo isomer, but in lesser amount than brevicomin. The simple mass spectral fragmentation patterns are different for the exo and endo isomers, and the occurrence of several metastables in the exo product is the most powerful proof of the authenticity of our synthetic material.

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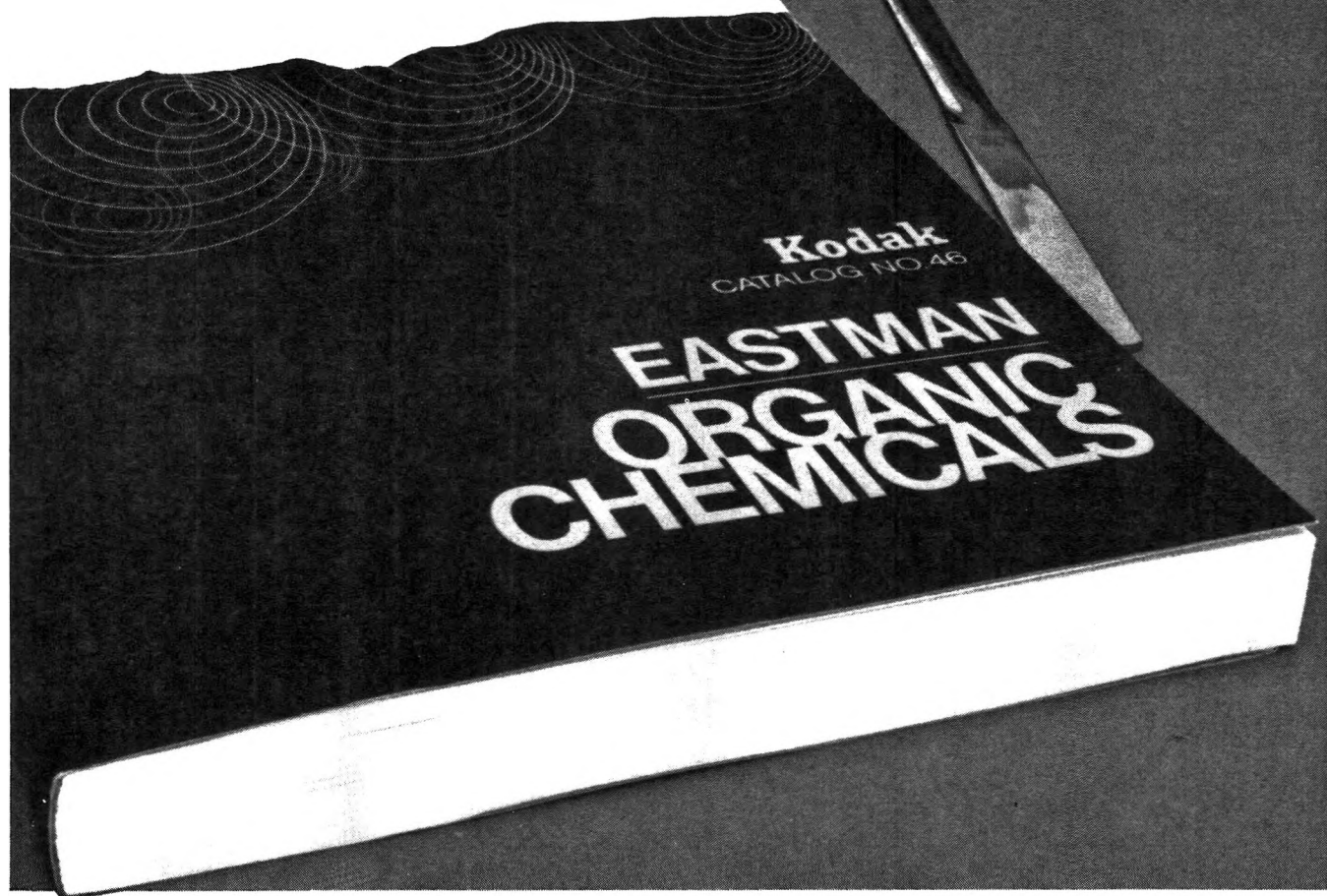
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