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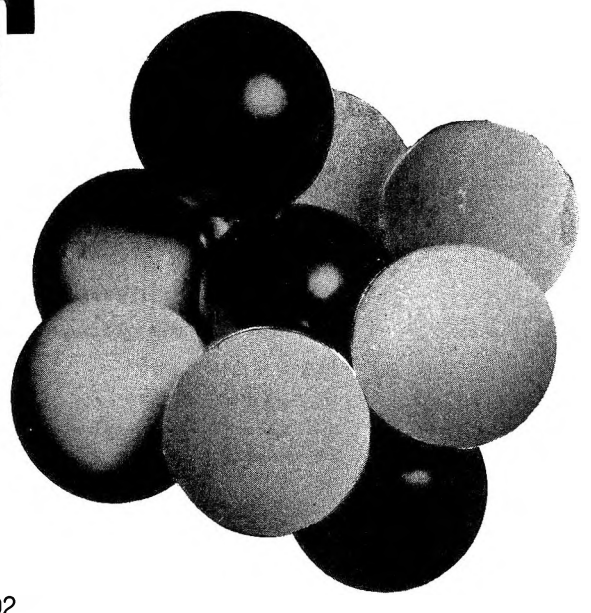

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DECEMBER 31, 1971

Keto–Enol Tautomerism in the Thiophene Analogs of Anthrone. I. Derivatives of Naphtho[2,3-*b*]thiophene and Naphtho[2,3-c]thiophene

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Department of Chemistry, West Virginia University, Morgantown, West Virgina 26506

Received June 1, 1971

The syntheses of 4,9-dihydronaphtho[2,3-*b*]thiophen-4-one (**2**), 4,9-dihydronaphtho[2,3-*b*]thiophen-9-one (**3**), and 4,9-dihydronaphtho[2,3-*c*]thiophen-4-one (**4**) are described. Keto–enol tautomerism in these compounds was studied by means of nmr spectroscopy and the results are compared with the calculated delocalization energy differences between the two tautomeric forms. Enol content in **2**–**4** was found to be dependent on the mode of fusion of the thiophene nucleus.

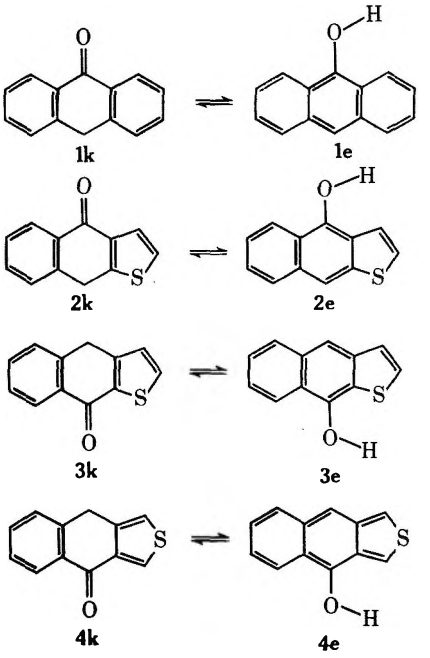
A comparison of the properties of polycyclic hydrocarbons with those of their thiophene analogs has provided some intriguing results. Anthracene and naphtho[2,3-*b*]thiophene proved to be very similar in physical and chemical properties;[2] however, the isomeric naphtho[2,3-*c*]thiophene has recently been shown to be a highly reactive species, whose transient existence could only be demonstrated in the form of two *N*-phenylmaleimide adducts.[3]

Keto–enol tautomerism has also been shown to be dependent on structure.[4] In the acene series, phenol and 1-naphthol have been isolated only in the enol form although the latter undergoes reactions which suggest the presence of both tautomers.[5] Even though both anthrone (**1k**) and anthrol (**1e**) have been isolated, the spectroscopically determined equilibrium constant ($K = 2.5 \times 10^{-3}$ at 20°) indicates that the keto form greatly predominates in benzene solution.[6] No evidence for enolization, in the absence of strong base, has been reported for the higher acene analogs.

There are three possible isomeric naphthothiophenones, **2**–**4**, analogous to anthrone.

In this paper we wish to report the preparation of these structurally related compounds and their corresponding keto–enol character.

Synthesis of 4,9-Dihydronaphtho[2,3-*b*]thiophen-4-one (2).—The synthesis of **2** was accomplished as outlined in Scheme I.



o-(2-Thenoyl)benzoic acid was prepared according to the procedure of Rajsner and coworkers[7] and converted to the known *o*-(2-thenyl)benzoic acid using zinc dust and aqueous ammonia as described by Schroeder and Weinmayr.[8] The overall yield was 80%. Cyclization of **6** *via* the acid chloride using stannic chloride afforded a mixture of the tautomers **2k** and **2e** in 75% yield after purification.

Synthesis of 4,9-Dihydronaphtho[2,3-*b*]thiophen-9-one (3).—The synthesis of **3** is outlined in Scheme II.

(1) NDEA Fellow, 1967–1970.

(2) (a) W. Carruthers, A. G. Douglas, and J. Hill, *J. Chem. Soc.*, 704 (1962); (b) W. Carruthers, *ibid.*, 4477 (1963).

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

(4) For a recent review on the subject of enolization, see S. Forsen and M. Nilsson in "The Chemistry of the Carbonyl Group," Vol. II, J. Zabicky, Ed., Intrscience, New York, N. Y., 1970, Chapter 3.

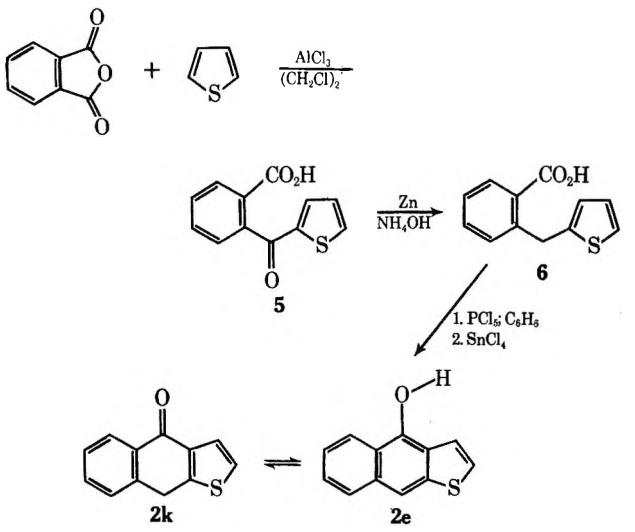
(5) Z. Majerski and N. Trinajstic, *Bull. Chem. Soc. Jap.*, **43**, 2648 (1970), and references contained therein.

(6) H. Baba and T. Takemura, *ibid.*, **37**, 1241 (1964).

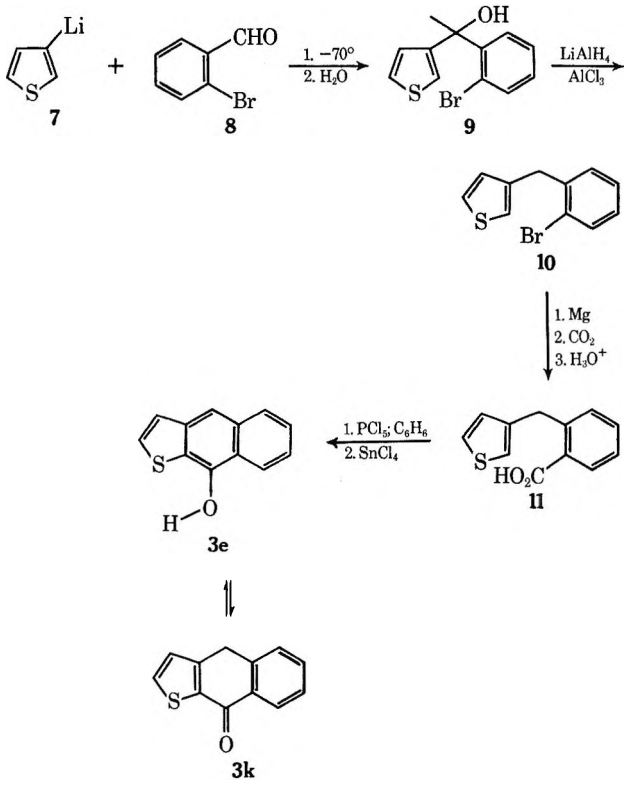
(7) M. Rajsner, J. Metysova, and M. Protiva, *Collect. Czech. Chem. Commun.*, **34**, 468 (1969).

(8) H. E. Schroeder and V. Weinmayr, *J. Amer. Chem. Soc.*, **74**, 4357 (1952).

Scheme I



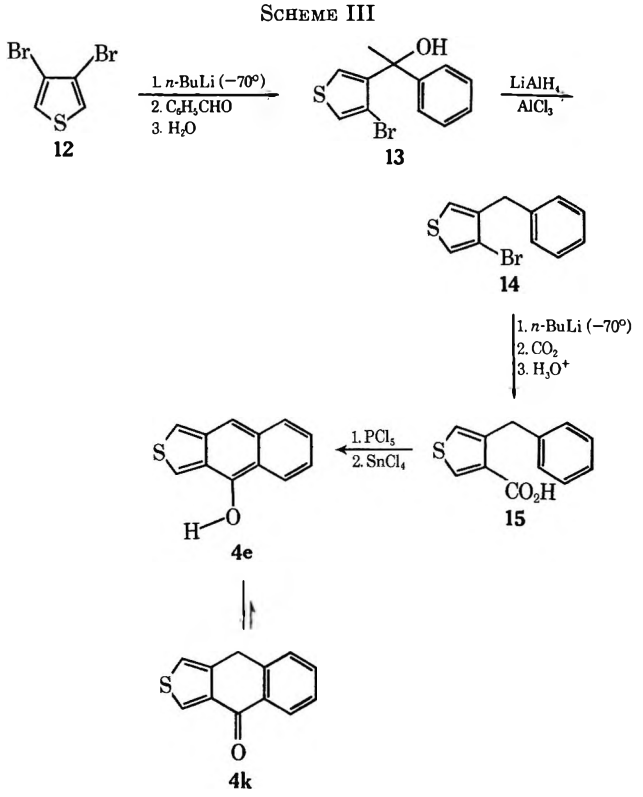
Scheme II



Treatment of 3-thienyllithium (**7**)[9] with *o*-bromobenzaldehyde (**8**) at −70° afforded *o*-bromophenyl-3-thienylcarbinol (**9**) in 61% yield. The reduction of **9** with equimolar amounts of lithium aluminum hydride and aluminum chloride in dry ether[10] provided *o*-bromophenyl-3-thienylmethane (**10**) in 82% yield. *o*-(3-Thenyl)benzoic acid (**11**) was obtained in 62% yield by carbonation of the Grignard reagent formed from **10**. Cyclization of **11** *via* the acid chloride using stannic chloride resulted in the formation of a mixture of the tautomers **3k** and **3e**. The ring closure proceeded in 78% yield.

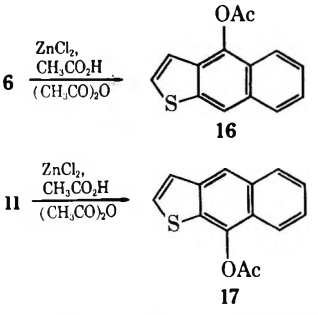
Synthesis of 4,9-Dihydronaphtho[2,3-*c*]thiophen-4-one (4).—The preparation of **4** is summarized in Scheme III.

Scheme III



4-Bromo-3-thienyllithium was allowed to react with benzaldehyde at −70° and the crude viscous product was promptly converted to 4-benzyl-3-bromothiophene (**14**) using an equimolar mixture of lithium aluminum hydride and aluminum chloride in dry ether. The overall yield was 73%. Halogen–metal exchange in **14** at −70°, followed by carbonation, afforded an 85% yield of 4-benzylthiophene-3-carboxylic acid (**15**), which was cyclized to **4k** *via* the acid chloride using stannic chloride in 82% yield.

The carboxylic acid, **6** and **11**, were also cyclized to the enol acetates **16** and **17** according to the method of Fieser and Hershberg.[11]

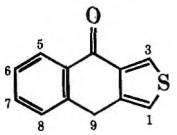


Spectral Data.—The nmr spectrum of **4k** was obobtained in both C_6D_6 and polysol-*d*[12] (see Table I).

The presence of the keto form (**4k**) in both solvents was confirmed by the appearance of a sharp singlet (2 H) in the methylene region. Neither spectrum contains a signal which can be assigned to an enol or meso proton in **4e**. The large chemical shift differences, which

(9) S. Gronowitz, *Ark. Kemi*, **7**, 361 (1954).
(10) J. Blackwell and W. J. Hickinbottom, *J. Chem. Soc.*, 1405 (1961).
(11) L. Fieser and E. B. Hershberg, *J. Amer. Chem. Soc.*, **59**, 1028 (1937).
(12) Available from Stohler Isotope Chemicals, Rutherford, N. J.; found to have solvent properties approximating those of dimethyl sulfoxide.

TABLE I



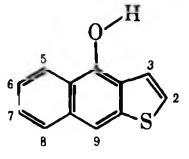
Solvent	Absorption, τ	Proton
Polysol-*d*	1.55 (d, 1 H), $J_{1,3}$ = 3 Hz	3
	1.62–1.85 (m, 1 H)	5
	2.17–2.73 (m, 4 H)	1, 6, 7, 8
	5.72 (s, 2 H)	9
Benzene-d_6	1.25–1.47 (m, 1 H)	5
	1.80 (d, 1 H), $J_{1,3}$ = 3 Hz,	3
	2.67–3.23 (m, 3 H)	6, 7, 8
	3.38–3.56 (m, 1 H), $J_{1,3}$ = 3 Hz, $J_{1,9}$ = 1 Hz	1
	6.48 (s, 2 H)	9

were induced by the utilization of an aromatic solvent, simplified the interpretation of these spectra. Since *only* the C_5 hydrogen exists on the deshielding side of a plane drawn through the C_4 carbon and perpendicular to the carbon–oxygen bond,[13] a downfield shift is observed for it while the remainder of the spectrum is shifted upfield.

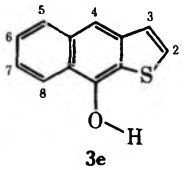
In polysol-*d* solution, both **2** and **3** give spectra which are consistent with the corresponding enol forms **2e** and **3e** (see Table II). Analogous results were obtained when acetone-d_6 was employed as the solvent. Since no absorption above τ 3.0 was observed, the existence of the keto forms **2k** and **3k** could not be verified.

TABLE II

NMR SPECTRA OF **2** AND **3** IN POLYSOL-*d*



2e



3e

Proton	τ	Proton	τ
-OH	−0.29 (s, 1 H)	OH	−0.29 (s, 1 H)
5	1.36–1.68 (m, 1 H)	8	1.40–1.71 (m, 1 H)
9	2.04 (s, 1 H)	4	2.08 (s, 1 H)
2, 8	1.94–2.26 (m, 2 H)	5	1.94–2.21 (m, 1 H)
3, 6, 7	2.32–2.68 (m, 3 H)	2, 3, 6, 7	2.27–2.69 (m, 4 H)

The nmr spectrum of **2** in C_6D_6 is composed of two complex multiplets in the aromatic region and a sharp singlet at τ 6.7 (see Table III). The singlet, due to the methylene protons in **2k**, furnishes a measure of the keto tautomer. The low field multiplet, which is assigned to the C_5 proton in both **2k** and **2e**, provides a measure of the sum of both tautomeric forms. The anisotropic effect of the ketone function results in a deshielding of the C_5 proton in **2k**. A similar deshielding by a phenolic oxygen has recently been reported[14] for the peri proton of hydroxynaphthalene systems. Analogously, the C_5 proton in **2e** appears downfield from the remainder of the aromatic absorptions.

TABLE III

NMR SPECTRA OF THE MIXTURE OF **2k** AND **2e**

Solvent	τ	Relative area[a] under absorption
C_6D_6	1.46–1.78 (m)	1.22
	2.26–3.55 (m)	6.77[b]
	6.73 (s)	1
C_6D_6	1.53–1.94 (m)	1
and	2.27–3.38 (m)	5.25[b]
CF_3CO_2H	6.75 (s)	1.71

[a] The values are an average of three experiments, none of which vary from the mean by more thn 3%. [b] Corrected for the residual signal from C_6D_6.

In order to ensure the establishment of an equilibrium condition, a drop of trifluoroacetic acid was added to the original solution and the spectrum was again recorded. The initial mixture was found to contain 40% ketone (**2k**) and 60% enol (**2e**). After equilibration, 85% of **2k** and 15% of **2e** were present in the solution. This proportion remained unchanged over the subsequent 48 hr. The appearance of two distinct doublets, τ 2.45 and 3.40 (J = 5 Hz), was an immediate indication that equilibration had taken place. These signals are assigned to the C_2 and C_3 protons of **2k**.

The presence of strong absorptions at 3400 and 1635 cm^{-1} in the ir spectrum of **2** confirms the presence of both the enol and ketone forms. The preference for the enol tautomer in polar solvents was verified by the striking similarities in the uv spectra (95% ethanol) of **2** and its enol acetate **16**.

The nmr spectrum of **3** in C_6D_6 (Table IV) shows a mixture of the keto and enol tautomers **3k** and **3e**. In this case a determination of the relative quantities is simplified by the fact that the signals due to the C_8 protons of the keto and enol forms are not superimposed upon each other. By a comparison of the peak areas, the original mixture was found to contain 50% of each tautomeric form. Equilibration was accomplished as before and the spectrum was recorded; 73% ketone and 27% enol are present in the equilibrium mixture. The ir and uv spectra of **3** substantiate the nmr data in the same manner as for the preceeding isomers.

TABLE IV

NMR SPECTRA OF THE MIXTURE OF **3k** AND **3e**

Solvent	τ	Relative area[a] under absorption
C_6D_6	1.34–1.58 (m)	1.00
	1.67–2.00 (m)	1.00
	2.10–3.35 (m)	10.05[b]
	3.67 (d), J = 5 Hz	1.00
	6.74 (s)	1.96
C_6D_6	1.53–1.83 (m)	2.75
and	1.87–2.04 (m)	1.00
CF_3CO_2H	2.21–3.42 (m)	16.67[b]
	3.67 (d), J = 5 Hz	2.67
	6.77 (s)	5.50

[a] The values are an average of three experiments, none of which vary from the mean by more than 3%. [b] Corrected for the residual signal from C_6D_6.

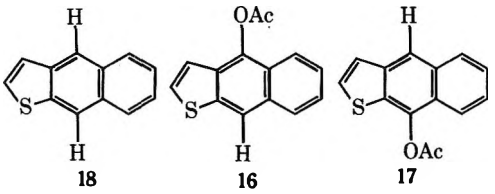
The enol acetates **16** and **17** were synthesized in order to compare their spectral properties with the

(13) E. D. Becker, "High Resolution NMR," Academic Press, New York, N. Y., 1969, p 230.

(14) G. Dudek, *Spectrochim. Acta*, **19**, 691 (1963).

corresponding enols **2e** and **3e**. Wynberg, *et al.*,[15] reported the nmr spectrum of naphtho[2,3-*b*]thiophene (**18**) and from a consideration of its 4-acetoxy derivative **16** concluded that the C_4 proton in **18** is more deshielded than the C_9 proton. As shown on Table V,

Table V



	18	**16**	**17**
Solvent	τ	τ	τ
Acetone-d_6	1.50, 1.56	1.65	1.73
CCl_4	1.68, 1.75	1.87	1.96

this conclusion appears to be erroneous, since the C_9 proton of **16** occurs at lower field than the C_4 proton of **17**.

Discussion

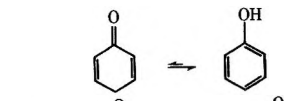
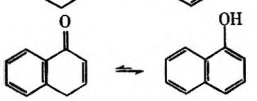
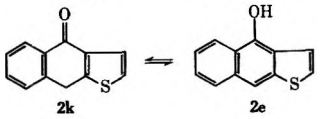
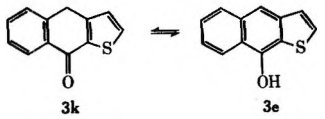
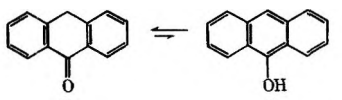
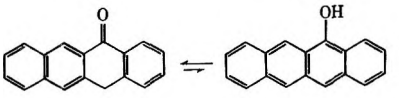
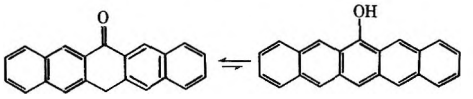
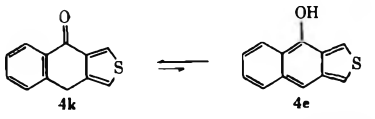
The keto–enol equilibrium position in hydroxyacene systems has been correlated with the free-energy loss which is experienced in the formation of the keto tautomer. For a series of structurally related compounds, this energy can be formulated as the π delocalization energy difference (ΔDE) between the two forms. The DE of the enol tautomer is taken as that of the parent system and the DE of the keto form as that of the corresponding *exo*-methylene derivative.[16] The values for ΔDE, which are given on Table VI, were computed using a general Hückel molecular orbital program.[17]

Compounds **2k**,**e** and **3k**,**e** possess calculated ΔDE values which are higher than the value for anthrone–anthrol (**1k**,**e**). This indicates an increased preference for the enol tautomer in the two systems which contain a *b*-fused thiophene ring. This prediction was supported experimentally by the observation that only **2e** and **3e** were present in hydrogen bonding solvents. Although both forms were detected in a benzene solution, the keto tautomer was found to predominate.

In contrast to the findings for the *b*-fused isomers **2** and **3**, compound **4**, which contains a *c*-fused thiophene ring, shows little tendency to enolize. Although **4k** was unaffected by 1 *M* sodium hydroxide, a deep red-orange solution was formed with ethanolic potassium hydroxide. The resulting solution soon exhibited the presence of a brown precipitate. The lack of enol character in **4** is reflected in a ΔDE value approximating that of 6-hydroxypentacene.

Since the keto forms **2k** and **4k** would be of equal energy according to this method of approximation, the difference in their ΔDE values is due to a difference in the calculated DE values for naphtho[2,3-*b*]thiophene and naphtho[2,3-*c*]thiophene.

Table VI

Compd	ΔDE (β units)	Preferred tautomer
	1.10	Enol
	0.83	Enol
 **2k** **2e**	0.66[a]	Mixture
 **3k** **3e**	0.62[a]	Mixture
 **1k** **1e**	0.50	Keto
	0.43	Keto
	0.38	Keto
 **4k** **4e**	0.37[a]	Keto

[a] The parameters for these calculations are $\alpha_s = \alpha + \beta$; $\beta_{cs} = 0.7\beta$.

Experimental Section[18]

Cyclization of *o*-(2-Thenyl)benzoic Acid (6).—A solution of *o*-(2-thenyl)benzoic acid (6.54 g, 30 mmol) in dry benzene (200 ml) was placed in a 500-ml, three-necked flask which was fitted with a reflux condenser and kept under a constant stream of nitrogen. After the solution was cooled to 4°, phosphorus pentachloride (6.24 g, 30 mmol) was added portionwise over 20 min with stirring. The mixture was then warmed until the evolution of hydrogen chloride ceased. The faintly yellow solution was then cooled to 4° and a solution of stannic chloride (4.0 ml, 8.9 g, 34 mmol) in dry benzene (50 ml) was added dropwise over a 1-hr period resulting in the formation of a yellow-green precipitate. Stirring was continued for an additional hour and the mixture was poured into ice and hydrochloric acid (200 ml, 2 *M*) and shaken vigorously. The layers were separated and the aqueous portion was extracted with benzene (100 ml). The combined benzene portions were washed successively with saturated sodium bicarbonate solution and water, then dried ($MgSO_4$), and concentrated to 50 ml. The resulting warm solution was chromatographed on a 15 × 2 cm column packed with neutral silica gel. Elution with benzene–chloroform (3:1) followed by concentration yielded 4.5 g (75%) of a yellow crystalline solid. Recrystallization from benzene–hexane afforded analytical sample (mp 130–132°): uv max (95% C_2H_5OH) 258 mμ (ε 49,800), 340 (6300), 352 (7400), and 367 (7310); ir (KBr) 3400 (OH) and 1635 cm^{-1} (ketone C=O); for nmr spectra (polysol-*d*) see Table II, (C_6D_6) see Table III.

(15) H. Wynberg, J. de Wit, and H. Sinnige, *J. Org. Chem.*, **35**, 711 (1970).

(16) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, p 250.

(17) HMO program written by Dr. J. Gruninger, West Virginia University.

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

Anal. Calcd for $C_{12}H_8OS$: C, 71.97; H, 4.02; S, 16.01. Found: C, 72.08; H, 4.11; S, 15.88.

o-Bromophenyl-3-thienylcarbinol (9).—Ethereal *n*-butyllithium (125 ml, 1.1 *M*, 0.138 mol) was transferred into a 500-ml, flame-dried, three-necked flask and kept under a constant stream of nitrogen. After cooling to −70°, a solution of 3-bromothiophene (25 g, 0.138 mol) in absolute ether (50 ml) was added over 15 min. The solution was stirred at −70° for an additional 30 min and a solution of *o*-bromobenzaldehyde (25.6 g, 0.138 mol) in absolute ether (50 ml) was added over a 1-hr period.

After the solution was stirred for an additional hour, it was allowed to slowly warm to 0°. Water (150 ml) was cautiously added to affect hydrolysis. The layers were separated and the aqueous layer was extracted with ether. The combined ether portions were washed neutral to litmus with copious quantities of water and dried ($MgSO_4$). Removal of the solvent left a viscous oil which crystallized on a short-path distillation. Recrystallization of the white solid from benzene–hexane gave an analytical sample of *o*-bromophenyl-3-thienylcarbinol (22.6 g, 61%): mp 58.5–60°; ir (melt) 3360 cm^{-1} (broad OH); nmr (CCl_4) τ 2.4-3.2 (m, 7 H, aromatic), 3.95 (d, J = 4 Hz, 1 H, methine), 6.90 (d, J = 4 Hz, 1 H, OH).

Anal. Calcd for $C_{11}H_9BrOS$: C, 49.08; H, 3.37; S, 11.91; Br, 29.69. Found: C, 48.91; H, 3.38; S, 11.73; Br, 29.83.

o-Bromophenyl-3-thienylmethane (10).—Lithium aluminum hydride (4.50 g, 0.118 mol) was suspended in absolute ether (50 ml) contained in a 500-ml, three-necked flask, which had previously been flame-dried under nitrogen and protected by a calcium chloride drying tube. The suspension was cooled in an ice bath while a solution of anhydrous aluminum chloride (15.6 g, 0.118 mol) in absolute ether (50 ml) was cautiously added. The ice bath was removed and a solution of *o*-bromophenyl-3-thienylcarbinol (21.0 g, 0.078 mol) in absolute ether (50 ml) was added at a rate such as to promote gentle reflux. The mixture was then refluxed for an additional 15 min and the ice bath replaced. Sulfuric acid (3 *M*) was added dropwise until vigorous refluxing subsided. The mixture was poured into ice and hydrochloric acid (200 ml, 2 *M*) and shaken. The layers were separated and the aqueous layer was extracted twice with ether (100 ml). The combined ethereal solution was successively washed with hydrochloric acid (2 *M*), saturated sodium bicarbonate solution, and water and then dried ($MgSO_4$). The liquid which remained after evaporation of the solvent was fractionally distilled giving 16.2 g (82%) of a clear colorless liquid, bp 95–97° (0.05 mm). On cooling the product crystallized as a white solid: mp 30–31°; nmr (CCl_4) τ 2.35–3.25 (m, 7 H, aromatic), 5.95 (s, 2 H, CH_2).

Anal. Calcd for $C_{11}H_9BrS$: C, 52.18; H, 3.58; Br, 31.51; S, 12.67. Found: C, 52.24; H, 3.50; Br, 31.75; S, 12.66.

o-(3-Thenyl)benzoic Acid (11).—The Grignard reagent, which was prepared from *o*-bromophenyl-3-thienylmethane (6.00 g, 24.7 mmol), magnesium metal (2.05 g, 84.5 g-atoms), 1,2-dibromoethane (8.92 g, 47.4 mmol), and ether (175 ml) according to the entrainment method,[19] was run onto excess Dry Ice and allowed to stand for 2 hr. Water (150 ml) was slowly added and the layers were separated. The organic layer was washed with 1 *M* sodium hydroxide solution (50 ml) and the aqueous portions were combined, cooled, and acidified with excess hydrochloric acid (1 *M*). The resulting precipitate was taken up in ether, washed with water, and dried ($MgSO_4$). The solvent was removed leaving a granular white solid, which was recrystallized from benzene–hexane to give white needles (3.2 g, 62%): mp 96–97°; ir (KBr) 1675 cm^{-1} (acid C=O); nmr (acetone-d_6) τ 0.4 (hump, 1 H, CO_2H), 1.9–2.1 (m, 1 H, aromatic), 2.4–3.2 (m, 6 H, aromatic), 5.6 (s, 2 H, CH_2).

Anal. Calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62; S, 14.69. Found: C, 65.99; H, 4.62; S, 14.48.

Cyclization of o-(3-Thenyl)benzoic Acid (11).—A solution of *o*-(3-thenyl)benzoic acid (2.00 g, 9.2 mmol) in dry benzene (75 ml) was run into a 300-ml, three-necked flask and kept at 4° under a constant stream of nitrogen. Phosphorus pentachloride (1.91 g, 9.2 mmol) was added portionwise with stirring over a 45-min period. The mixture was then warmed until the evolution of hydrogen chloride subsided. The resulting solution was cooled to 4° and a solution of stannic chloride (1.2 ml, 2.7 g, 10.3 mmol) in dry benzene (50 ml) was added over a 90-min period. The mixture was then stirred at room temperature for 2 hr, poured into ice and hydrochloric acid (1 *M*, 100 ml), and shaken vigorously. The layers were separated and the aqueous layer was extracted with benzene (100 ml). The benzene portions were combined, washed with saturated sodium bicarbonate solution and with water, dried ($MgSO_4$), and concentrated to 50 ml. The warm solution was chromatographed on a 15 × 2 cm column packed with neutral silica gel. Elution with benzene afforded 1.42 g (78%) of a yellow crystalline solid, mp 117–119°. An analytical sample was obtained by recrystallization from benzene–hexane: mp 120–121°; uv max (95% C_2H_5OH) 252 mμ (ϵ 52,100), 299 (5000), 338 (5070), 352 (6460), and 365 (6300); ir (KBr) 3400 (OH) and 1625 cm^{-1} (ketone C=O); for nmr spectra (polysol-*d*) see Table II, (C_6D_6) see Table III.

Anal. Calcd for $C_{12}H_8OS$: C, 71.97; H, 4.02; S, 16.01. Found: C, 72.13; H, 4.22; S, 16.22.

3-Bromo-4-thienylphenylcarbinol (13).—Ethereal *n*-BuLi (450 ml, 1.15 *M*, 0.52 mol) was run into a flame-dried, 1000-ml, three-necked flask under a constant stream of nitrogen. The solution was cooled to −70° and a solution of 3,4-dibromothiophene (125 g, 0.52 mol) in absolute ether (100 ml) was added dropwise. The resulting solution was stirred for an additional hour and then a solution of freshly distilled benzaldehyde (56 g, 0.53 mol) in absolute ether (75 ml) was added over a 1-hr period at −70°. The mixture was stirred for 30 min at −70°, allowed to warm to 0° slowly, poured into ice and water, and shaken vigorously. The layers were separated and the aqueous layer was extracted with ether (200 ml). The ether portions were combined, washed neutral to litmus with water, and dried ($MgSO_4$). The viscous oil (138 g, ~100%), which remained after evaporation of the solvent, was used withut further purification.

A small portion of the product obtained in a similar experiment was chromatographed on neutral alumina using benzene as the eluent. Repeated short-path distillation of the alcohol-containing fraction provided an analytical sample of 3-bromo-4-thienylphenylcarbinol as a slightly yellow, clear oil [100° bath (0.1 mm)]: ir (neat) 3350 cm^{-1} (broad OH); nmr (CS_2) τ 2.7–3.1 (m, 7 H, aromatic), 4.35 (d, J = 4 Hz, 1 H, methine), 7.52 (d, J = 4 Hz, 1 H, OH).

Anal. Calcd for $C_{11}H_9BrOS$: C, 49.08; H 3.37; Br, 29.69; S, 11.91. Found: C, 49.23; H, 3.46; Br, 29.50; S, 12.03.

4-Benzyl-3-bromothiophene (14).—Lithium aluminum hydride (29.5 g, 0.778 mol) was suspended in absolute ether (150 ml) contained in a 1000-ml, flame-dried, three-necked flask. The mixture was cooled in an ice–water bath while a solution of anhydrous aluminum chloride (104 g, 0.78 mol) in absolute ether (200 ml) was added over a 5-min period. External cooling was halted and a solution of crude 3-bromo-4-thienylphenylcarbinol (138.4 g, ~0.5 mol) in absolute ether (200 ml) was added at a rate such as to promote gentle reflux. The mixture was maintained at reflux for an additional 15 min and the ice bath was then replaced. Excess hydride was destroyed by cautious, dropwise addition of sulfuric acid (3 *M*). The mixture was poured into ice and hydrochloric acid (400 ml, 2 *M*) and shaken vigorously. The layers were separated and the aqueous layer was extracted twice with ether (150 ml). The combined ether portions were successively washed with hydrochloric acid (2 *M*), saturated sodium bicarbonate solution, and water, and dried ($MgSO_4$). After concentration, the liquid was fractionally distilled to give 94.7 g (73%) of a clear, colorless liquid: bp 105–110° (0.1 mm); nmr (CCl_4) τ 2.8 (broad s, 6 H, aromatic), 3.25–3.35 (m, 1 H, 5 position of thiophene), 6.11 (s, 2 H, CH_2).

Anal. Calcd for $C_{11}H_9BrS$: C, 52.18; H, 3.58; Br, 31.51; S, 12.67. Found: C, 52.37; H, 3.59; Br, 31.66; S, 12.70.

4-Benzylthiophene-3-carboxylic Acid (15).—Ethereal *n*-BuLi (84 ml, 1.32 *M*, 0.11 mol) was run into a 500-ml, three-necked, flame-dried flask under a constant stream of nitrogen. The solution was cooled to −70° and a solution of 4-benzyl-3-bromothiophene (25.3, g, 0.10 mol) in absolute ether (50 ml) was added dropwise over a 15-min period. The resulting mixture was maintained at −70° for 30 min and run onto excess Dry Ice under a stream of nitrogen. The mixture was allowed to warm to 0°, water (150 ml) was added, and the layers were separated. The ether layer was extracted with sodium hydroxide solution (100 ml, 1 *M*). The aqueous portions were combined, cooled, and acidified with excess hydrochloric acid (1 *M*). The white precipitate was taken up in ether and dried ($MgSO_4$). Removal of the solvent left 21.5 g of a white solid which was recrystallized as white needles (18.3 g, 85%) from acetonitrile: mp 143.5–

(19) E. C. Horning, Ed., "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 553.

144°; ir (KBr) 1675 cm^{-1} (acid C=O); nmr (polysol-*d*) τ 1.8 (d, J = 3.5 Hz, 1 H, thiophene 2 position), 2.78 (s, 5 H, C_6H_5), 3.02 (d, J = 3.5 Hz, 1 H, thiophene 5 position), 5.75 (s, 2 H, CH_2).

Anal. Calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62; S, 14.69. Found: C, 66.25; H, 4.64; S, 14.82.

Cyclization of 4-Benzylthiophene-3-carboxylic Acid (15).—Phosphorus pentachloride (2.72 g, 13 mmol) was added portionwise to a stirred solution of 4-benzylthiophene-3-carboxylic acid (2.85 g, 13 mmol) in dry benzene (15 ml) at 5°. The mixture was allowed to warm to room temperature and then heated on a steam bath until the evolution of hydrogen chloride had ceased.

The acid chloride solution was added dropwise to a solution of stannic chloride (1.6 ml, 3.5 g, 14 mmol) in dry benzene (75 ml) at 5° over a 30-min period. The mixture was allowed to stir at room temperature for 2 hr, refluxed for 15 min, allowed to cool, and poured into ice and hydrochloric acid (2 *M*). The layers were separated and the aqueous phase was extracted with benzene (100 ml). The combined organic portions were washed with saturated sodium bicarbonate solution and with water and dried ($MgSO_4$). The yellow solid which remained after removal of the solvent was chromatographed on neutral silica gel using benzene as the eluent. The benzene solution was concentrated and diluted with hexane. 4,9-Dihydronaphtho-[2,3-c]thiophen-4-one (2.15 g, 82%) was obtained as yellow plates: mp 103.5–105°; uv max (95% C_2H_5OH) 281 mμ (ϵ 13,700); ir (KBr) 1650 cm^{-1} (ketone C=O); for nmr spectra (polysol-*d*) and (C_6D_6) see Table I.

Anal. Calcd for $C_{12}H_8OS$: C, 71.97; H, 4.02; S, 16.01. Found: C, 71.99; H, 4.11; S, 15.85.

4-Acetoxynaphtho[2,3-*b*]thiophene (16).—A stirred mixture of *o*-(2-thenyl)benzoic acid (0.95 g, 4.3 mmol), glacial acetic acid (10 ml), acetic anhydride (7 ml), and anhydrous zinc chloride (0.10 g, 0.74 mmol) was heated at reflux for 15 min and while still hot was cautiously diluted with water (17 ml). The yellow crystalline solid was filtered and recrystallized from cyclohexane as yellow needles (0.82 g, 78%): mp 120–121° (lit.[2a] 119–120°); uv max (95% C_2H_5OH) 250 mμ (ϵ 63,100) 256 (63,200), 317 (sh, 4020), 331 (sh, 5930), 340 (7050), and 356 (8930); ir (KBr) 1755 cm^{-1} (acetate C=O); nmr (CCl_4) τ 1.87 (s, 1 H, aromatic 9 position), 2.05–2.4 (m, 2 H, aromatic 5 and 8 positions), 2.5–2.9 (m, 4 H, aromatic, 2, 3, 6, and 7 positions), 7.60 [s, 3 H, $CH_3C(=O)O$].

9-Acetoxynaphtho[2,3-*b*]thiophene (17).—A stirred mixture of *o*-(3-thenyl)benzoic acid (0.47 g, 2.2 mmol), glacial acetic acid (5 ml), acetic anhydride (3.5 ml), and anhydrous zinc chloride (50 mg, 0.37 mmol) was heated at reflux for 15 min and while still hot was slowly diluted with water (8.5 ml). The yellow crystalline solid was filtered and recrystallized from cyclohexane as yellow needles (0.41 g, 78%): mp 106–107°; uv max (95% C_2H_5OH) 249 mμ (ϵ 72,800), 255 (72,300), 316 (sh, 4640), 329 (6060), 338 (7270), and 354 (8890); ir (KBr) 1760 cm^{-1} (acetate C=O); nmr (CCl_4) τ 1.96 (s, 1 H, aromatic 4 position), 2.05–2.20 (m, 2 H, aromatic 5 and 8 positions), 2.35–2.90 (m, 4 H, aromatic 2, 3, 6, and 7 positions), 7.60 [s, 3 H, $CH_3C(=O)O$].

Anal. Calcd for $C_{14}H_{10}O_2S$: C, 69.39; H, 4.16; S, 13.24. Found: C, 69.56; H, 4.02; S, 13.09.

Registry No.—**2e**, 31926-61-1; **2k**, 31926-62-2; **3e**, 31926-63-3; **3k**, 31926-64-4; **4k**, 31926-65-5; **9**, 31926-66-6; **10**, 31926-67-7; **11**, 31926-68-8; **13**, 31981-25-6; **14**, 31926-69-9; **15**, 31926-70-2; **16**, 22566-41-2; **17**, 31926-72-4.

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Keto–Enol Tautomerism in the Thiophene Analogs of Anthrone. II. Benzodithiophenes

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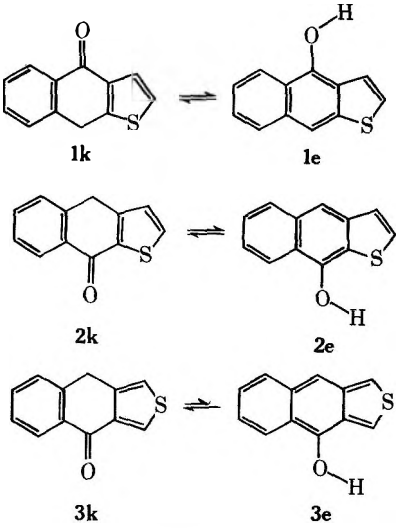
The syntheses of five benzodithiophene analogs of anthrone and anthrol are described. The keto–enol equilibrium position for each of these compounds was spectroscopically determined and a comparison of the experimental results with the calculated delocalization energy difference between the two tautomeric forms was made for each isomer. The results are explained in terms of the modes of fusion of the thiophene portions of the molecule.

As was demonstrated in the initial paper[2] in this series, substituting a thiophene nucleus for one of the benzene moieties of anthrone gives rise to a significant change in the conditions necessary to promote enolization. The direction of this change was found to be dictated by the mode of fusion of the thiophene ring.[2]

In order to further define the structural conditions which govern keto–enol tautomerism, the earlier study was extended to the benzodithiophene systems **4**–**9**.

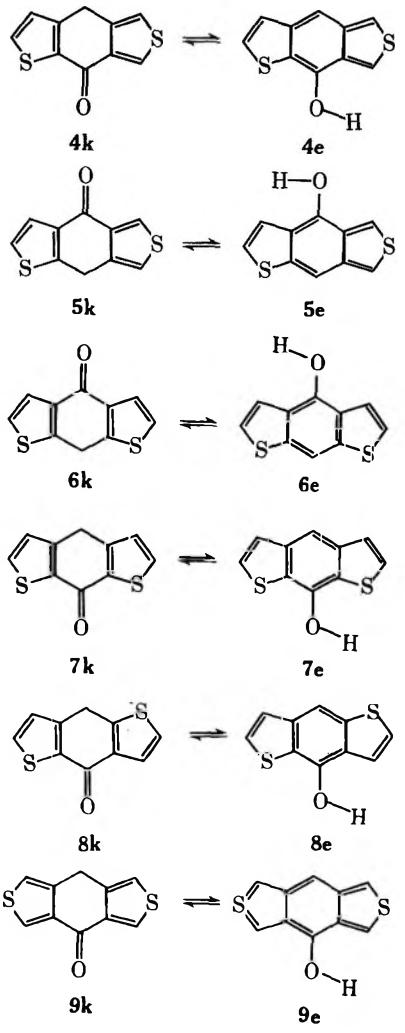
In this paper we wish to report the preparation of five of these compounds, **4**–**8**. The synthesis of the final isomer, 4,8-dihydrobenzo[1,2-*c*:4,5-*c*′]dithiophen-4-one (**9**), is underway and will be the subject of a future publication dealing with the chemistry of benzo-[1,2-*c*:4,5-*c*′]dithiophene.

Synthesis of 4,8-Dihydrobenzo[1,2-*b*:4,5-*c*′]thiophen-8-one (4k).—The reaction sequence which had been successfully employed in the preparation of the naphthothiophenones **2k** and **3k** was easily adapted to the synthesis of the first benzodithiophenone **4k** (see Scheme I).



(1) NDEA Fellow, 1967–1970.

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

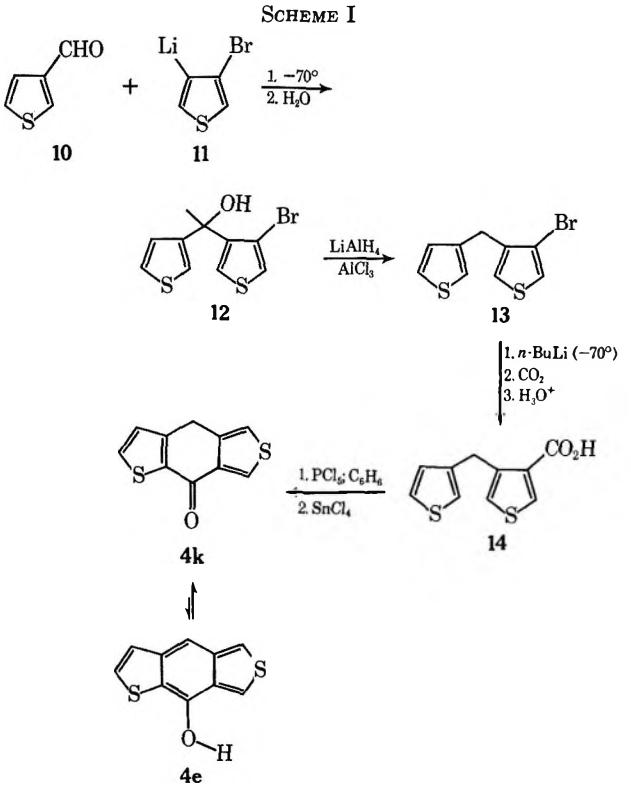


Treatment of 4-bromo-3-thienyllithium (**11**) with 3-thiophenecarboxaldehyde (**10**)[3] at −70° afforded 3-bromo-3′,4-dithienylcarbinol (**12**) in 95% yield. The reduction of **12** with lithium aluminum hydride and aluminum chloride in dry ether[4] provided 3-bromo-3′,4-dithienylmethane (**13**) in 91% yield. Halogen–metal exchange in **13** at −70°, followed by carbonation, resulted in an 84% yield of 3′,4-dithienylmethane-3-carboxylic acid (**14**) which was cyclized *via* the acid chloride using stannic chloride to **4k** in 63% yield. The presence of a sharp singlet (τ 6.67) in the methylene region of the nmr spectrum (C_6D_6) of **4k** (Table I) supports the keto structure for the cyclization product. The ir and uv spectra also uphold this assignment for the keto–enol character of **4**.

In cases where the free-energy difference between the two tautomeric forms is small, the enol content has been shown to be very solvent dependent, *i.e.*, **1k**,**e** and **2k**,**e**.[2] Both **1e** and **2e** were found to be present, exclusive of the corresponding keto forms, in a polysol-*d*[5] solution. However, no indication of the presence of **4e** was found in the nmr spectrum (polysol-*d*) of **4k** (Table I). The aromatic region of the spectrum, representing four hydrogens, shows the expected multiplicity and coupling constants. The methylene singlet appears at τ 5.82 and represents two hydrogens.

(3) S. Gronowitz, *Ark. Kemi*, **8**, 441 (1955).
(4) J. Blackwell and W. J. Hickinbottom, *J. Chem. Soc.*, 1405 (1961).
(5) Available from Stohler Isotope Chemicals, Rutherford, N. J.; it was found to have solvent properties, approximating those of dimethyl sulfoxide.

SCHEME I



In all its spectral properties, **4k** strongly resembles **3k**. However, unlike **3k** it is readily soluble in 1 *M* sodium hydroxide, giving rise to a bright yellow solution which rapidly darkens on standing.

Synthesis of 4,8-Dihydrobenzo[1,2-*b*:4,5-*c*′]dithiophen-4-one (5k).—The synthesis of **5k** is outlined in Scheme II.

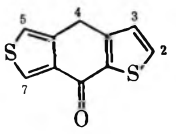
By simply substituting 2-thiophenecarboxaldehyde (**15**)[6] for 3-thiophenecarboxaldehyde (**10**) in Scheme I, the reaction sequence provided the same basic ring system as before with the ketone function now appearing in the 4 position. The individual reactions furnished compounds of unambiguous structure in yields of 56–86%.

The nmr spectrum (polysol-*d*) of **5k**, which is indicative of the keto tautomer, consists of a low field doublet for one hydrogen together with a complex multiplet for three hydrogens in the aromatic region and also a methylene singlet for two hydrogens at τ 5.58. The aromatic region was better resolved when C_6D_6 was employed as the solvent. The signal multiplicities and coupling constants support the presence of only the keto form (see Table I). The ir and uv spectra of **5k** also substantiate this conclusion. As was the case for **4k**, **5k** readily dissolves in 1 *M* sodium hydroxide solution.

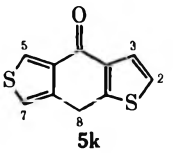
Synthesis of 4-Hydroxybenzo[1,2-*b*:5,4-*b*′]dithiophene (6e).—The synthesis of **6e** was accomplished in two steps from 3-bromo-2,2′-dithienylmethane (**21**) (see Scheme III). The alkylation of 3-bromothiophene (**19**) with 2-chloromethylthiophene (**20**)[7] under the influence of stannic chloride produced **21** in 29% yield. This compound was recently reported as a precursor in the preparation of benzo[1,2-*b*:5,4-*b*′]dithiophene,

(6) "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 915.
(7) "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 1955.

Table I



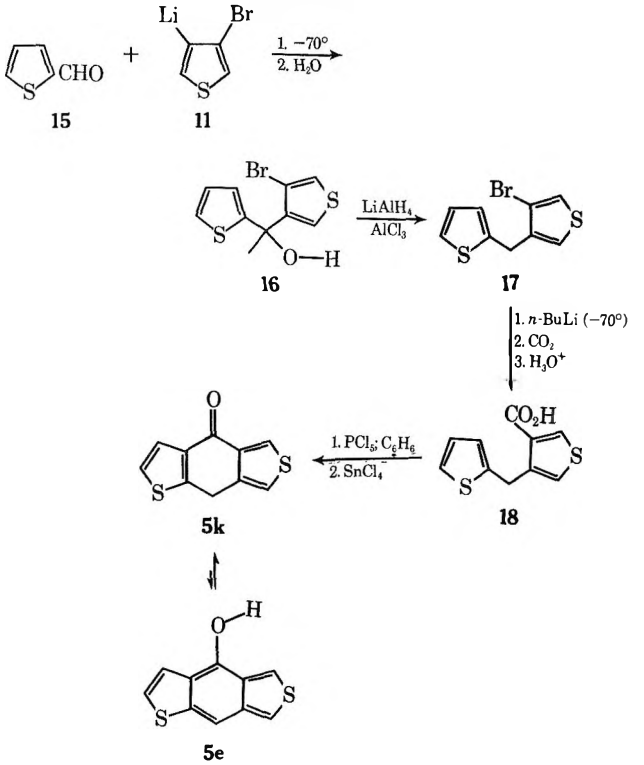
4k



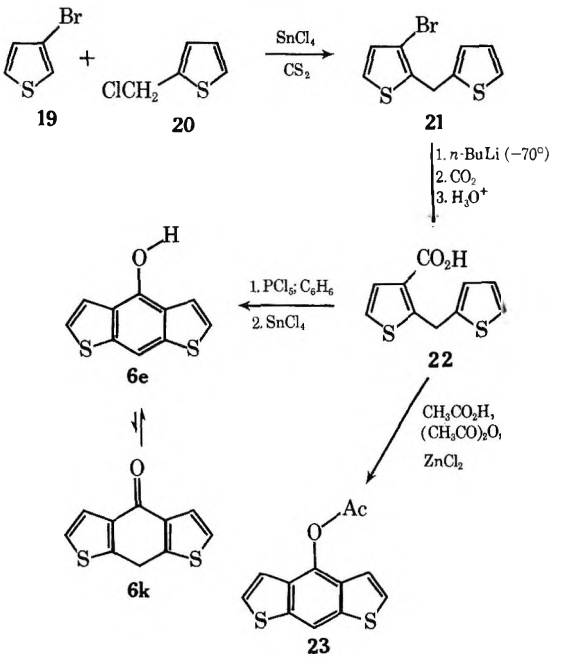
5k

Solvent	Proton	τ	Proton	τ
C_6D_6	7	1.87 (d, 1 H), $J_{5,7}$ = 3.5 Hz	5	1.88 (d, 1 H), $J_{5,7}$ = 3.5 Hz
	2	2.97 (d, 1 H), $J_{2,3}$ = 5 Hz	2	2.34 (d, 1 H), $J_{2,3}$ = 5 Hz
	3,5	3.31–3.58 (m, 2 H)	3	3.32 (d, 1 H), $J_{2,3}$ = 5 Hz
	4	6.67 (s, 2 H)	7	3.60 (m, 1 H), $J_{5,7}$ = 3.5, $J_{7,8}$ = 1 Hz
			8	6.62 (s, 2 H)
Polysol-*d*	7	1.69 (d, 1 H), $J_{5,7}$ = 3.5 Hz	5	1.64 (d, 1 H), $J_{5,7}$ = 3.5 Hz
	2	2.04 (d, 1 H), $J_{2,3}$ = 5 Hz	2, 3, 7	2.36–2.64 (m, 3 H)
	5	2.50 (m, 1 H), $J_{5,7}$ = 3.5, $J_{4,5}$ = 1 Hz	8	5.58 (s, 2 H)
	3	2.78 (d, 1 H), $J_{2,3}$ = 5 Hz		
	4	5.82 (s, 2 H)		

Scheme II



Scheme III



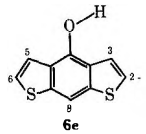
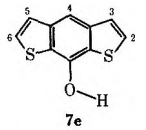
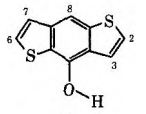
but its physical and spectral properties were not described.[8] Carbonation of **21** afforded 2,2′-dithienylmethane-3-carboxylic acid (**22**) in 64% yield. Cyclization of **22** *via* the acid chloride using stannic chloride provided a 40% yield of **6e**. The acid **22** was also converted to 4-acetoxybenzo[1,2-*b*:5,4-*b*′]dithiophene (**23**) according to the method of Fieser and Hershberg.[9]

The nmr spectrum (polysol-*d*) of **6e** consists of a broad singlet for the enol hydrogen, two doublets, $J_{2,3}$ = 5 Hz, which represent the four thiophene hydrogens, and a sharp singlet for the meso (C_8) hydrogen. No absorption above τ 2.7 was observed, thus indicating the absence of a significant quantity of the keto tautomer (see Table II). The spectrum of **6e** in C_6D_6 was also recorded. The signal multiplicities and coupling constants were identical with those in the spectrum which was obtained in polysol-*d*. The presence of the aromatic solvent caused a strong upfield shift of the entire spectrum. Trifluoroacetic acid had been used to ensure the formation of an equilibrium condition

(8) H. Wynberg, J. de Wit, and H. J. M. Sinnige, *J. Org. Chem.*, **35**, 711 (1970).

(9) L. Fieser and E. B. Hershberg, *J. Amer. Chem. Soc.*, **59**, 1028 (1937).

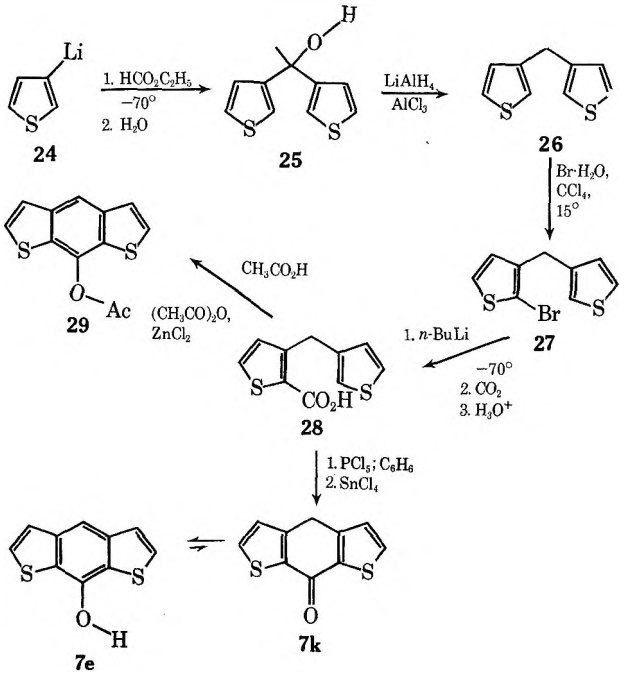
TABLE II

Compd	Polysol-*d* Proton	Polysol-*d* τ	C_6D_6 Proton	C_6D_6 τ
 6e	OH	−0.21 (s, 1 H)	OH	1.96 (s, 1 H)
	8	2.03 (s, 1 H)	2, 6	2.36 (d, 2 H), $J_{2,3}$ = 5 Hz
	2, 6	2.28 (d, 2 H), $J_{2,3}$ = 5 Hz	8	2.39 (s, 1 H)
	3, 5	2.62 (d, 2 H), $J_{2,3}$ = 5 Hz	3, 5	3.13 (d, 2 H), $J_{2,3}$ = 5 Hz
 7e	OH	−0.41 (s, 1 H)	4	2.32 (s, 1 H)
	4	2.10 (s, 1 H)	2, 6	2.92 (d, 2 H), $J_{2,3}$ = 5 Hz
	2, 6	2.43 (d, 2 H), $J_{2,3}$ = 5 Hz	3, 5	3.08 (d, 2 H), $J_{2,3}$ = 5 Hz
	3, 5	2.57 (d, 2 H), $J_{2,3}$ = 5 Hz	OH	4.87 (s, 1 H)
 8e	OH	0.33 (s, 1 H)		
	8	2.08 (s, 1 H)		
	2, 3, 6, 7	2.12–2.72 (m, 4 H)		

in C_6D_6 solutions of **1k,e** *and* **2k,e**.[2] The addition of a drop of this acid to the C_6D_6 solution of **6e** had no observable effect on the aromatic portion of the spectrum but only served to eliminate the enol (OH) absorption. Since no absorption above τ 3.2 was observed, the equilibrium position in **6k,e** must strongly favor the enol tautomer. The ir and uv spectra were also consistent with the assignment of **6e** for the structure of the cyclized product. The uv spectrum of **6e** was found to be very similar to that of its enol acetate (**23**).

Synthesis of 8-Hydroxybenzo[1,2-*b*:5,4-*b*′]dithiophene (7e).—The synthesis of **7e** is outlined in Scheme IV. The known 3,3′-dithienylmethane (**26**)[10] was

SCHEME IV



obtainable in fair quantity by way of high-yield reactions; therefore it presented itself as a logical starting material in the preparation of **7e**.

Gronowitz and Eriksson[11] have reported a two-step conversion of 3-bromothiophene to 3,3′-dithienylcarbinol (**25**) *via* 3-thiophenecarboxaldehyde. The same transformation was accomplished in one-step by treating ethyl formate with 2 equiv of 3-thienyllithium (**24**) at −70°. The yield of the alcohol was 77%. The reduction of **25** to 3,3′-dithienylmethane (**26**) was achieved in high yield according to the procedure of Wynberg, *et al.*[10] Since the dibromination of **26** had been shown[10] to produce 2,2′-dibromo-3,3-dithienylmethane, similar conditions were used to affect a monobromination. The conversion proceeded in 68% yield and provided the expected 2-bromo compound. Halogen–metal exchange at −70° in **27**, followed by carbonation, provided a good yield of 3,3′-dithienylmethane-2-carboxylic acid (**28**) which was cyclized *via* the acid chloride using stannic chloride to **7e**. The enol acetate of **7e** was also formed from **28** in order to compare its spectral properties with those of the enol.

The nmr spectrum of **7e** was obtained in polysol-*d* and in C_6D_6 and as expected both were very similar to those earlier described for **6e** (see Table II). No indication for the presence of the keto tautomer (**7k**) in either solvent was found. The uv spectrum of **7e** was compatible with that of its enol acetate (**29**). The lack of a carbonyl absorption in the ir spectrum of **7e** confirmed the presence of only the enol tautomer.

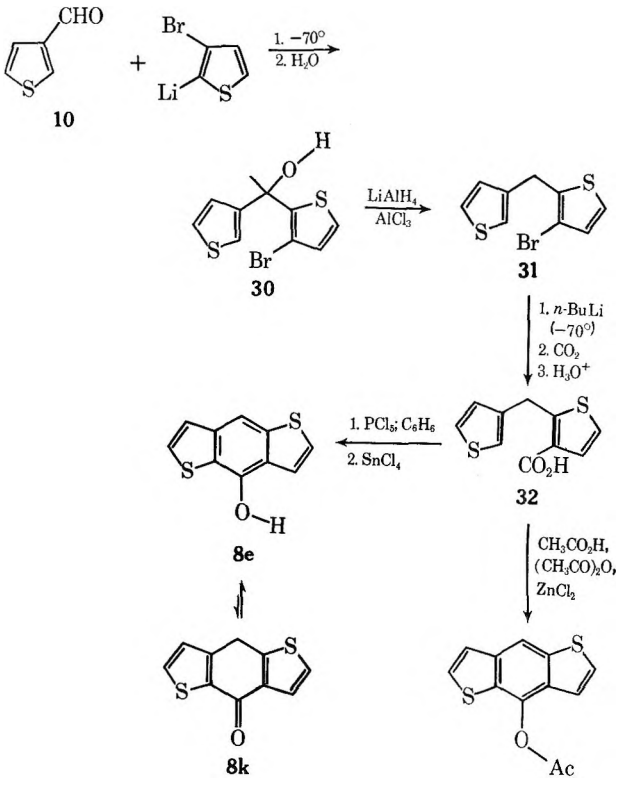
Synthesis of 4-Hydroxybenzo[1,2-*b*:4,5-*b*′]dithiophene (8e).—The preparation of the fifth isomer in this series was achieved by following a reaction sequence similar to that which proved successful in the synthesis of both **4k** and **5k** (see Scheme V).

Treatment of 3-bromo-2-thienyllithium with 3-thiophenecarboxaldehyde provided a 63% yield of 3-bromo-2,3-dithienylcarbinol (**30**) as a viscous oil. This alcohol had earlier been prepared by other workers,[10] who were unable to affect purification. Although we were successful in obtaining **30** as an analytically pure, low melting solid, the method was tedious. For this reason, the crude, viscous alcohol was allowed to react with equimolar quantities of lithium aluminum hydride and aluminum chloride, thus furnishing a 66% yield of 3-bromo-2,3′-dithienylmethane (**31**). The physical properties of **31** are comparable with those reported for it by Wynberg,[10] who obtained the bromide *via* an alternate route. Carbonation of **31** was affected in 83% yield and the resulting acid was cyclized to **8e** in 73% yield. The acid **32** was also converted to the enol acetate **33** of **8e**.

(10) A. Kraak, A. K. Wiersema, P. Jordens, and H. Wynberg, *Tetrahedron*, **24**, 3381 (1968).

(11) S. Gronowitz and B. Eriksson, *Ark. Kemi*, **21**, 335 (1964).

SCHEME V



The nmr spectrum (polysol-*d*) of **8e** revealed the presence of only the enol tautomer. A broad singlet due to the enol (OH) hydrogen was found at τ 0.33. The lack of a signal in the methylene region of the spectrum, τ 5–7, indicates the absence of a significant amount of the keto form **8k** (see Table II). Unlike **6e** and **7e**, **8e** possesses four nonequivalent thiophene protons. For this reason the aromatic portion of the spectrum is highly complex. The meso (C_8) proton appears slightly downfield from the remainder of the aromatic protons. Since **8e** was not readily soluble in benzene, its nmr spectrum in C_6D_6 could not be obtained. However, the information which was provided by the ir and uv spectra of **8e** justifies the assignment of the enol form for the cyclization product. The uv spectrum of **33** very closely resembles that of **8e**.

Discussion

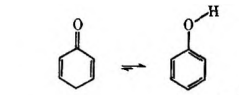
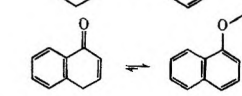
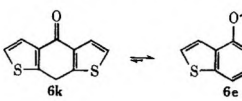
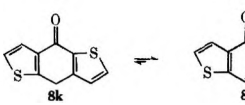
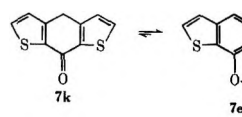
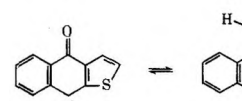
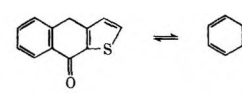
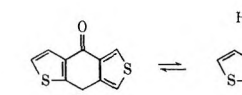
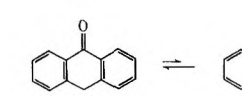
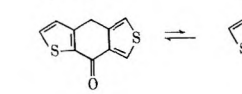
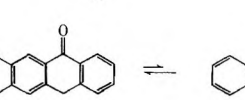
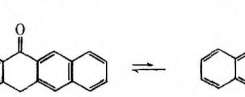
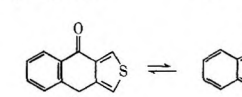
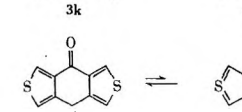
The keto–enol character of polycylic phenols is dictated by the free-energy difference between the two tautomeric forms. Since the individual compounds to be considered are very similar in structure, the change in σ bond energy for the transformation enol → ketone remains constant throughout the series. Thus the free-energy change can be represented by the π delocalization energy difference, ΔDE.

$$\Delta DE = DE_{enol} - DE_{keto}$$

In this approximation DE_{enol} is taken as the π delocalization energy of the parent system and DE_{keto} as that of the *exo*-methylene derivative.[12] A comprehensive list of ΔDE values was compiled and appears in Table III along with the experimentally determined equilibrium position for each substance.

(12) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, p 250.

TABLE III

Compd	ΔDE (β units)[a,b]	Preferred tautomer
	1.10	Enol
	0.83	Enol
 6k 6e	0.80	Enol
 8k 8e	0.76	Enol
 7k 7e	0.72	Enol
 1k 1e	0.66	Enol (polysol-*d*), mixture (C_6D_6)
 2k 2e	0.62	Enol (polysol-*d*), mixture (C_6D_6)
 5k 5e	0.53	Keto[c]
	0.50	Keto[c]
 4k 4e	0.49	Keto[c]
	0.43	Keto[d]
	0.38	Keto
 3k 3e	0.37	Keto[d]
 9k 9e	0.21	?[e]

[a] HMO program written by Dr. J. Gruninger, West Virginia University. [b] The parameters for these calculations are $\alpha_s = \alpha + \beta$; $\beta_{cs} = 0.7\beta$. [c] Soluble in hot 1 *M* sodium hydroxide solution. [d] Soluble in ethanolic potassium hydroxide solution. [e] Has not been prepared but keto form is predicted from the ΔDE value.

For the vast majority of the compounds which appear in Table III only one tautomeric form could be

spectroscopically detected. Only in the C_6D_6 solutions of the two *b*-fused naphthothiophene derivatives, **1k,e** and **2k,e**, was a coexisting keto–enol pair observed. The extent of the ΔDE region where this phenomenon occurs is still somewhat ill-defined and is currently under investigation.

Earlier,[2] we domonstrated that a compound of greatly enhanced enol content was produced by replacing one of the benzene rings of anthrone by a *b*-fused thiophene moiety. It logically follows that a still higher degree of enolization would be expected for the benzodithiophene derivatives related to anthrone if both heterocyclic rings were *b* fused. Hence, the fact that only the enol tautomers were detected in the equilibrium mixtures, **6k,e**, **7k,e**, and **8k,e**, is not unreasonable.

The benzodithiophene derivatives **4k** and **5k**, in which one of the thiophene rings is fused across its 3,4 bond, highly favor the keto tautomer since enolization would necessitate the formation of an energetically unfavorable benzo[*c*]thiophene system.

The correlation of the experimentally observed equilibrium position with computed ΔDE values provided excellent results in both the acene and "heteroacene" series.

Experimental Section[13]

3-Bromo-3′,4-dithienylcarbinol (12).—A solution of 3-thiophenecarboxaldehyde (46 g, 0.41 mol) in absolute ether (100 ml) was added dropwise to a solution of 4-bromo-3-thienyllithium, which had been prepared at −70° from ethereal *n*-butyllithium (300 ml, 1.5 *M*, 0.45 mol) and a solution of 3,4-dibromothiophene (110 g, 0.45 mol) in absolute ether (100 ml). The reaction mixture was stirred at −70° for 45 min and then allowed to warm to room temperature. Water (200 ml) was cautiously added with stirring. The layers were separated and the aqueous phase was extracted with ether (100 ml). The combined ether portions were washed neutral with copious quantities of water and dried ($MgSO_4$). The solvent was removed and the resulting viscous oil was warmed (70°) *in vacuo* for 2 hr. On cooling, the oil solidified giving an off-white solid which was recrystallized from hexane as white clusters (106.6 g, 95%), mp 64–68°. Two additional recrystallizations from hexane provided the analytical sample: mp 72.5–73.5°; ir (melt) 3390 cm^{-1} (OH); nmr ($CDCl_3$) τ 2.58–3.00 (m, 5 H, thiophene), 4.03 (d, 1 H, J = 3.5 Hz, methine), 7.47 (d, 1 H, J = 3.5 Hz, OH).

Anal. Calcd for $C_9H_7BrOS_2$: C, 39.28; H, 2.57; Br, 29.04; S, 23.30. Found: C, 39.10; H, 2.49; Br, 29.34; S, 23.03.

3-Bromo-3′,4-dithienylmethane (13).—A solution of aluminum chloride (64 g, 0.48 mol) in absolute ether (250 ml) was slowly added to a cooled suspension of lithium aluminum hydride (9.1 g, 0.24 mol) in absolute ether (100 ml). The mixture was allowed to come to room temperature and a solution of 3-bromo-3′,4-dithienylcarbinol (33 g, 0.12 mol) in absolute ether (100 ml) was added at such a rate as to promote a gentle reflux. The suspension was maintained at reflux for an additional 30 min and then cooled by means of an ice bath. The excess hydride was decomposed by dropwise addition of ethyl acetate (200 ml). The mixture was poured into ice and 1 *M* hydrochloric acid and shaken vigorously. The layers were separated and the aqueous phase was extracted with ether (two 100-ml portions). The combined organic portions were washed successively with 1 *M* hydrochloric acid, saturated sodium bicarbonate solution, and water and dried ($MgSO_4$). The solution was concentrated and the resulting liquid was fractionated giving 28.2 g (91%) of a colorless liquid, bp 98–103° (0.1 mm). An additional distillation provided the analytical sample: bp 94–95° (0.05 mm); nmr (CS_2) τ 2.74–3.32 (m, 5 H, thiophene), 6.15 (s, 2 H, CH_2).

Anal. Calcd for $C_9H_7BrS_2$: C, 41.70; H, 2.72; Br, 30.83; S, 24.74. Found: C, 41.89; H, 2.79; Br, 31.07; S, 24.89.

3′,4-Dithienylmethane-3-carboxylic Acid (14).—A solution of 3-bromo-3′,4-dithienylmethane (43 g, 0.17 mol) in absolute ether (100 ml) was added under a constant stream of nitrogen to an ethereal n-butyllithium solution (143 ml, 1.28 M, 0.18 mol) which was maintained at −70°. After stirring at −70° for 30 min, the solution was run onto excess Dry Ice. The mixture was allowed to come to room temperature and water (250 ml) was cautiously added with stirring. The layers were separated and the organic phase was washed with water (150 ml). The combined aqueous portions were acidified with excess 2 *M* hydrochloric acid. The resulting white precipitate was taken up in ether (two 250-ml portions) and the ethereal solution was washed with water, dried ($MgSO_4$), and concentrated. The white product was recrystallized from acetonitrile as white needles (31.1 g, 84%). An additional recrystallization from acetonitrile afforded the analytical sample: mp 138–139°; ir (KBr) 1675 cm^{-1} (acid C=O); nmr (acetone-d_6) τ 1.79 (d, 1 H, $J_{2,5}$ = 3.5 Hz, thiophene), 2.62–3.12 (m, 4 H, thiophene), 3.51 (broad s, 1 H, COOH), 5.75 (s, 2 H, $-CH_2-$).

Anal. Calcd for $C_{10}H_8O_2S_2$: C, 53.55; H, 3.59; S, 28.59. Found: C, 53.78; H, 3.68; S, 28.75.

4,8-Dihydrobenzo[1,2-*b*:4,5-*c*′]dithiophen-8-one (4k).—Phosphorus pentachloride (4.16 g, 20 mmol) was added portionwise to a stirred solution of 3′,4-dithienylmethane-3-carboxylic acid (4.48 g, 20 mmol) in dry benzene (150 ml) which was maintained at 4°. The mixture was then warmed until the evolution of hydrogen chloride ceased. The resulting solution was cooled to 4° and a solution of stannic chloride (3 ml, 6.7 g, 26 mmol) in dry benzene (50 ml) was dropwise added. The mixture was stirred at 4° for 1 hr and at room temperature for an additional hr, then poured into ice and 2 *M* hydrochloric acid. After vigorous shaking, the layers were separated and the aqueous phase was extracted with benzene (100 ml). The combined organic portions were washed with saturated sodium bicarbonate solution and with water, dried ($MgSO_4$), and concentrated to 75 ml. The resulting solution was chromatographed on a 20 cm × 2 cm column packed with neutral silica gel. Elution with benzene–chloroform (3:1), followed by concentration of the effluent, yielded a tan solid which was sublimed (100°, 0.05 mm) to give 2.6 g (63%) of a light-colored solid, mp 129–131°. Recrystallization from benzene–hexane provided an analytical sample: mp 132°; uv max (95% C_2H_5OH) 303 mμ (ε 15,900); ir (KBr) 1630 cm^{-1} (ketone C=O), no enol (OH) absorption was observed. Nmr spectra appear in Table I.

Anal. Calcd for $C_{10}H_6OS_2$: C, 58.22; H, 2.93; S, 31.09. Found: C, 58.16; H, 3.02; S, 30.92.

3-Bromo-2′,4-dithienylcarbinol (16).—A solution of 2-thiophenecarboxaldehyde (11.2 g, 0.10 mol) in absolute ether (50 ml) was dropwise added to a solution of 4-bromo-3-thienyllithium, which had been prepared at −70° from ethereal *n*-butyllithium (110 ml, 1.1 *M*, 0.12 mol) and a solution of 3,4-dibromothiophene (30 g, 0.12 mol) in absolute ether (50 ml). The mixture was stirred at −70° for 1 hr and then allowed to come to room temperature. Following normal work-up, the solvent was removed and the resulting liquid was dissolved in 50 ml of a 1:1 benzene–hexane solution. The solution was placed on a column of neutral alumina followed by 200 ml of the benzene–hexane solution. The eluent was then changed to chloroform and the alcohol containing fractions were combined and recrystallized from benzene–hexane giving 15.3 g (56%) of 3-bromo-4,2′-dithienylcarbinol as large white crystals. An additional recrystallization from benzene–hexane provided the analytical sample: mp 61.5–63°; ir (melt) 3380 cm^{-1} (OH); nmr (CS_2) τ 2.77–3.33 (m, 5 H, thiophene), 4.18 (d, 1 H, J = 4 Hz, methine), 7.22 (d, 1 H, J = 4 Hz, –OH).

Anal. Calcd for $C_9H_7BrOS_2$: C, 39.28; H, 2.57; Br, 29.04; S, 23.30. Found: C, 39.46; H, 2.36; Br, 29.20; S, 23.04.

3-Bromo-2′,4-dithienylmethane (17).—A solution of aluminum chloride (6.1 g, 46 mmol) in absolute ether (100 ml) was slowly added to a cooled suspension of lithium aluminum hydride (1.75 g, 46 mmol) in absolute ether (50 ml). The mixture was allowed to come to room temperature and a solution of 3-bromo-2′,4-dithienylcarbinol (11 g, 40 mmol) in absolute ether (50 ml) was added at such a rate as to promote a gentle reflux. The suspension was maintained at reflux for an additional 30 min and then cooled by means of an ice bath. The excess hydride was decom-

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

posed by dropwise addition of 3 *M* sulfuric acid. The mixture was poured into ice and 1 *M* hydrochloric acid. Work-up followed the procedure which was previously outlined in the preparation of **13**. The resulting liquid was fractionated giving 8.9 g (86%) of a colorless liquid: bp 94–98° (0.1 mm); nmr (CS_2) τ 2.79–3.33 (m, 5 H, thiophene), 5.95 (s, 2 H, $-CH_2-$).

Anal. Calcd for $C_9H_7BrS_2$: C, 41.70; H, 2.72; Br, 30.83; S, 24.74. Found: C, 41.75; H, 2.87; Br, 30.58; S, 24.92.

2′,4-Dithienylmethane-3-carboxylic Acid (18).—A solution of 3-bromo-2′,4-dithienylmethane (23 g, 89 mmol) in absolute ether (50 ml) was added under a constant stream of nitrogen to an ethereal *n*-butyllithium solution (85 ml, 1.18 *M*, 100 mmol) which was maintained at −70°. After stirring at −70° for 30 min, the solution was run onto excess Dry Ice. The mixture was allowed to come to room temperature and water (200 ml) was cautiously added. After normal work-up as previously described, the solvent was removed and the white solid was recrystallized from benzene–hexane as white needles (13.8 g, 69%). An additional recrystallization from benzene–hexane afforded the analytical sample: mp 136–137°; ir (KBr) 1675 cm^{-1} (acid C=O); nmr (acetone-d_6) τ 1.71 (d, 1 H, $J_{2,5}$ = 3.5 Hz, thiophene), 2.66–3.17 (m, 4 H, thiophene), 3.63 (broad s, 1 H, COOH), 5.52 (s, 2 H, $-CH_2-$).

Anal. Calcd for $C_{10}H_8O_2S_2$: C, 53.55; H, 3.59; S, 28.59. Found: C, 53.51; H, 3.61; S, 28.56.

4,8-Dihydrobenzo[1,2-*b*:4,5-*c*′]dithiophen-4-one (5k).—Phosphorus pentachloride (2.88 g, 14 mmol) was added portionwise to a stirred solution of 2′,4-dithienylmethane-3-carboxylic acid (3.1 g, 14 mmol) in dry benzene (25 ml) which was maintained at 4°. The mixture was then warmed on a steam bath until the evolution of hydrogen chloride had ceased. The resulting acid chloride solution was added dropwise to a stirred solution of stannic chloride (2.1 ml, 4.7 g, 18 mmol) in dry benzene (100 ml) at 4°. The mixture was allowed to come to room temperature and was stirred for 1 hr. The yellow suspension was poured into ice and 2 *M* hydrochloric acid (100 ml). The layers were separated and the aqueous phase was extracted with benzene (100 ml). The combined organic portions were washed with saturated sodium bicarbonate solution and with water, then dried ($MgSO_4$), and concentrated to 100 ml. The warm solution was chromatographed on neutral silica gel, using benzene (500 ml) as the eluent followed by benzene–chloroform (3:1) solution (1000 ml), which, after evaporation of the solvent, gave a slightly pink solid. Sublimation (90°, 0.1 mm) provided 1.65 g (58%) of a yellow solid. Recrystallization from ethanol–water afforded an analytical sample: mp 151–153°; uv max (95% C_2H_5OH) 279 mμ (ε 13,700); ir (KBr) 1635 cm^{-1} (ketone C=O), no enol (OH) absorption was observed. The nmr spectra of **5k** appear in Table I.

Anal. Calcd for $C_{10}H_6OS_2$: C, 58.22; H, 2.93; S, 31.09. Found: C, 57.99; H, 2.84; S, 30.80.

3-Bromo-2,2′-dithienylmethane (21).—A solution of 2-chloromethylthiophene (26.5 g, 0.20 mol) in carbon disulfide (120 ml) was dropwise added to a vigorously stirred solution of 3-bromothiophene (97.8 g, 0.60 mol) and stannic chloride (2 g, 7.7 mmol) in carbon disulfide (300 ml). The mixture was stirred for 4 hr, then poured into ice and 2 *M* hydrochloric acid, and shaken vigorously. Ether (500 ml) was added and the layers were separated. The aqueous phase was extracted with ether (200 ml) and the ethereal portions were combined and filtered. The solution was washed with saturated sodium bicarbonate solution and with water, then dried ($MgSO_4$), and concentrated. The resulting yellow liquid was fractionated giving a 3-bromothiophene (60 g), bp 60–62° (15 mm), and 3-bromo-2,2′-dithienylmethane (15.2 g, 29%), bp 91–98 (0.05 mm). The product was redistilled, bp 95–97° (0.1 mm), to given an analytical sample of the clear, colorless liquid: nmr (CS_2) τ 2.83–3.23 (m, 5 H, thiophene), 5.78 (d, 2 H, $-CH_2-$).

Anal. Calcd. for $C_9H_7BrS_2$: C, 41.70; H, 2.72; Br, 30.83; S, 24.74. Found: C, 41.78; H, 2.78; Br, 31.04; S 24.81.

2,2′-Dithienylmethane-3-carboxylic Acid (22).—A solution of 3-bromo-2,2′-dithienylmethane (23 g, 89 mmol) in absolute ether (50 ml) was added under a constant stream of nitrogen to an ethereal *n*-butyllithium solution (80 ml, 1.28 *M*, 102 mmol) which was maintained at −70°. After stirring at −70° for 30 min, the solution was run onto excess Dry Ice. The mixture was allowed to come to room temperature and stand for 10 hr. Water (200 ml) was cautiously added and the layers were separated. Following acidification and normal work-up, the solvent was removed and the resulting white solid was recrystallized from benzene–hexane. The yield was 16.2 g (81%). An additional recrystallization from benzene–hexane provided the analytical sample: mp 122.5–123.5°; ir (KBr) 1675 cm^{-1} (acid C=O); nmr (acetone-d_6) τ 2.46–3.15 (m, 5 H, thiophene), 4.08 (broad s, 1 H, COOH), 5.20 (s, 2 H, $-CH_2-$).

Anal. Calcd. for $C_{10}H_8O_2S_2$: C, 53.55; H, 3.59; S, 28.59. Found: C, 53.50; H, 3.54; S, 28.48.

Benzo[1,2-*b*:5,4-*b*′]dithiophen-4-ol (6e).—Phosphorus pentachloride (4.16 g, 20 mmol) was added portionwise to a stirred solution of 2,2′-dithienylmethane-3-carboxylic acid (4.48 g, 20 mmol) in dry benzene (50 ml) which was maintained at 4°. The mixture was then gently warmed until the evolution of hydrogen chloride had ceased. The resulting solution was cooled to 4° and a solution of stannic chloride (3 ml, 6.7 g, 26 mmol) in dry benzene (50 ml) was dropwise added during 30 min. The mixture was stirred at room temperature for 2 hr and then heated to reflux, cooled, and poured into ice and 2 *M* hydrochloric acid. Following a vigorous shaking, the layers were separated and the aqueous phase was extracted with ether (150 ml). The combined organic portions were washed with saturated sodium bicarbonate solution and with water, dried ($MgSO_4$), and concentrated to 50 ml. The resulting solution was chromatographed on a 20 cm × 2 cm column packed with neutral silica gel. Elution with benzene provided a white granular solid which was recrystallized from benzene–hexane as off-white clusters, 1.65 g (40%). An additional recrystallization from benzene–hexane provided the analytical sample: mp 179–180°; uv max (95% C_2H_5OH) 245 mμ (ε 58,600), 252 (66,500), 300 (8430), 325 (8000), 340 (9400); ir (KBr) 3330 cm^{-1} (OH), no carbonyl absorption was observed. The nmr spectra of **6e** appear in Table II.

Anal. Calcd for $C_{10}H_6OS_2$: C, 58.22; H, 2.93; S, 31.09. Found: C, 57.96; H, 3.00; S, 31.35.

4-Acetoxybenzo[1,2-*b*:5,4-*b*′]dithiophene (23).—A stirred mixture of 2,2′-dithienylmethane-3-carboxylic acid (10 g, 45 mmol), glacial acetic acid (100 ml), acetic anhydride (70 ml), and freshly fused zinc chloride (0.87, 6.4 mmol) was heated at reflux for 15 min and while still hot was cautiously diluted with water (170 ml). The resulting yellow-green crystalline solid was filtered, dried *in vacuo*, and sublimed (110°, 0.1 mm) to give 7.1 g (64%) of the yellow solid. An analytical sample was obtained by recrystallization from benzene–hexane: mp 131.5–133°; uv max (95% C_2H_5OH) 246 mμ (ε 66,000), 253 (76,200), 307 (9000), 328 (2650); ir (KBr) 1750 cm^{-1} (acetate C=O); nmr (CCl_4) τ 1.84 (s, 1 H, C_8 hydrogen), 2.68 (d, 2 H, $J_{2,3}$ = 5 Hz, thiophene), 2.82 (d, 2 H, $J_{2,3}$ = 5 Hz, thiophene), 7.60 [s, 3 H, $-OC(=O)CH_3$].

Anal. Calcd for $C_{12}H_8O_2S_2$: C, 58.04; H, 3.25; S, 25.83. Found: C, 57.81; H, 3.25; S, 25.80.

3,3′-Dithienylcarbinol (25).—A solution of freshly distilled ethyl formate (36 g, 0.49 mol) in absolute ether (100 ml) was dropwise added to a solution of 3-thienyllithium, which had been prepared at −70° from ethereal *n*-butyllithium (640 ml, 1.52 *M*, 0.97 mol) and a solution of 3-bromothiophene (170 g, 1.04 mol) in absolute ether (300 ml). The reaction mixture was stirred at −70° for 1 hr and then allowed to warm to 0°. Water (600 ml) was cautiously added with stirring. The layers were separated and the ethereal solution was washed neutral with copious quantities of water and dried ($MgSO_4$). The solvent was removed and the viscous oil which remained was warmed *in vacuo* for 3 hr. On cooling the oil solidified. The solid was recrystallized from hexane, to give 73.2 g (77%) of the alcohol: mp 65–68° (lit.[11] 68–69°); ir (melt) 3230 cm^{-1} (OH); nmr (CS_2) τ 2.79–3.27 (m, 6 H, thiophene), 4.40 (d, 1 H, *J* = 4 Hz, methine), 6.85 (d, 1 H, *J* = 4 Hz, OH).

2-Bromo-3,3′-dithienylmethane (27).—A solution of 3,3′-dithienylmethane (16.7 g, 93 mmol) in carbon tetrachloride (65 ml) was briskly added to a vigorously stirred mixture of bromine (14.85 g, 0.186 g-atom) and water (500 ml) at 15°. After 15 min the solution had turned colorless. Stirring was continued for an additional 10 min and ether (300 ml) was added. The layers were separated and the organic layer was extracted with ether (100 ml). The combined organic portions were washed with saturated sodium bicarbonate solution, then with water, and dried ($MgSO_4$). The ethereal solution was concentrated and the resulting oil was fractionated giving 3,3′-dithienylmethane (3.2 g), bp 65–75° (0.05 mm), and 2-bromo-3,3′-dithienylmethane (13.2, g, 68% based on unrecovered starting material), bp 85–95° (0.05 mm). An analytical sample was obtained by repeated distillation: bp 95–99° (0.1 mm); nmr (CS_2) τ 2.77–3.45 (m, 5 H, thiophene), 6.18 (s, 2 H, $-CH_2-$).

Anal. Calcd for $C_9H_7BrS_2$: C, 41.70; H, 2.72; Br, 30.83; S, 24.74. Found: C, 41.59; H, 2.50; Br, 30.62; S, 24.49.

Fair quantities of both 2,2-dibromo-3,3-dithienylmethane (mp 41–43°, lit.[10] 43°) and 2,2′,5,5′-tetrabromo-3,3′-dithienylmethane were isolated when the addition rate for 3,3′-dithienylmethane was slow. The tetrabromide was recrystallized from hexane as white needles: mp 102–103°; nmr (CS_2) τ 3.32 (s, 2 H, thiophene), 6.25 (s, 2 H, $-CH_2-$).

Anal. Calcd. for $C_9H_4Br_4S_2$: C, 21.80; H, 0.81; Br, 64.46; S, 12.93. Found: C, 21.76; H, 0.76; Br, 64.31; S, 13.05.

3,3′-Dithienylmethane-2-carboxylic Acid (28).—A solution of 2-bromo-3,3′-dithienylmethane (33 g, 0.13 mol) in absolute ether (75 ml) was added dropwise to an ethereal *n*-butyllithium solution (92 ml, 1.55 *M*, 0.14 mol) which was maintained at −70°. The mixture was stirred for 30 min and run to excess Dry Ice. After warming to room temperature, the reaction mixture was poured into ice and water (400 ml) and shaken vigorously. The layers were separated and the organic phase was washed with water (150 ml). The combined aqueous portions were acidified with excess 2 *M* hydrochloric acid. The resulting precipitate was taken up in ether and dried ($MgSO_4$). The solvent was evaporated leaving 25.8 g of white solid, which was recrystallized from acetonitrile as white clusters (24.2 g, 85%): mp 135–136°; ir (KBr) 1655 cm^{-1} (acid C=O); nmr (CS_2) τ −2.8 (s, 1 H, COOH), 2.67 (d, 1 H, $J_{2,3}$ = 5 Hz, thiophene), 2.82–3.02 (m, 1 H, thiophene), 3.07–3.29 (m, 3 H, thiophene), 5.72 (s, 2 H, $-CH_2-$).

Anal. Calcd. for $C_{10}H_8O_2S_2$: C, 53.55; H, 3.59; S, 28.59. Found: C, 53.33; H, 3.77; S, 28.77.

Benzo[1,2-*b*:5,4-*b*′]dithiophen-8-ol (7e).—Phosphorus pentachloride (6.24 g, 30 mmol) was added portionwise to a stirred solution of 3,3′-dithienylmethane-2-carboxylic acid (6.72 g, 30 mmol) in dry benzene (25 ml) which was maintained at 4°. The mixture was then warmed on a steam bath until the evolution of hydrogen chloride had ceased. The resulting acid chloride solution was dropwise added to a stirred solution of stannic chloride (4.8 ml, 10.6, g 40 mmol) in dry benzene (100 ml) at 4°. The mixture was allowed to come to room temperature and was stirred for 2 hr. The green suspension was heated to reflux, then was cooled, and poured into ice and 2 *M* hydrochloric acid (100 ml). The layers were separated and the aqueous phase was extracted with a benzene–ether solution (1:1, 150 ml). The combined organic portions were washed with saturated sodium bicarbonate solution and with water, then dried ($MgSO_4$), and concentrated to 100 ml. The warm solution was chromatographed on neutral silica gel, using benzene as the eluent. Evaporation of the solvent left a green-brown solid which was recrystallized from benzene–hexane giving large green-black clusters (1.6 g, 26%). An addition recrystallization from benzene–hexane provided an analytical sample: mp 140.5–142°; uv max (95% C_2H_5OH) 246 mμ (ϵ 54,500), 253 (61,600), 298 (7770), 309 (9500), 321 (8120), 335 (7550); ir (KBr) 3330 cm^{-1} (OH), no carbonyl absorption was observed. The nmr spectra of **7e** appear in Table II.

Anal. Calcd for $C_{10}H_6OS_2$: C, 58.22; H, 2.93; S, 31.09. Found: C, 58.07; H, 3.05; S, 30.97.

8-Acetoxybenzo[1,2-*b*:5,4-*b*′]dithiophene (29).— A stirred mixture of 3,3′-dithienylmethane-2-carboxylic acid (2.24 g, 10 mmol), glacial acetic acid (28 ml), acetic anhydride (20 ml), and dry zinc chloride (0.23 g, 1.7 mmol) was heated at reflux for 15 min and while still hot was cautiously diluted with water (48 ml). The resulting white crystalline solid was filtered, dried *in vacuo*, and sublimed (100°, 0.1 mm). The yield was 1.9 g, 77%. An analytical sample was obtained by recrystallization from acetic acid–water as long white needles: mp 127.5–128.5°; ir (KBr) 1765 cm^{-1} (acetate C=O); uv max (95% C_2H_5OH) 244 mμ (ϵ 53,600), 252 (57,600), 294 (7250), 303 (8160), 314 (sh, 4400), 328 (2210); nmr (acetone-d_6) τ 1.75 (s, 1 H, C_4 hydrogen), 2.36 (d, 2 H, $J_{2,3}$ = 5 Hz, thiophene), 2.50 (d, 2 H, $J_{2,3}$ = 5 Hz, thiophene), 7.52 [s, 3 H, $-OC(=O)CH_3$].

Anal. Calcd. for $C_{12}H_8O_2S_2$: C, 58.04; H, 3.25; S, 25.83. Found: C, 57.78; H, 3.31; S, 25.95.

3-Bromo-2,3′-dithienylcarbinol (30).—A solution of 2,3-dibromothiophene (95.3 g, 0.39 mol) in dry ether (100 ml) was added dropwise to a freshly prepared ethereal solution of *n*-butyllithium (250 ml, 1.65 *M*, 0.41 mol) at −70° under nitrogen. The mixture was stirred at −70° for 30 min and then a solution of 3-thiophenecarboxaldehyde (44 g, 0.39 mol) in dry ether (100 ml) was added. After the addition was complete, the mixture was allowed to warm slowly to room temperature. Stirring was continued for an additional 12 hr. The mixture was poured into ice and water and shaken vigorously. The layers were separated and the aqueous phase was extracted with ether (100 ml). The combined organic portions were washed neutral with water and dried ($MgSO_4$). The solvent was removed leaving 68 g (63%) of a reddish brown oil, which was used without further purification.

A small portion of the product obtained from a similar experiment was chromatographed on neutral alumina using benzene–hexane (1:1) as the eluent. Repeated short-path distillation of the alcohol containing fraction provided an analytical sample of 3-bromo-2,3′-dithienylcarbinol as a clear, slightly yellow-green oil (80° bath, 0.05 mm) which solidified during prolonged refrigeration: mp 39–40°; ir (neat) 3400 cm^{-1} (OH); nmr (CS_2) τ 2.75–3.25 (m, 5 H, thiophene), 4.15 (s, 1 H, methine), 7.40 (s, 1 H, OH).

Anal. Calcd for $C_9H_7BrOS_2$: C, 39.28; H, 2.57; Br, 29.04; S, 23.30. Found: C, 39.42; H, 2.70; Br, 28.84; S, 23.09.

3-Bromo-2,3′-dithienylmethane (31).—A solution of aluminum chloride (42 g, 0.31 mol) in absolute ether (150 ml) was cautiously added to a cooled suspension of lithium aluminum hydride (12 g, 0.31 mol) in absolute ether (100 ml). The mixture was allowed to come to room temperature and a solution of unpurified 3-bromo-2,3′-dithienylcarbinol (68 g, ~0.25 mol) in absolute ether (200 ml) was added at such a rate as to promote a gentle reflux. The suspension was maintained at reflux for an additional 30 min and then cooled by means of an ice bath. The excess hydride was decomposed by dropwise addition of 3 *M* sulfuric acid. The mixture was poured into ice and 1 *M* hydrochloric acid and worked up in the manner described for **13**. After the solvent was removed, the residue was fractionated yielding 3-bromo-2,3′ dithienylmethane (42 g, 66%) as a colorless liquid: bp 95–100° (0.1 mm) [lit.[10] bp 102–106° (0.2 mm)]; nmr (CS_2) τ 2.77 3.21 (m, 5 H, thiophene), 5.95 (s, 2 H, $-CH_2-$).

Anal. Calcd for $C_9H_7BrS_2$: C, 41.70; H, 2.72; Br, 30.83; S, 24.74. Found: C, 41.75; H, 2.56; Br, 30.59; S, 25.02.

2,3′-Dithienylmethane-3-carboxylic Acid (32).—A solution of 3-bromo-2,3′-dithienylmethane (32 g, 0.12 mol) in absolute ether (100 ml) was added under a nitrogen atmosphere to an ethereal *n*-butyllithium solution (135 ml, 1.05 *M*, 0.14 mol) which was maintained at −70°. After stirring at −70° for 30 min, the solution was run onto excess Dry Ice. The mixture was allowed to come to room temperature and water (300 ml) was cautiously added. The layers were separated and the organic phase was washed with water (100 ml). The combined aqueous portions were acidified and worked up as described in the preparation of **14**. The resulting ethereal solution was concentrated leaving 26.8 g of a white solid. Recrystallization from acetonitrile gave 23 g (83%) of a white crystalline solid. An additional recrystallization from benzene–hexane provided the analytical sample: mp 132–133.5; ir (KBr) 1665 cm^{-1} (acid C=O); nmr (acetone-d_6) τ 2.48–3.00 (m, 5 H, thiophene), 5.38 (s, 2 H, $-CH_2-$).

Anal. Calcd for $C_{10}H_8O_2S_2$: C, 53.55; H, 3.59; S, 28.59. Found: C, 53.71; H, 3.62; S, 28.30.

Benzo[1,2-*b*:4,5-*b*′]dithiophen-4-ol (8e).—A solution of 2,3′-dithienylmethane-3-carboxylic acid (4.48 g, 20 mmol) in dry benzene (50 ml) was transferred to a flame-dried, 300-ml, three-necked flask and maintained at 4° under a constant flow of nitrogen. Phosphorus pentachloride (4.16 g, 20 mmol) was added portionwise with stirring over a 45-min period. The mixture was then warmed until the evolution of hydrogen chloride ceased. The resulting solution was cooled to 4° and a solution of stannic chloride (3 ml, 6.7 g, 26 mmol) in dry benzene (50 ml) was added during 30 min. The mixture was stirred at room temperature for 2 hr and then heated to reflux, cooled, and poured into ice and 2 *M* hydrochloric acid. After vigorous shaking, the layers were separated and the aqueous phase was extracted with benzene (100 ml). The combined organic portions were washed with saturated sodium bicarbonate solution and with water, dried ($MgSO_4$), and concentrated to 50 ml. The resulting solution was chromatographed on a 20 cm × 2 cm column packed with neutral silica gel. Elution with benzene yielded a yellow-green solid, which was recrystallized from benzene–hexane to give 3.0 g (73%) of a lustrous black crystalline solid. Repeated recrystallization from benzene–hexane provided an analytical sample: mp 180–181°; uv max (95% C_2H_5OH) 227 mμ (ϵ 30,000), 246 (38,400), 253 (51,100), 276 (4600), 285 (6740), 296 (6370), 335 (10,450), 349 (12,450); ir (KBr) 3300 cm^{-1} (–OH), no carbonyl absorption was observed; nmr (polysol-*d*) τ 0.33

(broad s, 1 H, -OH), 2.08 (s, 1 H, C_8 hydrogen), 2.12–2.72 (m, 4 H, thiophene).

Anal. Calcd for $C_{10}H_6OS_2$: C, 58.22; H, 2.93; S, 31.09. Found: C, 58.37; H, 2.83; S, 30.90.

4-Acetoxybenzo[1,2-*b*:4,5-*b'*]dithiophene (**33**).—A stirred mixture of 2,3'-dithienylmethane-3-carboxylic acid (15 g, 67 mmol), glacial acetic acid (150 ml), acetic anhydride (105 ml), and freshly fused zinc chloride (1.3 g, 9.6 mmol) was heated at reflux for 15 min and while still hot was cautiously diluted with water (255 ml). The resulting yellow crystalline solid was filtered, dried *in vacuo* and purified by sublimation (90°, 0.1 mm). The yield was 12.5 g (75%). An analytical sample was obtained by recrystallization from benzene–hexane: mp 113–115°; uv max (95% C_2H_5OH) 231 mμ (ε 22,900), 246 (44,200), 254 (61,900), 289 (7680), 299 (8500), 323 (9620), 337 (14,900); ir (KBr) 1755 cm^{-1} (acetate C=O); nmr (CCl_4) τ 1.96 (s, 1 H, C_8 proton), 2.60–3.00 (m, 4 H, thiophene), 7.62 [s, 3 H, $-OC(=O)CH_3$].

Anal. Calcd. for $C_{12}H_8O_2S_2$: C, 58.04; H, 3.25; S, 25.83. Found: C, 57.97; H, 3.39; S, 25.83.

Registry No.—**4k**, 31936-79-5; **5k**, 31981-26-7; **6e**, 31936-80-8; **7e**, 31936-81-9; **8e**, 31936-82-0; **12**, 31936-83-1; **13**, 17965-66-1; **14**, 31936-85-3; **16**, 31936-86-4; **17**, 31936-87-5; **18**, 31936-88-6; **21**, 31936-89-7; **22**, 31936-90-0; **23**, 31936-91-1; **25**, 31936-92-2; **27**, 31936-93-3; **27** tetrabromide, 31936-94-4; **28**, 31936-95-5; **29**, 31936-96-6; **30**, 17964-88-4; **31**, 17965-56-9; **32**, 31936-99-9; **33**, 31937-00-5.

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Pteridines. XXVI. Preparation and Properties of Some 3,4- and 5,6-Dihydropteridines[1,2]

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Treatment of 8-alkyl-7(8*H*)-pteridinone-6-carboxylic acid derivatives (substituted at position 4 with hydrogen or methyl) with sodium borohydride leads to the formation in high yield of bright yellow dihydro compounds which are 10,000 times weaker acids, and exhibit uv absorption maxima some 50–60 nm higher, than the starting pteridinones. The influence of 2 and 4 substituents on this reduction has been carefully examined, and evaluation of both spectroscopic (uv, ir, and nmr) and chemical data has shown conclusively that these reduction products are 3,4-dihydro derivatives, and not 4,8- (or 5,8-) dihydro derivatives as previously suggested. By contrast, catalytic reduction of the same series of 8-alkyl-7(8*H*)-pteridinone-6-carboxylic acids and esters has been shown to give 5,6-dihydro compounds with very different chemical and physical properties. It has been demonstrated that the 3,4-dihydro compounds rearrange quantitatively and irreversibly to the 5,6-dihydro isomers in trifluoroacetic acid solution. The preparation of 22 new 8-alkyl-7(8*H*)-pteridinone-6-carboxylic acids and esters, as well as the requisite pyrimidine precursors, is described.

Dihydropteridines are attracting considerable current attention because of their role as naturally occurring cofactors in one-carbon transfer reactions involving the folic acid coenzymes,[3] the enzymatic hydroxylation of phenylalanine to tyrosine,[4] and a variety of other oxygenase reactions,[5] and as intermediates in photosynthetic electron transport processes in higher plants and photosynthetic bacteria.[6] Previous uncertainties as to the location of the hydrogen atoms in certain dihydropteridines (such as drosopterin, isodrosopterin, neodrosopterin, dihydrofolic acid, etc.)[7] have led to numerous efforts to prepare model dihydropteridines of known structure. For these reasons we have reinvestigated and extended our finding of several years ago[8,9] that a number of 7(8*H*)-pteridinone-6-carboxylic acid derivatives were reduced with sodium borohydride to dihydro compounds with unusual chemical and physical properties. The present work was undertaken in an effort to delineate the structural features (primarily the substitution pattern in the pyrimidine ring) necessary for sodium borohydride reduction of 7(8*H*)-pteridinone-6-carboxylic acids to these novel dihydro derivatives and to settle the controversy which has developed concerning their structure.[10] We describe herein the preparation of the requisite pteridine precursors, and the pyrimidine intermediates required for their preparation, the reduction experiments carried out on these pteridines, both with sodium borohydride and with hydrogen in the presence of various catalysts, and, finally, both spectroscopic and chemical evidence which firmly establishes the sodium borohydride reduction products as 3,4-dihydro derivatives, and the catalytic reduction products as their 5,6-dihydro isomers.

Synthesis of Intermediates. Pyrimidines.—Most of the requisite 4-alkylamino-5-aminopyrimidines required in this work were prepared by standard procedures and used directly in the pteridine preparations. Some special cases are described below.

(1) For the previous paper in this series, see E. C. Taylor and K. Lenard, *Justus Liebigs Ann. Chem.*, **726**, 100 (1969).

(2) A part of this work was supported by a grant (CA-02551) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.

(3) R. L. Blakley, "The Biochemistry of Folic Acid and Related Pteridines," Wiley–Interscience, New York, N. Y., 1969.

(4) S. Kaufman, *J. Biol. Chem.*, **242**, 3934 (1967).

(5) Summarized by S. Kaufman, *Ann. Rev. Biochem.*, **36**, 171 (1967).

(6) (a) N. A. Nugent and R. C. Fuller, in "Chemistry and Biology of Pteridines," K. Iwai, M. Akino, M. Goto, and Y. Iwanami, Ed., International Academic Printing Co., Ltd., Tokyo, 1970, pp 371–379. (b) R. C. Fuller and N. A. Nugent, *Proc. Nat. Acad. Sci. U. S.*, **63**, 1311 (1969).

(7) W. Pfleiderer and E. C. Taylor, Ed., "Pteridine Chemistry," Pergamon Press, Oxford, 1964.

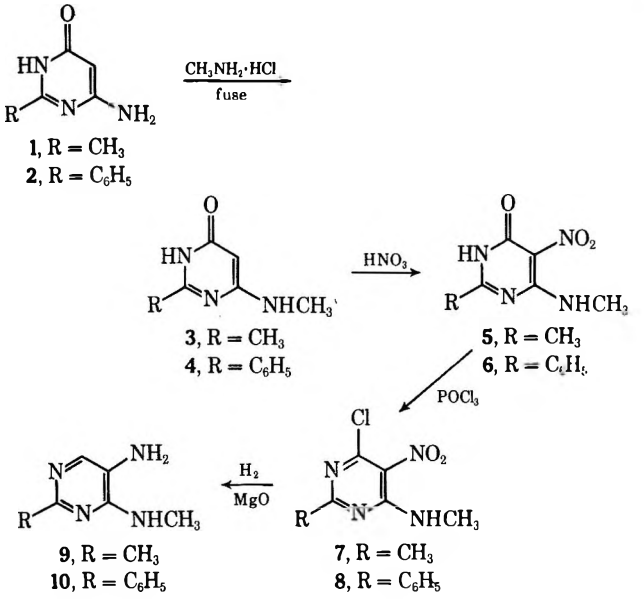
(8) W. Pfleiderer and E. C. Taylor, *J. Amer. Chem. Soc.*, **82**, 3765 (1960).

(9) E. C. Taylor, M. J. Thompson, and W. Pfleiderer, ref 7, pp 181–205.

(10) Reference 7, pp 205–210.

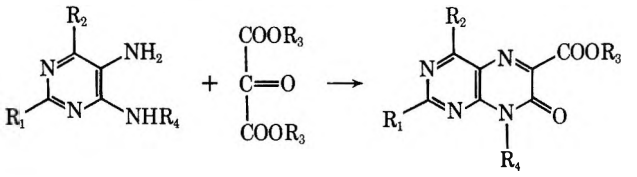
Although 2-methyl-4-methylamino-6(1*H*)-pyrimidinone (**3**) has been prepared previously[11] by a three-step sequence (21% overall yield) from 2-methyl-4,6(1*H*,3*H*)-pyrimidinedione,[12] it seemed that a simpler procedure would be transamidation[13-16] with the readily accessible 2-methyl-4-amino-6(1*H*)-pyrimidinone (**1**).[17] Fusion of this latter compound with methylammonium acetate gave a mixture containing the 4-amino-, 4-methylamino-, and 4-acetamido derivatives, but fusion with methylamine hydrochloride at 200° resulted in the formation of a more homogeneous product which, by nmr, consisted primarily of the desired 2-methyl-4-methylamino-6(1*H*)-pyrimidinone (**3**) (90%), along with a small amount of unreacted starting material. Nitration of this mixture with fuming nitric acid in glacial acetic acid, however, gave pure 2-methyl-4-methylamino-5-nitro-6(1*H*)-pyrimidinone (**5**). Treatment with phosphorus oxychloride then gave the 6-chloro compound **7** which upon reduction in aqueous ethanol containing magnesium oxide[18] underwent simultaneous dehalogenation and reduction of the nitro group to yield the desired 2-methyl-4-methylamino-5-aminopyrimidine (**9**). The same sequence of reactions, applied to 2-phenyl-4-amino-6(1*H*)-pyrimidinone (**2**),[19] gave 2-phenyl-4-methylamino-5-aminopyrimidine (**10**). These reactions are summarized in Scheme I.

SCHEME I



2-Dimethylamino-4-phenyl-5-amino-6-ethylaminopyrimidine (**16**) was prepared as follows. Condensation of dimethylguanidine with ethyl benzoylacetate in the presence of sodium ethoxide gave 2-dimethylamino-4-phenyl-6(1*H*)-pyrimidinone (**11**) in about 40% yield (a competing base-catalyzed cleavage of ethyl benzoylacetate to give acetophenone is apparently responsible for the low yield). This was converted to the 5-nitro compound **13** either by direct nitration with fuming nitric acid in glacial acetic acid at 20° (these conditions do not cause nitration of the 4-phenyl substituent) or by nitrosation to give 2-dimethylamino-4-phenyl-5-nitroso-6(1*H*)-pyrimidinone (**12**) followed by oxidation with pertrifluoroacetic acid.[20] Chlorination with phosphorus oxychloride to **14** followed by reaction with aqueous ethylamine then gave 2-dimethylamino-4-phenyl-5-nitro-6-ethylaminopyrimidine (**15**), which was reduced catalytically to the desired 5-amino derivative **16**. These reactions are summarized in Scheme II.

Pteridines.—All of the ethyl 8-alkyl-7(8*H*)-pteridinone-6-carboxylates utilized in the reduction experiments were prepared by the condensation of diethyl mesoxalate with the appropriate 4-alkylamino-5-aminopyrimidine (often prepared *in situ* by catalytic reduction of the appropriate 5-nitropyrimidine; see Experimental Section). The corresponding methyl esters were prepared from the ethyl esters by transesterification utilizing a large excess of methanol as solvent; this transesterification was particularly facile and complete because of the insolubility of the methyl esters in methanol. Free carboxylic acids were prepared either by condensation of the appropriate diaminopyrimidine with sodium mesoxalate or by alkaline hydrolysis of the esters. The 8-alkyl-7(8*H*)-pteridinone-6-carboxylic acid derivatives are listed, along with pertinent uv data, in Table I (for ir and nmr data, see Experimental Section).



Reduction Experiments with Sodium Borohydride.—Reduction of a series of 4-unsubstituted 8-alkyl-7(8*H*)-pteridinone-6-carboxylic acids and their corresponding ethyl (or methyl) esters, with the 2 position substituted by CH_3, C_6H_5, CH_3NH, $(CH_3)_2N$,[8] CH_3O, and HO, was effected by addition of sodium borohydride to a solution of the pteridinone in ethanol or dimethylformamide, followed by careful acidification with dilute acetic acid. In each instance, a yellow dihydro derivative, which exhibited a characteristic high wavelength absorption maximum between 402 and 453 nm, was obtained in high yield. Physical (see Table II and Experimental Section) and chemical evidence firmly establishing that these yellow compounds are 3,4-dihydro derivatives will be discussed later.

Substituents in the 4 position of the pyrimidine ring had a dramatic effect on the course of the sodium borohydride reduction. In fact, the only substituent besides hydrogen which yielded a 3,4-dihydro derivative under the above conditions was methyl; thus, methyl 2-methylamino-4,8-dimethyl-7(8*H*)-pteridinone-6-carboxylate (**27**) (and its corresponding acid **28**) underwent smooth reduction with sodium borohydride to give yellow 3,4-dihydro derivatives (**45** and **46**, respectively), but no reduction was observed when the 4 position was occupied by oxygen [2-amino-8-ethyl-4,7(3*H*,8*H*)-

(11) H. Hirano and H. Yonemoto, *J. Pharm. Soc. Jap.*, **76**, 234 (1956); *Chem. Abstr.*, **50**, 13043 (1956).
(12) H. R. Henze, W. J. Clegg, and C. W. Smart, *J. Org. Chem.*, **17**, 1320 (1953).
(13) E. C. Taylor and C. K. Cain, *J. Amer. Chem. Soc.*, **73**, 4384 (1951).
(14) D. J. Brown, *J. Appl. Chem.*, **7**, 109 (1957).
(15) W. V. Curran and R. B. Angier, *J. Org. Chem.*, **28**, 2672 (1963).
(16) C. W. Whitehead and J. J. Traverso, *J. Amer. Chem. Soc.*, **82**, 3971 (1960).
(17) A. Maggiolo, A. P. Phillips, and G. H. Hitchings, *ibid.*, **73**, 106 (1951).
(18) C. G. Overberger and I. C. Kogon, *ibid.*, **76**, 1879 (1954).
(19) R. Andrisano and L. Maioli, *Gazz. Chim. Ital*, **83**, 264 (1953).
(20) E. C. Taylor and A. McKillop, *J. Org. Chem.*, **30**, 3153 (1965).

SCHEME II

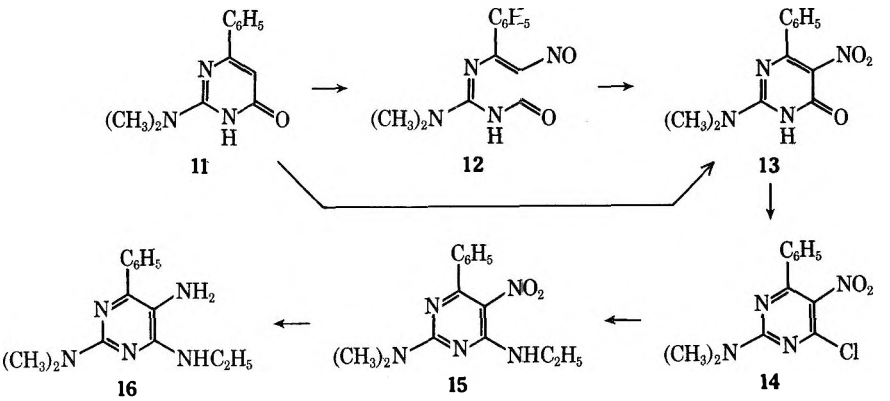
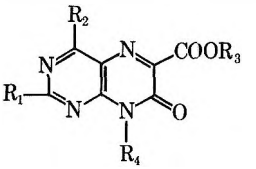


TABLE I

8-ALKYL-7(8*H*)-PTERIDINONE-6-CARBOXYLIC ACID DERIVATIVES



Compd no.	R_1	R_2	R_3	R_4	Uv spectra: λ_{max}, nm	Uv spectra: Log ϵ	Solvent
21	CH_3	H	C_2H_5	CH_3			
22	CH_3	H	CH_3	CH_3	245 (sh), 265, 275 (sh), 323	3.80, 3.55, 3.49, 4.01	C_2H_5OH
23	C_6H_5	H	C_2H_5	CH_3	228, 245 (sh), 290 (sh), 345	4.25, 3.92, 3.73, 4.27	C_2H_5OH
24	C_6H_5	H	CH_3	CH_3	227, 245 (sh), 290 (sh), 347	4.44, 3.97, 3.85, 4.29	C_2H_5OH
25	$(CH_3)_2N$	C_6H_5	C_2H_5	C_2H_5	230, 257 (sh), 295, 395	4.33, 4.16, 4.15, 4.35	C_2H_5OH
26	CH_3NH	CH_3	C_2H_5	CH_3	224, 245 (sh), 298, 378	4.50, 4.02, 3.72, 4.35	C_2H_5OH
27	CH_3NH	CH_3	CH_3	CH_3	222, 243 (sh), 295, 377	4.48, 3.98, 3.62, 4.36	C_2H_5OH
28	CH_3NH	CH_3	H	CH_3	222, 240, 293, 395	4.44, 4.07, 3.65, 4.36	C_2H_5OH
29	CH_3NH	H	C_2H_5	CH_3	238, 288, 354	4.47, 4.09, 4.10	pH −1
					225, 297, 387	4.50, 3.74, 4.40	pH 4
30	CH_3NH	H	CH_3	CH_3	225, 245 (sh), 303, 378	4.43, 3.97, 3.70, 4.37	C_2H_5OH
					238, 290, 355	4.48, 4.09, 4.11	pH −1
					225, 297, 388	4.51, 3.73, 4.41	pH 3
31	CH_3NH	H	H	CH_3	223, 245 (sh), 300, 385	4.16, 3.73, 3.56, 4.09	C_2H_5OH
					236, 288, 353	4.51, 4.10, 4.11	pH −1
					225, 288, 391	4.46, 3.86, 4.26	pH 2
					222, 240 (sh), 300, 366	4.45, 3.95, 3.80, 4.30	pH 6
32	CH_3O	H	C_2H_5	CH_3	257, 277 (sh), 283, 329	3.70, 3.66, 3.67, 4.17	C_2H_5OH
33	HO	H	H	CH_3	235 (sh), 291, 356	3.93, 3.72, 4.29	C_2H_5OH
34	HO	H	C_2H_5	CH_3	233 (sh), 291, 355	3.93, 3.72, 4.29	C_2H_5OH
35	H_2N	H	C_2H_5	CH_3	220, 294, 364	4.39, 3.53, 4.18	C_2H_5OH
					234, 280, 340	4.54, 4.0, 4.15	pH −1
					222, 290, 373	4.57, 3.72, 4.35	pH 7
36	H_2N	H	CH_3	CH_3	232, 280, 340	4.50, 4.01, 4.15	pH 1
					222, 290, 373	4.55, 3.71, 4.36	pH 3
37	H_2N	H	H	CH_3	291, 350	3.80, 4.18	pH 10
38	H	$(CH_3)_2N$	C_2H_5	CH_3	218, 230 (sh), 270, 380	4.31, 4.25, 4.00, 4.03	C_2H_5OH
39	H	$(CH_3)_2N$	H	CH_3	219, 272, 389	4.37, 4.03, 4.02	C_2H_5OH
40	H	C_2H_5NH	C_2H_5	C_2H_5	218, 264, 379	4.32, 3.97, 3.97	C_2H_5OH
41	H	C_2H_5NH	H	C_2H_5	219, 268, 335–350 (sh), 404	4.37, 3.96, 3.63, 4.01	C_2H_4OH
42	H	H	C_2H_5	CH_3	252 (sh), 258, 269 (sh), 319	3.59, 3.58, 3.48, 3.95	C_2H_5OH

pteridinedione-6-carboxylic acid (**64**)[21]], dimethylamino [ethyl 4-dimethylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (**38**), and the free acid **39**], ethylamino [ethyl 4-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (**40**), and the free acid **41**], or phenyl [ethyl 2-dimethylamino-4-phenyl-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (**25**)]. It should be noted that these substituents (methyl is a borderline case) are known to prevent covalent hydration at the site of substitution both in the quinazoline and pteridine ring systems.[22]

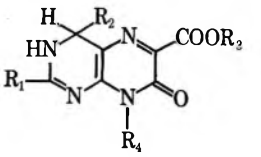
Catalytic Reduction Experiments.—In contrast to sodium borohydride, which yields yellow 3,4-dihydro derivatives exhibiting bathochromic ultraviolet absorption maxima, catalytic reduction of 8-alkyl-7(8*H*)-pteridinone-6-carboxylic acid derivatives yields isomeric 5,6-dihydro derivatives (*vide infra*) which exhibit

(21) E. C. Taylor and H. M. Loux, *J. Amer. Chem. Soc.*, **81**, 2474 (1959).

(22) A. Albert, *Angew. Chem. Int. Ed. Engl.*, **6**, 919 (1967).

TABLE II

3,4-DIHYDRO-8-ALKYL-7(8*H*)-PTERIDINONE-6-CARBOXYLIC ACID DERIVATIVES



Compd no.	R_1	R_2	R_3	R_4	Uv spectra: λ_{max}, nm	Uv spectra: Log ϵ	Solvent
43	CH_3	H	CH_3	CH_3	245, 270, 437	3.26, 3.09, 3.85	C_2H_5OH
44	C_6H_5	H	CH_3	CH_3	225 (sh), 260, 330 (sh), 453	3.96, 3.91, 3.54, 3.91	C_2H_5OH
45	CH_3NH	CH_3	CH_3	CH_3	263, 290, 410	3.59, 3.43, 3.99	C_2H_5OH
46	CH_3NH	CH_3	H	CH_3	265, 285, 412	3.80, 3.74, 4.20	C_2H_5OH
47	CH_3NH	H	CH_3	CH_3	245 (sh), 298, 402	3.40, 3.33, 3.64	C_2H_5OH
48	CH_3NH	H	H	CH_3	265, 288, 408	3.88, 3.78, 4.43	C_2H_5OH
49	CH_3O	H	C_2H_5	CH_3	263, 326–338 (sh), 416	3.79, 2.94, 4.34	C_2H_5OH
50	HO	H	H	CH_3	225 (sh), 253–260, 285, 402	3.85, 3.67, 3.66, 4.39	C_2H_5OH
51	HO	H	C_2H_5	CH_3	238, 269, 276–285 (sh), 425	3.88, 3.84, 3.82, 4.33	C_2H_5OH

marked hypsochromic shifts in their long wavelength absorption maxima and which are generally colorless. The preparation and properties of these latter dihydro derivatives, as well as experiments designed to probe possible interconversions between the two dihydro isomers, are described below.

Reduction of ethyl 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (**52**) with hydrogen and platinum oxide as catalyst resulted in the absorption of 1 mol of hydrogen and the formation of a precipitate which, upon isolation, proved to be identical with the sodium borohydride reduction product **53**[8] of the same pteridinone. However, examination of the uv spectrum of the filtrate showed the presence of a compound with an absorption maximum at 358 nm (compared with 390 nm for the nonreduced pteridinone **52** and 408 nm for the sodium borohydride reduction product **53**). Attempts to isolate and characterize this reduction product (which is shown later to be the 5,6-dihydro derivative **54**) led only to starting material. This lability toward air oxidation contrasts sharply with the stability of the borohydride reduction product **53**, which was indefinitely stable toward air.[8]

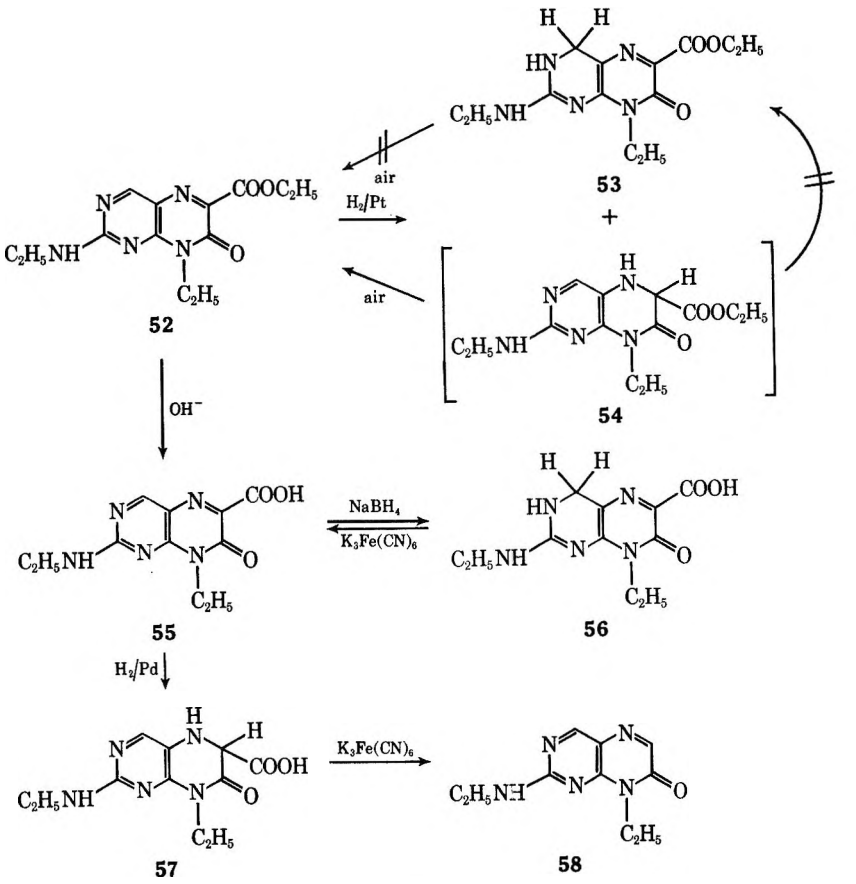
Since **53** was much less soluble than the product of catalytic reduction (*i.e.*, **54**), this system appeared to be a favorable one in which to explore possible isomerization of the latter into the former (it is conceivable that the 3,4-dihydro derivative may have been formed by initial borohydride reduction to give some other isomer, followed by tautomerization). However, the yield of the yellow 3,4-dihydro isomer **53** never exceeded 20% in catalytic reduction experiments, regardless of reaction conditions. Reductions were attempted under conditions designed to favor tautomerism (reduction in alkaline solution, reduction followed by addition of sodium borohydride), but in no case could an increase in the amount of the yellow, less soluble isomer be observed. One must conclude that, under the above conditions, there is no isomerization of the more soluble, colorless 5,6-dihydro isomer **54** to the less soluble, yellow 3,4-dihydro isomer **53**.

This conclusion was reinforced by an experiment carried out with the corresponding free acid [2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid, **55**]. Reduction with sodium borohydride has been shown to give the yellow 3,4-dihydro derivative **56**, which can be reoxidized to starting material with potassium permanganate or ferricyanide.[8] On the other hand, reduction of **55** with hydrogen in the presence of Pd/C resulted in the absorption of 1 mol of hydrogen and the formation of a colorless solution which exhibited a hypsochromic ultraviolet absorption maximum (354 nm, as contrasted with 365 nm for the starting material). Treatment of this reduction product (presumably the 5,6-dihydro derivative **57**) with potassium ferricyanide, however, resulted in loss not only of the two hydrogens but also of the carboxylic acid grouping giving 2-ethylamino-8-ethyl-7(8*H*)-pteridinone (**58**) (Scheme III). This difference in stability of the two isomeric dihydro acids is striking and emphasizes the lack of interconversion between them under the reaction conditions employed.

Isolation and characterization of the colorless 5,6-dihydro esters resulting from these catalytic reductions proved to be extremely difficult because of their lability toward reoxidation to starting material, particularly in the presence of alkali (see Experimental Section), and it was impossible to isolate the pure dihydro acids. For example, catalytic reduction of 4-dimethylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylic acid (**39**) gave 4-dimethylamino-8-methyl-7(8*H*)-pteridinone (**61**), presumably *via* initial reduction followed by spontaneous decarboxylation and subsequent reoxidation. Parallel results were obtained in attempts to reduce 4-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid (**41**); 4-ethylamino-8-ethyl-7(8*H*)-pteridinone (**63**) was the only product isolated. It is certain that decarboxylation in the above two instances takes place with the dihydro acids, and not prior to reduction, since the starting acids can be sublimed without decarboxylation.

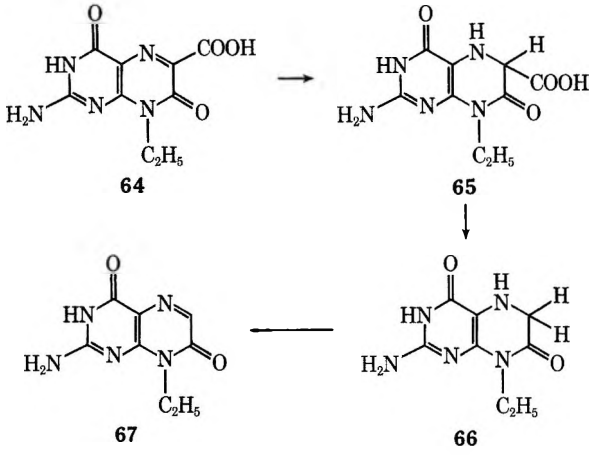
Analogous behavior was noted with 2-amino-8-ethyl-4,7(3*H*,8*H*)-pteridinedione-6-carboxylic acid (**64**),[21] which upon catalytic reduction with hydrogen and Pd in aqueous potassium hydroxide solution gave 2-amino-8-ethyl-4,7(3*H*,8*H*)-pteridinedione (**67**). The ultraviolet absorption spectrum of the initial alkaline solution before reduction showed a maximum at 366 nm which shifted to 325 nm immediately upon reduction. After acidification of the reduction mixture, however, it shifted slowly to 340 nm, and the resulting spectrum was identical with that given by a solution of 2-amino-8-ethyl-4,7(3*H*,8*H*)-pteridinedione (**67**) prepared by

SCHEME III



catalytic reduction of **64** followed by deliberate oxidation with potassium ferricyanide. Catalytic reduction of **67** resulted in loss of its bright blue fluorescence, but isolation of the (presumed) 5,6-dihydro derivative **66** was not possible because of rapid air oxidation back to starting material. We thus conclude (see Scheme IV)

SCHEME IV

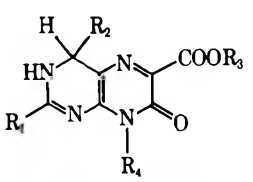


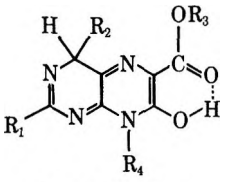
that catalytic reduction of **64** first yields the 5,6-dihydro derivative **65** (similar in structure to the other colorless 5,6-dihydro compounds, *i.e.*, **57**, discussed above), which first decarboxylates to **66** and then oxidizes to give the observed product **67**. Similar instability of dihydropteridine-6-carboxylic acids has been noted many times previously. For example, 2,4-diamino-7(8*H*)-pteridinone-6-carboxylic acid, on reduction with sodium amalgam or with zinc and alkali, yields an unstable dihydro acid which readily loses carbon dioxide to give the (presumed) 5,6-dihydro derivative.[23] Similarly, 2-amino-4,7(3*H*,8*H*)-pteridinedione-6-carboxylic acid has been reduced with zinc and alkali to give a mixture of the 5,6-dihydro acid and the decarboxylated 5,6-dihydro derivative; heating of either *in vacuo* at 150° results in ready decarboxylation and dehydrogenation to give isoxanthopterin.[23] Again, the contrast between the instability of the 5,6-dihydro acids (produced by catalytic reduction) and the stability of the isomeric 3,4-dihydro acids (produced by reduction with sodium borohydride) is remarkable.

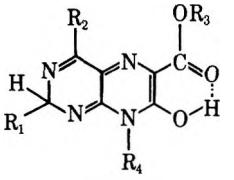
Structures of the Isomeric Dihydropteridines.—One of the most striking spectroscopic features of the dihydropteridines resulting from sodium borohydride treatment is their characteristic long wavelength uv absorption maxima, representing a bathochromic shift of some 50–60 nm as compared with the nonreduced pteridines. It is clear that a new, extended conjugated system has been introduced which, at the same time, must accommodate the observed 10,000-fold increase in base strength. Since borohydride does not normally reduce a carboxyl or amide carbonyl group (independent evidence, in any event, excludes reduction of the 6-carboxyl grouping[8]), there appear to be five structures (A–E) which must be considered (structure F is excluded by the uv data).

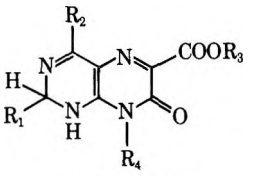
Nmr studies on the sodium borohydride reduction products clearly limit a choice to A or B. It will be seen from the data given in the Experimental Section that in a representative series of 4-unsubstituted 8-al-

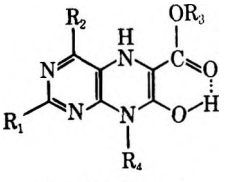
(23) G. B. Elion and G. H. Hitchings, *J. Amer. Chem. Soc.*, **74**, 3877 (1952).

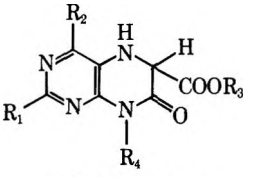

A (3,4-dihydro)


B (4,8-dihydro)


C (2,8-dihydro)


D (1,2-dihydro)


E (5,8-dihydro)


F (5,6-dihydro)

kyl-7(8*H*)-pteridinone-6-carboxylic acid derivatives the aromatic C-4 proton appears between 9.1 and 9.6 ppm, while in their respective dihydro derivatives resulting from borohydride reduction this signal disappears and is replaced by a two-proton singlet at *ca.* 5.0 ppm (CH_2 adjacent to N). Unequivocal evidence that C-4 is the site of reduction is provided by an examination of the spectrum of methyl 2-methylamino-4,8-dimethyl-7(8*H*)-pteridinone-6-carboxylate (**27**) and its sodium borohydride reduction product **45**. The C-4 methyl group, which appears as a sharp singlet at 2.96 ppm in the former compound, appears as a doublet (1.66 ppm) in the latter, while the methine proton introduced by reduction now appears as a quartet at 5.00 ppm. Analogous results were obtained with the corresponding carboxylic acid (*cf.* **28** and **46**). The nmr spectra of methyl 2,8-dimethyl-7(8*H*)-pteridinone-6-carboxylate (**22**) and its sodium borohydride reduction product **43** confirm the fact that reduction has indeed taken place at C-4 and that C-2 is unaffected.

The position of the second added hydrogen, which must reside either on nitrogen (structure A) or on oxygen (structure B), cannot be determined by nmr, since the dihydro compounds are insoluble in DMSO and other aprotic solvents, and spectra could only be obtained in trifluoroacetic acid solution. However, the ir spectra of the starting pteridinones and their sodium borohydride reduction products provide a possible criterion for this choice. All of the 7(8*H*)-pteridinone-6-carboxylic acid esters studied show the presence of two carbonyl bands, one in the 1724–1754-cm^{-1} region (ester) and the other in the 1667–1684-cm^{-1} region (cyclic lactam). In the yellow dihydro esters, however, only *one* carbonyl band appearing from 1692 to 1709 cm^{-1} is observed, and this must be due to the ester function, which is known from independent chemical evidence to be still present, unaffected by the borohydride reduction.[8] Interpreted in terms of the 4,8-dihydro structure B, the observed lowering of the frequency of the ester carbonyl band could be attributed to intramolecular hydrogen bonding of the 7-hydroxyl group to the carbonyl oxygen of the ester function.[24] It is striking (and fortuitous) that the amount of the observed shift is in approximate agreement with the shift observed in analogous systems when a hydroxyl group is introduced into a position ortho to an ester function.[25]

A similarly consistent interpretation in terms of structure B is possible when the corresponding carboxylic acids are considered. Thus, in contrast to the corresponding esters, all of the 7(8*H*)-pteridinone-6-carboxylic acids show only one carbonyl band between 1736 and 1767 cm^{-1}, which must be due to the carbonyl grouping. As a result of intramolecular hydrogen bonding between the amide carbonyl and the acid hydroxyl group, the amide band could be considered to be shifted to much lower frequencies where it would not be readily identified, with the acid carbonyl band occurring at the same frequency as the corresponding ester. In the reduction products, this single band would be shifted to much lower frequencies (1678–1706 cm^{-1}); in terms of structure B, this would be explicable as a result of a reversal of the hydrogen bonding so that the carbonyl oxygen participating is that of the carboxyl group.

On the other hand, the ir spectra of all of the sodium borohydride reduction products show a *sharp* new band at *ca.* 3300 cm^{-1}, certainly at variance with the broad band at lower frequencies expected of a strongly hydrogen-bonded –OH group.[24] This feature of their ir spectra is certainly more reasonably interpreted in terms of the 3,4-dihydro structure A. The observed shifts of the carbonyl frequencies upon reduction are also consistent with structure A; the lowered carbonyl frequency of the ester and carboxylic acid groupings is consistent with the change of environment to a vinylogous urethane, and the "disappearance" of the amide carbonyl band (present in the nonreduced pteridine esters at 1667–1684 cm^{-1}) could be due to a shift to lower frequencies because of its vinylogous urea character. The observed 10,000-fold increase in base strength[8] is better explained by the amidine structure A; this interpretation has strong precedent in the much greater base strength of the covalent hydrate of quinazoline, and of 3,4-dihydroquinazoline, as compared with quinazoline itself.[22]

The high wavelength uv absorption maxima found for all of the sodium borohydride reduction products are consistent with either structure A or B and appear to be characteristic of the system $-NR(CH{=}CH)_xC{=}O$; many examples are known which support this generalization.[26] Although the conjugated system present in structure A is considerably longer than in the examples cited,[26] competitive amide resonance involving the 7-carbonyl grouping and the 8 nitrogen must introduce dipole–dipole repulsions which would be expected to lower the importance of the former. An observation

(24) M. Tichy, *Advan. Org. Chem.*, **5**, 115 (1965).

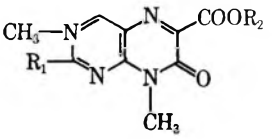
(25) The following examples are illustrative of this effect.

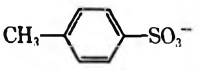
Ester	C=O band, cm^{-1}	Δ, cm^{-1}
Methyl benzoate	1730	47
Methyl salicylate	1683	
Methyl 1-naphthoate	1724	69
Methyl 2-hydroxy-1-naphthoate	1655	
Ethyl 2-naphthoate	1726	58
Ethyl 1-hydroxy-2-naphthoate	1668	

(26) See ref 7, p 204.

TABLE III

3,8-DIMETHYL-6-CARBALKOXY-7-OXO-7,8-DIHYDROPTERIDINIUM TOSYLATES

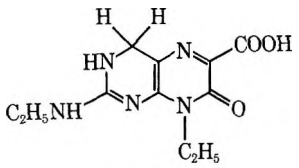




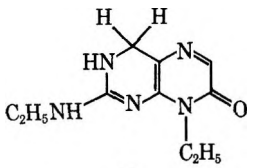
Compd no.	R_1	R_2	pK_a value[a]	Uv spectra: λ_{max}, nm	Uv spectra: Log ϵ	Solvent	Species
70	H_2N	CH_3	5.21 ± 0.06	229, 278, 339	4.56, 3.98, 4.17	pH 3	Cation
				262, 280 (sh), 393	3.97, 3.72, 4.51	pH 8	Pseudobase
71	H_2N	C_2H_5	5.13 ± 0.03	230, 278, 340	4.57, 4.00, 4.17	pH 3	Cation
				262, 280 (sh), 394	4.00, 3.75, 4.53	pH 8	Pseudobase
72	CH_3NH	CH_3	5.99 ± 0.03	230, 237, 289, 351	4.47, 4.46, 4.06, 4.14	pH 3	Cation
				264, 280 (sh), 394	4.05, 3.94, 4.47	pH 8	Pseudobase
73	CH_3NH	C_2H_5	6.06 ± 0.04	229, 237, 290, 352	4.47, 4.47, 4.07, 4.15	pH 3	Cation
				264, 280 (sh), 395	4.03, 3.85, 4.52	pH 8	Pseudobase

[a] Determined spectrophotometrically.

compatible only with structure A, and not with structure B, is the fact that 2-ethylamino-3,4-dihydro-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid (**68**) and its decarboxylation product **69** (formed by sublimation of **68** *in vacuo* at 175°) have approximately the same long wavelength uv maxima.[8,27]



68



69

Conclusive evidence that the sodium borohydride reduction products are 3,4-dihydro derivatives (A) and not the 4,8-dihydro tautomers (B) was obtained as follows. A series of 8-alkyl-7(8*H*)-pteridinone-6-carboxylates substituted at position 2 with $-NH_2$, $-NHCH_3$, and $-N(CH_3)_2$ was heated with methyl *p*-toluenesulfonate. In all cases except with ethyl 2-dimethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate,[8] crystalline monomethylated pteridinium tosylates **70**–**73** were obtained (see Table III). The fact that the 2-dimethylamino compound was recovered unchanged under the above reaction conditions indicates that methylation probably took place on one of the ring nitrogen atoms adjacent to the 2 position (*i.e.*, N-1 or N-3), which would be expected to be sterically affected by the bulky 2-dimethylamino grouping. (Methylation on oxygen was excluded by the observation that each of the four methylpteridinium tosylates **70**–**73** contained only one alkoxy (ester) group by a Zeisel determination.) The similarity of the uv spectra and the pK_a values (Table III) determined for all four compounds showed that they all possessed analogous structures. The position of alkylation was then firmly established as N-3 by the observations that (a) the methylation product **71** of ethyl 2-amino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (**35**) was smoothly converted by oxidation with potassium ferricyanide at pH 7 to the known 3,8-dimethylisoxanthopterin-6-carboxylic acid ethyl ester (**78**),[28] and (b) **71** underwent the Dimroth rearrangement[29] in sodium bicarbonate solution at room temperature to give ethyl 2-methylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (**29**), identical with an authentic sample. Furthermore, heating **71** in pH 9 buffer resulted in a Dimroth rearrangement with accompanying saponification of the ester grouping to give 2-methylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylic acid (**31**), again identical with an authentic sample. These conversions and rearrangements are summarized in Scheme V.[30]

Sodium borohydride reduction of these 3,8-dimethylpteridinium tosylates **70**–**73** then gave bright yellow 3,4-dihydro derivatives (**74**–**77**) whose uv spectra were essentially superimposable with the uv spectra of the sodium borohydride reduction products of the parent pteridinones (see Tables II and IV). We thus confidently assign the 3,4-dihydro structure to the yellow dihydro compounds resulting from sodium borohydride reduction of all of the pteridinones discussed above. The 4,8- and 5,8-dihydro structures previously discussed[7,8] are in error and should be amended accordingly.

The structures of the colorless dihydro derivatives obtained by catalytic (and occasionally zinc dust; see Experimental Section) reduction of the above series of 8-alkyl-7(8*H*)-pteridinones were evident by examination of their uv and ir spectra, and readily confirmed by examination of their nmr spectra (Table V) to be the 5,6-dihydro isomers (structure F). Thus, the only spectral change which occurred upon catalytic reduction (best carried out in trifluoroacetic acid) of the pteridinones **21**–**42**, apart from a shift of the C-4 proton singlet (when present) to lower field (from ~9 to 7.7–8.3 ppm) was the appearance of a new one-

(27) It was this observation that led one of us (W. P.) to question the originally assigned 5,8- and 4,8-dihydro structures for the sodium borohydride reduction products and to favor the 3,4-dihydro structure A (see ref 7, p 207). It should be noted that decarboxylation of **68** in aqueous acid gives the isomeric 5,6-dihydro derivative (see ref 8), which arises by rearrangement of the initially formed 3,4-dihydro isomer **69**.

(28) W. Pfleiderer and M. Rukwied, *Chem. Ber.*, **95**, 1591 (1962).

(29) D. J. Brown in "Mechanisms of Molecular Migrations," Vol. 1, B. S. Thyagarajan, Ed., Interscience, New York, N.Y., 1968, p 209.

(30) It is interesting to note that the nmr spectrum of 2-methylamino-3,8-dimethyl-6-earbomethoxy-7-oxo-7,8-dihydropteridinium tosylate (**72**) in trifluoroacetic acid shows the 2-methylamino grouping as a doublet. That the splitting of the methyl signal was due to coupling with the adjacent NH was demonstrated by a decoupling experiment (irradiation at −258 Hz). Apparently proton exchange at the 2-NH group is slow even in trifluoroacetic acid because of steric hindrance by the methyl group. Further evidence for this steric effect is seen in a comparison of the pK_a values for the 3,4-dihydro derivatives **74**–**77** (Table IV). The two 2-CH_3NH derivatives **76** and **77** are actually *weaker* bases than the 2-NH_2 derivatives **74** and **75**; this observation provides indirect evidence that protonation in these compounds occurs at N-1.

SCHEME V

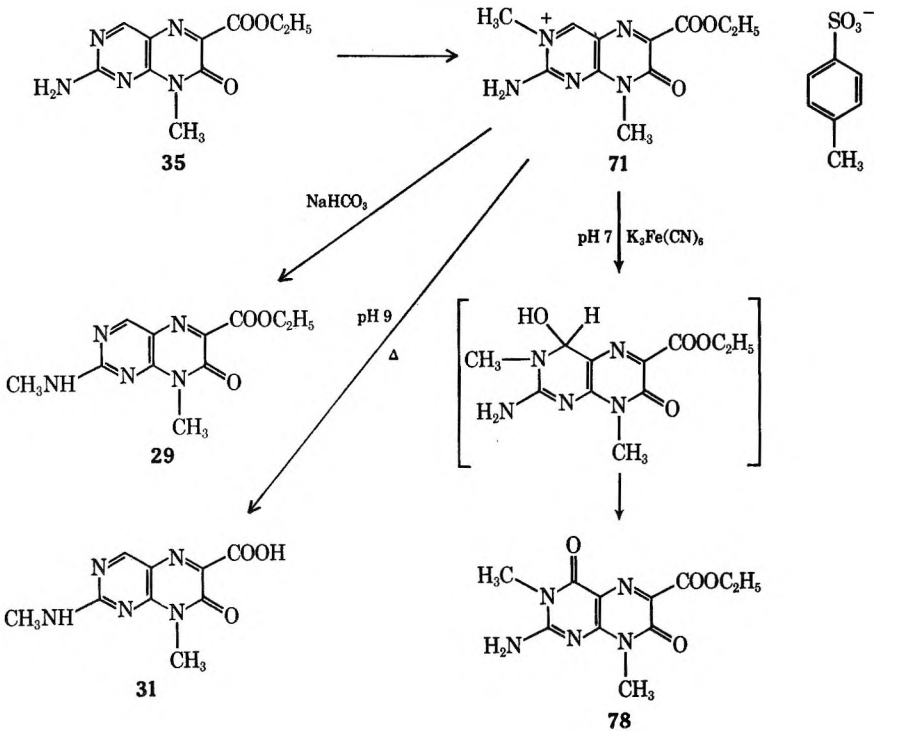
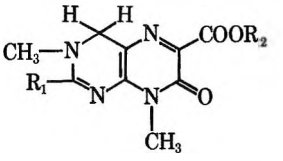


TABLE IV

3,8-DIMETHYL-3,4-DIHYDRO-7(8*H*)-PTERIDINONE-6-CARBOXYLATES



Compd no.	R_1	R_2	pK_a value[a]	Uv spectra: λ_{max}, nm	Uv spectra: Log ϵ	Solvent	Species[b]
74	H_2N	CH_3	1.66 ± 0.12	230, 392	4.05, 4.20	pH −1	Cation
				242, 269, 290 (sh), 408	4.0, 3.9, 3.69, 4.43	pH 6	O
75	H_2N	C_2H_5	1.85 ± 0.05	230, 392	4.05, 4.23	pH 0	Cation
				242, 268, 290 (sh), 408	3.99, 3.90, 3.67, 4.43	pH 6	O
76	CH_3NH	CH_3	0.55 ± 0.05	287, 390	3.61, 4.22	pH −1	Cation
				240, 272, 405	3.84, 4.00, 4.44	pH 4	O
77	CH_3NH	C_2H_5	0.65 ± 0.05	290, 390	3.62, 4.20	pH −1	Cation
				240, 373, 408	3.88, 3.99, 4.44	pH 5	O

[a] Determined spectrophotometrically. [b] O denotes the neutral species.

proton methine singlet at ~5.1 ppm, arising from reduction at C-6.

In an attempt to determine the nmr spectra of the yellow 3,4-dihydro isomers in trifluoroacetic acid, it was noted that a rapid change occurred even at room temperature; the 4-methine signal disappeared and was replaced by a one-proton methine singlet at about 5.1 ppm, while an aromatic one-proton singlet appeared at 7.7–8.3 ppm in the 4-unsubstituted compounds. Indeed, these latter spectra were identical with the spectra of solutions of the starting pteridinones in trifluoroacetic acid which had been reduced with hydrogen and platinum and with the spectra of trifluoroacetic acid solutions of the isolated, colorless 5,6-dihydro compounds obtained by catalytic reduction in water or ethanol (*vide supra*). It is thus evident that rearrangement of the 3,4- to the 5,6-dihydro isomers occurs in trifluoroacetic acid solution; this change represents the long sought isomerization (even if irreversible) between the two series of dihydro compounds.

The various interconversions among the 3,4- and 5,6-dihydro isomers discussed above are summarized in Scheme VI.

Experimental Section[31]

2-Methyl-4-methylamino-6(1*H*)-pyrimidinone (3).—A mixture of 30.0 g of 2-methyl-4-amino-6(1*H*)-pyrimidinone[17] and 120 g of methylamine hydrochloride was heated in an oil bath for 30 min

(31) All melting points were determined on a Thomas-Hoover silicone oil bath apparatus and are uncorrected. Microanalyses were performed by the Schwarzkopf Microanalytical Laboratories, Woodside, N. Y., Spang Microanalytical Laboratories, Ann Arbor, Mich., and Dr. G. Robertson, Florham Park, N. J. Uv spectra were determined on a Cary Model 11 recording ultraviolet spectrophotometer, ir spectra on a Perkin-Elmer Model 237B Infracord by the normal Nujol mull technique, and nmr spectra on a Varian A-60 instrument, using TMS as internal standard in CF_3COOH as solvent (unless otherwise indicated).

SCHEME VI

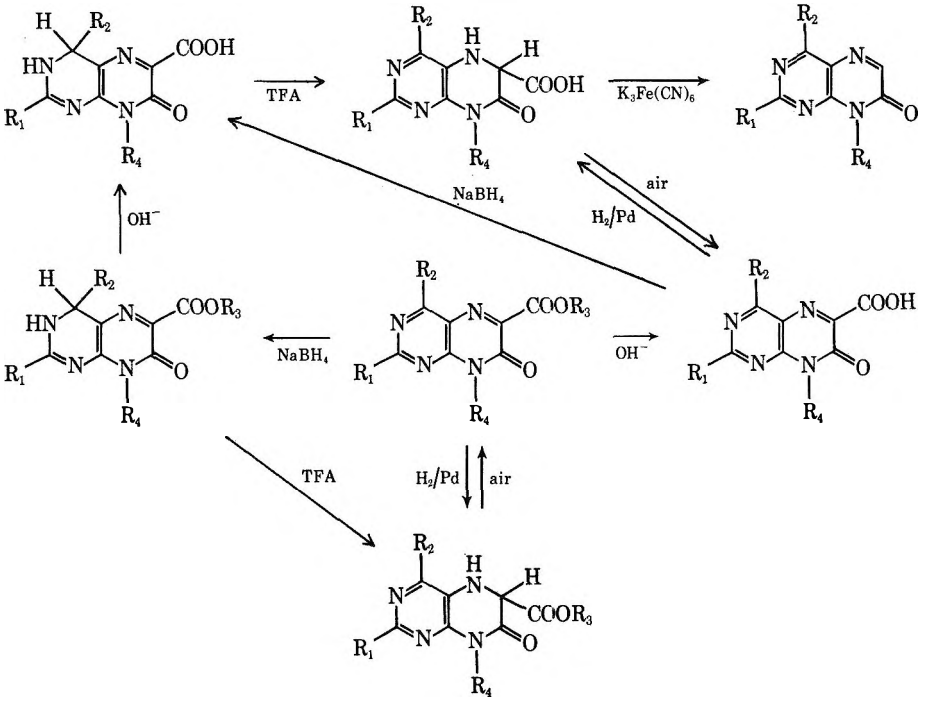
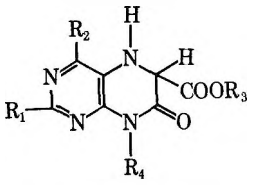


TABLE V

NMR SPECTRA OF REPRESENTATIVE 5,6-DIHYDRO-8-ALKYL-7(8*H*)-PTERIDINONE-6-CARBOXYLIC ACID DERIVATIVES[a]



Substrate compd no.	Chemical shift of substituent, ppm R1	R2	C6-H
22	2.83 (s, 3)	8.15 (s, 1)	5.28 (s, 1)
24	7.70 (m, 3)	8.30 (s, 1)	5.43 (s, 1)
	8.10 (m, 2)		
25	3.40 (s, 6)	7.70 (s, 5)	5.13 (s, 1)
27	3.18 (s, 3)	2.55 (s, 3)	5.15 (s, 1)
28	3.13 (s, 3)	2.50 (s, 3)	5.17 (s, 1)
30	3.20 (s, 3)	7.70 (s, 1)	5.15 (s, 1)
31	3.16 (s, 3)	7.70 (s, 1)	5.20 (s, 1)

[a] These 5,6-dihydro compounds were prepared in CF_3COOH solution by hydrogenation with H_2–Pd/C or H_2–PtO_2. Reduction was complete within 30 min; the catalyst was then removed by filtration and the nmr spectrum of the filtrate determined at room temperature [see A. Bobst and M. Viscontini, *Helv. Chim. Acta*, **49**, 875 (1966)].

with the internal temperature of the melt maintained at 190–195°. At the end of this time, the melt was cooled to about 100° and dissolved in 150 ml of warm water. The resulting solution was cooled to 0°, and the crystals which separated were collected by filtration (25 g) and recrystallized from water, mp 279–281° dec (lit.[11] mp 282° dec), yield 31.2 g (94%). Despite the agreement with the literature melting point, inspection of the nmr spectrum of this product indicated that it contains approximately 5–10% of unchanged 2-methyl-4-amino-6(1*H*)-pyrimidinone. This proved to be inconsequential, however, since the residual starting material was eliminated in the nitration step (see below).

2-Methyl-4-methylamino-5-nitro-6(1*H*)-pyrimidinone (5).—Over a period of 10 min, 6.0 g of 2-methyl-4-methylamino-6(1*H*)-pyrimidinone was added to a mixture of 60 ml of fuming nitric acid and 24 ml of glacial acetic acid at 30–32°. The mixture was stirred at this temperature for an additional 30 min and then poured into ice–water, and the precipitated solid was collected by filtration, washed with water, and dried, yield 4.3 g (55%), mp 301–302° dec. Recrystallization from dimethylformamide did not change the melting point.

Anal. Calcd for $C_6H_8N_4O_3$: C, 39.13; H, 4.38; N, 30.43. Found: C, 39.12; H, 4.51; N, 30.54.

Ethyl 2,8-Dimethyl-7(8*H*)-pteridinone-6-carboxylate (21).—A solution of 3.5 g of 2-methyl-4-methylamino-5-nitro-6(1*H*)-pyrimidinone in 35 ml of phosphorus oxychloride was heated under reflux, with stirring, for 1.5 hr, the excess phosphorus oxychloride removed by distillation under reduced pressure, and the residual gum crystallized from ether. The resulting yellow, crystalline 2-methyl-4-methylamino-5-nitro-6-chloropyrimidine (7) was dissolved in 40 ml of ethanol and 40 ml of water containing 10 g of magnesium oxide and 1 g of palladium-on-carbon catalyst, and the mixture was hydrogenated at 60 psi in a Parr shaker. Hydrogen uptake was very rapid and was complete within 10 min. The reduction mixture was filtered and 3.80 g of diethyl mesoxalate was added to the filtrate. The resulting solution was heated under reflux for 30 min, the ethanol evaporated under reduced pressure, and the residual solid recrystallized from ethanol to give 2.0 g (40%) of yellow crystals, mp 94–95°.

Anal. Calcd for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.87; N, 22.57. Found: C, 53.33; H, 4.93; N, 22.50.

Methyl 2,8-Dimethyl-7(8*H*)-pteridinone-6-carboxylate (22).—A solution of 1.0 g of ethyl 2,8-dimethyl-7(8*H*)-pteridinone-6-carboxylate in 25 ml of methanol containing a few crystals of thorium nitrate was heated under reflux for 24 hr and cooled, and the red crystals of the methyl ester were collected by filtration: yield 0.75 g (80%); mp 153–154°; ir 1675 (C_7-C=O), 1725 cm^{-1} (ester); nmr δ 9.41 (s, 1, C_4-H), 3.33 (s, 3, C_2-CH_3).

Anal. Calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.31; H, 4.37; N, 23.86.

2-Phenyl-4-methylamino-6(1*H*)-pyrimidinone (4).—A mixture of 20 g of 2-phenyl-4-amino-6(1*H*)-pyrimidinone[19] and 80 g of methylamine hydrochloride was stirred and heated at 235–240° (internal temperature) for 45 min. The melt was then cooled to about 100°, digested with 150 ml of warm water, and cooled, and the precipitate was collected by filtration, yield 14.7 g (70%), mp 255–257°. The compound was recrystallized for analysis from dimethylformamide; the crude product (containing some 10% of unchanged starting material by nmr) could be used directly in the next step.

Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.67; H, 5.51; N, 20.88. Found: C, 65.50; H, 5.27; N, 20.79.

2-Phenyl-4-methylamino-5-nitro-6(1*H*)-pyrimidinone (6).—To a mixture of 12 ml of fuming nitric acid and 60 ml of glacial acetic acid at 25–30° was added, over a period of 15 min, 10.8 g of

2-phenyl-4-methylamino-6(1*H*)-pyrimidinone. The mixture was stirred for an additional 15 min and then poured into 150 ml of ice–water. The resulting purple solid was collected by filtration, washed well with water, and then recrystallized from aqueous dimethylformamide to give 9.3 g (78%) of cream-colored crystals, mp 330–332° dec.

Anal. Calcd for $C_{11}H_{10}N_4O_3$: C, 53.64; H, 4.09; N, 22.76. Found: C, 53.47; H, 3.96; N, 22.51.

Ethyl 2-Phenyl-8-methyl-7(8*H*)-pteridinone-6-carboxylate (23).—A suspension of 6.0 g of 2-phenyl-4-methylamino-5-nitro-6-(1*H*)-pyrimidinone in 60 ml of phosphorus oxychloride was heated under reflux with stirring for 2.5 hr. A homogeneous solution resulted after about 1 hr of heating. The excess phosphorus oxychloride was removed by distillation under reduced pressure and the residual solid recrystallized from ether to give 4.35 g of 2-phenyl-4-methylamino-5-nitro-6-chloropyrimidine (8). This material was dissolved in 120 ml of 50% aqueous ethanol containing 12 g of magnesium oxide and 2.0 g of Pd/C catalyst and hydrogenated in a Parr apparatus until hydrogen uptake was complete (about 20 min). The reduction mixture was filtered, and to the filtrate was added 4.0 g of diethyl mesoxalate. The mixture was heated under reflux for 30 min and filtered, and the collected colorless solid recrystallized from ethanol to give 2.75 g (58%): mp 203–204°; ir 1690 (C_7-C=O), 1760 cm^{-1} (ester); nmr δ 9.51 (s, 1, C_4-H).

Anal. Calcd for $C_{16}H_{14}N_4O_3$: C, 61.93; H, 4.55; N, 18.06. Found: C, 62.05; H, 4.47; N, 18.15.

Methyl 2-Phenyl-8-methyl-7(8*H*)-pteridinone-6-carboxylate (24).—Heating a solution of 1.0 g of ethyl 2-phenyl-8-methyl-7(8*H*)-pteridinone-6-carboxylate for 24 hr in 100 ml of methanol resulted in the separation of 0.95 g of pure methyl ester: mp 202–203°; ir 1675 (C_7-C=O), 1750 cm^{-1} (ester); nmr δ 9.61 (s, 1, C_4-H).

Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.80; H, 4.08; N, 18.91. Found: C, 60.60; H, 4.20; N, 18.82.

2-Dimethylamino-4-phenyl-6(1*H*)-pyrimidinone (11).—A solution of 46 g (0.17 mol) of dimethylguanidine sulfate in 240 ml of methanol containing 8.5 g (0.37 mol) of sodium was heated under reflux for 30 min, the precipitated sodium sulfate filtered off, and 66 g (0.34 mol) of ethyl benzoylacetate added to the filtrate. The resulting solution was heated under reflux for 18 hr, the excess methanol removed by distillation under reduced pressure, and the semicrystalline residue dissolved in water. The pH was adjusted to 6–7 with acetic acid and the precipitated colorless crystals were collected by filtration, yield 26.7 g (37%), mp 240–241° (acetophenone separated from the filtrate as an oil). Recrystallization of the solid from methanol raised the melting point to 242–243°.

Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.95; H, 6.09; N, 19.52. Found: C, 66.95; H, 6.16; N, 19.80.

2-Dimethylamino-4-phenyl-5-nitroso-6(1*H*)-pyrimidinone (12).—To a solution of 10.5 g of 2-dimethylamino-4-phenyl-6(1*H*)-pyrimidinone in 40 ml of 5 *N* sulfuric acid was added 4.0 g of sodium nitrite dissolved in 15 ml of water. The mixture was stirred at room temperature for 4 hr, solid sodium acetate added to pH 6, and the precipitated solid collected by filtration and washed well with water, yield 11.3 g (92%). The analytical sample melted at 133–134° after recrystallization from ethanol.

Anal. Calcd for $C_{12}H_{12}N_4O_2$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.03; H, 5.07; N, 22.87.

2-Dimethylamino-4-phenyl-5-nitro-6(1*H*)-pyrimidinone (13). Method A.—Aqueous 30% hydrogen peroxide (8 ml) was added dropwise over a period of 1 hr to a stirred solution of 4.0 g of 2-dimethylamino-4-phenyl-5-nitroso-6(1*H*)-pyrimidinone in 40 ml of trifluoroacetic acid.[20] The temperature of the mixture was maintained below 40°. The initial brown solution had become pale yellow after 6 hr of stirring; it was then diluted with 200 ml of cold water and the precipitated solid collected by filtration and washed well with cold water, yield 2.2 g (52%), mp 277–278° dec (after recrystallization from dimethylformamide).

Method B.—To a cooled mixture of 50 ml of glacial acetic acid and 10 ml of fuming nitric acid was added slowly, and with stirring, 10 g of 2-dimethylamino-4-phenyl-6(1*H*)-pyrimidinone; the temperature of the mixture was maintained below 20°. The mixture was stirred at room temperature for 15 min and then poured into 150 ml of ice–water and filtered and the product was washed well with water, yield 9.8 g (75%), mp 274–276° dec.

Anal. Calcd for $C_{12}H_{12}N_4O_3$: C, 55.38; H, 4.65; N, 21.53. Found: C, 55.55; H, 4.72; N, 21.60.

2-Dimethylamino-4-phenyl-5-nitro-6-ethylaminopyrimidine (15).—A mixture of 5.5 g of 2-dimethylamino-4-phenyl-5-nitro-6(1*H*)-pyrimidinone and 55 ml of phosphorus oxychloride was heated under reflux for 2 hr and evaporated under reduced pressure, and the residual crystalline 6-chloro compound 14 was dissolved in 500 ml of ether and filtered (to remove a small amount of insoluble impurity). To the cooled, stirred ether solution was added 60 ml of 30% aqueous ethylamine, and the two-phase system was stirred overnight. The ether layer was evaporated, the aqueous solution was diluted with an additional 100 ml of water, and the precipitated yellow crystals were filtered, washed well with water, and dried, yield 5.5 g (92%), mp 123–125°.

Anal. Calcd for $C_{14}H_{17}N_5O_2$: C, 58.52; H, 5.96; N, 24.38. Found: C, 58.32; H, 5.95; N, 24.62.

Ethyl 2-Dimethylamino-4-phenyl-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (25).—A solution of 4.45 g of 2-dimethylamino-4-phenyl-5-nitro-6-ethylaminopyrimidine in 75 ml of ethanol containing 0.4 g of Pd/C catalyst was hydrogenated in a Parr apparatus at room temperature until hydrogen uptake was complete. The mixture was filtered, the filtrate evaporated to 35 ml, 4.0 g of diethyl mesoxalate added, and the solution then heated under reflux for 2 hr. Cooling resulted in the separation of 3.65 g (74%) of orange crystals, mp 132–134°, which were recrystallized from ethanol: ir 1675 (C_7-C=O), 1740 cm^{-1} (ester).

Anal. Calcd for $C_{19}H_{21}N_5O_3$: C, 62.11; H, 5.76; N, 19.06. Found: C, 62.26; H, 5.73; N, 19.19.

2,6-Bis(methylamino)-4-methyl-5-nitropyrimidine (17), mp 234–235°, was prepared by the procedure described[8] for the preparation of 2,6-bis(ethylamino)-4-methyl-5-nitropyrimidine, except that methylamine was employed instead of ethylamine.

Anal. Calcd for $C_7H_{11}N_5O_2$: C, 42.63; H, 5.62; N, 35.52. Found: C, 42.42; H, 5.69; N, 35.60.

Ethyl 2-Methylamino-4,8-dimethyl-7(8*H*)-pteridinone-6-carboxylate (26).—A suspension of 15.0 g of 2,6-bis(methylamino)-4-methyl-5-nitropyrimidine in 150 ml of ethanol containing 1.8 g of 10% Pd/C catalyst was hydrogenated in a Parr apparatus at room temperature until hydrogen uptake was complete (about 15 min). The catalyst was removed by filtration, and to the filtrate was added 14.5 g of diethyl mesoxalate. The mixture was heated under reflux for 15 min, cooled, and filtered to give 17.0 g (81%) of yellow crystals, mp 220–222°, which were recrystallized from ethanol: ir 1675 (C_7-C=O), 1745 cm^{-1} (ester).

Anal. Calcd for $C_{12}H_{15}N_5O_3$: C, 51.98; H, 5.45; N, 25.26. Found: C, 51.87; H, 5.41; N, 25.32.

The corresponding methyl ester **27**, mp 254–255°, was prepared in the usual manner by transesterification in methanol: nmr δ 2.96 (s, 3, C_2-CH_3).

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.61. Found: C, 50.22; H, 4.95; N, 26.62.

2-Methylamino-4,8-dimethyl-7(8*H*)-pteridinone-6-carboxylic acid (28) was prepared from the ethyl (or methyl) ester by heating for 30 min with 0.1 *N* sodium hydroxide, followed by acidification of the alkaline solution. The free acid was obtained as yellow crystals, mp 259–260° dec, upon recrystallization from dimethylformamide: ir 1765 cm^{-1} (acid); nmr δ 3.07 (s, 3, C_2-CH_3).

Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 48.38; H, 4.52; N, 28.12.

2,4-Bis(methylamino)-5-nitropyrimidine (18), mp 260–261°, was prepared as described[8] for the corresponding 2,4-bis(ethylamino) compound except that methylamine was used instead of ethylamine.

Anal. Calcd for $C_6H_9N_5O_2$: C, 39.34; H, 4.95; N, 38.24. Found: C, 39.58; H, 4.96; N, 38.30.

Ethyl 2-methylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (29) was prepared essentially by the method described[8] for the preparation of ethyl 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate except that the ethanol solution of 2,4-bis(methylamino)-5-aminopyrimidine (from the catalytic reduction) was treated directly with diethyl mesoxalate. The product was obtained as glistening yellow needles, mp 197–198° dec, upon recrystallization from ethanol.

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.61. Found: C, 50.35; H, 5.02; N, 26.48.

The methyl ester **30**, mp 245–246° (from water), was prepared by transesterification in the usual manner by refluxing in methanol with a crystal of thorium nitrate as catalyst: ir 1675 (C_7-C=O), 1750 cm^{-1} (ester); nmr δ 9.00 (s, 1, C_4-H).

Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 48.31; H, 4.44; N, 28.18.

2-Methylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylic acid (31) was prepared from the above methyl ester by heating in 0.5 *N* sodium hydroxide solution for 3 hr, followed by acidification. The free acid, mp 247–248° dec, was recrystallized from dimethylformamide for analysis: ir 1680 (C_7-C=O), 1712 cm^{-1} (acid); nmr δ 9.23 (s, 1, C_4-H).

Anal. Calcd for $C_9H_9N_5O_3$: C, 45.96; H, 3.86; N, 29.78. Found: C, 46.05; H, 3.95; N, 29.72.

Ethyl 2-Methoxy-8-methyl-7(8*H*)-pteridinone-6-carboxylate (32).—A solution of 1.5 g of 2-methoxy-4-methylamino-5-nitropyrimidine[32] in 50 ml of ethanol was reduced under 3 atm of hydrogen, using 5% Pd/C as catalyst. After hydrogen uptake had ceased, the mixture was filtered and 3 ml of diethyl mesoxalate was added to the filtrate. The solution was then heated under reflux for 2 hr and evaporated to a small volume, and 50 ml of water was added to the syrupy residue, whereupon the product separated as a pale yellow solid, mp 99–102°, yield 1.5 g (70%). Recrystallization from water gave white needles: mp 100–102°; ir 1677 (C_7-C=O), 1739 cm^{-1} (ester).

Anal. Calcd for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 49.68; H, 4.52; N, 20.94.

2-Hydroxy-8-methyl-7(8*H*)-pteridinone-6-carboxylic Acid (33). Method A.—A solution of 0.50 g of 2-hydroxy-4-methylamino-5-nitropyrimidine[33] in 50 ml of water containing 2 equiv of sodium hydroxide was reduced under 3 atm of hydrogen, using 5% Pd/C as catalyst, until hydrogen absorption had ceased. The mixture was filtered, 1.0 g of sodium mesoxalate added to the filtrate, and the resulting solution heated under reflux for 2 hr. The mixture was then cooled and hydrochloric acid added to pH 5. Filtration gave 0.46 g (65%) of an orange solid which was purified by reprecipitation from alkaline solution. The pale yellow solid turned green upon heating above 230° and then slowly decomposed without melting up to 320°.

Anal. Calcd for $C_8H_6N_4O_4 \cdot H_2O$: C, 40.00; H, 3.36; N, 23.33. Found: C, 40.32; H, 3.48; N, 23.60.

Method B.—Heating a solution of 0.50 g of ethyl 2-methoxy-8-methyl-7(8*H*)-pteridinone-6-carboxylate in 50 ml of 0.1 *N* sodium hydroxide for 30 min on a steam bath followed by acidification gave 0.40 g (88%) of a yellow solid identical in all respects with the product obtained by method A.

Ethyl 2-Hydroxy-8-methyl-7(8*H*)-pteridinone-6-carboxylate (34).—A solution of 0.50 g of 2-hydroxy-4-methylamino-5-nitropyrimidine in 50 ml of water was reduced as described above, the catalyst removed by filtration, 1.0 ml of diethyl mesoxalate added to the filtrate, and the mixture heated under reflux for 1.5 hr. The reaction mixture was evaporated to dryness under reduced pressure and the residue triturated with water and filtered to give 0.49 g (67%) of a gray solid, mp 253–256° dec. Recrystallization from ethanol gave small brown needles, mp 258–260° dec.

Anal. Calcd for $C_{10}H_{10}N_4O_4$: C, 48.00; H, 4.02; N, 22.39. Found: C, 47.92; H, 4.28; N, 22.62.

Ethyl 2-Amino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (35).—A suspension of 1.60 g of 2-amino-4-methylamino-5-nitropyrimidine[34] in 100 ml of ethanol was reduced under 3 atm of hydrogen, using 5% Pd/C as catalyst, until hydrogen absorption ceased. The reduction mixture was filtered, 3 ml of diethyl mesoxalate added to the filtrate, and the mixture heated under reflux for 1 hr. Evaporation to a small volume under reduced pressure followed by dilution with water and chilling resulted in the crystallization of 1.71 g (72%) of glistening yellow needles, mp 201–203°. Recrystallization from ethanol did not affect the melting point: ir ($HCCl_3$) 1681 (C_7-C=O), 1739 cm^{-1} (ester).

Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 48.18; H, 4.37; N, 28.19.

Methyl 2-Amino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (36).—This compound was prepared from 2-amino-4-methylamino-5-nitropyrimidine and dimethyl mesoxalate as described above, yield 54%, mp (from water) 237°.

Anal. Calcd for $C_9H_9N_5O_3$: C, 45.96; H, 3.86; N, 29.78. Found: C, 46.11; H, 3.84; N, 29.84.

2-Amino-8-methyl-7(8*H*)-pteridinone-6-carboxylic Acid (37).—A suspension of 1.10 g of 2-amino-4-methylamino-5-nitropyrimidine[34] in 80 ml of ethanol was reduced as described above and filtered, and the filtrate was evaporated to dryness. A solution of 1.5 g of sodium mesoxalate in 30 ml of water was added to the residue, and the mixture was heated under reflux for 2 hr. Acidification with hydrochloric acid resulted in the separation of 0.50 g (35%) of a yellow solid which was purified by acidification of a hot solution of the potassium salt. The product was obtained as fine, mustard-yellow needles, mp 258° dec, which then resolidified and remelted at 293–295°: ir 1754 cm^{-1} (acid).

Anal. Calcd for $C_8H_7N_5O_3$: C, 43.44; H, 3.19; N, 31.67. Found: C, 43.18; H, 3.35; N, 31.76.

4-Methylamino-5-nitro-6-dimethylaminopyrimidine (19).—A suspension of 3.0 g of 4-chloro-5-nitro-6-dimethylaminopyrimidine[35] in 50 ml of ethanol was treated with 10 ml of 25% aqueous methylamine. The reaction mixture became warm and the chloropyrimidine dissolved. Evaporation under reduced pressure followed by crystallization of the residue from water gave 1.7 g (58%) of fine, pale yellow needles, mp 101–101.5° (lit.[36] mp 96–97°).

Anal. Calcd for $C_7H_{11}N_5O_2$: C, 42.63; H, 5.62; N, 35.52. Found: C, 42.80; H, 5.79; N, 35.61.

Ethyl 4-Dimethylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (38).—A solution of 4.0 g of 4-methylamino-5-nitro-6-dimethylaminopyrimidine in 100 ml of ethanol was reduced with hydrogen, using 5% Pd/C as catalyst, until rapid hydrogen absorption ceased. The mixture was filtered to remove the catalyst, 8 ml of diethyl mesoxalate was added to the filtrate, and the resulting solution was heated under reflux for 1 hr. Evaporation under reduced pressure to 30 ml, dilution with water, and chilling to 0° resulted in the separation of 4.3 g (76%) of a bright yellow solid, mp 122–123°. Recrystallization from aqueous ethanol gave fine, canary-yellow needles: mp 124–125°; ir ($HCCl_3$) 1667 (C_7-C=O), 1733 cm^{-1} (ester).

Anal. Calcd for $C_{12}H_{15}N_5O_3$: C, 51.98; H, 5.45; N, 25.26. Found: C, 52.18; H, 5.54; N, 25.54.

4-Dimethylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylic Acid (39).—A mixture of 2.0 g of ethyl 4-dimethylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylate, 2 g of sodium hydroxide and 100 ml of water was allowed to stand at room temperature for 14 hr. The resulting solution was carefully acidified with hydrochloric acid. Filtration then gave 1.6 g (89%) of a yellow solid, mp 209–210°. Recrystallization from aqueous ethanol yielded fine, brilliant yellow needles, mp 210–211°. The acid could be sublimed *in vacuo* without decarboxylation: ir ($HCCl_3$) 1761 cm^{-1} (acid).

Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 47.94; H, 4.60; N, 28.22.

4,6-Bis(ethylamino)-5-nitropyrimidine (20).—A solution of 10.0 g of 4,6-dichloro-5-nitropyrimidine in 150 ml of ethanol was treated with an excess of aqueous ethylamine (70%). A vigorous reaction ensued with the separation of 8.2 g (76%) of pale yellow needles, mp 86–87°. Recrystallization from ethanol raised the melting point to 87–88°.

Anal. Calcd for $C_8H_{13}N_5O_2$: C, 45.49; H, 6.20; N, 33.16. Found: C, 45.50; H, 6.39; N, 33.42.

Ethyl 4-Ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (40).—A solution of 2.14 g of 4,6-bis(ethylamino)-5-nitropyrimidine in 100 ml of ethanol was reduced with hydrogen, using 5% Pd/C as catalyst. After hydrogen uptake had ceased, several milliliters of ethanolic hydrogen chloride were added, the mixture filtered, and 3.5 ml of diethyl mesoxalate added to the filtrate. The mixture was heated under reflux for 30 min, the ethanol removed by evaporation under reduced pressure, and the residue triturated with 50 ml of water. Filtration gave 2.30 g (81%) of a yellow-green solid, mp 88–93°. Recrystallization from aqueous ethanol gave long golden-yellow needles: mp 93–95°; ir ($HCCl_3$) 1667 (C_7-C=O), 1733 cm^{-1} (ester).

Anal. Calcd for $C_{13}H_{17}N_5O_3$: C, 53.60; H, 5.88; N, 24.04. Found: C, 53.85; H, 6.02; N, 24.01.

4-Ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic Acid. (41).—A solution of 0.60 g of ethyl 4-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate in 40 ml of water containing 0.6 g of sodium hydroxide was stirred at room temperature overnight, cooled, and acidified with hydrochloric acid. Filtration yielded 0.45 g (83%) of a bright yellow solid, mp 186–189°. Recrystallization from water gave bright yellow needles, mp 191–193°. The acid could be sublimed *in vacuo* without change: ir ($HCCl_3$) 1751 cm^{-1} (acid).

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Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.61. Found: C, 50.32; H, 5.14; N, 26.93.

Ethyl 8-Methyl-7(8*H*)-pteridinone-6-carboxylate (42).—A solution of 2.0 g of 4-methylamino-5-aminopyrimidine[32a] and 5.0 g of diethyl mesoxalate in 10 ml of ethanol was heated under reflux for 2 hr and then diluted with 10 ml of water. Chilling resulted in the separation of 3.5 g (93%) of white needles, mp 115–116°, which were recrystallized from aqueous ethanol: ir (CCl_4) 1695 (C_7-C=O), 1758 cm^{-1} (ester).

Anal. Calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.30; H, 4.52; N, 23.66.

Reduction with Sodium Borohydride. General Procedure.—A solution of 0.01 mol of the 7(8*H*)-pteridinone-6-carboxylate in 20 ml of dimethylformamide was treated with 0.015 mol of sodium borohydride. The resulting mixture was stirred at room temperature for 30 min and diluted with water and the excess sodium borohydride was decomposed by the cautious addition of dilute acetic acid. The precipitated orange solid was collected by filtration, washed well with water, and dried. The dihydro acids were reduced analogously but in 1 *N* sodium hydroxide solution. When solubility permitted, the 3,4-dihydro compounds were recrystallized from hot dimethylformamide.

Methyl 2,8-dimethyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (43): mp 265–266° dec (75% yield); ir 1705 cm^{-1} (ester); nmr δ 2.75 (s, 3, C_2-CH_3), 5.12 (br s, 2, C_4-H) (at −15°).

Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.61; H, 5.19; N, 23.91.

Methyl 2-phenyl-8-methyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (44): mp 210–211° dec (30% yield); ir (1720 cm^{-1} (ester); nmr δ 5.20 (br s, 2, C_4-H) (at −15°).

Anal. Calcd for $C_{15}H_{14}N_4O_3$: C, 60.39; H, 4.73; N, 18.78. Found: C, 60.12; H, 4.96; N, 18.65.

Methyl 2-methylamino-4,8-dimethyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (45): mp 242–244° dec (rapid heating) (90% yield); ir 1700 cm^{-1} (ester); nmr δ 5.00 (q, 1, C_4-H) (at room temperature), 1.66 (d, 3, C_4-CH_3) (at −15°).

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.80; H, 5.70; N, 26.40. Found: C, 49.72; H, 5.86; N, 26.48.

2-Methylamino-4,8-dimethyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylic acid (46): mp 235–237° dec (78% yield); ir 1720 cm^{-1} (acid); nmr δ 5.18 (q, 1, C_4-H), 1.83 (d, 3, C_4-CH_3) (at −15°).

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.22; N, 27.88. Found: C, 47.83; H, 5.09; N, 27.70.

Methyl 2-methylamino-8-methyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (47): mp 278–280° dec (35% yield); ir 1700 cm^{-1} (ester); nmr δ 4.98 (br s, 2, C_4-H) (at −15°).

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.22; N, 27.88. Found: C, 47.76; H, 5.39; N, 27.70.

2-Methylamino-8-methyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylic acid (48): mp 270–272° dec (60% yield); ir 1705 cm^{-1} (acid); nmr δ 4.98 (br s, 2, C_4-H) (at −15°).

Anal. Calcd for $C_9H_{11}N_5O_3$: C, 45.57; H, 4.67; N, 29.53. Found: C, 45.68; H. 4.71; N, 29.58.

Ethyl 2-methoxy-8-methyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (49): mp 267–268° dec (36% yield); ir 1709 cm^{-1} (ester).

Anal. Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.85; H, 5.42; N, 21.00.

8-Methyl-3,4-dihydro-2,7(1*H*,8*H*)-pteridinedione-6-carboxylic acid (50): mp 277–278° dec (70% yield; the same compound was prepared in 71% yield by alkaline hydrolysis of ethyl 2-methoxy-8-methyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate).

Anal. Calcd for $C_8H_8N_4O_4$: C, 42.86; H, 3.60; N, 24.99. Found: C, 43.03; H, 3.49; N, 25.21.

Ethyl 8-methyl-3,4-dihydro-2,7(1*H*,8*H*)-pteridinedione-6-carboxylate (51): mp 305–307° dec (75% yield).

Anal. Calcd for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.68; H, 4.92; N, 22.03.

Catalytic Reduction of Ethyl 2-Ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (52).—To a solution of 0.30 g of 52[8] in 250 ml of ethanol was added 0.2 g of PtO_2 catalyst and the mixture was shaken with hydrogen in a Parr apparatus for 2 hr at room temperature. It was then heated to boiling and filtered, and the filtrate was cooled and filtered to give 0.06 g (19%) of a bright yellow solid, mp 298°, identical with an authentic sample of ethyl 8-ethyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (53) prepared by the reduction of 52 with sodium borohydride.[8,37]

(37) This compound was described as the 5,8-dihydro derivative in the original publication.[8]

The uv spectrum of the filtrate exhibited a maximum at 358 nm, as contrasted with 390 nm for the starting material, and 405 nm for the 3,4-dihydro ester 53. An attempt to isolate this presumed 5,6-dihydro ester 54 by evaporation of the filtrate, however, gave only unchanged ethyl 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (52), mp 142–144°, resulting from rapid air oxidation of the extremely labile 5,6-dihydro derivative 54.

2-Ethylamino-8-ethyl-5,6-dihydro-7(8*H*)-pteridinone-6-carboxylic Acid (57).—A solution of 1.0 g of 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid (55) in 50 ml of water containing 2 equiv of sodium hydroxide was shaken with hydrogen and 5% palladium-on-carbon catalyst until 1 mol of hydrogen had been absorbed. The reduction mixture was filtered and the filtrate was acidified with concentrated hydrochloric acid and then evaporated to dryness under reduced pressure. The residue was triturated with ethanol and filtered to remove sodium chloride. Evaporation of the ethanol filtrate gave a gray-green solid which was dissolved in 10 ml of water. A yellow solid precipitated after a few minutes at 0°. Filtration gave 0.27 g (27%) of a light green solid, mp 175° dec. The product was unstable, for it rapidly turned brown upon standing in the air.

Anal. Calcd for $C_{11}H_{16}N_5O_3$: C, 49.80; H, 5.70; N, 26.40. Found: C, 49.06; H, 5.82; N, 26.70.

2-Ethylamino-8-ethyl-7(8*H*)-pteridinone (58).—A solution of 0.26 g of 2-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid (55) in 10 ml of water containing 1 equiv of sodium hydroxide was shaken with 3 atm of hydrogen, using 5% Pd/C catalyst, until 1 mol of hydrogen had been absorbed. The solution was filtered and 1.0 g of potassium ferricyanide in 10 ml of water was added to the filtrate. After 10 min, the white precipitate which had formed was collected by filtration to give 0.13 g (60%), mp 159–163°. Recrystallization from water raised the melting point to 164–165° (lit.[8] mp 155°).

Ethyl 2-Methoxy-8-methyl-5,6-dihydro-7(8*H*)-pteridinone-6-carboxylate (59).—To a solution of 0.50 g of ethyl 2-methoxy-8-methyl-7(8*H*)-pteridinone-6-carboxylate (32) in 25 ml of glacial acetic acid was added, with stirring, zinc dust until the initial yellow color of the solution had disappeared. The mixture was then filtered to remove excess zinc and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in 5 ml of ethanol, several pieces of ice were added, and the mixture was stirred until crystallization was complete. Filtration gave 0.40 g (80%) of a light yellow solid, mp 133–135°. Recrystallization from water then gave a white, microcrystalline solid, mp 138–139°. It is apparently stable in air but oxidizes extremely rapidly in solution in the presence of a trace of alkali to regenerate the starting material: $\lambda_{max}^{C_2H_5OH}$ 219 nm (log ϵ 4.44), 337 (3.79); ir ($HCCl_3$) 1709, 1739 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.77; H, 5.32; N, 21.25.

Ethyl 4-Dimethylamino-8-methyl-5,6-dihydro-7(8*H*)-pteridinone-6-carboxylate (60).—A solution of 1.2 g of ethyl 4-dimethylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (38) in 100 ml of ethanol was reduced with hydrogen, using 5% Pd/C as catalyst, until 1 mol of hydrogen had been absorbed. The reduction mixture was filtered to remove catalyst and the filtrate concentrated under reduced pressure to approximately 5 ml. Addition of 15 ml of water followed by several pieces of solid carbon dioxide resulted in the crystallization of 1.2 g (100%) of fine white needles, mp 76–78°. This dihydro ester is readily oxidized in solution back to the starting material but may be preserved in the solid state by storage in the absence of oxygen. It is considerably less stable than the corresponding 4-ethylamino derivative described below: $\lambda_{max}^{C_2H_5OH}$ 229 nm (log ϵ 4.26), 286 (3.80), 324 (3.79); ir ($HCCl_3$) 1695, 1739 cm^{-1}.

Anal. Calcd for $C_{12}H_{17}N_5O_3$: C, 51.60; H, 6.14; N, 25.08. Found: C, 51.26; H, 6.27; N, 25.35.

4-Dimethylamino-8-methyl-7(8*H*)-pteridinone (61).—A solution of 0.40 g of 4-dimethylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylic acid (39) in 30 ml of ethanol was reduced with hydrogen, using 5% Pd/C as catalyst, until 1 mol of hydrogen had been absorbed. This solution then exhibited ultraviolet absorption maxima at 260, 267, and 318 nm. Oxygen was bubbled through the reduction solution for 10 min, the ethanol was removed by evaporation under reduced pressure, and the residue was triturated with cold water. Filtration gave 0.26 g (79%) of fine pale green needles, mp 161–163°. The material was purified by sublimation at 140° (0.05 mm), followed by crystallization from ethanol, and was obtained as fine white needles, mp 161–163° (lit.[36] mp 159–161°). The product exhibited ultraviolet absorp-

tion maxima at 211, 232, 246, 264, 303, and 356 nm. Catalytic reduction of this compound in ethanol solution, using Pd/C catalyst, resulted in the uptake of 1 mol of hydrogen. The uv spectrum of this reduction solution was identical with the spectrum given by the reduction solution of the carboxylic acid, indicating that decarboxylation had apparently accompanied reduction of the latter. 4-Dimethylamino-8-methyl-5,6-dihydro-7(8*H*)-pteridinone was too readily oxidized by air to permit isolation and characterization as a solid.

Anal. Calcd for $C_9H_{11}N_5O$: C, 52.67; H, 5.40; N, 34.13. Found: C, 52.98; H, 5.61; N, 34.06.

Ethyl 4-Ethylamino-8-ethyl-5,6-dihydro-7(8*H*)-pteridinone-6-carboxylate (62).—A solution of 1.0 g of ethyl 4-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylate (**40**) in 50 ml of ethanol was reduced with hydrogen, using 5% Pd/C as catalyst, until 1 mol of hydrogen had been absorbed. The resulting colorless solution was filtered, the filtrate was evaporated to dryness under reduced pressure, and the residue was dissolved in water. Chilling resulted in the separation of 1.0 g (100%) of small white plates, mp 129–131°. Recrystallization from aqueous ethanol raised the melting point to 132–133.5°. This dihydro ester was readily oxidized in solution by air back to the starting material, but the solid was more stable and could be preserved without difficulty by storing in the absence of oxygen: $\lambda_{max}^{C_2H_5OH}$ 216 nm (log ϵ 4.32), 228 sh (4.25), 275 (3.89), 317 (3.70); ir ($HCCl_3$) 1689, 1742 cm^{-1}.

Anal. Calcd for $C_{13}H_{19}N_5O_3$: C, 53.23; H, 6.53; N, 23.88. Found: C, 53.42; H, 6.62; N, 23.68.

4-Ethylamino-8-ethyl-7(8*H*)-pteridinone (63).—A solution of 0.20 g of 4-ethylamino-8-ethyl-7(8*H*)-pteridinone-6-carboxylic acid (**41**) in 20 ml of ethanol was reduced with hydrogen, using 5% Pd/C as catalyst, until 1 mol of hydrogen had been absorbed. This solution exhibited uv maxima at 215, 276, and 317 nm. Evaporation of the ethanol, addition of water to the residue, and filtration give 0.10 g (60%) of a white solid, mp 126.5–127.5°, which exhibited uv maxima at 226, 259, and 353 nm in ethanol solution. Isolation of this material is facilitated if oxygen is bubbled through the reduction solution prior to evaporation. Catalytic reduction of this compound in ethanol solution, using Pd/C catalyst, resulted in the uptake of 1 mol of hydrogen. The uv spectrum of this reduction solution was identical with the spectrum of the reduction solution of the carboxylic acid. However, 4-ethylamino-8-ethyl-5,6-dihydro-7(8*H*)-pteridinone could not be isolated because of the ease with which it is reoxidized by air to 4-ethylamino-8-ethyl-7(8*H*)-pteridinone (**63**).

Anal. Calcd for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.95. Found: C, 55.05; H, 6.08; N, 31.70.

2-Amino-8-ethyl-4,7(3*H*,8*H*)-pteridinedione (67).—A solution of 1.0 g of 2-amino-8-ethyl-4,7(3*H*,8*H*)-pteridinedione-6-carboxylic acid (**64**)[21] in 100 ml of water containing 0.6 g of potassium hydroxide was reduced under 3 atm of hydrogen, using 5% Pd/C as catalyst. After 4 hr, the catalyst was removed by filtration and the filtrate treated with a solution of potassium ferricyanide until the color persisted. The solid which precipitated was collected by filtration, washed well with water, and dried to give 0.7 g (78%), mp >300°. An alkaline solution of this material exhibited a bright blue fluorescence. Recrystallization from aqueous ethanol gave colorless plates. The same product was formed in lower yield and more slowly when the reduction mixture was acidified with acetic acid rather than treated with potassium ferricyanide solution.

Anal. Calcd for $C_8H_9N_5O_2 \cdot H_2O$: C, 42.66; H, 4.92; N, 31.10. Found: C, 42.90; H, 5.18; N, 30.94.

2-Ethylamino-8-ethyl-3,4-dihydro-7(8*H*)-pteridinone (69).—2-Ethylamino-8-ethyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylic acid[8] (1 g) was heated for 3 days at 175° under vacuum (0.1 mm). The sublimate (0.3 g) was identified as 2-ethylamino-8-ethyl-7(8*H*)-pteridinone by comparison with an authentic sample.[8] The orange-yellow residue was repeatedly recrystallized from water with the use of a small amount of decolorizing charcoal to give 0.3 g (36%) of glittering orange-yellow crystals: mp 243–244°; λ_{max}^{pH7} 242 nm (log ϵ 3.76), 280 (3.54), 390 (4.26); pK_a = 3.75 ± 0.04.

Anal. Calcd for $C_{10}H_{15}N_5O$: C, 54.28; H, 6.83; N, 31.66. Found: C, 53.96; H, 6.66; N, 31.78.

2-Amino-3,8-dimethyl-6-carbomethoxy-7-oxo-7,8-dihydropteridinium Tosylate (70).—A mixture of 0.50 g of methyl 2-amino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (**36**) and 10 ml of methyl *p*-toluenesulfonate was heated for 1 hr at 120°, cooled, and filtered. The collected solid was washed well with ether and then dried at 100°, yield 0.72 g (81%), mp 233°. The analytical sample was prepared by dissolution of the above solid in methanol followed by precipitation by addition of ether: nmr δ 4.17 (s, 3, N^+-CH_3), 9.03 (s, 1, C_4-H).

Anal. Calcd for $C_{10}H_{12}N_5O_3 \cdot C_7H_7SO_3$: C, 48.45; H, 4.55; N, 16.62; OCH_3, 7.37. Found: C, 48.19; H, 4.65; N, 16.42; OCH_3, 7.58.

2-Amino-3,8-dimethyl-6-carbethoxy-7-oxo-7,8-dihydropteridinium Tosylate (71).—A mixture of 0.70 g of ethyl 2-amino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (**35**) and 14 g of methyl *p*-toluenesulfonate was heated for 1.5 hr at 120°, and the fine colorless needles which had separated were collected by filtration (hot) and washed well with ether, yield 0.80 g (66%), mp 245°. An additional 0.25 g of product, mp 240°, was obtained by cooling of the filtrate followed by filtration. The analytical sample, mp 245°, was prepared in the form of colorless, silky needles by recrystallization from ethanol: nmr δ 4.2 (s, 3, N^+-CH_3), 9.00 (s, 1, C_4-H).

Anal. Calcd for $C_{11}H_{14}N_5O_3 \cdot C_7H_7SO_3$: C, 49.65; H, 4.86; N, 16.09; OC_2H_5, 10.13. Found: C, 49.67; H, 4.79; N, 15.84; OC_2H_5, 10.91.

2-Methylamino-3,8-dimethyl-6-carbomethoxy-7-oxo-7,8-dihydropteridinium Tosylate (72).—In the same manner as described above, methyl 2-methylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (**30**) was methylated by heating with methyl *p*-toluenesulfonate: yield 75%; mp (by precipitation from methanol solution with ether) 246°; nmr δ 4.13 (s, 3, N^+-CH_3), 9.05 (s, 1, C_4-H).

Anal. Calcd for $C_{11}H_{14}N_5O_3 \cdot C_7H_7SO_3$: C, 49.65; H, 4.86; N, 16.09; OCH_3, 7.13. Found: C, 49.80; H, 4.80; N, 15.89; OCH_3, 7.30.

2-Methylamino-3,8-dimethyl-6-carbethoxy-7-oxo-7,8-dihydropteridinium Tosylate (73).—This compound was prepared as described above from ethyl 2-methylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (**29**) and methyl *p*-toluenesulfonate: yield 73%; mp (from methanol) 249°; nmr δ 4.1 (s, 3, N^+-CH_3), 9.01 (s, 1, C_4-H).

Anal. Calcd for $C_{12}H_{16}N_5O_3 \cdot C_7H_7SO_3$: C, 50.78; H, 5.16; N, 15.58; OC_2H_5, 9.81. Found: C, 50.50; H, 5.11; N, 15.65; OC_2H_5, 11.10.

Methyl 2-Amino-3,8-dimethyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (74).—To a suspension of 0.27 g of **70** in 10 ml of ethanol was added 0.15 g of sodium borohydride, and the mixture was diluted with 10 ml of water and stirred at room temperature for 12 hr. The yellow needles which had separated were collected by filtration, washed well with ether, and dried to give 0.12 g (75%), mp 230–233°. The analytical sample, mp 240°, was prepared by recrystallization first from water and then from methanol: nmr (in DMSO-d_6) δ 2.96 (s, 3, N_3-CH_3), 4.36 (s, 2, C_4-CH_2).

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.22; N, 27.88. Found: C, 47.63; H, 5.33; N, 27.59.

Ethyl 2-Amino-3,8-dimethyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (75).—To a solution of 0.20 g of 71 in 10 ml of water was added 0.10 g of sodium borohydride. The solution foamed slightly and turned yellow. After a few minutes a yellow solid started to separate. The mixture was stirred at room temperature for 3 hr and filtered, and the collected solid was washed well with ether and dried to give 0.12 g (96%), mp 181°. The analytical sample was prepared in the form of yellow, silky needles, mp 194°, by recrystallization from ethanol: nmr (in DMSO-d_6) δ 2.97 (s, 3, N_3-CH_3), 4.36 (s, 2, C_4-CH_2).

Anal. Calcd for $C_{11}H_{15}N_5O_3 \cdot {}^1/_2H_2O$: C, 48.52; H, 5.91; N, 25.37. Found: C, 48.22; H, 5.89; N, 25.56.

Methyl 2-Methylamino-3,8-dimethyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (76).—A solution of 0.50 g of **72** and 0.10 g of sodium borohydride in 20 ml of methanol was stirred at room temperature for 30 min and evaporated to dryness, and the residue was triturated with 10 ml of water. Filtration then gave 0.30 g of a yellow solid which was dissolved in 10 ml of hot water; neutralization with a few drops of hydrochloric acid and cooling gave 0.20 g (66%) of yellow needles, mp 233°. The analytical sample, mp 240°, was prepared by recrystallization from methanol: nmr (in DMSO-d_6) δ 2.93 (s, 3, N_3-CH_3), 4.31 (s, 2, C_4-CH_2).

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.80; H, 5.70; N, 26.40. Found: C, 49.77; H, 5.61; N, 26.24.

Ethyl 2-Methylamino-3,8-dimethyl-3,4-dihydro-7(8*H*)-pteridinone-6-carboxylate (77).—To a suspension of 1.1 g of **73** in 50 ml of ethanol was added 0.5 g of sodium borohydride. The mixture foamed slightly and turned greenish yellow and the

suspended solid dissolved. Dilution with 150 ml of water, followed by evaporation under reduced pressure to a small volume, cooling, and filtering gave 0.7 g (97%) of yellow needles, mp 201°. The analytical sample, mp 213°, was prepared by recrystallization from water: nmr (DMSO-d_6) δ 2.94 (s, 3, N_3-CH_3), 4.32 (s, 2, C_4-CH_2).

Anal. Calcd for $C_{12}H_{17}N_5O_3$: C, 48.47; H, 6.44; N, 23.56. Found: C, 48.57; H, 6.13; N, 23.88.

3,8-Dimethylisoxanthopterincarboxylic Acid Ethyl Ester (78).—A solution of 0.108 g of 2-amino-3,8-dimethyl-6-carbethoxy-7-oxo-7,8-dihydropteridinium tosylate (71) and 0.165 g of potassium ferricyanide in 27 ml of pH 7 buffer was stirred at room temperature for 4 days and the light yellow precipitate was collected by filtration, washed with ether, and dried, yield 0.033 g (49%), mp 305° (lit.[28] mp 308°). The product was identical (tlc) with an authentic sample of 3,8-dimethylisoxanthopterincarboxylic acid ethyl ester, and its uv spectrum was also in agreement with published data: λ_{max}^{pH6} 266 nm (log ϵ 3.92), 290 (3.87), 375 (4.38) [lit.[28] 265 (3.94), 289 (3.81), 374 (4.38)].

Dimroth Rearrangement of 2-Amino-3,8-dimethyl-6-carbethoxy-7-oxo-7,8-dihydropteridinium Tosylate (71).—A solution of 75 mg of 71 in 10 ml of saturated sodium bicarbonate solution was stirred at room temperature for 3 hr, and the bright yellow solid which had separated was collected by filtration, washed well with water, and dried, yield 19 mg (42%), mp 197–198°. The product was identical with an authentic sample of ethyl 2-methylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylate (29).

Heating 100 mg of 71 in 10 ml of pH 9 buffer under reflux for 20 min, followed by acidification, gave 25 mg (46%) of 2-methylamino-8-methyl-7(8*H*)-pteridinone-6-carboxylic acid (31), identical in every respect with an authentic sample.

Registry No.—4, 31937-01-6; 5, 31937-02-7; 6, 31937-03-8; 11, 31937-04-9; 12, 31937-05-0; 13, 31937-06-1; 15, 31937-07-2; 17, 31937-08-3; 18, 5177-26-4; 20, 31937-10-7; 21, 31937-11-8; 22, 31937-12-9; 23, 31937-13-0; 24, 31937-14-1; 25, 31937-15-2; 26, 31937-16-3; 27, 31937-17-4; 28, 31937-18-5; 29, 31937-19-6; 30, 31937-20-9; 31, 31937-21-0; 32, 2046-74-4; 33, 2046-73-3; 34, 2046-72-2; 35, 2539-49-3; 36, 31937-26-5; 37, 2046-69-7; 38, 2046-68-6; 39, 2235-77-0; 40, 2046-67-5; 41, 2235-76-9; 42, 2047-23-6; 43, 31934-03-9; 44, 31934-04-0; 45, 31934-05-1; 46, 31934-06-2; 47, 31981-27-8; 48, 31934-07-3; 49, 31934-08-4; 50, 31934-09-5; 51, 31934-10-8; 52, 2144-73-2; 53, 31934-12-0; 57, 31934-13-1; 59, 1471-66-5; 60, 1471-87-0; 61, 1639-38-9; 62, 1471-67-6; 63, 1471-81-4; 67, 31934-17-5; 69, 31934-18-6; 70, 31934-19-7; 71, 31981-30-3; 72, 31981-31-4; 73, 31934-20-0; 74, 31934-21-1; 75, 31934-22-2; 76, 31934-23-3; 77, 31934-24-4.

Synthesis of the 1,4-Dihydropyrazine Ring System. A Stable 8-π-Electron Heterocycle

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A previous report on the synthesis of the 1,4-dihydropyrazine ring system by the reaction of carboxylic anhydrides with dihydropyrazine 4 has been shown to be incorrect. The tetrahydropyrazine 6 is the product of this reaction. A stable dihydropyrazine 5a has been prepared from 4 using acetyl chloride. Chemical reactions and physical properties of this 8-π-electron heterocycle are reported.

It has been known since the last century that certain conjugated cyclic molecules, such as benzene, possess unusual properties not consistent with those of simple open-chain conjugated olefins. However, it remained until the 1930's with the advent of quantum mechanics, for a theoretical understanding of these molecules to be developed. Now, due initially to the investigations of Hückel,[1] conjugated cyclic molecules can be divided into two groups. The first group contains molecules possessing $(4n + 2)$ π electrons (where $n = 0, 1, 2, \ldots$). Those molecules are predicted to have additional stability due to the cyclic delocalization of π electrons and should display aromatic properties analogous to benzene. Considerable research effort in recent years has verified this original prediction.[2]

The second group consists of molecules containing $4n$ π electrons (where $n = 1, 2, 3 \ldots$) which were originally predicted not to be stabilized by the cyclic delocalization of π electrons. Therefore, molecules in this group were designated simply as nonaromatic. The best and most classical representative of this group is cyclooctatetraene which behaves as a cyclic polyene.

Molecules containing $4n$ π electrons where the cyclic delocalization of π electrons can occur have recently attracted attention. Simple HMO theory predicts that monocyclic molecules containing $4n$ π electrons should possess zero delocalization. Since some delocalization is predicted for the open-chain analogs containing $4n$ π electrons, the cyclic compared to the noncyclic structures are actually destabilized. For this reason cyclic molecules containing $4n$ π electrons have been designated as antiaromatic.[3]

Most work on the concept of antiaromaticity has been concerned with electronic systems containing 4 π electrons. However, antiaromaticity should also be observed in molecules containing 8 π electrons *if* electron delocalization can occur.

Cyclooctatetraene, 1*H*-azepine, and 1,4-dihydropyrazine potentially all contain 8 π electrons. Since the π overlap of two p orbitals is proportional to cos θ (where θ = angle between the axis bisecting each p orbital),[4] molecular models indicate that little delocalization should occur in cyclooctatetraene. The smaller seven-membered 1*H*-azepine ring is more planar and more delocalization should be possible compared to cyclooctatetraene. However, molecular models indi-

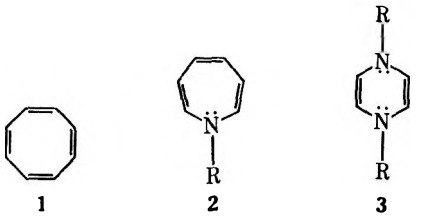
(1) (a) E. Hückel, *Z. Phys.*, **70**, 204 (1931); (b) *Z. Electrochem.*, **43**, 752 (1937).

(2) J. P. Snyder, "Nonbenzenoid Aromatics," Academic Press, New York, N. Y., and London, 1969.

(3) (a) R. Breslow, J. Brown, and J. Grajewski, *J. Amer. Chem. Soc.*, **89**, 4383 (1967); (b) R. Breslow, *Angew. Chem., Int. Ed. Engl.*, **7**, 565 (1968).

(4) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., and London, 1961, p 16.

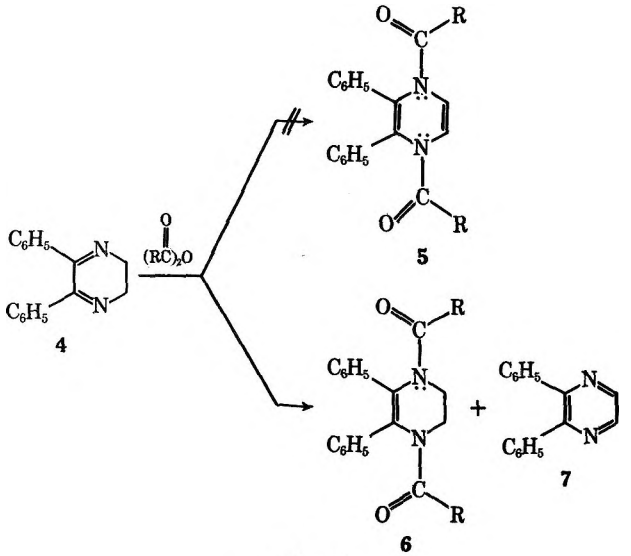
cate that the magnitude of this delocalization still must be small and it is unlikely that there is a large degree of antiaromatic character associated with 1*H*-azepine.[5] In contrast to cyclooctatetraene and 1*H*-azepine, molecular models indicate that the 1,4-dihydropyrazine ring system is nearly planar and that substantial delocalization of π electrons can occur. Clearly, the 1,4-dihydropyrazine ring system would be a suitable model for a study of antiaromaticity in 8-π-electron molecules.



1 2 3

The 1,4-dihydropyrazine ring system is reported in the older literature to be a known structure. Because of our interest in this ring system as a potential synthetic intermediate for the preparation of large heterocyclic molecules, we have repeated what would appear to be the most plausible syntheses. We have been unable to reconfirm any of these earlier claims.[6]

One logical approach to the 1,4-dihydropyrazine ring system has been reported by Mason and Dryfoos.[7] They state that when 2,3-diphenyl-5,6-dihydropyrazine is heated with either acetic or benzoic anhydride a derivative of the 1,4-dihydropyrazine ring system is produced. The melting points of the products from these reactions that we obtain, in addition to an equivalent amount of 2,3-diphenylpyrazine, are consistent with those originally reported. However, the nmr spectrum and elemental analysis are not in agreement with the proposed structures. The elemental analysis of the



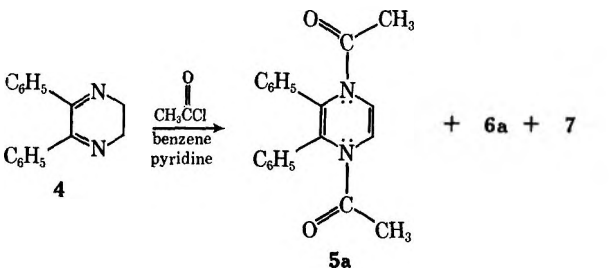
4 5 6 7

a, R = CH_3
b, R = C_6H_5

product from the reaction of **4** with acetic anhydride suggests a formula $C_{20}H_{20}N_2O_2$ which contains two additional hydrogens compared to **5a**. This is confirmed by the nmr spectrum, which shows a four-hydrogen singlet at τ 5.90. We conclude from this data that the product must possess the 1,4,5,6-tetrahydropyrazine structure **6a**. Although the mechanism for the formation of **6** is unknown, it is likely that an intermediate leading to **5** is reduced by the 5,6-dihydropyrazine **4** to **6**. This would also explain the formation of 1 equiv of 2,3-diphenylpyrazine.

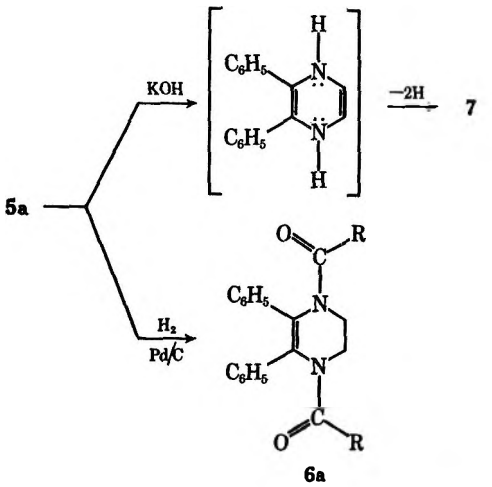
We have prepared what we believe to be the first characterized derivative of the 1,4-dihydropyrazine ring system[8] by the slow addition of acetyl chloride to 5,6-dihydropyrazine **4** in benzene containing 2 equiv of pyridine. In addition to a 30% yield of **5a**, **6a** and **7** are also produced. The nmr spectrum shows olefinic hydrogens occurring as a two-hydrogen singlet at τ 3.15. Hydrolysis of **5a** with potassium hydroxide in diethylene glycol gave 2,3-diphenylpyrazine. This reaction probably involves the intermediate dihydropyrazine, which is rapidly oxidized in air. An attempt to carry out the hydrolysis at $-20°$ using methyllithium and working up the reaction in an inert atmosphere gave only a small quantity of pyrazine **7** and a red polymer.

Confirmation of the proposed structure was obtained by catalytic hydrogenation (Pd/C). This resulted in



4 5a

the rapid uptake of 1 mol of hydrogen with the formation of 1,4,5,6-tetrahydropyrazine **6a** previously prepared from **4** and acetic anhydride.

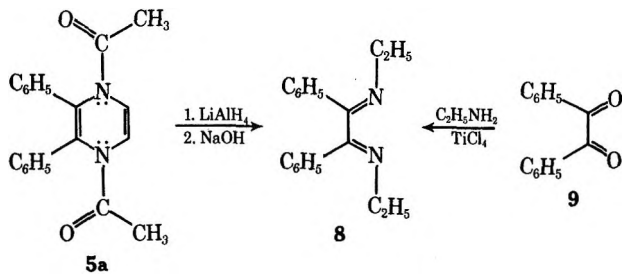


5a 6a 7

Reduction of **5a** with lithium aluminum hydride did not give the expected *N*,*N*′-diethyl derivative. The major product was *N*,*N*′-diethylbenzilimine **8**, in addition to a small amount of pyrazine **7** and benzil which was probably formed by hydrolysis of **8** in the work-up procedure. The structure of **8** was indicated by the

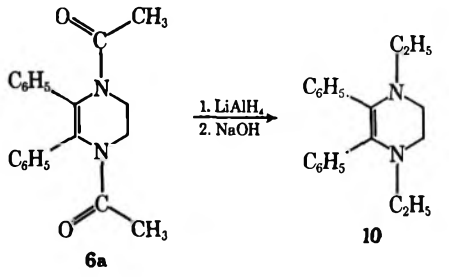
(5) L. A. Paquette in "Nonbenzenoid Aromatics," J. P. Snyder, Ed., Academic Press, New York, N. Y., 1969, p 250.
(6) S.-J. Chen and F. W. Fowler, *J. Org. Chem.*, **35**, 3987 (1970).
(7) A. T. Mason and L. Dryfoos, *J. Chem. Soc.*, **63**, 1293 (1893).
(8) After this work was written up for publication, another report of a 1,4-dihydropyrazine derivative appeared: R. A. Sulzbach and A. F. M. Agbal, *Angew. Chem., Int. Ed. Engl.*, **10**, 127 (1971).

spectral data and chemical analysis. The structure was confirmed by independent synthesis.[9]



5a 8 9

The unusual course of this reduction is probably due to the presence of the completely conjugated π system, since the reduction of partially hydrogenated ring systems (**6a**) occurs normally.

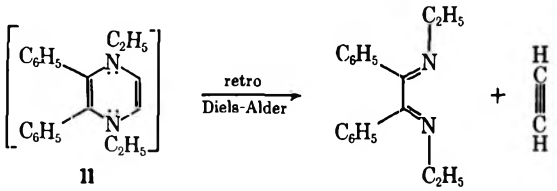


6a 10

It is possible that the *N,N'*-diethyl-1,4-dihydropyrazine ring system **11** is being formed in the reaction but is extremely reactive, decomposing to give imine **8**. Instability of **11** would be expected compared to the diacetyl derivative **5**, since the ethyl groups would allow the nonbonding electrons on nitrogen to interact with the π system. Even with azepine the *N*-methyl derivative is extremely reactive and it can only be isolated at low temperatures.

Attempts to carry out the reduction at lower temperature changed the course of the reaction completely. Only 2,3-diphenylpyrazine could be isolated. Also, carrying out the reaction in the more polar tetrahydrofuran gave only 2,3-diphenylpyrazine.

Although imine **8** could be explained as being the product from a retro Diels–Alder reaction of **11**, all attempts to detect acetylene in this reaction have been unsuccessful.



11

Dihydropyrazine **5a** does not undergo thermal cycloadditions with either dimethyl acetylenedicarboxylate or tetracyanoethylene. An attempted photochemical cycloaddition between **5a** and dimethyl acetylene dicarboxylate gave 2,3-diphenylpyrazine as the only isolable product.

In summary, dihydropyrazine **5a**, which has strong electron-withdrawing substituents on the nitrogen, does not appear to possess any significant antiaromatic character.

(9) H. Weingarten, J. P. Chupp, and W. A. White, *J. Org. Chem.*, **32**, 3246 (1967).

Experimental Section[10]

2,3-Diphenyl-1,4-dibenzoyl-1,4,5,6-tetrahydropyrazine (6b).—A mixture of 2.34 g (0.01 mol) of 2,3-diphenyl-5,6-dihydropyrazine (**4**) with 4.52 g (0.02 mol) of benzoic anhydride, in the proportion of 1 mol to 2 was heated over a naked flame under diminished pressure (20–30 mm). The mixture was slowly brought to boiling, and, after being allowed to cool, it was dissolved in hot alcohol and left overnight. A yellow solid was removed by filtration. The solvent was stripped from the filtrate, the residue was dissolved in ether, and the crystals formed were recrystallized from ethanol: mp 192–195°; yield 0.846 g; nmr ($CDCl_3$) τ 2.55–2.75 (m, 20 H), 5.7 (s, 4 H); ir (KBr) 2929, 1660 (C=O), 1470, 1380, 725, and 700 cm^{-1}.

Anal. Calcd for $C_{30}H_{24}N_2O_2$: C, 81.06; H, 5.44; N, 6.30. Found: C, 80.99; H, 5.42.

2,3-Diphenyl-1,4-diacetyl-1,4,5,6-tetrahydropyrazine (6a).—2,3-Diphenyl-5,6-dihydropyrazine (10 g) was heating to boiling under reduced pressure (20–30 mm), and allowed to cool to about 100°; 10 g (0.98 mol) of acetic anhydride was then added, and the mixture was boiled in a reflux apparatus for 15 min. The product was digested on a water bath with 10% sodium hydroxide solution until the excess of anhydride was decomposed. The residue was dissolved in ethanol and the yellow solid was removed by filtration. The solvent was stripped from the filtrate, and the residue was chromatographed on tlc plate (1.5 mm silica gel, eluted with ether). The first band eluted was recrystallized from ethanol, giving 2,3-diphenylpyrazine: nmr ($CDCl_3$) τ 1.41 (s, 2 H), 2.4–2.8 (m, 10 H); mp 113–115° (lit.[11] 112–116°). The second band eluted was recrystallized from ethyl acetate: mp 131–132°; nmr ($CDCl_3$) τ 2.52–2.92 (m, 10 H), 5.9 (s, 4 H), and 8.2 (s, 6 H); ir (KBr) 1660 (C=O), 1385, 1300, 1225 cm^{-1}.

Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.97; H, 6.29; N, 8.74. Found: C, 74.95; H, 6.53; N, 8.72.

2,3-Diphenyl-1,4-diacetyl-1,4-dihydropyrazine (5a).—To a mixture of 3.16 g (0.04 mol) of pyridine and 3.95 g (0.05 mol) of acetyl chloride in refluxing benzene stirred with magnetic stirrer was slowly added over 3 hr 4.68 g (0.02 mol) of 2,3-diphenyl-5,6-dihydropyrazine in 30 ml of chloroform, and the mixture refluxed for 12 hr. The reaction mixture was cooled and washed thoroughly with water. The organic layer was dried with magnesium sulfate, the solvent was stripped off, and the residue was chromatographed on tlc (1.5 mm silica gel, eluted with ether). The first band gave a compound possessing an nmr spectrum identical with that of 2,3-diphenylpyrazine (**7**) from previous work. The second band was crystallized from ethanol and from ethyl acetate and gave **5a**: mp 194–195°; nmr ($CDCl_3$) τ 2.54–2.92 (m, 10 H), 3.12 (s, 2 H), and 8.20 (s, 6 H); ir (KBr) 1680 (C=O), 1624, 1380, 780, and 700 cm^{-1}.

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.12; H, 5.99; N, 8.56.

The third band gave 2,3-diphenyl-1,4-diacetyl-1,4,5,6-tetrahydropyrazine (**6a**). The relative yield of each compound **4**, **5a**, and **6a** was determined to be 34:32:34 from the nmr spectrum of the crude product. Pure **5a** can more conveniently be prepared by recrystallizing the crude product several times from ethyl acetate–ethanol (7:5).

Hydrogenation of 2,3-Diphenyl-1,4-diacetyl-1,4-dihydropyrazine (5a).—2,3-Diphenyl-1,4-diacetylpyrazine (0.136 mg) was added to a solution with 0.02 g of 10% Pd/C in 20 ml of ethyl acetate. The mixture was subjected to microhydrogenation at room temperature for up to 2 hr. The nmr spectrum showed 90% conversion to 2,3-diphenyl-1,4-diacetyl-1,4,5,6-tetrahydropyrazine (**6a**).

Alkali Hydrolysis of 5a.—2,3-Diphenyl-1,4-diacetylpyrazine (0.318 g) and 0.5 g of potassium hydroxide was added to 11 ml of diethylene glycol and refluxed for 1.5 hr. The reaction mixture was cooled to room temperature, extracted with ether, and washed thoroughly with water. The ethereal solution was evaporated and the residue was crystallized from *n*-pentane, mp 112–116°; nmr ($CDCl_3$) shows this to be pyrazine **7**.

Reduction of 5a.—To 0.3 g of lithium aluminum hydride in 21 ml of anhydrous ether was slowly added 0.478 g (0.0015 mol) of 2,3-diphenyl-1,4-diacetylpyrazine (**5a**) and the mixture was

(10) Melting points are uncorrected. The microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were determined with a Perkin-Elmer Model 137 Infracord. The nmr spectra were determined with a Varian A-60 spectrophotometer.

(11) L. H. Amundsen, *J. Chem. Educ.*, **16**, 567 (1939).

stirred for 1 hr. The reaction mixture was cooled in an ice bath and 3 ml of 20% sodium hydroxide solution was carefully added. Stirring was continued for another hour at room temperature and the white precipitate was removed by filtration. The filtrate was dried with magnesium sulfate and the ether was removed. Chromatography of the residue on a thin layer plate (1.5 mm silica gel eluted with 10% ether in benzene) gave 0.119 g of benzil (yield 37%), nmr ($CDCl_3$) τ 1.9–2.8 (only aromatic hydrogens), mp 94–95° (lit.[12] 94°), and 0.177 g of 2,3-diphenyl-1,4-diethyl-1,4-diaza-1,3-butadiene (**8**): yield 44%; mp 37–39°; nmr ($CDCl_3$) τ 2.1–2.35 and 2.55–2.85 (m, 10 H), 3.61 (q, 4 H), and 8.75 (t, 6 H); ir (KBr) 1630, 1580, 1450, 775, and 700 cm^{-1}. A small amount of 2,3-diphenylpyrazine (0.022 g) is also produced.

1,4-Diethyl-2,3-diphenyl-1,4-diaza-1,3-butadiene (8).—The method of imine synthesis by Weingarten[9] was modified as described below.

Benzil (4.2 g, 0.02 mol) was placed in a 250-ml flask and mixed with a solution of 100 ml of ether containing 15 ml of anhydrous ethylamine at −10°. A solution of 20 ml of pentane containing 3.6 ml of $TiCl_4$ (6.2 g, 0.0326 mol) was then added over 45 min. After all of the $TiCl_4$ was added, the material was allowed to warm up to room temperature over 1 hr, then heated to reflux for 0.5 hr. The solvent was removed and 4.0 g of **8** was obtained (76% yield). The analytical sample was purified by recrystallization from ether: mp 37–39°; nmr ($CDCl_3$) τ 2.1–2.35 and 2.55–2.85 (m, 10 H), 3.61 (q, 4 H), and 8.75 (t, 6 H); ir (KBr) 1630, 1580, 1450, 775, and 700 cm^{-1}.

Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.77; H, 7.63; N, 10.60. Found: C, 81.61; H, 7.77; N, 10.62.

Reduction of 6a.—To 0.3 g of lithium aluminum hydride in 21 ml of anhydrous ether was slowly added 0.48 g (0.0015 mol) of 2,3-diphenyl-1,4-diacetyl-1,4,5,6-tetrahydropyrazine (**6a**) and the mixture was stirred for 1 hr. The reaction mixture was cooled in an ice bath and 3 ml of 20% sodium hydroxide was carefully added. Stirring was continued for another hour at room temperature and the white precipitate was removed by filtration. The filtrate was dried with magnesium sulfate and the ether was removed. The residue was crystallized on standing and recrystallized from ethyl acetate: mp 100–102°; 0.43 g (98% yield); nmr ($CDCl_3$) τ 2.65–3.06 (m, 10 H), 7.03 (s, 4 H), 7.33 (q, 4 H), and 9.0 (t, 6 H); ir (KBr) 2970, 2850, 1590, 1445, 1380, 1128, 755, and 700 cm^{-1}.

Anal. Calcd for $C_{20}H_{24}N_2$: C, 82.14; H, 8.27; N, 9.58. Found: C, 82.28; H, 8.43.

Registry No.—**5a**, 32174-84-8; **6a**, 32174-85-9; **6b**, 32174-86-0; **7**, 1588-89-2; **8**, 32174-88-2; **10**, 32174-89-3.

Acknowledgment.—We are indebted to the Research Foundation of the State University of New York, The Research Corporation, and the National Science Foundation (GP-20099) for financial support of this work.

(12) "Handbook of Chemistry and Physics," 40th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1958–1959, p 844.

Reactions of Phosphorus Compounds. 28. Mechanism of the Formation of 2-Methyl-2*H*-1-benzopyran by the Reaction of 3-(o-Formylphenoxy)propylphosphonium Salts in Alcoholic Alkoxide

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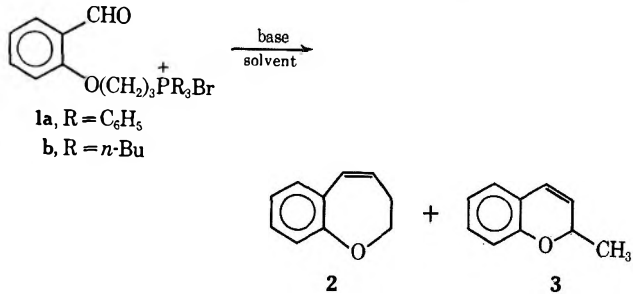
Received May 4, 1971

A mechanism is proposed for the formation of 2-methyl-2*H*-1-benzopyran (**3**) by the reaction of 3-(o-formylphenoxy)propylphosphonium salts (**1**) in alcoholic alkoxide. 2,3-Dihydro-1-benzoxepin-4-tri-*n*-butylphosphonium bromide (**17b**) and 2-methyl-2*H*,1-benzopyran-3-triphenylphosphonium bromide (**15a**) were prepared using catalytic amounts of base in alcoholic solvent and their reactions were observed. The reaction of o-vinyloxybenzaldehyde (**10**) with methylene triphenylphosphorane (**11**) yielded 1-phenyl-2-(*o*-vinyloxyphenyl)ethyldiphenylphosphine oxide (**13**).

In a previous paper[1] we have discussed and discarded a number of possible mechanisms for the unexpected formation of 2-methyl-2*H*-1-benzopyran (**3**) from 3-(*o*-formylphenoxy)propyltriphenylphosphonium bromide (**1a**) under normal Wittig[2] reaction conditions. An alternate mechanism (Scheme I) has recently been proposed.[3] It is supported by (a) the data[1] which indicate that the rearrangement of **1** to **3** is favored in more highly protonic solvents, *i.e.*, inhibiting decomposition of betaine **5** to the expected benzdihydrooxepin (**2**) by protonation of **5** to **6**; (b) the β elimination (**6** → **7**) which would also be favored by a more electrophilic phosphonium species, *i.e.*, **1a** *vs.* **1b** (see Table I).



(1) E. E. Schweizer, C. J. Berninger, D. M. Crouse, R. A. Davis, and R. S. Logothetis, *J. Org. Chem.*, **34**, 207 (1969); E. E. Schweizer and R. Schepers, *Tetrahedron Lett.*, 979 (1963).

(2) A. Maercker, *Org. Reactions*, **14**, 272 (1965).

(3) Proposed by Professor H. T. Bestmann at the Chemical Societies International Symposium on Ylides, Leicester, England, July 14, 1970. Although Professor Bestmann did not really believe that this would be the right mechanism, we felt compelled to find supporting evidence or disprove it.

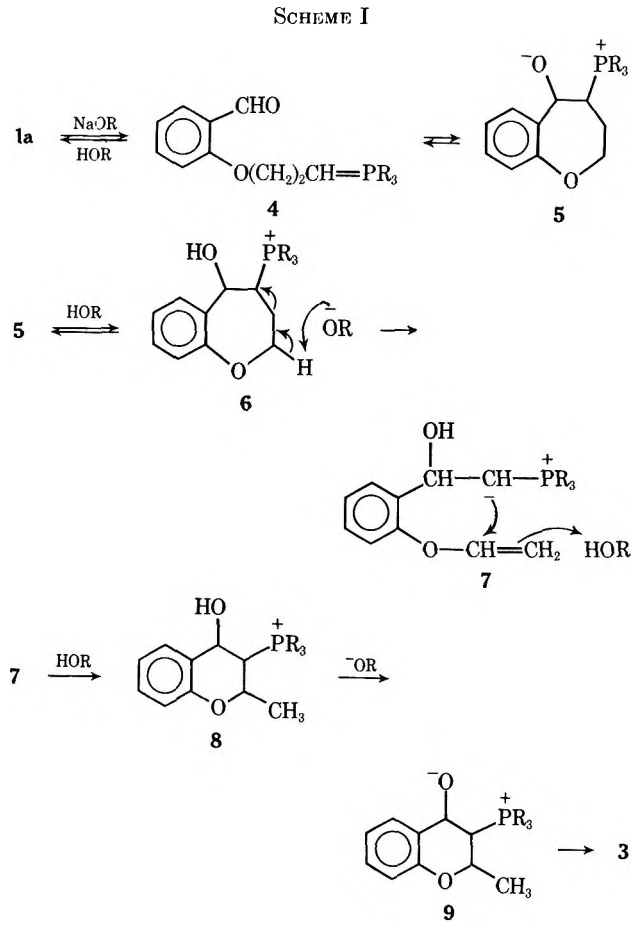
TABLE I

SOLVENT AND PHOSPHORUS SUBSTITUENT EFFECTS ON RATIOS OF 2 AND 3 FROM SALTS 1[a]

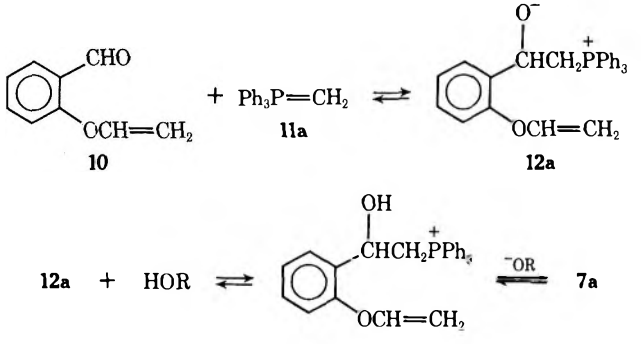
R in salt 1	Solvent	Overall yield of 2 + 3, %	Ratio of 2:3
Ph	DMF	70	100:0
n-Bu	DMF	43	48:52
Ph	MeOH	65	0:100
Ph	MeOH[b]	88	0:100
n-Bu	MeOH[c]	0	
n-Bu	MeOH[b,c]	0	
n-Bu	MeOH–DMF 20:80	10	1:99
n-Bu	MeOH–DMF 10:90	31	4:96
n-Bu	DMF[d]	50	78:22

[a] At 64° for 24 hr under N_2 with 1.0 equiv of NaOMe except as noted. [b] As in *a* except 4.44 equiv of NaOMe. [c] Only starting salt 1 and 17b recovered on work-up after HBr neutralization. [d] Base used is NaH.

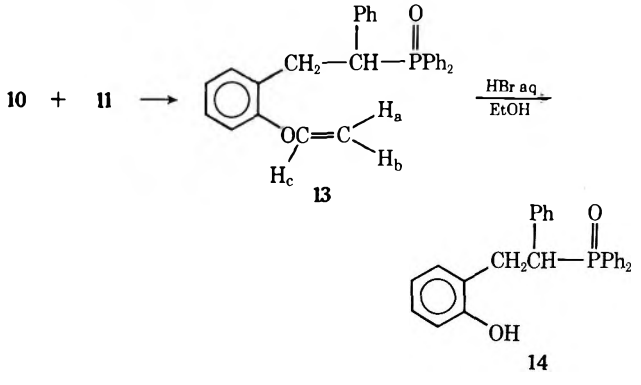
SCHEME I



If the mechanism in Scheme I is feasible, one would expect to be able to produce **3** from *o*-vinyloxybenzaldehyde (**10**) and methylene triphenylphosphorane (**11**), since the proposed intermediate **7** would be in equilibrium with the betaine **12** which would be formed from the reaction of **10** and **11**.



The reaction of **10** and **11** was allowed to take place and the product was shown to contain no trace of 2-



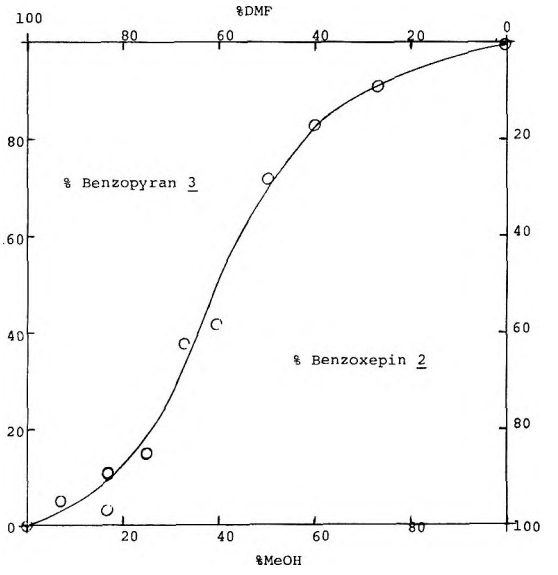


Figure 1.—Phosphonium salt (**1a**) decomposition in mixed solvents.

methyl-2*H*-1-benzopyran (**3**) (by vpc) and only 1-phenyl-2-(*o*-vinyloxyphenyl)ethyldiphenylphosphine oxide (**13**) was found in 70% yield.

The formation of the oxide **13** is consistent with some alcoholic alkoxide reactions of phosphonium salts with aldehydes;[4,5] however, it is not consistent with the mechanism shown in Scheme I. The structure of **13** was also supported by obtaining and characterizing **14** as its hydrolysis product.

It has been shown that the reaction of salt **1a** to give **3** is highly solvent dependent[1] and that more acidic solvents enhance the formation of the rearranged product **3**. The results obtained by using a variable ratio of only two solvents (DMF–MeOH) with the triphenylphosphonium salt (**1a**), sodium methoxide as a base, are shown in Figure 1.

The tri-*n*-butylphosphonium salt (**1b**) (prepared in the same manner as **1a**[1]) was significantly more sensitive to the effects of MeOH in DMF than the salt **1a**. If pure DMF was used as solvent with NaOMe as the base (thus 1 equiv of MeOH would be present per 1 equiv of ylide formed) the ratio of **2** to **3** was 48:52 (Table I). Elimination of all of the MeOH by employing NaH as a base gave mainly the expected 2,3-dihydrobenzoxepin (**2**). Using pure MeOH (no DMF) as solvent, none of the cyclized products **2** or **3** were observed, and on work-up only the starting material **1b** and a vinyl phosphonium salt (**17b**) were recovered. Thus a reduction of the electrophilic nature of the phosphonium moiety both reduced the overall yield of the reaction and increased the ratio of the 2-methyl-2*H*-1-benzopyran (**3**) to **2** formed.

The search for a vinyl salt as a possible intermediate in the reaction of **1** was pursued by lowering the concentration of the base used (Table II). Isolation of large quantities of vinyl salt **17b** (90% yield) and **15a** (76%) were accomplished by using 0.25 equiv or less of base per 1 equiv of the corresponding salt **1**.

When salt **15a** was treated with 1 equiv of NaOH in anhydrous MeOH, 2-methyl-2*H*-1-benzopyran (**3**) was

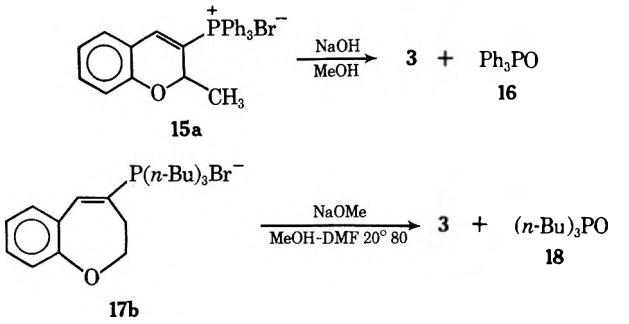
(4) E. M. Richards and J. C. Tebby, *Chem. Commun.*, 494 (1969); S. Trippett and B. J. Walker, *J. Chem. Soc. C*, 887 (1966).
(5) E. E. Schweizer, unpublished results.

TABLE II

REACTION OF 3(*o*-FORMYLPHENOXY)PROPYLPHOSPHONIUM SALTS (1) WITH SODIUM METHOXIDE

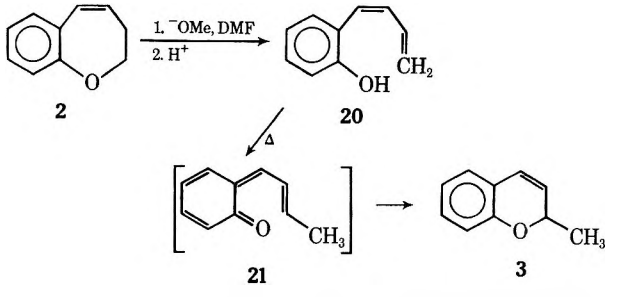
R in 1	Solvent	Ratio of NaOMe:1	Yield of 2 + 3 %	Ratio of 2:3	Yield of 15a, %[a]	Ratio of 1b:17b
Ph	MeOH	4.0	88[a]	*b*		
Ph	MeOH	1.0	65[a]	*b*		
Ph	MeOH	0.40	31[a]	*b*	53	
Ph	MeOH	0.23	15[c]	8:92[d]	77	
Ph	MeOH	0.10	9[c]	44:56[d]	76	
n-Bu	MeOH	1.0				83:17[c]
n-Bu	MeOH	0.8				83:17[c]
n-Bu	MeOH	0.62				81:19[c]
n-Bu	MeOH	0.39				94:6[c]
n-Bu	MeOH–DMF 20:80	1.1	9[d]	4:96[d]		0:87[a]
n-Bu	MeOH–DMF 20:80	0.25	4[d]	64:36[d]		0:90[a]

[a] Isolated and purified. [b] 100% of **3**. [c] Yields based on nmr; accuracy ±2% for salts **1b**:**17b**. [d] Ratio determined by vpc.

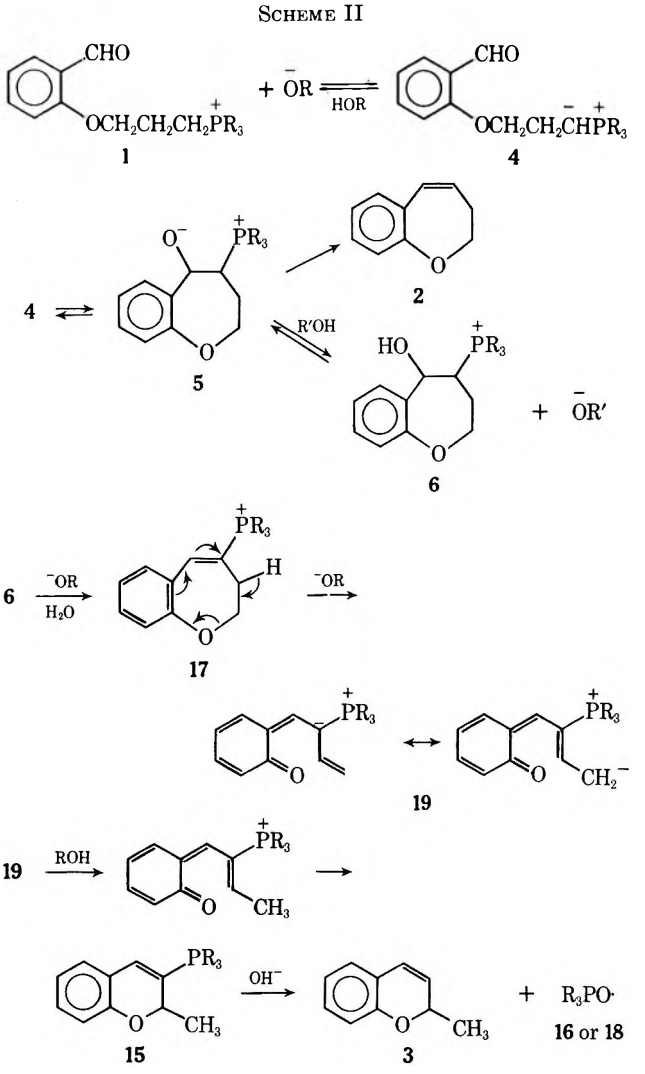


isolated in 82% yield and triphenylphosphine oxide **16** was isolated in 92% yield, whereas aqueous NaOH gave **3** and **16** in 88 and 97% yields, respectively. These data compel us to write the mechanism shown in Scheme II for the formation of **3** from **1**.

The postulation is that the initial reaction is that of a phosphonium salt under basic conditions giving an ylide (**4**) which forms the normal "Wittig" betaine (**5**). The expected collapse of the betaine (**5**) yields the 2,3-dihydrobenzoxepin-1 (**2**). However, the more acidic the solvent system becomes,[1] the more the alkoxide in **5** is protonated to afford **6**. The hydroxyphosphonium salt is readily dehydrated to give the conjugated vinylphosphonium salt (**17**).[4,5] The lower electrophilicity of the tri-*n*-butylphosphonio group in salt **1b** allows us to stop the reaction at the *non*ring-contracted salt **17b** (Table II), whereas in the reaction of **1a** the β-elimination step that initiates the sequence converting **17a** to **15a** must be faster than the conversion of **6a** to **17a**, since we have been unable to obtain **17a**. Even without the assistance of the phosphonium moiety, 2,3-dihydrobenzoxepin-1 (**2**) has been found to be readily converted to **20**.[6] The conversion of **20** to **3** occurs[6,7]



SCHEME II



via an allylidenecyclohexadienone intermediate **21** as shown in the conversion of **17** to **15** *via* **19**.

The aqueous (or methanolic) hydrolysis of **17b** with NaOH produces 2-methyl-2*H*-1-benzopyran (**3**) and salicylaldehyde, but never any of the expected oxepin **2** (Table II). The lack of **2** shows that the ring contraction of **17b** to **15b** must be considerably faster than the hydrolysis of **17b** to **2**. It also indicates that, although the *n*-butyl groups (instead of phenyl) on the phosphorus lower the electrophilicity of phosphorus so that hydroxide attack is slower at that site, the predominant

(6) E. E. Schweizer, D. M. Crouse, and D. L. Dalrymple, *Chem. Commun.*, 354 (1969).

(7) R. Hug, H. J. Hansen, and H. Schmid, *Chimia*, **23**, 108 (1969).

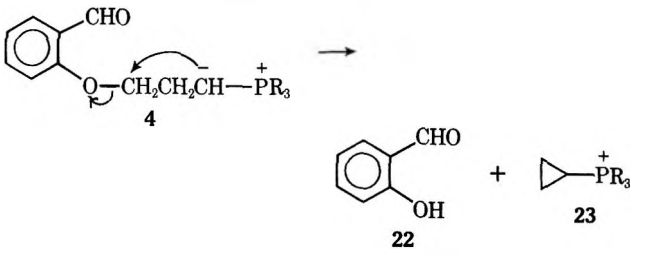
TABLE III

AQUEOUS ALKALINE HYDROLYSIS OF PHOSPHONIUM SALTS

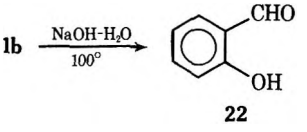
Salt	Ratio (equiv) of NaOH:salt	Solvent	Temp, °C	Time, hr	Products (yield, %)[a]
15a	1	MeOH	64	24	**3** (82) + **16** (92)
15a	2	H_2O	100	4	**3** (88) + **16** (97)
17b	1	MeOH	64	24	**3** (5) + **17b** (75)
17b	2	H_2O	100	4	**3** (trace) + **22** (26) + **17b** (64)
17b	2	H_2O	100	18	**3** (4) + **22** (40) + **17b** (37)
1b	2	H_2O	100	4	**22** (8) + **18** (5) + **1b** (68)
1b	2	H_2O	100	18	**22** (16) + **18** (7) + **1b** (65)
1b	2	H_2O	100	45	**22** (61) + **18** (24) + **1b** (25) + **3** (9)

[a] Yields based on nmr of isolated materials.

reaction of **17b** with hydroxide is undoubtedly a reversal of the pathway back to **4** which then gives salicylaldehyde, probably as shown below (Table III). Previous



work from this group has shown that this is a common reaction.[8] We have also shown that treatment of **1b** with aqueous NaOH gives salicylaldehyde as the main identifiable product (Table III).



Thus a mechanism has been proposed, which is supported by all of the data, for the conversion of 3-(*o*-formylphenoxy)propylphosphonium salt (**1**) to 2-methyl-2*H*-1-benzopyran (**3**). Also of considerable interest is the first isolation of vinylphosphonium salts in a reaction of a phosphorane with a carbonyl reagent, thus showing a pathway (in protonic solvents) which is not that of a normal Wittig[2] reaction to give olefins.[4]

Experimental Section

Preparation of *o*-Formylphenyl Vinyl Ether (10).—A mixture of 22.9 g (0.1 mol) of *o*-formylphenyl β-bromoethyl ether and 6.7 g (0.12 mol) of KOH was refluxed for 24 hr in 40 ml of ethanol. After ethanol was removed, the residue was distilled to give 4.25 g (28.7%) of **10**: bp 59° (0.3 mm); ir ν 1680 (C=O) and 1640 cm^{-1} (-OCH=CH_2); nmr (CCl_4) δ 4.5 (dd, 1 H, J_{bc} = 6.3 Hz, H_b), 4.75 (dd, 1 H, J_{ac} = 13.7 Hz, H_a), 6.65 (dd, 1 H, H_c); 6.85–7.87 (m, 4 H, phenyl protons), 10.30 (s, 1 H, aldehyde proton).

Anal. Calcd for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 73.05; H, 5.33.

Reaction of 10 with Triphenylmethylenephosphorane (11).—Sodium metal (0.58 g, 0.025 g-atom) was added to a refluxing solution of 8.93 g (0.025 mol) of methyltriphenylphosphonium bromide dissolved in 100 ml of anhydrous MeOH. To this was added dropwise 3.70 g (0.025 mol) of vinyl ether **10** dissolved in 50 ml of MeOH. The reaction mixture was allowed to reflux for 24 hr under dry N_2. After MeOH was removed, the residue was poured into 300 ml of H_2O and extracted with benzene. The benzene extract was washed with water, dried over $CaSO_4$, and evaporated to give 7.50 g (70%) of **13**: ir (KBr) ν 1640 (C=C), 1435 (P-C), 1220 (Ph-O), 1180 cm^{-1} (P=O); nmr ($CDCl_3$) δ 3.13–3.58 (m, 2 H, $-CH_2CPhHPPh_2$), 3.75–4.17 (m, 1 H, $-CH_2CPhHPPh_2$), 4.41 (dd, 1 H, J_{bc} = 5.4 Hz, H_b), 4.67 (dd, 1 H, J_{ac} = 13.4 Hz, H_a), 6.50 (dd, 1 H, H_c), 6.63–8.30 (m, 19 H, phenyl protons); mass spectrum (75 eV) *m/e* 424.

Anal. Calcd for $C_{28}H_{25}O_2P$: C, 79.23; H, 5.94; P, 7.29. Found: C, 79.47; H, 5.69; P, 7.09.

Hydrolysis of 13.—Hydrobromic acid (48%), 1 ml, was added to a solution of **13** (1.06 g, 2.5 mmol) in 35 ml of ethanol. The solution was refluxed for 22 hr. After the ethanol was removed by distillation, the residue was dissolved in 100 ml of methylene chloride. The methylene chloride extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to give 0.90 g (91%) of product **14** as white crystals. The analytical sample was prepared by recrystallization from benzene–alcohol to give white crystals: mp 213–214°; ir (KBr) ν 3000 cm^{-1} (OH); nmr (CD_3SOCD_3) δ 2.90–3.40 (m, 3 H, OH and methylene, one D_2O exchangeable proton), 4.08–4.62 (m, 1 H, methine), 6.25–8.35 (m, 19 H, phenyl).

Anal. Calcd for $C_{26}H_{23}O_2P$: C, 78.38; H, 5.82; P, 7.78. Found: C, 78.62; H, 5.69; P, 7.66.

Standard Reaction Procedure (for Figure 1).—Into a 250-ml, flame-dried, three-necked flask fitted with reflux condenser, mechanical stirrer (sometimes a magnetic stirrer), and glass stopper and containing 4.1 g (0.0083 mol) of triphenylphosphonium salt **1a** in 150 ml of dried solvent was added 0.5 g (0.0091 mol) of NaOMe. The reaction mixture was heated at 64° for 24 hr under nitrogen, then poured into 300 ml of distilled water and extracted four times with ether. The combined ether extracts (150 ml) were washed two times with water, dried ($MgSO_4$), filtered, and concentrated at room temperature on a rotary evaporator to give an oil. Glc of the oil yielded the values for Figure 1.

3-(*o*-Formylphenoxy)propyltri-*n*-butylphosphonium Bromide (1b).—Tri-*n*-butylphosphine (110 g, 0.36 mol) was dissolved in 600 ml of acetonitrile. While mechanically stirring under nitrogen, 88 g (0.36 mol) of 3-(o-formylphenoxy)propyl bromide was added dropwise (20 min). The yellow solution was refluxed for 24 hr. The solvent was removed under aspirator vacuum. After cooling, *ca.* 500 ml of anhydrous ether was added with fast stirring. In 5 min the semiliquid crystallized, causing the ether to reflux. After decanting the ether and adding 500 ml of fresh anhydrous ether, the salt was stirred overnight. Filtering and recrystallizing from methylene chloride–ethyl acetate gave 151 g (78%) of **1b**: mp 107–108°; ir (Nujol) 1680 (C=O), 1240 cm^{-1} (C-O-C); nmr ($CDCl_3$) δ 0.97 (t, 9, $-CH_3$), 1.2–1.9 (broad, 12), 2.1–3.1 (broad, 10), 4.30 (t, 2, $-OCH_2-$), 6.8–7.8 (m, 4, aromatic), 10.43 ppm (s, 1, -CHO).

Anal. Calcd for $C_{22}H_{38}BrO_2P$: C, 59.32; H, 8.59; Br, 17.71. Found: C, 59.48; H, 8.74; Br, 17.65.

General Procedure for the Reaction of 3-(*o*-Formylphenoxy)-propylphosphonium Salt (1) with NaOMe (Data for Table II).—To a solution of 0.432 g (8 mmol) of sodium methoxide in 100 ml of dried MeOH was added 3.60 g (8 mmol) of phosphonium salt **1b**. The reaction was allowed to stir at the MeOH refluxing temperature for 24 hr under dry N_2. After the reaction mixture was cooled to room temperature, it was neutralized with hydrobromic acid. The alcoholic solution was poured into 350 ml of H_2O and extracted with ether (four 150-ml portions) and CH_2Cl_2 (four 150-ml portions), respectively. The ether and the methylene chloride extractions were washed with water and dried over $CaSO_4$. No product was detected in the ether extraction.

(8) E. E. Schweizer, C. J. Berninger, and J. G. Thompson, *J. Org. Chem.*, **33**, 336 (1968); E. E. Schweizer and J. G. Thompson, *Chem. Commun.*, 666 (1966).

The methylene chloride extraction was concentrated until 50 ml of solvent remained.

The concentrated solution was added to 1 l. of anhydrous ether to give 3.0 g of a white precipitate. The precipitate (80% yield) was identified as a mixture of the starting material **1b** (83%) and the contracted product **17b** (17%) by nmr. Data was entered in Table II.

This technique was also used to obtain salt **15a**, with the yield and ratio of **2** and **3** coming from examination of the ether extract.

Reaction of 3-(o-Formylphenoxy)propyltributylphosphonium Bromide (1b) with NaOMe in MeOH–DMF.—Sodium metal (0.10 g, 4.35 g-atoms) was placed into 40 ml of anhydrous MeOH. After the evolution of hydrogen gas stopped, 160 ml of anhydrous DMF was added to the NaOMe solution. Then 8.20 g (18.5 mmol) of phosphonium salt **1b** was added to the NaOMe solution in MeOH–DMF. The reaction was allowed to stir at 64° for 24 hr under dry Na. The work-up followed was that used in the general procedure for the reaction of phosphonium salt with NaOMe in MeOH. Vinylphosphonium salt **17b** (7.10 g, 90%) and 0.25 g of a mixture of benzopyran **3** (1.44%), benzoxepine **2** (2.56%), and tributylphosphine oxide (4%) were obtained. All compounds were identified by comparison with authentic samples.

2,3-Dihydro-1-benzoxepin-4-tri-*n*-butylphosphonium Bromide (17b).—The salt from experiment 10 in Table II was recrystallized from methylene chloride–ethyl acetate, giving an analytically pure sample: mp 157–158°; ir (KBr) 1220 (C–O–C) and 1130 cm^{-1} (C–P); nmr ($CDCl_3$) δ 1.00 (t, 9, $-CH_3$), 1.23–2.10 (broad, 12), 2.35–3.16 (broad, 8), 5.52 (t, 2, J_{HH} = 6 Hz), 6.78–7.72 (m, 4, aromatic), 8.10 ppm (d, 1, J_{PH} = 18 Hz, vinyl); mass spectrum (70 eV) *m/e* 347.

Anal. Calcd for $C_{22}H_{36}BrOP$: C, 61.82; H, 8.49; P, 7.24; Br, 18.69. Found: C, 62.20; H, 8.67; P, 7.38; Br, 18.45.

Hydrolysis of Vinylphosphonium Salt 17b in Methanol.—Dried NaOH (0.32 g, 8 mmol) was added to a solution of 3.42 g (8 mmol) of phosphonium salt **17b** in 80 ml of dried MeOH and the mixture was allowed to stir at 64° for 24 hr under dry Na. The work-up followed the procedure of the reaction of phosphonium salt **1b** with NaOH. The ether extract gave 0.15 g of the mixture of benzopyran **3** (5%) and tributylphosphine oxide (16%) by nmr. The methylene chloride extract afforded 2.55 g (74.5%) of the unreacted starting salt **17b**. All compounds were identified by comparison with authentic samples.

Hydrolysis of Vinylphosphonium Salt 17b in Water.—Sodium hydroxide (0.64 g, 16 mmol) was added to a solution of 3.42 g (8 mmol) of phosphonium salt **17b** in 100 ml of water and the mixture was allowed to stir at 100° for 18 hr under a nitrogen atmosphere. The mixture was neutralized with aqueous hydrobromic acid and extracted with three 200-ml portions of ether and then three 300-ml portions of methylene chloride. The ether extract was washed with three 150-ml portions of water and dried ($CaSO_4$). A mixture of salicylaldehyde **5** (40%), benzopyran **3** (4%), and tributylphosphine oxide (3.6%) was obtained by removing ether (total wt 0.50 g). The methylene chloride was similarly washed with two 200-ml portions of water and dried ($CaSO_4$). The methylene chloride extract was concentrated until 50 ml of methylene chloride remained. The concentrated methylene chloride extract was added dropwise to 1 l. of anhydrous ether; 1.25 g (37%) of white crystals of salt **17b** were recovered. All compounds were identified by comparison with authentic samples.

2-Methyl-2*H*-1-benzopyran-3-triphenylphosphonium Bromide (15a).—The solid from experiment 5 listed in Table II, run in a manner similar to the reaction for the preparation of **17b**, was recrystallized from chloroform–ethyl acetate to give analytically pure **15a**: mp 264–266°; ir (KBr) 1210 (C–O–C), 1100 cm^{-1} (C–P); nmr ($CDCl_3$) δ 1.17 (d, 3, J_{HH} = 6 Hz, decoupled, $-CH_3$), 5.20 (pentuplet, 1, $J_{HH} = J_{HP}$ = 6 Hz, –OCH–), 6.9–8.1 (m, 19, aromatic), 8.30 ppm (d, 1, J_{PH} = 13 Hz, vinyl); mass spectrum (70 eV) *m/e* 262.

Anal. Calcd for $C_{28}H_{24}BrOP$: C, 69.00, H, 4.96; Br, 16.39; P. 6.36. Found: C, 68.80; H, 4.93; Br, 16.64; P, 6.17.

Hydrolysis of Phosphonium Salt 15a in MeOH.—Dried NaOH (0.40 g, 0.01 mol) was added to a solution of 4.87 g (0.01 mol) of phosphonium salt **15a** in 100 ml of dried MeOH and the reaction mixture was allowed to stir at reflux temperature for 24 hr under dry Na. The reaction mixture was poured into 2 l. of anhydrous ether. The ether was washed with water and dried over $CaSO_4$. After the solvent ether was removed under reduced pressure, the reaction product was distilled to give 1.20 g (82%) of 2-methyl-2*H*-1-benzopyran (**3**). The residue was chromatographed to give 2.55 g (92%) of triphenylphosphine oxide. Comparison with authentic samples provided positive identification.

Hydrolysis of Phosphonium Salt 15a in Water.—Sodium hydroxide (0.20 g, 5 mmol) was added to an aqueous solution of 1.22 g (2.5 mmol) of phosphonium salt **15a** dispersed in 50 ml of water and the reaction mixture was allowed to stir at 100° for 4 hr. The reaction mixture was cooled to room temperature and extracted with ether (four 100-ml portions). The ether extract was washed with water and dried over $CaSO_4$. After the solvent ether was removed under reduced pressure, 1.0 g of residue was obtained. It was shown to be a mixture of **3** (88%) and triphenylphosphine oxide (97%) by nmr.

Aqueous Hydrolysis of 3-(*o*-Formylphenoxy)propyltributylphosphonium Bromide (1b).—In a 250-ml flask equipped with magnetic stirrer, a mixture of phosphonium salt **1b** (4.44 g, 0.01 mol) and NaOH (0.80 g, 0.02 mol), dissolved in 100 ml of water, was allowed to stir at 100° for 18 hr under a nitrogen atmosphere. The mixture was cooled to room temperature and neutralized with aqueous HBr. The aqueous mixture was extracted with three 150-ml portions of ether and then three 150-ml portions of CH_2Cl_2. The ether extract gave a mixture (0.35 g) of salicylaldehyde **2** (16%) and tri-*n*-butylphosphine oxide **3** (7%), identified by comparison with authentic samples. The methylene chloride extract was concentrated to 50 ml and added dropwise into 1 l. of anhydrous ether. The starting phosphonium salt (2.90 g, 65%) was recovered (nmr showed a trace of impurity as a contaminant).

Registry No.—NaOMe, 124-41-4; **1a**, 17954-76-6; **1b**, 31600-73-4; **2**, 14949-49-6; **3**, 2513-24-8; **10**, 31600-76-7; **13**, 31600-77-8; **14**, 31600-78-9; **15a**, 31600-79-0; **17b**, 31600-80-3.

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Reactions of Phosphorus Compounds.[1] 29. Preparation and Reactions of Pyrazolinyltriphenylphosphonium Salts

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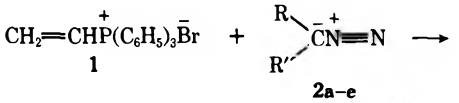
Received May 24, 1971

Unsubstituted and substituted pyrazolinyltriphenylphosphonium salts are prepared by 1,3-dipolar cycloaddition of diazoalkanes to vinyltriphenylphosphonium bromide. Thermal decomposition, aqueous basic hydrolysis, alkylation, and Wittig olefination reactions are examined.

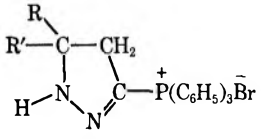
Synthetic methods for the preparation of heterocyclic compounds by 1,3-dipolar cycloadditions have been reviewed recently by Huisgen.[2] Pyrazolinylphosphonates,[3-9] pyrazoylphosphonates,[10,11] and pyrazolinyldialkylphosphine oxides and sulfides[12] have been prepared by 1,3-dipolar cycloadditions. Zbiral[13] investigated the preparation of triazoles from 1,3-dipolar cycloaddition reactions of acyl-substituted vinyltriphenylphosphonium chlorides and sodium azide.

We wish to report the preparations and reactions of unsubstituted and 5-substituted 2-pyrazolin-3-yltriphenylphosphonium salts.[14] The uniqueness of these salts over the products mentioned above,[3-12] which retain the phosphorus moiety, is that they provide an intermediate of great synthetic utility which may undergo a number of interesting conversions as depicted generally in Scheme I.

Vinyltriphenylphosphonium bromide (1), on reaction with diazoalkanes **2a–e** at room temperature for 1–2 hr, gave only the corresponding 2-pyrazolin-3-yltriphenylphosphonium bromides, **3a–e**, in excellent yields (84–100%). None of the corresponding 4-substituted salts



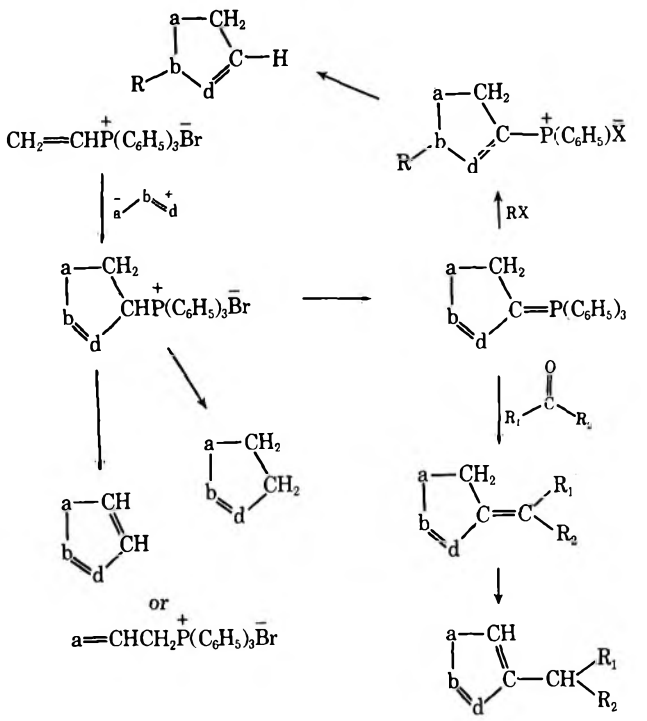
1 **2a–e**



3a, R = R′ = H
b, R = H; R′ = CH_3
c, R = R′ = CH_3
d, R = H; R′ = C_6H_5
e, R = R′ = C_6H_5

were obtained. Undoubtedly steric factors inhibit the formation of 4-substituted salts which would require the phosphonium moiety of the vinyl salt **1** to be adjacent to the substituted diazoalkane carbon moiety. Allylphenylphosphonium or β-substituted vinyltriphenylphosphonium salts did not react with diazoalkanes to give 1,3-dipolar cycloaddition products. Only starting salts were recovered even under more vigorous reaction conditions.

SCHEME I



Only species with the 2-pyrazoline structures were isolated, from the reaction of **1** and **2**, even when mild conditions were employed similar to those which were used by Pudovik[9] to obtain 1-pyrazolin-3-yldialkylphosphonates instead of the 2-pyrazolin-3-yldialkylphosphonates, on reaction of diphenyldiazomethane with vinylphosphonates. The rapid isomerization of the 1- into the 2-pyrazoline structure during the reaction is due to the greater stability of the 2-pyrazoline structure engendered by overlapping between the π electrons of the C=N bond and a vacant d orbital of the positive phosphorus atom.[8]

If the diazoalkane was not added in excess, or all at once, phosphonioethylated compounds[15] were also formed, and the separation of the mixed salts was very difficult. The reaction, however, was readily controlled by rapid addition of diazoalkanes **2a–e** in excess to **1** in order to obtain pure pyrazolinyl salts, **3a–e**.

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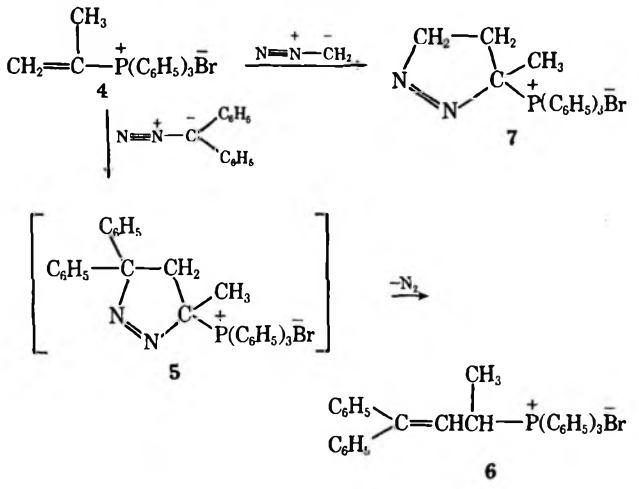
(10) B. C. Saunders and P. Simpson, *J. Chem. Soc.*, 3351 (1963).
(11) A. N. Pudovik and N. G. Khusaimova, *Zh. Obshch. Khim.*, **40**, 697 (1970).
(12) I. G. Kolokol, *et al.*, *ibid.*, **40**, 667 (1970).
(13) von E. Zbiral, *et al.*, *Justus Liebigs Ann. Chem.*, **725**, 22 (1969).
(14) E. E. Schweizer, C. S. Kim, and R. A. Jones, *Chem. Commun.*, **39**, 1584 (1970).
(15) Part 30: E. E. Schweizer and C. S. Kim, *J. Org. Chem.*, **36**, 4041 (1972).

The ir spectra of **3a–e** show a strong, broad band at 3050–3150 cm^{-1} which indicates a strong intermolecular interaction between amine proton and bromine anion (N—H···$\bar{B}r$). This type of interaction is supported[16] by the observation that the N–H stretching vibration band shifted into higher frequencies (3200–3250 cm^{-1}) when the bromine anion was replaced by tetraphenylborate anion in compound **3a**. The nmr data for **3a–e** are consistent with the structures assigned.[12,17–22]

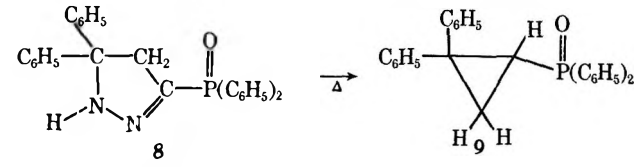
When the isopropenyl salt **4** was allowed to react with diphenyldiazomethane (**2e**) for 1 week at room temperature, a decomposition product, **6**, of the initially formed adduct, **5**, was obtained in 45% yield. On the other hand, a 1-pyrazoline adduct, **7**, was isolated from the reaction of **4** and diazomethane, **2a** (Scheme II). This

SCHEME II



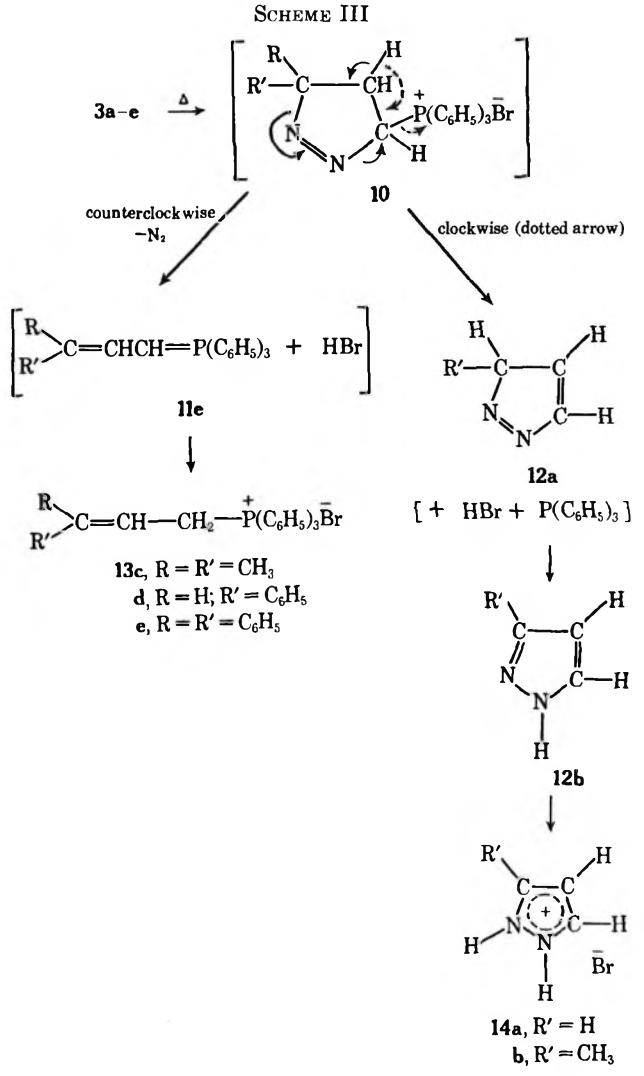
latter adduct slowly decomposed on standing at room temperature into 3-methylpyrazole hydrobromide (**14a**) and triphenylphosphine. Attempts to purify **7** without decomposition proved unsuccessful. Only in CD_3OD solution could an acceptable nmr spectrum be obtained before the salt would undergo spontaneous decomposition. Immediate decomposition was observed in deuterated chloroform or in trifluoroacetic acid.

Thermal Decomposition of 3a–e.—It has been known[2] that 2-pyrazolines decompose thermally to give cyclopropanes and olefins with varying product distributions. In most cases, the corresponding cyclopropanes were observed, either as a major product or as a contaminant. Pudovik reported[8] that he only isolated the corresponding cyclopropane product **9** in 92% yield by heating **8** to 160–170°. The catalyzing effect



of the bromine anion in the present system was suggested by the fact that the corresponding cyclopropane compounds were not observed as thermal decomposition products of the salts **3a–e** and **7**. The salts **3a**, **3b**, and **7** eliminated triphenylphosphine to form the corresponding pyrazole hydrobromides (**14a,b**) while **3c–e** resulted in the formation of the corresponding allyltriphenylphosphonium bromides, **13c–e**, by loss of nitrogen (Scheme III).

SCHEME III



In the mechanism of the thermal decomposition of 2-pyrazolines, the isomerization of 2- into 1-pyrazoline before losing nitrogen has been generally accepted as a first step.[23] The isomerized 1-pyrazoline, **10**, will decompose by two unique pathways (see Scheme III). In **3c–e** the allylphosphonium salts, **13c,e**, are expected since the intermediate, **12a**, formed by clockwise electron transfer would not be able to isomerize into a stable pyrzole, **12b**, due to the absence of a proton at C-5. Isomerization (to **12a**) is possible if one of the C-5 substituents is a hydrogen, as in **3a,b**, *via* a 1,3-hydrogen shift. The formation of **13d**, rather than the alternate pyrazole salt, **14** (from **3d**), may be due to the electron-withdrawing effect of the phenyl ring at C-5. This effect would result in the formation of the double bond in conjugation with the phenyl giving **11**, rather than the

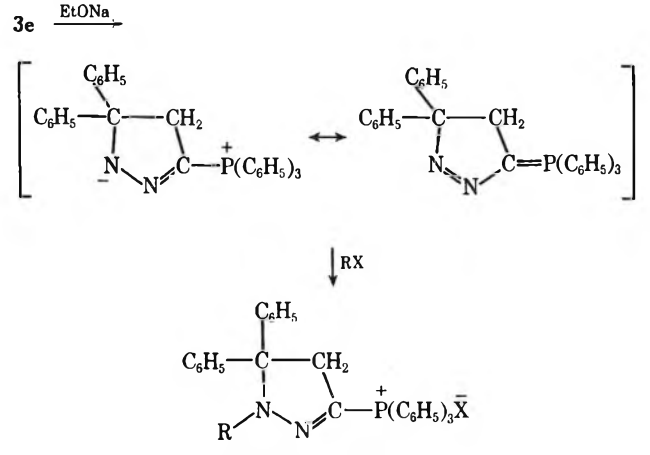
(16) L. B. Senyavina, *et al.*, *Zh. Obshch. Khim.*, **37**, 499 (1967).
(17) K. B. Sloan and N. Rabjohn, *J. Heterocycl. Chem.*, **7**, 1273 (1970).
(18) R. Sustmann, R. Huisgen, and H. Huber, *Chem. Ber.*, **100**, 1802 (1967).
(19) A. Hassner and M. J. Michelson, *J. Org. Chem.*, **27**, 3974 (1962).
(20) R. C. Cookson, *et al.*, *Tetrahedron Suppl.*, No. 7, 355 (1967).
(21) J. R. Dyer, "Application of the Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, p 108.
(22) G. L. Vecchio, M. Crisafulli, and M. C. Aversa, *Tetrahedron Lett.*, 1909 (1966).
(23) R. H. Wiley, "Chemistry of Heterocyclic Compounds (Pyrazolines)," Interscience, New York, N. Y., 1967, p 209.

intermediate **12a** where the double bond formed is not in conjugation with the phenyl.

The structure of **13e** was supported by allowing the phosphorane produced from **13e** to react with benzophenone. This resulted in the known 1,1,4,4-tetraphenylbutadiene (62%).

Attempted Alkylation of 3a–e.—Only N-alkylated compounds, **15a–c,** were obtained upon treatment of reactive alkyl halides by the ylide formed from the salt **3e** in the presence of ethanolic sodium ethoxide (Scheme IV). Only the corresponding pyrazoles were

SCHEME IV

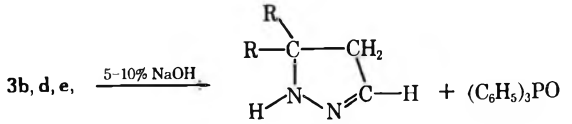


15a, R = CH_3; X = I (84%)
b, R = CH_2–COOEt, X = Br (69%)
c, R = COOEt, X = Cl (43%)

observed on attempting to alkylate salts **3a,b,d**, under basic conditions, *i.e.*, when **3** contained one or more protons in the C-5 position.

In addition to the spectra data, which supported the structures assigned, hydrolysis of **15a–c** gave the corresponding N-alkylated 2-pyrazolines, **16a,b**. Where the intermediate anion **17** is stabilized (in **15c**), the cyanourethane, **18**, was obtained by N–N bond cleavage as well as **16c** (Scheme V) in a ratio of 7 to 3, respectively (overall yield 67%). The saponified acid, **16b**, was thermally decarboxylated into **16a** (100%).

Hydrolysis of 3a–e.—When compounds **3b,d,e** were treated with 5–10% aqueous NaOH, the corresponding 2-pyrazolines, **19b,d,e,** and triphenylphosphine oxide were isolated.

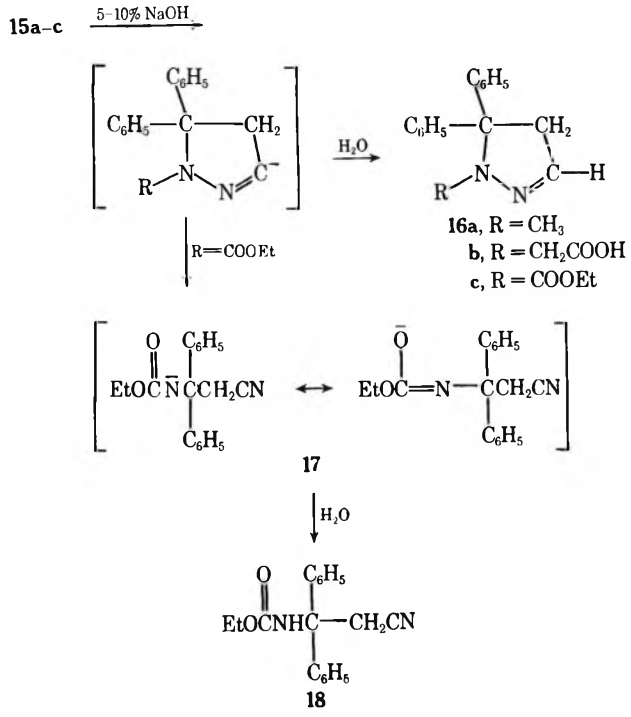


19b, R = H; R′ = CH_3
d, R = H; R′ = C_6H_5
e, R = R′ = C_6H_5

Triphenylphosphine oxide was similarly isolated, in 90–95% yield, on basic hydrolysis of **3a** and **3c**; the corresponding 2-pyrazolines were not isolated.

Wittig Olefination Reaction of 3a–e.—The salts **3a–e** undergo the Wittig olefination reaction. Reactions of **3a–e** with ethanolic sodium ethoxide and benzaldehyde gave different types of products, and the yields depend on the order of mixing the starting materials (Scheme VI).

SCHEME V



16a, R = CH_3
b, R = CH_2COOH
c, R = COOEt

17

18

Three orders of mixing were employed for these reactions: (a) benzaldehyde was added to a mixture of the salt and ethanolic sodium ethoxide, (b) the salt was added to a mixture of benzaldehyde and ethanolic sodium ethoxide, and (c) ethanolic sodium ethoxide was added to an ethanolic solution of the salt and benzaldehyde.

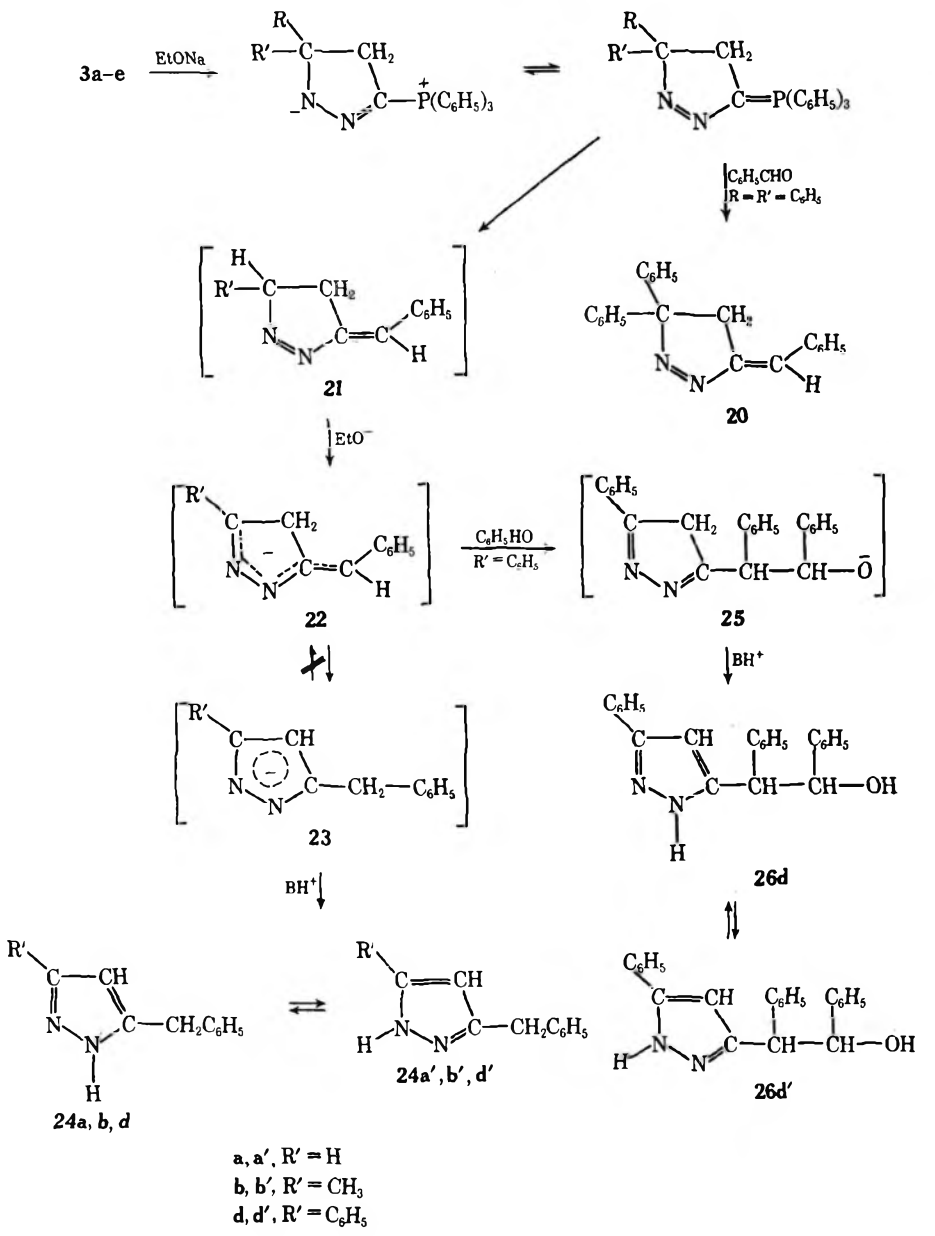
Only **3e** furnished the expected benzilidene product, **20**, regardless of the order of mixing (78% by method c). The structure of **20** was supported by its spectral data.[21,24,25]

When **3a,b,d** were treated in manner "a," no Wittig olefination products were observed. The corresponding pyrazoles were isolated as observed previously on attempting the alkylation reactions. If, however, **3a,b,d** were allowed to react under method b or c, Wittig olefination products, **24a,b** and **26**, were obtained in good yields. Generally method c gives the best yields. Further isomerization or addition of benzaldehyde to the initial product, **21**, is undoubtedly caused by the relative stability of the anion intermediate, **22**. Thus, if R′ = H or CH_3, **22** will isomerize rapidly to the more stable anion, **23**, which has aromatic character. On the other hand, if R′ is phenyl, **22** has a long enough lifetime to be able to react with another mole of benzaldehyde and give adduct **26**. In both cases the alternate products were observed in trace amounts. The reversibility of **23** to **22** was ruled out by experiments in which 3(5)-methyl- (**24b**) or phenyl-5(3)-benzylpyrazoles (**24d**) were observed to give unchanged starting materials and none of adducts of type **26** upon treatment with benzaldehyde in the presence of ethanolic sodium ethoxide.

Several reactions were carried out in order to support structure **26**. Thermal decomposition of **26** by heating

(24) von P. Bosshard, *et al.*, *Helv. Chim. Acta*, **47**, 769 (1964).
(25) R. J. Crawford, A. Mishra, and R. J. Dummel, *J. Amer. Chem. Soc.*, **88**, 3959 (1966).

SCHEME VI



to 260–290° gave 1 mol of 3(5)-benzyl-5(3)-phenylpyrazole [**24d**(**d'**)] and benzaldehyde (Scheme VII).

Treatment of **26** with 48% aqueous hydrogen bromide furnished an unstable bromine-substituted salt, **27**, whose analysis was not consistent with the structure. When **27** was recrystallized from methanol, it underwent a solvolysis reaction to give **28** (**29** was obtained in ethanol.)

The ir spectrum of **26** in KBr indicates that **26d** is in equilibrium with **26d'**, since a sharp and strong band appears at 3365 ± 5 cm^{-1} due to free NH and a strong broad band at 3310–3325 cm^{-1} due to hydrogen-bonding hydroxy group. The nmr spectrum also suggests the existence of the hydrogen-bonded structure of type **26d**, since a free NH shows at δ 5.30 with one of the benzal hydrogens and a hydrogen-bonded OH as part of the phenyl proton region.

The salt **3c** gave benzaldehyde diethyl acetal in 80% yield (isolated) when it was treated under condition c and worked up in the standard manner. The mechanism of acetal formation is not clear at present. A similar result was observed during an intramolecular Wittig olefination reaction by Minami and Schweizer.[26]

Experimental Section

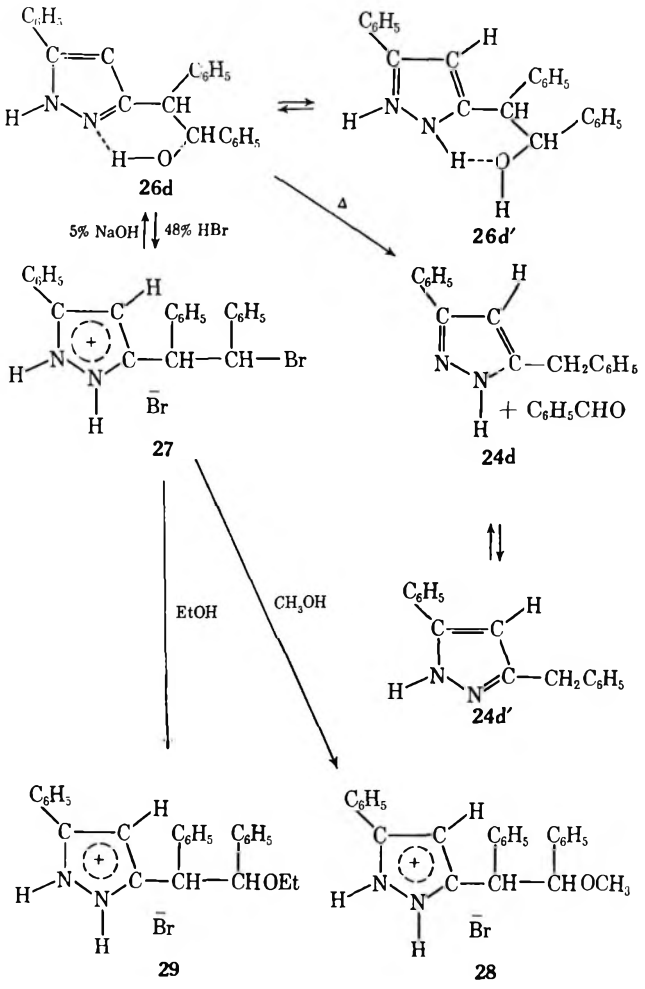
Indices of refraction were obtained on a Bausch and Lomb refractometer, ultraviolet spectra on a Perkin-Elmer Model 202 spectrometer, infrared spectra on a Perkin-Elmer 137 spectrophotometer or a Perkin-Elmer Model 421 grating spectrophotometer, and nmr spectra on a Varian A-60A spectrometer using tetramethylsilane as internal standard. All melting points were uncorrected and obtained on a Thomas–Hoover capillary melting point apparatus. Elemental analyses are by Micro-Analysis Inc., Wilmington, Del., and MHW Laboratories, Garden City, Mich. Any analytical and spectral data not included in the text may be found in the tables. All reactions were run under dry nitrogen except for aqueous reactions. All solvents used were anhydrous.

Warning. Diazoalkanes are skin irritants and reactions for their preparation and use should be done in a hood, wearing gloves.

2-Diazopropane (2c).—Reagent grade acetone (52 g, 1.0 mol) was added to 32 g (1.0 mol) of 95% hydrazine in the course of

(26) T. Minami and E. E. Schweizer, unpublished results.

SCHEME VII



2 hr with cooling. After all the acetone was added, the mixture was allowed to stir for an additional 1 hr at room temperature. The resultant mixture was extracted with 300 ml of ether and filtered through anhydrous magnesium sulfate into a 500-ml flask equipped with a magnetic stirrer. The extract was cooled to −5° in an ice–salt mixture, and yellow mercuric oxide (50 g) was added portionwise while keeping the temperature below 0°. After all of the mercuric oxide had been added, the reaction mixture was stirred until a deep pink color developed. The ethereal solution was filtered immediately through a cotton plug. The filtrate was used immediately for a further reaction and the yield was not determined.

Phenyldiazomethane (2d).[27]—Benzaldehyde (110 g, 1.03 mol) was added dropwise over a period of 1 hr with vigorous stirring to a mixture of 100 ml of ether and 95% hydrazine (32 g, 1.0 mol). The reaction was cooled with cold water in order to prevent the ether from boiling. The solution was diluted with 100 ml of ether, and cooled to below 5° in an ice–salt mixture. Yellow mercuric oxide (113 g) was added slowly, making sure that no nitrogen was evolved. Bubbling indicates a too rapid rate of oxide addition. The deep red mixture was allowed to stir vigorously for 2 hr at room temperature, filtered through a cotton plug, and dried ($MgSO_4$). The dried ethereal solution was allowed to react immediately with vinyl salts.

2-Pyrazolin-3-yltriphenylphosphonium Bromide (3a).—A freshly distilled ethereal solution of diazomethane[28] was added as rapidly as possible, at room temperature, to a solution of vinyltriphenylphosphonium bromide[29] (1) (56 g, 0.15 mol) dissolved in 400 ml of methylene chloride. Addition was continued until the orange color persisted. The mixture was allowed to stir for an additional 2 hr at room temperature. Ether was added to the solution in order to precipitate white crystals which were collected (61.0 g, 97%) by filtration. The crystals were dissolved in methylene chloride and precipitated with ethyl acetate to give an analytically pure sample: mp 162–164° dec; ir (KBr) 3100 (hydrogen bonded NH), 2850 (CH), 1580 (C=N, phenyl), 1115 (CP), 725, 690 cm^{-1} (phenyl); uv (MeOH) λ_{max} 231 mμ (ε 26,000), 301 (9800); nmr ($CDCl_3$) δ 2.88–3.30 (m, 2, C_4), 3.70–4.30 (m, 2, C_5), 7.45–8.20 (m, 15, C_6H_5), 9.90 ppm (s, 1, NH). The NH proton chemical shift depends on concentration and its exchangeable with D_2O for all **3a–e** species.

Anal. Calcd for $C_{21}H_{20}BrN_2P$: C, 61.32; H, 4.90. Found: C, 61.17; H, 5.08.

2-Pyrazolin-3-yltriphenylphosphonium Tetraphenylborate.—Methylene chloride (10 ml) was added to a solution of **3a** (1 g) and sodium tetraphenylborate (0.7 g). The mixed solution was boiled for 5 min and filtered. The filtrate was concentrated while adding EtOAc to precipitate 1.0 g of needlelike crystals. Recrystallization from acetone–ether gave an analytically pure sample: mp 181–185°; ir (KBr) 3250 (NH), 2980 (CH), 1580 (C=N, phenyl), 1115 (CP), 735, 710 cm^{-1} (phenyl).

Anal. Calcd for $C_{45}H_{40}BN_2P$: C, 83.07; H, 6.19. Found: C, 83.15; H, 6.21.

5-Methyl-2-pyrazolin-3-yltriphenylphosphonium bromide (3b) was prepared by the above procedure using a freshly distilled ethereal solution of diazoethane,[30] 200 ml of methylene chloride, and 23.48 g (0.0635 mol) of vinyltriphenylphosphonium bromide (1). On filtration, 26.7 g (99%) of white crystals were collected. An analytical sample was obtained as in the previous experiment: mp 174–175° dec; ir (KBr) 3050 (hydrogen bonded NH, CH), 1115 (CP), 755, 730, 693 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 1.42 (d, 3, CH_3, J = 6.5 Hz), 2.54 (dd, 1, C_4, $J_{vic\text{-}trans}$ = 10 Hz, J_{gem} = 16 Hz), 3.17 (dd, 1, C_4, $J_{vic\text{-}cis}$ = 11.5 Hz), 4.46 (m, 1, C_5, J = 6.5 Hz), 7.40–8.20 (m, 15, C_6H_5), 10.18 ppm (s, 1, NH).

Anal. Calcd for $C_{22}H_{22}BrN_2P$: C, 62.12; H, 5.21. Found: C, 62.28; H, 5.32.

5,5-Dimethyl-2-pyrazolin-3-yltriphenylphosphonium Bromide (3c).—A freshly prepared deep pink ethereal solution of 2-diazopropane was added to a solution of 1 (5 g, 0.0135 mol) in 100 ml of methylene chloride while keeping the temperature below 5° until the color persisted. The pink-colored mixture was stirred for 1 hr at room temperature, and precipitated 5.0 g (84%) of white crystals by adding ether. The product was recrystallized from CH_2Cl_2–EtOAc: mp 180–183° dec; ir (KBr) 3150, 3100 (hydrogen bonded NH), 1575 (C=N, phenyl), 1115 (CP), 760, 695 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 1.53 (s, 6, CH_3), 2.80 (s, 2, C_4), 7.30–8.10 (m, 15, C_6H_5), 10.22 ppm (s, 1, NH).

Anal. Calcd for $C_{23}H_{24}BrN_2P$: C, 62.88; H, 5.50. Found: C, 62.99; H, 5.14.

5-Phenyl-2-pyrazolin-3-yltriphenylphosphonium Bromide (3d).—An ethereal solution of phenyldiazomethane was added to a solution of 1 (60.1 g, 0.16 mol) in 400 ml of methylene chloride with vigorous stirring at room temperature until the color persisted. After 30 min of stirring, ether was added slowly to precipitate white crystals (79 g, 100%). An analytical sample was recrystallized from CH_2Cl_2–MeOH–EtOAc: mp 202–203° dec; ir (KBr) 3050 (hydrogen bonded NH), 1608, 1580 (C=N, phenyl), 1115 (CP), 753, 530, 690 cm^{-1} (phenyl); nmr (CF_3CO_2H) δ 3.22 (dd, 1, C_4, $J_{vic\text{-}trans}$ = 9 Hz, J_{gem} = 18 Hz), 3.73 (1, C_4, $J_{vic\text{-}cis}$ = 10 Hz), 5.38 (dd, 1, C_5), 7.07 (s, 5, CC_6H_5), 7.20–7.83 ppm (m, 15, PC_6H_5).

Anal. Calcd for $C_{27}H_{24}BrN_2P$: C, 66.59; H, 4.97. Found: C, 66.54; H, 5.02.

5,5-Diphenyl-2-pyrazolin-3-yltriphenylphosphonium Bromide (3e).—To a solution of 1 (40 g, 0.108 mol) dissolved in 300 ml of methylene chloride was added crystalline diphenyldiazomethane[31] (23 g, 0.118 mol) in 50 ml of ether or a dark red petroleum ether (bp 30–60°) solution of diphenyldiazomethane[32] in excess. The mixture was vigorously stirred at room temperature for 1 hr. Ether (200 ml) was added slowly to complete the precipitation of the product (53.9 g, 97.5%). The crude salt was placed in boiling CH_2Cl_2 (250 ml) and methanol was added until it dissolved. The solution was filtered and ethyl acetate was added while concentrating to give analytically pure white crystals. An analytical sample had mp 213–216° dec: ir (KBr) 3050 (hydrogen bonded NH), 1580 (C=N, phenyl), 1110 (CP), 750, 720, 690 cm^{-1}

(27) This synthesis was a modification of C. G. Overberger, *J. Amer. Chem. Soc.*, **86**, 658 (1964).

(28) J. A. Moore and D. E. Reed, *Org. Syn.*, **41**, 16 (1961).

(29) E. E. Schweizer and R. D. Bach, *ibid.*, **48**, 129 (1969).

(30) A. L. Wilds and A. L. Meader, *J. Org. Chem.*, **13**, 763 (1948).

(31) J. B. Miller, *ibid.*, **24**, 560 (1959).

(32) L. I. Smith and K. L. Howard, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 351.

(phenyl); uv (EtOH) λ_{max} 216 mμ (ε 30,100), 302 (ε 10,050); nmr (CF_3CO_2H) δ 3.92 (s, 2, CH_2), 7.37 (s, 10, CC_6H_5), 7.5–8.1 ppm (m, 15, PC_6H_5).

Anal. Calcd for $C_{30}H_{28}BrN_2P$: C, 70.34; H, 5.01. Found: C, 70.24; H, 4.75.

3-Methyl-1-pyrazolin-3-yltriphenylphosphonium Bromide (7).—The reaction was run by the same manner as in **3a**, using 100 ml of methylene chloride, an ethereal solution of diazomethane, and isopropenyltriphenylphosphonium bromide[33] (4) while keeping the temperature below 20° during addition. White crystals (9 g, 81.5%) were obtained by filtration. This salt slowly decomposed even at room temperature. In a protonic solvent like chloroform or trifluoroacetic acid, the salt decomposed into 3-methylpyrazole hydrobromide and triphenylphosphine. No analytical sample was obtained by recrystallization. Nmr, ir, and uv spectra were taken immediately after reprecipitation from MeOH with EtOAc: mp 100–102°; ir (KBr) 3000, 2940 (CH), 1550 (C=N), 1115 (CP), 757, 730, 692 cm^{-1} (phenyl); uv (MeOH) λ_{max} 235, 332 mμ; nmr (CD_3OD) δ 1.85 (d, t, 2, protons at C-4, J_{gem} = 15, J_{vic} = 8 Hz), 4.85 (m, 2, protons at C-5), 7.65–8.25 ppm [m, 15, $P(C_6H_5)_3$].

Anal. Calcd for $C_{22}H_{22}BrN_2P$: C, 62.11; H, 5.21; N, 6.58. Found: C, 61.03; H, 5.34; N, 6.17.

3,3-Diphenyl-1-methylallyltriphenylphosphonium Bromide (6).—A mixture of 4 (2.0 g, 0.0053 mol) and an excess amount of diphenyldiazomethane (1.3 g, 0.0061 mol) in 10 ml of methylene chloride was allowed to stand for 1 week at room temperature (reaction is too slow at 5°) and precipitated into ether to obtain 1.3 g (45%) of 6. An analytical sample was recrystallized from CH_2Cl_2–EtOAc: mp 194–196°; ir (KBr) 2950 (CH), 1480 (phenyl), 1430 ($-CH_3$), 1110 cm^{-1} (CP); nmr ($CDCl_3$) δ 1.80 (d d, 3, $-CH_3$, J_{HP} = 18.5, J = 7 Hz), 4.55 (m, 1, proton at C-1), 5.77 ppm (d d 1, vinyl proton at C-2, J = 7.5, J_{HP} = 10.5 Hz).

Anal. Calcd for $C_{34}H_{30}PBr$: C, 74.97; H, 5.50. Found: C, 74.83; H, 5.50.

Thermal Decomposition of 3a–e. Method A.—A sample of **3a–e** was heated to its melting point temperature for 15–30 min in an oil bath (temperature maintained 10° over melting point). After cooling, the solidified decomposition product was worked up by individual procedure.

Method B.—A sample of the salt was refluxed in mesitylene for 12–24 hr under dry nitrogen. After cooling the mixture, the solvent was removed by decantation and the solid material was purified.

Pyrazole Hydrobromide (14a).—Compound **3a** (4.2 g, 0.01 mol) was treated by method A. The solidified residue was washed with anhydrous ether several times under nitrogen atmosphere. The ether-insoluble solid was dissolved in methylene chloride and concentrated while adding EtOAc to precipitate 1.4 g (93.5%) of **14a**. The product was extremely hygroscopic. An analytical sample was prepared by sublimation at 60° under vacuum. Spectral data and melting point were the same as as those of an authentic sample prepared from pyrazole: mp 164–166°; nmr ($CDCl_3$) δ 6.82 (t, 1, proton at C-4, J = 2.5 Hz), 8.42 (d, 2, proton at C-3 and C-5), 13.04 ppm (broad s, 2, NH, chemical shift depends on concentration, exchangeable with D_2O).

3(5)-Methylpyrazole Hydrobromide (14b).—The residue resulting from the reaction of **3b** by method A or B was washed with EtOAc. Triphenylphosphine was obtained in quantitative yield by concentration of the EtOAc wash. The insoluble residue (2 g, 100%) was sublimed (50°) to obtain an extremely hygroscopic analytical sample: mp 98–101°; nmr ($CDCl_3$) δ 6.69 (d, 1, proton at C-4, J = 2.5 Hz), 2.66 (s, 3, $-CH_3$), 8.25 [d, 1, proton at C-3 (5)], 14.65 ppm (s, 2, NH, exchangeable with D_2O, and chemical shift depends on concentration).

Anal. Calcd for $C_4H_7BrN_2$: C, 29.46; H, 4.26; N, 17.18. Found: C, 29.52; H, 4.31; N, 16.92.

3,3-Dimethylallyltriphenylphosphonium Bromide (13c).—A sample of **3c** (2 g, 0.0045 mol) was treated by method B, refluxing for 12 hr. The solid residue (1.8 g, 98%) was recrystallized from CH_2Cl_2–EtOAc: mp 234–236° (lit.[34] mp 242°); ir (KBr) 1380, 1385 (geminal methyl), 1120 (CP) 895, 845 (vinyl), 755, 725, 695 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 1.32 (d, 3, cis methyl to vinyl proton, J = 4.0 Hz), 1.70 (d, 3, trans methyl to vinyl proton, J = 6.0 Hz), 7.40–8.25 ppm [m, 15, $-P(C_6H_5)_3$].

3-Phenylallyltriphenylphosphonium Bromide (13d).—A 5-g (0.0102 mol) quantity of sample, **3d**, was heated by method A for 20 min. A pale yellow solid (4.6 g, 100%) was recrystallized from CH_2Cl_2–EtOAc: mp 249–250° (lit. mp 240°[35], 256–258°[36]); ir (KBr) 1125 (CP), 980 (trans vinyl), 760, 745, 695 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 4.95 (d d, 2, $-CH_2-$, J = 7 Hz, J_{HP} = 15.5 Hz), 6.01 (d d, t, 1, vinyl proton at C-2 J_{trans} = 15.5, J_{HP} = 5 Hz, 687 ppm (d d, 1, vinyl proton at C-3, J_{HP} = 5.5 Hz). The nmr spectrum indicated a trans configuration between the phenyl at C-3 and the methylene group.

3,3-Diphenylallyltriphenylphosphonium Bromide (13e).—A quantitative yield of the crude salt was obtained by method A (15 min heating) or method B (refluxing 24 hr). An analytical sample was recrystallized from CH_2Cl_2–EtOAc: mp 248–250°; ir (KBr) 3000 (CH), 1110 cm^{-1} (CP); uv (MeOH) λ_{max} 212 mμ (ε 46,000), 270 (17,600); nmr ($CDCl_3$) δ 4.77 (d d, 2, $-CH_2-$, J_{HP} = 15.5 Hz), 6.00 (d d, 1, vinyl proton at C-2, J = 8 Hz), 6.67–7.50 (m, 10, phenyl protons at C-3), 7.50–8.18 ppm [m, 15, $-P(C_6H_{28})_3$].

Anal. Calcd for $C_{23}H_{28}BrP$: C, 73.80; H, 5.28; Br, 14.93. Found: C, 73.95; H, 5.36; Br, 14.88.

Thermal Decomposition of 7.—On heating **7** for 5 min (method A), **14b** and triphenylphosphine were obtained in a quantitative yield. The salt **7** was also decomposed completely during drying at 60° under vacuum for 1 day.

5,5-Diphenyl-1-methyl-2-pyrazolin-3-yltriphenylphosphonium Iodide (15a).—To a solution of 0.23 g (0.01 g-atom) of sodium dissolved in 150 ml of ethanol was added 5.63 g (0.01 mol) of **3e** under dry nitrogen. The solution was stirred at room temperature for 10 min. The resulting yellow mixture was allowed to stir with 4.2 g (0.03 mol) of methyl iodide at room temperature for 18 hr. The solution was precipitated by adding to ether (500 ml), filtered, and the residue dissolved in CH_2Cl_2. Insoluble sodium bromide was eliminated by filtration and the filtrate was concentrated and precipitated by adding EtOAc; 5.2 g (84%) of **15a** was obtained and recrystallized from methylene chloride–ethyl acetate: mp 249–254°; ir (KBr) 1580 (C=N, phenyl), 1080 (CP), 760, 730, 690 cm^{-1} (phenyl); uv (MeOH) λ_{max} 215 mμ (ε 37,200), 321 (11,600); nmr ($CDCl_3$) δ 3.15 (s, 3, $-CH_3$), 3.78 (s, 2, $-CH_2-$), 7.43 (s, 10, phenyl protons at C-5), 7.55–8.10 ppm [m, 15, $P(C_6H_5)_3$].

Anal. Calcd for $C_{34}H_{30}IN_2P$: C, 65.39; H, 4.85. Found: C, 65.26; H, 4.97.

5,5-Diphenyl-1-ethylaceto-2-pyrazolin-3-yltriphenylphosphonium bromide (15b) was prepared by the same procedure as **15a** using 0.23 g (0.01 mol) of sodium, 5.63 g (0.01 mol) of **3e**, and 3.7 g (0.02 mol) of ethyl bromoacetate. The precipitate was partially dissolved in boiling acetone, and the sodium bromide and unreacted starting salt were removed by filtration. The acetone solution was concentrated while adding ethyl acetate to precipitate 4.4 g (69%) of **15b**, recrystallized from acetone–ethyl acetate: mp 207–210°; ir (KBr) 1750 (C=O), 1210 (CO), 1115 (CP), 770, 730, 700 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 1.08 (t, 3, $-CH_3$, J = 7.0 Hz), 3.88 (q, 2, $-OCH_2-$), 3.88 (s, 2, two protons at C-4), 4.32 (s, 2, $-NCH_2-$), 7.38 (s, 10, phenyl protons at C-5), 7.50–8.10 ppm [m, 15, $P(C_6H_5)_3$].

Anal Calcd for $C_{37}H_{34}BrN_2O_2P$: C, 68.40; H, 5.28. Found: C, 68.58; H, 5.18.

1-Carbethoxy-5,5-diphenyl-2-pyrazolin-3-yltriphenylphosphonium Chloride (15c).—A mixture of 0.42 g (0.01 mol) of NaH (57% mineral oil dispersion) and 5.63 g (0.01 mol) of **3e** in 100 ml of acetonitrile was allowed to stir at room temperature for 3 hr. To the resulting yellow solution was added ethyl chloroformate (1.5 g, 0.015 mol) and the mixture was stirred at room temperature for 8 hr. After filtering the reaction mixture, the filtrate was precipitated by adding to ether; 2.5 g (43%) was collected of **15c**. An analytical sample was recrystallized from CH_2Cl_2–EtOAc: mp 179–180° dec; ir (KAr) 1750 (C=O), 1350 ($-CH_2-$, CN), 1200 (CO), 1115 (CP), 760, 730, 700 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 1.00 (t, 3, $-CH_3$, J = 7.0 Hz), 4.06 (q, 2, $-CH_2O-$), 4.08 (s, 2, protons at C-4), 7.40 (s, 10, phenyl protons at C-5), 7.45–8.00 ppm [m, 15, $P(C_6H_5)_3$].

Anal. Calcd for $C_{36}H_{32}ClN_2OP$: C, 73.15; H, 5.46. Found: C, 73.35; H, 5.56.

Aqueous Basic Hydrolysis of 15a,b. General Methods.—A sample of the salt was allowed to stir with a volume of 10% aqueous sodium hydroxide by warming the mixture to *ca.* 80° for

(33) P. T. Keough and M. Grayson, *J. Org. Chem.*, **29**, 631 (1964).
(34) R. Rüegg, *et al.*, *Helv. Chim. Acta*, **44**, 994 (1961).
(35) K. Friedrich and H. G. Henning, *Chem. Ber.*, **92**, 2756 (1959).
(36) E. T. Shaffer, Ph.D. Thesis, University of Delaware, 1967, p 32.

1 hr. The resulting mixture was cooled to room temperature and worked up as described in the individual procedures.

5,5-Diphenyl-1-methyl-2-pyrazoline (16a).—The resultant heterogeneous reaction mixture from the treatment by the general method, using 6.3 g (0.01 mol) of **15a** and 50 ml of 10% aqueous sodium hydroxide, was diluted with an equal volume of water, and extracted with ether (300 ml). The ether extract was washed with water several times and dried ($MgSO_4$). The dried ether extract was concentrated to give an oily liquid which was chromatographed (silica gel–ether) to obtain 1.8 g (76%) of **16a**. An analytical sample was collected by a microscale distillation under vacuum: $n^{23}D$ 1.5998; ir (neat) 3050, 2950 (CH), 1600 (phenyl, C=N), 1230 (CN), 760, 700 cm^{-1} (phenyl); uv (MeOH) λ_{max} 217 mμ (ε 12,700), 273 (4700); nmr ($CDCl_3$) δ 2.55 (s, 3, $-CH_3$), 3.37 (d, 2, $-CH_2-$, J = 1.7 Hz), 6.68 (t, 1, vinyl proton at C-3), 7.25 ppm (s, 10, phenyl protons).

Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.30; H, 6.82. Found: C, 81.49; H, 6.82.

5,5-Diphenyl-2-pyrazolin-1-ylacetic Acid (16b).—Compound **15b** (4.5 g, 0.0069 mol) was treated with 20 ml of 10% aqueous sodium hydroxide by the general method. The cooled mixture was filtered to collect 1.4 g (73%) of triphenylphosphine oxide. The aqueous filtrate was washed with ether several times to eliminate dissolved phosphine oxide. The aqueous alkaline layer was neutralized with dilute hydrochloric acid to precipitate 1.6 g of a pale yellow crude product, which was recrystallized from ether–methanol–hexane to obtain 1.4 g (71.5%) of **16b**: mp 164–167°; ir (KBr) 3050–3100 (hydrogen bonded OH), 1720 (C=O), 1600 (C=N, phenyl), 1250 (CO), 760, 710 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 3.37 (s, 2, $-NCH_2-$), 3.55 (d, 2, protons at C-4, J = 1.7 Hz), 7.06 (t, 1, vinyl proton at C-3), 7.36 (s, 10, phenyl protons), 11.37 ppm (m, 1, –OH, exchangeable with D_2O, chemical shift depends on concentration).

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75. Found: C, 72.93; H, 5.98.

Thermal Decomposition of 16b.—A small amount of **16b**, in an nmr tube, was heated to 180° for 40 min in an oil bath (bath temperature 170–190°). After cooling, the orange solid was dissolved in deuterated chloroform and its nmr spectrum was shown to be identical with that of **16a**.

Aqueous Basic Hydrolysis of 15c.—The salt **15c** (4.0 g, 6.8 mmol) was stirred with 50 ml of 5% aqueous sodium hydroxide for 4 hr at room temperature. The cooled reaction mixture was extracted with ether (300 ml), dried ($MgSO_4$), and concentrated to furnish an oily liquid. The oily liquid was chromatographed (silica gel–ether) to obtain 0.96 g (47%) of **18** and 0.40 g (20%) of **16c**.

An analytically pure sample of each compound was furnished by recrystallization from ether–petroleum ether.

β-Cyano-α,α-diphenylethylurethane (18).—An analytically pure sample had mp 114–116°; ir (KBr) 3230 (NH), 2230 (CN), 1710 (C=O), 1245 (CO), 770, 703 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 1.15 (t, 3, $-CH_3$, J = 7.0 Hz), 3.74 (s, 2, $-CH_2CN$), 3.98 (q, 2, $-OCH_2-$), 5.88 (s, 1, NH, exchangeable with D_2O slowly and chemical shift depends on concentration), 7.25 ppm (s, 10, phenyl protons).

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.51. Found: C, 73.30; H, 6.21; N, 9.41.

1-Carbethoxy-5,5-diphenyl-2-pyrazoline (16c).—An analytically pure sample melted at 157–158°: ir (KBr) 1705 (C=O), 1608 (C=N phenyl), 1165 (CO), 850 (vinyl), 762, 700 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 1.14 (t, 3, $-CH_3$, J = 7.0 Hz), 3.58 (d, 2, protons at C-4, J = 1.3 Hz), 3.96 (q, 2, $-OCH_2-$), 6.83 (t, 1, proton at C-3), 7.25 ppm (s, 10, phenyl protons).

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16. Found: C, 73.93; H, 6.19.

Attempted Alkylation of 3a and 3d.—A 0.01-mol sample of the individual salt was treated under the same procedure as **15a**. The precipitated salt in ether was identified as methyltriphenylphosphonium iodide in 50–70% yield. No alkylated salt was observed in each case. From the ether solution the corresponding pyrazole was isolated in over 70% yield and identified by comparing its nmr spectrum with that of the reported nmr spectrum.[37]

Reaction of 3d,e with Ethanolic Sodium Ethoxide. 3(5)-Phenylpyrazole.—Compound **3d** (4.87 g, 0.01 mol) was added to a solution of 0.23 g (0.01 g-atom) of sodium in 150 ml of ethanol. The mixture was allowed to reflux for 10 hr. After cooling, the resultant mixture was concentrated to 20 ml, and 200 ml of ether was added. The resulting solution was washed with two 20-ml portions of ether. The ether layer was vigorously shaken with dilute hydrochloric acid (150 ml), and the acidic aqueous layer was separated and washed with ether–ethyl acetate (1:1) mixture which was combined with the former ether layer. The combined organic layers furnished triphenylphosphine (2.6 g, 97%). The acidic aqueous solution was basified with 10% aqueous sodium hydroxide. The heterogeneous resultant solution was extracted with ether (100 ml), dried ($MgSO_4$), and concentrated to obtain 1.5 g (80%) of an oil which crystallized on standing, mp 77–78° (lit.[38] mp 78°). The nmr spectrum is identical with that found in the literature.[39]

3(5)-Phenylpyrazole Picrate.—To a solution of 1.0 g (0.007 mol) of pyrazole in 10 ml of ether was added a saturated ether solution of picric acid (2.13 g, 0.01 mol). The solution was brought to a boil and then cooled immediately. Cooling overnight gave 2.2 g (91%) of yellow crystals: mp 170–172° (lit.[40] mp 168–170°); nmr ($CDCl_3$) δ 6.92 (d, 1, proton at C-4, J = 2.5 Hz), 8.09 [d, 1, proton at C-3(5)], 7.32–7.62 (m, 3, meta and para protons of phenyl ring), 7.62–7.96 (m, 2, ortho protons of phenyl ring), 8.71 (s, 2, protons of picric acid ring), 14.84 ppm (broad s, 2, NH, exchangeable with D_2O, chemical shift depends on concentration).

5,5-Diphenyl-2-pyrazoline, (19).—This reaction was run in the same manner as the reaction with **3d** using 0.23 g (0.01 g-atom) of sodium and 5.63 g (0.01 mol) of **3e**. Refluxing for 3 hr gave triphenylphosphine oxide instead of triphenylphosphine from the combined organic layers. After the usual work-up procedure, 1.4 g (72.5%) of an oily product was obtained. All spectral data and melting point were identical with those of **19e** obtained by basic hydrolysis of **3e**: ir (KBr) 3330 (NH), 1600 (C=N, phenyl), 780, 740, 700 (phenyl), 545 cm^{-1} (vinyl); nmr ($CDCl_3$) δ 3.23 (d, 2, $-CH_2-$, J = 1.6 Hz), 6.67 (t, 1, proton at C-3), 5.9 (broad s, 1, NH, exchangeable with D_2O, chemical shift depends on concentration), 7.21 ppm (s, 10, phenyl protons).

Aqueous Basic Hydrolysis of 3a–e. General Procedure.—A sample (0.01 mol) of **3a–e** was allowed to stir with a specified volume of 10% aqueous sodium hydroxide at room temperature or warmed and then immediately cooled to room temperature. The resultant reaction mixture was diluted with an equal volume of water and extracted with ether (200 ml). The ether extract was washed with dilute hydrochloric acid (two 100-ml portions). The separated acidic aqueous layer was washed with ether (50 ml), and the organic layers were combined, dried ($MgSO_4$), and concentrated to give triphenylphosphine oxide. The aqueous solution was basified and extracted with ether (200 ml). The dried ($MgSO_4$) ether extract was concentrated to obtain the individual 2-pyrazoline (see results in Table I).

TABLE I

AQUEOUS BASIC HYDROLYSIS OF COMPOUNDS **3a–e**

Salt	Base, ml	Time, min	Temp, °C	$(C_6H_5)_3PO$, %	2-Pyrazoline (**19**), %	Ref
3a	50	30	25	99	[a]	
3b	70	60	25	95	62.5[b]	43
3c	60[c]	120	25	100	[a]	
3d	50[c]	80	40	96	83[d]	44
3e	100	60	80	97	83.3[d]	44, 45

[a] 2-Pyrazoline was not observed. [b] Picrate was prepared, mp 124–126° [mp 126°, von K. Freudenberg and W. Stoll, *Justus Liebigs Ann. Chem.*, **440**, 44 (1924)]. [c] 5% aqueous sodium hydroxide. [d] Mp 70–73° [mp 72–78.5°, D. S. Matteson, *J. Org. Chem.*, 27, 4293 (1962); 64.5–65.5°, M. Hamada, *et al.*, *Bull. Inst. Chem. Res., Kyoto Univ.*, **24**, 81 (1951)]; see the nmr and ir data in **19e**. [e] Nmr ($CDCl_3$) δ 2.38 (ddd, 1, cis proton at C-4 to phenyl, J_{gem} = 16.5 Hz, J_{trans} = 9.5 Hz), 2.90 (ddd, 1, trans proton at C-4 to phenyl, J_{cis} = 10 Hz), 4.52 (t, 1, proton at C-5), 6.56 (t, 1, proton at C-3, J = 1.5 Hz), 7.19 (s, 5, phenyl protons), 5.20 ppm (broad, s, 1, NH, exchangeable with D_2O, chemical shift depends on concentration).

(37) N. S. Bhacca, *et al.*, "NMR Spectra Catalog," Vol. II, Varian Associates, Palo Alto, Calif., 1963.

(38) K. Bowden and E. R. H. Jones, *J. Chem. Soc.*, 953 (1946).

(39) L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966).

(40) I. I. Grandberg, *Zh. Obshch. Khim.*, **31**, 2793 (1961).

Attempted Wittig Olefination Reaction of 3a–e.[41] **General Method A.**—Sodium was dissolved in ethanol and the salt was added. After stirring the mixture for 10 min, freshly distilled carbonyl compound was added to the yellow ylide solution and allowed to stir at room temperature for 12 hr. The reaction mixture was worked up by the individual procedure cited.

General Method B.—To a solution of sodium dissolved in ethanol was added freshly distilled carbonyl compound and then the salt was added portionwise through a wide rubber tube which is connected to an erlenmeyer flask. The reaction mixture was allowed to stir at room temperature and worked up as described.

General Method C.—To a mixture of salt and carbonyl compound in ethanol was slowly added ethanolic sodium ethoxide through a dropping funnel. After stirring the reaction mixture for a defined time at room temperature, the mixture was worked up as described.

3(5)-Benzylpyrazole [24a(a′)].—The reaction was carried out by method B, using 250 ml of ethanol, 0.69 g (0.03 g-atom) of sodium, 3.67 g (0.035 mol) of benzaldehyde, and 12.3 g (0.03 mole) of **3a**. Reaction time was 8 hr. The resultant reaction mixture was concentrated to 50 ml, poured into water (100 ml), extracted with ether–ethyl acetate (3:2) mixture (150 ml), and dried ($MgSO_4$). After removing the solvent, the pale yellow oily liquid was distilled (short path) under vacuum. A colorless oil (3.0 g, 65%) was collected at 140–150° (0.05 mm Hg): $n^{20}D$ 1.5762; ir (neat) 3300 (free NH), 3100 (hydrogen bonded NH), 1608 (C=N, phenyl), 950 (vinyl), 765, 720 700 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 3.95 (s, 2, $-CH_2-$), 5.96 (d, 1, proton at C-4, J = 2 Hz), 7.18 (s, 5, phenyl protons), 7.28 ppm [d, 1, proton at C-3(5)]. The chemical shift of the NH proton depends on concentration of sample and is exchangeable with D_2O.

Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.91; H, 6.36; N, 17.71. Found: C, 75.96; H, 6.49; N, 17.67.

3(5)-Benzylpyrazole Picrate.—To a solution of 0.2 g (1.33 mmol) of **24a(a′)** in 5 ml of ethanol was added 0.458 g (2.0 mmol) of picric acid. The solution was boiled for 5 min. To the orange-colored mixture was added enough hexane to double the volume, and it was cooled in the refrigerator overnight. Yellow crystals (0.5 g, 99.5%) were collected and recrystallized from ethanol–petroleum ether: mp 125–127°; nmr (DMSO-d_6 + $CDCl_3$) δ 4.17 (s, 2, $-CH_2-$), 6.42 (d, 1, proton at C-4, J = 2.5 Hz), 7.30 (s, 5, phenyl protons), 8.01 [d, 1, proton at C-3(5)], 8.76 (s, 2, protons of picric acid ring), 15.54 ppm (s, 2, NH, chemical shift depends on concentration, exchangeable with D_2O).

Anal. Calcd for $C_{16}H_{13}N_5O_7$: C, 49.61; H, 3.38; N, 18.08. Found: C, 49.60; H, 3.24; N, 18.14.

3(5)-Benzyl-5(3)-methylpyrazole [24b(b′)].—The reaction was run according to method C using 150 ml of ethanol, 8.5 g (0.02 mol) of **3b**, 2.5 g (0.025 mol) of benzaldehyde, and 0.46 g (0.02 g-atom) of sodium. The ethanolic sodium ethoxide was added over the period of 2 hr and the reaction mixture was subsequently stirred for 10 hr. The resultant mixture was concentrated to 20 ml and ether (300 ml) was added. The solution was washed with water (two 200-ml portions). The ether layer was shaken with 10–20% hydrochloric acid (100 ml) for 10 min. The acidic aqueous layer was separated and washed with ether and ethyl acetate, basified with 20% aqueous sodium hydroxide, and extracted with two 200-ml portions of ether. The combined, dried ($MgSO_4$) ether extracts were concentrated to give 3.3 g (96%) of a pale yellow oil. An analytical sample of **24b(b′)** was obtained by distillation at 135–145° (0.05 mm). The distillate solidified on standing: mp 71–73° (lit. mp 72–73.5°,[42] 77–78° [43]); ir (KBr) 3370 (free NH), 3170–3070 (hydrogen bonded NH), 1600, 1580 (C=N, phenyl), 1030 (vinyl), 735, 700 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 2.17 (s, 3, $-CH_3$), 3.91 (s, 2, $-CH_2-$), 5.75 (s, 1, vinyl proton at C-4), 7.20 (s, 5, phenyl protons), 12.40 ppm (s, 1, NH, exchangeable with D_2O and chemical shift depends on concentration). Compound **28b(b′)** was also obtained by method B (95%).

3-Benzyl-5-methylpyrazole Picrate.—To a solution of 1.0 g (5.9 mmol) of **24b(b′)** in 20 ml of ether and a few drops of EtOAc was added 2.0 g (8.7 mmol) of picric acid dissolved in EtOAc (3 ml). The mixture was boiled for 10 min and petroleum ether was added. After cooling in a refrigerator, one obtained 2.2 g (93%) of yellow crystals, recrystallized from ethanol: mp 119–121°; nmr (DMSO-d_6 + $CDCl_3$) δ 2.42 (s, 3, $-CH_3$), 4.11 (s, 2, $-CH_2-$), 6.17 (s, 1, proton at C-4), 7.30 (s, 5, phenyl protons), 8.88 ppm (s, 2, protons of picric acid ring). Two NH protons are exchangeable with D_2O and their chemical shifts depend on concentration.

Anal. Calcd for $C_{17}H_{15}N_5O_7$: C, 50.87; H, 3.77; N, 17.45. Found: C, 50.74; H, 3.69; N, 17.39.

3(5)-α,β-Diphenyl-β-hydroxyethyl-5(3)-phenylpyrazole [26d-(d′)].—The reaction was carried out by method B using ethanol (200 ml), 0.69 g (0.03 g-atom) of sodium, 7.42 g (0.07 g-atom) of benzaldehyde, and 15 g (0.031 mol) of **3d**. The reaction was run for 11 hr. The resultant reaction mixture was concentrated to half its volume, poured into water, and extracted with 300 ml of ether. The dried ($MgSO_4$) ether extract was concentrated to furnish an oily liquid. The oily liquid was chromatographed on silica gel (hexane–ethyl acetate). Compound **26d(d′)**, was obtained (9.0 g, 88%), recrystallized from CH_2Cl_2–EtOAc: mp 183–185°; ir (KBr) 3360 (free NH), 3225–3125 (hydrogen bonded NH and OH), 1580, 1550 (C=N, phenyl), 1050 (CO), 770, 700 cm^{-1} (phenyl); nmr (DMSO-d_6) δ 4.35 [d, 1, $-CH(C_6H_5)$, J = 8.0 Hz], 5.30 [d, 2, NH and $-CH(C_6H_5)OH$], 6.59 (s, 1, proton at C-4), 7.00–7.58 [m, 14, OH phenyl protons at side chain and meta and para protons of the phenyl ring at C-5(3)], 7.58–7.90 ppm [m, 2, ortho protons of phenyl ring at C-5(3)]. After added D_2O, the integration of the phenyl proton region was 13 and 1 at 5.30.

Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 81.36; H, 5.63; N, 8.30.

3-(α,β-Diphenyl-β-hydroxyethyl)-5-phenylpyrazole Picrate.—To a solution of 0.5 g (1.45 mmol) of **26d(d′)** dissolved in EtOAc (10 ml) was added 0.6 g (2.00 mmol) of picric acid in EtOAc (5 ml). After boiling for 5 min, the resultant yellow solution was concentrated while adding hexane to precipitate 0.8 g (100%) of the picrate, recrystallized from EtOAc–hexane: mp 183–185°; nmr (DMSO-d_6 + $CDCl_3$) δ 4.52 [d, 1, $-CH(C_6H_5)-$, J = 6.0 Hz], 5.45 [d, 1, $-CH(C_6H_5)OH$], 6.84 (s, 1, proton at C-4), 7.19–7.35 (d, 10, phenyl protons at side chain), 7.35–7.60 (m, 3, meta and para protons of phenyl ring at C-5), 8.81 (s, 2, protons of picric acid ring), 10.39 ppm (s, 2, NH and OH, exchangeable with D_2O and chemical shift depends on concentration).

Anal. Calcd for $C_{29}H_{23}N_5O_8$: C, 61.15; H, 4.06; N, 12.02. Found: C, 61.03; H, 4.15; N, 12.13.

3(5)-Benzyl-5(3)-phenylpyrazole [24d(d′)] by Thermal Decomposition of 26d(d′).—A sample of **26d(d′)** (2 g, 5.8 mmol) was heated to 270–290° for 90 min in a microscale distillation apparatus. In the center section of the apparatus, 0.53 g (91.3%) of benzaldehyde was collected. The residue was dissolved in ether and concentrated while adding petroleum ether until crystals formed. The white crystalline **24d,d′** (1.3 g, 93.5%) was obtained: mp 89–90° (lit. mp 89–90°,[44] 90.5–91° [45]); ir (neat) 3250–3150 (NH), 1595, 1575 (phenyl, C=N), 1040, 1015 (vinyl), 970 (vinyl), 770, 720, 700 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 3.75 (s, 2, $-CH_2-$), 6.15 (s, 1, proton at C-4), 7.0–7.4 (m, 8, para and meta proton of phenyl ring at C-5 and phenyl protons at side chain), 7.5–7.7 (m, 2, ortho protons of phenyl ring at C-5), 13.48 ppm (s, 1, NH, exchangeable with D_2O, chemical shift depends on concentration).

Attempted Reactions of 3(5)-Methyl- [24b(b′)] or Phenyl-5(3)-benzylpyrazole[46] **[24d(d′)] with Benzaldehyde.**—A sample (0.005 mol) of **24b(b′)** or **24d(d′)** was added to 30 ml of ethanol in which an equimolar amount of benzaldehyde and a catalytic amount of sodium had been dissolved. The resultant solution was allowed to stir at room temperature for 12 hr. The reaction mixture was poured into water, extracted with ether (100 ml), and dried ($MgSO_4$). The dried ether extract was concentrated to obtain an oily liquid which was shown by nmr to be only a mixture of starting materials in each case. No additional products were observed.

3-(α,β-Diphenyl-β-bromoethyl)-5-phenylpyrazole Hydrobromide (27).—A sample of **26d(d′)** (0.5 g, 1.47 mmol) was allowed to stir with 48% hydrogen bromide (20 ml) at room temperature for 1 hr. The mixture was filtered to furnish wet solids which were dissolved in chloroform. The chloroform solution was dried ($MgSO_4$) and concentrated while adding ether to pre-

(41) Attempted reactions with benzophenone, cyclohexanone, or cyclopentanone gave the same results as the reactions with refluxing ethanolic sodium ethoxide alone.

(42) J. B. Wright, *et al.*, *J. Med. Chem.*, **7**, 102 (1964).

(43) V. Y. Grinshtein, *et al.*, *ibid.*, **32**, 1077 (1962).

(44) D. G. Farnum and P. Yates, *J. Amer. Chem. Soc.*, **84**, 1399 (1962).

(45) C. Bürow and H. Grotowsky, *Chem. Ber.*, **34**, 1479 (1901).

(46) Prepared by a method reported by D. S. Matteson, *J. Org. Chem.*, **27**, 4293 (1962).

cipitate 0.4 g (56.5%) of white crystals. Even after numerous attempts at recrystallization, an analytical sample could not be obtained. The best sample we could obtain had mp 210–212°; ir (KBr) 3250 (NH), 2650, 2900 (amine salt); nmr (DMSO-d_6) δ 4.50 [d, 1, -CH(C_6H_5)-, J = 8.0 Hz], 5.43 [d, 1, -CH(C_6H_5)-Br], 7.10 (s, 1, proton at C-4), 7.10–8.00 (m, 15, phenyl protons), 9.6 ppm (s, 2, NH, exchangeable with D_2O, chemical shift depends on concentration).

3-(α,β-Diphenyl-β-methoxyethyl)-5-phenylpyrazole Hydrobromide (28).—Reagent grade methanol (5 ml) was added to a boiling solution of 0.4 g (0.83 mmol) of **27** dissolved in 10 ml of CH_2Cl_2. The clear solution was concentrated while adding hexane to precipitate 0.35 g (98%) of **28**. Recrystallization from methanol–hexane gave an analytical sample: mp 150–153°; ir (KBr) 3200 (NH), 2700 (amine salt), 1070 (CO), 750, 705, 695 cm^{-1} (phenyl); nmr (DMSO-d_6) δ 3.35 (s, 3, -OCH_3), 4.61 [d, 1, -CH(C_6H_5)-, J = 6.5 Hz], 5.58 [d, 1, -CH(C_6H_5)O-), 6.99 (s, 1, proton at C-4), 7.08–7.66 (m, 13, meta and para protons of phenyl ring at C-5, protons of phenyl ring at side chain), 7.66–8.00 (m, 2, ortho protons of phenyl ring at C-5), 9.00 ppm (s, 2, NH, exchangeable with D_2O and chemical shift depends on concentration).

Anal. Calcd for $C_{24}H_{23}BrN_2O$: N, 6.43. Found: N, 6.29.

3-(α,β-Diphenyl-β-ethoxyethyl)-5-phenylpyrazole hydrobromide (29) was prepared in the same manner as described above but using reagent grade ethanol instead of methanol. A 0.36-g (94%) sample of **29** was obtained. Recrystallization from ethanol–hexane gave an analytically pure sample: mp 154–156°; ir (KBr) 3200 (NH), 2700 (amine salt), 1630 (C=N, phenyl), 1040 (CO), 1005 (-CH_2CH_3), 745, 700 cm^{-1} (phenyl); nmr (DMSO-d_6 + $CDCl_3$) δ 1.18 (t, 3, -CH_3, J = 6.0 Hz), 3.62 (q, 2, -OCH_2-), 4.60 [d, 1, -CH(C_6H_5)-, J = 6.2 Hz], 5.57 [d, 1, -CH(C_6H_5)O-], 6.92 (s, 1, proton at C-4), 7.00–7.58 (m, 13, meta and para protons of phenyl ring at C-5 and phenyl protons at side chain), 7.58–8.00 (m, 2, ortho protons of phenyl ring at C-4), 8.33 ppm (s, 2, NH, exchangeable with D_2O and chemical shift depends on concentration).

Anal. Calcd for $C_{25}H_{25}NrN_2O$: N, 6.23. Found: N, 6.25.

3-Benzilidene-5,5-diphenyl-1-pyrazoline (20) was prepared by following method C using 13.8 g (0.025 mol) of **3e**, 200 ml of ethanol, 2.75 g (0.026 mol) of benzaldehyde, and 0.57 g (0.025 g-atom) of sodium. The reaction mixture was allowed to stir 15 hr. The resultant mixture was concentrated to 50 ml, poured into water (100 ml), and extracted with ether (300 ml). The dried $Mg(SO_4)$ ether extract furnished a pale yellow, oily liquid on concentration. To the oily liquid was added methanol (20 ml) and water (5 ml), and the mixture was allowed to stand in a refrigerator overnight. Needlelike crystals (6 g, 78%) were obtained. Recrystallization from ether–methanol gave an analytically pure sample of **20**: mp 123–124°; ir (KBr) 1575 (-N=N-), 1100 (CN, vinyl), 780–700 cm^{-1} (phenyl); uv (MeOH) λ_{max} 212 mμ (ϵ 21,800), 316 (19,400); nmr ($CDCl_3$) δ 3.23 (d, 2, -CH_2-, J = 2.5 Hz), 7.00–7.55 (m, 15, phenyl protons), 7.64 ppm (t, 1, benzilidene proton).

Anal. Calcd for $C_{21}H_{18}N_2$: C, 84.80; H, 6.15. Found: C, 84.78; H, 5.98.

From the mother liquor, 5,5-diphenyl-2-pyrazoline (**19e**) was identified in trace amount by nmr spectrum. By method A **24** was also prepared in 65% yield.

1,1,4,4-Tetraphenyl-1,3-butadiene.—The reaction was carried out by method A using 50 ml of ethanol, 0.23 g (0.01 g-atom) of sodium, 5.4 g (0.01 mol) of **13e** and 1.8 g (0.01 mol) of benzophenone in the course of 7 hr. The resultant reaction mixture was diluted with 10 ml of water and cooled in a refrigerator overnight. Collected was 2.2 g (61.5%) of white crystals of the product: mp 195–196°; ir (KBr) 2950 (CH), 910 (vinyl), 765, 703 cm^{-1} (phenyl). The nmr spectrum was identical with that reported in the literature.[37]

Registry No.—**3a**, 32251-61-9; **3a** tetraphenylborate, 32237-61-9; **3b**, 32251-62-0; **3c**, 32251-63-1; **3d**, 32251-64-2; **3e**, 32251-65-3; **6**, 32251-66-4; **7**, 32251-67-5; **13c**, 1530-34-3; **13d**, 7310-74-9; **13e**, 25201-67-6; **14a**, 27981-65-3; **14b**, 32251-72-2; **15a**, 32251-73-3; **15b**, 32251-74-4; **15c**, 32251-75-5; **16a**, 32251-76-6; **16b**, 32251-77-7; **16c**, 32251-78-8; **18**, 32251-79-9; **19e**, 25201-66-5; **20**, 25201-65-4; **24a(a′)**, 32251-82-4; **24a(a′)** picrate, 32251-83-5; **24b(b′)**, 32251-84-6; **24b(b′)** picrate, 32251-85-7; **24d(d′)**, 21917-99-7; **26d(d′)**, 32251-87-9; **26d(d′)** picrate, 32304-10-2; **27**, 32251-88-0; **28**, 32251-89-1; **29**, 32251-90-4; 3(5)-phenylpyrazole picrate, 6456-07-1; 1,1,4,4-tetraphenyl-1,3-butadiene, 1450-63-1.

Acknowledgment.—This work was supported by a U. S. Public Health Service Grant (CA 11000) for which we are most grateful.

Reactions of Phosphorus Compounds.[1,2] 30. Preparation and Basic Hydrolysis of 1-(β-Triphenylphosphonioethyl)-2-pyrazolin-3-yltriphenylphosphonium Dibromides

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Received May 24, 1971

Unsubstituted or 5-substituted 1-(β-triphenylphosphonioethyl)-2-pyrazolin-3-yltriphenylphosphonium dibromides were prepared by the phosphonioethylation reaction of vinyltriphenylphosphonium bromide and unsubstituted or 5-substituted 2-pyrazolinyltriphenylphosphonium bromides. Their basic hydrolysis was investigated and unusual phenyl migration and N–N bond cleavage were observed on the hydrolysis of phosphonium moiety attached at C-3.

During investigations of the preparations and reactions of pyrazolinyltriphenylphosphonium salts,[2] we found that vinyltriphenylphosphonium bromide easily undergoes Michael-type additions[3] (phosphonioethylation) with 2-pyrazolinyltriphenylphosphonium salts. In the preparation of pyrazolinyltriphenylphosphonium salts, when diazoalkanes were added slowly (not in excess) to vinyltriphenylphosphonium bromide, the phosphonioethylated salts were observed as contaminants. On the other hand, the phosphonioethylated salts, **3a–d** were prepared (>95% yield) by treatment of equal molar amounts of vinyltriphenylphosphonium bromide (**1**) and 2-pyrazolin-3-yltriphenylphosphonium bromides (**2a–d**) in the presence of a catalytic amount of base (potassium *tert*-butoxide) (Scheme I).

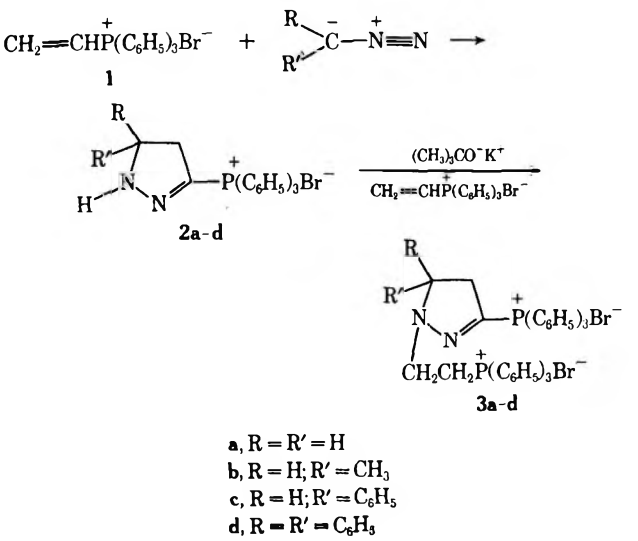
The phosphonioethylation reactions of 5-substituted salts of **2a** necessitated more vigorous reaction conditions in order to achieve comparable yields to that of the unsubstituted salt. This sluggishness is postulated as being due to the steric hindrance of substituents next to the reaction site.

(1) Part 28: E. E. Schweizer, T. Minami, and D. M. Crouse, *J. Org. Chem.*, **36**, 4028 (1971).

(2) Part 29: E. E. Schweizer and C. S. Kim, *ibid.*, **36**, 4033 (1971).

(3) E. E. Schweizer and R. D. Bach, *ibid.*, **29**, 1746 (1964).

SCHEME I



a, R = R′ = H
b, R = H; R′ = CH_3
c, R = H; R′ = C_6H_5
d, R = R′ = C_6H_5

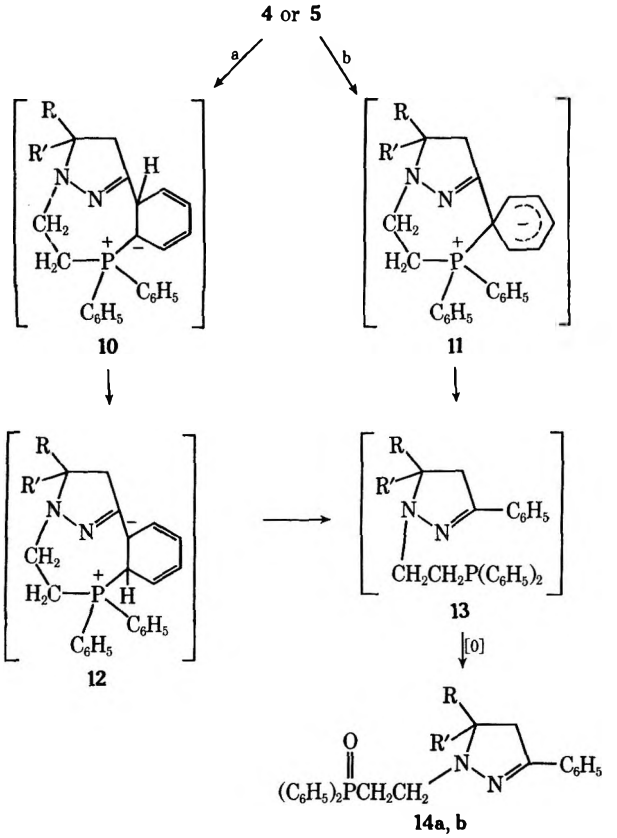
In the nmr spectrum the chemical shifts for protons at C-4, C-5, and the ethyl group attached to nitrogen could not be assigned individually, except for the single proton at C-5 in **3d**.

The basic hydrolysis of **3a–d** gave a series of unique products whose relative abundance could be varied by changing the acidity of the solvent used (Scheme II).

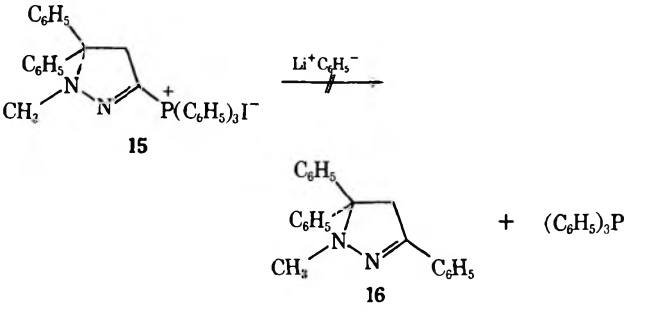
Hydrolysis in anhydrous methanolic sodium hydroxide gave relatively greater amounts of phenyl migrated product **14** (60%) over protonated compound **7** (40%). Hydrolysis in aqueous sodium hydroxide gave **14** (40%) and **7** (60%). If the carbanion **5** is assumed to be an intermediate during the hydrolysis reaction, the carbanion **5** will be protonated less readily in methanol than in the more acidic aqueous medium, as shown by the above ratio. The carbanion **5** attacks the phenyl moiety (attached to the phosphorus atom at the β-ethyl position) more readily in methanol (where it is longer lived) than in water. We have, however, no data which would allow us to say that the free carbanion **5** is indeed an intermediate in this reaction or that a concerted reaction, similar to that postulated by Trippett,[4] takes place. Similarly, the yield of **9** was also increased on hydrolysis of **3d** in methanol (47%) in comparison to the yield of **9** observed in water (<10%).

The phosphorus atom attached to C-3 was expected to be more electrophilic than the phosphonium group attached at the β-ethyl position. This expectation was borne out by the fact that at no time could it be shown that basic hydrolysis would form a diphenylphosphine oxide moiety at the β-ethyl position prior to the cleavage of the phosphonium moiety attached at C-3. The phosphonium salts, **8b** and **6c**, were, however, isolated, thus clearly showing precedence of hydrolysis. This difference is attributed to the greater electrophilicity imparted by the –N=C< group attached to the former (C-3) phosphonium moiety in contrast to the $-CH_2CH_2-$ group attached to the latter (β-ethyl).

The phenyl migration in this system is quite unusual, comparable only to 1,2-phenyl migrations reported by earlier workers.[5,6] The migrated (to C-3) phenyl moiety is one of the phenyl substituents attached to the phosphorus atom at the β-ethyl position. The two migrating pathways (a and b) are possible from the



intermediate **4** or the free carbanion **5** described in Scheme II. Attempts to isolate the assumed intermediate **13** were fruitless. This intermediate was presumably easily oxidized to give **14** under the hydrolysis condition, similar to the oxidation of ethyldiphenylphosphine.[7] The possibility of the nucleophilic attack (SN2) on C-3 by the phenyl anion formed by the hydrolysis of the phosphonium moiety attached to the β-ethyl position was ruled out by two facts: (a) no triphenylphosphine was observed; (b) 1-methyl-5,5-diphenyl-2-pyrazolin-3-yltriphenylphosphonium iodide (**15**) did not give the phenyl-substituted compound (**16**) at C-3, when it was allowed to react with phenyllithium. No reaction is observed.



The phenyl migrated structure, **14** (where R = R′ = H), was characterized by its comparison with an authentic sample prepared by aqueous basic hydrolysis of

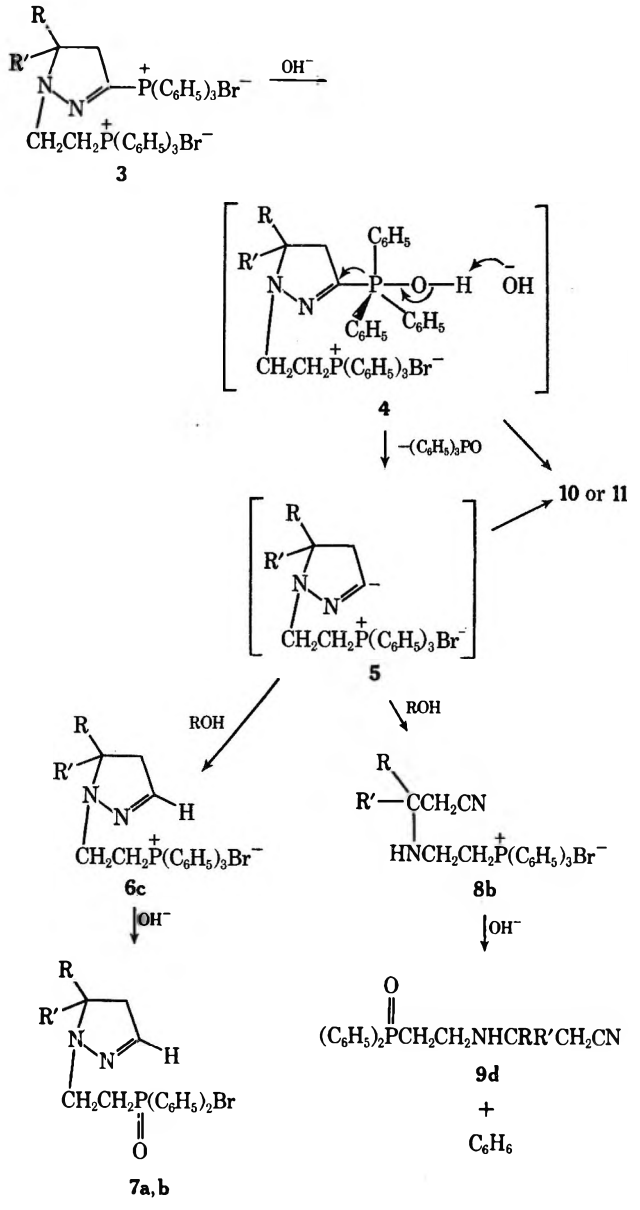
(4) J. R. Corfield and S. Trippett, *Chem. Commun.*, 1267 (1970).

(5) J. J. Brophy, K. L. Freeman, and M. J. Gallagher, *J. Chem. Soc.*, 2260 (1968).

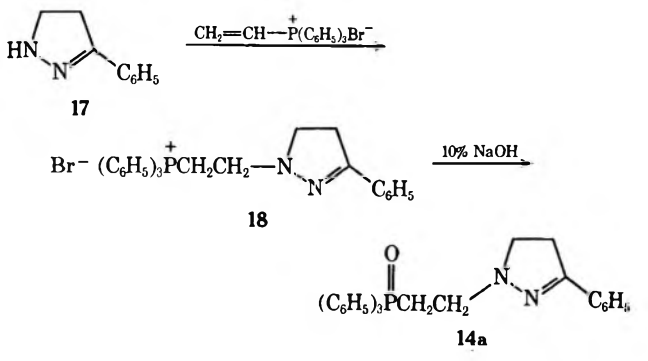
(6) E. Zbiral and L. Werner, *Justus Liebigs Ann. Chem.*, **707**, 130 (1967).

(7) von A. Michaelis and A. Link, *ibid.*, **207**, 214 (1881).

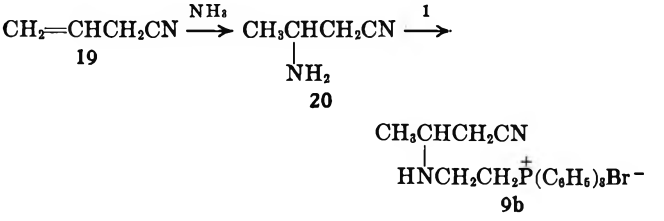
SCHEME II



3-phenyl-2-pyrazolin-1-ylethyltriphenylphosphonium bromide (**18**), which was synthesized from 3-phenyl-2-pyrazoline (**17**) and **1**.



The formation of nitrile compounds by N–N bond cleavage of 3-unsubstituted 2-pyrazolines under basic conditions was reported in the literature.[8-10] This cleavage during basic hydrolysis of **3** may be considered to take place *via* intermediate **4** or **5** by β elimination. Kost[10] reported that 3-alkyl substituted 2-pyrazoline did not give any N–N bond cleavage product (nitrile compound) under conditions which gave nitrile products from the 3-H species. The alkyl substituent at C-3 obviously blocked the formation of the anion at C-3. The structure of **9b** was shown to be identical with that of an authentic sample prepared by the phosphonioethylation of **1** and 2-aminobutyronitrile (**20**), which was synthesized by the ammonolysis of allyl cyanide (**19**).



Experimental Section

Infrared spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer or a Perkin-Elmer Model 421 grating spectrophotometer, and nmr spectra were obtained on a Varian A-60A spectrometer using tetramethylsilane as internal standard. All melting points were uncorrected and obtained on a Thomas–Hoover capillary melting point apparatus. Elemental analyses are by M. H. W. Laboratories, Garden City, Mich., and Micro-Analysis Inc., Wilmington, Del.

Any analytical and spectral data not included in the text may be found in the tables. All reactions were run under dry nitrogen except for aqueous reactions, and solvents used were anhydrous.

Preparation of Phosphonioethylated Salts. General Method A.—A catalytic amount of potassium *tert*-butoxide was added to a mixture of the salt (0.01 mol) and vinyltriphenylphosphonium bromide (3.7 g, 0.01 mol) in acetonitrile (50 ml) and allowed to stir at room temperature for 6 hr. To the resultant reaction mixture was added EtOAc (100 ml) slowly to precipitate the phosphonioethylated salt. An analytically pure sample was obtained by recrystallization from CH_2Cl_2–EtOAc.

General Method B.—The reaction was carried out in the same manner as method A using 0.03 mol of the starting materials, and refluxed for 12 hr. The reaction mixture was worked up by the general procedure of method A.

1-(β-Triphenylphosphonioethyl)-2-pyrazolin-3-yltriphenylphosphonium dibromide (3a) was prepared by method A in 95% yield: mp 251–253°; ir (KBr) 1570 (C=N, phenyl), 1340 (-CH_2-), 1115, 1100 (CP), 730, 695 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 2.85–3.35 (m, 2, protons at C-4), 3.75–4.68 (m, 6, protons at C-5 and ethyl group), 7.45–8.19 (m, 30, phenyl protons).

Anal. Calcd for $C_{41}H_{38}Br_2N_2P_2$: C, 63.09; H, 4.89; P, 7.93. Found: C, 63.11; H, 4.90; P, 8.06.

5-Methyl-1-(β-triphenylphosphonioethyl)-2-pyrazolin-3-yltriphenylphosphonium Dibromide (3b).—The salt prepared by method A in quantitative yield had mp 251–252°: ir (KBr) 1590 (C=N, phenyl), 1150, 1100 (CP), 725, 690 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 1.32 (d, 2, -CH_3, J = 6.0 Hz), 2.35–5.15 (m, 7, protons at C-4, C-5, and ethyl group), 7.40–8.20 (m, 30 phenyl protons).

Anal. Calcd for $C_{42}H_{40}Br_2N_2P_2$: P, 7.79. Found: P, 7.72.

5-Phenyl-1-(β-triphenylphosphonioethyl)-2-pyrazolin-3-yltriphenylphosphonium Dibromide (3c).—The salt prepared by method B (94%) had mp 262–264° dec: ir (KBr) 3000 (CH), 1580 (C=N, phenyl), 1440 (-CH_2), 1115–1105 (CP), 730, 695 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 2.50–5.25 (m, 6, protons at C-4 and ethyl group), 6.19 (d, d, 1, protons at C-5, J_{cis} = 13, J_{trans} = 12 Hz), 7.25–8.20 (m, 35, phenyl protons).

Anal. Calcd for $C_{47}H_{42}Br_2N_2P_2$: C, 65.89; H, 4.94; N, 3.27. Found: C, 65.92; H, 5.01; N, 3.18.

5,5-Diphenyl-1-(β-triphenylphosphonioethyl)-2-pyrazolin-3-yltriphenylphosphonium dibromide (3d) was prepared by method B in 94% yield. Recrystallized salt by the general method had mp 182–185°: ir (KBr) 1580 (C=N, phenyl), 1340 (-CH_2-), 1115–

(8) N. Rabjohn, H. R. Havens, and J. L. Rutter, *J. Heterocycl. Chem.*, **3**, 413 (1966).

(9) J. J. Grandberg and A. V. Potanova, *Zh. Obshch. Khim.*, **32**, 651 (1962).

(10) A. N. Kost, *et al.*, *Dokl Akad. Nauk SSSR*, **144**, 359 (1962).

1105 (CP), 727, 695 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 3.50–4.30 (broad s, 6, protons at C-4 and ethyl group), 7.45 (s, 10, phenyl protons at C-5), 7.50–8.20 (m, 30, protons attached to phenyl on phosphorus atoms).

Anal. Calcd for $C_{53}H_{46}Br_2N_2P_2$: C, 68.24; H, 4.97; P, 6.53. Found: C, 68.07; H, 5.11; P, 6.34.

Basic Hydrolysis of 3a–d. General Method A.—A sample of the salt (0.01 mol) was allowed to stir with 10% aqueous sodium hydroxide (100 ml) at 60° for 2 hr. The resultant heterogeneous solution was diluted with water to double its volume and extracted with EtOAc–ether (3:1) mixed solvent (300 ml). The dried ($MgSO_4$) extract was concentrated to obtain a white solid which was chromatographed (silica gel–EtOAc) to give compounds **7**, **14**, and ring-opened products.

General Method B.—A mixture of the salt (0.01 mol) and NaOH (1.2 g, 0.03 mol) in methanol (100 ml) was allowed to reflux for 1 day. The cooled reaction mixture was poured into water (200 ml) and extracted with EtOAc–ether (3:1) mixed solvent (300 ml). The dried ($MgSO_4$) extract was worked up by the same procedure as the above.

β-(2-Pyrazolin-1-yl)ethyldiphenylphosphine oxide (7a) was prepared by method A (25% yield) or by method B (16%): mp 114–116°; ir (KBr) 2800 (CH), 1580 (C=N, phenyl), 1180 (PO), 1125 (CP), 810 (vinyl), 720, 700 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 2.30–3.50 (m, 8, protons at C-4, C-5, and ethyl group), 6.77 (t, 1, vinyl proton at C-3, J = 1.5 Hz), 7.25–8.10 (m, 10, phenyl protons).

Anal. Calcd for $C_{17}H_{19}N_2OP$: C, 68.79; H, 6.43; P, 10.82. Found: C, 68.59; H, 6.53; P, 10.88.

β-(3-Phenyl-2-pyrazolin-1-yl)ethyldiphenylphosphine oxide (14a) was prepared by method A (17%) or by method B (26%), mp 153–155°.

Preparation of Authentic Sample of 14a.—The salt **18** (1.5 g, 2.9 mmol) was allowed to warm with 10% aqueous sodium hydroxide (30 ml) for 1 hr. The cooled reaction mixture was filtered and washed with water and gave 1 g (92%) of pale yellow crystals. An analytically pure sample was obtained by recrystallization from EtOAc–ether: mp 152–154°; mmp with **14a**, 151–154°; ir (KBr) 2800 (CH), 1580 (C=N, phenyl), 1180 (PO), 1125 (CP), 765, 700 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 2.35–3.70 (m, 8, protons at C-4, C-5, and ethyl group), 7.00–8.10 (m, 15, phenyl protons).

Anal. Calcd for $C_{23}H_{23}N_2OP$: C, 73.78; H, 6.46; N, 7.48. Found: C, 73.85; H, 6.48; N, 7.50.

β-(3-Phenyl-2-pyrazolin-1-yl)ethyltriphenylphosphonium Bromide (18).—A mixture of 1 (7.2 g, 0.02 mol) and 3-phenyl-2-pyrazoline[11] (3.0 g, 0.0206 mol) was allowed to stir in acetonitrile (60 ml) and a catalytic amount of potassium *tert*-butoxide at room temperature for 7 hr. The resulting reaction mixture was precipitated by pouring into ether to collect pale yellow solids (6.2 g, 60%). An analytically pure sample was recrystallized from CH_2Cl_2–acetone: mp 192–196°; ir (KBr) 1553 (C=N), 1120 (CP), 760, 740, 695 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 2.50–4.52 (m, 8, protons at C-4, C-5, and ethyl group), 7.10–8.20 (m, 20, phenyl protons).

Anal. Calcd for $C_{29}H_{28}BrN_2P$: C, 67.57; H, 5.47; N, 5.43. Found: C, 67.80; H, 5.37; N, 5.32.

β-(5-Methyl-2-pyrazolin-1-yl)ethyldiphenylphosphine oxide (7b) was prepared by method A (26%) or by method b (23%): mp 98–100°; nmr ($CDCl_3$) δ 1.15 (d, 3, $-CH_3$, J = 5.5 Hz), 1.95–3.75 (m, 7, protons at C-4, C-5, and ethyl group), 6.70 (t, 1, proton at C-3, J = 1.5 Hz), 7.20–8.00 (m, 10, phenyl protons).

Anal. Calcd for $C_{18}H_{21}N_2OP$: C, 69.21; H, 6.77. Found: C, 69.45; H, 6.83.

β-(5-Methyl-3-phenyl-2-pyrazolin-1-yl)ethyldiphenylphosphine oxide (14b) was prepared by method A (18%) or method B (30%): mp 144–147°; ir (KBr) 3000, 2900, 2800 (C–H), 1555 (C=N), 1180 (PO), 1120 (CP), 760, 690 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 1.25 (d, 3, $-CH_3$ J = 5.5 Hz), 2.35–3.90 (m, 7, protons at C-4, C-5, and ethyl group), 7.00–8.00 (m, 15, phenyl protons).

(11) von K. Auwers and P. Heimke, *Justus Liebigs Ann. Chem.*, **458**, 211 (1927).

Anal. Calcd for $C_{24}H_{25}N_2OP$: C, 74.26; H, 6.48. Found: C, 74.31; H, 6.25.

β-[N-(β-Cyano-α-methyl)ethyl]aminoethyltriphenylphosphonium Bromide (8b).—The salt **3b** (16.0 g, 0.02 mol) was allowed to stir with 5% aqueous NaOH at room temperature for 5 hr. The heterogeneous reaction mixture was diluted with water (100 ml), neutralized with dilute HCl, and extracted with EtOAc (500 ml). The dried ($MgSO_4$) extract was concentrated to 10 ml and ether was added to precipitate white crystals (1.2 g, 13%). A pure sample was recrystallized from CH_2Cl_2–EtOAc, mp 175–177°. This sample was identical in all respects with an authentic sample.

Preparation of 8b from 1 and β-Aminobutyronitrile.—A mixture of 1 (16.8 g, 0.045 mol) and β-aminobutyronitrile[12] (3.8 g, 0.045 mol) was allowed to stir in acetonitrile (50 ml) at room temperature for 10 hr. Ethyl acetate (20 ml) was added to the solution and the mixture was stirred for 30 min. White crystals (19.5 g, 85%) were collected. A recrystallized sample from CH_2Cl_2–EtOAc gave analytically pure **8b**: mp 175–176°; ir (KBr) 3200 (NH), 2230 (C≡N), 1120 (CP), 760, 755, 730, 680 cm^{-1} (phenyl); nmr ($CDCl_3$) obtained after adding D_2O, δ 1.01 (d, 3, $-CH_3$, J = 6.0 Hz), 2.37 (d, 2, $-CH_2CN$, J = 5.5 Hz), 3.03 (d, t, 2, NCH_2-, J_{HP} = 17.5, J = 6.0 Hz), 3.93 (d, t, 2, $-CH_2P$; J_{HP} = 11.5 Hz), 2.55–3.35 (m, 1, >$CHCH_3$), 7.50–8.15 (m, 15, phenyl protons).

Anal. Calcd for $C_{24}H_{26}BrN_2P$: C, 63.57; H, 5.78; P, 6.83. Found: C, 63.55; H, 5.90; P, 6.71.

β-(5-Phenyl-2-pyrazolin-1-yl)ethyltriphenylphosphonium Bromide (6c).—The salt **3c** (4.2 g, 5.0 mmol) was allowed to react with 0.2 g (5.0 mmol) of NaOH in refluxing water (20 ml) for 12 hr. The reaction mixture was extracted with EtOAc (300 ml), dried ($MgSO_4$), and concentrated to obtain an oily liquid. The oily liquid was partly dissolved in EtOAc–ether (1:1) mixed solvent (100 ml) and filtered to collect crystals (1.0 g, 40%). Recrystallization from CH_2Cl_2–EtOAc gave an analytically pure sample: mp 194–196°; ir (KBr) 2950, 2800 (CH), 1580 (C=N, phenyl), 1115 (CP), 755, 725, 690 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 2.25–4.85 (m, 7, protons at C-4, C-5, and ethyl group), 6.85 (t, 1, protons at C-3, J = 1.5 Hz), 6.95–7.45 (m, 5, phenyl protons at C-5), 7.45–8.00 (m, 15, protons attached to phenyl on phosphorus atom).

Anal. Calcd for $C_{29}H_{28}BrN_2P$: C, 67.57; H, 5.47; N, 5.43; P, 6.00. Found: C, 67.73; H, 5.62; N, 5.38; P, 6.17.

β-[N-(β-Cyano-α,α-diphenyl)ethyl]aminoethyldiphenylphosphine oxide (9d).—The salt **3d** (3 g, 3.12 mmol) was allowed to reflux in 10% aqueous NaOH (50 ml) for 2 hr. The cooled mixture was extracted with EtOAc (100 ml); the extract was dried ($MgSO_4$) and concentrated to 5 ml. Ether (100 ml) was added to the concentrated solution, and the solution was allowed to stand overnight in a refrigerator. Collected were white crystals of **9d** (0.65 g, 47%). Recrystallization from EtOAc gave an analytically pure sample: mp 176–178°; ir (KBr) 3250 (NH), 2250 (C≡N), 1200 (PO), 1130 (CP), 730, 725, 700 cm^{-1} (phenyl); nmr ($CDCl_3$) δ 2.18–3.00 (m, 5, $-CH_2CH_2-$ and NH, after adding D_2O integration decreased to four protons), 3.17 (s, 2, $-CH_2CN$), 7.26 (s, 10, protons attached to phenyl on carbon), 7.30–7.95 (m, 10, protons attached to phenyl on phosphorus).

Anal. Calcd for $C_{29}H_{27}N_2OP$: N, 6.22; P, 6.87. Found: N, 6.23; P, 6.71.

Registry No.—**3a**, 32247-17-9; **3b**, 32247-18-0; **3c**, 32247-19-1; **3d**, 32304-09-9; **6c**, 32247-20-4; **7a**, 32247-21-5; **7b**, 32247-22-6; **8b**, 32247-23-7; **9d**, 32247-24-8; **14a**, 32247-25-9; **14b**, 32247-26-0; **18**, 32247-27-1.

Acknowledgment.—The authors gratefully acknowledge a grant (CA 11000) from the U. S. Public Health Service.

(12) T. Kurihara and K. Ro, *J. Pharm. Soc. Jap.*, **75**, 1267 (1955).

6,11-Dihydro-11-hydroxy-6-oxo-2,2,5-trimethyl-2*H*-naphtho[1,2-*b*]pyran. A Stable Quinone Hemiketal Related to Vitamin K and of Special Interest Concerning Oxidative Phosphorylation

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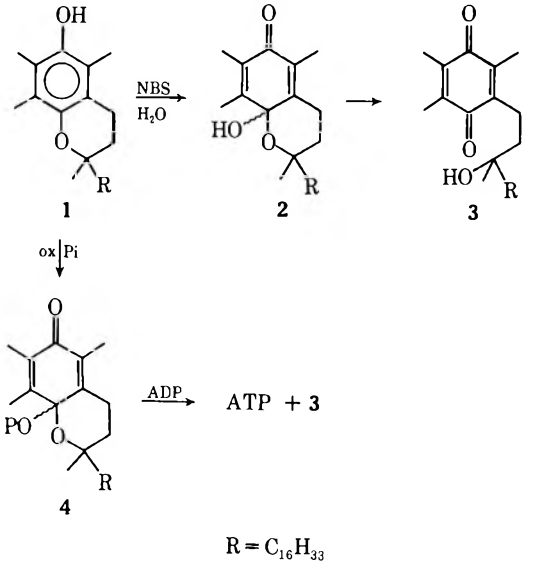
Argentic oxide oxidation of 6-methoxy-2,2,5-trimethyl-2*H*-naphtho[1,2-*b*]pyran gives the title compound in 35% yield. The latter is a stable hemiketal of special interest because it is structurally analogous to an intermediate proposed for oxidative phosphorylation. The hemiketal is isolated from an acidic medium and is isomerized only slowly and partially by triethylamine in refluxing benzene. Various attempts to prepare phosphate esters of the ketal hydroxyl function were unsuccessful.

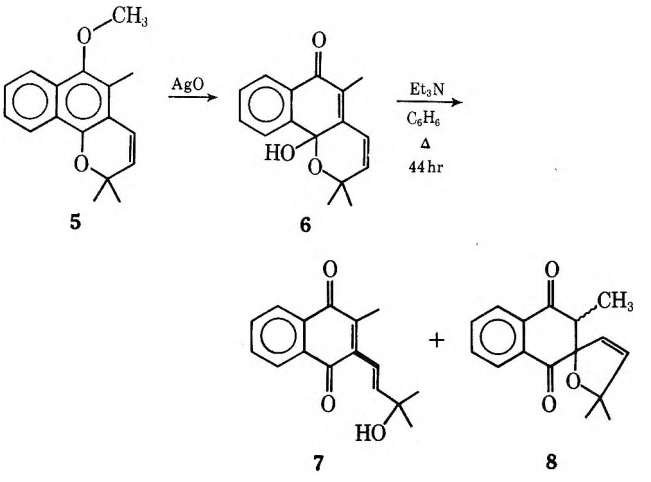
Although the involvement of quinones in oxidative phosphorylation has been decisively demonstrated, the detailed mechanism whereby electron transport (oxidation–reduction or respiration) is coupled to phosphorylation (the conversion of ADP to ATP) remains speculative. Several plausible mechanistic proposals have recently been found inconsistent with the isotope labeling experiments performed in the phylloquinone–*Mycobacterium phlei* system.[1,2] One of the several remaining possibilities consistent with the aforementioned experiments is that proposed by Durckheimer and Cohen (Scheme I).[3] The hemiketal **2** was identified as a

SCHEME I



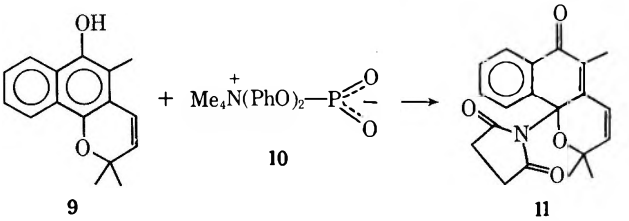
transient intermediate in the NBS oxidation of α-tocopherol (**1**) in the presence of water. The corresponding phosphate (**4**), which might be formed by oxidation of **1** in the presence of inorganic phosphate (P_i), was proposed as an analog of a possible ADP phosphorylating agent, and arguments were advanced in support of this possibility. In this context it is especially interesting that a relatively stable quinone hemiketal (**6**) has been isolated as a product of the oxidation of chromene **5** by argentic oxide (35% yield).[4] The hemiketal is amazingly stable for its structural type, as indicated by its isolation from an acidic aqueous medium and from the fact that long heating with triethylamine in benzene leads to a 27% yield of recovered **6**, along with two other interesting compounds, **7** (10%) and **8** (29%, all isolated yields, Scheme II). The special stability of **6** relative

SCHEME II



to Durckheimer and Cohen's hemiketal may be attributed to the conjugation energy of the pyranyl double bond with the aromatic ring, which could be diminished in the open chain form, and/or to the formation of a naphthoquinone system in the present instance as contrasted to a benzoquinone system in the earlier one. This extraordinary stability provided encouragement for attempts to prepare the phosphate of **6** of interest for oxidative phosphorylation experiments, as mentioned earlier.

The naphthopyranol **9** was oxidized by NBS in the presence of excess tetramethylammonium diphenyl phosphate (**10**). The desired phosphate was not found



among the products, but the novel molecule **11** was. It was considered possible that the phosphate had been formed but had undergone SN1 substitution by succinimide, giving **11**. To reduce the SN1 reactivity of any

(1) S. J. DiMari, C. D. Snyder, and H. Rapoport, *Biochemistry*, **7**, 2301 (1968).
(2) C. D. Snyder and H. Rapoport, *ibid.*, **7**, 2318 (1968).
(3) W. Durckheimer and L. A. Cohen, *J. Amer. Chem. Soc.*, **86**, 4388 (1964).
(4) W. E. Bondinell, C. D. Snyder, and H. Rapoport, *ibid.*, **91**, 6889 (1969).

phosphate formed, the more basic and nucleophilic salt ditetramethylammonium phenyl phosphate was substituted for **10** in a similar reaction. Still, none of the desired product was observed. The methyl group at the 5 position provides a convenient means for decomposition of such phosphates, by elimination. It therefore seems possible that model studies on a suitable unmethylated system might be to more avail.

Experimental Section

Melting points were determined without correction using a Mel-Temp apparatus. Infrared spectral measurements utilized a Beckman IR-5, nmr spectra a Varian A-60 spectrometer, unless otherwise specified. A consolidated Electrodynamics 21-102 spectrometer was used for obtaining mass spectra.

6,11-Dihydro-11-hydroxy-6-oxo-2,2,5-trimethyl-2*H*-naphtho[1,2-*b*]pyran (6).—To a stirred solution of 1.7 g (6.7 mmol) of the chromenol methyl ether **5** dissolved in dioxane (77 ml) and 85% phosphoric acid (7.7 ml) was added 2.5 g (20 mmol) of argentic oxide. After stirring for 2.5 hr at room temperature, the mixture was diluted with 200 ml of water and 100 ml of ether and worked up in the usual way. The ether solvent was evaporated cold, leaving an oil, which crystallized from 10% ether–hexane. There was obtained 0.584 g (35.4% yield) of the hemiketal **6**: mp 128–130° dec; ir ($CDCl_3$) ν 3600, 3400, 1650, 1605, 1340 cm^{-1}; mass spectrum m/e 256 (M), 238 (M − H_2O); nmr (10% DMSO-d_6–$CDCl_3$) τ 8.68 (s, 3 H), 8.32 (s, 3 H), 8.0 (s, 3 H), 5.9 (br s, 1 H), 3.74, 3.35 (q, 2 H, J_{AB} = 10.0 Hz), 2.47 (m, 2 H), and 2.04 (m, 2 H). Analytical purity could not be achieved because of the decomposition accompanying attempted recrystallizations.

Triethylamine Experiment.—A solution of 0.194 g (0.759 mmol) of the hemiketal **6** in benzene (20 ml) and triethylamine (0.32 ml, 2.27 mmol, 3 equiv) was refluxed for 44 hr under nitrogen and cooled, and the solvent was evaporated. Crystallization of the resulting gum from 4:1 hexane–ether afforded 52 mg (26.8%) of unreacted **6**. The mother liquor was evaporated cold and chromatographed on Florisil. The combined 1:1 benzene–hexane eluates were evaporated and gave 57 mg (29.4%) of **8** as a yellow gum: ir ($CHCl_3$) ν 1700, 1650, 1600 cm^{-1}; mass spectrum m/e 256 (M); nmr ($CDCl_3$, HA-100) τ 8.73 (several sharp lines, 9 H, among which are two doublets at 8.83 and 8.63, J = 7.0 Hz), 6.85 (sextet representing two overlapped quartets, 1 H, J = 7.0 Hz), 4.74 and 4.14 (q, 1 H, J = 6.0 Hz), 4.45 and 4.12 (q, 1 H, J = 6.0 Hz), 2.39 (m, 2 H), and 2.05 (m, 2 H).

The chloroform eluate yielded another gum which crystallized from 1:1 ether–hexane, affording 20 mg (10.3%) of the ring-opened quinone alcohol **7** as a tan solid: mp 81–85°; ir (CS_2) ν 3600, 1665, 1295, 713 cm^{-1}; mass spectrum m/e 256 (M); nmr ($CDCl_3$, HA-100) τ 8.55 (s, 6 H), 7.74 (s, 3 H), 3.35 (s, 2 H), 2.35 (m, 2 H), and 1.95 (m, 2 H); nmr (DMSO-d_6, 500 Hz sweep) showed the 3.35 singlet to be a doublet separated by about 1 Hz. The initially formed quinone alcohol must certainly have the cis geometry, but may isomerize by reversible addition of triethylamine to the terminal end of the dienone system. Because of the spectral similarity between **7** and the previously reported trans compound,[5] the assignment of the trans geometry is made, pending further evidence.

Tetramethylammonium *O,O*-Diphenyl Phosphate (10).—To a stirring solution of 0.616 g (4.0 mmol) of tetramethylammonium bromide in 4 ml of water was added 0.927 g (4.0 mmol) of silver(I) oxide. The mixture was stirred for 3 hr, filtered, and washed three times with 1-ml portions of water. Diphenyl phosphate (1.0 g, 4.0 mmol) was added to the filtrate, and the solution was stirred for 12 hr and then evaporated to a solid. This crude product was stirred in acetone, filtered, washed (acetone), and dried. There was obtained 1.17 g (91%) of **10** as a white solid, nmr (DMSO-d_6) τ 6.90 (s, 12 H) and 2.95 (m, 10 H).

NBS Oxidation of 9 in the Presence of 10.—To a stirring solution of 0.24 g (1 mmol) of **9** in acetonitrile (20 ml) was added 1.14 g (3.52 mmol) of tetramethylammonium diphenyl phosphate (**10**) and then 0.18 g (1.0 mmol) of *N*-bromosuccinimide. The mixture was stirred for 0.5 hr at room temperature, filtered under nitrogen, and evaporated cold under reduced pressure to afford a solid. The latter was leached several times with carbon tetrachloride, the washes were evaporated, and the crude solid was chromatographed on Florisil. Elution with 3:1 benzene–chloroform gave a product which formed yellow crystals in 1:1 ether–hexane. There was obtained 32 mg (9.4%) of the succinimidyl derivative **11**: mp 136° (with resolidification); ir ($CHCl_3$) ν 1700, 1650, 1600, 1205 cm^{-1}; mass spectrum m/e 239 (M − succinimidyl); nmr (CCl_4, HA-100) τ 8.68 (s, 3 H), 8.52 (s, 3 H), 8.20 (s, 3 H), 7.36 (s, 4 H), 4.59, 4.10 (q, 2 H, J_{AB} = 10.0 Hz), and 2.0 (d, 1 H, J = 8.0 Hz).

Recrystallization from ether–hexane gave **11** as yellow crystals, mp 144–145°.

Anal. Calcd for $C_{20}H_{19}O_4N$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.06; H, 5.81; N, 4.40.

Registry No.—**6**, 31819-55-3; **7**, 22268-05-9; **8**, 31819-57-5; **10**, 31819-58-6; **11**, 31883-40-6.

(5) C. D. Snyder and H. Rapoport, *J. Amer. Chem. Soc.*, **91**, 731 (1969).

Neutral and Positively Charged Azonitriles. Decomposition Rates and Efficiencies of Radical Production[1]

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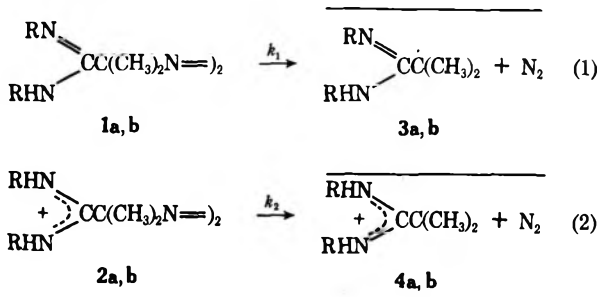
The uncharged azonitrile, 4,4′-azobis-4-cyano-1-methylpiperidine (ACMP), and its monopositive *N*-methyl and dipositive *N,N*′-dimethyl derivatives (MACMP and DACMP) have been synthesized. Their decomposition rates and efficiencies of radical production have been measured in the solvent DMSO and compared with the analogous data for 1,1′-azobis-1-cyanocyclohexane (ACC) and the new compound, 1,1′-azobis-1-cyano-4,4-dimethylcyclohexane (ACDC). The resulting activation parameters follow [azonitrile, ΔH^* (kcal/mol), ΔS^* (eu), ΔF^* (kcal/mol)]: ACMP, 32.6, 10.4, 28.8; MACMP, 31.7, 9.2, 28.4; DACMP, 29.8, 4.6, 28.1; ACC, 32.4, 9.7, 28.9; ACDC, 31.6, 8.6, 28.5. The efficiencies of radical production from ACC, ACDC, and DACMP are *ca.* 0.6, 0.5, and 0.4, respectively. These data are discussed in terms of electrostatic interactions between the positively charged ends of the molecules and the resultant geminate radicals. It is concluded that electrostatic effects are of minimal importance and that rate differences are largely the result of steric and/or solvation effects.

In order to determine whether positively charged geminate radicals possess a significant "cage effect," Hammond studied the thermal decomposition reactions of a pair of azobisisobutyramidines (**1a**, R = H; **1b**, R = $-CH_2-$) and their conjugate acids (**2a** and **2b**).[3] Products were consistent with radical formation (**3** and

(1) Support by the National Science Foundation (GP-8670) is gratefully acknowledged.

(2) NDEA Predoctoral Fellow, 1968–1971.

(3) G. S. Hammond and R. C. Neuman, Jr., *J. Amer. Chem. Soc.*, **85**, 1501 (1963).



1a, b 3a, b (1)

2a, b 4a, b (2)

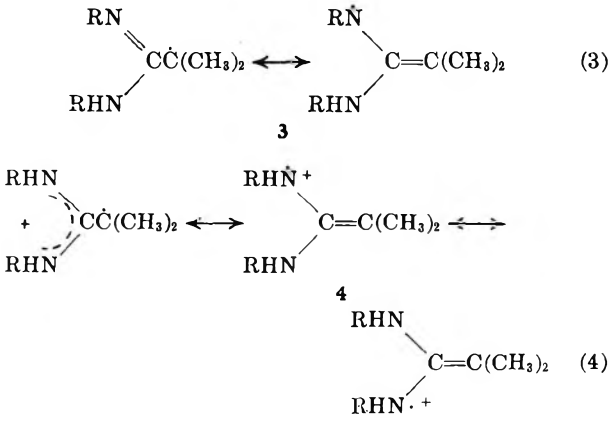
4) and efficiency measurements indicated that the neutral and positively charged systems had cage effects similar to each other and to that for azobisisobutyronitrile (AIBN) (Table I).

TABLE I
EFFICIENCY OF RADICAL PRODUCTION FROM 1, 2, AND AIBN[a,b]

Compd	Temp, °C	Solvent	Efficiency[c]
1a	70	DMSO–cumene	0.4
1b	80	DMSO–cumene	0.4
	70	DMSO–MMA[d]	0.4
2a	70	DMSO–cumene	0.60
2b	60	DMSO–tetralin	0.66
AIBN	70	DMSO–cumene	0.58

[a] Taken from ref 3. [b] From hydrocarbon oxidation unless otherwise indicated. [c] Fraction of azo compound yielding scavengeable radicals. [d] Efficiency from methyl methacrylate (MMA) polymerization.

It was suggested that the smaller cage effects (greater efficiencies of radical production) for **2a** and **2b** could reflect electrostatic repulsion between the positively charged geminate radicals (**4**). However, it was also recognized that this difference could be due to a greater stability of the radicals **4** compared to the neutral species **3**. In both cases the conjugate acids decomposed faster than the neutral azoamidines (k_{2a}/k_{1a} *ca.* 50, and k_{2b}/k_{1b} *ca.* 20). Since decomposition rates of azo compounds (RN=NR) reflect the stabilities of the product radicals (R·),[4,5] it was suggested that the positive radicals **4** were more stable than the neutral radicals **3**. This is consistent with the contributing forms which can be written for these species (eq 3 and 4).



3 (3)

4 (4)

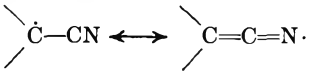
(4) For reviews see (a) C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957, pp 511–516; (b) C. G. Overberger, J.-P. Anselme, and J. G. Lombardino, "Organic Compounds with Nitrogen-Nitrogen Bonds," Ronald Press, New York, N. Y., Chapter 4.

(5) See also R. C. Neuman, Jr., and E. S. Alhadeff, *J. Org. Chem.*, **35**, 3401 (1970).

To resolve this uncertainty, it was proposed[6] that a similar study be carried out using azo compounds such as **5** and **6**. While the geminate product radicals from

5 6

these systems would be expected to possess different electrostatic interactions, their stabilities should be essentially the same due to delocalization into the α-cyano group (**7**). Also, because of the expected simi-



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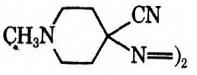
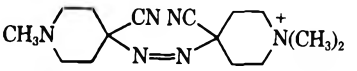
larities in radical stabilities, electrostatic repulsive interactions in the dipositive azo compound might be reflected in differences in the decomposition rate constants of **5** and **6**.

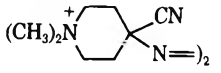
In this manuscript, we report such a study using the neutral, monopositive, and dipositive azo compounds **5**, **8**, and **9**. The results are compared with those for the reference compounds **10** and **11**.[7,8]



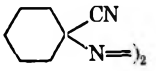
5
ACMP



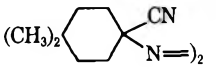
8
MACMP



9
DACMP



10
ACC



11
ACDC

Results and Discussion

Decomposition Kinetics. Rates of thermal decomposition of these azo compounds in DMSO were determined at 80, 85, 90, and 95° by monitoring the evolution of molecular nitrogen. An automatic pressure-equilibrating "gas apparatus" was utilized in these studies.[9] In all cases, the kinetic plots were first order and rate constants were calculated by least-squares analysis of the data. Rate constants reported in Table II are the result of least-squares analysis of the data from several runs and errors reported are standard deviations. Activation parameters were calculated from these data (Table II).

Acid–base titration data and microanalytical results indicated that the sample of MACMP nitrate used in

(6) Proposition V submitted by R. C. N. in partial fulfillment of the requirements for the Ph.D. degree, California Institute of Technology, 1963; see Ph.D. dissertation of R. C. N.

(7) All kinetic data in this study were obtained using the nitrate salts of MACMP and DACMP.

(8) Compounds **5** and **10** were synthesized by W. Snider and M. Amrich, respectively.

(9) (a) T. G. Traylor and C. A. Russell, *J. Amer. Chem. Soc.*, **87**, 3698 (1965). (b) We thank Professor Traylor for his help in providing us information about construction of the gas apparatus.

TABLE II

KINETIC DATA FOR THERMAL DECOMPOSITION OF ACMP, MACMP, DACMP, ACC, AND ACDC IN DMSO[a]

	$k \times 10^5$ sec^{-1}				
Temp, °C	ACMP	MACMP	DACMP	ACC	ACDC
80	0.97 ± 0.03	1.83 ± 0.02	2.84 ± 0.02	1.01 ± 0.01	1.51 ± 0.02
85	1.75 ± 0.07	3.36 ± 0.07	5.11 ± 0.05	2.01 ± 0.11	2.79 ± 0.08
90	3.64 ± 0.05	6.62 ± 0.34	9.87 ± 0.25	3.89 ± 0.05	5.40 ± 0.08
95	6.47 ± 0.06	11.80 ± 0.10	16.26 ± 0.24	6.83 ± 0.16	9.77 ± 0.04
ΔH^*	32.6 ± 0.9	31.7 ± 0.6	29.8 ± 1.0	32.4 ± 0.9	31.6 ± 0.5
ΔS^*	10.4 ± 2.6	9.2 ± 1.5	4.6 ± 2.7	9.7 ± 2.4	8.6 ± 1.3
ΔF^*	28.8	28.4	28.1	28.9	28.5

[a] Rate constants determined from nitrogen evolution.

these kinetic studies was contaminated by about 6 mol % DACMP dinitrate. Based on this and the known rate constants for decomposition of DACMP dinitrate, corrected rate constants for decomposition of MACMP nitrate were calculated from the kinetic data.[10] These and the resulting activation parameters are compared in Table III with those obtained by

TABLE III

A COMPARISON OF CORRECTED AND UNCORRECTED KINETIC DATA FOR MACMP NITRATE

	$k \times 10^5$ sec^{-1}	
Temp, °C	Uncorrected[a]	Corrected[b]
80	1.83 ± 0.02	1.76 ± 0.04
85	3.36 ± 0.07	3.31 ± 0.09
90	6.62 ± 0.34	6.23 ± 0.16
95	11.80 ± 0.10	11.56 ± 0.12
ΔH^*	31.7 ± 0.6	31.7 ± 0.4
ΔS^*	9.2 ± 1.5	9.2 ± 1.0
ΔF^*	28.4	28.4

[a] Experimental results based on nitrogen evolution. [b] Calculated from experimental data assuming 6 mol % contamination by DACMP dinitrate.

least-squares analysis of the uncorrected kinetic data (*i.e.*, those reported in Table II). Their similarity suggests that the contamination of MACMP nitrate can be ignored.

The differences in rate constants between the dipositive (DACMP) and neutral compound (ACMP) are substantially smaller than those found between the compounds 1 and their conjugate acids 2. This supports the arguments presented relative to radical stability in the azoamidine series (*vide supra*) and suggests that only a small fraction of the rate difference observed by Hammond could have been due to electrostatic repulsion between the positively charged ends of the azobisamidinium molecules.[3] That electrostatic repulsion is probably not responsible for even the small differences between ACMP and DACMP is indicated by the intermediate values of the decomposition rate constants for the monopositive compound MACMP.

The regular trend in rate constants and ΔF^* values for ACMP, MACMP, and DACMP suggests that their differences are the result of steric and/or specific solvation effects. A comparison of the rate data for ACC and ACDC shows that dimethyl substitution in the 4 positions increases the decomposition rate constants. Molecular models indicate that rehybridization of the ring carbon bearing the cyano group from sp^3 to sp^2 decreases steric interactions between the axial methyl in the 4 position and the *ring methylene groups in the 2 positions*. Since such rehybridization should occur to some extent in the transition state for decomposition of the azo compounds, the observed rate (and ΔF^*) differences between ACC and ACDC are reasonably explained on this basis.

In terms of these 1,3-steric interactions and their rate effects, it seems proper to compare the difference between ACDC and ACC with that between DACMP and ACMP. While the latter already has one methyl group on each ring nitrogen, these should be in equatorial positions[11] and this is supported by the similar rates and ΔF^* values for ACC and ACMP. Addition of the two methyl groups to form DACMP might then be expected to lead to the same rate enhancement as observed on going from ACC to ACDC. The effect is bigger, however, suggesting that other factors may be involved. Since DMSO is a good cation solvator, perhaps the increase in bulk around the positive ring nitrogens increases steric interactions in the ground state which are relieved somewhat in the decomposition transition state.

Examination of the values of ΔH^* and ΔS^* suggests that the rate variations are enthalpic and this does not conflict with the explanations proposed. While the value of ΔS^* for DACMP appears to be lower than those for the other systems, the magnitude of the difference does not seem to warrant special consideration.

Efficiencies of Radical Production.—The efficiencies of radical production from ACC (**10**), ACDC (**11**), and DACMP dinitrate (**9**) were determined from studies of inhibition of hydrocarbon oxidation.[3,12] The solvent system was a 2:1 v/v mixture of dimethyl sulfoxide and cumene;[3] the inhibitor was di-*tert*-butyl-*p*-cresol (DBPC). The neutral azo compound ACMP functioned as an oxidation inhibitor, and data could not be obtained for this system.[13] The efficiencies were cal-

(10) (a) The best values of the rate constant for decomposition of MACMP (k_1) were calculated from the known values (Table II) for DACMP (k_2) using the equation[10b] $V_\infty - V_t = V_{\infty 1}e^{-k_1 t} + V_{\infty 2}e^{-k_2 t}$, where V_∞ and V_t are the experimental volumes of nitrogen at infinite time and time t, and $V_{\infty 1}$ and $V_{\infty 2}$ are infinite time volumes from MACMP and DACMP, respectively; it was assumed that $V_\infty = V_{\infty 1} + V_{\infty 2}$ and that $V_{\infty 1} = 0.94\ V_\infty$. (b) See, *e.g.*, I. Amdur and G. G. Hammes, "Chemical Kinetics," McGraw-Hill, New York, N. Y., 1966, pp 15–16.

(11) While the relative "sizes" of the NH hydrogen and the nitrogen lone pair in piperidine are not certain [G. A. Yousif and J. D. Roberts, *J. Amer. Chem. Soc.*, **90**, 6428 (1968)] it seems accepted that the methyl group on nitrogen in *N*-methylpiperidine should occupy an equatorial position [J. B. Lambert, R. G. Keske, R. E. Carhart, and A. P. Jovanovich, *ibid.*, **89**, 3761 (1967); J. L. Sudmeier and G. Occupati, *ibid.*, **90**, 154 (1968)].

(12) (a) C.-H. S. Wu, G. S. Hammond, and J. M. Wright, *ibid.*, **82**, 5386 (1960). (b) Inhibition times (t_i) were sufficiently short to preclude complications from ketenimine formation.

(13) The tertiary amino groups must be acting as the inhibitors. Similar results were observed in attempts to study neutral azoamidines.[3]

TABLE IV

EFFICIENCIES OF RADICAL PRODUCTION FROM ACC, ACDC, AND DACMP DINITRATE IN 2:1 DMSO–CUMENE BY INHIBITION OF CUMENE AUTOXIDATION (80°)

RN_2R	$k \times 10^5$,[a] sec^{-1}	$(RN_2R)_0$, $M \times 10^2$	$(DBPC)_0$, $M \times 10^3$	t_i, min	Efficiency[a]
ACC	1.03	6.57	5.20	215.8	0.64
		6.40	1.40	58.2	0.62
		6.85	1.40	54.0	0.63
ACDC	1.40	6.44	1.40	51.6	0.51
		6.04	0.866	33.7	0.51
		5.13	0.866	37.9	0.54
DACMP· $2NO_3$	3.28	1.10	0.253	31.7	0.38
		0.87	0.174	26.3	0.40

[a] Rate constant for decomposition of RN_2R in DMSO–cumene solvent system; determined from nitrogen evolution.

culated (Table IV) using eq 5 in which $(DBPC)_0$ and $(RN_2R)_0$ are the initial concentrations of inhibitor and

$$a = (DBPC)_0/(RN_2R)_0(1 - e^{-kt_i}) \quad (5)$$

initiator, respectively; k is the rate constant for decomposition of RN_2R in 2:1 DMSO–cumene (Table IV),[14] and t_i is the duration of the inhibition period.[3,12]

The a values for ACC (Table IV) are in reasonable agreement with those reported by Hammond (0.61).[12] In comparison, the values of a for ACDC are smaller than those for ACC, while those for the dipositive azo compound, DACMP nitrate, are the *smallest* of the three. These data imply that any electrostatic repulsion between the positively charged geminate neighbors must be balanced by contributions which tend to decrease k_d. We suggest that among such factors, the mass of the radicals is of substantial importance. Increasing radical mass should lead to lower values of k_d, and a decrease in the efficiency of radical production. If it is assumed that the nitrate anions contribute to the mass of the product radicals from DACMP dinitrate, the data in Table IV follow the expected trend. These results indicate that the variation in the data in Table I is largely due to relative radical stability.

Experimental Section

Syntheses. 4,4′-Hydrazobis-4-cyano-1-methylpiperidine.—A 64.3-g (0.569 mol) sample of *N*-methyl-4-piperidone (Aldrich) was dissolved in 283 ml of water containing 56 g of concentrated hydrochloric acid. To this solution was carefully added with stirring 45.7 g of hydrazine sulfate followed by 31.3 g of sodium cyanide. After stirring for 24 hr, sufficient concentrated aqueous sodium hydroxide was added to bring the pH of the solution above 10. The resultant white precipitate was collected, washed with three portions of water, and dried *in vacuo* over P_2O_5, yield 57.0 g (72.6%).

4,4′-Azobis-4-cyano-1-methylpiperidine (ACMP) (5).—The 57.0-g sample of the hydrazo compound was dissolved in 347 ml of water containing 68.6 ml of concentrated hydrochloric acid in a three-necked, round-bottom flask fitted with an immersion thermometer, dropping funnel, and drying tube. While stirring this solution, 12.1 ml (35.3 g) of bromine was added dropwise over a period of 45 min. During the addition a small amount of red solid material was formed and at the end of the addition a white solid precipitated from solution. The latter was redissolved by warming the flask briefly and the red material was removed by filtration. The pH of the clear solution was raised above 10 by the addition of concentrated aqueous sodium hydroxide and the resultant white precipitate was collected by filtration, washed with water, and dried *in vacuo* over P_2O_5, yield 44.8 g (79.2%). The azo compound was recrystallized from 95% ethanol: mp 137–138° dec; uv λ_{max} (95% EtOH) 349.5 mμ (ε 16). *Anal.* Calcd for $C_{14}H_{22}N_6$: C, 61.29; H, 8.08; N, 30.63. Found: C, 61.30; 8.24; N, 30.20. The yield of nitrogen gas on thermal decomposition was *ca.* 99.9% of theoretical.

***N,N′*-Dimethyl-4,4′-azobis-4-cyano-1-methylpiperidine Dinitrate (DACMP Dinitrate) (9).**—A 3.4-g (0.014 mol) sample of recrystallized ACMP was dissolved in 300 ml of 95% ethanol. To this was added a solution consisting of 2 ml (*ca.* 0.032 mol) of CH_3I diluted to 30 ml with 95% ethanol. The flask was stoppered, covered with aluminum foil, and stirred at room temperature for 48 hr. The resultant white precipitate was filtered from solution, shaken with 100 ml of 95% ethanol, refiltered, and rinsed with three 10-ml portions of 95% ethanol. The 2.5 g (36.6% yield) of DACMP diiodide was dried *in vacuo* over phosphorus pentoxide: mp 187–190° dec; uv λ_{max} (50% EtOH) 349.0 mμ (ε 9.0). *Anal.* Calcd for $C_{16}H_{28}N_6I_2$: C, 34.42; H, 5.06; N, 15.06; I, 45.46. Found: C, 35.13; H, 5.61; N, 15.04; I, 42.70.

A 2.2-g sample of DACMP diiodide was dissolved in 50 ml of water and carefully titrated with stirring by 0.25 *M* aqueous silver nitrate until formation of silver iodide ceased. Tests on the resultant solution indicated the virtual absence of ionic iodide or silver. The solution was lyophilized, yielding 1.7 g (99%) of DACMP dinitrate: mp 183–185° dec; uv λ_{max} (H_2O) 351.2 mμ (ε 11.6). *Anal.* Calcd for $C_{16}H_{28}N_8O_6$: C, 44.85; H, 6.59; N, 26.15; O, 22.41. Found: C, 44.91; H, 6.91; N, 24.99. The yield of nitrogen gas on thermal decomposition was *ca.* 99.8% of theoretical.

***N*-Methyl-4,4′-azobis-4-cyano-1-methylpiperidine Nitrate (MACMP Nitrate) (8).**—A 22.3-g (0.081 mol) sample of recrystallized ACMP was dissolved in 300 ml of anhydrous methanol and to this was added a solution of 0.50 ml (0.008 mol) of methyl iodide in 25 ml of methanol. The solution was stirred for 2 days in a stoppered flask covered with aluminum foil. Subsequently, the methanol was evaporatively distilled giving white crystals with a yellowish tinge. Excess ACMP was removed using a Soxhlet extractor with ether as the solvent. The solid was continuously extracted until no more ACMP was found in the ether solvent. The remaining 2.6 g of solid material was canary yellow and tests with aqueous $AgNO_3$ showed that it contained ionic iodide. Titration with standard hydrochloric acid indicated that the solid was the iodide salt of MACMP contaminated with about 3 mol % DACMP diiodide.

The nitrate salt was obtained by ion exchange. A 15.2-g sample of wet Dowex 1-10X anion-exchange resin (33.4 mequiv exchangeable anions) was placed in a standard 100-ml buret. The column was treated with a solution of 28.3 g of sodium nitrate in 100 ml of water and rinsed with 200 ml of water. A solution made up of 1.86 g of MACMP iodide in 50 ml of water was slowly run through the column followed by an additional 50 ml of water. The solution was lyophilized, giving white crystals. Titration with standard hydrochloric acid indicated that MACMP nitrate was contaminated by *ca.* 6 mol % (8 wt %) DACMP dinitrate. *Anal.* Calcd for $C_{15}H_{25}N_7O_3$: C, 51.27; H, 7.17; N, 27.90; O, 13.66. Found: C, 50.86; H, 7.50; N, 26.80. Calcd for 92 wt % $C_{15}H_{25}N_7O_3$ and 8 wt % $C_{16}H_{28}N_8O_6$: C, 50.76; H, 7.12; N, 27.77; O, 14.35. Based on 92 wt % MACMP nitrate in the samples used in the kinetic study, the yield of nitrogen gas on thermal decomposition was *ca.* 97% of theoretical.

4,4-Dimethyl-2-cyclohexen-1-one.[15]—A solution of 58.5 g (0.81 mol) of distilled isobutyraldehyde and 56.9 g (0.81 mol) of distilled methyl vinyl ketone in 300 ml of anhydrous methanol was placed in a 1-l. single-neck round-bottom flask fitted with a condenser, drying tube, and magnetic stirrer. A 30-ml portion of 1 *N* sodium methoxide in methanol was added and the resulting solution started to reflux immediately. After 1 hr, the solution was neutralized with 1.8 ml of glacial acetic acid, mixed with 1 l. of water, and extracted eight times with 20-ml portions of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, and evaporatively distilled. The resulting liquid was vacuum distilled and the desired product was collected in 37% yield over the range 84–87° (20 mm): ir 1680 cm^{-1} (C=O) (lit.[15] 1680 cm^{-1}); uv λ_{max} (95% EtOH) 318.5 mμ (ε 29.5) [lit.[15] λ_{max} (EtOH) 318.0 mμ (ε 30)]; semicarbazone mp 207–208° (lit.[15] 209°).

(14) The rate constants for decomposition of ACC and ACDC are about the same in 2:1 DMSO–cumene as in pure DMSO (Table II); however, that for DACMP is slightly larger. It is possible that this reflects an electrostatic repulsion effect.

(15) J. M. Conia and A. Le Craz, *Bull. Soc. Chim. Fr.*, 1934 (1960).

4,4-Dimethylcyclohexanone.[15]—A mixture of 15.4 g of 4,4-dimethyl-2-cyclohexen-1-one, 50 ml of ether, and 1 g of platinum black was hydrogenated at room temperature using an initial hydrogen pressure of 24 psi. The mixture was allowed to react for 14 hr, filtered, and evaporatively distilled. The ir showed an absorption at 1710 cm^{-1} (C=O) (lit.[15] 1710 cm^{-1}). Another absorption was observed at 3390 cm^{-1} (OH) indicating that a part of the ketone had been reduced to the corresponding alcohol. To reoxidize the alcohol to the ketone, the procedure of Auwers and Lange was used.[16] A solution consisting of 10 g of potassium dichromate and 8.5 g of concentrated sulfuric acid in 50 ml of water was prepared and the crude reaction mixture containing both alcohol and ketone was added. This mixture was stirred for 0.5 hr, heated on a steam bath for 10 min, and steam distilled. The distillate was saturated with sodium chloride, extracted with ether, dried over anhydrous magnesium sulfate, and evaporatively distilled, resulting in the recovery of 12.1 g of white needle crystals: uv λ_{max} (EtOH) 281.0 mμ (ϵ 31) [lit.[15] λ_{max} (EtOH) 281.0 mμ (ϵ 32)].

1,1′-Hydrazobis-1-cyano-4,4-dimethylcyclohexane.—A solution of 19.0 g (0.15 mol) of 4,4-dimethylcyclohexanone, 7.4 g (0.15 mol) of sodium cyanide, 9.8 g (0.075 mol) of hydrazine sulfate, and 15 ml of dioxane in 100 ml of water was stirred for 50 hr at room temperature. The resulting solid was filtered and recrystallized from 95% ethanol, 2.19 g (97% yield), mp 148–149°.

1,1′-Azobis-1-cyano-4,4-dimethylcyclohexane (ACDC) (11).—A 15.1-g (0.05 mol) sample of the hydrazo compound was stirred with 25 ml of 2 *N* HCl, and bromine was added in 0.5-ml portions to the resulting slurry with cooling until the mixture retained a yellowish color. A total of 2.58 ml of bromine was added (94.5% of theoretical). The yellowish, fluffy solid was removed by filtration, recrystallized first from methanol, and then from low-boiling petroleum ether (bp 30–60°). The azo compound was obtained in 79% yield: mp 132–133° dec; uv λ_{max} (95% EtOH) 351.0 mμ (ϵ 18.3). *Anal.* Calcd for $C_{18}H_{28}N_4$: C, 71.96; H, 9.39; N, 18.65. Found: C, 71.75; H, 9.38; N, 18.24. The yield of nitrogen gas on thermal decomposition was *ca.* 100% of theoretical.

1,1′-Azobis-1-cyanocyclohexane (ACC) (10).—This compound was synthesized by Mr. M. Amrich according to the procedure reported by Overberger (see Hammond)[12] and recrystallized from methanol: mp 113–115° dec (lit.[12] 113–114°, 114–115°); uv ϵ at 350.0 mμ (95% ethanol), 18.2 (lit.[12] 17.9, ethanol; 19.4, chlorobenzene).

Kinetic Studies.—Nitrogen evolution was monitored using a constant-pressure gas apparatus based on a design by Professor T. Traylor.[9]

Efficiency Studies.—Oxygen uptake was monitored using the gas apparatus employed in the kinetic studies.

Registry No.—**5**, 32174-90-6; **8**, 32174-91-7; **8** nitrate, 32174-92-8; **9**, 32174-93-9; **9** dinitrate, 32256-09-0; **9** diiodide, 32174-94-0; **11**, 32174-95-1; 1,1′-hydrazobis-1-cyano-4,4-dimethylcyclohexane, 32174-96-2.

(16) K. v. Auwers and E. Lange, *Justus Liebigs Ann. Chem.*, **401**, 303 (1913).

Ion Radicals. XXIII. Some Reactions of the Perylene Cation Radical[1,2]

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Solid perylene cation radical perchlorate has been prepared (a) in admixture with perylene by anodic oxidation of perylene, and (b) in admixture with silver iodide by oxidation of perylene with iodine–silver perchlorate. Each of these preparations is usable for studying reactions of the cation radical. Reaction with water led to perylene and 3,10-perylenequinone (**3**). The stoichiometry of this reaction is $6C_{20}H_{12}\cdot^+ + 2H_2O \rightarrow 5C_{20}H_{12} + C_{20}H_{10}O_2 + 6H^+$. Reaction with pyridine gave *N*-(3-perylenyl)pyridinium perchlorate (**9**), degradation of which by the Zincke method gave 3-aminoperylene. Compound **9** was also obtained easily by the direct reaction of perylene, iodine, silver perchlorate, and pyridine. Perylene cation radical was reduced quantitatively by iodide ion. Reduction by bromide ion also appeared to be quantitative. Reaction with chloride ion also led mostly to perylene. Reaction with fluoride ion did not occur; reaction with unremoved small amounts of water occurred slowly instead. Reaction with acetate and benzoate ion led to the 3-perylenyl esters. The overall picture is that nucleophilic substitution occurs where the nucleophile is not easily oxidized, and substitution occurs at the position in the cation radical which has the highest positive charge density according to simple HMO calculations.

Although the perylene cation radical has been known for some time and has been well characterized spectroscopically,[4] hardly anything is known about its chemistry. Some years ago it was found that perylene was recovered from dilution of a solution of the cation radical in 96% sulfuric acid with water.[5] Since conversion of perylene into the cation radical in 96% sulfuric acid is high,[5] the re-formation of perylene by dilution with water was, apparently, a chemical rather than physical reaction.

Cation radicals are frequently made in strong acid solutions. Chemical studies in such cases are almost impossible. Antimony pentachloride is also frequently used, both for spectroscopic, solution studies[4] and for precipitating cation radicals as antimony halide salts.[6] The composition of the perylene cation radical salt has been reported as $C_{20}H_{12}SbCl_5$, for example.[6] The use of antimony pentachloride systems for chemical studies, however, does not seem to be suitable. Complications are caused by the antimony halide, and, in reaction with nucleophiles, organoantimony compounds or complexes are formed.[7]

Recently, the perylene cation radical was prepared in the solid state by two methods which we have adapted fruitfully to chemical studies. Williams prepared a 1:1 complex of perylene and perylene perchlorate by anodic oxidation,[8] while Sato and coworkers[6] precipitated the perchlorate in admixture with silver iodide by treating perylene with iodine and silver perchlorate. We have already shown that the cation radical isolable by each of these methods can be used

(1) Part XXII: J. J. Silber and H. J. Shine, *J. Org. Chem.*, **36**, 2923 (1971).

(2) Supported by the National Science Foundation Grant No. GP-25989X.

(3) Postdoctoral fellow.

(4) I. C. Lewis and L. S. Singer, *J. Chem. Phys.*, **43**, 2712 (1965).

(5) W. I. J. Aalbersberg, G. J. Hoijtink, E. L. Mackor, and W. P. Weijland, *J. Chem. Soc.*, 3049 (1959).

(6) Y. Sato, M. Kinoshita, M. Sano, and H. Akamatu, *Bull. Chem. Soc. Jap.*, **42**, 3051 (1969).

(7) Unpublished work in these laboratories by T. Okuyama.

(8) D. F. Williams, Abstracts, Fourth Molecular Crystal Symposium, Enschede, Holland, July 1968. We thank Dr. Williams for further details by private communications. T. C. Chiang, A. H. Reddoch, and D. F. Williams, *J. Chem. Phys.*, **54**, 2051 (1971).

for a convenient, new preparation of 3-nitroperylene.[9] We now report a number of other studies.

Results

Electrochemical Preparation.—We have not been able to grow large, well-defined crystals of perylene–perylene perchlorate complex.[8] In our hands, anodic oxidation of perylene gave deposits of small crystals containing both perylene and its cation radical perchlorate, but in varying proportions. Both elemental and iodimetric analysis showed the cation-radical content to be between 60–70%. A 1:1 complex requires 58% by weight. Repeated washing of the solid mixture removed perylene. Attempts to remove all of the perylene only resulted in eventual decomposition of the cation radical. In spite of its composition, the electrochemically prepared product was easily usable for chemical studies. In most reactions of the perylene cation radical perylene itself is one of the products. Therefore, in using the electrochemical preparation for quantitative chemical studies it is necessary to know its perylene content. We have found that iodimetric analysis is very easy and reliable. Electron transfer between the cation radical and iodide ion is quantitative, and potentiometric titration of the iodine gives a quick assay of cation-radical content.

Chemical Preparation with Iodine–Silver Perchlorate.—By mixing a concentrated solution of perylene and silver perchlorate with one of iodine a well-dispersed mixture of silver iodide and cation radical perchlorate precipitates.[6] The solid mixture is easily analyzed iodimetrically, and has been found to contain at least 95% of the required cation radical perchlorate. This method of preparing cation-radical salts has also been used for heterocyclic and amino compounds by Ledwith,[10] who was able to extract the cation radical with solvent. We have found that perylene cation radical perchlorate can be extracted from admixture with silver iodide, but losses occur because of the impossibility of having perfectly dry solvents. Instead of extracting the cation radical for later use we have found that the mixed solids can be used for many preparative chemical reactions. We have also found that in some cases reaction of the cation radical can be achieved in one step by mixing a solution of perylene, silver perchlorate, and reactant with a solution of iodine. Reaction with nitrite ion is a case in point, and in that we have also achieved reaction by using only perylene, silver nitrite, and iodine.[9]

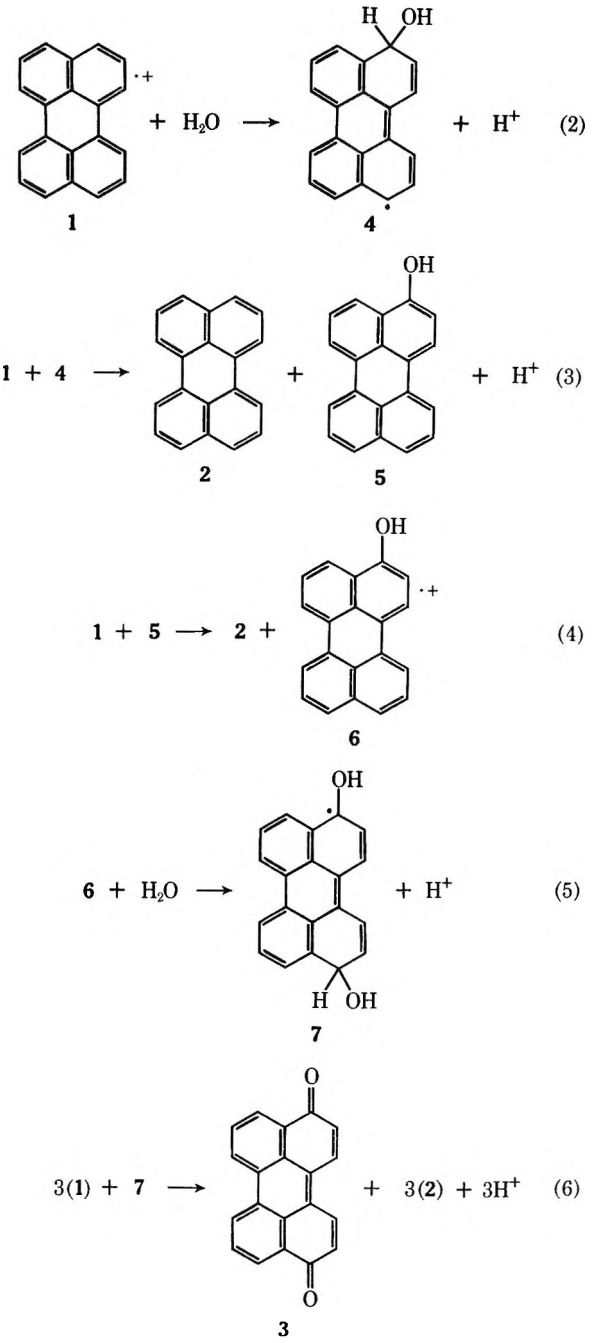
Reaction with Water.—Reactions of cation radicals with water are not well documented and are still not well understood. It has been thought in some instances that one-electron exchange occurred.[11,12] More recently, the water molecule has been represented as a nucleophile attacking a cationic rather than a radical center, but there is no general agreement on mechanistic details. Reaction of water with thianthrene cation radical is second order in cation radical, and has been interpreted as involving the thianthrene dication rather than the cation radical directly.[13] The role of the dication in this reaction has also been examined electrochemically.[14,15] Reaction of the 9,10-diphenylanthracene cation radical is first order in cation radical and has been interpreted as occurring by direct attack of water on the cationic 9 position of the cation radical.[16]

Several other examples of *in situ* reaction of water with a cation radical formed at an anode have been interpreted analogously as ECE reactions.[17]

No detailed chemical study of the reaction of a hydrocarbon cation radical with water has been reported.

$$\underset{1}{6C_{20}H_{12}\cdot^{+}} + 2H_2O \longrightarrow 5\underset{2}{C_{20}H_{12}} + \underset{3}{C_{20}H_{10}O_2} + 6H^{+} \quad (1)$$

Scheme I

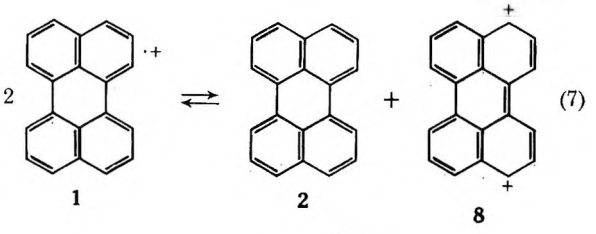


(9) C. V. Ristagno and H. J. Shine, *J. Amer. Chem. Soc.*, **93**, 1811 (1971).
(10) F. A. Bell, A. Ledwith, and D. C. Sherrington, *J. Chem. Soc. B*, 2719 (1969).
(11) G. Cauquis, *Bull. Soc. Chim. Fr.*, 1618 (1968).
(12) H. J. Shine and L. Piette, *J. Amer. Chem. Soc.*, **84**, 4798 (1962).
(13) Y. Murata and H. J. Shine, *J. Org. Chem.*, **34**, 3368 (1969).
(14) V. D. Parker and L. Eberson, *J. Amer. Chem. Soc.*, **92**, 7488 (1970).
(15) L. S. Marcoux, personal communication.
(16) R. Sioda, *J. Phys. Chem.*, **72**, 2322 (1968).
(17) (a) L. Jeftic and R. N. Adams, *J. Amer. Chem. Soc.*, **92**, 1332 (1970); (b) E. J. Majeski, J. D. Stuart, and W. E. Ohnesorge, *ibid.*, **90**, 633 (1968).

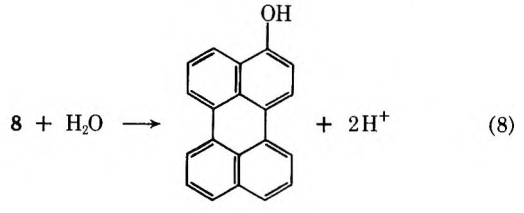
Anodic oxidation studies ordinarily rely on electrochemical data without isolation of products. Sioda isolated one of the products (9,10-dihydroxy-9,10-diphenylanthracene) but not the other (the original hydrocarbon).[16] In our present work we have isolated the final products quantitatively and can write the overall stoichiometry for the reaction of the perylene cation radical (**1**) with water (eq 1). We have not attempted kinetic work yet. According to eq 1, 82 mol % of cation radical reverts to perylene (**2**). It is not surprising, therefore, that perylene was recovered by previous workers.[5] The only other product obtained by us was 3,10-perylenequinone (**3**). Our results with electrochemically prepared cation radical gave 91% of the perylene and 86% of the quinone required by eq 1. Analogous results with the silver iodide mixture were 87 and 70%.

It is possible to explain the results in two ways (Schemes I and II), and a distinction cannot be made

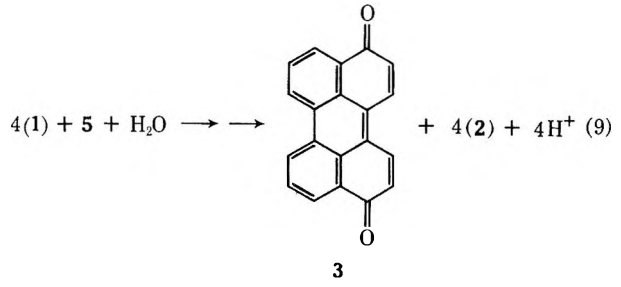
SCHEME II



(7)



(8)

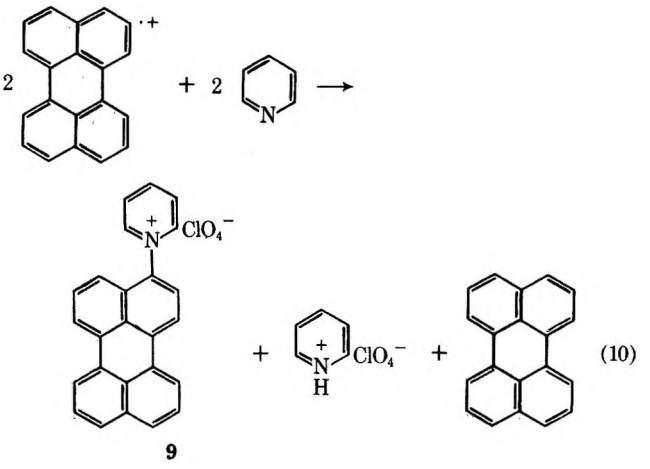


(9)

until, possibly, kinetic data for the series of reactions are obtained. Each of these schemes has 3-hydroxyperylene (**5**) as an intermediate. We have written the schemes in this way rather than having the initial formation of 3,10-dihydroxyperylene (or 3,10-dihydro-3,10-dihydroxyperylene) on the basis of our work with **1** and pyridine. Only one pyridine unit is introduced into the perylene nucleus (see later) in a very rapid reaction. It does not seem reasonable that, in contrast, reaction with water, a poorer nucleophile, would go directly to the dihydroxy compound.

In Scheme I, attack of water (eq 2) occurs at the position in the cation radical which simple HMO calculations[18] show as having the highest positive charge density. It is to be expected that 3-hydroxyperylene would be oxidized by the perylene cation radical (eq 4), and under our experimental conditions, therefore, would not survive. The possibilities that 3-hydroxyperylene is further oxidized by air to the quinone, or that either 3,10-dihydroxyperylene or 3,10-dihydro-3,10-dihydroxyperylene are formed and similarly oxidized do not seem to be serious, since our quantities of isolated perylene would not fit large-scale incursions of those oxidation reactions.

Reaction with Pyridine.—Reaction of perylene cation radical with pyridine is fast and clean, and has the stoichiometry of eq 10. On the basis of this stoichiometry, reaction with the electrochemically prepared cation radical gave 92% of the required perylene and 87% of the required substitution product (**9**). Reaction with the silver iodide mixture gave 98% of the required perylene and 84% of **9**.



(10)

Compound **9** was identified by elemental analysis and by Zincke degradation to 3-aminoperylene.

The difference between the pyridine and water reactions is probably attributable to the difficulty one might expect of oxidizing **9**, which bears an electron-withdrawing group, as compared with oxidizing **5** (eq 4) which bears an electron-donating substituent. Rochlitz[19] has isolated monopyridinium substitution products from reaction of polynuclear aromatic hydrocarbons with iodine and pyridine, while Lund obtained 9,10-dihydroanthracenyldipyridinium diperchlorate from anthracene.[20]

Reaction with Acetate and Benzoate Ions.—The reactions of perylene cation radical with sodium acetate and sodium benzoate are fast and give relatively low yields of the corresponding esters. Reaction of the cation radical with sodium acetate and sodium benzoate gave 26 and 33% of the corresponding 3-perylenyl esters, **10** and **11**, and 105 and 113% of perylene based on the stoichiometry in eq 11. It is believed that the

$$2C_{20}H_{12}\cdot^{+} + RCO_2^{-} \longrightarrow \underset{\substack{\mathbf{10},\ R = Me \\ \mathbf{11},\ R = C_6H_5}}{C_{20}H_{11}O_2CR} + C_{20}H_{12} + H^{+} \qquad (11)$$

relatively low yields of the esters can be attributed in part to hydrolysis in the presence of the perchloric acid which is generated. The hydrolysis product, 3-hydroxyperylene, was not identified positively, but is thought, from spectroscopic evidence, to have comprised one of the fractions removed from the chromatography col-

(18) C. A. Coulson and A. Streitwieser, Jr., "Dictionary of π-Electron Calculations," Pergamon Press, New York, N. Y., 1965.

(19) J. Rochlitz, *Tetrahedron*, **23**, 3043 (1967).

(20) H. Lund, *Acta Chem. Scand.*, **11**, 1323 (1957).

umn. Some 3,10-perylenequinone was formed also, and this might account for the high yield of perylene (see stoichiometry for the formation of the quinone by reaction of $P\cdot^{+}ClO_4^{-}$ with water). The acetate and benzoate esters are rapidly hydrolyzed by base.

Electron Exchange Reactions.—Perylene cation radical is reduced quantitatively by iodide ion. The reaction is a good way of assaying cation-radical purity. Reduction by bromide ion also occurs. Anodic bromination of anthracene has been reported by Millington.[21] We had thought that reaction between perylene cation radical and bromide ion might give 3-bromoperylene, but none could be detected by tlc. Bromine formed in reaction was determined iodimetrically. The quantities of perylene and bromine formed (eq 12, X = Br) from both the electrochemical product and the silver iodide mixture gave results consistent with eq 12, that is, 92 and 84% of the anticipated perylene and 87 and 90% of the bromine.

$$2C_{20}H_{12}\cdot^{+} + 2X^{-} \longrightarrow 2C_{20}H_{12} + X_2 \qquad (12)$$

The facts that the color of both preparations of cation radical was discharged by addition of bromide ion and both preparations gave similar analytical results establish reliability in the results. It is possible with the use of the silver iodide mixture and a nucleophile X^- that, if the solubility product of AgX were significantly smaller than or comparable with that of AgI ($K_{sp} = 8.5 \times 10^{-17}$), exchange between X^- and I^- may occur. In that case reduction of cation radical by iodide ion would follow. This does not seem to be the case when bromide ion (K_{sp} AgBr $= 5.0 \times 10^{-13}$) is used. Reaction between chloride ion (K_{sp} AgCl $= 1.7 \times 10^{-10}$) and the silver iodide mixture led to 84% of the anticipated perylene and 90% of the anticipated halogen (eq 11), while the electrochemically produced cation radical gave 95% of the anticipated perylene and 84% of the anticipated halogen.

Reaction with cyanide ion remains unsettled. Use of potassium cyanide with the silver iodide mixture was accompanied by almost total reduction of the cation radical to perylene. Use of electrochemical product, however, gave a mixture of perylene and a green, fluorescent compound which has not as yet been characterized. It appears that the use of the silver iodide mixture and cyanide may lead to halide exchange (K_{sp} AgCN $= 1.6 \times 10^{-14}$) through the complex $Ag(CN)_2^-$.

It is recognized, of course, that data on solubility products and complex formation relate to aqueous solutions and may have limited validity in the reactions we have examined.

Reaction with fluoride ion failed to occur. We had hoped that since electron transfer was not to be expected, nucleophilic substitution by fluoride ion would occur. However in none of the many attempts with various fluorides was an organic fluoride formed. The only products isolated were perylene and its 3,10-quinone, and these are presumed to have been formed from slow reaction with small amounts of water remaining in the reactants or finding ingress from the atmosphere. We conclude that fluoride ion is too weakly nucleophilic to react with perylene cation radical.

(21) J. P. Millington, *J. Chem. Soc. B*, 982 (1969).

Summary

Perylene cation radical reacts with certain nucleophiles at the 3 position. Other nucleophiles, *e.g.*, iodide and bromide ion, usually acknowledged as "good" nucleophiles do not attack at carbon but donate an electron to perylene cation radical. Earlier work showed that pyrene cation radical is "nitrated" by nitrite ion in the 1 position.[9] The overall picture is that a cation radical will undergo nucleophilic substitution at the position of highest positive charge density provided that the nucleophile is itself not easily oxidized by the cation radical. Thus, in their reactions with cation radicals, nucleophiles are controlled by their nucleophilicity and oxidation potentials. It is hoped that further work will bring out the relationships more quantitatively.

Experimental Section

Perylene was purified by chromatography on an alumina column followed by crystallization from benzene. Tetrahydrofuran (THF) was dried by distilling over lithium aluminum hydride.

Electrochemical Preparations.—Controlled potential oxidations were performed with a Princeton Applied Research Electrochemistry System, Model 170. An H cell with compartments separated by a fritted glass disk, and with a platinum gauze anode and a copper wire cathode, was used. In a typical procedure about 25 ml of THF containing 1.2 g of dried tetrabutylammonium perchlorate (TBAP) (an approximately 0.2 *M* solution) was placed in each compartment of the cell. Perylene was then added to the anode compartment to saturate the solution. Electrolysis was carried out at 1.25 V (*vs.* sce) while the anolyte was stirred continuously magnetically. A black solid began depositing on the anode as soon as electrolysis was begun. Electrolysis was interrupted at 15-min intervals and the anode deposit was carefully scraped off. Perylene was added to the anode compartment at each interval. In this way it was possible to collect quantities of deposit of the order of 1 g in 5 hr. The deposit was washed with 10-ml portions of THF and dried under vacuum. Washing removed perylene from the deposit, but perylene removal was never complete. Attempts to completely extract perylene ended only in slow decomposition of the cation radical salt. As a typical example, 563 mg of deposit was washed with ten 10-ml portions of THF, leaving 475 mg of solid.

Anal. Calcd for $C_{20}H_{12}ClO_4$: C, 68.2; H, 3.41; Cl, 10.10. Found: C, 70.15; H, 4.36; Cl, 7.10.

Analysis indicated that the composition of the solid was 70% $C_{20}H_{12}ClO_4$ and 30% $C_{20}H_{12}$. This was confirmed by potentiometric iodimetric titration, as follows. A solution of the solid in 100 ml of dry acetonitrile was deaerated by nitrogen bubbling for 5 min. Addition of 100 mg of tetrabutylammonium iodide immediately discharged the purple color of the ion radical. The yellow iodine solution was titrated potentiometrically with thiosulfate, using the PAR instrument. Two analyses, beginning with 55 and 57 mg of solid, respectively, showed the solid to contain 68 and 71% of its weight as cation radical perchlorate. In the latter case perylene was extracted from the solution with benzene after titration was complete. The perylene was placed on a silica gel column and eluted with benzene, a solvent capable of separating perylene and its 3,10-quinone. The amount of perylene recovered was 41 mg. If the electrochemical solid was a mixture of 70% cation radical perchlorate and 30% perylene, the amount of perylene anticipated after reduction with iodide ion is 45.8 mg. Stripping of the silica gel column with benzene–methanol (3:1) gave a solution whose visible spectrum indicated the presence of some perylene-3,10-quinone (**3**).

Chemical Preparation ($P\cdot^{+}ClO_4^{-}$, AgI).—To a solution of 504 mg of perylene in a minimum of dry methylene chloride was added a solution of 414 mg of dry silver perchlorate in a minimum of acetonitrile. To this mixture was added a solution of 203 mg of iodine in a minimum of methylene chloride. All operations were carried out under nitrogen to exclude moisture. A dark precipitate formed immediately. After stirring for 3 min the mixture was filtered and dried under vacuum, giving 912 mg

(97%) of $P\cdot^{+}ClO_4^{-}$, AgI. Potentiometric iodimetry showed the solid to contain 95% of the required amount of $P\cdot^{+}ClO_4^{-}$.

Reaction with Water. A. Electrochemical Product.—To 75 mg of solid product was added 150 ml of acetonitrile containing 0.1 ml of water. The mixture was stirred under a nitrogen bubbler for 7 hr. Five grams of silica gel was added and the solvent was evaporated. The silica gel was placed on the top of a column of silica gel for chromatography. Perylene was removed with benzene, and the column was next eluted with benzene–methanol (3:1). Evaporation of the benzene solutions gave 51 mg (96%) of solid, found to be perylene by ultraviolet and visible spectroscopy. Evaporation of the benzene–methanol solution gave 6 mg (86%) of solid identified by visible spectrum as perylene-3,10-quinone. On the basis that the electrochemical product was 70% cation radical perchlorate and 30% perylene, the anticipated products from reaction with water are 53 mg of perylene and 7 mg of quinone (see discussion for stoichiometry).

B. $P\cdot^{+}ClO_4^{-}$, AgI.—A suspension of 151 mg of solid in 60 ml of acetonitrile containing 0.5 ml of water was stirred for 3 hr under nitrogen. Filtration gave 44 mg (73%) of silver iodide. The acetonitrile was evaporated and the residue was chromatographed on alumina, using benzene to remove perylene, and 3:1 benzene–methanol to remove the 3,10-quinone. Isolation of solutes gave 47 mg (87%) of perylene and 8.5 mg (70%) of the quinone.

Reaction with Pyridine. A. Electrochemical Product.—A solution of 0.1 ml of pyridine in 150 ml of acetonitrile was added to 75 mg of electrochemical product under nitrogen. The reaction mixture turned yellow immediately. After 30 min of stirring, the solvent was pumped off and the residue was extracted with 50 ml of hot benzene. Evaporation of the benzene gave 38 mg (92%) of perylene, identified and assayed by its absorption spectrum. The benzene-insoluble portion was 39 mg of yellow solid. This was washed with 100 ml of water to remove pyridinium perchlorate, leaving 28 mg (87%) of yellow-brown solid, which was identified as *N*-(3-perylenyl)pyridinium perchlorate (9) as described later.

On the basis that the electrochemical product contained only 52.5 mg (70%) of cation radical perchlorate, reaction with pyridine should have given 32.2 mg of *N*-(3-perylenyl)pyridinium perchlorate and a total of 41.4 mg of perylene.

B. $P\cdot^{+}ClO_4^{-}$, AgI.—A solution of 0.1 ml of pyridine in 100 ml of acetonitrile was added to 123 mg of the mixture of salts. After stirring, a yellow solution and a yellow precipitate (silver iodide) were obtained. Filtration gave 48.7 mg (99%) of silver iodide. Evaporation of the acetonitrile solution and benzene extraction gave 30 mg of benzene-soluble and 59 mg of benzene-insoluble material. Chromatography of the benzene-soluble solid on silica gel column gave 26 mg (98%) of perylene.

C. By Direct, Iodine–Silver Ion Initiated Reaction.—To a mixture of 300 mg (1.2 mmol) of perylene, 606 mg (2.4 mmol) of iodine, and 1.0 g (4.8 mmol) of silver perchlorate in 200 ml of acetonitrile was added 2 ml (26 mmol) of pyridine. The mixture turned yellow immediately. Work-up as above gave 125 mg (32%) of *N*-(3-perylenyl)pyridinium perchlorate (9). A sample of 9 was crystallized from benzene–methanol: mp 309° dec; λ_{max} (methanol) 442, 419, 400 (s), 252, 247 nm (s).

Anal. Calcd for $C_{25}H_{16}ClNO_4$: C, 70.0; H, 3.73; N, 3.26; Cl, 8.25. Found: C, 70.1; H, 4.24; N, 3.22; Cl, 7.73.

Degradation of 50 mg (0.12 mmol) of 9 to 3-aminoperylene was carried out by Zincke's method.[22] The organic product was extracted with benzene and chromatographed on silica gel with 50:50 benzene–ether as eluent, giving 8 mg (26%) of 3-aminoperylene, mp 218° dec, shown to be identical with an authentic sample.

3-Aminoperylene.—3-Nitroperylene was prepared by the reaction of perylene cation radical with nitrite ion,[9] and reduced with hydrazine and a palladium/charcoal catalyst,[23] mp 222° dec (lit. mp 220–230° dec.)[23]

Reaction with Sodium Acetate.—A solution of 328 mg (4 mmol) of sodium acetate in 100 ml of acetonitrile was deaerated by nitrogen bubbler. To this was added 401 mg (0.68 mmol) of $P\cdot^{+}ClO_4^{-}$, AgI. Immediately the reaction mixture turned yellow. The mixture was stirred for 15 min under nitrogen, filtered, and chromatographed on silica gel. Perylene was removed with benzene–petroleum ether (1:1) and the blue-fluorescent ester was removed with benzene. Evaporation of the benzene–petroleum ether fraction gave 111 mg (105%) of perylene. Evaporation of the benzene solution gave 22 mg (26%) of a bright yellow solid, mp 182–187°, which was identified as 3-perylenyl acetate (10). A sample was recrystallized from ethanol: mp 193–194°; λ_{max} (methanol) 438, 412, 390 (s), 253, 246 nm.

Anal. Calcd for $C_{22}H_{14}O_2$: C, 85.16; H, 4.52. Found: C, 84.92; H, 4.41

The ester bands on the column were followed by a small yellow band having a strong green fluorescence. This was eluted and had ultraviolet and visible spectra identical with those attributed to 3-hydroxyperylene (see below). Continued elution with benzene–methanol (3:1) gave some 3,10-perylenequinone.

Reaction with Sodium Benzoate.—A mixture of 331 mg (0.56 mmol) of $P\cdot^{+}ClO_4^{-}$, AgI, and sodium benzoate was treated as described above; 80 mg (113%) of perylene and 34 mg (33%) of 3-perylenyl benzoate (11) were obtained. A sample of the benzoate was recrystallized from ethanol: mp 209–210°; λ_{max} (methanol) 439, 412, 391 (s), 253, 247 nm.

Anal. Calcd for $C_{27}H_{16}O_2$: C, 87.09; H, 4.30. Found: C, 86.89; H, 4.14.

Treatment of either 10 or 11 with 5% sodium hydroxide in methanol caused a rapid change in the ultraviolet spectrum resulting, we believe, from hydrolysis to the anion of 3-hydroxyperylene, λ_{max} (methanol) 488, 345, 330, 300 (s), 270 (s), 264 nm. Acidification of the basic solution gave, we believe, 3-hydroxyperylene, λ_{max} (methanol) 448, 426, 258, 252 nm (s).

Reaction with Bromide Ion. A. Electrochemical Product.—The electrochemical product was found to be 60% cation radical perchlorate by iodimetry. Of this, 49.8 mg in 50 ml of acetonitrile was deaerated by nitrogen bubbler and capped with a serum cap. A solution of 100 mg of tetrabutylammonium bromide in acetonitrile was injected. The solution turned yellow. After 5 min a solution of tetrabutylammonium iodide in acetonitrile was injected. The yellow-orange solution was removed for potentiometric titration with thiosulfate, and found to contain 87% of theoretical iodine. The titrated solution was extracted with benzene and gave 38 mg (92%) of perylene. Based on electron exchange between bromide ion and 29.9 mg of cation radical perchlorate (60% of the solid used), the expected yield of perylene was 41.4 mg.

B. With $P\cdot^{+}ClO_4^{-}$, AgI.—A sample of 109 mg of salt was treated as above. Titration gave 90% of theoretical iodine. Extraction gave 39 mg (84%) of perylene.

Reaction with Chloride Ion. A. Electrochemical Product.—The electrochemical product was found to be 63% cation radical perchlorate by iodimetry; 75 mg of the cation radical salt and 144 mg of tetrabutylammonium chloride were placed in a one-neck, 100-ml round-bottom flask under nitrogen and sealed with a serum cap; and 40 ml of CH_3CN was injected. The solution turned yellow. After 5 min a solution of tetrabutylammonium iodide in acetonitrile was injected. The solution turned yellow-orange. The solution was removed for potentiometric titration with thiosulfate and found to contain 84% of theoretical iodine. The titrated solution was extracted with benzene and chromatographed on silica gel to give 58 mg (95%) of perylene.

B. With $P\cdot^{+}ClO_4^{-}$, AgI.—A sample of 103 mg of salt was treated as above. Titration gave 90% of theoretical iodine. Extraction gave 37 mg (84%) of perylene.

Attempted Reaction with Fluoride Ion.—$P\cdot^{+}ClO_4^{-}$, AgI was used in all attempts. The cation radical salt was added to the fluoride salt, which was either dissolved or suspended in acetonitrile. The mixture was stirred under nitrogen until the color of the cation radical either disappeared or failed to disappear over a period of 36 hr. In the latter case reaction was presumed not to have occurred. When hydrogen fluoride was used at room temperature the gas was bubbled through the acetonitrile solution. Liquid hydrogen fluoride was used at 0°. A reaction mixture was worked up by first evaporating the solution and next chromatographing on a column of silica gel, using benzene and 3:1 benzene–methanol for elution as described earlier. These solvents were chosen for separating perylene and its 3,10-quinone when considerable exploratory work showed that these two compounds were the only ones formed. In no case was any evidence found by tlc for the presence of any other compound than these two. Further search for the presence of an organic fluoride was made by subjecting each organic fraction isolated from the silica gel column to sodium fusion and the zirconium–alizarin

(22) T. Zincke, *Justus Liebigs Ann. Chem.*, **330**, 361 (1903); **333**, 296 (1904).

(23) M. J. Dewar and T. Mole, *J. Chem. Soc.*, 1441 (1956).

test for fluoride ion.[24] This method was successful when applied to small amounts of 1-fluoronaphthalene. All of the isolated organic fractions failed to show the presence of a fluoride.

Perylene and its 3,10-quinone were isolated from attempted reaction with AgF (97%, 46%); AgF, HF (gas) (90%, 47%); and KF (97%, 50%). The figures in parentheses refer to products formed in reaction with unremoved water according to the stoichiometry of eq 1. The use of HF (gas), KF, HF (gas), KF, HF (liquid), and $(n\text{-}C_4H_9)_4NF$ failed to discharge the color of the cation radical during a 36-hr period.

(24) A. I. Vogel, "Practical Organic Chemistry," Wiley, New York, N. Y., 1956, p 1043.

Iodimetric Assay.—In a typical iodimetric analysis, 124.8 mg of $P\cdot^+ClO_4^-$, AgI (2.13×10^{-4} equiv) was placed in 150 ml of deaerated, dry acetonitrile and 200 mg (5.42×10^{-4} equiv) of tetra-*n*-butylammonium iodide was added. The purple reaction mixture *immediately* turned yellow. The reaction mixture was then titrated potentiometrically using a 0.0566 *N* sodium thiosulfate solution. An end point corresponding to 2.13×10^{-4} equiv of I_2 was obtained. The titrated solution was then poured into water and extracted with benzene. The benzene extract was chromatographed on silica gel giving 48 mg of perylene (89.6% of theory).

Registry No. 1, 12576-62-4; 1 perchlorate, 12576-63-5; 9, 32174-97-3; 10, 32174-98-4; 11, 32174-99-5.

Electrophilic and Homolytic Cleavage of 5-Aryl-5*H*-dibenziodoles[1]

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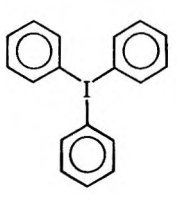
The organometallic character of triaryliodine compounds has been demonstrated by the reactivity of 5-phenyl-5*H*-dibenziodole toward water, protonic acids, and Lewis acids. Cleavage of 5-phenyl-5*H*-dibenziodole by electrophilic reagents is rapid and gives both cyclic dibenziodolium and acyclic 2-biphenylylphenyliodonium salts. The product ratio was found to be dependent on the electrophile used. Thermal decomposition and rearrangement of 5-phenyl-5*H*-dibenziodole have also been studied. A free-radical mechanism is suggested to account for the complexity of the products in the presence of alkyl and acyl halides. In contract, heating in hexane gives 2-iodo-*o*-terphenyl in good yield and suggests a molecular rearrangement. Various new 5*H*-dibenziodoles have been prepared with aryl groups attached to iodine: *p*-tolyl, *m*- and *p*-chlorophenyl, and 1-naphthyl. Cleavage of these species with ethereal hydrogen chloride has also been studied.

Since the first isolation of triphenyliodine (1) by Wittig[2] in 1952, little work has been reported on the relatively unstable triorganoiodine compounds. In 1955, Clauss[3] prepared from dibenziodolium iodide and phenyllithium the first triaryliodine, 5-phenyl-5*H*-dibenziodole (2) that is stable at room temperature.



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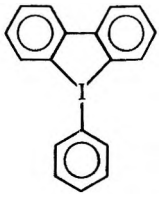

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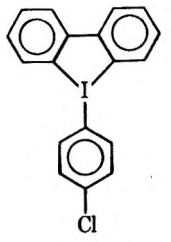
Using the method of Clauss, we have successfully prepared three previously unknown 5-aryl-5*H*-dibenziodoles, *i.e.*, 5-(*p*-chlorophenyl)-5*H*-dibenziodole (**3**), 5-(*p*-tolyl)-5*H*-dibenziodole (**4**), and 5-(1-naphthyl)-5*H*-dibenziodole (**5**), in 75–85% yield. Attempts to isolate 5-(*m*-chlorophenyl)-5*H*-dibenziodole (**6**) from the reaction mixture of dibenziodolium chloride and *m*-chlorophenyllithium solution were unsuccessful because of its high solubility in the reaction medium. Therefore, **6** was often used immediately without isolation for further reaction. 5-Phenyl-5*H*-dibenziodole was also successfully prepared by the present authors from dibenziodolium chloride and phenylmagnesium bromide in 90% yield.



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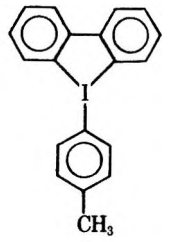

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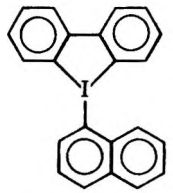

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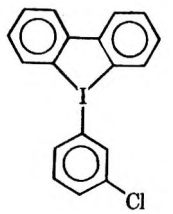


6

Thermal Decomposition and Rearrangement.—It has been long known that trisubstituted organoiodine compounds on heating decompose homolytically to complex products.[4–6] When a suspension of 5-phenyl-5*H*-dibenziodole (2) in hexane was decomposed gradually at room temperature, the products were benzene, iodobenzene, biphenyl, 2-iodobiphenyl, and 2,2′-diiodobiphenyl, all in 10–15% yield, and 2-iodo-*o*-terphenyl in about 10% yield. At higher temperature (refluxing hexane), 2-iodo-*o*-terphenyl was formed as the major product (*ca.* 80%). Adapting the radical mechanism proposed previously[4,5] for the thermal cleavage of Ph_2IR[6] and Ph_2ISR, one can envision free-radical sequences initiated by homolysis to account for the complexity of the products from **2**. Path L, in-

(1) (a) Taken from the dissertation of L. L. Chang submitted to the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Doctor of Philosophy (Chemistry), 1971. (b) Supported by National Institutes of Health, 1968–1969, through Grant No. 5-SO5-FR-07063-04.

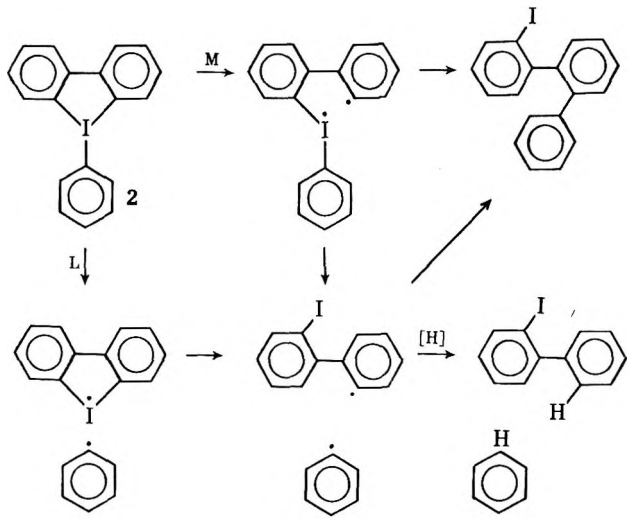
(2) G. Wittig and K. Clauss, *Justus Liebigs Ann. Chem.*, **578**, 136 (1952).

(3) K. Clauss, *Chem. Ber.*, **88**, 268 (1955).

(4) F. M. Beringer, J. W. Dehn, Jr., and M. Winicov, *J. Amer. Chem. Soc.*, **82**, 2948 (1960).

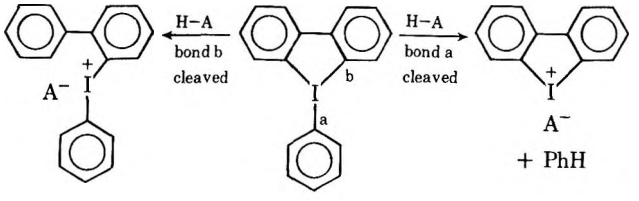
(5) J. W. Greidanus, W. J. Rebel, and R. B. Sandin, *ibid.*, **84**, 1504 (1962).

(6) M. C. Caserio, D. L. Glusker, and J. D. Roberts, *ibid.*, **81**, 336 (1959).



volving the cleavage of the phenyl–iodine bond, is probably the process of the lowest activation energy and is therefore favored at low temperature. Path M, involving a ring opening, seemed to compete better at high temperature with a statistical limit of 67%. However, it seems unlikely that the high yield of 2-iodo-*o*-terphenyl arises from homolysis followed by coupling; a direct migration of the phenyl group from iodine to carbon seems more likely.

Heterolytic Cleavage.—The first example[2] of the heterolytic cleavage of a triaryliodine was the regeneration of the starting diphenyliodonium salt from triphenyliodine (**1**) by cleavage with hydrogen chloride. Similarly, Clauss[3] reported the recovery of dibenziodolium salts from 5-phenyl-5*H*-dibenziodole (**2**) by cleavage with a number of electrophilic reagents. However, contrary to the findings of Clauss, we have found that the cleavage of **2** with electrophiles gave



two iodonium salts. The cyclic dibenziodolium salt from the cleavage of bond a (the phenyl–iodine bond) and the previously unknown acyclic 2-biphenylylphenyliodonium salt from the cleavage of bond b (the biphenylene–iodine bond) were both formed. A fully random cleavage of both types of bonds would give 66.7% of the cyclic salt and 33.3% of the acyclic salt.

Reaction of **2** with cold water was very slow. Only when the suspension of **2** in degassed water was heated at 60–70° under argon for 3 hr did reaction occur, giving iodonium hydroxides which contained only traces of acyclic iodonium ions. A solution of **2** in tetrahydrofuran under fully anhydrous condition was essentially inert to carbon dioxide gas.

Cleavage of **2** with protonic and Lewis acids (Table I) was fast and gave both cyclic and acyclic iodonium salt, with product distribution dependent on the acid used. The weak carboxylic acids (acetic and benzoic) reacted predominantly with the phenyl group. The stronger inorganic acids showed low selectivity in the

TABLE I

REACTION[a] OF 5-PHENYL-5*H*-DIBENZIODOLE WITH PROTONIC AND LEWIS ACIDS

Acid	Solvent	Reaction[b] time, hr	% of iodonium ions Cyclic[c]	Acyclic[d]	Total $-I^+-$ yield, %
CH_3CO_2H	THF	0.1	89.5[e]	10.5	87
$C_6H_5CO_2H$	THF	0.5	78.5[e]	21.5	98
HF	THF	0.5	79.5[e]	20.5	104
HCl	THF	0.5	50.0[e]	50.0	96
HNO_3	THF	0.5	37.0[e]	63.0	101
CH_3SO_3H	THF	0.5	42.5[e]	57.5	93
HBF_4	THF	0.5	44.6[e]	55.4	92
I_2[e]	THF	0.5	62.0[e]	38.0	94
Ph_3B	PhH	3.0	100.0	0.0	77
$AlCl_3$	PhH	0.5	31.5	68.5	80

[a] Inverse addition of a solution of **2** to the acids. [b] The reaction was completed at the end of addition of **2**. However, the mixture was stirred totally for 0.5 hr before work-up. [c] Percentage of 2,2′-diiodobiphenyl based on the number of millimoles in the pyrolysate of the iodonium salt mixture. While benzene was identified as a reaction product, quantitative determination by vpc was not successful because of overlapping with solvent (THF). [d] Percentage of iodobenzene based on the number of millimoles in the pyrolysate of the iodonium salt mixture. [e] Two equivalents of iodine to 1 equiv of **2** was used.

cleavage of bonds to iodine. As for Lewis acids, the large triphenylboron cleaved the carbon–phenyl bond slowly and selectively to form dibenziodolium tetraphenylborate. At the other end of the scale, the strong electrophile aluminum chloride cleaved 5-phenyl-5*H*-dibenziodole in a completely random manner. Finally, molecular iodine cleaved both bond a and b; however, the former cleavage was favored.

The reaction of 5-phenyl-5*H*-dibenziodole with borane in tetrahydrofuran gave not iodonium salts but reduced products such as biphenyl and 2-iodobiphenyl.

Concerning the relative stability of the carbon–iodine bonds in the molecule of 5-phenyl-5*H*-dibenziodole, one might suggest that the iodine–phenyl bond is the most labile bond in the molecule. Bearing in mind that solid 5-phenyl-5*H*-dibenziodole is stable to around 100° while triphenyliodine decomposes at −10°, one sees that the joining of the two phenyl rings contributes some special stability to the molecule. It has also been found that the dibenziodolium ion is much less reactive than the diphenyliodonium ion.[7]

Cleavage of other 5-aryl-5*H*-dibenziodoles with hydrogen chloride in tetrahydrofuran has also been studied (Table II). Both 5-(*p*-chlorophenyl)-5*H*-dibenziodole (**3**) and 5-(*m*-chlorophenyl)-5*H*-dibenziodole (**6**) have yielded only cyclic dibenziodolium cation with benzoic acid and with hydrogen chloride. In other words, both a weak and a strong acid cleaved off the chlorophenyl group exclusively. A comparison of the results of acid cleavage of **2**, 5-(*p*-tolyl)-5*H*-dibenziodole (**4**), and 5-(1-naphthyl)-5*H*-dibenziodole (**5**), has suggested that the *p*-tolyl group was cleaved with about the same ease as the phenyl group, while the 1-naphthyl group was cleaved with greater ease than a phenyl group.

The effect of substituents on the benzene nucleus in the protodemetalation of organometallic compounds has been most exhaustively explored in the group IV elements. Accumulated results have been excellently

(7) J. Nachtigal, Ph.D. Dissertation, Polytechnic Institute of Brooklyn, 1967.

TABLE II

REACTION[a] OF 5-ARYL-5*H*-DIBENZIODOLES WITH HYDROGEN CHLORIDE IN TETRAHYDROFURAN

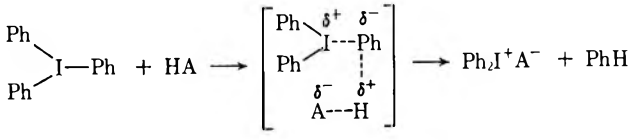
Ar	% of iodonium salts Cyclic	Acyclic	Total $-I^+-$ yield, %	Other product
Ph	50	50	96	PhH (Table I)
p-ClPh	100[b]	0	85–97[c]	PhCl[d]
m-ClPh	100[e]	0	70	PhCl[f]
p-Tolyl	52[g]	48[h]	100	$PhCH_3$[i]
1-Naphthyl	76[g]	24[j]	93	Naphthalene[k]

[a] Inverse addition of triaryliodine to the acid. [b] Results from three identical experiments with hydrogen chloride and two with benzoic acid. [c] Range of the yield in five experiments. [d] The yield was 95 ± 5%. [e] Results from duplicate runs. [f] The yield was 61%. [g] Based on 2,2′-diiodobiphenyl in the pyrolysate of the mixture of iodonium iodides. [h] Based on 4-iodotoluene in the pyrolysate of the mixture of the iodonium iodides. [i] The yield was 47%. [j] Based on 1-iodonaphthalene in the pyrolysate of the mixture of iodonium iodides. [k] The yield was 67%.

organized by Dessy and Kitching,[8] Reutov and Beletskaya,[9] and MacDiarmid.[10] In general, the mechanism proposed for the cleavage of metal–carbon bonds is electrophilic attack at carbon with or without nucleophilic participation at metal; often the latter is an important factor. In the cases where nucleophile and electrophile are combined in the same molecule, a multicenter pathway is available. The effect of substituents in the aryl groups usually can be correlated with those in electrophilic aromatic substitution; *i.e.*, electron-releasing substituents increase the ease of cleavage and electron-withdrawing substituents decrease it.

However, according to Table II, a *p*-methyl group seems to exert only a slight influence on the ease of the cleavage of phenyl–iodine bonds. Most striking is the observation that both *m*- and *p*-chlorophenyl groups were cleaved exclusively. Exclusive cleavage of a *p*-chlorophenyl group from an acyclic triaryliodine has been also observed.[1]

The authors do not have any fully satisfactory rationalization of the enhancement of reactivity by *m*- or *p*-chlorine in the heterolysis of the phenyl–iodine bond by acids. The transition state might be pictured as involving a weakened carbon–iodine bond with partial charge separation. If the leaving phenyl group has a partial negative charge, a *m*- or *p*-chlorine might favor this process.



Attempted alkylation and acylation of 5-phenyl-5*H*-dibenziodole with methyl iodide, carbon tetrachloride, and acetyl chloride failed to give a clean reaction yielding alkylated or acylated product. Even though in each case a good yield (70–80%) of dibenziodolium salt was obtained, the organic phase was always a very complex mixture. With acetyl chloride, a low yield (13%) of acetophenone was detected among products derived from homolytic decomposition. With methyl iodide, the formation of toluene was either in trace amount or in question. With carbon tetrachloride, chlorobenzene and 2-chloro-2′-iodobiphenyl were identified among other products. In summary, reaction of 5-phenyl-5*H*-dibenziodole with organic halides probably went largely by a homolytic process. The small yield of acetophenone may have arisen from a competitive electrophilic attack by acetyl chloride. Similarly, reactions of diphenylmercury with an excess of acetyl or benzoyl chloride led to complex organic mixtures in which only small amounts of acetophenone or benzophenone were found.[11]

Experimental Section

Analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by Chemalytics, Tempe, Ariz. Gas chromatography was done on 6-ft columns, packed with 20% OV-1 on 60–80 Chromosorb W with an Aerograph 1520-A gas chromatograph. Melting points were taken in capillary tubes on a Thomas–Hoover apparatus and corrected. The technique involved in taking the melting points of iodonium salts has previously been discussed.[12] All reactions involving the handling of organometallic reagent and triorganoiodine compounds were performed under argon atmosphere unless otherwise stated.

Organometallic Reagents.—*n*-Butyllithium in hexane, phenyllithium in 70:30 benzene–ether, phenylmagnesium bromide, and triphenylboron were purchased from Alfa Inorganics. *trans*-Chlorovinylmercuric chloride was prepared by the addition of mercuric chloride to acetylene.[13–16]

Concentrations of *n*-butyllithium and phenyllithium solution were frequently checked by the double titration method[17] using benzal chloride and water.

p-Tolyllithium,[4] 3-chlorophenyllithium,[18] 4-chlorophenyllithium,[19] 1-naphthyllithium,[20] *p*-dimethylaminophenyllithium,[21] and 2-lithiobiphenyl were prepared by the exchange reactions of corresponding aryl bromides or iodides with *n*-butyllithium. 2,2′-Dilithiobiphenyl[20] was prepared by the action of *n*-butyllithium on 2,2′-diiodobiphenyl, obtained in turn from the thermal decomposition of dibenziodolium iodide.[22]

Iodonium Salts.—Phenyl(*trans*-chlorovinyl)iodonium chloride[23] and dibenziodolium chloride[24] were prepared by known procedures.

5-Aryl-5*H*-dibenziodoles.—Because of their instability, 5-aryl-5*H*-dibenziodoles can be kept at room temperature even under vacuum for only a few days; decomposition is more rapid in the presence of air. Recrystallization from anhydrous tetrahydrofuran was accomplished by preparing and filtering a solution of the sample under argon at room temperature and partially removing the solvent under vacuum at Dry Ice–acetone temperature. The crystals were collected by rapid filtration under air. Analytical samples were shipped in sealed tubes, degassed, then filled with argon and covered with aluminum foil.

5-Phenyl-5*H*-dibenziodole (2).—The procedure described by Clauss[3] was modified as follows. To a suspension of 3.14 g (10

(8) R. E. Dessy and W. Kitching, *Advan. Organometal. Chem.*, **4**, 267 (1966).

(9) O. A. Reutov and I. P. Beletskaya, "Reaction Mechanisms of Organometallic Compounds," Wiley, New York, N. Y., 1968, Chapter 5.

(10) A. G. MacDiarmid, Ed., "The Bond to Carbon," Marcel Dekker, New York, N. Y., 1968.

(11) H. O. Calvery, *J. Amer. Chem. Soc.*, **48**, 1009 (1926).

(12) F. M. Beringer, R. A. Falk, N. Karniol, I. Lillien, G. Massulo, M. Mausner, and E. Sommer, *ibid.*, **81**, 324 (1952).

(13) A. N. Nesmeyanov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 239 (1945); *Chem. Abstr.*, **40**, 2122 (1946).

(14) R. Kh. Freidlina and A. N. Nesmeyanov, *C. R. Acad. Sci. USSR*, **29**, 567 (1940).

(15) A. N. Nesmeyanov and L. S. Isaeva, *Dokl. Akad. Nauk SSSR*, **117**, 996 (1957); *Chem. Abstr.*, **52**, 8090*g* (1958).

(16) D. L. Chapman and W. J. Jenkins, *J. Chem. Soc.*, **115**, 847 (1919).

(17) H. Gilman and F. K. Cartledge, *J. Organometal. Chem.*, **2**, 447 (1964).

(18) H. Gilman and S. M. Spatz, *J. Amer. Chem. Soc.*, **66**, 621 (1944).

(19) H. Gilman in "Organic Reactions," Collect. Vol. III, Wiley, New York, N. Y., 1954, p 285.

(20) F. M. Beringer and R. A. Nathan, *J. Org. Chem.*, **34**, 685 (1969).

(21) H. Gilman and I. Banner, *J. Amer. Chem. Soc.*, **62**, 344 (1940).

(22) L. Mascarelli and G. Benati, *Gazz. Chim. Ital.*, **38**, 619 (1908).

(23) E. M. Brainina and R. Kh. Freidlina, *Bull. Acad. Sci. USSR, Cl. Sci. Chim.*, 623 (1947); *Chem. Abstr.*, **42**, 5863*b* (1948).

(24) J. Collete, D. McGreer, R. Crawford, F. Chubb, and R. B. Sandin, *J. Amer. Chem. Soc.*, **78**, 3819 (1956).

mmol) of dibenziodolium chloride in 100 ml of anhydrous ether held at 0° under argon, 12 mmol of phenyllithium solution was added dropwise. The resulting citrus-yellow suspension was further stirred at 0° under argon for 3 hr. The yellow solid was quickly collected, washed with a small amount of ether once, with water a few times, and finally with hexane, and dried under vacuum over P_2O_5 overnight. The yield of the crude product was 3.2 g (90%).

An analytical sample was prepared by recrystallization from anhydrous tetrahydrofuran under argon. The bright yellow crystals decomposed vigorously at around 100°. Reported[3] decomposition range was 105–115°.

Anal. Calcd for $C_{18}H_{13}I$: C, 60.70; H, 3.68; I, 35.63. Found: C, 60.49; H, 3.95; I, 35.37.

This compound was also successfully prepared by treating a suspension of 3.14 g (10 mmol) of dibenziodolium chloride in anhydrous ether at 0° with 12 mmol of phenylmagnesium bromide solution. The yellow solid collected was washed first with 10 ml of anhydrous ether, then a few times with water, and finally with dilute aqueous ammonium chloride. After drying, 3.0 g (85%) of the lemon-yellow 5-phenyl-5*H*-dibenziodole, mp 105° dec, was obtained.

5-(*p*-Chlorophenyl)-5*H*-dibenziodole (3).—A suspension of 3.14 g (10 mmol) of dibenziodolium chloride was treated with 13 mmol of freshly prepared *p*-chlorophenyllithium solution. The resulting yellow solid was collected and worked up as described above to give 2.6 g (66.5%) of 5-(4-chlorophenyl)-5*H*-dibenziodole, mp 85–90° dec.

Anal. Calcd for $C_{19}H_{12}ICl$: C, 55.10; H, 3.06. Found: C, 55.37; H, 3.12.

The bright yellow color of the filtrate indicated some solubility of 5-(*p*-chlorophenyl)-5*H*-dibenziodole in benzene–ether mixture. Titration with standard hydrochloric acid, using the disappearance of the yellow color as the end point, showed that approximately 10% of the product remained in the filtrate. The crude iodonium salts weighed 0.29 g.

5-(*m*-Chlorophenyl)-5*H*-dibenziodole (6).—When the suspension of dibenziodolium chloride was treated, as above, with *m*-chlorophenyllithium solution, a bright yellow, semitransparent solution resulted. By filtration, 0.04 g (1.2%) of unreacted dibenziodolium chloride was recovered. The yellow filtrate, presumably containing the triaryliodine, was used immediately for further reactions. Reaction with hydrogen chloride etherate gave 2.2 g (7.0 mmol, 71%) of dibenziodolium chloride, mp 280° dec; its iodide decomposed at 225° to give only 2,2′-diiodobiphenyl.

5-(*p*-Tolyl)- and 5-(1-Naphthyl)-5*H*-dibenziodole (4 and 5).—These compounds were prepared in 70–80% yield as described above for compound 2 and decompose vigorously at about 100 and 90°, respectively.

Anal. Calcd for $C_{19}H_{15}I$: C, 61.62; H, 4.05; I, 34.33. Found: C, 61.95; H, 4.10; I, 34.10. Calcd for $C_{22}H_{15}I$: C, 65.02; H, 3.69; I, 31.29. Found: C, 64.96; H, 3.72; I, 31.59.

Thermal Rearrangement of 2 in Hexane.—A suspension of 3.2 g (9 mmol) of 2 in 150 ml of hexane was heated under reflux with stirring under argon for 6 hr. The bright citrus-yellow color of 2 faded completely. After a trace of insoluble material was removed by filtration, the filtrate was condensed and by vpc analysis was shown to contain iodobenzene (0.2 mmol, 2.2%), biphenyl (0.35 mmol, 3.9%), 2-iodobiphenyl (0.48 mmol, 5.7%), 2,2′-diiodobiphenyl (0.31 mmol, 3.4%), and a high-boiling material (*ca.* 80% by peak height). Purification of this high-boiling product was accomplished by chromotography of the mixture of neutral alumina with hexane and cyclohexane. The cyclohexane fraction that contained more than 95% of this material (detected by vpc) was condensed to a colorless oil which was then triturated with cyclohexane and slowly crystallized to give a white solid. The mass spectrum of this solid gave a molecular ion at 356; isotopic analysis was in good agreement with the formula $C_{18}H_{13}I$; and fragmentation was consistent with that expected of an iodoterphenyl. The melting point of 53–54° agrees with that of 2-iodo-*o*-terphenyl (lit.[26] mp 55–57°).

Anal. Calcd for $C_{18}H_{13}I$: C, 60.69; H, 3.68; I, 35.63. Found: C, 60.79; H, 3.53; I, 35.69.

Repeated attempts at synthesis of an authentic sample by the reported procedure[25] from fluorobenzene and phenyllithium were unsuccessful.

(25) G. Wittig and D. Hellwinkel, *Chem. Ber.*, **97**, 769 (1964).

Cleavage of 5-Aryl-5*H*-dibenziodole with Electrophilic Reagents. Determination of Concentration of Triaryliodine Compounds.—Because of the instability of triaryliodine compounds in solution, their concentration was best established by dissolving a weighed amount of sample in anhydrous tetrahydrofuran and filtering through a sintered-glass funnel into a three-necked round-bottomed flask containing a weighed amount of benzoic acid in tetrahydrofuran under argon. The color of triaryliodine solution was usually immediately discharged by the acid solution. After the reaction, the excess benzoic acid was titrated with dilute standard sodium hydroxide solution. The difference between the concentrations of the starting acid and the unreacted acid gave the number of millimoles of the weighed sample of triaryliodine. Then another solution of the identical batch of the sample was prepared and allowed to react with other electrophilic reagents in the same fashion as described above.

General Reaction Procedure.—A solution of triaryliodine compound of known concentration was prepared and added dropwise with stirring and gentle cooling under argon to a solution of the electrophilic reagent. In cases where the resulting iodonium salts were insoluble in the reaction media, an appropriate solvent such as acetone, methanol, or water was added, and the reaction mixture was treated with a concentrated solution of potassium iodide. The iodonium iodides were collected, washed with dilute aqueous sodium thiosulfate, water, and ether, and dried over P_2O_5. The composition of the iodonium iodide mixture was determined as described in the following section. The filtrate was extracted a few times with ether, and the combined organic layers were washed with dilute sodium hydroxide solution, dried over $MgSO_4$, and analyzed by vpc.

In order to obtain samples of iodonium salts from the above reactions, duplicates were run. After removal of tetrahydrofuran, the mixed salts were separated by fractional recrystallization from appropriate solvents.

Analysis of the Mixture of Iodonium Salts.—On heating, iodonium iodides are known to give high yields of aryl iodides.[12,22,26,27] Therefore, the amounts of aryl iodides determined by vpc were used to calculate the composition of two-component mixtures of iodonium salts. The mixture of iodonium iodides from the reaction of triaryliodine with electrophiles was heated at decomposition temperature under argon in a round-bottomed flask equipped with a condenser. After cooling, the contents were transferred with methylene chloride into a flask, and a weighed amount of dibenzofuran was added as internal standard. The mixtures were analyzed by vpc. The area under each peak was read by a planimeter. Calibration factors were determined using standard mixtures of authentic samples with dibenzofuran, and averaged calibration factors were used to determine the weights in grams of all products obtained from the reactions.

An authentic sample of **2-biphenylylphenyliodonium iodide** was prepared by application of a newly developed synthesis.[20] To a cooled (−78°) stirred suspension of 3.01 g (10 mmol) of phenyl(*trans*-chlorovinyl)iodonium chloride, a solution of 12 mmol of 2-lithiobiphenyl was added dropwise. The lemon-yellow suspension was stirred at −78° for 2 hr and allowed to warm slowly. At −40° the bright yellow color began to fade. The mixture was further stirred at room temperature overnight. The pale yellow solid was collected, washed with ether and water, and dried to give 1.233 g of crude salt. Metathesis of the crude salt with potassium iodide gave 0.97 g (2 mmol, 20%) of 2-biphenylylphenyliodonium iodide, mp 148–149° dec. Recrystallization from ethanol gave an analytically pure sample, mp 148–149° dec.

Anal. Calcd for $C_{18}H_{19}I_2$: C, 44.64; H, 2.90; I, 52.46. Found: C, 44.29; H, 2.85; I, 52.80.

Pyrolysis of the iodide gave 1 mol of iodobenzene with 0.95 mol of 2-iodobiphenyl.

Pyrolysis of a mixture of 0.8 g (1.94 mmol) of dibenziodolium iodide and 0.1 g (0.203 mmol) of 2-biphenylylphenyliodonium iodide, after work-up and vpc analysis, gave iodobenzene (0.202 mmol, 99%), 2-iodobiphenyl (0.253 mmol), and 2,2′-diiodobiphenyl (1.8 mmol, 93%).

Reaction of 2 with Hot Water.—A suspension of 3.2 g (9 mmol) of 2 in 200 ml of degassed distilled water was heated at 65–70° under argon with stirring for 3 hr. The yellow color of 2

(26) F. M. Beringer, L. Kravetz, and G. B. Topliss, *J. Org. Chem.*, **30**, 1141 (1965).

(27) F. M. Beringer and M. Mausner, *J. Amer. Chem. Soc.*, **80**, 4535 (1958).

gradually disappeared, giving a colorless solution. This hot, strongly basic solution was neutralized with 7.02 ml of 1 *N* hydrochloric acid (7.02 mequiv, 78% of hydroxide ion). The white precipitate that formed immediately in the hot solution was collected after the mixture was cooled to room temperature to give 2.3 g (6.75 mmol, 75%) of dibenziodolium chloride, mp 290–291° dec (lit.[24] mp 293–294° dec).

Treatment of this hot basic solution with aqueous potassium iodide solution yielded iodonium iodides which thermally decomposed to 94% of 2,2′-diiodobiphenyl, 2% of iodobenzene, and 1.7% of 2-iodobiphenyl.

Crude dibenziodolium hydroxide was obtained by cooling of the hot basic solution. It has a melting point between 165 and 220° with decomposition and its infrared spectrum showed strong, broad peaks at 3600–3200, 1700–1550, and 1450–1200 cm^{-1}, indicative of hydroxide and bicarbonate ions. The filtrate was extracted three times with 20 ml of ether. The combined organic layers were analyzed by vpc and shown to contain approximately 55% of benzene (based on **2**).

Reaction of 2 with Carbon Dioxide.—Through a bright citrus-yellow solution of 2.15 mmol of **2** in THF, which was carefully dried and freshly distilled over lithium aluminum hydride, a stream of dry carbon dioxide gas was passed with stirring. The yellow color of **2** persisted for 2 hr. Quenching of **2** with ethereal hydrogen chloride gave approximately 70% of iodonium salts.

Cleavage by Protic Acids.—A solution of 5-phenyl-5*H*-dibenziodole of known concentration in tetrahydrofuran was prepared and added immediately with stirring to a tetrahydrofuran solution of glacial acetic acid, benzoic acid, hydrofluoric acid, hydrogen chloride, nitric acid, methanesulfonic acid, or hydrofluoroboric acid. Stirring with gentle cooling was continued for a half hour except with acetic acid, where the product was worked up immediately (5 min). Analysis of product distribution were performed according to the general procedure described above.

In parallel runs, removal of the solvent gave crude iodonium salt mixtures. The following salts were obtained in pure form from the mixtures by repeated recrystallizations.

Dibenziodolium acetate (one recrystallization from water) turned dark at 185° and decomposed at 195–196° [lit.[28] 187° (darkens), mp 195.5° dec].

Anal. Calcd for $C_{14}H_{11}IO_2$: C, 49.70; H, 3.25; I, 37.57. Found: C, 49.81; H, 3.32; I, 37.29.

Dibenziodolium benzoate (two recrystallizations from water) darkens at 190° and decomposes at 198–199° (lit.[28] turns dark at 177°, mp 184° dec). This salt is soluble in organic solvents such as tetrahydrofuran and methanol and partially soluble in cold water.

Anal. Calcd for $C_{19}H_{13}IO_2$: C, 57.00; H, 3.25; I, 31.75. Found: C, 56.98; H, 3.25; I, 31.71.

Dibenziodolium fluoride (two recrystallizations from water) is very soluble in water, mp 269° dec (lit.[28] mp 166°). Because of the large discrepancy in the melting point with the reported value, the identity of this compound was carefully established by an independent synthesis from dibenziodolium chloride and silver fluoride to give, after careful recrystallization, pure dibenziodolium fluoride.[29] Samples obtained both ways have identical melting points and satisfactory elementary analysis.

Anal. Calcd for $C_{12}H_8IF$: C, 48.33; H, 2.69; I, 42.62; F, 6.36. Found: C, 48.67; H, 2.81; I, 42.27; F, 6.29 (from acidic cleavage of **2**); C, 48.30; H, 2.76; I, 42.31; F, 6.37 (from metathesis with AgF).

Dibenziodolium nitrate was obtained after three recrystallizations from water, mp 243.5–244° dec (lit.[28] mp 230°).

Anal. Calcd for $C_{12}H_8INO_3$: C, 42.24; H, 2.35; N, 4.11; I, 37.22. Found: C, 42.62; H, 2.35; N, 4.25; I, 36.94.

2-Biphenylylphenyliodonium fluoroborate was obtained after six recrystallizations from water as colorless, crystalline needles, mp 200–201°.

Anal. Calcd for $C_{18}H_{14}IBF_4$: C, 48.68; H, 3.15; I, 28.59; F, 17.13. Found: C, 49.00; H, 3.24; I, 28.92; F, 16.94.

Dibenziodolium fluoroborate was isolated, after condensation of the mother liquor of the recrystallizations of 2-biphenylylphenyliodonium fluoroborate, in crude form. Three recrystallizations of the crude salt from water gave crystalline needles of dibenziodolium fluoroborate, mp 247–248°.

Anal. Calcd for $C_{12}H_8IBF_4$: C, 39.35; H, 2.18; I, 34.70; F, 20.78. Found: C, 39.18; H, 2.12; I, 35.69; F, 20.45.

(28) L. Mascarelli, D. Gatti, E. Jons, and V. Leoncini, *Gazz. Chim. Ital.*, **59**, 867 (1929).

(29) Unpublished work by S. Messing in this laboratory.

Another sample has also been prepared by metathesis of dibenziodolium chloride with $AgBF_4$ in 20% H_2O–80% MeOH. The infrared spectrum was identical with that of the sample prepared above.

Dibenziodolium Methanesulfonate.—The white gummy material obtained from the reaction of **2** with methanesulfonic acid was dissolved in methanol and filtered. The filtrate was condensed to give a viscous oil, which, upon standing, gave colorless crystals. Trituration with acetone of the crude crystals yielded pure dibenziodolium methanesulfonate, mp 231–232°, decomposition point 285°.

Anal. Calcd for $C_{13}H_{11}ISO_3$: I, 32.55; S, 8.56. Found: I, 32.78; S, 8.75.

Reactions with Lewis Acids. A. With Iodine.—Addition of a solution of **2** (3.08 mmol) in tetrahydrofuran to a solution of 1.58 g (6.2 mmol) of iodine in tetrahydrofuran gave a dark brown suspension, from which a brown solid was separated and stirred with dilute aqueous $Na_2S_2O_3$ for a few hours to give 0.93 g (2.33 mmol, 61.3%) of crude dibenziodolium iodide. One recrystallization from dimethylformamide gave pure iodide, mp 220° dec (lit.[22] mp 210–215°). Condensation of the filtrate to 15 ml yielded a brown residue, which was redissolved in methylene chloride. After shaking with aqueous $Na_2S_2O_3$, the methylene chloride layer was condensed slowly to 20 ml, giving pale yellow crystalline 2-iodo-2′-biphenylylphenyliodonium iodide (0.67 g, 1.1 mmol, 29%), mp 165–170° dec. Pyrolysis of this salt gave 1 equiv of iodobenzene for each 0.95 equiv of 2,2′-diiodobiphenyl. Recrystallization of the salt from hot ethanol did not raise the melting point and sometimes caused decomposition of the salt.

Anal. Calcd for $C_{18}H_{13}I_3$: C, 35.42; H, 2.15; I, 62.43. Found: C, 35.47; H, 1.97; I, 62.55.

The filtrate contained 1.54 mmol (66.6%) of iodobenzene according to vpc analysis.

B. With Triphenylboron.—After a solution of **2** (2.43 mmol) and triphenylboron (0.726 g, 3 mmol) in benzene had been stirred at room temperature for a few hours, the yellow precipitate was collected, washed with benzene, and dried to give 1.21 g (2.03 mmol, 83.7%) of dibenziodolium tetraphenylborate, mp 196–197° (lit.[3] mp 195–196°). Recrystallization from 50% aqueous DMF produced yellow, crystalline, analytically pure salt, mp 196° dec. There was no depression of melting point on admixture with an authentic sample prepared by treating dibenziodolium hydroxide solution[28] with sodium tetraphenylborate. Their infrared spectra were identical.

C. With Aluminum Chloride.—A solution of 2.7 mmol of **2** in benzene was prepared and added under argon with gentle cooling to a suspension of 0.8 g (6 mmol) of aluminum chloride in 50 ml of benzene. The light brown solution was stirred at room temperature under argon for 0.5 hr and hydrolyzed by pouring into cold dilute hydrochloric acid. The white precipitate was collected, dissolved in hot water, and treated with KI to give iodonium iodides. The aqueous layer of the filtrate was also treated with KI. The combined mixture of iodonium iodides (0.85 g) was decomposed by heating to 1.25 mmol of iodobenzene, 1.13 mmol of 2-iodobiphenyl, and 0.83 mmol of 2,2′-diiodobiphenyl. Total yield of iodonium salt was 2.08 mmol (76%), in which there were 68.5% of 2-biphenylylphenyliodonium salt and 31.5% of dibenziodolium salt. In the organic phase, 0.14 mmol of iodobenzene, 0.59 mmol of biphenyl, 0.19 mmol of 2-iodobiphenyl, and 0.05 mmol of 2,2′-diiodobiphenyl were found. The total recovery of iodine atom was 2.51 mg-atoms (93.5%).

D. With Borane.—After a solution of 2.8 mmol of **2** in tetrahydrofuran was added to 4 mmol of borane in tetrahydrofuran, the pale yellow mixture was stirred for 0.5 hr and hydrolyzed with cold dilute hydrochloric acid (gas evolution). After concentration by solvent removal, the reaction mixture was extracted a few times with ether. The aqueous layer gave no iodonium iodide when treated with KI solution. Vpc analysis of the ether layer showed iodobenzene (0.074 mmol, 2.6%), biphenyl (0.52 mmol, 18.6%), 2-iodobiphenyl (1.72 mmol, 61.5%), and 2,2′-diiodobiphenyl (0.046 mmol, 1.6%). The total recovery of iodine atom was 68% (1.9 mg-atoms)

Reactions with Acyl and Alkyl Halides. A. With Acetyl Chloride.—Pure dibenziodolium chloride (0.62 g, 1.96 mmol, 72%) was isolated from the mixture of 2.73 mmol of **2** and 4 mmol of freshly distilled acetyl chloride in benzene and stirred for 12 hrs under argon at room temperature. Infrared spectrum and thermal decomposition product of this salt were completely in accord with those of an authentic sample. The organic phase showed iodobenzene (0.30 mmol, 11%), acetophenone (0.35

mmol, 12.8%), biphenyl (0.6 mmol, 22.2%), 2-iodobiphenyl (0.07 mmol, 2.55%), 2,2′-diiodobiphenyl (0.5 mmol, 1.8%), 2-iodo-*o*-terphenyl (0.125 mmol, 4.25%), and small amounts of unidentified high-boiling products.

B. With Carbon Tetrachloride.—A yellow suspension of 0.86 (2.24 mmol) of **2** in 30 ml of carbon tetrachloride was stirred under Ar at room temperature in the dark for 6 hr. The white precipitate was collected, washed with carbon tetrachloride, and dried to give 0.563 g (1.8 mmol, 80%) of dibenziodolium chloride, mp 295° dec. The mother liquor was shown by peak enhancement with authentic samples to be a complex mixture of chlorobenzene, iodobenzene, benzotrichloride, biphenyl, 2-iodobiphenyl, 2-chloro-2′-iodobiphenyl, 2,2′-diiodobiphenyl, and traces of unidentified high-boiling products.

C. With Methyl Iodide.—A suspension of 1 g (2.08 mmol) of **2** in 50 ml of methyl iodide was stirred for 12 hr to yield 0.83 g (1.97 mmol, 70%) of dibenziodolium iodide, mp 220° dec. In the complex organic phase, benzene, toluene, iodobenzene, biphenyl, 2-iodobiphenyl, and 2,2′-diiodobiphenyl have been identified.

Cleavage of 5-Aryl-5*H*-dibenziodole with Hydrogen Chloride.—5-(*p*-Tolyl)-, 5-(*p*-chlorophenyl)-, 5-(*m*-chlorophenyl)-, and 5-(1-naphthyl)-5*H*-dibenziodole have been cleaved by benzoic acid and by hydrogen chloride in tetrahydrofuran. The mixtures of iodonium salts formed were all precipitated as iodides and analyzed as described previously.

Iodonium iodides obtained from 5-(*p*-tolyl)-5*H*-dibenzoidole decomposed to 4-iodotoluene (48%), 2-iodobiphenyl (45%), and 2 2′-diiodobiphenyl (52%). From 5-(1-naphthyl)-5*H*-dibenziodole, the iodides were pyrolyzed to 1-iodonaphthalene (23.8%), 2-iodobiphenyl (21.0%), and 2,2′-diiodobiphenyl (76.3%). 5-(*p*-Chlorophenyl)- and 5-(*m*-chlorophenyl)-5*H*-dibenziodole were cleaved by hydrogen chloride to form pure dibenziodolium chloride and with benzoic acid to give pure dibenziodolium benzoate.

Registry No.—**2**, 32174-73-5; **3**, 32174-74-6; **4**, 32174-75-7; **5**, 32174-76-8; **6**, 32174-77-9; 2-biphenylylphenyliodonium iodide, 32174-78-0; 2-biphenylylphenyliodonium fluoroborate, 32174-79-1; dibenziodolium fluoroborate, 18116-06-8; dibenziodolium methanesulfonate, 6478-21-8; 2-iodo-2′-biphenylylphenyliodonium iodide, 32174-81-5; dibenziodolium chloride, 4673-26-1; dibenziodolium iodide, 1010-76-0.

Transannular Interactions of the Silyl Center with Distant Keto Groups in the Mass Spectra of Medium-Sized Organosilicon Heterocycles. Improved Synthetic Routes to Six-, Seven-, and Eight-Membered Silicon Ring Systems

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The mass spectra of 4,4-dimethylsilacyclohexanone (I), 4,4-dimethylsilacycloheptanone (II), and 5,5-dimethylsilacyclooctanone (III) are discussed. I was prepared by a modified Dieckmann cyclization. II and III were prepared by use of a modified acyloin reaction. Significantly improved yields over previous synthetic routes were obtained.

Only a limited amount of work has been done so far on the mass spectra of functionally substituted organosilicon compounds. Significant differences from the behavior of analogous organic molecules in which silicon is replaced by carbon have been observed. These differences may arise due to strong interaction of the silyl center with electron-rich functional groups. Such interaction often leads to rearranged ions, in which the silyl center and the previously distant electron-rich functional group become directly bonded.[2,3] Two major types of rearrangements involving silyl centers have been observed. The first involves the direct transfer of an intact trimethylsilyl group from one part of the ion to another with concurrent fragmentation in a manner similar to certain types of specific hydrogen migrations frequently observed in mass spectrometry.[3,4] The second involves interaction of a siliconium ion center formed by loss of a methyl group from the quaternary silyl center with a distant electron-rich center in the molecule.[3]

We were interested in the mass spectral behavior of medium-sized organosilicon heterocyclic ketones, since it is well known that strong transannular interactions often play a dominant role in the carbonium ion chemistry of analogous medium-sized organic compounds.[5-7] We propose to discuss the mass spectra of three compounds in which transannular interaction of a silyl center with a remote keto functionality appears to play a dominant role. The compounds are 4,4-dimethylsilacyclohexanone (I),[8] 4,4-dimethylsilacycloheptanone (II),[9] and 5,5-dimethylsilacyclooctanone (III).[9]

Most of the major ions in the mass spectrum of I are probably formed by interaction of the silyl center with the carbonyl functionality. The fragmentation pattern of I is outlined in Figure 1. Metastable peaks at appropriate masses $m^* = (m_2)^2/m_1$ were observed for all fragmentation rearrangement processes discussed (see Table I).

The peak at mass 142 is the parent ion. Loss of a methyl radical from the parent leads to a siliconium ion at mass 127. Cleavage at a quaternary silyl center

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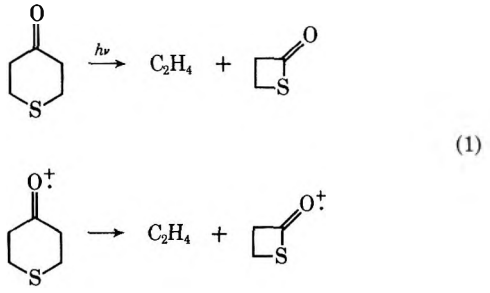
TABLE I
METASTABLE IONS OBSERVED

Possible process	Mass of metastable ion
4,4-Dimethylsilacyclohexanone	
142 → 127	113.6
142 → 114	91.5
114 → 99	85.9
127 → 99	77.2
114 → 86	64.8
4,4-Dimethylsilacycloheptanone	
156 → 141	127.5
156 → 128	105
128 → 113	99.5
141 → 113	90.5
5,5-Dimethylsilacyclooctanone	
170 → 155	141.4
170 → 142	118.6
142 → 127	113.6
155 → 127	104
142 → 114	91.5
114 → 99	85.9
127 → 99	77.2

is a favored process.[10,11] The parent ion also fragments by loss of C_2H_4 to yield an ion of mass 114. Deuterium labeling indicates specific loss of ethylene. The four hydrogens α to the carbonyl group were exchanged by base-catalyzed equilibration of I with D_2O. In the mass spectrum of I-d_4, the parent loses 30, *i.e.*, $C_2H_2D_2$, rather than 28, C_2H_4. A structure for this ion consistent with this result is the 1,1-dimethylsilacyclobutan-2-one cation radical. By analogy, Berchtold has reported that photolysis of the analogous γ-keto sulfide yields thiacyclobutan-2-one. A prominent ion formed by loss of C_2H_4 is also observed in the mass spectrum of this compound (eq 1).[12]



(1)

Loss of a methyl radical from the ion of mass 114 leads to an ion of mass 99. This α-keto siliconium ion is also formed by rearrangement of the mass 127 ion with specific loss of C_2H_4. Both the high resolution data and the mass spectrum of I-d_4 are consistent with these conclusions. Finally, the ion at mass 86 is formed by loss of carbon monoxide from the ion of mass 114 (see Tables II and III).

Clearly, the mass spectrum of 4,4-dimethylsilacyclohexanone is very different from that of cyclohexanone where major fragmentation processes are controlled by the initial cleavage α to the carbonyl group.[13,14]

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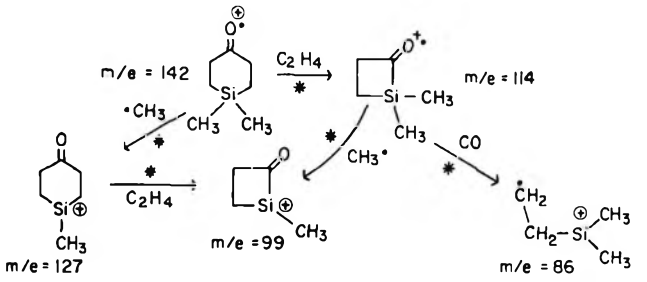


Figure 1.—Mass spectral fragmentation scheme for 4,4-dimethylsilacyclohexanone (*, metastable ion observed).

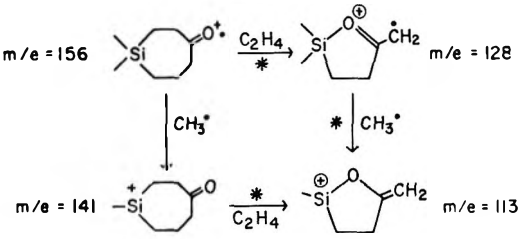


Figure 2.—Mass spectral fragmentation scheme for 4,4-dimethylsilacycloheptanone (*, metastable ion observed).

The mass spectrum of II (Table IV) is dominated by ions which may be formed by transannular interaction of the silyl center with the keto group. The fragmentation pattern of II is outlined in Figure 2. Metastable peaks were observed for all fragmentation–rearrangement processes discussed (see Table I). Loss of a methyl group from the silyl center of the parent ion at mass 156 leads to the expected siliconium ion at mass 141. The parent ion also fragments by loss of C_2H_4 to yield an ion of mass 128. Evidence for the specific loss of C_2H_4 was obtained by deuterium labeling. Exchange of the four hydrogens α to the keto group by base-catalyzed equilibration in D_2O leads to II-d_4. All four deuterium atoms are retained in the (parent $- C_2H_4$)$\cdot^+$ ion. Evidence that the P $-$ 28 ion did not involve loss of carbon monoxide was obtained from high-resolution mass spectrometry (see Table V). Hence the P $-$ 28 ion is probably formed by an intramolecular rearrangement in which the silyl center interacts with the positively charged carbonyl group with simultaneous loss of C_2H_4 specifically from the C_5–C_6 carbons of the three-carbon methylene bridge.[3]

Loss of a methyl radical from this ion of mass 128 leads to a siliconium ion of mass 113. This ion is also formed from the ion of mass 141, by loss of C_2H_4. In this case, the siliconium ion center interacts with the oxygen of the carbonyl group with simultaneous loss of C_2H_4. The spectrum of II-d_4 proves that C_2H_4 is specifically lost from C_5–C_6.

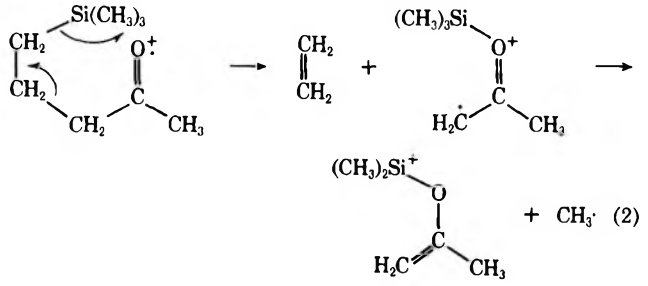
A note of caution must be sounded. In mass spectrometry one never absolutely knows the structure of an ion The transannular formation of an Si–O bond as shown in Figure 2 provides an economical explanation of the data consistent with the high silicon–oxygen bond strength.

A similar silyl-McLafferty rearrangement (eq 2) is observed to be a dominant fragmentation pathway in the mass spectrum of 5-trimethylsilylpentan-2-one (see Table VI).

TABLE II

MASS SPECTRUM OF 4,4-DIMETHYLSILACYCLOHEXANONE

Mass *m/e*	(I) 70 eV	(I) 20 eV	(I-d_4) 70 eV	(I-d_4) 20 eV	Mass *m/e*	(I) 70 eV	(I) 20 eV	(I-d_4) 70 eV	(I-d_4) 20 eV
39	2.5				97	1.5			
					98			0.25	
41	2.5				99	16.0	27.2	1.1	0.5
42	8.0		6.0		100	1.0	2.6	4.3	8.6
43	51.0		36.0		101	0.5	0.9	10.0	25.3
44	7.0		8.3		102			2.3	3.8
45	14.0		7.0		103			1.2	1.6
46	0.5		5.0		104			0.3	
47	1.5		1.0		105			0.3	
53	5.5		2.5		109	0.5			
54	1.5		2.0		110				
55	11.5		4.5		111	0.8		0.3	
56	2.5		6.0		112			0.5	
57	4.5		4.0		113	5.5	44.0	0.8	4.8
58	100.0	1.7	100.0	2.7	114	12.0	100.0	3.5	42.5
59	32.5		17.3	0.5	115	1.8	12.9	3.5	44.7
60	6.0		14.7		116	0.5	3.4	8.0	100.0
61	10.0		5.0		117	0.3		0.5	13.5
62			5.4		118			0.5	4.3
63			2.0		119				
66	0.5								
67	4.5				125	0.8	0.4		
68	0.5				126	0.3	0.4		
69	1.0		0.5		127	3.8	22.0	0.3	
70	1.5		2.0		128	0.5	2.6	0.5	2.7
71	7.5		2.0		129	0.3	0.9	0.5	6.5
72	1.5		3.5		130			1.3	11.8
73	1.0		4.5		131			2.0	14.0
74			0.5		132			0.3	1.6
75	8.5	6.5	4.0	4.3	133			0.3	1.6
76	0.5	0.4	3.5	6.5	134			0.3	0.5
77				0.5					
					141	2.8	16.4		
85	5.0		0.5		142	8.5	65.9		0.5
86	34.5	62.1	2.0	1.6	143	1.5	11.2	0.5	4.3
87	10.5	18.5	9.3	22.1	144	0.5	3.0	1.8	18.8
88	2.0	3.9	28.5	86.0	145			3.5	45.2
89		0.4	5.0	14.0	146			5.3	72.6
90			4.0	13.5	147			0.8	10.8
					148			0.3	2.7



The mass spectrum of III is also dominated by ions which probably arise by transannular interactions of the silyl center and the keto group. The fragmentation pattern of III is outlined in Figure 3. Metastable peaks were observed for all pathways discussed (see Table I). Loss of a methyl radical from the silyl center of the parent ion at mass 170 leads to a siliconium ion of mass 155. The parent ion also fragments by specific loss of C_2H_4 to yield an ion of mass 142. The four hydrogens α to the carbonyl group were exchanged by base-catalyzed equilibration with D_2O. The (parent $- C_2H_4$)$\cdot^+$ ion of III-d_4 retained all the deuterium. This demonstrates that the fragmentation process is similar to that observed in II. Loss of a methyl radical from this ion of mass 142 leads to a

TABLE III

HIGH-RESOLUTION MASS SPECTRAL DATA AT 70 EV FOR 4,4-DIMETHYLSILACYCLOHEXANONE

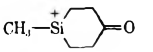
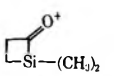
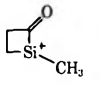
Elemental composition	Calcd mass	Obsd mass	Possible structure of ion
$C_7H_{14}SiO$	142.08139	142.0836	Parent
$C_7H_{13}SiO$	141.07356	141.0728	P − 1
$C_6H_{11}SiO$	127.05791	127.0573	
$C_5H_{10}SiO$	114.05009	114.0514	
C_5H_9SiO	113.04226	113.0407	
C_4H_7SiO	99.02662	99.0245	
$C_4H_{11}Si$	87.06300	87.0599	$(CH_3)_2$—Si—CH_2CH_3
$C_4H_{10}Si$	86.05518	86.0558	$(CH_3)_2$Si—$CH_2\dot{C}H_2$

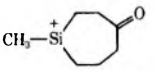
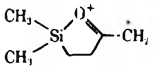
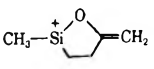
TABLE IV

MASS SPECTRUM OF 4,4-DIMETHYLSILACYCLOHEPTANONE

Mass m/e	(II) 70 eV	(II) 20 eV	(II-d_4) 70 eV	(II-d_4) 20 eV	Mass m/e	(II) 70 eV	(II) 20 eV	(II-d_4) 70 eV	(II-d_4) 20 eV
55			15		113	100	38	2	1
56			11		114	11	4	8	7
57			16		115	4	2	14	10
58	9		55		116		1	35	12
59	16		57		117			83	24
60			23		118			9	3
61	7		12		119			3	1
62			16						
63			8		126				
64			1		127	22	18	1	
65	3		1		128	76	100	5	16
					129	8	13	3	6
69					130	3	4	6	13
70			7		131			19	53
71	5		8	1	132			38	100
72	43	5	100		133			5	14
73	4	1	35	1	134			2	5
74			65	1					
75	27	4	29	1	139	1			
76			38		140				
77	5		6		141	18	15		
78			2		142	2	2		1
					143		1	1	4
81			1		144			3	9
82			1		145			4	12
83			2		146			1	2
84			2						
85	14		6		155	3	1		
86	5	1	12		156	16	10		
87	3		29		157	2	1		
88			13		158			1	2
89			6		159			2	6
					160			4	11
95	6				161			1	2
99	9	2	2						
100	7	6	6	1					
101	4	1	6	1					
102			10	6					
103			3	1					
104			2						

TABLE V

HIGH-RESOLUTION MASS SPECTRAL DATA AT 70 eV FOR 4,4-DIMETHYLSILACYCLOHEPTANONE

Elemental composition	Calcd mass	Obsd mass	Possible structure of ion
$C_8H_{16}SiO$	156.09704	156.0950	Parent
$C_7H_{13}SiO$	141.07356	141.0721	
$C_6H_{12}SiO$	128.06574	128.0697	
$C_6H_{11}SiO$	127.05791	127.0612	
C_5H_9SiO	113.04226	113.0457	

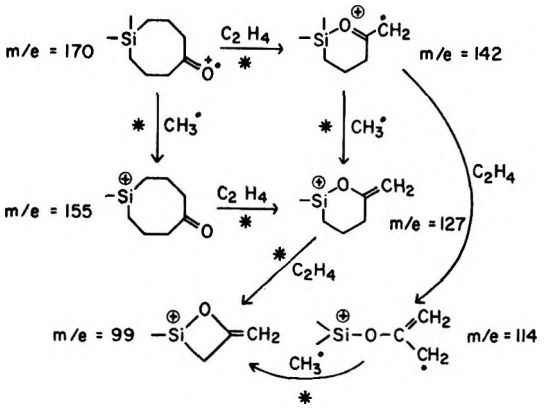


Figure 3.—Mass spectral fragmentation scheme for 5,5-dimethylsilacyclooctanone (*, metastable ion observed).

siliconium ion of mass 127. This ion is also formed by interaction of the siliconium ion center of the mass 155 ion with the carbonyl functionality with simultaneous specific loss of C_2H_4 from C_3–C_4 of the three-carbon methylene bridge. The ion of mass 142 fragments further by specific loss of C_2H_4 to yield an ion of mass 114. All four deuterium atoms of III-d_4 are retained in this ion as is required by the proposed mechanism.

Loss of a methyl group from the silyl center of the mass 114 ion leads to an ion of mass 99. The ion of mass 127 also specifically loses C_2H_4 to yield the ion of mass 99. However, the spectrum of III-d_4 indicates

TABLE VI

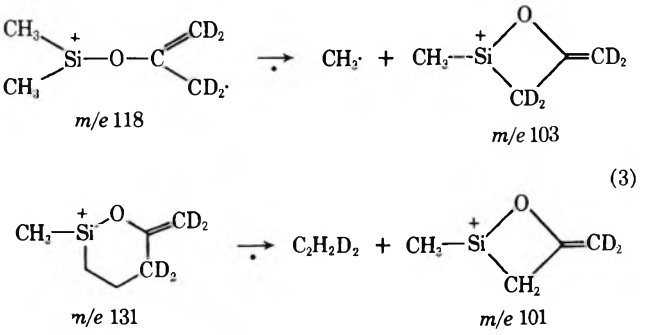
5-TRIMETHYLSILYLPENTAN-2-ONE

Mass m/e	70 eV	20 eV	d_5 70 eV	d_5 20 eV
67	1.7			
68				
69	1.1			
70	1.7		3.5	
71	2.8		5.0	
72	17.9		22.3	
73	81.6	4.9	100.0	5.6
74	7.8		16.1	
75	76.0	25.8	26.2	3.5
76	5.6	1.5	65.3	11.7
77	2.2	0.5	13.8	17.7
78			6.9	11.2
79			1.2	3.0
85	2.8		1.9	
99	2.8			
100			1.5	
101			1.2	
115	100.0	66.3		
116	9.5	6.3		
117	2.8	2.0	6.2	7.6
118			24.6	26.9
119			64.2	46.1
120			57.3	34.0
121			7.3	4.1
122			1.9	
130	33.5	100.0		
131	3.4	11.2		
132	0.6	3.4		3.0
133			5.8	27.4
134			18.5	91.9
135			21.9	100.0
136			2.7	13.7
137				3.0
143	14.5	42.0		
144	1.1	4.9		
145	0.5	1.5		1.5
146			2.7	12.7
147			8.8	41.1
148			9.6	44.2
149			1.2	6.1
150				1.0

that these processes are complicated. In addition to an ion at mass 103, there is also observed a second peak of almost equal intensity at mass 101. It appears that the mass 103 ion is formed by loss of a methyl radical specifically from the mass 118 ion. A metastable peak at mass 89.9 = $(103)^2/118$ is observed. On the other hand, it appears that the mass 101 ion is formed by specific loss of $C_2H_2D_2$ from the mass 131 ion. In support of this a metastable peak is observed at 77.8 = $(101)^2/131$. No evidence in the form of metastable peaks indicates that the mass 118 ion rearranges to the mass 101 or that the mass 131 rearranges to the mass 103 ions. However, it is possible that both of these additional processes could be occurring (eq 3) (see Tables VII and VIII).

Again a final note of caution must be sounded. The structures of ions proposed are consistent with the mass spectral data but cannot be absolutely known by present methods.

In all the compounds discussed transannular interactions of the silyl center with the electron-rich carbonyl group dominate the spectra. The simplicity of the spectra supports the view that these interactions



(3)

are powerful enough to suppress the usual complex fragmentation patterns of cyclic ketones.[13-15]

Synthesis.—All of the compounds have been previously reported by Benkeser.[8,9] However, our synthetic routes lead to improved overall yields.

Our route to I began with the preparation of dimethyldiallylsilane[16] by the *in situ* trapping of allyl Grignard by dimethyldichlorosilane. Dimethyldiallylsilane was converted to dimethyldi(3-hydroxypropyl)silane by a hydroboration–oxidation sequence.[17-19] This reaction is highly specific due to the directive effect of the γ-silyl center. The diol can be oxidized to the expected diacid by Jones reagent;[20,21] however, the yield is only 55%.[8] After esterification with methanol–H_2SO_4, the diester, dimethyldi(2-carbomethoxyethyl)silane,[8] was cyclized to the basic six-membered ring skeleton by a modified Dieckmann reaction.[22] This is of interest since a carbon–silicon bond is considerably longer than a carbon–carbon single bond. For this reason, preparing a six-membered ring containing silicon may be like preparing an all-carbon seven-membered ring system.[23] To achieve reasonable yields, the enolate anion formed in the Dieckmann cyclization must be trapped by rapid addition of trimethylchlorosilane to yield the corresponding silyl enol ether.[22] This prevents the reverse reaction which occurs if quenching of the anion is slow as by addition of water. This silyl enol ether is refluxed overnight in aqueous methanolic HCl to effect hydrolysis of the trimethylsilyl protecting group and decarboxylation of the β-keto acid. The overall yield was 27%.

The basic seven-membered ring skeleton of II is formed by an acyloin reaction on dimethyldi(2-carbomethoxyethyl)silane.[9] We have used the modification of adding trimethylchlorosilane.[22,24] A large excess of sodium is thus no longer required. Further, the reaction conditions remain essentially neutral instead of becoming strongly basic due to the presence of alkoxides. This is particularly useful for organo-

(15) J. H. Benyon, R. A. Saunders, and A. E. Williams, *Appl. Spectrosc.*, **14**, 95 (1960).
(16) C. A. Burkhard, *J. Amer. Chem. Soc.*, **72**, 1078 (1950).
(17) (a) H. C. Brown, K. J. Murry, L. J. Murry, J. A. Snover, and G. Zweifel, *ibid.*, **82**, 4233 (1960). (b) H. C. Brown and B. C. Subba Rao, *ibid.*, **81**, 6428 (1959).
(18) D. Seyferth, H. Yamazaki, and Y. Sato, *Inorg. Chem.*, **2**, 734 (1963).
(19) J. L. Speier, *J. Amer. Chem. Soc.*, **74**, 1003 (1952).
(20) K. Boden, I. M. Heibron, E. R. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1943).
(21) A. Bowors, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2555 (1953).
(22) U. Schräpler and K. Rühlmann, *Chem. Ber.*, **97**, 1383 (1964).
(23) J. P. Schaefer and J. J. Bloomfield, "Organic Reactions," Vol. 15, Wiley, New York, N. Y., 1967.
(24) J. J. Bloomfield, *Tetrahedron Lett.*, 587, 591 (1968).

TABLE VII

MASS SPECTRUM OF 5,5-DIMETHYLSILACYCLOOCTANONE

Mass m/e	(III) 70 eV	(III-d_4) 70 eV	Mass m/e	(III) 70 eV	(III) 20 eV	(III-d_4) 70 eV	(III-d_4) 20 eV
50	6	2	109	2			
51	1	5	110				
52	1		111	3		1	
53	7	4	112			1	
54	2	2	113	6		2	
55	15	11	114	100	26	5	1
56	3	7	115	11	3	4	
57	10	9	116	4	1	7	2
58	15	18	117	1		33	12
59	42	38	118			100	31
60	5	12	119			12	4
61	24	11	120			4	1
62	2	11					
63	1	4	125	2		1	
64	1		126				
65	2	1	127	96	35	5	2
66	2	1	128	12	4	8	6
67	6	3	129	4	2	12	6
68	1	2	130			31	12
69	5	4	131			98	31
70	5	6	132			12	4
71	11	8	133			5	1
72	58	3					
73	11	12	141	1	1	2	2
74	4	35	142	58	100	2	3
75	39	19	143	8	11	1	1
76	3	25	144	2	3	4	7
77	3	5	145			22	36
78		2	146			62	100
79	1		147			8	14
80			148			3	4
81	5						
82			155	6	7		
83	4	2	156	1	1		
84	2	2	157			1	2
85	23	7	158			3	4
86	5	8	159			4	6
87	3	12	160				1
88		7	161				
89		3					
90		2	167				
			168				
95	1		169	0.3	0.3		
96	1		170	0.3	0.3		
97	3	1	171		0.1		
98	2	2	172				
99	60	6	173				
100	7	9	174				
101	2	27	175				
102		19					
103		32					
104		4					
105		1					

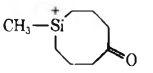
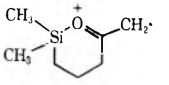
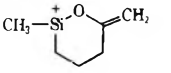
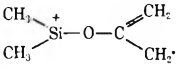
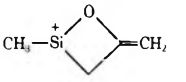
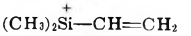
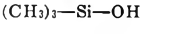
silicon compounds, since alkoxides can cleave certain carbon–silicon bonds.[25] The product is not the acyloin but rather a bis-silyl enol ether. The bis-silyl enol ether is converted to the α-acetoxy ketone by hydrolysis in acetic acid–acetic anhydride.[26] The α-acetoxy ketone is reduced to the desired ketone by

(25) C. Eaborn, "Organosilicon Compounds," Butterworths, London, 1959, pp 129–140.

(26) K. Rühlmann, H. Seefluth, and H. Becker, *Chem. Ber.*, **100**, 3820 (1967).

TABLE VIII

HIGH-RESOLUTION MASS SPECTRAL DATA AT 70 EV FOR 5,5-DIMETHYLSILACYCLOOCTANONE

Elemental composition	Calcd mass	Obsd mass	Possible structure of ion
$C_8H_{15}OSi$	155.08921	155.0870	
$C_7H_{14}OSi$	142.08139	142.0815	
$C_6H_{11}SiO$	127.05791	127.0585	
$C_6H_{10}OSi$	114.05009	114.0503	
C_4H_7OSi	99.02662	99.0291	
C_4H_9Si	85.04735	85.0456	
C_2H_7OSi	75.02662	75.0286	
C_3H_9Si	72.03953	72.0402	
C_2H_7Si	59.03170	59.0315	

treatment with zinc dust in acetic acid.[27] The overall yield is 12%.

The basic eight-membered ring skeleton of 4,4-dimethylsilacyclooctanone and III was prepared by use of an acyloin reaction. This required preparation of a suitable precursor diester. The problem is basically one of connecting unsymmetrical groups to silicon. Our sequence starts with the bromination of trimethylchlorosilane to yield dimethylbromomethylchlorosilane.[28] Addition of allyl Grignard to this yields dimethylallylbromomethylsilane. This is expected, since a silicon–chlorine bond is much more reactive than a carbon–bromine bond. Dimethylallylbromomethylsilane was then converted to the corresponding Grignard reagent, to which was added allyl bromide. The product, dimethylallyl-3-butenylsilane, was converted to dimethyl(3-hydroxypropyl)(4-hydroxybutyl)silane by hydroboration–oxidation in excellent yield.[17] The diol was oxidized to the corresponding diacid by use of the Jones reagent.[20,21] The diacid was esterified with methanolic HCl to yield dimethyl(2-carbomethoxyethyl)(3-carbomethoxypropyl)silane. This was then cyclized to the basic eight-membered ring skeleton by use of the modified acyloin reaction.[22,24] The bis-silyl enol ether was hydrolyzed to the corresponding pair of isomeric α-acetoxy ketones as before.[26] They were not separated but were converted directly to the ketones by treatment with zinc dust in acetic acid.[27] The ketones were separated by gas chromatography. The overall yield was 3%.

The greater accessibility of these medium-sized organosilicon heterocycles opens the possibility of studying many types of transannular interactions in these systems.

Experimental Section

All reactions were carried out under a nitrogen atmosphere. All products were distilled through a 25-cm vacuum jacketed

(27) R. S. Rosenfeld and T. F. Gallagher, *J. Amer. Chem. Soc.*, **77**, 4367 (1955).

(28) J. L. Speier, *ibid.*, **73**, 826 (1951).

Vigreux column unless otherwise noted. All compounds were purified for mass spectral study by preparative gas chromatography on a 0.25 in. × 10 ft SE-30 column unless otherwise noted. Ir spectra were determined in CCl_4 solution on a Perkin-Elmer 337. Nmr spectra were run on a Varian HA-100 using 10% solutions in CCl_4. Chloroform or methylene chloride was used as internal standard. Microanalysis was done by Elek Microanalytical Laboratory.

Conditions in determining low-resolution mass spectra on a Hitachi RMU-6E instrument were source temperature 200°; all-glass inlet temperature 200°; ionizing voltage 70 and 20 eV; filament emission 70 μA; target current 50 μA. Comparisons were made between unlabeled compounds and labeled compounds at 20 eV under identical conditions.

Conditions used in determining high resolution spectra on the AEI MS-902 instrument were as follows. Exact mass determination of the composition of important ions were carried out at a resolution of at least 10,000 by peak matching with peaks of known mass of perfluorokerosene: ionizing voltage 70 eV; filament emission 480 μA; source temperature 150°.

Dimethyldiallylsilane was prepared by the *in situ* trapping of allylmagnesium bromide by dimethyldichlorosilane in THF. The product was distilled; a central fraction, bp 134°, was obtained in 94% yield.[16]

Dimethyldi(3-hydroxypropyl)silane was prepared by hydroboration–oxidation of dimethyldiallylsilane.[17] The diol was purified by distillation; a central fraction, bp 133–135° (1.5 mm), was obtained in 92% yield. Its physical properties were in agreement with literature values.[7,19] Nmr spectrum follows: s (6 H) δ 0.1; m (4 H) 0.4; m (4 H) 1.4, t (4 H) 3.4, J = 7 Hz; s(2 H), 3.6.

Dimethyl(2-carbomethoxyethyl)silane.—In a 5-l. flask equipped with a mechanical stirrer, a thermometer, and an addition funnel was placed 100 g (0.57 mol) of dimethyldi(3-hydroxypropyl)silane dissolved in 700 ml of reagent acetone. The flask was cooled to 0° in an ice–salt bath; 1.14 l. of Jones reagent[20,21] was then added at a rate such that the reaction temperature remained below 20°. The reaction mixture was then stirred for an additional 15 min. The organic layer was separated, and the aqueous layer was extracted with three 500-ml portions of ether. The combined organic layers were extracted with 20% sodium hydroxide until the extract was basic. This basic solution was then acidified and extracted with three 500-ml portions of ether. The ether extracts were dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed by evaporation under reduced pressure. The crude diacid was then refluxed overnight with 600 ml of methanol containing 5 ml of concentrated H_2SO_4. The volume was then reduced to one-third by evaporation under reduced pressure; 500 ml of ether was added; and the organic layer was extracted twice with 100-ml portions of water followed by 100-ml portions of 10% sodium hydroxide until the extracts were basic. The organic layer was then dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed by evaporation under reduced pressure. The residue was distilled, a fraction, bp 90–100° (0.3 mm), 70 g, was obtained, 53% yield. This diester had properties in agreement with reported values.[8]

1,1-Dimethyl-4-trimethylsiloxy-3-carbomethoxy-1-silacyclohexa-3-ene.—A 2-l., three-necked, round-bottom flask equipped with a mechanical stirrer, a pressure-equalizing addition funnel, and a reflux condenser was flamed out under nitrogen. In the flask was placed 24 g (1 mol) of NaH and 1 l. of dry toluene. The mixture was stirred at reflux while 54 g (0.23 mol) of dimethyldi(2-carbomethoxyethyl)silane was added over 4 hr. The reaction was then quenched by the addition of 66 g (0.6 mol) of trimethylchlorosilane.[22] The reaction mixture was then filtered and the solvents were removed by distillation at atmospheric pressure. The residue was distilled; a fraction, bp 80–85° (0.15 mm), 36 g (56% yield), was obtained. The ir had a C–C double bond stretch at 1600 cm^{-1} and a carbonyl band at 1710 cm^{-1}: nmr s (6 H) δ −0.15; s (9 H) −0.03; t (2 H) 0.50, J = 7 Hz; s (2 H) 1.27; t (2 H) 2.07; s (3 H) 3.39, J = 7 Hz. The exact mass of the parent ion was found to be 272.1222; calculated for $C_{12}H_{24}O_3Si_2$, 272.1257. The exact mass of the (P − CH_3) ion was found to be 257.0992; calculated for $C_{11}H_{21}O_3Si_2$, 257.1023.

4,4-Dimethylsilacyclohexanone.—A mixture of 30 ml of concentrated HCl, 300 ml of methanol, 100 ml of H_2O, and 33 g (0.12 mol) of 1,1-dimethyl-4-trimethylsiloxy-3-carbomethoxy-1-silacyclohexa-3-ene was stirred at reflux for 24 hr. The solution was then extracted with two 100-ml portions of ether. The organic layer was dried over anhydrous $MgSO_4$ and filtered and solvent was removed by evaporation under reduced pressure. The residue was then distilled; a fraction, bp 110° (25 mm), was collected, 17 g (95% yield). All properties were in agreement:[7] nmr spectrum s (6 H) δ 0.13; t (4 H) 0.88, J = 7.5 Hz; t (4 H) 2.40, J = 7.5 Hz.

1,1-Dimethyl-4,5-di(trimethylsiloxy)-1-silacyclohept-4-ene.—A 1-l., three-necked flask equipped with a high speed stirrer, pressure-equalizing addition funnel, and a reflux condenser was flamed out under nitrogen. In the flask was placed 16.0 g (0.7 g-atom) of sodium and 300 ml of dry toluene. After the toluene was heated to reflux, stirring was begun. To this Na dispersion was added a mixture of 90 ml of trimethylchlorosilane (0.7 mol) and 25.9 g of dimethyldi(2-carbomethoxyethyl)silane over several hours.[22,24] The reaction was stirred for 2 hr after the addition was complete. The mixture was then filtered. The solvent was removed by distillation at atmospheric pressure. The residue was then distilled, a fraction boiling at 90–100° (0.1 mm), 20 g, was obtained, 60% yield: nmr spectrum s (6 H) δ 0.0; s (18) 0.2; m (4 H) 0.6; m (4 H) 2.2. Its ir has a C–C double bond stretch at 1680 cm^{-1}. The mass spectrum of such bis-silyl enol ethers are quite interesting in that the parent ion carries a high portion of the total ion current. The exact mass of the parent ion was found at 316.1770 (calcd for $C_{14}H_{32}O_2Si_3$: 316.1701).

5,5-Dimethyl-2-acetoxy-5-silacycloheptanone.—A mixture of 13.0 g (41.2 mmol) of 1,1-dimethyl-4,5-di(trimethylsiloxy)-1-silacyclohepta-4-ene, 12 ml of glacial acetic acid, 12 ml of acetic anhydride, and 150 mg of sodium acetate[26] was stirred at reflux for 3 hr. After removal of 18 ml of solvent by distillation at atmospheric pressure, the residue was taken up in 50 ml of ether. The solution was extracted with 50 ml portions of water, followed by 20-ml portions of 10% sodium hydroxide solution until the extracts were basic. The organic layer was then dried over anhydrous $MgSO_4$ and filtered, and the solvents were removed by evaporation under reduced pressure. The residue was distilled; a central fraction, bp 80–85° (0.25 mm), 7 g, was collected, 80% yield. Its ir had two carbonyl bands at 1720 and 1740 cm^{-1}; nmr spectrum s (3 H), δ 0.8; s (3 H) 0.12; m (4 H) 0.8; m (2 H) 2.00; s (3 H) 2.07; m (2 H) 2.50; and m (1 H) 5.40. *Anal.* Calcd for $C_9H_{18}O_2Si$: C, 56.04; H, 8.45. Found: C, 55.69; H, 8.39.

4,4-Dimethylsilacycloheptanone.—In a 200-ml, three-necked round-bottom flask equipped with a Hirshberg mechanical stirrer and a reflux condenser was placed 7.8 g (36.5 mmol) of 5,5-dimethyl-2-acetoxy-5-silacycloheptanone dissolved in 100 ml of glacial acetic acid. The reaction mixture was heated to reflux, while 24 g (0.4 mol) of reagent zinc dust was added in several small batches over 4 hr.[27] The solution was then decanted from the solids, which were washed with 100 ml of ether. The organic layer was extracted with two 50-ml portions of water, and then with 20-ml portions of 10% NaOH until the aqueous extracts were basic. The organic layer was then dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed by evaporation under reduced pressure. The residue was distilled. Two fraction were collected: the first, bp 115° (25 mm) (1.5 g), was largely the desired ketone; the second, bp 140° (25 mm) (4 g), was largely recovered α-acetoxy ketone. The yield of ketone based on converted α-acetoxy ketone is 50%. All physical properties were in agreement with those reported.[8]

Dimethylbromomethylchlorosilane was prepared by the bromination of trimethylchlorosilane following the method of Speier.[28] The product was purified by distillation. A central fraction, bp 134°, was collected: yield 50%; nmr spectrum s (6 H) δ 0.50; s (2 H) 2.35.

Dimethylallylbromomethylsilane was prepared by the addition of allylmagnesium bromide to dimethylbromomethylchlorosilane in ethyl ether. After work-up, the residue was distilled, and a fraction, bp 84–88° (25 mm), was collected, yield 65%. Its ir is characterized by a C–C double bond stretch at 1625 cm^{-1}; nmr spectrum s (6 H) δ 0.14; d (2 H) 1.64, J = 7 Hz; s (2 H) 2.43; a pair of multiplets (2 H) 4.80 and 4.92; and m (1 H) 5.77. *Anal.* Calcd for $C_6H_{13}BrSi$: C, 37.31; H, 6.78. Found: C, 37.16; H, 6.74.

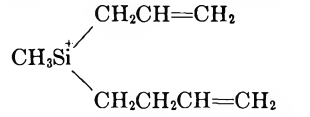
Dimethylallyl-3-butenylsilane.—A 1-l. three-necked flask equipped with a pressure-equalizing addition funnel, a reflux condenser, and a magnetic stirring bar was flamed out under nitrogen. In the flask was placed 200 ml of dry THF and 5.2 g (0.22 g-atom) of Mg turnings. To this was added 34.8 g (0.18 mol) of

dimethylallylbromomethylsilane dropwise with stirring. When formation of the Grignard reagent was complete 36 g (0.3 mol) of allyl bromide was added. When the coupling reaction had ceased 100 ml of water was added. The layers were separated and the organic layer was washed with two 100-ml portions of water. The organic layer was then dried over anhydrous $MgSO_4$ and filtered, and the solvents were distilled at atmospheric pressure. The residue was distilled; a central fraction, bp 62–64° (25 mm), 20 g, was collected, 80% yield. Its ir is characterized by a C–C double bond stretch at 1630 cm^{-1}; nmr spectrum s (6 H) δ 0.0; m (2 H) 0.63; d (2 H) 1.50; m (2 H) 2.00, J = 8 Hz; m (4 H) 4.90; m (2 H) 5.70.

The mass spectrum of the compound is characterized by siliconium ions produced by fragmentation at the quaternary silyl center. High-resolution mass spectral data are shown below.

parent ion $\cdot^+$

Calcd for $C_9H_{18}Si$ 154.11777
Found 154.1226



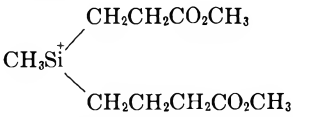
Calcd for $C_8H_{15}Si$ 139.09430
Found 139.0938

$(CH_3)_2\overset{+}{S}iCH_2CH_2CH{=}CH_2$
Calcd for $C_6H_{13}Si$ 113.07865
Found 113.0810

$(CH_3)_2\overset{+}{S}iCH_2CH{=}CH_2$
Calcd for $C_5H_{11}Si$ 99.0630
Found 99.0642

Dimethyl(3-hydroxypropyl)(4-hydroxybutyl)silane was prepared by the hydroboration and oxidation of dimethylallyl-3-butenylsilane in THF.[17,18] The residue was distilled, a central fraction, bp 145–150° (0.1 mm), was obtained in 90% yield. Its ir has a strong OH stretch at 3600–3200 cm^{-1}; nmr spectrum s (6 H) δ −0.1; m (4 H) 0.40; m (6 H) 1.40; m (4 H) 3.40; and a broad singlet at 3.70 (2 H). This last resonance disappeared after exchange with D_2O. The diol was converted to the corresponding diacetate by treatment with acetyl chloride in pyridine. This was done to have a volatile derivative which could be purified by gas chromatography. Its ir has a carbonyl stretch at 1740 cm^{-1}: nmr spectrum s (6 H) δ 0.0; m (4 H) 0.50; m (6 H) 1.55; s (6 H) 2.00; t (2 H) 3.94; J = 7 Hz; t (2 H) 4.00, J = 7 Hz. *Anal.* on diacetate. Calcd for $C_{13}H_{26}O_4Si$: C, 56.90; H, 9.59. Found: C, 57.05; H, 9.43.

Dimethyl (2-carbomethoxyethyl)(3-carbomethoxypropyl)silane was prepared by Jones oxidation[20,21] of dimethyl(3-hydroxypropyl)(4-hydroxybutyl)silane to the corresponding diacid followed by esterification with methanolic H_2SO_4. The procedure is the same as was used to prepare dimethyldi(2-carbomethoxyethyl)silane. The residue was distilled, a central fraction, bp 105° (0.2 mm), was collected in average yield (45%). The ir has a carbonyl stretch at 1745 cm^{-1}; nmr spectrum s (6 H) δ 0.00; m (4 H) 0.80; m (2 H) 1.60; m (4 H) 2.20; and s (6 H) at 3.70. Its mass spectrum is characterized by siliconium ions formed by fragmentation at the quaternary silyl center. The parent ion is quite small. The exact masses of the following three siliconium ions were determined.



Calcd for $C_{10}H_{19}O_4Si$ 231.10525
Found 231.1019

$(CH_3)_2\overset{+}{S}iCH_2CH_2CH_2CO_2CH_3$
Calcd for $C_7H_{13}O_2Si$ 159.08413
Found 159.0830

$(CH_3)_2\overset{+}{S}iCH_2CH_2CO_2CH_3$
Calcd for $C_6H_{13}O_2Si$ 145.06848
Found 145.0667

1,1-Dimethyl-4,5-di(trimethylsiloxy)-1-silacycloocta-4-ene was prepared by an acyloin reaction of dimethyl(2-carbomethoxyethyl)(3-carbomethoxypropyl)silane. The same procedure was used to prepare the corresponding seven-membered ring compound.[22,24] The residue was distilled, a central fraction, bp 95° (0.1 mm), was collected, average yield 60%. The ir has a characteristic C–C double bond stretch at 1680 cm^{-1}; nmr s (6 H) δ 0.00; s (9 H) 0.18; s (9 H) 0.22; m (4 H) 0.85; m (2 H) 1.75; and m (4 H) 2.16. The mass spectrum of such bissilyl enol ethers are quite interesting in that the parent ion carries a quite high percentage of the total ion current. The exact mass of the parent ion was found to be 330.1928 (calculated for $C_{15}H_{34}O_2Si_3$, 330.1857).

5,5-Dimethyl-2-acetoxy-5-silacyclooctanone and 6,6-Dimethyl-2-acetoxy-6-silacyclooctanone.—A mixture of the two compounds was prepared by reaction of 1,1-dimethyl-4,5-di(trimethylsiloxy)-1-silacyclooct-4-ene with a mixture of glacial acetic acid and acetic anhydride by the same procedure used to prepare 2-acetoxy-5,5-dimethylsilacycloheptanone.[26] The residue was distilled; a fraction, bp 90° (0.1 mm), 13 g, was collected, 85% yield. Preparative gas chromatography served to purify the mixture, but not to separate the isomeric acetoxy ketones. The ir of the mixture was characterized by two carbonyl bands, one at 1720 and the other at 1745 cm^{-1}. *Anal.* Calcd for $C_{11}H_{20}O_3Si$: C, 57.85; H, 8.83. Found: C, 57.99; H, 8.80.

4,4-Dimethylsilacyclooctanone and 5,5-dimethylsilacyclooctanone were prepared by the reduction of the mixture of acetoxy ketones by Zn and acetic acid.[27] The procedure was the same as was used to prepare 4,4-dimethylsilacycloheptanone. The residue was distilled; a fracton, bp 115° (25 mm), was collected, yield 55%. The isomeric ketones were separated on a 0.25 in. × 15 ft TCEP column at 135°. The component with the shorter retention time (48 min) was the symmetrical ketone. The component with the longer retention time (55 min) was the unsymmetrical ketone. They were present in a ratio of 60:40 symmetrical to unsymmetrical.

Properties of 4,4-Dimethylsilacyclooctanone.—Its ir has a carbonyl band at 1710 cm^{-1}; nmr spectrum s (6 H) δ 0.00; m (2 H) 0.56; m (2 H) 1.00; m (4 H) 1.82; m (4 H) 2.40. The exact mass of the parent ion determined by peak matching. Calcd for $C_9H_{18}OSi$: 170.1122. Found: 170.1072.

Properties of 5,5-Dimethylsilacyclooctanone.—Its ir showed a carbonyl band at 1710 cm^{-1}; nmr spectrum s (6 H) δ −0.07; m (4 H) 0.68; m (4 H) 1.91; m (4 H) 2.34. For high-resolution mass spectral data, see Table VIII.

5-Trimethylsilylpentan-2-one was prepared following the procedures of Sommer.[29] Its ir was characterized by a carbonyl stretch at 1720 cm^{-1}. Its nmr spectrum showed s (9 H) δ 0.0; m (2 H) 0.5; m (2 H) 1.6; s (3 H), 2.1; t (2 H) 2.4, J = 6.8 Hz.

Deuterium Exchange.—The various ketones were deuterium labeled by the following procedure: 0.5 g of the desired ketone, 6 ml of D_2O (99.8% deuterium), 0.2 g of sodium carbonate, 15 ml of dioxane, and 5 ml of THF were placed in a small round-bottom flask equipped with a magnetic stirring bar and a reflux condenser. The reaction was stirred at reflux for 24 hr. The solution was then extracted with two 30-ml portions of pentane. The organic layer was then washed with two 10-ml portions of water, dried over anhydrous $MgSO_4$, and filtered, and finally the solvents were removed by evaporation under reduced pressure. Final purification was by preparative gas chromatography.

Deuterium content was determined at 20 eV using low-resolution mass spectral data. The analysis was complicated by a significant (P − 1) peak associated with the parent ion in the spectra of the unlabeled compounds. For this reason, the analysis was done using the (P − 15) peak due to cleavage of a methyl group from silicon which has no complicating (P − 15 − 1) ion associated with it.[30]

Deuterium contents determined were as follows: 4,4-dimethylsilacyclohexanone, d_4 38.7%, d_3 33.7%, d_2 19.2%, d_1 8.4%; 4,4-dimethylsilacycloheptanone, d_4 44.4%, d_3 35.2%, d_2 16.2%, d_1 4.2%; 5,5-dimethylsilacyclooctanone, d_4 48.9%, d_3 33.2%, d_2 17.9%; 5-trimethylsilylpentan-2-one, d_5 42.1%, d_4 42.8%, d_3 13.5%, d_2 1.6%.

Registry No.—I, 18276-42-1; II, 10325-26-5; III, 10325-31-2; 1,1-dimethyl-4-trimethylsiloxy-3-carbo-

(29) L. H. Sommer, F. P. Mackay, O. W. Steward, and P. G. Campbell, *J. Amer. Chem. Soc.*, **79**, 2764 (1967).

(30) K. Biemann, "Mass Spectrometry—Organic Chemical Applications," McGraw-Hill, New York, N. Y., 1962; see Chapter 5 for treatment of data for deuterium-labeled compounds.

methoxy-1-silacyclohexa-3-ene, 32297-02-2; 1,1-dimethyl-4,5-di(trimethylsiloxy)-1-silacycloheptene, 32297-03-3; 5,5-dimethyl-2-acetoxy-5-silacycloheptanone, 32297-04-4; dimethylbromomethylchlorosilane, 16532-02-8; dimethylallylbromomethylsilane, 32367-49-0; dimethylallyl-3-butenylsilane, 24171-43-5; dimethyl(3-hydroxypropyl)(4-hydroxybutyl)silane, 32367-50-3, 32367-51-4 (diacetate); dimethyl(2-carbomethoxyethyl)(3-carbomethoxypropyl)silane, 32367-52-5; 1,1-dimethyl-4,5-di(trimethylsiloxy)-1-silacyclocta-4-ene, 32296-53-0; 5,5-dimethyl-2-acetoxy-5-silacyclooctanone, 32296-54-1; 6,6-dimethyl-2-acetoxy-6-silacyclooctanone, 32296-55-2; 4,4-dimethylsilacyclooctanone, 32296-56-3; 5-trimethylsilylpentan-2-one, 17012-93-0.

Acknowledgments.—This work was supported in part by a Biomedical Sciences Support Grant RR-07012-04 from the National Institutes of Health. We also thank the Caltech President's Fund and NASA Contract NAS 7-100.

Reactions of 2-Methylchloroferrocene. Evidence for the Ferrocyne Intermediate[1]

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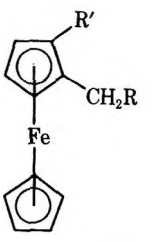
Received May 27, 1971

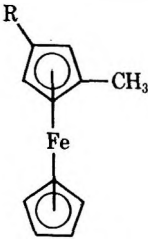
In an effort to investigate the possibility of aryne intermediates in the metallocene series, 2-methylchloroferrocene (2) was prepared by reduction of the methiodide of 2-chloro-*N*,*N*-dimethylaminomethylferrocene (3). Reaction of 2 with butyllithium in tetrahydrofuran gave α-lithiation, while excess butyllithium in hexane gave a mixture of approximately equal parts of 2-methyl- and 3-methylbutylferrocene (7 and 8) in addition to recovered 2 and methylferrocene (6). Similar results were obtained using the butyllithium–tetramethylethylenediamine complex. For reference samples, 7 and 8 were synthesized by alternative routes, and 1'-methylbutylferrocene (9) was also prepared. The results from the reaction of 2 with butyllithium provide the first strong evidence for an aryne intermediate in the ferrocene series.

Several years ago, in work carried out in these laboratories, reactions of chloroferrocene with butyllithium and butyllithium–lithium piperidide were carried out.[2] The products obtained in this study indicated that these reactions were probably proceeding *via* a ferrocyne intermediate, but alternative paths involving prior halogen–metal interconversion could not be excluded.[2] Following our earlier publication, there have been no additional studies on the intermediacy of arynes in the metallocene series, and the only related work appears to be the recent preparation and subsequent trapping of dehydrocyclopentadiene[3] and the selective α-lithiation experiments carried out on haloferrocenes by Hedberg and Rosenberg.[4]

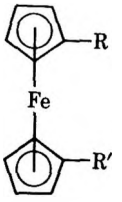
In order to establish whether the reaction of chloroferrocene with *n*-butyllithium to give butylferrocene was an example of an aryne reaction or simply Wurtz–Fittig coupling, a substrate which would give an unsymmetrical aryne was needed. The classical work in the benzene series was carried out using such compounds as *o*-bromoanisole and the halotoluenes,[5] and by analogy it appeared that the reaction of a 2- or 3-substituted chloroferrocene with butyllithium should serve to either establish or refute the existence of the ferrocyne intermediate. In view of the limited synthetic methods available for preparing 1,3-disubstituted ferrocenes, a 2-substituted chloroferrocene seemed to be the substrate of choice. Since it has been noted that the reaction of *N*,*N*-dimethylaminomethylferrocene (1) with *n*-butyllithium proceeds to



1, R = $N(CH_3)_2$; R' = H
2, R = H; R' = Cl
3, R = $N(CH_3)_2$; R' = Cl
4, R = $N(CH_3)_2$; R' = $B(OH)_2$
5, R = $N(CH_3)_3^+I^-$; R = Cl
6, R = R' = H
7, R = H; R' = C_4H_9
12, R = $N(CH_3)_2$; R' = $CH=CHC_2H_5$
13, R = H; R' = COC_3H_7



8, R = C_4H_9
14, R = COC_3H_7



9, R = C_4H_9; R' = CH_3
10, R = $CON(C_6H_5)$; R' = H
11, R = $CON(C_6H_5)$; R' = COC_3H_7
15, R = CH_3; R' = COC_3H_7

give almost exclusively lithiation at the 2 position[6] and since the replacement of the dimethylamino group by hydrogen was quite feasible, 2-methylchloroferrocene (2) was chosen as the subject of our study. Initially

(1) (a) Abstracted from the Ph.D. Dissertation of J. F. Cope, Clemson University, May 1971; (b) supported in part by Career Development Award GM-5433 from the National Institutes of Health.

(2) J. W. Huffman, L. H. Keith, and R. L. Asbury, *J. Org. Chem.*, **30**, 1600 (1965).

(3) J. C. Martin and D. R. Block, *J. Amer. Chem. Soc.*, **93**, 451 (1971).

(4) (a) F. L. Hedberg and H. Rosenberg, *Tetrahedron Lett.*, 4011 (1969). (b) A. N. Nesmeyanov, B. A. Sazonova, and N. S. Sazonova, *Dokl. Akad. Nauk SSSR*, **176**, 598 (1967), reported the preparation and thermal decomposition of 2-chloroferrocenylsilver, but observed no products indicative of an aryne reaction.

(5) (a) T. L. Gilchrist and C. W. Rees, "Carbenes, Nitrenes and Arynes," Appleton-Century-Crofts, New York, N. Y., 1969, pp 42–54 and 103–119, (b) H. Heaney, *Chem. Rev.*, **62**, 81 (1962), and (c) R. Huisgen in "Organometallic Chemistry," H. Zeiss, Ed., Reinhold, New York, N. Y., 1960, pp 36–88, have all reviewed the work which establishes the fact that arynes are intermediates in the reactions of halobenzenes with strong bases.

(6) D. W. Slocum, B. W. Rockett, and C. R. Hauser, *J. Amer. Chem. Soc.*, **87**, 1241 (1965).

2-chloro-*N*,*N*-dimethylammomethylferrocene (**3**) was prepared by means of a halogen–metal interconversion utilizing 3,3,3-trichloropropylene oxide as a halogen source;[7] however, the yields were rather poor and the product difficult to isolate. Subsequently the preparation of this compound by way of 2-(*N*,*N*-dimethylamino)ferrocenylboronic acid (**4**) was reported[8] and this method was used for the preparation of the bulk of the material used in this study. The conversion of the dimethylamine to the methiodide (**5**) and the sodium amalgam reduction to 2-methylchloroferrocene proceeded smoothly.

Initial reactions of **2** with butyllithium in hexane–tetrahydrofuran, even for prolonged periods at reflux, gave no evidence for either aryne reactions or coupling. The only volatile (glc) compounds which could be isolated were recovered **2** and methylferrocene (**6**), probably the result of halogen–metal interconversion.[1a] In order to ensure that lithiation was occurring at the position adjacent to the halogen atom[2,4] the reactions with *n*-butyllithium–tetrahydrofuran were repeated, and either quenched with deuterium oxide or carbonated. Quenching with deuterium oxide gave a 7:1 mixture of **2** and **6**, with 44% incorporation of deuterium in **2**. The only nmr peak which was affected by deuteration was the low-field multiplet at δ 4.22, which may be assigned to the proton α to the chlorine in **2**. Carbonation gave an unstable acid, the spectral data for which (see Experimental Section) were in accord with the structure 2-chloro-3-methylferrocenecarboxylic acid.

Since it was apparent that lithiation α to the halogen was taking place, but the lithioferrocene was not decomposing, the reaction conditions were varied in an effort to obtain the aryne. The use of an alternative solvent, tetrahydropyran, and a more reactive organometallic, *tert*-butyllithium in *n*-butyl ether, were explored. The latter reaction gave no identifiable products except methylferrocene (**6**), while the former gave **2**, **6**, and traces of compounds which were subsequently identified as 2- and 3-methylbutylferrocene.

It has been noticed recently that the *n*-butyllithium–tetramethylethylenediamine complex is a very powerful lithiating agent,[9] which is highly selective for reactions ortho to an electron-rich substituent on an aromatic ring.[9b] Reaction of **2** with this reagent in hexane–tetrahydrofuran, under conditions which favored first formation of the lithio derivative, and then prolonged heating with excess complex, gave a mixture which contained 40% of **6**, 52% of recovered **2**, and 8% of a 5:3 mixture of 2-methylbutylferrocene (**7**) and 3-methylbutylferrocene (**8**). Finally, since it had been noted that lithiation was occurring in tetrahydrofuran, but decomposition to the aryne was not, **2** was lithiated in tetrahydrofuran, and the lithioferrocene was treated with excess butyllithium in hexane and then heated at reflux for several hours. By this method a mixture containing 45% of **6**, 40% of **2**, and 15% of a 2:3 mixture of **7** and **8** was obtained. The overall yield of **7** plus **8** by this procedure was 6%. Various reactions of **2** with butyllithium in the presence of lithium piperidide gave only traces of material which may have been piperidylmethylferrocene, in contrast to the similar reaction of chloroferrocene which affords isolable quantities of piperidylferrocene.[2]

The mixture of **7** and **8** could be isolated by preparative glc, but could not be separated into its components. The infrared and nmr spectra of the mixture were indentical with the sum of the spectra of pure **7** and **8**, prepared as described below, as were the retention times on glc. In addition, the mass spectrum of the mixture was the same as that of **7** and **8**, while markedly different from that of 1′-methylbutylferrocene (**9**).[10] The mass spectral data are summarized in Table I.

TABLE I[a]

MASS SPECTRA OF METHYLBUTYLFERROCENES

			Compd	
m/e	**7**	**8**	**7** + **8**[b]	**9**
257	24	20	21	20
256	100	100	100	100
254	18	31	18	16
214	18	12	17	
213	88	60	79	97
135	10	10	9	27
134	9	8	10	15
121	48	28	34	15
56	21	18	22	26

[a] All peaks reported in relative abundances. [b] From preparative glc of the reaction product of **2** and *n*-butyllithium.

Since the preparation of the three isomeric butylmethylferrocenes had not been reported, and it was necessary to have samples available in order to rigorously assign structures to the products of the above reactions, the syntheses of these compounds was carried out. The most accessible of the three isomers is 1′-methylbutylferrocene, which was prepared in a straightforward sequence from *N*,*N*-diphenylcarbamylferrocene (**10**).[11] Acylation of **10** with butyryl chloride gave keto amide **11**, which on hydrolysis followed by lithium aluminum hydride–aluminum chloride reduction gave **9**. It has been clearly established that electrophilic substitution reactions carried out on **10** proceed to give exclusively the heteroannular product.[11]

The most attractive approach to 2-methylbutylferrocene seemed to be *via* 2-lithio-*N*,*N*-dimethylaminomethylferrocene. However, the reaction with *n*-butyraldehyde did not proceed particularly well, and on isolation of the product it was found that the intermediate carbinol had dehydrated to a mixture of cis and trans butenyl compounds (**12**), contaminated with considerable **1**. The mixture was converted to the methiodides and reduced first with sodium amalgam and then catalytically to give a 1:1 mixture of **2** and **7**.

The only route available for the preparation of 3-methylbutylferrocene (**8**), and one which also afforded an alternative route to the 2 and 1′ isomers (**7** and **10**, respectively), was from the reaction of methylferrocene with butyryl chloride–aluminum chloride, which gave a mixture of 2-methylbutyrylferrocene (**13**, 18%), 3-methylbutyrylferrocene (**14**, 30%), and 1′-methylbutyrylferrocene (**15**, 52%). The heteroannular product **15** was easily distinguished due to the lack of

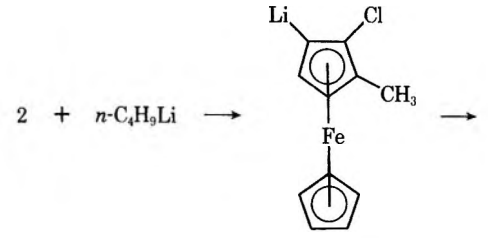
(7) W. Reeve and E. F. Group, Jr., *J. Org. Chem.*, **32**, 22 (1967).
(8) G. R. Marr, E. Moore, and B. W. Rockett, *J. Chem. Soc. C*, **24** (1968).
(9) (a) G. G. Eberhardt and W. A. Butler, *J. Org. Chem.*, **29**, 2928 (1964); (b) R. E. Ludt, G. P. Crowther, and C. Hauser, *ibid.*, **33**, 1288 (1970).

(10) The authors would like to thank the Research Triangle Institute for Mass Spectrometry, Research Triangle Park, N. C., for carrying out these determinations.
(11) W. F. Little and R. Eisenthal, *J. Amer. Chem. Soc.*, **82**, 1577 (1960).

"9–10 bands" in the infrared, and the presence of an A_2B_2 pattern in the aromatic region of the nmr, with two-proton multiplets centered about δ 4.38 and 4.60. The 2-methyl ketone **13** shows a deshielded aryl methyl singlet at δ 2.24, while that of the 3-methyl isomer **14** shows a methyl singlet at δ 1.98. Also, the aromatic region of the spectrum of **13** shows only one proton at significantly lower field, δ 4.40, than the other aromatic protons, while **14** shows a two-proton multiplet at δ 4.55.[12] These structural assignments were strengthened by the chromatographic behavior of these compounds, which paralleled that of the acetylmethylferrocenes,[13] and were confirmed by reduction of each isomer to the corresponding methylbutylferrocene, the structures of two of which had been established by the routes described above.

The three methylbutylferrocenes show slightly different but reproducible retention times on glc (two columns), and, although the mass spectra of the 2- and 3-methyl isomers (**7** and **8**) are very similar, that of 1′-methylbutylferrocene (**9**) is considerably different (see Table I). A comparison of these three compounds with the products of the reaction of 2-methylchloroferrocene (**2**) and butyllithium clearly shows that only the 2-methyl and 3-methylbutyl isomers are obtained. No trace of the 1′ isomer is found.

The results of the reaction of 2-chloromethylferrocene with butyllithium provide very strong evidence for intervention of an aryne intermediate, as outlined in eq 1. It is very difficult to envision any other mech-



methylferrocyne → **7** + **8** (1)

anism which is consistent with the formation of approximately equimolar quantities of 2- and 3-methylbutylferrocenes, from these reactions.[14] The methylferrocene (**6**) obtained probably arises from halogen–metal interconversion to 2-lithiomethyl ferrocene which would afford methylferrocene on hydrolysis, or perhaps by way of a β-hydride transfer from butyllithium to the aryne.[15] On the basis of the data available, it is not possible to differentiate between these two reaction paths.

Although the overall yields of butylmethylferrocenes from these reactions are not high, there is strong evidence that they proceed, at least in part, through an aryne intermediate, and indicate that the earlier reactions of chloroferrocene reported from these laboratories[2] probably proceed by a similar route.

Experimental Section[16]

2-Chloro-*N*,*N*-dimethylaminomethylferrocene. A.—The lithiation of 5.0 g of *N*,*N*-dimethylaminomethylferrocene was carried out following the published procedure.[6] The resulting solution of 2-lithio-*N*,*N*-dimethylaminomethylferrocene in 60 ml of dry ether and 5 ml of hexane was added dropwise to a chilled solution of 2.80 ml of 3,3,3-trichloropropylene oxide in 20 ml of anhydrous tetrahydrofuran. The reaction mixture was allowed to warm to room temperature, stirred for 6 hr, and then poured into water. The aqueous phase was drawn off, and the organic layer was extracted with 10% aqueous sulfuric acid. The acidic solution was made basic with 10% potassium hydroxide and extracted with ether. The ether extracts were washed with water and dried and the solvent was removed to give an orange oil. Tlc (alumina-G) indicated that the reaction product consisted of two compounds, one of which was *N*,*N*-dimethylaminomethylferrocene. Integration of the nmr spectrum indicated that this accounted for 60% of the product mixture, with the chloro compound accounting for the remaining 40%. Repeated chromatography on Bio-Rad neutral alumina and elution with hexane–benzene (2:1) gave a small quantity of pure 2-chloro-*N*,*N*-dimethylaminomethylferrocene, which formed crystals from pentane, mp 42–43° (lit.[8] mp 42–43°). The nmr spectrum of this compound was essentially the same as that reported subsequently by Slocum and Engelmann.[17]

Anal. Calcd for $C_{13}H_{16}NClFe$: C, 56.21; H, 5.80; N, 5.05; Cl, 12.78. Found: C, 56.40; H, 5.69; N, 4.95; Cl, 12.97.

B.—2-Chloro-*N*,*N*-dimethylaminomethylferrocene could be prepared more effectively from 2-(*N*,*N*-dimethylaminomethyl)-ferrocenylboronic acid by the following modification of the published procedure.[8] A suspension of 1.68 g of the aminoboronic acid in 50 ml of water was added to a solution of 2.1 g of cupric chloride dihydrate in 50 ml of water, which had been warmed to 40°. The solution was stirred mechanically and the temperature was raised to 55° for 1.5 hr. After cooling to room temperature, the reaction mixture was treated with excess concentrated ammonium hydroxide and extracted with ether. The organic solution was washed with water and saturated sodium chloride solution and dried over magnesium sulfate. Removal of solvent at reduced pressure gave 1.34 g (83%) of an orange oil which slowly crystallized, mp 41–42°, mmp 42.43° with material from part A. Both samples had identical infrared and nmr spectra.

2-Chloro-*N*,*N*,*N*-trimethylammonium Methylferrocene Methiodide.—To a solution of 0.210 g of 2-chloro-*N*,*N*-dimethylaminomethylferrocene in methanol at room temperature was added 0.50 ml of methyl iodide. The mixture was stirred for 20 min at room temperature and then heated on the steam bath with stirring for an additional 5 min. Ether was added and the crystals were collected, washed with anhydrous ether, and dried under reduced pressure, giving 0.290 g (92%) of yellow crystals, mp 186–189° dec (lit. darkening from 185°).[8]

Anal. Calcd for $C_{14}H_{19}NClFeI$: C, 40.07; H, 4.56; N, 3.34; Cl, 8.45; I, 30.25. Found: C, 40.03; H, 4.45; N, 3.28; Cl, 8.50; I, 30.48.

2-Methylchloroferrocene.—To sodium amalgam, formed from 65 g of mercury and 5 g of sodium maintained at 0°, was added

(12) M. I. Levenberg and J. H. Richards, *J. Amer. Chem. Soc.*, **86**, 2634 (1964), have used a more or less similar argument in assigning the structure to a series of acetylated alkylferrocenes.

(13) J. H. Richards and E. A. Hill, *ibid.*, **83**, 4216 (1961).

(14) One can postulate a series of halogen–metal interconversions and coupling reactions leading to **7**. To arrive at **8**, 2-chloro-3-methyllithioferrocene would react with butyl chloride to give 3-methyl-2-chlorobutylferrocene, which would then undergo halogen–metal interconversion to give on hydrolysis 3-methylbutylferrocene. This route is highly unlikely for two reasons. First, **7** and **8** are formed in approximately equal amounts, while a preponderance of **7** would be predicted if this mechanism were operative. Second, no trace of a methylchlorobutylferrocene was found. Since a significant amount of **2** survives the reaction, a significant amount of chlorobutyl compound would be expected to be present in the final product mixture. The glc techniques used would have permitted the detection of even very small quantities of this substance if it were present.

(15) V. Franzen and H. I. Joschek, *Angew. Chem.*, **72**, 564 (1964).

(16) All melting points were taken on a Kofler hot stage and are uncorrected. The analytical vapor phase chromatography was carried out with an F & M research chromatograph, Model 810; unless otherwise noted a 6 ft × 0.125 in. SE-30 silicon gum column was employed. Preparative glc was carried out on an Aerograph Autoprep, Model A-700 using a 5-ft, 20% SF-96 silicone fluid column. All infrared spectra were taken on a Perkin-Elmer Model 137 spectrophotometer, as liquid or potassium bromide pellets, and are reported in microns. Nuclear magnetic resonance spectra were obtained on a Varian Associates A-60 nuclear magnetic resonance spectrophotometer using either deuteriochloroform or carbon tetrachloride as a solvent. All spectra are reported in parts per million relative to tetramethylsilane (δ). Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Unless otherwise noted, all reactions were carried in an atmosphere of dry nitrogen.

(17) D. W. Slocum and T. R. Engelmann, *J. Org. Chem.*, **34**, 4101 (1969).

0.416 g of methiodide 5 in 10 ml of water. The reaction was allowed to proceed for 10 min, after which 20 ml of benzene was added and the mixture was heated at reflux for 2 hr, at which point the aqueous phase was colorless. The organic phase was extracted with 10% aqueous sulfuric acid and dried and the solvent was removed at reduced pressure. The residue was dissolved in hexane and chromatographed on Merck alumina. Elution with hexane gave an orange oil which crystallized on standing. Recrystallization from pentane gave 0.052 g of yellow crystals (64%): mp 54–57°; nmr δ 2.05 (s, 3 H, CH_3), 3.91 (m, 2 H, FCH), 4.06 (s, 5 H, FCH), 4.22 (m, 1 H, FCH).

Anal. Calcd for $C_{11}H_{11}ClFe$: C, 56.33; H, 4.73; Cl, 15.12. Found: C, 56.29; H, 4.90; Cl, 15.00.

Reactions of 2-Methylchloroferrocene with *n*-Butyllithium. A.—To a solution of 0.270 g of 2-methylchloroferrocene, containing 8% methylferrocene in 25 ml of freshly distilled tetrahydrofuran, cooled to 0°, was added 1.6 ml of 0.9 *N* *n*-butyllithium in hexane. The mixture was stirred for 1.5 hr at this temperature and 25 ml of the reaction solution were withdrawn and mixed with 4 ml of deuterium oxide. After stirring for 5 min, the phases were separated, the organic solution was dried, and the solvent was removed at reduced pressure. Following chromatography on Bio-Rad neutral alumina and elution with hexane, the crystalline material was analyzed by glc and nmr. The former showed the sample to consist of 87% 2-methylchloroferrocene and 13% methylferrocene; nmr showed a 44% decrease in the intensity of the resonance at 4.22 assigned to the proton adjacent to the chloro substituent.

B.—The reaction of 0.970 g of 2-methylchloroferrocene with 2.0 ml of 2.1 *N* *n*-butyllithium was carried out as described above; however, the reaction was heated at reflux for 6.5 hr. A 25-ml aliquot of the reaction solution was removed and added, under nitrogen, to a slurry of anhydrous ether and Dry Ice. The carbonation mixture was extracted with 10% sodium hydroxide until the extracts were colorless. The extracts were washed with ether, acidified with 10% hydrochloric acid, extracted with ether, and dried and the solvent was removed to give 0.168 g of soft crystals. Recrystallization from ether gave orange crystals: mp 178–183°; ir 3.75 br, 5.98; nmr δ 2.14 (s, 3 H, CH_3), 4.25 (s, 5 H, FCH), 4.30 (m, 1 H, FCH), 4.76 (m, 1 H, FCH). Tlc (ethyl acetate, silica gel-G) showed a single spot with an R_f value only slightly different than that of ferrocenecarboxylic acid. This material, 2-chloro-3-methylferrocenecarboxylic acid, decomposed in 12 hr when stored under nitrogen at −10 and could not be submitted for analysis.

The balance of the original reaction mixture was treated with 4 ml of deuterium oxide as described above to give 0.240 g of a mixture of methylferrocene and 2-methylchloroferrocene in which 15% deuterium incorporation in the chloro compound was observed.

C.—To a stirred solution of 0.215 g of freshly sublimed 2-methylchloroferrocene in 25 ml of tetrahydrofuran at 0° was added 3 ml of a mixture of 1.37 ml of tetramethylethylenediamine, 3.6 ml of hexane, and 10 ml of 0.9 *N* *n*-butyllithium. The reaction mixture was heated at reflux for 15 min and the remaining butyllithium solution was added dropwise to the hot reaction mixture. After heating for 18 hr the dark brown solution was poured into ice water and the aqueous layer was drawn off. The aqueous solution was treated with ascorbic acid and extracted with ether and the extracts were combined with the original organic phase. The combined extracts were washed with water and dried, and the solvent was removed to give a yellow oil. The oil was dissolved in hexane and chromatographed on Merck alumina to give 0.20 g of yellow oil which by glc contained 40% methylferrocene, 52% 2-methylchloroferrocene, 5% 2-methylbutylferrocene, and 3% 3-methylbutylferrocene.

D.—The reaction of 0.130 g of 2-methylchloroferrocene with *n*-butyllithium–tetramethylethylenediamine was carried out essentially as described in C above; however, the chloro compound was dissolved in 10 ml of hexane to which had been added 0.12 ml of piperidine. After heating at reflux for 11 hr the reaction mixture was poured over ice and the phases were separated. The organic phase was washed with water and extracted with 10% hydrochloric acid. The acidic extracts were cooled in an ice bath and made basic with 10% sodium hydroxide. Extraction with ether gave a yellow organic phase which was washed with with saturated sodium chloride and dried over magnesium sulfate. Removal of the solvent gave 0.032 g of brown material. Tlc (alumina-G, benzene–hexane 1:1) left most of the sample at the origin; however, two spots appeared, the R_f values of which were slightly greater than that of piperidylferrocene,[2] which was simultaneously chromatographed.

The neutral fraction was washed with saturated brine and dried, and the solvent removed to give 0.070 g of dark oil which was dissolved in hexane and chromatographed on 20 g of Merck alumina. Elution with hexane gave 0.030 g of yellow oil which was analyzed by glc and found to contain 79% methylferrocene, 9% 2-methylchloroferrocene, and 11% butylmethylferrocenes. A second fraction was eluted with benzene and was nonvolatile under glc conditions. Tlc showed that it had an R_f value virtually identical with that of biferrocenyl.[2] The infrared spectrum showed both alkyl and aromatic carbon hydrogen bands as well as the 9 and 10 bands characteristic of unsubstituted rings in ferrocene derivatives.

E.—To a solution of 1.00 g of feshly sublimed 2-methylchloroferrocene in 10 ml of tetrahydrofuran at 0° was added 2.5 ml of 2.18 *N* *n*-butyllithium in hexane. After 1.5 hr at 0°, 20 ml of purified hexane and an additional 10 ml of *n*-butyllithium in hexane were added. The reaction mixture was allowed to warm to room temperature and then heated at reflux for 6 hr. The products were isolated as described above, and on chromatography 0.386 g of material was obtained from the hexane fraction. This mixture was found to contain 45% (19% yield) methylferrocene, 40% (17% recovery) 2-methylchloroferrocene, 6% (2%) 2-methylbutylferrocene, and 9% (4%) 3-methylbutylferrocene. Preparative glc of this material gave 0.010 g of the mixture of 2- and 3-methylbutylferrocenes, the infrared, nmr, and mass spectra of which were identical with the summation of the spectra of the pure isomers.

1′-Butyldiphenylcarbamylferrocene.—To a chilled (−40°) solution of 2.19 g of diphenylcarbamylferrocene[11] in 50 ml of anhydrous dichloroethane was added 0.90 g of aluminum chloride and then a mixture of 6.87 ml of butryl chloride and 0.90 g of aluminum chloride was added dropwise. The mixture was stirred for 2 hr in the cooling bath and was then warmed to room temperature and stirred for an additional 1.5 hr. The reaction mixture was poured into water, the aqueous layer was drawn off, and the organic material was washed with two portions of 10% hydrochloric acid, sodium bicarbonate, and finally water. The dark organic solution was dried and the solvent was removed to give a dark oil which partially crystallized after standing under nitrogen at room temperature for several days. Crystallization from ether gave 1.48 g (56%) of dark red crystals: mp 125–127°; nmr 0.98 (t, 3 H, CH_3), 1.70 (m, 2 H, $CH_2CH_2C{=}O$), 2,70 (t, 2 H, $CH_2CH_2C{=}O$), 4.18 (s, 4 H, FCH), 4.52, 4.78 (A_2 B_2, FCH), 7.28 (s, 10 H, Ar H).

Anal. Calcd for $C_{27}H_{25}NO_2Fe$: C, 71.85; H, 5.58; N, 3.10. Found: C, 72.04; H, 5.94; N, 3.06.

1′-Butyrylferrocenecarboxylic Acid.—A suspension of 0.490 g of diphenyl amide 11 in 25 ml of 10% ethanolic potassium hydroxide was heated at reflux for 7 hr. The reaction mixture was poured into ice water and washed with methylene chloride. The aqueous layer was acidified with 10% hydrochloric acid and extracted with three portions of methylene chloride. The organic extracts were combined, washed with water, and dried and the solvent was removed to give 0.263 g (70%) of orange crystals. Recrystallization from ether gave an analytical sample: mp 109–110°; resolidification then mp 119–120°; nmr δ 1.01 (t, 3 H, CH_3), 1.78 (m, 2 H, $CH_2CH_2C{=}O$), 2.78 (t, 2 H, $CH_2CH_2C{=}O$), 4.58 (m, 4 H, FCH), 4.89 (br s, 4 H, FCH).

Anal. Calcd for $C_{15}H_{16}O_3Fe$: C, 60.02; H, 5.37. Found: C, 60.00; H, 5.41.

Butyrylmethylferrocenes.—To a solution of 3.57 g of methylferrocene[18] in 25 ml of methylene chloride was added dropwise a mixture of 1.34 ml of butyryl chloride and 2.38 g of aluminum chloride in 30 ml of methylene chloride. The mixture was stirred at room temperature for 4 hr and the poured over ice. The organic layer was drawn off and the aqueous solution was extracted with methylene chloride. The organic extracts were combined, washed with water and saturated aqueous sodium bicarbonate, and dried and the solvent was removed to give 4.06 g of red oil. This oil was dissolved in hexane and chromatographed on Merck acid-washed alumina. Elution with hexane gave 0.637 g (18%) of recovered ferrocene, while 2:1 hexane–benzene gave 0.400 g (10%) of **2-methylbutyrylferrocene** as a red oil: nmr δ 0.99 (t, 3 H, CH), 1.70 (m, 2 H, $CH_2CH_2C{=}O$),

(18) A. N. Nesmeyanov, E. G. Prevalova, L. S. Shilovtseva, and Z. N. Beinoreivichata, *Dokl. Akad. Nauk SSSR*, **121**, 117 (1958); *Chem. Abstr.*, **53**, 323 (1959).

2.21 (s, 3 H, FC CH_3), 2.55 (m, 2 H, $CH_2CH_2C{=}O$), 3.98 (s, 5 H, FCH), 4.15 (m, 2 H, FCH), 4.39 (m, 1 H, FCH).

Anal. Calcd for $C_{15}H_{18}FeO$: C, 66.60; H, 6.72. Found: C, 66.92; H, 6.48.

Later fractions eluted with hexane–benzene mixtures gave 2.30 g (57%) of a mixture of 2-, 3-, and 1′-methylbutyrylferrocene. The major fraction (1.68 g) of this mixture, which as relatively rich in the 3 and 1′ isomers, was dissolved in benzene and rechromatographed on Woelm activity I neutral alumina. Elution with 2:1 methylene chloride–ether gave 0.370 g of a mixture of 94% 1′-methyl ketone and 6% of the 3 isomer, while later fractions eluted with the same solvent pair gave first 0.440 g of a mixture of 44% of the 1′ and 56% of the 3′ compound and finally 0.500 g containing 84% of 3-methylbutyrylferrocene and 16% of the 1′ isomer. The nmr assignments could be made on the enriched fractions and follow: **1′-methylbutyrylferrocene**, δ 1.00 (t, 3 H, CH_3), 1.75 (m, 2 H, $CH_2CH_2C{=}O$), 1.82 (s, 3 H, FC CH_3), 2.59 (t, 2 H, $CH_2CH_2C{=}O$), 3.91 (s, 4 H, FCH), 4.24 (m, 2 H, FCH), 4.60 (m, 2 H, FCH); **3-methylbutyrylferrocene**, 0.98 (t, 3 H, CH_3), 1.68 (m, 2 H, $CH_2CH_2C{=}O$), 1.99 (s, 3 H, FCH), 2.55 (m, 2 H, $CH_2CH_2C{=}O$), 3.96 (s, 5 H, FCH), 4.21 (m, 2 H, FCH), 4.59 (m, 2 H, FCH). The middle fraction consisting of the 44:56 mixture was submitted for analysis.

Anal. Calcd for $C_{15}H_{18}FeO$: C, 66.69; H, 6.72. Found: C, 66.89; H, 6.67.

2-Methylbutylferrocene. A.—To a chilled suspension of 0.080 g of aluminum chloride and 0.265 of lithium aluminum hydride in 20 ml of dry ether was added dropwise 0.100 g of 2-methylbutyrylferrocene in 20 ml of ether. The reaction mixture was allowed to warm to room temperature and stirred for 30 min, and ice water was added cautiously. The aqueous layer was drawn off, the organic layer was dried, and the solvent was removed to give a yellow oil which was dissolved in hexane and filtered through a column of Woelm neutral alumina to give 0.048 g (50%) of 2-methylbutylferrocene, homogenous to glc: nmr δ 0.92 (m, 3 H, CH_3), 1.32 (m, 4 H, $-CH_2CH_2-$), 1.98 (s, 3 H, $FcCH_3$), 2.28 (m, 2 H, $FcCH_2-$), 3.78 (m, 3 H, FCH), 3.81 (s, 5 H, FCH).

Anal. Calcd for $C_{15}H_{20}Fe$: C, 70.33; H, 7.87. Found: C, 70.63; H, 7.91.

B.—To a solution of 2-lithio-*N*,*N*-dimethylaminomethylferrocene, from 1.67 g of *N*,*N*-dimethylamminomethylferrocene, was added 3.1 g of redistilled *n*-butyraldehyde and the reaction was stirred at reflux for 5 hr. Ice water was added and the layers were separated. The ethereal solution of products was extracted with 10% hydrochloric acid, and the acid extracts were made basic with 10% sodium carbonate and extracted with ether. The ether extracts were washed with water and dried, and the solvent was removed to give 2.56 g of various viscous oil. Tlc (alumina-G; 1:1 benzene–ether) indicated the presence of starting material and a second compound of similar polarity. The ir showed no hydroxyl absorption and the nmr showed vinyl protons in the δ 5.85–6.18 region. Attempted chromatographic separation was unsuccessful and the mixture was converted to the methiodides and reduced with sodium amalgam as described above for the preparation of 2-methylchloroferrocene. From 2.56 g of starting mixture, 1.50 g of amber oil was obtained. Glc analysis showed that the product consisted of 49% methylferrocene, 45% 2-methylbutenylferrocenes (cis and trans), and 6% of a third component: nmr 1.83–2.42 (m, $-CH_2$, CH_3), 3.60, 3.65 (s, $FeCH_3$), 3.95–4.34 (m, FCH), 5.96 (m, CH=CH).

Again, chromatographic separation was unsuccessful and 1.00 g of the mixtue was dissolved in 40 ml of methanol and hydrogenated at 30 psig using 0.100 g of Adams catalyst. The catalyst was filtered off and the solvent was removed to leave 0.802 g of yellow oil. Glc showed that the product contained 42% methylferrocene, 45% 2-methylbutylferrocene, and 13% minor components. The retention time of material prepared in this manner was identical with that prepared in part A, and differed from that of the other two isomers.

3-Methylbutylferrocene.—This compound was prepared from the corresponding ketone contaminated with 15% of the 1′ isomer, by the procedure described above. From 0.100 g there was obtained 0.060 g (63%) of reduced material: nmr 0.91 (m, 3 H, CH_3), 1.32 (m, 4 H, CH_2CH_2), 1.98 (s, 3 H, $FcCH_3$), 2.21 (m, 2 H, $FcCH_2$), 3.79 (m, 3 H, FCH), 3.85 (s, 5 H, FCH).

Anal. Calcd for $C_{15}H_{20}Fe$: C, 70.33; H, 7.87. Found: C, 70.42; H, 7.71.

1′-Methylbutylferrocene. A.—The reduction of 1′-butyrylmethylferrocene, contaminated with 5% of the 3 isomer, was carried out as described above for the preparation of 2-methylbutylferrocene. From 0.100 g of ketone there was obtained 0.73 g (75%) of 1′-methylbutylferrocene, contaminated with 5% of the 3 isomer: nmr δ 0.90 (m, 3 H, CH_3), 1.34 (m, 4 H, CH_2CH_2), 1.91 (s, 3 H, $FcCH_3$), 2.22 (m, 2 H, $FcCH_2$), 3.80 (br s, 8 H, FCH).

Anal. Calcd for $C_{15}H_{20}Fe$: C, 70.33; H, 7.87. Found: C, 69.64; H, 7.33.[19]

B.—The reduction of 1′-butyrylferrocenecarboxylic acid was carried out by the same procedure used for the reduction of the methylbutyryl compounds. From 0.030 g of acid 0.032 g of product, which was homogenous to glc, was obtained. The retention time of this material was identical with that of material prepared by method A, as were the ir and nmr spectra.

Registry No.—2, 31852-03-6; 7, 32241-91-1; 8, 32241-92-2; 9, 32241-93-3; 11, 32241-94-4; 13, 32241-95-5; 14, 32241-96-6; 15, 32241-97-7; *n*-butyllithium, 109-72-8; 2-chloro-3-methylferrocenecarboxylic acid, 32241-98-8; 1′-butyrylferrocenecarboxylic acid, 32241-99-9.

(19) Completely acceptable analytical data could not be obtained for this compound; however, ir, nmr, and mass spectral data (see Table I) are in accord with the assigned structure.

Electrochemical Generation of Homogeneous Nickel(0) Catalysts for Butadiene Oligomerization

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Electrolytic reduction has been used successfully to prepare nickel catalysts which will convert butadiene to principally 4-vinylcyclohexene and 1,5-cyclooctadiene. The effects upon conversion and product distribution of (a) initial nickel compound, (b) added ligands, (c) solvent, (d) electrolyte, and (e) reduction potential were investigated. Of particular significance was a successful reduction in the absence of any supporting electrolyte. Evidence that the catalytic species contained nickel(0) was obtained by the isolation of $Ni(Ph_2PCH_2CH_2PPh_2)_2$ when the reduction was effected in the presence of this chelating phosphine. The electrochemically reduced species were also shown to undergo reactions typical of nickel(0) leading to organonickel derivatives.

Transition metals in low oxidation states (particularly zerovalent) are known to be the active species in a number of homogeneous catalytic reactions of unsaturated hydrocarbons.[1,2] In a number of cases, the action of a cocatalyst capable of acting as a reducing agent is necessary for catalyst formation. The objective of this research was to investigate the feasibility of *in situ* electrochemical reduction as a method of generating low-valent metal species capable of functioning, without isolation or further treatment, as homogeneous catalysts. We have chosen as a model system the oligomerization of butadiene by reduced nickel species.

Yamazaki and Murai have reported[3] that electrolysis of $[Ni(py)_4][ClO_4]_2$ or $NiCl_2$ in the presence of butadiene yields a red-brown complex which upon decomposition by sulfuric acid or heat yields *trans,trans,trans-n*-hexadecatetraene. The tetraene presumably arises by tetramerization of the butadiene by a reduced nickel species. The reaction, however, was not catalytic. Shortly after completion of this work, a communication appeared describing the electrochemical synthesis of organonickel compounds.[4] It was also mentioned that the reduced nickel species would convert butadiene to cyclododecatrienes or (with triphenylphosphine present) to 4-vinylcyclohexene and 1,5-cyclooctadiene.

Results

The experimental procedure consisted of two phases: (1) catalyst generation and (2) reaction with butadiene. Catalyst generation involved the controlled-potential electrolysis of a solution of the nickel compound, electrolyte, and added ligand, if any, until the cell current decreased essentially to 0 mA. The initial current was arbitrarily limited to 100 mA. The reductions were generally accompanied by a series of striking color changes. Thus, in the system $NiCl_2$·dimethoxyethane–Ph_3P–Bu_4NClO_4–*N*,*N*-dimethylformamide, the initially royal blue solution changed to dark green to red-brown to dark yellow-brown.

After completion of the electrolysis, the solution containing the reduced nickel species was transferred to a pressure vessel, butadiene was added, and the mixture was heated. The effect of a number of variables on the product distribution and per cent conversion were investigated and are discussed individually below. Under our experimental conditions, heating a mixture of butadiene and acetonitrile alone gave 3% of 4-vinylcyclohexene, a trace of 1,5-cyclooctadiene, and 2% of polymer. In some cases, the per cent VCH includes small amounts of octatrienes. The reduction potentials quoted below are referred to the $Ag|Ag^+$ couple.

Effect of Nickel Source.—Table I lists the results obtained with several types of nickel(II) compounds. The first three entries indicate that several combinations of nickel(II) chloride and triphenylphosphine may be used. Enhanced solubility in organic solvents makes nickel(II) chloride–tertiary phosphine complexes preferred sources of nickel (the phosphine is also necessary to prevent deposition of metallic nickel; *vide infra*). For convenience, prior preparation of the phosphine complexes can be circumvented by using the 1:1 complex of nickel(II) chloride and 1,2-dimethoxyethane (DME) which is also somewhat soluble in organic solvents. Addition of the appropriate phosphine results in the rapid *in situ* formation of the phosphine complex. The low conversions in experiments 1 and 4 are believed to be due to the very low solubilities of $NiCl_2$ and $NiCl_2(Cy_3P)_2$ resulting in a very low concentration of reduced nickel. The five-coordinate complex, $Ni(CN)_2(PhPMe_2)_3$, when reduced in acetonitrile gave an active catalyst; this reaction, however, was not analyzed quantitatively.

Effect of Added Ligand.—The effect of various added ligands on the catalyst system obtained from $NiCl_2$·DME in acetonitrile is shown in Table II.

The reduction must be carried out in the presence of a ligand capable of stabilizing the reduced nickel species. Thus, as indicated by expt 7, metallic nickel is precipitated when $NiCl_2$·DME alone is subjected to electrolysis. Nickel metal was also formed when triphenylarsine and 1,5-cyclooctadiene were the added ligands (expt 8 and 9). Acrylonitrile prevented the formation of metallic nickel but did not give a catalytic system (expt 14). The triphenyl- and trialkylphosphines were effective in stabilizing the reduced nickel. The chelating phosphine, bis(1,2-diphenylphosphino)-ethane, gave a catalyst of low activity. The effect of varying the Ph_3P:Ni ratio from 2:1 to 4:1 is demonstrated by expt 10 and 11, respectively. A higher concentration of triphenylphosphine increases the conversion and the selectivity to VCH while decreasing the amounts of heavier materials, *i.e.*, CDT and poly-

(1) I. Wender and P. Pino, "Organic Synthesis via Metal Carbonyls," Interscience, New York, N. Y., 1968.

(2) C. W. Bird, "Transition Metal Intermediates in Organic Synthesis," Academic Press, New York, N. Y., 1967.

(3) N. Yamazaki and S. Murai, *Chem. Commun.*, 147 (1968).

(4) H. Lehmkuhl and W. Leuchte, *J. Organometal. Chem.*, **23**, C30 (1970).

TABLE I[a]

EFFECT OF NICKEL SOURCE[b]

Expt no.	Nickel compd, mmol	Added ligand, mmol	C_4H_6, g	Yield, % VCH	COD	CDT	Polymer
1	$NiCl_2$, 0.4	Ph_3P, 4.6	11.5	7	0.5	~0	2
2	$NiCl_2$·DME,[c] 1.0	Ph_3P, 2.0	11.9	25	36	5	11
3	$NiCl_2(Ph_3P)_2$, 1.0	None	17.3	18	29	5	2
4	$NiCl_2(Cy_3P)_2$,[d] 0.4	None	10.1	6	3	2	3
5	$NiCl_2(Et_3P)_2$, 0.4	None	10.7	12	24	1	3
6	$NiCl_2(Bu_3P)_2$, 0.4	Bu_3P, 4.8	11.2	16	43	1	*e*

[a] The following abbreviations are used throughout the tables below: VCH = 4-vinylcyclohexene, COD = 1,5-cyclooctadiene, and CDT = cyclododecatrienes. The per cent yield is the chemical yield. [b] Conditions: CH_3CN (25 ml), Bu_4NClO_4 (0.1 *M*), −2.0 V. [c] DME = 1,2-dimethoxyethane. [d] Cy = Cyclohexyl. [e] Not determined.

TABLE II

EFFECT OF ADDED LIGAND[a]

Expt no.	Added ligand, mmol	C_4H_6, g	Yield, % VCH	COD	CDT	Polymer
7	None[b,c]		Metallic nickel			
8	Ph_3As,[b] 4.6		Metallic nickel			
9	1,5-COD,[b] 5.1		Metallic nickel			
10	Ph_3P,[d] 2.0	11.9	25	36	5	11
11	Ph_3P,[d] 4.0	11.6	40	43	3	8
12	Bu_3P,[d] 2.0	7.3	14	28	2	11
13	diphos,[e] 1.0	11.4	8	Trace	Trace	*g*
14	CH_2=CHCN,[d,f] 0.4	8.9	No catalysis			

[a] Conditions: CH_3CN (25 ml), Bu_4NClO_4 (0.1 *M*), −2.0 V. [b] 0.4 mmol of $NiCl_2$·DME. [c] Bu_4NBr as electrolyte. [d] 1.0 mmol of $NiCl_2$·DME. [e] diphos = bis(1,2-diphenylphosphino)ethane. [f] *N*,*N*-Dimethylformamide solvent. [g] Not determined.

mer. The substitution of tributylphosphine for triphenylphosphine enhances the selectivity to COD.

Effect of Solvent.—Several solvents were found to be suitable media both for the electrolytic reduction and the subsequent oligomerization reaction (Table III).

TABLE III

EFFECT OF SOLVENT[a]

Expt no.	Solvent[b]	Reduction V	Reduction Min	Yield, % VCH	COD	CDT	Polymer
15	CH_3CN	−2.0	40	25	36	5	11
16	DMF[c]	−2.0	42	17	32	8	7
17	DME[d]	−2.0	196	6	2	~0	13
18	DME[d]	−3.0	189	5	4	~0	*e*
19	DME[d,f]	−3.0	118	15	30	2	4

[a] Conditions: $NiCl_2$·DME (1.0 mmol), Ph_3P (2.0 mmol), Bu_4NClO_4 (0.1 *M*). [b] 25 ml. [c] DMF = *N*,*N*-dimethylformamide. [d] DME = 1,2-dimethoxyethane. [e] Not determined. [f] 0.5 mmol of $NiCl_2$·DME.

Acetonitrile and *N*,*N*-dimethylformamide are, however, the solvents of choice. The solubilities of the starting nickel complexes are much higher in these solvents. Much higher current densities can, therefore, be achieved in these solvents and the reductions can thus be effected much more rapidly (*cf.* expt 15 and 16 with expt 17–19). In acetonitrile and *N*,*N*-dimethylformamide, a lower Ph_3P:Ni ratio (2:1 *vs.* 4:1) was sufficient to obtain catalysts of satisfactory activity than was the case with 1,2-dimethoxyethane. It is likely that the former solvents are effective in stabilizing the reduced nickel species through coordination. Under the same experimental conditions, *N*,*N*-dimethylformamide gives a higher selectivity to COD than does acetonitrile. This is additional evidence that the solvent may be acting as a ligand in the catalytic nickel species. Sulfolane was also shown to be a suitable solvent, but the reaction was not analyzed quantitatively.

Effect of Electrolyte.—The results obtained with several different supporting electrolytes are shown in Table IV.

TABLE IV

EFFECT OF SUPPORTING ELECTROLYTE[a]

Expt no.	Supporting electrolyte[b]	C_4H_6, g	Yield, % VCH	COD	CDT	Polymer
20	Bu_4NClO_4	11.9	25	36	5	11
21	Bu_4NCl	12.3	10	17	5	13
22	Bu_4NBr	15.6	26	39	5	12
23	None[c]	13.6	26	34	5	9

[a] Conditions: $NiCl_2$·DME (1.0 mmol), Ph_3P (2.0 mmol), CH_3CN (25 ml), −2.0 V. [b] 0.1 *M*. [c] Bu_4NClO_4 present in anode compartment.

Tetra-*n*-butylammonium perchlorate is a commonly used supporting electrolyte in electrochemical studies because of the poor coordinating ability of the perchlorate ion which minimizes interactions of the electrolyte with the metal-containing species. We have found that halide anions can be tolerated by the nickel catalyst systems (expt 21 and 22). The results obtained in the oligomerization reaction are very similar for the bromide and perchlorate salts; however, a lower conversion and a somewhat higher proportion of polymer resulted with the chloride derivative. Of significance, is the result of expt 23 in which supporting electrolyte was omitted. This could be useful in cases where interference from the electrolyte in subsequent reactions is a problem. With the exception of the Bu_4NCl system, essentially the same results are obtained with or without supporting electrolyte present.

Effect of Reduction Potential.—The reduction of a 2:1 Ph_3P:$NiCl_2$·DME mixture in acetonitrile was carried out at several different potentials (Table V).

TABLE V

EFFECT OF REDUCTION POTENTIAL[a]

Expt no.	Reduction V	Reduction Min	C_4H_6, g	Yield, % VCH	COD	CDT	Polymer
24	−1.5	57	12.6	8	<1	Trace	10
25	−2.0	40	11.9	25	36	5	11
26	−2.5	78	12.2	14	25	2	16

[a] Conditions: $NiCl_2$·DME (1.0 mmol), Ph_3P (2.0 mmol), Bu_4NClO_4 (0.1 *M*), CH_3CN (25 ml).

At −1.5 V a green solution and yellow solid were formed; this mixture exhibited lower activity for the oligomerization of butadiene (expt 24). At −2.0 V a

dark red-brown solution resulted which showed high catalytic activity. A more negative potential (−2.5 V) had a deleterious effect on the catalyst system when employing acetonitrile as the solvent. It is likely that at −2.5 V some reduction of solvent is beginning to occur (the cathodic limit for acetonitrile has been reported[5] to be −2.84 V *vs.* $Ag|Ag^+$) which yields species that deactivated the catalyst.

Discussion

The distribution of products in the butadiene oligomerization reaction catalyzed by electrochemically reduced nickel species is generally in accord with the results obtained with chemically reduced catalysts. Thus, the catalyst obtained from the interaction of nickel(II) acetylacetonate and ethoxydiethylaluminum in the presence of triphenylphosphine gave (after 5 hr at 80°) 30% of VCH, 62% of COD, and 4% of CDT.[6] The results obtained in the electrochemical system $Ni(acac)_2$–pyridine–R_4NBr are comparable to those we have obtained. The above system gives 44% of VCH and 56% of COD.[4]

A number of zerovalent nickel compounds are known to catalyze the oligomerization of butadiene.[7] Direct evidence for the presence of nickel(0) species in the systems of this research was obtained by the following experiment. Reduction of a solution of $NiCl_2(Ph_2PCH_2CH_2PPh_2)$ in acetonitrile at −2.0 V in the presence of 1 equiv of $Ph_2PCH_2CH_2PPh_2$ resulted in the precipitation of $Ni(Ph_2PCH_2CH_2PPh_2)_2$ in 89% yield.

The nickel(0) complexes, Ni(1,5-cyclooctadiene)$_2$, Ni(cyclooctatetraene), Ni(*all-trans*-cyclododecatriene), and $Ni(Ph_3P)_4$, were prepared by Lehmkuhl and Leuchte from $Ni(acac)_2$ and the appropriate ligand.[4] Recently, the electrochemical synthesis of two rhodium(0)–tertiary phosphine complexes has been described.[8]

Additional evidence for the presence of nickel(0) in our system was obtained by the following experiments. Reduction of $NiCl_2(Ph_3P)_2$ in acetonitrile followed by treatment of the solution with pentafluorobromobenzene gave $NiBr(C_6F_5)(Ph_3P)_2$. Similarly, a reduced solution of $NiCl_2(Et_3P)_2$ reacted with tetrachloroethylene to give $NiCl(CCl{=}CCl_2)(Et_3P)_2$. These organonickel(II) derivatives arise from the oxidative addition of the organic halide to a nickel(0) species.[9]

Experimental Section

Reagents.—The following chemicals were obtained from the source indicated in parentheses and used as received: $AgClO_4$ (K and K Laboratories), Bu_4NClO_4 (G. Frederick Smith), Bu_4NX(X = Cl, Br) (Eastman), Hg (National Zinc Co.), $NiCl_2$·DME (Alfa Inorganics), Ph_3P and Bu_3P (Carlisle), and $Ph_2PCH_2CH_2PPh_2$ (Arapahoe). The following complexes were prepared by established literature methods: $NiCl_2(Bu_3P)_2$, $NiCl_2(Ph_2PCH_2CH_2PPh_2)$, $NiCl_2[(C_6H_{11})_3P]_2$, $NiCl_2(Et_3P)_2$, and $NiCl_2(Ph_3P)_2$. The Ph_3As (M and T) was recrystallized from MeOH. The COD (Columbia Carbon) and $CH_2{=}CHCN$ (Eastman) were distilled materials. The acetonitrile (Mallinckrodt) was dried over Davidson Type 4A molecular sieves. The DME (Eastman) and DMF (Mallinckrodt) were distilled from CaH_2. The solvents were degassed by sparging with prepurified nitrogen before use.

Apparatus.—All electrochemical work was carried out in a Vacuum Atmospheres Corp. Dry-Lab/Dry-Train containing an atmosphere of 96% nitrogen and 4% hydrogen.

Controlled-potential electrolyses were conducted in a U-shaped cell consisting of two compartments separated by a sintered-glass disk. One compartment (the cathode) was equipped with a ground-glass joint to hold the reference electrode assembly. Electrical contact with the cathode and anode compartments was made *via* platinum wires pinch-sealed through the base of the cell. The reference electrode assembly consisted of two parts: an upper tube containing a silver wire and a 0.001 *M* solution of $AgClO_4$ in 0.1 *M* Bu_4NClO_4 in CH_3CN and a lower tube containing 0.1 *M* electrolyte in the reduction solvent. The upper tube was separated from the lower and the lower tube from the catholyte by sintered-glass disks.

Controlled-potential electrolysis was effected with a Kepco Model 60-0.5 power supply used in conjunction with a Heath voltage reference source.

The butadiene reactions were conducted in Fisher–Porter aerosol compatibility bottles equipped with a pressure gauge and fitting for admitting gaseous butadiene. All equipment was dried at 105–110° before use.

Analysis.—The reactions were analyzed by glpc on a F & M Scientific Model 5750 chromatograph using a flame ionization detector. The analysis for VCH and COD was conducted on a 20 ft × 1/8 in. column containing 20% tris(cyanoethoxy)propane on 35/80 mesh Chromosorb P at 120°. Analysis for cyclododecatrienes was carried out on a 6 ft × 1/8 in. column containing 20% SE-30 on Chromosorb P at 120°. The polymer content of the reaction mixture was taken as the material which would not distil into a Dry Ice cooled receiver at 100° (0.075–0.1 mm). The VCH, COD, and CDT were isolated in an experiment using a catalyst obtained by reducing (at −2.0 V) 0.4 mmol of $NiCl_2$·DME and 4.5 mmol of Ph_3P in 0.1 *M* Bu_4NClO_4-CH_3CN. They were identified by their ir and nmr spectra.

Catalyst Generation.—The following general procedure was used in all the experiments discussed above. The nickel compound, electrolyte, added ligand, and solvent were mixed (total volume 25 ml). The resulting solution or suspension was transferred to the cathode compartment of the elctrolysis cell. A solution (0.1 *M*) of electrolyte was placed in the anode compartment. Mercury was added to both compartments in an amount sufficient to cover the platinum wires sealed in the base. The reference electrode assembly was allowed to contact the solution in the cathode compartment. The mercury pool electrodes were stirred magnetically. Current was then passed through the cell at the desired reduction potential until a residual value of <5 mA was reached.

Butadiene Oligomerization.—After completion of the electrolysis, the mercury was drained from the cathode *via* a stopcock located in the base of the cell and the solution containing the reduced nickel species was transferred to a Fisher–Porter bottle. Butadiene was added at room temperature and the reaction mixture was stirred and heated to 130° over 2 hr. After an additional 3 hr at this temperature, heating was discontinued. The reaction mixture was cooled in an ice bath, then analyzed by glpc. A weighed quantity of VCH was added to the reaction mixture followed by reanalysis. The increase in area of the VCH peak (relative to the COD peak) was used to determine the quantities of these materials present.

Preparation of $Ni(Ph_2PCH_2CH_2PPh_2)_2$.—A solution of 0.26 g (0.49 mmol) of $NiCl_2(Ph_2PCH_2CH_2PPh_2)$, 0.20 g (0.50 mmol) of $Ph_2PCH_2CH_2PPh_2$, and 0.86 g of Bu_4NClO_4 in 25 ml of CH_3CN was reduced at −2.0 V over an 18-min period. The solution changed from red-brown to yellow and a gold solid precipitated. The solid was recovered by filtration and washed with pentane to give 0.38 g. The infrared spectrum of this material was identical with that of a sample of $Ni(Ph_2PCH_2CH_2PPh_2)_2$ prepared by the procedure of Chatt and Hart.[10] A sample recrystallized from benzene–methanol gave orange crystals. *Anal.* Calcd for $C_{52}H_{48}P_2Ni$: C, 73.0; H, 5.7; Ni, 6.9. Found: C, 73.0; H, 5.7; Ni, 7.0.

Preparation of $NiBr(C_6F_5)(Ph_3P)_2$.—A solution of 1.30 g (2.0 mmol) of $NiCl_2(Ph_3P)_2$ in 50 ml of 0.1 *M* Bu_4NClO_4 in 1,2-dimethoxyethane was reduced at −3.6 V for 4.75 hr. Pentafluorophenyl bromide, 2.20 g (8.9 mmol), was added to the reduced

(5) E. O. Sherman and D. C. Olson, *Anal. Chem.*, **40**, 1174 (1968).
(6) G. Wilke, H. Muller, and M. Kroner, *Angew. Chem.*, **73**, 33 (1961).
(7) G. Wilke, *Angew. Chem., Int. Ed. Engl.*, **2**, 105 (1963).
(8) D. C. Olson and W. Keim, *Inorg. Chem.*, **8**, 2028 (1969).
(9) D. R. Fahey, *J. Amer. Chem. Soc.*, **92**, 402 (1970).
(10) J. Chatt and F. A. Hart, *J. Chem. Soc.*, 1378 (1960).

solution after transfer from the cell to a 7-oz bottle. After heating at 60° for *ca.* 10 min, the reaction mixture was filtered through alumina. Concentration of the filtrate gave a green oil. Extraction with pentane left a green gum. The addition of 30 ml of methanol resulted in the formation of a yellow solid, 0.19 g. An infrared spectrum of this material showed it to be $NiBr(C_6F_5)(Ph_3P)_2$.

Preparation of $NiCl(CCl{=}CCl_2)(Et_3P)_2$.—A solution of 0.3 g (0.8 mmol) of $NiCl_2(Et_3P)_2$ and 0.86 g of Bu_4NClO_4 in 25 ml of CH_3CN was reduced at −2.0 V over a 52-min period. The solution changed from dark red to brownish-gold. The solution was transferred to a 7-oz beverage bottle and treated with 1.82 g (11.0 mmol) of tetrachloroethylene. After standing overnight at room temperature, a 2-ml aliquot of the solution was chromatographed on alumina. Elution with 50% ether in pentane gave a yellow solid which had an infrared spectrum identical with that of authentic $NiCl(CCl{=}CCl_2)(Et_3P)_2$. Chromatography of the remainder of the solution on alumina gave, with pentane elution, 0.19 g of the yellow solid. Recrystallization from methanol–water gave gold crystals, mp 89–91° (lit.[11] mp 92–92.8°).

Registry No.—Butadiene, 106-99-0; $NiCl_2(Ph_3P)_2$, 14264-16-5; $NiCl_2(Cy_3P)_2$, 19999-87-2; $NiCl_2(Et_3P)_2$, 17523-24-9; $NiBr(C_6F_5)(Ph_3P)_2$, 14154-59-7.

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(11) R. G. Miller, D. R. Fahey, and D. P. Kuhlman, *J. Amer. Chem. Soc.*, **90**, 6243 (1968).

Interaction of Silver Ion with Some Strained Olefins

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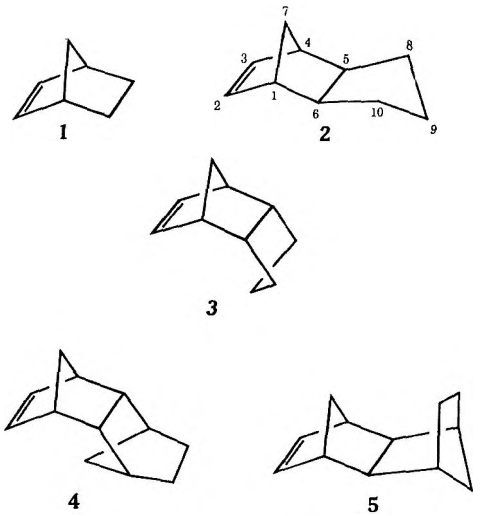
The interaction of silver ion with olefins that would have hindrance at the back of the complexed π orbital was studied. Hindrance causes a small decrease in complex formation indicating a slight dependance on solvation at the back of the complex.

Steric effects have long been recognized as an important factor influencing complex formation of silver(I) with olefins.[1] In an attempt to further elucidate the nature of steric effects in these complexes, a variety of olefins were investigated in which backside (the face of the double bond opposite to that complexed with silver) steric hindrance to the incipient complex was varied. Norbornene type ring systems were used for this because the relatively rigid ring system would prevent differences due to conformational variations. Silver ion has been shown to be largely complexed on the exo face of the norbornene ring[1c,d] so that substitution at the endo 5,6 positions would sterically block the back side of the complexed π orbital.

Conceivable blockage of solvation on the backside could drastically reduce complex formation. The interactions of silver(I) ion with norbornene (**1**), *exo*-5,6-trimethylene-2-norbornene (**2**), *endo*-5,6-trimethylene-2-norbornene (**3**), 1,2,3,4,4a,5,8,8a-octahydro-1,4,-5,8-*exo*,*endo*-dimethanonaphthalene (**4**), and 1,2,3,4,4a,-5,8,8a-octahydro-1,4,5,8-*endo*,*exo*-dimethanonapththalene (**5**) were investigated by the Muhs and Weiss procedure[1a] and by the Winstein and Lucas method.[1b]



The equilibrium constants determined by the Muhs and Weiss[1a] procedure (Table I) depend upon the difference in glpc retention time of olefin on an ethylene glycol column *vs.* its retention time on a silver nitrate impregnated ethylene glycol column.

TABLE I

EQUILIBRIUM CONSTANTS FOR SILVER COMPLEXES WITH OLEFINS BY MUHS AND WEISS TECHNIQUE AT 60°

Compd	K_L[a]	K_{eq}[b]	Rel K_{eq}
1	15.1	16.9[c]	1.0[c]
2	82.9	15.8	0.94
3	90.1	9.84	0.58
4	369	11.5	0.68
5	406	13.9	0.82
Norbornadiene	25.9	6.75	0.40[d]

[a] K_L is the partition coefficient for olefin on pure ethylene glycol. [b] K_{eq} is the equilibrium constant (l./mol) for formation of silver nitrate–olefin complex in ethylene glycol. [c] See discussion in Experimental Section. [d] Reference 1a gives 0.54 for this result at 40°.

In Table II are the equilibrium constants determined by distribution of olefin between carbon tetrachloride and an aqueous 1.0 *M* silver nitrate solution by the Winstein and Lucas[1b] treatment. The equilibrium constants are defined as follows.

$$K_0 = [\text{complex}]_{H_2O}/[\text{olefin}]_{CCl_4}[Ag^+]_{H_2O}$$

$$K_D = [\text{olefin}]_{CCl_4}/[\text{olefin}]_{H_2O}$$

(1) (a) M. A. Muhs and F. T. Weiss, *J. Amer. Chem. Soc.*, **84**, 4697 (1962); (b) S. Winstein and H. J. Lucas, *ibid.*, **60**, 836 (1938); (c) H. C. Brown and J. H. Kawakami, *ibid.*, **92**, 201 (1970); (d) C. F. Wilcox and W. Gaal, *ibid.*, **93**, 2453 (1971).

Table II

Equilibrium Constants for Formation of Complexes of Silver with Olefins by Distribution between Aqueous Silver Nitrate and Carbon Tetrachloride at 0.3°

Olefin	K_D	Std dev	K_0	Std dev	K_1	Std dev
1	4,696	±400	0.961	±0.041	4513	±430
2	131,625	±13100	0.033	±0.002	4396	±512
3	145,818	±13600	0.020	±0.002	2989	±408
4	>500,000		<0.005			
5	>500,000		<0.005			

This equals distribution of olefin between carbon tetrachloride and 1.0 M aqueous potassium nitrate.

$$K_1 = [\text{complex}]_{H_2O}/[\text{olefin}]_{H_2O}[Ag^+]_{H_2O}$$

$K_1 = K_0K_D$. In the discussion below it is K_1 that is used for the comparisons.

From Tables I and II it can be seen that steric blockage at the back side of the complex decreases the extent of complex formation slightly. Within the rather wide limits of error inherent in method II the relative equilibrium constants obtained by the two methods agree in the cases (**1**–**3**) where it is experimentally possible to compare them. The data in both methods support the conclusion that there is a small amount of charge developed on the vinyl carbon atoms which is stabilized by solvation. This is suggested by the lower value of K_{eq} for **3** when compared to the value found for **1** and **2** and the lower value of **4** when compared to **5**. The relatively small differences are in agreement with previous work suggesting little charge development on the olefinic carbons in the complex.[2,3]

In the Muhs and Weiss technique there appears to be one result that is inconsistent. The value of K_{eq} for **5** is a little lower than seems reasonable when compared to **1**. Conceivably this could be due to differences in solvation of the complex of **5** due to the much greater size of **5** compared to **1**. Perhaps a more reasonable model might be **4**. A comparison of **5** with **4** shows that blockage at the endo side of the double bond does decrease complex formation, which is consistent with the results found in a comparison of **1**–**3**.

Another aspect of interest is the use of silver ions as a means of purifying olefins. During the course of synthetic work involving norbornene type of ring systems, whose preparation utilizes Diels–Alder reactions, it is often necessary to separate 1:1 adducts from higher molecular weight materials. The value of K_0 from Table II is indicative of the amount of olefin that could be extracted from a carbon tetrachloride solution by aqueous silver nitrate when the olefin is largely insoluble in water. As the molecular weight increases the value of K_0 decreases very significantly. In **1**–**3** it is clear that this is very largely due to the partition coefficient (K_D) of olefin in carbon tetrachloride–water increasing in favor of carbon tetrachloride as the molecular weight of olefin increases. There are other factors but of much smaller magnitude such as the decrease due to blockage of solvation. Very probably for **4** and **5** the major factor is also an increase in K_D, but this is not proven since experimental evaluation of the extremely high K_D and extremely low K_0 was not considered reliable.

(2) (a) R. D. Bach and H. F. Henneike, *J. Amer. Chem. Soc.*, **92**, 5589 (1970); (b) T. Fueno, T. Okuyama, T. Deguchi, and J. Furukawa, *ibid.*, **87**, 170 (1965).

(3) R. G. Parker and J. D. Roberts, *ibid.*, **92**, 743 (1970).

Experimental Section

General.—All near-infrared spectra were determined using a Cary 14 spectrophotometer. All glpc determinations were made on a Hewlett–Packard Model 5750 instrument with a flame ionization detector. Norbornene was purchased from Aldrich Chemical Co. and used without further purification. *exo*-5,6-Trimethylene-2-norbornene (**2**),[4] 1,2,3,4,4a,5,8,8a-octahydro-1,4,5,8-*exo*,*endo*-dimethanonaphthalene (**4**),[5] and 1,2,3,4,4a,5,8,-8a-octahydro-1,4,5,8-*endo*,*exo*-dimethanonaphthalene (**5**)[6] were known compounds and prepared essentially according to literature procedures. *endo*-5,6-Trimethylene-2-norbornene (**3**) was prepared essentially according to the procedure of Cristol[4] except that final purification to remove a small amount of **2** was carried out by repeated equilibration of an ether solution of **3** with 15% aqueous silver nitrate solutions. After three equilibrations no **2** could be detected in **3** by glpc on the silver nitrate column described below.

Conditions for Glpc Determinations.[1a]—The ethylene glycol column was a 6-ft (0.25-in. o.d.) aluminum column packed with 40.0% by weight of ethylene glycol on Chromosorb P (60–80 mesh). The silver nitrate column was a 1.5-ft (0.25-in. o.d.) aluminum column packed with 40.0% by weight of 0.325 M silver nitrate in ethylene glycol on Chromosorb P (60%). Determinations were carried out at 60°. To check for deterioration of the column with time, the retention time of norbornene was checked at various intervals. No change in retention time for norbornene was found in either ethylene glycol or the silver nitrate column after 72 hr at 60°. The samples were dissolved in pentane and the retention time was measured as the time from the solvent to the sample peak. The values of K_{eq} are reproducible to 5%. We could not reproduce the absolute values of K_{eq} for norbornene reported by Muhs and Weiss at 40°. We could not obtain C-22 firebrick used by Muhs and Weiss and perhaps this is the cause of the differences. We obtained similar results on Chromosorb W and also using a stainless steel column with Chromosorb P and W. However, relative values for K_{eq} were very similar to relative values reported by Muhs and Weiss. These values did not change after heating at 60° for 72 hr. Some comparisons of relative K_{eq} at 40° are given below.

	Rel K_{eq} (this study)	Rel K_{eq} (Muhs and Weiss)
Norbornene	1.0	1.0
2,5-Norbornadiene	0.47	0.54
Camphene	0.046	0.050

Conditions for Carbon Tetrachloride–Aqueous Silver Nitrate Method.[1b,7]—The aqueous phase was maintained at 1.0 M ionic strength by using 1.0 M potassium nitrate or 1.0 M silver nitrate. The olefin in carbon tetrachloride was varied from 0.1 to 1 M. No variation in the values for the equilibrium constant could be detected in this range of concentrations. Equilibration was carried out by shaking 10.0 ml of aqueous phase with 4.0 ml of organic phase at 0.3° for 1 hr with a mechanical shaker. A sample of the olefin was shaken with silver nitrate solution and an identical sample was shaken with 1.0 M potassium nitrate. The difference in the concentration of olefin in the carbon tetrachloride phase equilibrated with silver nitrate and that equilibrated with potassium nitrate was evaluated and K_0 was determined as described by Traynham and Olechowski.[7] In cases where K_0 was less than 0.005 no complex formation could be detected. A value of 0.005 for K_0 could have been detected. All of the compounds were examined by ir, nmr, and glpc before and after treatment with aqueous silver nitrate. In each case the compounds were homogeneous and the spectral properties were

(4) S. J. Cristol, W. K. Seifert, and S. B. Soloway, *ibid.*, **82**, 2351 (1960).

(5) S. B. Soloway, *ibid.*, **74**, 1027 (1952); J. K. Stille and D. R. Witherell, *ibid.*, **86**, 2188 (1964).

(6) J. K. Stille, P. R. Kasper, and D. R. Witherell, *J. Org. Chem.*, **28**, 682 (1963); J. K. Stille and D. A. Frey, *J. Amer. Chem. Soc.*, **81**, 4273 (1959); K. Alder and H. F. Rickert, *Justus Liebigs Ann. Chem.*, **543**, 1 (1939).

(7) J. G. Traynham and J. R. Olechowski, *J. Amer. Chem. Soc.*, **81**, 571 (1959).

completely in agreement with the proposed structures. No change in properties could be detected after treatment with silver nitrate.

The value of K_D was determined largely by the procedure of Wilcox and Gaal.[1d] Olefin was dissolved in 2.00 ml of carbon tetrachloride and shaken with 100.0 ml of 1.0 *M* potassium nitrate at 0.3° for 1 hr. The layers were separated in a separatory funnel and the aqueous layer was centrifuged and then filtered through a Whatman No. 5 filter paper. A 90.00-ml aliquot of aqueous solution was cooled in an ice bath and extracted with 2.00 ml of ice-cold pentane. The pentane solution was then evaluated by gas chromatography on a 10-ft (0.25-in. o.d.) column of 10% UCC-W-982 Silicone on Chromosorb W (60–80). The values for **4** and **5** were greater than five times the value for **3**. However, we do not feel that a reliable estimate could be made for the absolute value of K_D. The extremely high value of K_D for **4** and **5** leads to a high susceptibility to error due to traces of impurities and through incomplete separation of the phases. We obtained variations in the results for these two compounds which we attribute to these factors.

Registry No.—**1**, 498-66-8; **2**, 10466-50-9; **3**, 2826-19-9; **4**, 15914-93-9; **5**, 15914-93-9; silver ion, 14701-21-4.

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Autoxidation of Cyclohexene with *tert*-Butyl Hydroperoxide and Chromium(III) Acetylacetonate

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The system chromium(III) acetylacetonate–*tert*-butyl hydroperoxide has been used to initiate autoxidation of cyclohexene in 1-chlorooctane solvent in the temperature range 30–60°. Oxygen absorption rates and peroxide decomposition rates are presented and contrasted to a similar study of 1-octene. Disappearance rates of chromium(III) acetylacetonate could not be determined spectrophotometrically because of the rapid appearance of an interfering absorption.

In connection with a study of the effectiveness of chromium(III) acetylacetonate and *tert*-butyl hydroperoxide as a free-radical initiator system,[2] an investigation of the autoxidation of cyclohexene initiated by this system has been undertaken. Some kinetic data for the autoxidation and for *tert*-butyl hydroperoxide decomposition in the temperature range 30–60° are presented and compared to that reported earlier for 1-octene.[2]

Experimental Section

Chemicals.—Eastman "White Label" cyclohexene was distilled under nitrogen prior to use. Samples of autoxidized cyclohexene were prepared by bubbling oxygen through cyclohexene (neat) at 30° in the presence of azobisisobutyronitrile for 3 days and analyzed[3] for peroxide content (2.9×10^{-2} *M*). No attempt was made to purify the peroxide formed. Aliquots of this autoxidized cyclohexene were added to solutions of pure cyclohexene in chlorooctane prior to chromium(III) acetylacetonate–*tert*-butyl hydroperoxide initiated autoxidation. All other chemicals have been described previously.[4]

Kinetics.—All kinetic measurements have been described previously.[4] Attempts to study chromium(III) acetylacetonate disappearance rates spectrophotometrically[2] were foiled by the rapid appearance of an absorption of unknown origin in the 336-mμ region. No absorption peak was observed in the 438–440-mμ region [Cr(VI)] during the course of this work, although at higher initial concentrations ($\sim 10^{-3}$ *M*) of chromium(III) acetylacetonate, Cr(VI) was detected in reaction mixtures.

Products.—Products were identified by comparison with gas chromatographic retention times of previously analyzed reaction mixtures[5] or with authentic samples of known reaction products. Analyses were performed on a Perkin-Elmer Model 154D gas chromatograph using a 6-ft stainless steel column packed with silicone grease on "GC-20" (Perkin-Elmer column type O). Helium flow was 8.0 psi, column temperature 148°. Gas chromatograph analyses were performed on three reaction mixtures: one cyclohexene sample was autoxidized by chromium(III) acetylacetonate–*tert*-butyl hydroperoxide at 50°; one cyclohexene sample was autoxidized by azobisisobutyronitrile at 50° similar to the procedure of Mayo, *et al.*;[5] one cyclohexene sample was permitted to react at 50° in the presence of chromium(III) acetylacetonate–*tert*-butyl hydroperoxide *in vacuo*.

Results and Discussion

Tables I and II present initial oxygen absorption rates and *tert*-butyl hydroperoxide decomposition rates

TABLE I
CYCLOHEXENE AUTOXIDATION[a,b] RATES IN THE PRESENCE OF CHROMIUM(III) ACETYLACETONATE AND *tert*-BUTYL HYDROPEROXIDE

$[Cr(acac)_3]_0 \times 10^6$ *M*	[*tert*-BuOOH]$_0$, *M*	[Cyclohexene]$_0$, *M*	Rate × 10^6 *M* sec^{-1} 30°	40°	50°
0.00	0.00	4.95	0.0	0.0	0.0
0.00	0.99	4.95	5.26	28.9	56.3
1.35	0.99	4.95	6.76	n[c]	n
2.69	0.00	4.95	0.0	n	n
2.69	0.50	4.95	6.80	n	n
2.69	0.99	0.99	1.29	n	n
2.69	0.99	1.98	3.76	n	n
2.69	0.99	4.95	9.05	n	n
2.69	2.97	4.95	13.5	n	n
2.69	3.96	4.95	14.5	n	n
3.92	0.99	4.95	10.0	17.9	29.2
5.38	0.99	4.95	11.2	n	n
6.10	0.99	4.95	6.66	n	n
7.83	0.50	4.95	n	22.9	25.3
7.83	0.99	1.98	n	21.4	51.9
7.83	0.99	4.95	3.91	35.4, 28.0,[d] 5.50[e]	46.9
7.97	0.00	4.95	0.0	n	n
15.66	0.99	4.95	5.95	28.2	46.8

[a] 1-Chlorooctane solvent. [b] Oxygen pressure = 1 atm. [c] n = no data. [d] Autoxidized cyclohexene added. [e] 1.0×10^{-2} *M* cyclohexenone added.

(1) Brooklyn College of Pharmacy, Long Island University.
(2) N. Indictor, T. Jochsberger, and D. Kurnit, *J. Org. Chem.*, **34**, 2855 (1969).
(3) W. F. Brill and N. Indictor, *ibid.*, **29**, 710 (1964).
(4) N. Indictor and T. Jochsberger, *ibid.*, **31**, 4271 (1966).
(5) D. E. Van Sickle, F. R. Mayo, and R. M. Arluck, *J. Amer. Chem. Soc.*, **87**, 4824 (1965).

TABLE II
tert-BUTYL HYDROPEROXIDE DECOMPOSITION[a,b] RATES IN THE PRESENCE OF CHROMIUM(III) ACETYLACETONATE AND CYCLOHEXENE

[Cr(acac)$_3$]$_0$, $\times 10^5$ M	[*tert*-BuOOH]$_0$, M	[Cyclohexene]$_0$, M	Rate $\times 10^7$ M sec^{-1} 40°	50°	61°
0.00	0.99	1.98	0.34	0.44	n[c]
3.05	0.99	1.98	0.667	3.74	n
3.92	0.99	1.98	n	4.62	7.70
6.10	0.99	1.98	2.27[d]	10.2	n
7.83	0.50	1.98	2.45	9.40	12.4
7.83	0.99	0.00	n	11.1	52.6
7.83	0.99	1.98	4.88	12.8	33.6
7.83	0.99	4.95	4.42	13.0	33.4

[a] 1-Chlorooctane solvent. [b] *In vacuo*. [c] n = no data. [d] Reaction temperature = 30°.

The dependence of the rate on chromium(III) acetylacetonate at low concentrations ($<4 \times 10^{-5}$ M) is kinetically first order but is rapidly reduced as the metal concentration increases. Indeed at some concentrations the chelate retards the reaction (Table I). The lowering of kinetic dependence on initiator with increasing concentration has been observed in other systems.[4,6,7]

In this system the inhibitory effect of added chromium(III) acetylacetonate may arise from several sources. The first of these involves a reaction in which nonradical and therefore nonchain-carrying species are produced (eq 1). It should be pointed out that an

$$\mathrm{Cr(III)} + \mathrm{R}\cdot \longrightarrow \mathrm{Cr(III} \pm n) + \mathrm{R}^{\mp n} \qquad (1)$$

TABLE III
COMPARISON OF *tert*-BUTYL HYDROPEROXIDE DECOMPOSITION RATES AND OLEFIN AUTOXIDATION RATES IN THE PRESENCE OF CHROMIUM(III) ACETYLACETONATE

Temp, °C	[Cr(acac)$_3$]$_0$ $\times 10^5$ M	[*tert*-BuOOH]$_0$, M	[Olefin]$_0$, M	R_0[a] CHE[c]	R_0[a] Oct[d]	R_p[b] CHE[c]	R_p[b] Oct[d]
30	0.00	0.8	5.0–6.0	5.26	0.0		0.0
30	8.0	0.0	3.0–5.0	0.0	0.17		
30	8.0	0.8	5.0–6.0	3.91	0.53		
30	6.1–9.0	0.8–1.0	2.0–3.0			0.227	25.7
40	6.0–8.0	0.8–1.0	2.0–3.0	21.4	1.15	0.488	56.5
50	6.0–8.0	0.8–1.0	2.0–3.0			1.28	224

[a] R_0 = rate of autoxidation $\times 10^6$ M sec^{-1}. [b] R_p = rate of *tert*-BuOOH decomposition $\times 10^6$ M sec^{-1}. [c] Cyclohexene data from this work. [d] 1-Octene data from ref 2 and 4.

TABLE IV
EFFECT OF VARIOUS INITIATORS ON THE RELATIVE AUTOXIDATION RATES OF CYCLOHEXENE AND 1-OCTENE

Temp, °C	Initiator	R_{CHE}/R_{Oct}[a]	Ref
80–85	Cobalt propionate	20–30[b]	*c*
60	Azo initiated[d]	13.8[b]	5, *c*
55	Benzoyl peroxide	10.3	*f*
45	Benzoyl peroxide	14.7	*g*
30	Photoinitiated[h]	37	14
40	Cr(acac)$_3$/*tert*-BuOOH	18.6[i]	2, present work
30	Cr(acac)$_3$/*tert*-BuOOH	7.4[i]	2, present work

[a] Estimated on the basis of reported rate constants for propagation and termination. [b] Value for 1-hexene in place of 1-octene. [c] S. J. Moss and H. Steiner, *J. Chem. Soc.*, 2372 (1965). [d] 2,2′-Azobis(2-methylpropionitrile) or 1,1′-azobis(cyclohexane-1-carbonitrile). [e] D. E. Van Sickle, F. R. Mayo, R. M. Arluck, and M. G. Syz, *J. Amer. Chem. Soc.*, **89**, 967 (1967). [f] L. Bateman, *Quart. Rev., Chem. Soc.*, **8**, 147 (1954). [g] J. L. Bolland, *Trans. Faraday Soc.*, **46**, 358 (1950). [h] 1,1′-Azobis(cyclohexane-1-carbonitrile) used as photoinitiator. [i] Based on rate of O_2 absorption.

respectively. Tables III and IV contrast kinetic data for 1-octene and cyclohexene obtained under similar conditions.

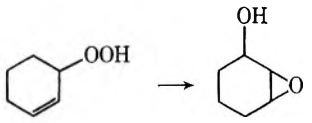
Autoxidations.—Unlike the 1-octene system[2] the presence of chromium(III) acetylacetonate is apparently not required for cyclohexene autoxidation. However, addition of small amounts of the chelate do enhance the rate under most conditions. Under comparable conditions of chromium(III) acetylacetonate–*tert*-butyl hydroperoxide concentration, cyclohexene autoxidizes 7–19 times faster than 1-octene. Relative cyclohexene–1-octene autoxidation rates using other initiators are compiled in Table IV and are seen to be roughly comparable.

increase in the concentration of chromium(III) acetylacetonate does not decrease the rate of *tert*-butyl hydroperoxide decomposition which occurs in part by a chain mechanism.[2,8] However, the chain-carrying radical may be different in the two cases. It has been shown[9,10] that cyclohexene and its derivatives undergo rapid (relative to 1-octene) polar epoxidation with *tert*-butyl hydroperoxide and metal acetylacetonates. The addition of chromium(III) acetylacetonate may therefore deplete the peroxide concentration *via* a nonradical mechanism. Depletion of peroxide both in the presence[9] and absence[3] of added chromium(III) acetylacetonate in epoxide-forming reactions (performed in the absence of oxygen) has accounted for 10–60% of the decomposed peroxide in the formation of the monoring epoxide of 4-vinylcyclohexene. At high enough metal concentrations the decrease in peroxide concentration might reduce the autoxidation rate. Furthermore, since a product of *tert*-butyl hydroperoxide decomposition is molecular oxygen,[11] an increased rate of O_2 production *in situ* would lead to an apparent decrease in the rate of oxygen uptake.[4] However, it should be noted that O_2 evolution was not found to be a significant factor in 1-octene autoxidation.[12]

It is known[6] that products of an autoxidation often

(6) K. U. Ingold, *Chem. Rev.*, **61**, 563 (1961).
(7) A. E. Woodward and R. B. Mesrobian, *J. Amer. Chem. Soc.*, **75**, 6189 (1953).
(8) N. Indictor, T. Jochsberger, and D. Kurnit, *J. Org. Chem.*, **34**, 2861 (1969).
(9) N. Indictor and W. F. Brill, *ibid.*, **30**, 2074 (1965).
(10) M. N. Sheng and J. G. Zajacek, International Oxidation Symposium, San Francisco, Calif., Aug 1967.
(11) A. V. Tobolsky and R. B. Mesrobian, "Organic Peroxides," Interscience, New York, N. Y., 1954, p 93.
(12) T. Jochsberger, Ph.D. Thesis, City University of New York, 1968, unpublished results.

inhibit the reaction. During the period of temperature and concentration equilibration of reactants, before kinetic measurements are made, autoxidation products may be built up. Increasing chromium(III) acetylacetonate concentration probably increases product formation and may therefore diminish the reaction rate. Indeed, the respective introduction of small amounts of autoxidized cyclohexene or cyclohexenone, a known product of cyclohexene autoxidation,[5] significantly reduces the autoxidation rate (Table I, footnotes *d* and *e*). The addition of the normally chain-branching cyclohexenyl hydroperoxide in the form of autoxidized cyclohexene might cause depletion of the chromium reactivity by participation in metal-catalyzed rearrangement,[13] by competitive complex formation with the chromuim(III) acetylacetonate, or by producing further decomposition products (such as cyclohexenone) which act as inhibitors. Cyclohexenone may inhibit the reaction by forming phenols or their precursors.



As the concentration of chromium(III) acetylacetonate is increased above a certain value, the inhibitory effect, whatever its source, appears to be overcome and the rate increases. This suggests a higher order initiation process which only becomes important at higher metal concentrations.

The inhibitory effect of chromium(III) acetylacetonate appears to be temperature dependent, increasing in importance with a rise in temperature. At 50° the reaction rate is faster in the absence of metal than in its presence at all concentrations studied. Therefore, whatever the mode of inhibition, it clearly has a higher activation energy than the initiation process.

Unlike the 1-octene system,[2] no reaction occurs in the absence of *tert*-butyl hydroperoxide. The data of Table I indicate that, while the autoxidation rate increases, the apparent kinetic order in peroxide diminishes with increasing peroxide concentration. With 1-octene it was observed that increased *tert*-butyl hydroperoxide–olefin ratios retarded the reaction due to an increase in the concentration of *tert*-butyl peroxy radicals.[12] With cyclohexene this effect is somewhat less dramatic, perhaps due to the more rapid formation of cyclohexenyl compared to octenyl radicals.[14]

The autoxidation rate is kinetically first order with respect to cyclohexene under most conditions. This is again somewhat different from the 1-octene system in which the reaction was first order in olefin only at low concentrations (<0.3 *M*) and dropped off rapidly with increasing amounts of olefin.[2] This decrease in order is due to an increase in termination *via* unoxidized octenyl radicals. The fact that no decrease is observed with cyclohexene is consistent with the observation that propagation competes more favorably with termination for cyclohexene autoxidation than for 1-octene (eq 2).[14]

$$k_{\text{1-octene}}/k_{\text{cyclohexene}} = 0.027 \qquad (2)$$

where

$$k = k_{\text{propagation}}/(2k_{\text{termination}})^{1/2} \text{ at } 30°$$

(13) K. Allison, P. Johnson, G. Foster, and M. B. Sparks, *Ind. Eng. Chem. Prod. Res. Develop.*, **5**, 166 (1966).

(14) J. A. Howard and K. U. Ingold, *Can. J. Chem.*, **45**, 793 (1967).

As in the case of 1-octene the data indicate that the chromium(III) acetylacetonate–*tert*-butyl hydroperoxide initiated autoxidation of cyclohexene proceeds *via* a multistep mechanism. This leads to a complex kinetic equation of several terms, each one having its own concentration and temperature dependence.

Decomposition of *tert*-Butyl Hydroperoxide.—The rate of *tert*-butyl hydroperoxide decomposition in the absence of metal is consistent with previous work,[3] as is rate enhancement due to the presence of chromium(III) acetylacetonate.[2,4,9] The decomposition of *tert*-butyl hydroperoxide in the presence of metal acetylacetonates may be due to either a radical[2] or nonradical[9,10] process or a combination of both. Although the reaction was observed to proceed almost entirely by a radical-chain mechanism in the presence of 1-octene,[2,8] other olefins apparently undergo a nonradical reaction with the hydroperoxide, especially in the presence of metals,[9,10] to form epoxides.

Tables II and III present *tert*-butyl hydroperoxide decomposition data both in the presence and absence of cyclohexene or 1-octene. It is noted that the presence of cyclohexene retards the decomposition at 61° but has a small accelerating effect at 50°. In the 1-octene system the reverse was observed, *i.e.*, the retarding effect of the olefin diminished with increasing temperature. In the latter case the temperature effect on retardation was attributed to a lower activation energy for the termination process than for hydrogen abstraction. It is known[14] that hydrogen abstraction from cyclohexene is much more facile than from 1-octene, while termination by cyclohexenyl peroxy radicals is some 40 times slower than for octenyl peroxy radicals. It is therefore probable that in the case of cyclohexene the activation energy for termination is not significantly lower than that for propagation. Indeed, from the data of Howard and Ingold[14] and Sajus,[15] the estimated activation energies for propagation and termination in cyclohexene autoxidation are almost identical (~3 kcal/mol).[16] Furthermore, the observation[3,9,10] that cyclohexene and its derivatives interact to a greater extent than 1-octene with *tert*-butyl hydroperoxide in nonradical reactions implies that the two olefins might retard decomposition by different mechanisms.

It is interesting to note that with both cyclohexene and 1-octene there is a relatively large difference in peroxide decomposition rate upon addition of small amounts of olefin. Once the olefin is present the rate is no longer affected by changes in concentration. It was observed in the 1-octene system[2] and in other systems[17-19] that complex formation plays an important role in metal-induced peroxide decompositions. Therefore the whole effect of the olefin might be as a competitive ligand[20-22] for a site on the chromium. The large excess of olefin relative to the metal produces a kinetically "zero" order effect.

(15) L. Sajus, *Advan. Chem. Ser.*, **75**, 59 (1968).

(16) Minimum value of $E_{\text{termination}}$ based on the estimates in ref 15. Some data in this reference lead to higher values.

(17) N. G. Ariko and B. V. Erofeev, *Usp. Khim. Org. Perekisnykh Soedin. Autookisleniya, Dokl. Vses. Konf.*, **3rd**, 354 (1965) (Pub 1969); *Chem. Abstr.*, **72**, 42520m (1970).

(18) W. H. Richardson, *J. Amer. Chem. Soc.*, **87**, 247 (1965).

(19) E. J. Y. Scott, *J. Phys. Chem.*, **74**, 1174 (1970).

(20) P. M. Henry, *J. Amer. Chem. Soc.*, **87**, 990 (1965).

(21) R. Cramer, *ibid.*, **87**, 4717 (1965).

(22) R. J. Cvetanovic, F. J. Duncan, W. E. Falconer, and R. S. Irwin, *ibid.*, **87**, 1827 (1965).

Although autoxidation rates are of the order of ten times faster for cyclohexene relative to 1-octene, the data of Table III indicate that *tert*-butyl hydroperoxide decomposes some hundred times faster in 1-octene than in cyclohexene. It is suggested that this effect is due to the greater ease of hydrogen abstraction from cyclohexene,[14] the greater stability of the cyclohexenyl radical, and the statistical factor (four allylic hydrogen atoms in cyclohexene *vs.* two in 1-octene).

An effort to observe the disappearance of chromium(III) acetylacetonate *via* its ultraviolet absorption peak at 336 mμ[23] was thwarted by the appearance of an absorption of unknown origin at that wavelength. None of the known[5] products of cyclohexene autoxidation were observed to absorb in that region. Since this absorption of unknown origin occurs even in the absence of metal acetylacetonate, it is suggested that the peak arises from a complex between the peroxide and either cyclohexene or product(s). In the 1-octene system[2] the presence of Cr(VI) was detected both chemically and spectrophotometrically; only at higher initial chromium(III) acetylacetonate concentrations ($\sim 10^{-3}$ *M*) than runs reported in this communication was Cr(VI) detected in the cyclohexene system. This implies that the oxidation state of chromium remains essentially unchanged over the course of the reaction[24] probably *via* the usual oxidation–reduction scheme proposed[26] for metal–peroxide reactions (eq 3 and 4). In the presence of 1-octene a similar scheme was proposed[2] in which, however, Cr(III) does not survive but is oxidized eventually to Cr(VI). Since the Cr(III) disappearance rate is essentially zero in cyclohexene the chain lengths for these reactions must be extremely large based on initiation solely *via* reactions 3 and 4. However, unlike the 1-octene system, the data for cyclohexene autoxidation indicate that an initiation process involving only *tert*-butyl hydroperoxide is also important.

$$\mathrm{Cr(III) + ROOH \longrightarrow Cr(IV) + RO\cdot + OH^-} \quad (3)$$

$$\mathrm{Cr(IV) + ROOH \longrightarrow Cr(III) + RO_2\cdot + H^+} \quad (4)$$

The products detected in cyclohexene autoxidations initiated by chromium(III) acetylacetonate–*tert*-butyl hydroperoxide were the same as those found using azobisisobutyronitrile initiator[5] (cyclohexenone, cyclohexenol, and cyclohexene epoxide) and analyzed under identical gas chromatograph conditions. Results with azobisisobutyronitrile gave good agreement with other product studies[5] made under somewhat different conditions. More ketone was found in the presence of chromium than in the presence of azobisisobutyronitrile; more epoxide was found *in vacuo* than under autoxidation conditions. Although chromium(III) acetylacetonate enhances epoxide formation, the presence of oxygen either causes further reaction of the epoxide or adversely affects complexes that favor epoxide formation.

Registry No.—Cyclohexene, 110-83-8; *tert*-butyl hydroperoxide, 75-91-2; chromium(III) acetylacetonate, 13681-82-8; 1-octene, 111-66-0.

Acknowledgment.—Equipment grants from the City University of New York are gratefully acknowledged.

(23) R. H. Holm and F. A. Cotton, *J. Amer. Chem. Soc.*, **80**, 5658 (1958).

(24) Although no effort was made to detect other chromium oxidation states (*e.g.*, +2, +4, and +5), these states are known to be unstable relative to the +3 and +6 states (*cf.* ref 25).

(25) J. Kleinberg, Wm. J. Argersinger, Jr., and E. Griswold, "Inorganic Chemistry," D. C. Heath, Boston, Mass., 1960, p 513 ff.

(26) R. Hiatt, K. C. Irwin, and C. W. Gould, *J. Org. Chem.*, **33**, 1430 1968).

Kinetics of Reactions of Amines with Tricarbonyl(fluorobenzene)chromium[1a]

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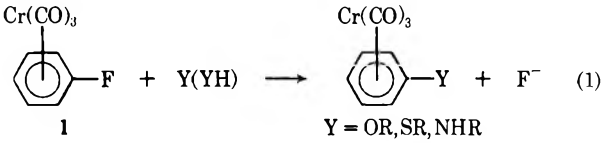
These aminodefluorination reactions occur at convenient rates in dipolar, aprotic solvents. Third-order terms predominate in their rate laws. These terms are first order in substrate, first order in the reacting nucleophilic amine, and first order in a catalytic amine which may or may not be the same as the "reacting" amine. The catalytic effect is taken to be base catalysis, and as an indication that expulsion of fluorine from the intermediate complex is the rate-limiting step, whereas in analogous reactions of *p*-fluoronitrobenzene the initial nucleophilic attack is rate limiting. The data are consistent with the hypothesis that the amine attacks exo to the chromium tricarbonyl moiety and that steric hindrance in the general acid catalyzed expulsion of fluorine from the conjugate base of the intermediate complex is a critical factor.

Chromium tricarbonyl complexes (CTC complexes) of aryl halides undergo nucleophilic replacement of halogen by moieties such as OR, SR, and NR_2 much more rapidly than does the parent halobenzene.[2]



(1)

A similar effect is found in the pK_a's of the CTC complexes of phenol, aniline, and benzoic acid; the acid dissociation constant is considerably increased by complexing. In its effects on pK_a's,[2a,3a] on rates of saponification of methyl benzoates,[3b] and on substitution rates with methoxide,[4] the chromium tricarbonyl moiety demonstrates approximately the same electron-attracting effect as the nitro group. However, the activating effects of the nitro group and of the chromium tricarbonyl moiety are not closely correlated. The activating effect of the latter is sometimes greater

(1) (a) This investigation was supported in part by Public Health Service Research Grant No. GM 14647 from the National Institute of General Medical Sciences; (b) NATO Fellow, 1967–1968, on leave from University of Göttingen, Germany.

(2) (a) B. Nichols and M. C. Whiting, *J. Chem. Soc.*, 551 (1959). (b) M. C. Whiting, U. S. Patent 3,225,071 (1965); *Chem. Abstr.*, **64**, 6694 (1966). (c) U. S. Patent 3,317,522 (1967); *Chem. Abstr.*, **67**, 64543 (1967).

(3) (a) E. O. Fischer, K. Öfele, H. Essler, W. Fröhlich, J. P. Mortensen, and W. Semmlinger, *Chem. Ber.*, **91**, 2763 (1958); (b) G. Klopman and F. Calderazzo, *Inorg. Chem.*, **6**, 977 (1967).

(4) D. A. Brown and J. R. Raju, *J. Chem. Soc. A*, 40 (1966).

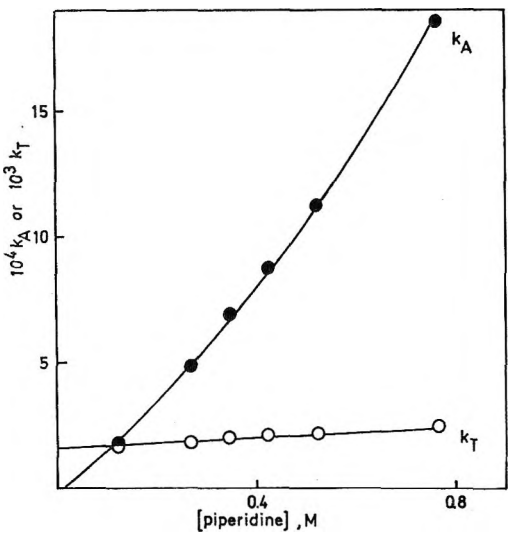


Figure 1.—Reaction of CTC–fluorobenzene with piperidine in acetonitrile at 25°. Second-order (k_A) and third-order (k_T) rate coefficients as functions of piperidine concentration.

than, sometimes less than, and sometimes nearly equal to that of the nitro group. This suggests that, besides its electronic effect, the chromium tricarbonyl moiety exerts a large steric effect.

It is known that nucleophiles may attack metal carbonyl complexes with conjugated systems such as cyclopentadiene or benzene in three ways: on carbonyl carbon, on the conjugated ligand, or on the metal atom (to effect replacement of ligands). Which pathway is followed depends on the metal atom and on the nucleophile.[5,6] In the cases of the complexes of Cr, Mo, and W with a benzene ring bearing a leaving group,[2,4] and with the tropylium cation,[7] and even in the case of the cationic manganese tricarbonyl–benzene complex,[8] nucleophiles attack almost exclusively on the aromatic moiety, but cleavage of the aromatic moiety from the metal by phosphine nucleophiles[6] and displacement of one carbonyl group by an amine in the presence of light[9] also have been observed.

Previous studies of aromatic nucleophilic substitution in CTC complexes are chiefly those of Whiting and coworkers[2] and of Brown and Raju.[4] These studies have demonstrated several similarities with familiar aromatic nucleophilic substitutions activated by nitro groups.[10] Substitutions occur without change of ring position; this testifies against an aryne mechanism. The order of halogen mobility is F ≫ Cl.

A further similarity is that reactions of CTC–fluorobenzene with amines are strongly catalyzed by amines. This is reported by Whiting in a published lecture[11] and in a patent,[2c] but we have been unable to find any fully documented report on these catalytic effects in the journal literature. Reactions of amines with 2,4-dinitrofluorobenzene are base catalyzed in some situations[12,13] but not in others.[14] Inasmuch as base catalysis of aromatic nucleophilic substitution reactions involving amine reagents is a matter of considerable interest in this laboratory,[15–17] we undertook to study the phenomenon in reactions of CTC–fluorobenzene.

Kinetic Results

Reactions of tricarbonyl(fluorobenzene)chromium (CTC–fluorobenzene) with amines in several solvents were followed photometrically. CTC–fluorobenzene has an absorption maximum at *ca.* 311 nm, and the CTC complexes of *N*-phenylpiperidine, *N*-phenylpyrrolidine, and *N*-*n*-butylaniline have maxima at *ca.* 316–320 nm. The most satisfactory difference in extinction coefficients is at 350 nm, the wavelength used in the kinetic studies. Reactions were run with the amine in large excess, so as to afford pseudo-first-order kinetics. The spectra of infinity solutions matched those of the expected aminodefluorination products, showing that side reactions did not occur to any appreciable extent. A few runs were also followed by titration of fluoride ion. The infinity titers showed the reactions to be essentially quantitative, and the rate coefficients were in agreement with those from photometric runs under the same conditions.

The pseudo-first-order rate coefficients (k_ψ) were divided by the amine concentration to afford second-order coefficients (k_A), and in some cases the k_A values were again divided by amine concentration to afford third-order coefficients (k_T).

Reactions of CTC–Fluorobenzene with Piperidine.—This reaction was studied in three solvents. In *acetonitrile*, the solvent favored by Whiting,[2b,c,10] the rate was determined at from two to six piperidine concentrations at each of three temperatures. Results at 25° are plotted in Figure 1, and data for all three temperatures are set forth in Table IV.[18] It is to be noted that the second-order rate coefficient (k_A) rose steeply with increasing amine concentration, and that ever the third-order coefficient (k_T) increased to some extent. Extrapolation of k_A to zero amine concentration (Figure 1) gives an intercept which is zero or nearly zero; this shows that piperidino defluorination is essentially wholly catalyzed by piperidine. Whiting's report[10] of overall third-order kinetics is thus confirmed. The moderate rise in k_T with increase in amine concentration evidently represents the same kind of mild augmentation that has been observed in numerous other investigations.[14,19,20]

The variation of rate with temperature was remark-

(5) (a) D. A. White, *Organometal. Chem. Rev.*, *A*, **3**, 497 (1968); (b) P. H. Treichel and R. L. Shubkin, *Inorg. Chem.*, **6**, 1328 (1967).

(6) (a) F. Zingales, A. Chiesa, and F. Basolo, *J. Amer. Chem. Soc.*, **88**, 2707 (1966); (b) A. Pidcock, J. D. Smith, and B. W. Taylor, *J. Chem. Soc. A*, 872, 877 (1967); (c) H. Werner, *Angew. Chem.*, **80**, 1026 (1968).

(7) P. L. Pauson, G. H. Smith, and J. H. Valentine, *J. Chem. Soc. C*, 1057 (1967).

(8) D. Jones, L. Pratt, and G. Wilkinson, *ibid.*, 4458 (1962); D. Jones and G. Wilkinson, *ibid.*, 2479 (1964).

(9) W. Strohmeier, *Angew. Chem., Int. Ed. Engl.*, **3**, 730 (1964).

(10) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1961); J. F. Bunnett, *Quart. Rev., Chem. Soc.*, **12**, 1 (1958).

(11) M. C. Whiting, *Chem. Weekbl.*, **59**, 119 (1963).

(12) J. F. Bunnett and J. J. Randall, *J. Amer. Chem. Soc.*, **80**, 6020 (1958).

(13) C. F. Bernasconi and H. Zollinger, *Helv. Chim. Acta*, **49**, 103 (1966); **50**, 3 (1967).

(14) J. F. Bunnett and R. H. Garst, *J. Amer. Chem. Soc.*, **87**, 3875 (1965).

(15) J. F. Bunnett, T. Kato, and N. S. Nudelman, *J. Org. Chem.*, **34**, 785 (1969).

(16) J. F. Bunnett and D. H. Hermann, *Biochemistry*, **9**, 816 (1970).

(17) J. A. Orvik and J. F. Bunnett, *J. Amer. Chem. Soc.*, **92**, 2417 (1970).

(18) Tables IV–VIII, inclusive, appear only in the microfilm edition of this journal. These tables 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 check or money order for $3.00 for photocopy or $2.00 for microfiche.

(19) T. C. Bruice and S. J. Benkovic, *J. Amer. Chem. Soc.*, **86**, 418 (1964).

(20) C. F. Bernasconi and H. Zollinger, *Helv. Chim. Acta*, **49**, 2570 (1966).

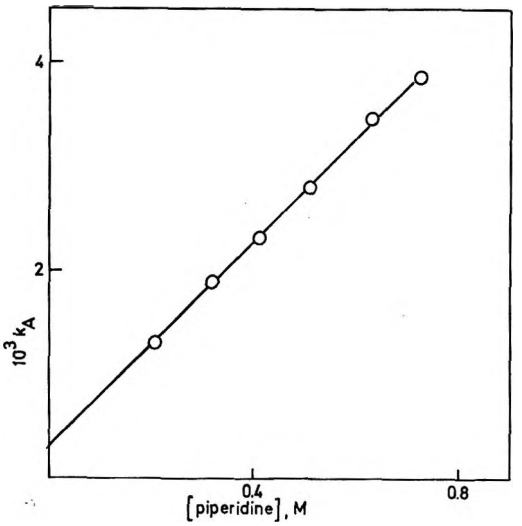


Figure 2.—Second-order rate coefficient for reaction of CTC–fluorobenzene with piperidine in DMF as function of piperidine concentration.

ably small. The extrapolated k_T at zero piperidine concentration increased only from 1.19×10^{-3} M^{-2} sec^{-1} at 10° to 1.87×10^{-3} M^{-2} sec^{-1} at 40°. This effect was previously noted by Whiting.[10] The Arrhenius plot is linear; $\Delta H^{\ddagger}$ is 2.1 kcal/mol and $\Delta S^{\ddagger}$ is −64 gibbs/mol. There is precedent for exceedingly large negative entropies of activation for third-order reactions of very low activation energy.[19] The fact that translational and rotational entropy of two molecules are lost in forming the transition state is largely responsible for the low activation entropy.

In dimethylformamide (DMF) solvent (Table V[18]), k_A again rose with increasing amine concentration. The plot of k_A *vs.* piperidine concentration (Figure 2) is linear. In this case the intercept is not zero. The plot conforms to eq 2 in which S is the substrate and

$$-d[S]/dt = k'[S][A] + k''[S][A]^2 \quad (2)$$

A the amine. Clearly the k'' term, representing catalysis by piperidine, is the dominant one, but a small fraction of the reaction occurs uncatalyzed or with catalysis only by solvent.

A plot of the third-order coefficient, k_T, *vs.* piperidine concentration, analogous to Figure 1, was tried. It was approximately linear and had negative slope of modest magnitude; *cf.* Table V.[18] This suggests the alternative view that the reaction is for the most part third order and that the third-order rate coefficient, k_T, is somewhat depressed by increasing piperidine concentration through a medium effect. Although analogies to such an interpretation appear in data presented below, representation with respect to eq 2 seems on the whole to be more legitimate.

The situation *in dimethyl sulfoxide* (DMSO) solvent (Table I) is similar to that in DMF. The correlation of k_A with piperidine concentration is cleanly linear while the plot of k_T against amine concentration has obvious curvature. Neither plot is shown, but correlation coefficients appear in Table II. Representation according to eq 2 is clearly indicated.

Reactions with piperidine in DMSO in the presence of varying concentrations of 1,4-diazobicyclo[2.2.2]octane (DABCO), *quinuclidine, or N-methylpiperidine* were also investigated. In each set of experiments, piperidine concentration was held essentially constant. *N*-Methylpiperidine depressed the reaction rate. There was a gentle, linear increase of k_A with increase in DABCO concentration, and a much sharper, linear augmentation with quinuclidine concentration. Plots for all three amines are presented in Figure 3, and full data appear in Table VI.[18]

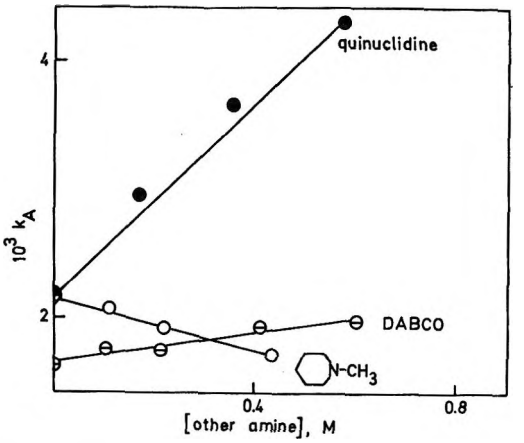


Figure 3.—Second-order rate coefficients for reactions of CTC–fluorobenzene with piperidine in DMSO, in the presence of diverse concentrations of other amines. Piperidine was 0.15 *M* in the DABCO runs and 0.20 *M* in the others.

TABLE I

REACTION OF CTC–FLUOROBENZENE WITH PIPERIDINE IN DMSO AT 25°

$[C_5H_{10}NH]$	$10^4 k_\psi$, sec^{-1}	$10^3 k_A$, M^{-1} sec^{-1}	$10^3 k_T$, M^{-2} sec^{-1}
0.103	1.30	1.26	12.2
0.108	1.31	1.22	11.3
0.108[a]	1.23	1.13	10.5
0.158	2.63	1.66	10.5
0.208	4.51	2.16	10.4
0.223	4.89	2.19	9.83
0.313	9.05	2.89	9.24
0.425	16.4	3.87	9.10
0.525	23.2	4.42	8.43
0.627	33.8	5.40	8.61

[a] Piperidine hydrochloride, 0.108 *M*, also present.

The behavior with *N*-methylpiperidine suggests a negative medium effect, while that with DABCO or quinuclidine might be interpreted either as a positive medium effect or as catalysis of the reaction of piperidine with CTC–fluorobenzene by the added amine as well as by piperidine, according to eq 3, in which B

$$-d[S]/dt = k'[S][A] + k''[S][A]^2 + k'''[S][A][B] \quad (3)$$

stands for DABCO or quinuclidine. In other situations in which such modest positive slopes as for that with DABCO in Figure 3 have appeared,[14,20,21] interpretation as a medium effect appears better justified than as catalysis. However, in the present case there is good evidence for catalysis by piperidine, and therefore interpretation of positive slopes as catalysis by other amines is admissible, though not compelled.

Reactions with piperidine in DMSO in the presence of varying concentrations of tert-butylamine were studied at three levels of piperidine concentration. Whiting[2c,10] has recommended *tert*-butylamine as a catalyst for

(21) (a) O. L. Brady and F. R. Cropper, *J. Chem. Soc.*, 507 (1950); (b) J. F. Bunnett and C. C. King, unpublished experiments.

TABLE II

SUMMARY OF CORRELATIONS OF k_A OR k_T *vs.* AMINE CONCENTRATION

Reagent amine	Other amine	Solvent	Temp. °C	Quantities correlated y^a	x^b	No. of points	Slope × 10^3	Intercept × 10^3	Slope/intercept ratio	r^c
$C_5H_{10}NH$		CH_3CN	10	k_T	$[C_5H_{10}NH]$	4	1.17	1.19		0.811
			25	k_T		6	0.95	1.58		0.847
			40	k_T		2	0.79	1.87		
$C_5H_{10}NH$		DMF	25	k_A	$[C_5H_{10}NH]$	6	5.03	0.26	19	0.9994
			25	k_T		6	−1.44	6.35		0.965
$C_5H_{10}NH$		DMSO	25	k_A	$[C_5H_{10}NH]$	9	7.85	0.44	18	0.999
				k_T		9	−5.9	11.7		0.881
$C_5H_{10}NH^d$	Quinuclidine	DMSO	25	k_A	[Quinuclidine]	4	3.68	2.25[f]		0.994
$C_5H_{10}NH^e$	DABCO	DMSO	25	k_A	[DABCO]	5	0.56	1.65[f]		0.967
$C_5H_{10}NH^d$	$C_5H_{10}NCH_3$	DMSO	25	k_A	$[C_5H_{10}NCH_3]$	4	−1.09	2.17[f]		0.997
C_4H_8NH		DMSO	25	k_A	$[C_4H_8NH]$	8	38.7	0.52	74	0.997
$C_5H_{10}NH^g$	*tert*-$BuNH_2$[h]	DMSO	25	k_A	[*tert*-$BuNH_2$]	4	8.3 (initial segment)			
						7	5.5 (final segment)			
$C_5H_{10}NH^e$	*tert*-$BuNH_2$[h]	DMSO	25	k_A	[*tert*-$BuNH_2$]	3	11.1 (initial segment)			
						4	6.3 (final segment)			
$C_5H_{10}NH^d$	*tert*-$BuNH_2$[h]	DMSO	25	k_A	[*tert*-$BuNH_2$]	3	12.6 (initial segment)			
						5	5.9 (final segment)			

[a] Dependent variable. [b] Independent variable. [c] Correlation coefficient. [d] 0.20 *M*. [e] 0.15 *M*. [f] This intercept includes substantial catalysis by piperidine. [g] 0.10 *M*. [h] *tert*-Butylamine.

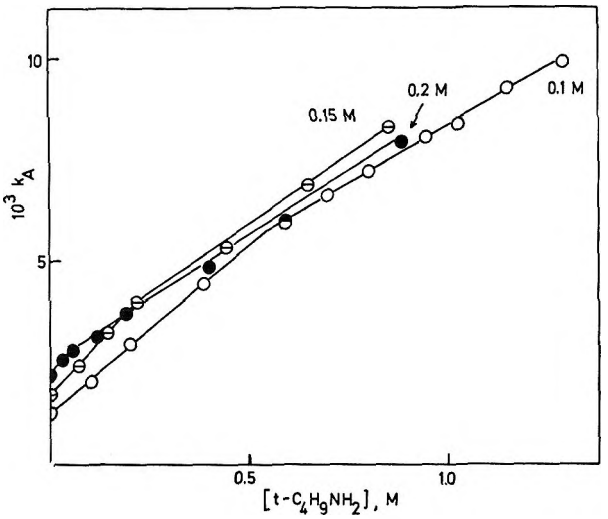


Figure 4.—Second-order rate coefficients for reaction of CTC–fluorobenzene with piperidine in DMSO in the presence of various concentrations of *tert*-butylamine. Three series of experiments are shown, each at a different piperidine concentration as indicated.

preparative purposes. Our data are plotted in Figure 4, and appear in full in Table VII.[18] At each level of piperidine concentration, the increase of k_A with *tert*-butylamine concentration is nonlinear but can be represented by two segments, each linear, the segment at lower *tert*-butylamine concentrations having the greater slope. The initial segment is shorter and steeper the higher the level of piperidine concentration, while the final slopes are nearly the same in all three plots; see Table II. The second-order rate coefficients (k_A), defined as $k_\psi/[C_5H_{10}NH]$, are dependent mainly on *tert*-butylamine concentration and only slightly on piperidine concentration.

Reactions of CTC–Fluorobenzene with Pyrrolidine in DMSO.—There are some remarkable differences between aromatic nucleophilic substitution reactions of piperidine and pyrrolidine. For example, reaction of 2,4-dinitrophenyl phenyl ether with piperidine in 10% dioxane–90% water is strongly (but curvilinearly) catalyzed by NaOH,[22] whereas the corresponding reaction with pyrrolidine is not catalyzed by NaOH.[16] It was therefore conceivable that differences would be found between their reactions with CTC fluorobenzene.

It was found that k_A increases linearly with pyrrolidine concentration. The plot (not shown) resembles Figure 2. The slope, intercept, etc., are listed in Table I[illegible], and full data are given in Table VIII.[18] The intercepts in the plots for pyrrolidine and piperidine in DMSO are nearly the same (*cf.* Table II), but the slope in the plot for pyrrolidine is about five times greater.

Reactions of CTC–Fluorobenzene with *n*-Butylamine in DMSO.—In several cases it has been observed that reactions of aromatic substrates with secondary amines are base catalyzed whereas reactions with closely related primary amines under the same conditions are not.[14,23]

In the present investigation a difference is also observed, as evident in Figure 5. The numerical data appear in Table III. k_A rises with *n*-butylamine concentration, but in curvilinear fashion. In cases somewhat related to this,[16,22-24] such curvature has been

TABLE III

REACTION OF CTC–FLUOROBENZENE WITH *n*-BUTYLAMINE IN DMSO AT 25°

[*n*-Butylamine], *M*	$10^4 k_\psi$, sec^{-1}	$10^3 k_A$, M^{-1} sec^{-1}
0.101	0.675	0.668
0.203	2.73	1.34
0.301	5.28	1.75
0.406	8.66	2.13
0.605	16.7	2.76
0.698	20.9	2.99
0.818	26.1	3.19
0.958	32.8	3.42
1.195	45.6	3.82

(22) J. F. Bunnett and C. F. Bernasconi, *J. Amer. Chem. Soc.*, **87**, 5209 (1965).
(23) C. F. Bernasconi, *J. Org. Chem.*, **32**, 2947 (1967).
(24) J. F. Bunnett and R. H. Garst, *J. Amer. Chem. Soc.*, **87**, 3879 (1965).

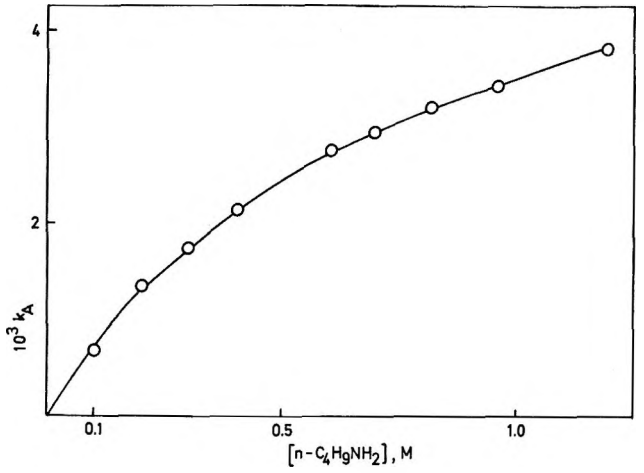
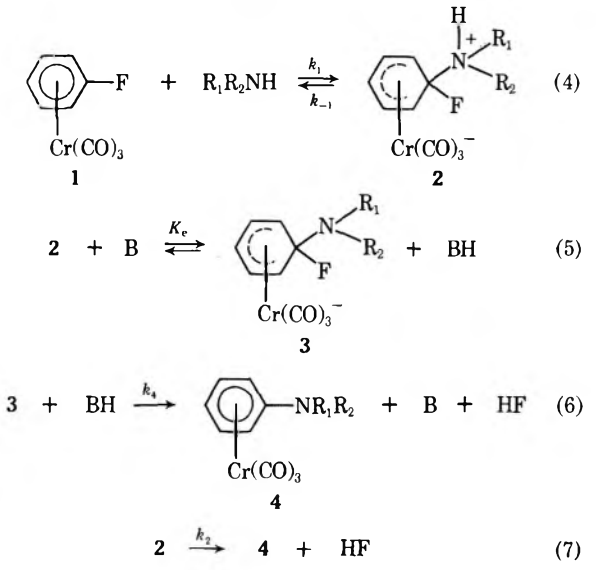


Figure 5.—Second-order rate coefficients for reaction of CTC–fluorobenzene with *n*-butylamine in DMSO at 25° as function of *n*-butylamine concentration.

attributed to a change in rate-limiting step with change of amine concentration.

A mechanistic model which serves well for other aromatic nucleophilic substitution reactions involving amine reagents[17] is sketched in Scheme I for reactions

SCHEME I



of CTC–fluorobenzene. By the usual steady-state assumption, one may derive from this mechanism an expression for k_A

$$k_A = \frac{k_1k_2 + [k_1k_3B]}{k_{-1} + k_2 + k_3[B]} \tag{8}$$

in which k_3 represents the product, k_4K_e, regardless of whether equilibrium 5 lies mainly on the right or on the left.[22]

Equation 8 is qualitatively consistent with the curvature in Figure 5, if a molecule of *n*-butylamine is playing the role of base B. A more searching test involves inverting eq 8 to obtain

$$\frac{1}{k_A} = \frac{k_{-1}}{k_1k_2 + k_1k_3[B]} + \frac{1}{k_1} \tag{9}$$

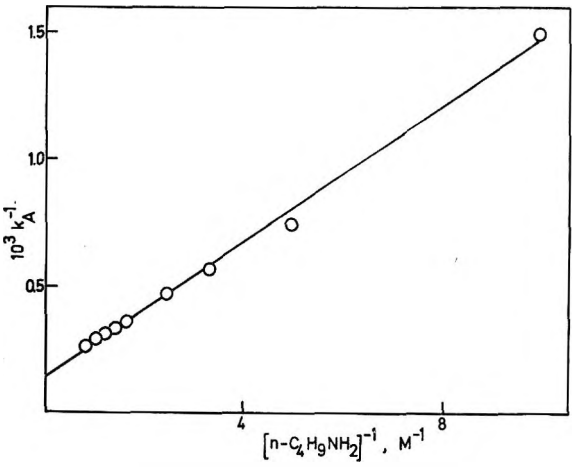


Figure 6.—Reaction of CTC–fluorobenzene with *n*-butylamine in DMSO at 25°. Inversion plot.

If $k_3[B] \gg k_2$, which is likely except at low base concentrations

$$\frac{1}{k_A} = \frac{k_{-1}}{k_1k_3}\frac{1}{[B]} + \frac{1}{k_1} \tag{10}$$

An "inversion plot" according to eq 10, based on the data in Table III, is presented as Figure 6. It closely approximates linearity, and the negative deviations at lower amine concentrations (higher $1/[n\text{-BuNH}_2]$) are as expected if the assumption whereby eq 9 is transformed into eq 10 is not fully justified. (The conformity of the point at the far right to the linear regression line is perhaps fortuitous.) From the intercept in Figure 6, k_1 is evaluated as 7.25×10^{-3} M^{-1} sec^{-1}, and from dividing the slope by the intercept the ratio k_{-1}/k_3 is evaluated as 1.03 M.

To evaluate also the ratio k_2/k_{-1}, one rearranges eq 8 into

$$\frac{k_A}{k_1 - k_A} = \frac{k_2}{k_{-1}} + \frac{k_3[B]}{k_{-1}} \tag{11}$$

The plot (not shown) of the data of Table III (excepting that for 0.1 M *n*-$BuNH_2$) according to eq 11 is linear (r = 0.998). From the intercept, k_2/k_{-1} is evaluated as 0.04 and from the slope k_3/k_{-1} is 0.910 M^{-1}, or k_{-1}/k_3 is 1.09 M. The ratio k_3/k_2 is 24 M^{-1}.

According to the model of Scheme I, with attention especial to eq 8, linear dependence of k_A on base concentration is observed when $k_{-1} \gg (k_2 + k_3[B])$, independence is observed when $(k_2 + k_3[B]) \gg k_{-1}$, and curvilinear dependence in the sense of Figure 5 when k_{-1} and $(k_2 + k_3[B])$ are of similar magnitude. The frequently observed shift from linear or curvilinear dependence on base with secondary amines to independence with primary amines is understood as a consequence of an increase in the relative magnitude of $(k_2 + k_3[B])$ over k_{-1}. The present shift from linear dependence (Figures 2 and 3) to curvilinear dependence (Figure 5) may be attributed to the same cause.

Summary of Correlations.—In the foregoing presentation, we have described several linear correlations (or attempted correlations) between k_A or k_T and amine concentration. These are summarized in Table II.

Experiments with Other Leaving Groups.—Efforts were made to observe reactions of amines with analogs of CTC–fluorobenzene in which the (intended) leaving

group was chlorine, nitro, dimethylsulfonio, or trimethylammonio. These were unsuccessful, but some chemistry of qualitative interest was encountered.

It is reported that the dimethylsulfonio and trimethylammonio groups of, respectively, *p*-nitrophenyldimethylsulfonium ion and *p*-nitrophenyltrimethylammonium ion are exceptionally mobile in reactions with sodium methoxide in methanol.[25a] We obtained CTC–phenyldimethylsulfonium fluoroborate easily by methylation of CTC–thioanisole with trimethyloxonium fluoroborate. However, reactions of this sulfonium salt with piperidine in water, methanol, or acetonitrile and with sodium thiophenoxide in water or methanol afforded CTC–thioanisole in high yield, but no other CTC-complexed aromatic. CTC–thioanisole was also the chief product from reaction with sodium methoxide in methanol; the infrared and mass spectra of the crude product mixture suggested the presence also of about 2% of CTC–anisole. Thus nucleophilic displacement on methyl carbon, releasing CTC–thioanisole as leaving group, was the predominant reaction. Displacement on methyl carbon occurs on reaction of *p*-nitrophenyldimethylsulfonium ion with thiocyanate ion[25b] or piperidine (this work), but methoxide ion attacks to form *p*-nitroanisole.[25a]

In contrast to the behavior of CTC–thioanisole, CTC–dimethylaniline was not methylated by trimethyloxonium fluoroborate. Several attempts were made, but only unreacted CTC–dimethylaniline or decomposition products were obtained. Trimethyloxonium fluoroborate did, however, smoothly methylate both *p*-nitrophenyl methyl sulfide and *N*,*N*-dimethyl-*p*-nitroaniline. Thus the unreactivity of CTC–dimethylaniline with trimethyloxonium fluoroborate contrasts sharply with the facility of analogous reactions.

Reactions of CTC–chlorobenzene with 2 *M* piperidine in DMSO afforded little chloride ion, and only decomposition products. This was a surprise, because CTC–chlorobenzene reacts smoothly with $NaOCH_3$ in CH_3OH,[2a] and the reaction rate has been measured.[4]

The nitro group is exceptionally mobile in many aromatic nucleophilic substitution reactions. However, like Whiting,[2a] we were unable to prepare CTC–nitrobenzene. We attempted the preparation under nonoxidizing conditions, by allowing sodium nitrite to act upon CTC–fluorobenzene.[26]

Discussion

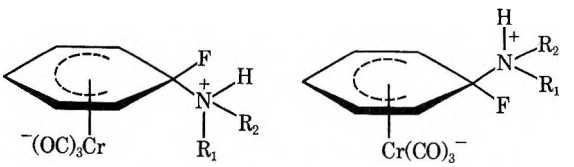
We shall give a large measure of attention to the form of the rate law, and especially to the pattern and extent of variation of the second-order rate coefficient, k_A, with the concentration of the reacting nucleophilic amine and/or the concentration of an accompanying "catalytic" amine. It is a fact that third-order terms predominate in the rate laws for these reactions, being first order in substrate, first order in the reacting amine, and first order in a "catalytic" amine which may be the reacting amine or another one. Although we have not specifically demonstrated that the observed catalytic effects represent base catalysis, as contrasted, say, to a general medium effect, we shall interpret them as base catalysis because (a) base catalysis is well established for closely related reactions of benzene derivatives,[17,22,24] and (b) the accelerations produced by most amines in the present work are quite large.

In this type of reaction, the incidence and form of base catalysis are instructive as to which step of the intermediate complex mechanism, as sketched in Scheme I for reaction of CTC–fluorobenzene with an amine, is rate-limiting.[24] By analogy to reactions of analogous benzene derivatives, the second stage of reaction, from intermediate **2** to product **4**, is catalyzed by base but the first step is not. Therefore, if the reaction is not catalyzed by base, the first step is rate limiting, that is $(k_2 + k_3[B]) \gg k_{-1}$. Base catalysis with linear dependence of k_A on base concentration indicates that expulsion of fluorine from complex **3** is rate limiting, that is that $k_{-1} \gg (k_2 + k_3[B])$. Base catalysis with curvilinear dependence of k_A on base concentration indicates that each stage is partially rate limiting, that is that k_{-1} and $(k_2 + k_3[B])$ are of similar magnitude, depending on the base concentration.

The salient outcome of the present study is that reactions of CTC–fluorobenzene with amines in dipolar, aprotic solvents are quite sensitive to catalysis by amines. In contrast, reactions of *p*-fluoronitrobenzene with amines in the same solvents are not base catalyzed.[27] We conclude that the second stage of the intermediate complex mechanism is largely or wholly rate limiting in these reactions of CTC–fluorobenzene, while the first is rate limiting for corresponding reactions of *p*-fluoronitrobenzene.

The reaction of CTC–fluorobenzene with piperidine is wholly base catalyzed in acetonitrile (Figure 1), and mainly base catalyzed in DMF (Figure 2) and in DMSO (Figure 3). In DMSO, the reaction with piperidine is catalyzed strongly by quinuclidine and weakly by DABCO (a weaker base), but is repressed by *N*-methylpiperidine (Figure 4). The same reaction is accelerated by *tert*-butylamine, but in a curious nonlinear fashion (Figure 4) which is not understood. The reaction of CTC–fluorobenzene with pyrrolidine in DMSO is strongly catalyzed by pyrrolidine, in linear fashion, but that with *n*-butylamine in DMSO shows a curvilinear dependence of k_A on amine concentration (Figure 5). With *n*-butylamine the first and second stages of the mechanism are both partially rate limiting, while in all other cases expulsion of fluoride ion from intermediate complex **2** or **3** is rate limiting.

Whiting[10] has pointed out that, conceptually, an amine might attack CTC–fluorobenzene either endo (syn) or exo (anti) with respect to the chromium tricarbonyl moiety to form, respectively, intermediate **5** or **6**. He judged the evidence to support endo at-



5 **6**

(25) (a) B. A. Bolto and J. Miller, *Aust. J. Chem.*, **9**, 79 (1956); (b) *J. Org. Chem.*, **20**, 558 (1955).

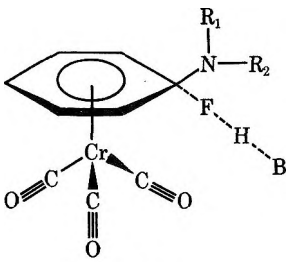
(26) *Cf.* T. J. Broxton, Thesis, University of Western Australia, 1967.

(27) H. Suhr, *Ber. Bunsenges. Phys. Chem.*, **67**, 893 (1963); *Justus Liebigs Ann. Chem.*, **687**, 175 (1965); *ibid.*, **689**, 109 (1965).

tack, largely because piperidine is about 100,000-fold more reactive than diethylamine toward CTC–fluorobenzene but only about 100-fold more reactive with ordinary aromatic substrates such as 1-chloro-2,4-dinitrobenzene.

On the other hand, related complexes bearing a positive charge, such as the tropylium cation–CTC complex[6] and the cationic tricarbonyl(benzene)–manganese complex,[7] add nucleophiles on the less hindered exo side. Also, the reduction of CTC–1-indanone by $LiAlH_4$ or $NaBH_4$ occurs almost exclusively by exo attack of the reducing agent,[28a] and the Friedel–Crafts acylation of CTC–alkylbenzenes is believed to involve exo attack of the electrophile.[28b]

A number of observations in the present research and in the earlier work of Whiting[10] are compatible with the hypothesis that the amine attacks CTC–fluorobenzene on the exo side. The lack of catalytic activity by *N*-methylpiperidine (Figure 3) or by triethylamine[10] may be ascribed to steric hindrance when the *N*-methylpiperidium or triethylammonium ion, with its comparatively large steric requirements, attempts to approach the endo fluorine atom in order to provide electrophilic assistance to its severance from carbon.[29] By analogy with reactions of substrates such as 2,4-dinitro-1-naphthyl ethyl ether with amines,[17] the mechanism of general base catalysis of fluorine expulsion from intermediate complex 2 (Scheme I) is general acid catalysis of departure of the leaving group from the conjugate base intermediate complex (3). The transition state for fluorine expulsion, if the original nucleophilic attack is exo, may then be represented by structure 7. If the amine moiety,



7

B, has large steric requirements, structure 7 will present obvious problems of fit.

In similar terms, the fact that diethylamine is enormously less reactive than piperidine in reaction with CTC–fluorobenzene may be understood. If the reacting amine is also the catalytic amine, its steric requirements will affect the rate of the fluorine expulsion step, as well as having some effect on the equilibrium concentration of intermediate complex 3 through steric interactions with the benzene moiety.

The very circumstance that reactions of CTC–fluorobenzene with amines of modest steric requirements, such as piperidine, pyrrolidine, and *n*-butylamine, in DMSO solvent are base-catalyzed whereas corresponding reactions of *p*-fluoronitrobenzene are not[27] also finds explanation in the hypothesis of exo attack and ultimate expulsion of fluorine *via* transition state 7. With the nitro-activated substrate, leaving group expulsion from the intermediate complex is much faster than rejection of the amine moiety, but with CTC–fluorobenzene fluorine dismissal is the slower step. Steric problems evident in transition state 7, even when the steric requirements of the amine are not great, are a plausible cause. If endo attack of amine were postulated, steric interactions between the amine and chromium tricarbonyl moieties would surely accelerate amine rejection, but they would also find relief in fluorine expulsion which would allow the amino group to move into coplanarity with the benzene ring carbons. If the latter factor predominated, no base catalysis would be observed.

The fact that *tert*-butylamine is an effective catalyst for reaction of CTC–fluorobenzene with piperidine, although not effective as a nucleophilic amine with this substrate, calls for comment. The bulkiness of *tert*-butylamine is about its α carbon, not about the nitrogen atom as in triethylamine. Although its bulkiness does adversely affect exo attack by *tert*-butylamine to form complexes of type 2 or 3 (its reactivity with ordinary aromatic substrates is also very low), the fact that in 7 the bulkiness is about an atom four atoms removed from aromatic carbon allows the *tert*-butyl group to be adjusted into conformations in which it does not experience formidable compressions against other moieties in the transition state.

The unreactivity of CTC–phenyldimethylsulfonium ion with methoxide ion, insofar as replacement at aromatic carbon is concerned, is also consistent with the hypothesis of exo attack by the nucleophile. In this case the intended leaving group is large, and in the intermediate complex it would be forced against the chromium tricarbonyl moiety. No such problem is involved in attack at aromatic carbon in *p*-nitrophenyldimethylsulfonium or *p*-nitrophenyltrimethylammonium ion.

Experimental Section

Preparations.—All tricarbonyl(arene)chromium complexes were prepared from the corresponding benzene derivative and chromium hexacarbonyl in an apparatus designed by Strohmeier,[30] which allows back-transport of the sublimed chromium hexacarbonyl to the reaction solution. The complexes were purified by recrystallization from *n*-heptane or better by high-vacuum sublimation.

CTC–fluorobenzene[2a] was obtained from fluorobenzene and chromium hexacarbonyl, mp 116–117° (lit.[2a] 122.5–124°). The melting point of the literature could not be obtained, even after extended purification by crystallization from *n*-heptane and sublimation. The complex was pure according to its mass spectrum; uv–visible in acetonitrile λ_{max} 310.5 nm (ϵ 9050); in DMF λ_{max} 310.5 (9360); in DMSO λ_{max} 311.5 (9020).

CTC–chlorobenzene[2a] was obtained from chlorobenzene and chromium hexacarbonyl, mp 98° (lit.[2a,31] 102–103°, 97–100°).

CTC–anisole was obtained from anisole and chromium hexacarbonyl, mp 86° (lit.[2a] 86–87°).

CTC–dimethylaniline was obtained from dimethylaniline and chromium hexacarbonyl, mp 146° (lit.[2a] 146–146.5°).

CTC–phenylpiperidine was obtained from phenylpiperidine and chromium hexacarbonyl, in 70% yield after sublimation, or from CTC–fluorobenzene and piperidine in acetonitrile[3] in 99% yield: mp 126–127° (lit.[2c] 125–126.5); uv–visible λ_{max} in acetonitrile 320 nm (ϵ 7800); in DMF 320 (8030); in DMSO 320 (7750).

CTC–phenylpyrrolidine was obtained from CTC–fluorobenzene and pyrrolidine in acetonitrile in 99% yield: mp 161–162° (lit.[2c] 161–162°); uv–visible λ_{max} in DMSO 317.5 nm (ϵ 7550).

(28) (a) W. R. Jackson and T. R. B. Mitchell, *J. Chem. Soc. B*, 1228 (1969); (b) W. R. Jackson and W. B. Jennings, *ibid.*, 1221 (1969).

(29) *Cf.* F. Covitz and F. H. Westheimer, *J. Amer. Chem. Soc.*, **85**, 1773 (1963).

(30) W. Strohmeier, *Chem. Ber.*, **94**, 2490 (1961).

(31) M. C. Whiting, British Patent 941,061 (1963); *Chem. Abstr.*, **60**, 3006 (1964).

CTC–*N*-*n*-butylaniline was obtained from CTC–fluorobenzene and *n*-butylamine in acetonitrile in 94% yield: mp 67°; uv-visible λ_{max} in DMSO 316 nm (ϵ 6650). *Anal.* Calcd for $C_{13}H_{15}CrNO_3$: C, 54.73; H, 5.30; N, 4.91. Found: C, 55.04; H, 5.01; N, 4.80.

CTC–thioanisole was obtained from thioanisole and chromium hexacarbonyl in 71% yield (after the first sublimation) or from CTC–fluorobenzene and sodium methyl mercaptide in DMSO after 24 hr at room temperature in 50% yield (after the first sublimation). The complex slightly decomposes during sublimation: mp 101°; ir (KBr) $\nu_{C=O}$ 1940, 1880, 1850 cm^{-1}. *Anal.* Calcd for $C_{10}H_8CrO_3S$: C, 46.15; H, 3.10; S, 12.32; mol wt ,260. Found:[32] C, 46.48; H, 3.23; S, 12.12; mol wt (mass spectrum, parent peak), 260.

CTC–Phenyldimethylsulfonium Fluoroborate.—A mixture of 4.2 g of CTC–thioanisole and 10 g of trimethyloxonium fluoroborate in 50 ml of dichloromethane was kept at room temperature for 15 hr. After evaporation of the solvent the residue was crystallized from ethanol (under N_2). The yield was 5.2 g (89%): on heating, it decomposed at 170–180°; ir (KBr) $\nu_{C=O}$ 1980, 1915, 1890, 1855 cm^{-1} (shoulder); nmr (CD_3SOCD_3) S, 6 H, τ 6.24 (CH_3); multiplet, 5 H, τ 3.24–4.10 (aromatic protons). *Anal.* Calcd for $C_{11}H_{11}BCrF_4O_3S$: C, 36.49; H, 3.06. Found:[32] C, 36.25; H, 3.00.

Reactions of CTC–Phenyldimethylsulfonium Fluoroborate. With Piperidine in Water.—From 10-hr reaction at room temperature, after which time the water phase was colorless, only CTC–thioanisole in a yield of 95% could be isolated. The result was the same when the reaction was carried out in acetonitrile as solvent. No CTC–phenylpiperidine was detectable (by ir) in either experiment.

With sodium methoxide in methanol, a mixture of CTC–thioanisole and CTC–anisole was obtained, but, according to ir and mass spectra, the yield of the latter was less than 5%. The yield of CTC–thioanisole was 97%.

Attempts to Prepare CTC–Phenyltrimethylammonium Fluoroborate.—Under the same conditions as for the preparation of the corresponding sulfonium salt, only starting material was detectable after a reaction time of 24 hr. Heating a solution of CTC–dimethylaniline with an excess of trimethyloxonium fluoroborate in ethylene chloride for 5 hr caused partial decomposition of the complex, but only starting material could be isolated. Carrying out the same experiment in tetrachloroethylene at its reflux temperature (140°) caused complete decomposition of the complex to form ill-defined products.

Attempts to Prepare CTC–Nitrobenzene.—CTC–Fluorobenzene (320 mg) in 5 ml of a saturated solution of sodium nitrite in DMSO was heated for 40 min at 80°. The dark brown reaction mixture was diluted with water and extracted with ether. After removal of the ether, the oily residue did not contain a trace of CTC–nitrobenzene, but only starting material according to ir and mass spectra. From the same reaction carried out in acetonitrile (2 hr under reflux), the only isolable substance was starting material. No CTC–nitrobenzene was detectable by mass spectrum in the reaction mixture after careful removal of the solvent by evaporation at room temperature.

***p*-Nitrophenyldimethylsulfonium Fluoroborate.**—A mixture of 2.3 g of *p*-nitrothioanisole[24] and trimethyloxonium fluoroborate (tenfold excess) in dichloromethane was kept at room temperature for 12 hr. The solvent was evaporated and the residue was crystallized twice from methanol; the product formed white plates, mp 118°, in 60% yield.

Reactions of *p*-Nitrophenyldimethylsulfonium Fluoroborate. With Piperidine in Water.—The sulfonium salt (305.5 mg) was kept for 10 hr at room temperature in a 15% solution of piperidine in water. The only isolable product, in 91% yield, was *p*-nitrothioanisole. The same reaction carried out in methanol in the presence of piperidine hydrochloride gave *p*-nitrothioanisole in 85% yield. With sodium methoxide in methanol, *p*-nitroanisole was formed in 86% yield.

Solvents.—DMSO (Crown Zellerbach) was purified by repeated fractional freezing until its ultraviolet spectrum was constant. DMF was purified by distillation from P_2O_5 at 45° in the dark. Acetonitrile was purified after O'Donnell, Ayres, and Mann.[33]

(32) Elemental analysis by Micro-Tech Laboratories, Skokie, Ill.

(33) J. F. O'Donnell, J. T. Ayres, and C. K. Mann, *Anal. Chem.*, **37**, 1161 (1965).

Kinetic Measurements.—Runs were conducted spectrophotometrically under conditions to afford pseudo-first-order kinetics. A few crystals of CTC–fluorobenzene were placed in a nitrogen-flushed 10-mm cuvette with neck. The cuvette was flushed again with nitrogen and closed under a nitrogen stream with a cap made from silicone rubber tubing which was stoppered at the top with a flat-ended piece of glass rod. (Other types of rubber tubing were slowly attacked by solvent vapor.) After injection of a solution, prepared under nitrogen, of all reaction ingredients except CTC–fluorobenzene through the wall of the silicone rubber tubing by means of a syringe, the cap was pushed down, so that the planar end of the glass rod was attached to the neck of the cuvette as tightly as possible, so as to minimize direct contact of the silicone rubber tubing with the reaction solution. Then the reaction solution was thoroughly mixed and placed in the thermostated cell compartment of a Gilford 2000 automated kinetics spectrophotometer. Absorbance was then determined as a function of time, and the data were treated according to standard methods.

Ultraviolet spectra were determined by a similar procedure, by injecting solutions of the complexes in appropriate solvents. The spectra obtained in this way were reproducible and stable for several hours, an indication that this technique effectively excluded oxygen. In DMSO and DMF all complexes slowly decomposed, but too slowly to interfere with the kinetic measurements. All reaction solutions were light sensitive and had to be kept in the dark, because the photolytic decomposition of the complexes is quite rapid.

That reactions with amines in DMSO were entirely aminodefluorination was shown in two ways. First, ultraviolet–visible spectra taken during the course of the reaction with piperidine showed two isosbestic points, at 285 and 322 nm. The final spectrum was identical with that of CTC–phenylpiperidine, and intermediate spectra could be mimicked by combination of the spectra of CTC–fluorobenzene and CTC–phenylpiperidine. Only at low concentrations of piperidine (0.1*M* and below) was there a slight deterioration of the isosbestic points after the first half-life, owing to the slow deterioration of these CTC complexes in DMSO, but the error caused in the infinity absorbance was not more than 3%. Similar observations were made in respect to reactions with pyrrolidine and *n*-butylamine.

The second type of evidence showing that the reactions occurred in the expected sense was from fluoride ion titration against lanthanum nitrate solutions with reference to a fluoride ion-selective electrode (Orion Model 94-09). Kinetic runs were performed, with CTC–fluorobenzene (0.01 *M*) and piperidine (0.158 *M*) in DMSO, under nitrogen, with samples being removed at recorded times by syringe. The samples were quenched with HCl in water to pH 3, extracted with ether to remove CTC complexes, diluted with isopropyl alcohol and water to constant volume of 50% isopropyl alcohol content by volume, adjusted to pH 4 by addition of a few drops of piperidine solution in DMSO, and titrated with $La(NO_3)_3$ solution. The end-point potential was found to depend on the volume of titrant added. It was therefore necessary to employ several $La(NO_3)_3$ solutions for each run in order to get meaningful results, and to perform numerous test titrations with solutions of known fluoride ion concentration. Two identical runs at 25° afforded k_ψ values of 2.74 and 2.59 $\times$ 10^{-4} sec^{-1}, and infinity fluoride ion yields of 90 and 91%. The photometric k_ψ under the same conditions (Table I) was 2.63 $\times$ 10^{-4} sec^{-1}.

The infinity solutions from runs in acetonitrile and DMF had ultraviolet–visible spectra which matched that of CTC–phenylpiperidine. Reactions in DMF showed well-defined isosbestic points at 220 and 283 nm (with piperidine 0.134 *M*). A preparative run in acetonitrile afforded CTC–phenylpiperidine in 99% yield.

Registry No.—1, 12082-05-2; piperidine, 110-89-4; pyrrolidine, 123-75-1; *n*-butylamine, 109-73-9; quinuclidine, 100-76-5; DABCO, 280-57-9; *N*-methylpiperidine, 626-67-5; *tert*-butylamine, 75-64-9; CTC–*N*-*n*-butylaniline, 32104-33-9; CTC–thioanisole, 32104-34-0; CTC–phenyldimethylsulfonium fluoroborate, 32104-35-1.

Kinetics and Mechanisms of the Spontaneous and Metal-Modified Oxidations of Ethanol by Peroxydisulfate Ion[1a,b]

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The oxidation of ethanol by peroxydisulfate has been found to proceed by three distinct paths, the first in the presence of O_2 (path A), the second in the absence of oxygen (path B), and the third in the presence of several metal ions, particularly Cu(II) (path C). The first two paths are similar to those observed for the 2-propanol and methanol oxidations; however, some differences are noted. Included are results showing inhibition by O_2, by allyl acetate, and by product acetaldehyde. After minimization of effects due to catalysts and inhibitors, the observed rate law for path B was found to be rate $= k[S_2O_8^{2-}]^{3/2}$. A survey of metal salts as potential catalysts has shown that copper and silver ions act as catalysts while ammonium molybdate apparently acts as an inhibitor. A detailed study of the effect of cupric ion on the oxidation showed that the stoichiometry (including secondary oxidation of aldehyde product) was not changed by the metal ion, but that the rate law became rate $= k_{3/2}'[S_2O_8^{2-}][Cu(II)]^{1/2}$. Radical chain mechanisms which are consistent with stoichiometry, rate laws, and other kinetic effects are presented.

As a part of our continuing study of the peroxydisulfate oxidation of alcohols, we decided to look at a primary alcohol, specifically ethanol, as reductant. This alcohol presents the possibility of finding a behavior intermediate between those of 2-propanol[2] and methanol.[3]

A number of investigations which bear on the ethanol oxidation have been carried out.[4-7] Prior to our study, however, there existed an inconsistency between the apparent rate law which suggested the bimolecular initiation step (eq 1) while the results from

$$CH_3CH_2OH + S_2O_8^{2-} \longrightarrow CH_3\dot{C}HOH + HSO_4^- + SO_4\cdot^- \quad (1)$$

the use of radical traps (allyl acetate[3b,4] and diphenylpicrylhydrazyl[5]) were consistent only with the unimolecular initiation step (eq 2). Further, since our

$$S_2O_8^{2-} \xrightarrow{k_{1a}} 2SO_4\cdot^- \quad (2)$$

previous studies[2,3] showed that oxygen inhibition, aldehyde inhibition, and copper ion catalysis must be considered in alcohol oxidations (but had not been in the ethanol case), a careful study of the oxidation of ethanol by peroxydisulfate was warranted; in the course of this study, we have made the first detailed study of metal ion catalysis in such reactions.

Experimental Section

Distilled 95% ethanol was used for both kinetic and stoichiometric determinations. The $K_2S_2O_8$ was Baker and Adamson reagent grade, recrystallized twice from demineralized water. The acetaldehyde and allyl acetate were Eastman Organic Chemicals, usually distilled just before use. The cupric sulfate, anhydrous powder, was Baker and Adamson reagent grade and was used with no further purification. The 2,2,2-trifluoroethanol was K & K, and the 2,3-butanediol was Matheson Coleman and Bell; both alcohols were distilled (Vigreux column) before use. All other chemicals were reagent grade and were used without further purification. The demineralized water was obtained from a Bantam demineralizing column of the Barnstead Still and Sterilizer Co.

For the most part, kinetic runs were carried out spectrophotometrically using techniques similar to those of the previous studies.[2,3c] As both acetaldehyde and peroxydisulfate absorb in the ultraviolet, only a limited choice of convenient wavelengths was available. Most of the data was taken in the range below 240 nm, where a significant change in absorption obtains during the course of a kinetic run. Details are reported elsewhere.[8] With allyl acetate present, it was necessary to use a titrimetric technique.[3b,8]

Depending on the wavelength chosen, it was possible to analyze spectrophotometrically for peroxydisulfate (below 240 nm) or for acetaldehyde (ϵ 12.0 at λ_{max} 280 nm and 70°). Knowledge of the concentration of aldehyde was particularly important because of the stoichiometric complications.

The stoichiometric experiments that were performed in order to determine the total acid produced as a function of the ethanol-to-peroxydisulfate ratio were carried out in 5- or 10-cc ampoules and the reaction solution was titrated at infinite time with 0.05 or 0.1 *M* sodium hydroxide to the thymol blue (basic range pH 8.0–9.6) end point.

The vpc detection data for the glycol (2,3-butanediol) were obtained on a flame ionization Aerograph 200 vpc using a 6 ft × 0.125 in. aluminum tubing using FFAP (10%) as the liquid phase and Chrom W as the solid support.

A Fortran program, similar to that of Wiberg,[9] was written[8] to facilitate the calculations of rate constants from spectrophotometric data.

Results

General.—A number of characteristics of the ethanol oxidation by peroxydisulfate are akin to those characteristics reported[2-4,6] for oxidations of other alcohols; these will be mentioned here without further substantiation. Oxygen gas is an inhibitor; the rate of oxidation while oxygen is present is barely above the rate due to spontaneous decomposition of peroxydisulfate. At the instant the last bit of oxygen is used up, a sudden end to the "induction period" (denoted part A) is observed, and the faster rate of part B commences. In Figure 1, the fashion by which oxygen gas influences the behavior of this oxidation reaction is clearly seen. Product aldehyde is known to be a mild inhibitor.[1b,3a] Allyl acetate, both in the presence and absence of copper ion, lowers the rate of loss of peroxydisulfate to the level of the spontaneous decomposition; allyl

(1) (a) Abstracted from the Ph.D. thesis of A. R. Gallopo, Brown University, 1967. (b) A preliminary account of some of this work has been published: J. O. Edwards, A. R. Gallopo, and J. E. McIsaac, Jr., *J. Amer. Chem. Soc.*, **88**, 3891 (1966). (c) NASA Fellow, 1965–1966.

(2) D. L. Ball, M. M. Crutchfield, and J. O. Edwards, *J. Org. Chem.*, **25**, 1599 (1960); see also references therein.

(3) (a) J. E. McIsaac, Jr., and J. O. Edwards, *ibid.*, **34**, 2565 (1969); (b) P. D. Bartlett and J. D. Cotman, *J. Amer. Chem. Soc.*, **71**, 1419 (1949).

(4) I. M. Kolthoff, E. J. Meehan, and E. M. Carr, *ibid.*, **75**, 1439 (1953).

(5) C. E. H. Bawn and D. Margerison, *Trans. Faraday Soc.*, **51**, 925 (1955).

(6) M. Santappa and L. R. Subbaraman, *Curr. Sci.*, **33**, 208 (1964).

(7) (a) L. R. Subbaraman and M. Santappa, *Proc. Indian Acad. Sci.*, **64**, 345 (1966); (b) *Z. Physik. Chem.*, **48**, 163 (1966).

(8) Ph.D. thesis of A. R. G.; see ref 1a. Procedures, results, and discussion in considerable detail can be found therein.

(9) K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, p 560.

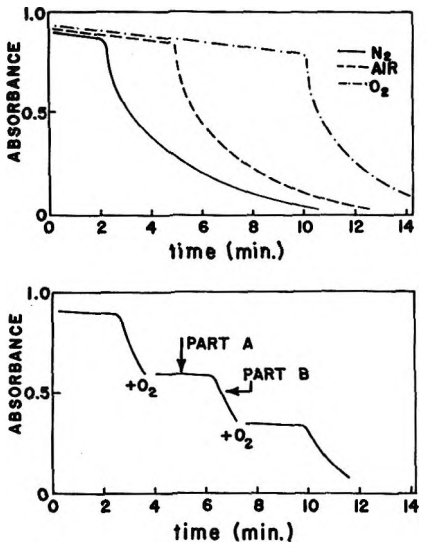

Figure 1.—The relative length of the induction period (part A) as a function of oxygen concentration (as established by nature of gas bubbled through solution before start of reaction) and a spectrophotometric plot showing how part B of reaction can be changed back to part A on reintroduction of oxygen.

alcohol also lowers the rate, but it is not quite so effective as allyl acetate. As expected, copper(II) under certain conditions is a catalyst for the reaction.

Under some conditions (carefully purified reactants and water, etc.), the rate of reaction during the induction period gave a rate constant value of 1.4×10^{-5} min^{-1} at 70°,[10] which is the constant reported for loss of peroxydisulfate in pure water. This indicates that the rate of radical formation is the same when alcohol is present as when alcohol is absent.

A search using glc for 2,3-butanediol as a possible product of the ethanol oxidation gave conclusive results. The standards used in the analysis showed that the amount of glycol formed even by chain termination alone would be readily detectable (approximately ten times background). We found none; thus the predominant (90%) termination product must also be aldehyde. No ethyl acetate was detected in either glc or the stoichiometric studies.

It is appropriate to discuss this oxidation reaction in three sections. The initial period during which the reaction is inhibited by dissolved oxygen is designated part A and the reaction is said to proceed by path A. The reaction after initiation of the faster section is termed part B, and is subdivided on the basis of copper additive. The mechanism in the absence of copper(II) is termed path B, and the mechanism when copper is present is termed path C.

Stoichiometry.—Because of the complications during the initial period (see below), a careful study of the stoichiometry was not feasible. On the other hand, the stoichiometry during the second part for both paths B and C was carefully investigated, and these data supply an important clue as to mechanism.

The predominant stoichiometry of the reaction in the absence of oxygen, with and without the presence of copper(II), was confirmed to be

$$S_2O_8^{2-} + CH_3CH_2OH \longrightarrow CH_3CHO + 2HSO_4^- \quad (3)$$

(10) I. M. Kolthoff and I. K. Miller, *J. Amer. Chem. Soc.*, **73**, 3055 (1951).

This was based on yields of acetaldehyde, on titration of the total acid produced, and on the unchanging absorbance at an isoabsorptive point (270 nm at 70°) for the production of acetaldehyde and the disappearance of peroxydisulfate.

The yields of acetaldehyde and initial rates of reaction as a function of the ethanol-to-peroxydisulfate ratio are listed in Table I. The yields of acetaldehyde

TABLE I

INITIAL RATES AND PER CENT YIELD OF ALDEHYDE AS A FUNCTION OF ETHANOL-TO-PEROXYDISULFATE RATIO AT 70°[a]

$[EtOH]_0$, M	$[S_2O_8^{2-}]_0$, M	$[EtOH]_0/[S_2O_8^{2-}]_0$	Initial rate, M min^{-1}	Yield, %
4.2	0.0314	134	2.05×10^{-4}	
3.9	0.0326	120	2.22×10^{-2}	100
3.5	0.0328	107	2.34×10^{-2}	99
3.1	0.0339	92	2.51×10^{-2}	100
3.1	0.0362	86	2.48×10^{-2}	
2.6	0.0354	74	2.79×10^{-2}	101
2.2	0.0365	60	2.68×10^{-2}	100
2.2	0.0372	59	2.34×10^{-2}	
1.7	0.0374	45	2.50×10^{-2}	100
1.2	0.0392	31	2.76×10^{-2}	98
0.61	0.0403	15	2.00×10^{-2}	93
0.31	0.0415	7.5	1.80×10^{-2}	83
0.16	0.0406	4.0	1.29×10^{-2}	71
0.063	0.0426	1.5	7.96×10^{-3}	
0.013	0.0418	0.31	4.40×10^{-3}	

[a] Further data may be found in ref 8.

are essentially constant at 100 ± 1% when the ethanol-to-peroxydisulfate ratio is 40 or above, and the yields are seen to decrease when this ratio falls below about 40. This indicates that the mole ratio of acetaldehyde produced to peroxydisulfate reacted is 1:1 when the ethanol-to-peroxydisulfate ratio is 40 or above.

The above stoichiometry (eq 3) predicts that 2 mol of monohydrogen sulfate will be produced for every mole of peroxydisulfate reacted. Under some conditions, however, a higher ratio of acid produced to peroxydisulfate reacted was observed; these conditions were the same as those for which the yield of acetaldehyde was less than 100%. Separate experiments[8] showed that the reaction of peroxydisulfate with acetaldehyde to form acetic acid (eq 4) can take place

$$S_2O_8^{2-} + CH_3CHO + H_2O \longrightarrow CH_3CO_2H + 2HSO_4^- \quad (4)$$

under our conditions. It can be seen that for this reaction 3 mol of titratable acid are produced per mol of peroxydisulfate reacted.

In Table II, data relevant to this point are presented. In this table, 100% yield of total acid represents 2 mol of H^+ released per $S_2O_8^{2-}$ mole used up. It is clear that the deviation from 100% when the ethanol-to-peroxydisulfate ratio is less than 40 represents aldehyde oxidation. The limiting value, based on the complete conversion of ethanol to acetic acid, would be 1.25. Therefore, at low reactant ratios, a significant fraction of ethanol is transformed into acetic acid. A number of experiments[8] in which the initial concentrations of reactants were varied by a factor of four showed that both the "per cent yield total acid" and the initial rates were a function only of the ratio of reactants rather than a function of the individual concentrations.

The important conclusion from the data in Table II and in Figure 2 is that addition of copper ion does

TABLE II

PER CENT YIELD OF TOTAL ACID AS A FUNCTION OF ETHANOL-TO-PEROXYDISULFATE RATIO FOR SPONTANEOUS AND COPPER(II)-MODIFIED REACTIONS AT 70°

$[EtOH]_0$, M[a]	$([EtOH]_0/[S_2O_8^{2-}]_0)$[a]	Yield[b] total acid, %	Yield[c] total acid, %	Yield[d] total acid, %
3.9	130	100	100	100
3.4	113	100	100	100
2.9	98	100	100	100
2.4	81	101	100	100
1.9	64	100	100	101
1.4	48	101	101	101
0.97	33	101	102	101
0.48	16	103	102	103
0.24	8.1	106	104	105
0.12	4.0	109	109	108
0.097	3.2	111	111	109
0.072	2.4	111	111	111
0.048	1.6	114	114	115
0.024	0.80	117	120	119

[a] $[S_2O_8^{2-}]_0 = 3.0 \times 10^{-2}$ M for all runs. [b] No added Cu(II). [c] $[Cu(II)] = 5.0 \times 10^{-5}$ M. [d] $[Cu(II)] = 3.0 \times 10^{-4}$ M.

not change the stoichiometry. The relative yields of acetaldehyde and acetic acid are independent of the amount of copper ion in the solution, even though, as will be seen below, the rate and rate law are significantly changed. The fact that unchanging absorbance at the isoabsorbtive point (270 nm) as a function of time was observed both in the presence and absence of copper ion also indicates that the stoichiometry is unchanged.

Part A.—The general features of the part A reaction, which occurs when dissolved oxygen is present, are similar to the features of the analogous parts of the 2-propanol[2] and methanol[3a] oxidations. The length of part A increases as the amount of dissolved oxygen increases. When the oxygen present is exhausted, the rate changes dramatically to the much faster part B, during which the oxygen inhibition can be made to reintrude by opening the reaction vessel to air. These phenomena are demonstrated by the curves in Figure 1. Trace metals also affect this part of the reaction. The water solvent had to be carefully purified, as did the sample of $K_2S_2O_8$; in both cases, purification decreased the rate, which is the behavior expected if trace amounts of active metals were present. Addition of EDTA also decreased the rate.

Some variables affecting part A are (1) the peroxydisulfate concentration, (2) the ethanol concentration, (3) the temperature, and (4) the nature and concentration of the metal ion. Both the rate of decrease of peroxydisulfate concentration and the time length τ (the "induction period") for part A can be studied; however, we shall limit the data discussed here to those things which are presently explicable. In Table III, the length of induction period is presented as a function of peroxydisulfate concentration and of temperature. Assuming that the amount of oxygen is the same in all solutions and that the oxygen reacts at every collision with an organic radical (details given below), the disappearance of oxygen should be more rapid (smaller τ) as peroxydisulfate concentration increases and as temperature increases. This is what is observed. The temperature-dependence data make possible a calculation of apparent activation energy; the value obtained from the plot of $1/\tau$ *vs.* $1/T$ is 26 ± 2 kcal

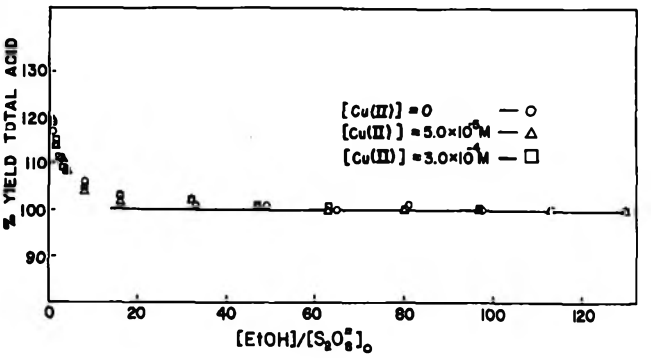

Figure 2.—The yield of total acid (HSO_4^- plus CH_3CO_2H) as a function of the ethanol-to-persulfate ratio for both path B (circles) and path C [triangles and squares for two different concentrations of copper(II) ion].

TABLE III

LENGTH OF THE INDUCTION PERIOD AS A FUNCTION OF PEROXYDISULFATE CONCENTRATION AND TEMPERATURE

Dependence on $[S_2O_8^{2-}]_0$, M[a]		Dependence on temp	
$[S_2O_8^{2-}]_0$, M[a]	τ, min[b]	Temp, °C	τ, min[a,c]
2.80×10^{-2}	2.0	55	25
1.58×10^{-2}	3.0	60	12
8.27×10^{-3}	5.0	65	7.5
5.72×10^{-3}	7.0	70	5.0
3.42×10^{-3}	7.5	75	3.0
1.96×10^{-3}	9.0	80	2.5
1.49×10^{-3}	10.5		
1.11×10^{-3}	11.5		

[a] $[EtOH]_0 = 1.4$ M. [b] At 70°. [c] $[S_2O_8^{2-}]_0 = 8.9 \times 10^{-3}$ M.

mol^{-1}, which is in agreement with the value of 26 ± 1 for the 2-propanol case[2] and 29 ± 2 for the methanol case.[3a] The value of τ increased from 4.0 to 8.0 min as the ethanol concentration decreased from 2.3 to 0.23 M ($[S_2O_8^{2-}] = 8.7 \times 10^{-3}$ M at 70°). A similar dependence was observed with the other alcohols. With purified reagents and addition of EDTA, the rate of loss of peroxydisulfate is close to that for spontaneous decomposition of $S_2O_8^{2-}$ in pure water.

In Table IV, the influence of Cu(II) concentration on the initial rate of part A, the amount of peroxydisulfate

TABLE IV

EFFECT OF COPPER(II) ON THE RATE OF PART A AT 70°[a]

$[Cu(II)]$, M	Initial rate, M min^{-1}	$S_2O_8^{2-}$ lost in A, %	τ, min
None	$0.2\text{–}1.8 \times 10^{-4}$	1–2	4.5–5.0
1.0×10^{-8}	1.8×10^{-4}	5.8	5.5
5.0×10^{-8}	1.8×10^{-4}	3.5	6.0
1.0×10^{-7}	3.2×10^{-4}	13	5.6
5.0×10^{-7}	4.5×10^{-4}	23	6.5
1.0×10^{-6}	4.9×10^{-4}	30	6.0
1.5×10^{-6}	5.5×10^{-4}	31	6.5
1.0×10^{-5}	6.2×10^{-4}	43	6.5
2.0×10^{-5}	6.6×10^{-4}	45	6.0
4.0×10^{-5}	6.2×10^{-4}	42	6.5
6.0×10^{-5}	6.6×10^{-4}	44	6.0
8.0×10^{-5}	6.4×10^{-4}	43	6.5
1.0×10^{-4}	6.4×10^{-4}	43	6.5

[a] $[EtOH]_0 = 1.4$ M; $[S_2O_8^{2-}]_0 = 8.7 \times 10^{-3}$ M.

lost in part A, and the length of the induction period τ are presented. The first horizontal row gives ranges of values of these observables found in a number

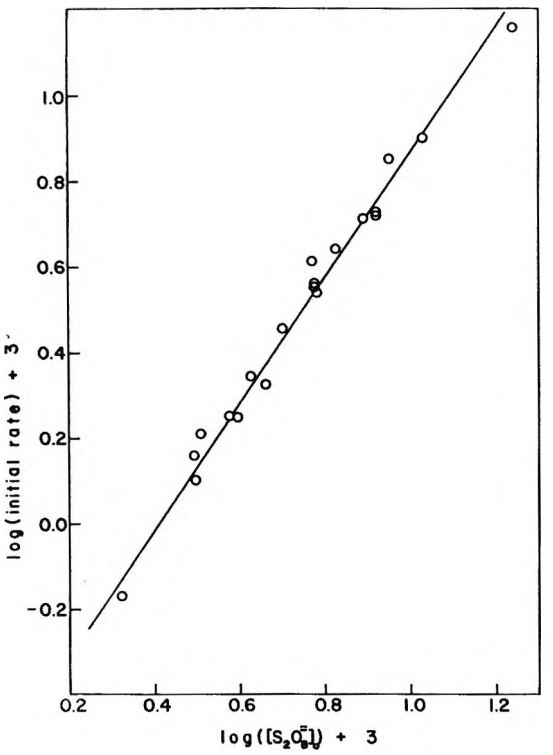

Figure 3.—Data for evaluation of kinetic order (path B) in persulfate concentration. Points are log initial rate against log initial $[S_2O_8^{2-}]$; for $[C_2H_5OH]$ = 1.4 M, no added acetaldehyde, and T = 70°.

of experiments carried out in the absence of added Cu(II) ion. It is noted that 10^{-8} M copper ion has a barely observable effect. The initial rate of reaction (second column) increases with copper concentration, but the rate variation is much smaller than the variation in metal ion concentration. The amount of peroxydisulfate lost in part A also increases with copper concentration, but not in a simple manner. An important observation is the lack of a strong inverse dependence of τ on copper concentration; this indicates that the metal ion does not increase the rate of radical production. Explanations for some of these observations will be given in the Discussion.

Data on the effect of a number of other metal ions on part A of the reaction are given in Table V. Ten metal ions [Ni(II), Fe(II), Cr(III), Hg(II), Sn(II), Sn(IV), Ag(I), Ce(IV), Co(II), and Ti(III)] increase (sometimes marginally) the rate of part A, while five others [Mn(II), Mg(II), Cd(II), Sr(II), and Zn(II)] show no detectable catalytic activity at a level of 10^{-5} M. In part, the existence of a redox couple (*e.g.*, $Hg_2^{2+} \rightleftarrows 2\ Hg^{2+} + 2e^-$) seems to be a factor in the catalytic activity; however, the complete explanation must be more complex. No significant influence on the τ values was observed.

Path B.—The oxidation of ethanol by peroxydisulfate in the absence of oxygen and of metal ions follows the stoichiometry mentioned above. The problems uncovered in the order determination have been briefly discussed earlier,[1b] and it was shown there that the oxidation of ethanol is inhibited by the product acetaldehyde when the concentration of aldehyde becomes equal to or larger than 1×10^{-3} M.

In order to minimize the problem of aldehyde inhibition while determining the order of the reaction,

TABLE V

EFFECT OF SOME METAL IONS ON THE RATE OF PART A AT 70° [a]

Metal ion[b]	Initial rate, M min^{-1}	$S_2O_8^{2-}$ lost in A, %
Ni(II)	3.2×10^{-4}	13
Fe(II)	2.9×10^{-4}	10
Cr(III)	5.0×10^{-4}	32
Hg(II)	4.5×10^{-4}	26
Sn(II)	5.0×10^{-4}	33
Sn(IV)	6.5×10^{-4}	31
Mn(II)	8.4×10^{-5}	5.8
Mg(II)	5.5×10^{-5}	4.2
Ag(I)	4.8×10^{-4}	26
Ag(I)	1.3×10^{-4}	5.7
Ce(IV)	3.2×10^{-4}	29
Cd(II)	3.1×10^{-5}	2.5
Sr(II)	4.5×10^{-5}	3.0
Zn(II)	6.3×10^{-5}	4.0
Co(II)	2.5×10^{-4}	14
Ti(III)	3.2×10^{-4}	16

[a] $[EtOH]_0$ = 1.4 M; $[S_2O_8^{2-}]_0 = 8.7 \times 10^{-3}$ M. [b] Metal ion concentration is 1.0×10^{-5} M, except for Ag^+ where it is 1.0×10^{-6} M.

the method of initial rates was employed. The rate was determined as a function of peroxydisulfate concentration at the commencement of part B with the ethanol concentration constant and in large excess. A plot of log (initial rate) against log ($[S_2O_8^{2-}]_0$) was made in order to determine the kinetic order; see Figure 3. The slope was 1.52 ± 0.05 (correlation coefficient of 0.990) and hence the order in peroxydisulfate is three halves.

This method was also used to determine the order in ethanol (see Table VI). The value of $k_{3/2}$ appears to be

TABLE VI

DETERMINATION OF INITIAL RATES OF PATH B AS A FUNCTION OF ETHANOL

$[EtOH]_0$, M	$[S_2O_8^{2-}]_0$ (B)[a]	Initial rate, M min^{-1}	$k_{3/2}$[b]
2.3	7.67×10^{-3}	4.78×10^{-3}	7.53
2.3	8.15×10^{-3}	6.04×10^{-3}	8.23
2.0	7.90×10^{-3}	5.43×10^{-3}	7.75
2.0	7.93×10^{-3}	4.92×10^{-3}	6.97
1.8	7.84×10^{-3}	5.63×10^{-3}	8.68
1.8	8.34×10^{-3}	4.84×10^{-3}	6.34
1.6	8.08×10^{-3}	4.50×10^{-3}	6.21
1.4	7.88×10^{-3}	5.24×10^{-3}	7.48
1.1	7.96×10^{-3}	4.57×10^{-3}	6.47
0.91	8.08×10^{-3}	6.18×10^{-3}	8.54
0.68	7.96×10^{-3}	5.78×10^{-3}	8.17

[a] Concentration (M) of $S_2O_8^{2-}$ at initiation of part B; note the essential constancy. [b] Units are $M^{-1/2}$ min^{-1}.

independent of ethanol concentration and hence the order in ethanol is zero in this concentration range.

The rate law for path B is

$$-d[S_2O_8^{2-}]/dt = k_{3/2}[S_2O_8^{2-}]^{3/2}$$

Confirmation of this is seen in Figure 4 which is a typical integrated rate plot covering 89% reaction.

The apparent activation energy for path B was determined from the values of $k_{3/2}$ at 55, 60, 65, 70, 75, and 80° to be found in the middle column of Table VII. A linear Arrhenius plot was obtained (correlation coefficient 0.993) with a slope corresponding to an activation energy of 17.2 ± 0.8 kcal mol^{-1}.

TABLE VII
SUMMARY OF RATE CONSTANTS FOR PATH B AND PATH C AS A FUNCTION OF TEMPERATURE

Temp, °C	$k^{3/2}$, $M^{-1/2}$ min^{-1} [b]	$k'^{3/2}$, $M^{-1/2}$ min^{-1} [c]
55	2.30	
60	3.88	70.3
65	5.97	116
70	8.48	177
75	11.0	288
80	16.1	393

[a] $[S_2O_8^{2-}]_0$(B) = 1.0×10^{-2} M; $[EtOH]_0$ = 1.4 M. [b] Reaction in absence of Cu(II); *i.e.*, path B. [c] [Cu(II)] = 5.0×10^{-5} M; *i.e.*, path C.

Path C.—In our initial experiments, it was found that rates in part B of the reaction were not significantly influenced by small amounts of EDTA (ethylenediaminetetraacetic acid); therefore, catalysis by adventitious metal ions was not considered important. However, further investigation showed that copper(II) ion at concentrations of 10^{-5} M or higher changed the kinetic behavior without dramatically increasing the rate. A similar effect of copper(II) had been noted in the methanol oxidation.[3a] This was interesting because part B of the 2-propanol system was not influenced by any of the metal ions tried.[2] This basic difference suggested that a study of the behavior of copper(II) in the ethanol oxidation would be worthwhile.

It should be noted that metal ions may enter into a chain reaction and not change the rate appreciably but change the mechanism significantly. This was found to be the case here. For this reason the reaction in the presence of copper(II) might better be called "the copper(II)-modified mechanism" rather than "the copper(II)-catalyzed mechanism." For the sake of simplicity, however, it will be called path C. In a series of kinetic runs, the concentration of copper(II) was varied over a factor of 50,000 in order to determine in which fashion the metal ion modifies the mechanism. Some results are presented in Table VIII. At concentrations of 10^{-6} M or lower, the rate was about the same as in the absence of metal ion. At concentrations of 10^{-5} M or higher, the rate is more rapid and increases with increasing copper concentration.

TABLE VIII
VARIATION IN RATE COEFFICIENTS WITH VARIATION IN COPPER(II) CONCENTRATION FOR PATH AT 70°

[Cu(II)], M	$[EtOH]_0$, M	$[S_2O_8^{2-}]_0$(B), M	$R^{3/2}$ [a]	R_1 [b]
5.1×10^{-4}	1.1	6.85×10^{-3}	22.3	1.73
1.5×10^{-4}	1.1	6.43×10^{-3}	30.0	1.98
1.0×10^{-4}	1.1	6.20×10^{-3}	20.6	1.28
5.0×10^{-5}	1.4	5.00×10^{-3}	21.9	1.29
5.1×10^{-5}	1.1	6.25×10^{-3}	18.3	1.08
1.0×10^{-5}	1.1	5.87×10^{-3}	13.3	0.793
1.0×10^{-5}	1.4	5.10×10^{-3}	14.8	0.868
1.5×10^{-6}	1.4	6.00×10^{-3}	9.32	0.601
1.0×10^{-6}	1.4	6.10×10^{-3}	9.17	0.574
1.0×10^{-6}	1.4	6.46×10^{-3}	8.02	0.522
5.0×10^{-7}	1.4	6.77×10^{-3}	9.25	0.626
1.0×10^{-7}	1.4	7.63×10^{-3}	8.55	0.591
5.0×10^{-8}	1.4	8.40×10^{-3}	7.79	0.575
1.0×10^{-8}	1.4	8.18×10^{-3}	9.32	0.632

[a] Units are $M^{-1/2}$ min^{-1}, assuming three-halves order in $S_2O_8^{2-}$. [b] Units are min^{-1}, assuming first order in $S_2O_8^{2-}$.

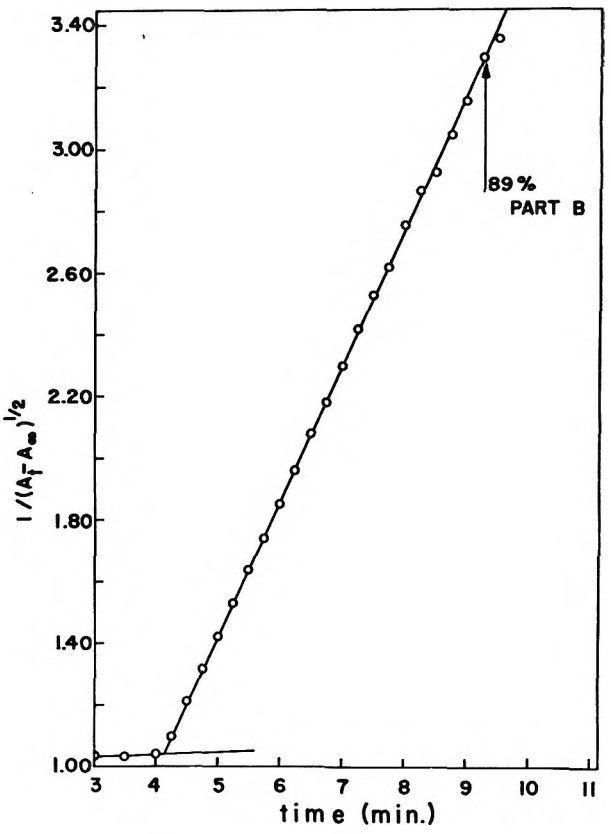

Figure 4.—A typical $^3/_2$-order integrated plot for path B; $[S_2O_8^{2-}]_0 = 1.0 \times 10^{-2}$ M, $[C_2H_5OH]$ = 1.4 M, and T = 70°.

In view of the fact that chain mechanims such as are seen in the present reaction are not additive (see Discussion), the assumption that path C is dominant when the copper concentration is greater than 10^{-5} M was made. The internal consistency of the results below indicates that the assumption is probably valid.

Path C was found to be first order in peroxydisulfate. The rate coefficient R_1 was evaluated over an eightfold concentration range (see Table IX) and the value is constant. Further, plots using the integrated first-order rate equation were linear to between two and three half-lives. A typical plot is shown in Figure 5. Path C was found to be zero order in ethanol; the results are shown in Table X. In this copper-modified mechanism, it was found[8] that product aldehyde does not act as an inhibitor as it does in the path B mechanism.

TABLE IX
VARIATION OF RATE COEFFICIENT WITH PEROXYDISULFATE CONCENTRATION AT CONSTANT ETHANOL AND COPPER(II) CONCENTRATIONS[a]

$[S_2O_8^{2-}]_0$(B), M	R_1, min^{-1}	$[S_2O_8^{2-}]_0$(B), M	R_1, min^{-1}
2.80×10^{-2}	1.40	1.10×10^{-2}	1.42
2.38×10^{-2}	1.33	8.27×10^{-3}	1.51
1.58×10^{-2}	1.45	6.57×10^{-3}	1.29
1.43×10^{-2}	1.42	5.72×10^{-3}	1.54
1.16×10^{-2}	1.35	3.42×10^{-3}	1.41
1.14×10^{-2}	1.34		

[a] $[EtOH]_0$ = 1.4 M; [Cu(II)] = 5.0×10^{-5} M; at 70°.

The order in copper(II) ion for path C was found to be one-half. The copper(II) concentration was varied over a factor of 5 and the observed first-order rate

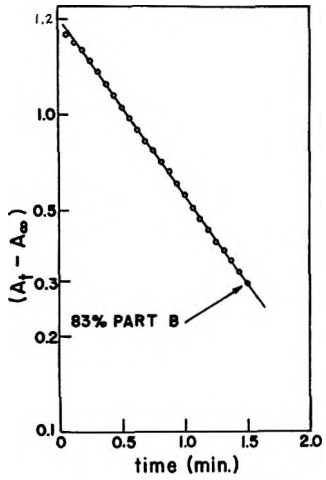

Figure 5.—A typical first-order integrated plot for path C; $[S_2O_8^{2-}]_0 = 1.5 \times 10^{-2}$ *M*, $[C_2H_5OH] = 1.4$ *M*, $[Cu^{2+}] = 5.0 \times 10^{-5}$ *M*, and $T = 70°$.

TABLE X
VARIATION OF RATE COEFFICIENT WITH ETHANOL CONCENTRATION AT CONSTANT PEROXYDISULFATE AND COPPER(II) CONCENTRATIONS[a]

$[EtOH]_0$, *M*	$[S_2O_8^{2-}]_0$(B), *M*	R_1, min^{-1}
1.8	5.12×10^{-3}	1.36
1.6	4.82×10^{-3}	1.52
1.4	4.74×10^{-3}	1.23
1.1	4.74×10^{-3}	1.52
0.91	4.71×10^{-3}	1.55
0.68	4.82×10^{-3}	1.36
0.46	4.96×10^{-3}	1.55
0.23	5.17×10^{-3}	1.23
0.091	5.83×10^{-3}	1.21

[a] $[Cu(II)] = 5.0 \times 10^{-5}$ *M*; at 70°.

constants appear to be dependent upon the copper(II) ion concentration to the one-half power (see Figure 6). The rate law for part C is, at least over a limited range, therefore

$$\text{rate} = k_{1/2}'[S_2O_8^{2-}][Cu(II)]^{1/2}$$

It should be noted that all kinetic runs in the study of path C were done at or above an ethanol-to-peroxydisulfate ratio of 40, so that the yields of aldehyde in all cases should be 100 ± 1%, as in Figure 2.

The apparent activation energy for path C was determined from kinetic runs at five temperatures (see last column in Table VII). A linear Arrhenius plot was obtained (correlation coefficient = 0.996) with a slope corresponding to an activation energy of 20.2 ± 0.8 kcal mol^{-1}.

In order to find out if the Cu(II) ion changes oxidation state during the course of the reaction, several experiments were carried out, as follows. Copper(II) ion in aqueous solution has an extinction coefficient of 390 M^{-1} cm^{-1} at 228 nm and 70°; consequently, there is a significant absorbance at high copper(II) concentrations (1.00×10^{-3} *M*). If one performs a kinetic run at this copper(II) concentration (such that the only absorbing species are peroxydisulfate and copper) and if copper(II) undergoes no chemical change, the absorbance at infinite time should be due to copper(II) alone. On performing such a kinetic run and using the extinction coefficient of copper(II) the absorbance at time infinity was predicted well within experimental

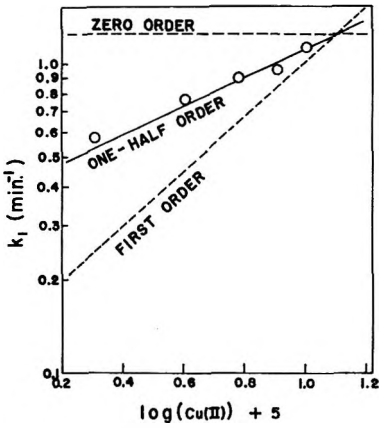

Figure 6.—The dependence of the pseudo-first-order rate constant on $[Cu^{2+}]$ for path C; $[S_2O_8^{2-}]_0 = 2.5 \times 10^{-2}$ *M*, $[C_2H_5OH] = 2.3$ *M*, and $T = 60°$.

error (±2%), indicating that copper(II) has undergone no net chemical change.

The second experiment was carried out to show that the expression below is valid. Two runs at [Cu(II)] = 1×10^{-3} *M* were made. In the first run, the same concentration of copper(II) was put in both the sample and reference cells. In the second run, copper(II) was put only in the sample cell. If the expression in question is valid, the absorbance in the first run should be due to persulfate alone. Initial rates and rate constants were calculated from both runs, assuming in the second run that the expression in question was valid and the concentration of persulfate calculated assuming that all the copper(II) still existed mainly in the plus two state. The rate constants agreed within experimental error (±5%) indicating that the equation is valid.

$$[Cu(II)]_{added} - [Cu(II)]_{during\ run} \simeq 0$$

It seemed worthwhile to find out if other metal ions had comparable effects to copper(II). Considerable scatter in the rate constant values were obtained in these experiments, but no significant alteration in rate was observed except for the cases of Ag(I) and $(NH_4)_6Mo_7O_4$. The silver acted as a catalyst, as expected,[11] but only when increased in concentration to 10^{-4} *M*. The molybdate acted as an inhibitor; the observed rate was lower by a factor of two when the molybdate salt concentration was 10^{-5} *M*. The reason for this inhibition is not understood.

Discussion

Comparison of Rates.—Before proceeding with the discussion of mechanism, it is helpful to make a summary of the relative rates of the various paths involved (see Table XI). These relative rates are based on the rates of the spontaneous thermal decomposition of peroxydisulfate[10,11] as unity. The rate in part A, in some runs, was essentially identical with the basis rate. For path B, the chain length (as given by the

(11) (a) W. K. Wilmarth and A. Haim in "Peroxide Reaction Mechanisms," J. O. Edwards, Ed., Wiley-Interscience, 1962, p 204; (b) D. A. House, *Chem. Rev.*, **62**, 185 (1962); (c) E. J. Behrman and J. E. McIsaac, Jr., in "Mechanisms of Sulfur Reactions," Vol. 2, N. Kharasch, Ed., Interscience, Los Angeles, Calif., 1968, p 193.

TABLE XI
COMPARISON OF RELATIVE REACTION RATES (CHAIN LENGTH) OF VARIOUS PATHS STUDIED (70°)

Alcohol	Alcohol concn	$[S_2O_8^{2-}]$, M	[Cu(II)], M	Part of reaction	k_1, min^{-1}	Initial rate, $M\ min^{-1}$	Rel rate[a,d]
					1.45×10^{-3}[a]		1
EtOH	1.4	1.0×10^{-2}		A		1.30×10^{-5}[b]	1
EtOH	1.4	1.0×10^{-2}		B		8.60×10^{-3}	590
EtOH	1.4	8.7×10^{-3}	1.0×10^{-5}	A		6.4×10^{-4}	51[c]
EtOH	1.4	1.0×10^{-2}	5.0×10^{-5}	C			870
CF_3CH_2OH	1.3	9.36×10^{-3}				5.91×10^{-5}[e]	4.3

[a] References 4, 10, and 11. The value of relative rate may be defined as the chain length under the conditions of the experiment. The chain length for this reaction is dependent on concentrations. [b] See General under Results. [c] See Table IV. [d] Defined by the relative rate of loss of peroxydisulfate under the conditions. [e] After correction for spontaneous thermal decomposition.

relative rate) is about 600; this value falls between those for methanol (about 50)[3] and 2-propanol (about 1800).[2] The relative rates for path B and path C are not greatly different, but, as mentioned above and discussed below, there is a definite change in the kinetics.

Included in Table XI is the rate of oxidation of 2,2,2-trifluoroethanol.[8] The powerful electron-withdrawing effect of the trifluoromethyl group appears to have an enormous retarding effect upon the rate of loss of peroxydisulfate, decreasing it to only four times the rate of the spontaneous thermal decomposition. The rate of oxidation of ethanol under these same conditions is about 140 times faster.

Evidence for Free Radical Nature.—The evidence for the free radical nature of the mechanisms of the oxidation of various alcohols is vast and has been commented on in many articles and reviews.[2-8,10] In the course of our work, we found no reason to doubt this general conclusion. For example, we observed the following: (a) inhibition by oxygen gas, and marked increase in rate at the time of oxygen disappearance, (b) inhibition by allyl acetate and allyl alcohol, (c) fractional orders in the rate laws, (d) inhibition by product aldehyde, and (e) change in kinetic pattern and rate on addition of copper(II) ion. All of these phenomena are characteristic of free radical chain reactions. We shall, therefore, postulate mechanisms of this type.

Chain Initiation Step.—The apparent discrepancy mentioned in the introduction between the allyl acetate experiments[4] and the tentative rate laws[3b,4] was first pointed out by Kolthoff, Meehan, and Carr,[4] although not resolved at that time. The difficulty, essentially, is that the allyl acetate experiments indicate that chain initiation is occurring by way of the unimolecular initiation step (eq 2) while the overall second-order nature of the tentative rate law, which as reported was

$$-d[S_2O_8^{2-}]/dt = k[S_2O_8^{2-}]^{1/2}[RCH_2OH]^{1/2} \qquad (R = CH_3 \text{ or } H)$$

indicates that initiation is occurring by way of the bimolecular initiation step (eq 1). It is to be noted, however, that the early kinetic experiments were carried out in the concentration ranges where aldehyde is now known to be an inhibitor.[1b,8] Further, it has been observed here that the rate appears to be a function of the ethanol concentration when the yields of aldehyde are less than 100%. These observations suggest that the apparent half-order dependence on alcohol concentration in the second-order rate law is related to the aldehyde inhibition. The results would be explicable if there is a competition between ethanol and acetaldehyde for the very reactive sulfate radical ion; the competition steps would be

$$SO_4\cdot^- + CH_3CH_2OH \xrightarrow{k_{2a}} HSO_4^- + CH_3\dot{C}HOH$$
$$SO_4\cdot^- + CH_3CHO \longrightarrow HSO_4^- + CH_3\dot{C}O$$

Under conditions where $[CH_3CH_2OH] \gg [CH_3CHO]$, the ethanol would compete successfully and any aldehyde inhibition would be minimized. Therefore, the order in ethanol which is observed at high concentrations of ethanol would be the true order. As seen in Table VI, this order is zero. We conclude that the proper rate law for part B of the reaction is

$$\text{rate} = k_{3/2}[S_2O_8^{2-}]^{3/2}$$

and that the unimolecular initiation step k_{1a} is the correct one. The apparent discrepancy is therefore resolved.

Recently, the evidence for a unimolecular initiation step in the oxidation of a number of organic compounds has been supported by the careful studies of Crematy[12] on oxidation of organic detergents by peroxydisulfate.

Path B. Mechanism.—The mechanism of the reaction in the absence of either oxygen or copper can now be formulated. The proposed steps are k_{1a}, k_{2a}, and

$$CH_3\dot{C}HOH + S_2O_8^{2-} \xrightarrow{k_{3a}} CH_3CHO + HSO_4^- + SO_4\cdot^-$$
$$2CH_3\dot{C}HOH \xrightarrow{k_{4a}} CH_3CHO + CH_3CH_2OH$$
$$H_2O + CH_3CHO \rightleftharpoons CH_3CH(OH)_2$$

The first step (constant k_{1a}) is the unimolecular homolytic scission of the peroxydisulfate ion. The second step (constant k_{2a}), which is the abstraction of a hydrogen atom on the carbon having a hydroxyl group, is analogous to the second step in the 2-propanol and methanol oxidations. The rate constants for these hydrogen atom abstractions have recently been measured[13] and found to be very large. Little is known of the third step (k_{3a}), but it is a reasonable one and it fits both stoichiometry and kinetics. The type of termination step (k_{4a}) is demanded by the kinetics, it is consistent with the absence of 2,3-butanediol, and it has recently been reported[14] in the photolytic oxidation of ethanol by hydrogen peroxide. The final step is the known, rapid hydration equilibrium of acetaldehyde. Upon application of the steady-state approximation and neglect of the term due to the

(12) E. P. Crematy, Ph.D. Thesis, University of Sydney, Australia, 1970.
(13) L. Dogliotti and E. Hayon, *J. Phys. Chem.*, **71**, 2511 (1967).
(14) J. Barrett, A. L. Mansell, and R. J. M. Ratcliffe, *Chem. Commun.*, 48 (1968).

spontaneous thermal decomposition of peroxydisulfate, the following rate law is obtained.

$$-d[S_2O_8^{2-}]/dt = k_{3a}(k_{1a}/k_{4a})^{1/2}[S_2O_8^{2-}]^{1/2}$$

This is consistent with the observed rate law. In view of the fact that $SO_4\cdot^-$ reacts directly with alcohols,[13] there is no need to postulate the intermediacy of hydroxyl radicals OH·.

It is a necessary condition of such a chain mechanism that the observed activation energy be greater than one-half the activation energy (33.5 kcal mol^{-1}) of the initiation step. The values are 17.2 and 16.7, respectively; the difference is small and in the proper direction. We conclude that the chain propagation step k_{3a} has a very small activation energy.

When acetaldehyde is present in kinetically significant amounts, the mechanism must be modified to include appropriate steps. For several reasons, the most important of which is the obvious activation of α-hydrogen extraction by hydroxyl groups, we feel that the hydrate form of the aldehyde is the reactive form. The new steps are

$$SO_4\cdot^- + CH_3CH(OH)_2 \xrightarrow{k_{2b}} HSO_4^- + CH_3\dot{C}(OH)_2$$

$$CH_3\dot{C}(OH)_2 + S_2O_8^{2-} \xrightarrow{k_{3b}} CH_3CO_2H + HSO_4^- + SO_4\cdot^-$$

$$CH_3\dot{C}(OH)_2 + CH_3\dot{C}HOH \xrightarrow{k_{4b}} \text{termination products}$$

These three steps plus the k_{1a}, k_{2a}, and k_{3a} steps mentioned above provide a derived rate law which is consistent with the observations concerning aldehyde inhibition. Since this type of inhibition has been adequately discussed elsewhere,[1b,3a,8] further discussion on aldehyde inhibition is not deemed necessary.

Path C. Mechanism.—The influence of copper ion on the kinetics turns out to be readily analyzed. The rate law is

$$\text{rate} = k_{3/2}'[S_2O_8^{2-}][Cu(II)]^{1/2}$$

Therefore, since the overall order is $^3/_2$ and the τ values do not depend on [Cu(II)], the initiation step is again k_{1a}. The data in Table II, along with much other data reported elsewhere,[8] show that the copper ion does not influence the stoichiometry. Since the product distribution between acetaldehyde and acetic acid is not a function of [Cu(II)], one can conclude that copper ion does not enter at the k_2 stage. The copper(II) must, therefore, react with the organic radicals formed in the k_2 stage.

The postulated mechanism for path C is then k_{1a}, k_{2a}, and the new steps

$$CH_3\dot{C}HOH + Cu(II) \xrightarrow{k_5} CH_3CHO + H^+ + Cu(I)$$

$$Cu(I) + S_2O_8^{2-} \xrightarrow{k_6} Cu(II) + SO_4^{2-} + SO_4\cdot^-$$

$$Cu(I) + CH_2\dot{C}HOH \xrightarrow{k_7} Cu(O) + CH_3CHO + H^+$$

$$Cu(O) + S_2O_8^{2-} \xrightarrow{k_8} Cu(II) + 2SO_4^{2-}$$

Step k_{1a} is again initiation, steps k_{2a}, k_5, and k_6 are the propagation steps, and k_7 is the new termination. Using the steady-state approximation for concentrations of $SO_4\cdot^-$, $CH_3\dot{C}HOH$, Cu(0), and Cu(I), the rate law

$$\text{rate} = (k_{1a}k_5k_6/k_7)^{1/2}[S_2O_8^{2-}][Cu(II)]^{1/2}$$

is obtained; this derived law is in agreement with the observed law. The observed activation energy 20.2 kcal mol^{-1} also is consistent with expectations for it is less than E_a for the k_{1a} step but greater than half of that value.

In view of the fact that aldehyde is oxidized to acid in the presence of copper ion, other steps involving $CH_3\dot{C}(OH)_2$ and Cu(II), etc., could be postulated. There appears no necessity for doing so. One point is, nevertheless, important. Since the termination step no longer involves the aldehyde radical $CH_3\dot{C}(OH)_2$, inhibition by aldehyde is not expected. Within our experimental error, no influence of acetaldehyde on the rate of path C was observed.

Part A.—The results obtained for part A are explicable in terms of oxygen inhibition and its consequences. We feel, however, that lengthy discussion here is unwarranted as the general behavior of part A has been developed in earlier papers.[2,3a] Suffice it to say that steps k_{1a} and k_{2a} are followed by the step

$$O_2 + CH_3\dot{C}CHOH \longrightarrow \cdot OOC(CH_3)HOH$$

or its kinetic equivalent

$$O_2 + CH_3\dot{C}HOH \longrightarrow HO_2\cdot + CH_3CHO$$

Recombination of peroxy radicals can then occur to terminate the chain at short chain length. This provides an entirely satisfactory explanation of the rate inhibition by oxygen gas.

Interconnection of Reactions.—The continuing problem of interpretation of the mechanisms of peroxydisulfate ion oxidations can be attributed, in part, to the implicit, but often employed, assumption that the mechanisms of these reactions are independent. For example, it has been felt that the oxidation of water will go on in the presence of alcohols in the same way that it goes in their absence. Also, it has been assumed that the alcohol oxidation can be treated identically when aldehyde is present as when it is absent. The invalidity of the assumption can be clearly recognized in one experimental result, namely, the inhibition of the oxidation of ethanol when acetaldehyde is present. If the product aldehyde were being oxidized independently, then the rate of disappearance of peroxydisulfate would of necessity be greater, rather than smaller. Even if alcohol and aldehyde compete for the sulfate radical ions, the rate of disappearance of peroxydisulfate must still be greater when the aldehyde is present. The fact that there is inhibition can only be explained if the termination step for the ethanol oxidation is altered when aldehyde is present.

Registry No.—Cu(II), 15158-11-9; Ni(II), 14701-22-5; Fe(II), 15438-31-0; Cr(III), 16065-83-1; Hg(II), 14302-87-5; Sn(II), 22541-90-8; Sn(IV), 22537-50-4; Mn(II), 16397-91-4; Mg(I), 14581-92-1; Mg(II), 22537-22-0; Ag(I), 14701-21-4; Ce(IV), 16065-90-0; Cd(II), 22537-48-0; Sr(II), 22537-39-9; Zn(II), 23713-49-7; Co(II), 22541-53-3; Ti(III), 22541-75-9; ethanol, 64-17-5; peroxydisulfate ion, 15092-81-6.

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Hydrogen Chloride Catalyzed Oxygen-18 Exchange between Para-Substituted Phenyl Methyl Sulfoxides and Water[1]

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Para-substituted phenyl methyl sulfoxides-^{18}O undergo oxygen-18 exchange with water in aqueous dioxane solutions of most mineral acids (reduction of the sulfoxides to sulfides takes place with hydrobromic and hydroiodic acids), but hydrochloric acid is a more effective catalyst by at least a factor of ten than other mineral acids at the same concentration. A much slower base-catalyzed exchange has also been detected. For the hydrogen chloride catalyzed exchange, the relative rates for *p*-methoxy-, *p*-methyl-, unsubstituted, *p*-chloro-, and *p*-nitrophenyl methyl sulfoxides are 2.18, 1.61, 1.00, 0.52, and 0.21, respectively. A Hammett plot of log k/k_0 *vs.* σ is linear with $\rho = 1.046$. Coupled with the work of others, these results indicate that there are at least four mechanisms for oxygen-18 exchange between sulfoxides and water.

In the past few years Oae and coworkers have carried on an extensive and intensive investigation of the oxygen-18 exchange between sulfoxides and water,[2] other acidic[3] and basic reagents,[4] and other sulfoxides;[5] and many features of the varied mechanisms of these reactions have been worked out. In the initial[6] oxygen-18 study of sulfoxides, exchange with the oxygen atoms of sulfuric acid was demonstrated, but there was no incorporation of oxygen-18 into diphenyl sulfoxide when a solution of it in 97% sulfuric acid was diluted with water-^{18}O. Following other reports that sulfoxides did not undergo oxygen-18 exchange reactions in acidic[7,8] or basic[8] solution (under mild conditions), Mislow, Simmons, Melillo, and Ternay showed[9] that such an exchange does take place quite readily with *p*-tolyl phenyl sulfoxide in an aqueous dioxane solution of hydrogen chloride. Furthermore, the rate of oxygen-18 exchange was found to be equal to the rate of racemization of (+)-*p*-tolyl phenyl sulfoxide, indicating the presence of a symmetrical intermediate in the reaction. Since that time Oae and coworkers have shown that sulfoxides

$$(+)\text{-}p\text{-ToS}^{+}(O^{-})\text{Ph} + H_2{}^{18}O \xrightarrow[\text{dioxane}]{\text{HCl}} (\pm)\text{-}p\text{-ToS}^{+}(\,{}^{18}O^{-})\text{Ph} + H_2O$$

$$k_{ex} = k_{rac}$$

undergo acid-catalyzed oxygen exchange reactions with water in solutions of phosphoric acid,[10] various chloroacetic acids,[11] hydrobromic acid in aqueous acetic acid,[12] and sulfuric acid at various concentrations.[2,13,14] These exchange studies have frequently involved comparative measurements of the rates of racemization of optically active sulfoxides under the same conditions.[2,3,10,11,13,14] The effects of various para substituents on the rates of oxygen-18 exchange[2,3,10,11,13] or racemization[10,13] of para-substituted phenyl sulfoxides were also determined in several cases. Some of the findings of these research efforts are summarized in Table I.

On the assumption that there is an intimate relationship between the exchange and racemization reactions, examination of the data in Table I reveals that there are at least two distinct mechanistic patterns for acid-catalyzed exchange of oxygen-18 between sulfoxides and water, one where $k_{ex}/k_{rac} \cong 1$, and another where $k_{ex}/k_{rac} \cong 0.5$. In addition, special, frequently closely related mechanisms are indicated for oxygen-18 exchange between sulfoxides and N_2O_4,[3b] carboxylic acids,[11] acetic anhydride,[3a] other sulfoxides,[5] potassium *tert*-butoxide,[4] and the oxygens of sulfuric acid.[6,14] The data in Table I reveal no clear pattern of substituent effects, the most noteworthy feature perhaps being the relative insensitivity of these reactions to substituents.

In investigating the substituent effect on the hydrogen chloride catalyzed oxygen-18 exchange between para-substituted phenyl methyl sulfoxides and water in dioxane solution, the special role of hydrochloric acid immediately became apparent, as shown in Table II. Except for hydrobromic and hydriodic acids, which reduced *p*-methoxyphenyl methyl sulfoxide to *p*-methoxyphenyl methyl sulfide, all mineral acids investigated catalyzed the oxygen-18 exchange, but hydrochloric acid was more effective[15] than any other acid by at least a factor of 10. Under conditions (50°, 24 hr) where 0.12 *N* HCl resulted in 40.5% exchange, there was no detectable exchange in 0.12 *N* $HClO_4$. At higher concentrations, however, perchloric acid shows a normal increasing fraction of exchange with increasing acid concentration. Clearly, at least two different exchange mechanisms are required by these results, one faster reaction specifically catalyzed by HCl, and another slower reaction catalyzed by other mineral acids. Since the k_{ex}/k_{rac} data of Table I require at least two sulfuric acid catalyzed exchange mechanisms in the absence of chloride ion, at least three different mechanisms must be involved in acid-catalyzed exchange of oxygen-18 between sulfoxides and water.

(1) Supported by Atomic Energy Commission Contract AT-(40-1)-3234; presented at the Southwest–Southeast Regional Meeting of the American Chemical Society, New Orleans, La., Dec 2–4, 1970; taken from the doctoral dissertation of I. O., St. Paul's University, Tokyo, Japan, 1971.

(2) For leading references see N. Kunieda and S. Oae, *Bull. Chem. Soc. Jap.*, **42**, 1324 (1969), and other papers of this research group cited below.

(3) (a) S. Oae and M. Kise, *ibid.*, **43**, 1416, 1421 (1970); (b) N. Kunieda, K. Sakai, and S. Oae, *ibid.*, **42**, 1090 (1969), and references cited therein.

(4) S. Oae, M. Kise, N. Furukawa, and Y. H. Khim, *Tetrahedron Lett.*, 1415 (1967).

(5) S. Oae, M. Yokoyama, M. Kse, and N. Furukawa, *ibid.*, 4131 (1968).

(6) S. Oae, T. Kitao, and Y. Kitaoka, *Chem. Ind. (London)*, 291 (1961).

(7) N. J. Leonard and C. R. Johnson, *J. Amer. Chem. Soc.*, **84**, 3701 (1962).

(8) D. Samuel and M. Weiss-Broday, in "Advances in Physical Organic Chemistry," Vol. 3, V. Gold, Ed., Academic Press, New York, N. Y., 1965, p 180.

(9) K. Mislow, T. Simmons, J. T. Melillo, and A. L. Ternay, Jr., *J. Amer. Chem. Soc.*, **86**, 1452 (1964); see also K. Mislow, *Rec. Chem. Progr.*, **28**, 217 (1967).

(10) N. Kunieda and S. Oae, *Bull. Chem. Soc. Jap.*, **41**, 1025 (1968).

(11) S. Oae, M. Yokoyama, and M. Kise, *ibid.*, **41**, 1221 (1968).

(12) W. Tagaki, K. Kikukawa, and N. Kunieda, and S. Oae, *ibid.*, **39**, 614 (1966).

(13) S. Oae and N. Kunieda, *ibid.*, **41**, 696 (1968).

(14) S. Oae, T. Kitao, Y. Kitaoka, and S. Kawamura, *ibid.*, **38**, 546 (1965).

(15) Whether there are actual differences in the catalytic effects of the other mineral acids was not investigated further.

TABLE I

COMPARISON OF SULFOXIDE OXYGEN-18 EXCHANGE AND RACEMIZATION RATES, AND THE EFFECTS OF SUBSTITUENTS ON THOSE RATES

Compounds used	Reaction medium	k_{ex}/k_{rac}	Substituents and relative rates	Ref
p-XC_6H_4SOPh	Concd HCl, dioxane	1[a]		9
p-XC_6H_4SO-p-Tol	85% H_3PO_4	0.98[b]	k_{ex}: H, 1.0; Cl, 0.6	10
		1.02[c]	k_{rac}: H, 1.0; Cl, 0.6	
p-XC_6H_4SOPh	CCl_3COOH	1.01[a]	k_{ex}: Me, 1.1; H, 1.0; Cl, 0.7	11
p-XC_6H_4SOPh	N_2O_4 in CCl_4	0.98[a]	k_{ex}: MeO, 7.4; Me, 1.9; H, 1.0; Cl, 0.4	3b
p-XC_6H_4SO-p-Tol	96.7% H_2SO_4		k_{rac}: NH_2, 0.7; H, 1.0; Cl, 1.1	13
p-XC_6H_4SOPh	95.5% H_2SO_4	0.97[a]	k_{ex}: Me, 3.0; H, 1.0; Cl, 1.4	13
p-XC_6H_4SOPh	91% H_2SO_4	0.75[a]		2
	86.9% H_2SO_4	0.65[a]		
	83.4% H_2SO_4	0.64[a]		
	80.5% H_2SO_4	0.52[a]		
	75.4% H_2SO_4	0.49[a]	k_{ex}: MeO, 6.0; Me, 0.8; H, 1.0; Cl, 1.1; NO_2, 1.3	
p-XC_6H_4SOPh	Ac_2O	0.50[a]	k_{ex}: Me, 1.1; H, 1.0; Cl, 0.8	3a
p-$XC_6H_4SOCH_2Ph$	Ac_2O	0.36[a]	k_{ex}: MeO, 0.9; Me, 0.9; H, 1.0; Cl, 0.8; NO_2, 1.1	3a

[a] X = Me. [b] X = H. [c] X = Cl.

TABLE II

PRELIMINARY EXPERIMENTS ON THE CATALYTIC EFFECTS OF VARIOUS ACIDS ON THE OXYGEN-18 EXCHANGE BETWEEN p-METHOXYPHENYL METHYL SULFOXIDE-^{18}O AND WATER IN DIOXANE SOLUTION[a]

Catalyst	Catalyst concn, N	Temp, °C	% exchange after 24 hr
$HClO_4$	0.12	75	6.0
HNO_3	0.12	75	3.0
H_2SO_4	0.12	75	3.0
H_3PO_4	0.12	75	1.5
HF	0.12	75	9.9
HCl	0.12	75	95.5
HBr	0.12	75	Reduction[b]
HI	0.12	75	Reduction[b]
HCl	0.12	50	40.5
$HClO_4$	0.12	50	0.0
HCl	0.36	50	88.8
$HClO_4$	0.35	50	4.5
$HClO_4$	0.59	50	10.5
$HClO_4$	0.82	50	20.3
$HClO_4$	1.18	50	45.8

[a] 88% dioxane, 12% aqueous acid, by volume, [RSOR'] = 0.195 M. [b] The sulfoxide was reduced to p-methoxyphenyl methyl sulfide.

More quantitative data on the effects of various concentrations of hydrochloric acid and various other reagents on the rate of exchange are given in Table III.

TABLE III

RATE CONSTANTS FOR THE OXYGEN-18 EXCHANGE BETWEEN p-METHOXYPHENYL METHYL SULFOXIDE-^{18}O AND WATER IN DIOXANE SOLUTION[a] AS A FUNCTION OF CONCENTRATION OF HCl AND OTHER REAGENTS

Catalyst and concn	Temp, °C	$k_{ex} \times 10^4$, sec^{-1}
0.12 N HCl	75	2.42
0.24 N HCl	75	7.13
0.36 N HCl	75	21.8
0.48 N HCl	75	38.6
0.12 N HCl + 0.12 N NH_4ClO_4	50	0.046
0.12 N HCl + 0.12 N NH_4Cl	50	0.059
0.12 N HCl + 0.12 N $HClO_4$	50	0.184
0.05 N NaOH	125	0.006

[a] 88% dioxane, 12% aqueous solution, by volume, [RSOR'] = 0.195 M.

There is a clear, greater than first-order dependence of the exchange rate on hydrochloric acid concentration. Addition of 0.12 N ammonium chloride to 0.12 N hydrochloric acid gives more effective catalysis than addition of 0.12 N ammonium perchlorate, demonstrating again the specific catalytic effect of chloride ion. However, substitution of 0.12 N perchloric acid for the 0.12 N ammonium chloride results in much faster reaction, a fact which is probably best interpreted in terms of a mechanism involving higher order catalytic dependence on hydrogen ion than on chloride ion (see below). In the absence of activity coefficient or acidity function data for these aqueous dioxane solutions, and since the experimental limitations of the exchange procedure precluded the use of either very dilute solutions or large excesses of catalyst relative to sulfoxide, no attempt was made to put the hydrogen ion and chloride ion catalytic effects on a more quantitative basis. However, in closely related work, Landini, Montanari, Modena, and Scorrano reported[16] that the racemization of (+)-p-tolyl methyl sulfoxide in aqueous perchloric acid was near first order with respect to added chloride or bromide ion over a wide range of acidities, and that the slopes of the linear log k_{rac} $vs.$ H_0 plots at constant halide ion concentration had slopes of near unity at high acidities and near two at low acidities, Allenmark and Hagberg reported[17] a similar first-order dependence of the rate of racemization of the same compound on halide ion concentration in aqueous acetic acid. Kunieda and Oae also reported that plots of $-H_0$ $vs.$ log k_{rac}[2,13] or log k_{ex}[2] for (+)-p-tolyl phenyl sulfoxide-^{18}O in aqueous sulfuric acid were linear with slopes near unity at high acidities, but no halide ion catalysis was involved in those cases.

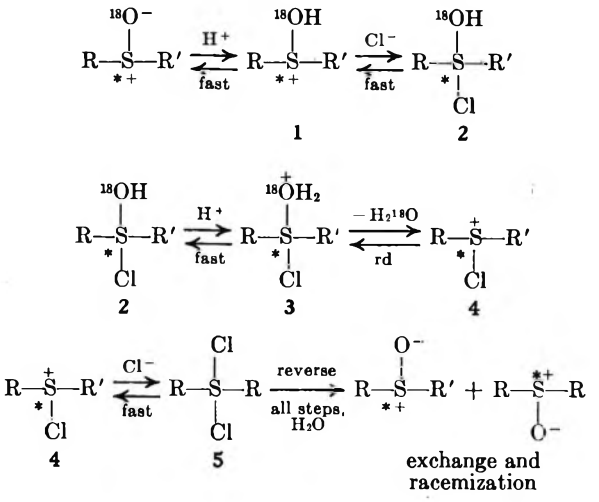
Our data on the catalytic effects of hydrogen ion and chloride ion on the rate of oxygen-18 exchange between p-methoxyphenyl methyl sulfoxide-^{18}O and water, coupled with the related work of Landini and coworkers and

(16) D. Landini, F. Montanari, G. Modena, and G. Scorrano, *Chem. Commun.*, 86 (1968); in a very recent report [*J. Amer. Chem. Soc.*, **92**, 7168 (1970)] these authors have given more details of this research, utilizing other acidity function data, but the basic conclusions regarding orders of reaction remain unchanged.

(17) S. Allenmark and C. Hagberg, *Acta Chem. Scand.*, **22**, 1461, 1694 (1968).

Allenmark and Hagberg on the racemization of sulfoxides, seems to be best interpreted in terms of the mechansim of Scheme I (* indicates asymmetric

Scheme I



sulfur). Sulfoxides react with concentrated sulfuric acid to yield their conjugate acids,[18] **1**, rather than dications, R–$^{+}$S^{+}–R′, as shown by oxygen-18 exchange experiments[6,18,19] and by freezing point depression measurements.[6,19–21] Suggestion that the conversion of **3** to **4** is rate determining is consistent with higher order H^+ than Cl^- dependence of the exchange rate as observed in this research and as noted by Landini and coworkers[16] for the racemization reaction. These workers point out that at very high acidities where the sulfoxide is essentially all converted to its conjugate acid, a plot of log k_{rac} *vs.* $-H_0$ would be expected to have a slope of about unity as observed.[16] Since **5** is a symmetrical intermediate which inevitably leads to *exchange and racemization*, k_{ex} should equal k_{rac} as observed.[9] Finally, the reversible formation of dibromo and dichloro compounds from the corresponding sulfoxides by treatment with hydrobromic and hydrochloric acids is well known.[22]

Additional significant support for this mechanism is provided by the data on the effects of substituents on the oxygen-18 exchange rate as presented in Table IV. Clearly, electron-donating substituents accelerate the exchange reaction, while electron-withdrawing substituents slow it down. A Hammett plot of log k/k_0 *vs.* σ is linear with $\rho = -1.046$. A negative ρ would certainly be expected for the first step of the above mechanism, and the basicity measurements of Landini, Modena, Scorrano, and Taddei[23] on a series of para-substituted phenyl methyl sulfoxides ($\rho = -0.85$) are in accord with this view. Similarly, for para-substituted diphenyl sulfoxides[24] and para-substituted acetophenones,[25] plots of σ^+ *vs.* pK_{BH^+} are linear with ρ values of -2.00 and -2.17. For the equilibrium constants for the conversion of **1** to **2**, on the other hand, a positive ρ would be expected; perhaps a very small negative ρ would be expected for the conversion of **2** to **3**; and a relatively large negative ρ would be expected for the rate-determining conversion of **3** to **4**. The net result of this combination of substituent effects should almost certainly be a negative ρ, as observed.

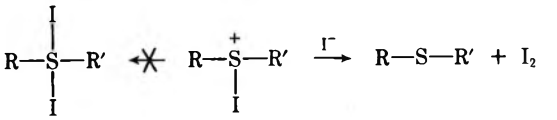
Table IV

Rate Constants for the Hydrochloric Acid Catalyzed Oxygen-18 Exchange of Para-Substituted Phenyl Methyl Sulfoxides-^{18}O and Water in Aqueous Dioxane[a] at 75°

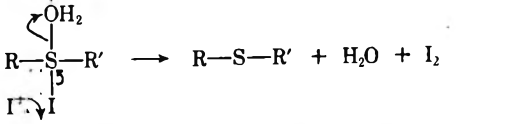
Para substituent	Registry no.	$k_{ex} \times 10^4$, sec^{-1}	Relative k_{ex}
CH_3O	3517-99-5	2.87	2.18
CH_3	934-72-5	2.12	1.61
H	1193-82-4	1.32	1.00
Cl	934-73-6	0.685	0.52
NO_2	940-12-5	0.275	0.21

[a] 88% dioxane, 12% aqueous acid, by volume; [RSOR′] = 0.19 *M*; [HCl] = 0.14 *M*.

The validity of these arguments is further supported by consideration of substituent effects and likely mechanisms for related reactions, selected data for which are summarized in Table V. It is seen that the substituent effect data for the reduction of sulfoxides to sulfides by hydriodic acid[26,27] follow almost exactly the same pattern as that observed in this research. An attractive possibility for the mechanism of the reduction reaction (which was also observed with HBr and HI in aqueous dioxane in the present research) is the rate-determining formation of R–$^{+}$SI–R′ (corresponding to **4**) by a sequence of steps corresponding exactly to that given in the above mechanism for exchange and racemization. Under conditions favoring reduction, iodide ion would then attack iodine to form the sulfide and iodine rather than attacking sulfur to give the di-



iodide. Alternatively, a reduction mechanism[26] involving rate-determining attack of iodide ion on iodine in a species corresponding to **3** would probably have much the same substituent effect behavior, providing O–S bond rupture proceeds "ahead" of the electron transfer from iodine to sulfur. Such a mechanism would require second-order dependence on iodide ion for the reduction



(18) G. A. Olah, A. T. Ku, and J. A. Olah, *J. Org. Chem.*, **35**, 3904 (1970), have reported that sulfoxides protonate on sulfur rather than on oxygen in HSO_3F–SbF_5 solutions in SO_2ClF. It is difficult to see how the oxygen-18 exchange, racemization, or reduction reactions of sulfoxides in more conventional acid solutions could proceed through such sulfur protonated species.

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(20) H. J. Shine and D. R. Thompson, *Tetrahedron Lett.*, 1591 (1966).

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(22) T. Zincke and W. Frohneberg, *Chem. Ber.*, **43**, 837 (1909); K. Fries and W. Vogt, *Justus Liebigs Ann. Chem.*, **381**, 337 (1911); E. Fromm, *ibid.*, **396**, 75 (1913); K. Issleib and M. Tzschach, *Z. Anorg. Allg. Chem.*, **305**, 198 (1960).

(23) D. Landini, G. Modena, G. Scorrano, and F. Taddei, *J. Amer. Chem. Soc.*, **91**, 6703 (1969).

(24) S. Oae, K. Sakai, and N. Kunieda, *Bull. Chem. Soc. Jap.*, **42**, 1964 (1969).

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(26) D. Landini, F. Montanari, H. Hogeveen, and G. Maccagnani, *Tetrahedron Lett.*, 2691 (1964).

(27) R. A. Strecker and K. K. Andersen, *J. Org. Chem.*, **33**, 2234 (1968).

TABLE V

COMPARISON OF SUBSTITUENT EFFECTS ON VARICUS REACTIONS OF SULFOXIDES

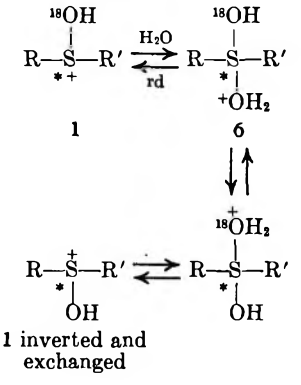
X	p-XC6H4SOMe, rel k_{ex} in HCl–dioxane[a]	p-XC6H4SOMe, rel $k_{reduction}$ in HOAc–H2O–HI[b]	p-XC6H4SOMe, rel $k_{reduction}$ in HClO4–H2O–HI[c]	p-XC6H4SOPh, rel k_{ex} in 75.4% H2SO4[d]	p-XC6H4SOCH2Ph, rel k_{ex} in Ac2O[e]
CH3O	2.2	1.5	1.2	6.0	0.9
CH3	1.6	1.4	1.4	0.8	0.9
H	1.0	1.0	1.0	1.0	1.0
Cl	0.5	0.5	0.5	1.1	0.8
NO2	0.2	0.2	0.2	1.3	1.1

[a] This research. [b] Reference 26. [c] Reference 27. [d] Reference 2. [e] Reference 3a.

reaction, in contrast to the known[16] first-order iodide ion dependence in a somewhat different reaction medium, but this mechanism could account for the fact that rates of racemization are lower than rates of reduction by a factor of about 30 in some cases.[28]

For racemization and exchange reactions of sulfoxides in 75.4% sulfuric acid in acetic anhydride, $k_{ex}/k_{rac} \cong 0.5$, in contrast to the value of about one for the hydrochloric acid catalyzed reaction (see Table I). The substituent effect pattern is also very different, as can be seen by comparing the smooth trend in the first column of Table V with the erratic results in the last two columns. These two lines of evidence complement each other and are probably best rationalized by a mechanism in which 1 (or the –OAc analog in Ac_2O) can react with water (or AcO^- in Ac_2O) in a rate-determining step to give rapidly equilibrating sulfoxide hydrate conjugate acids (or a symmetrical sulfoxide–Ac_2O addition compound in Ac_2O) (Scheme II). In such a mechanism, every exchange would result in *inversion* at sulfur, so the *racemization* rate would be twice the exchange rate, as observed.[2,3a] Since substituents should have opposite effects on the formation of 1 and its reaction with a nucleophile (Cl^-, H_2O, AcO^-, see above), it is not surprising that erratic substituent effect results should be observed.[2,3a] The results obtained in this research and those of others in dilute acids in the absence of chloride ion seem to be best explained by a mechanism of this type. In the presence of chloride ion, a much better nucleophile than water toward sulfur, 1 reacts to form primarily 2 rather than 6.

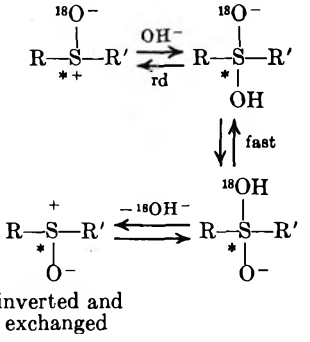
SCHEME II



In more concentrated sulfuric acid,[13] and apparently also in phosphoric acid,[10] trichloroacetic acid,[11] and N_2O_4,[3b] yet another racemization and exchange mechanism is involved, in which 1 is further protonated on oxygen to give, by loss of water or the radical cation $H_2O\cdot^+$ in a rate-determining step, a transitory dication, R–$^+$S$^+$–R′, or radical cation, R–$\dot{S}^+$–R′. Oae and coworkers have discussed the evidence for this mechanism quite extensively.[2,3b,10,11,13,14] A negative ρ behavior would certainly be expected for reactions taking place by this mechanism, and most of the scattered data available are in accord with this view,[3b,10,11,13] although the variation with substituent is surprisingly small, even for radical cation formation. Some esr data appear to favor the radical cation rather than the dication mechanism.[2,13,20]

In addition to the three distinct acid-catalyzed mechanisms for oxygen-18 exchange between sulfoxides and water discussed above, the last entry in Table III makes it clear that a base-catalyzed mechanism is also operative. The simplest mechanism for such a reaction would involve addition of hydroxide ion to the sulfoxide sulfur (numerous other mechanisms, *e.g.*, one involving rate-determining proton abstraction from the sulfoxide methyl group, might be considered, but the one bit of data available does not justify extensive speculation); see Scheme III. Although no substituent effect or comparative k_{ex} *vs.* k_{rac} studies have as yet been carried out under basic conditions, reaction by the above mechanism would be predicted to give $k_{ex}/k_{rac} = 0.5$ and a positive ρ. In a similar manner, a neutral path for the exchange might also be envisioned, but reaction by it should certainly be very slow, and there is currently no experimental evidence to support such speculation.

SCHEME III



It is perhaps noteworthy to mention that the nmr chemical shifts of the methyl protons of the para-substituted phenyl methyl sulfoxides show the expected correlation with substituent, the $\delta_{TMS}^{CHCl_3}$ values being 2.55, 2.55, 2.66, 2.69, and 2.75 for the substituents CH_3O, CH_3, H, Cl, and NO_2, respectively.

(28) D. Landini, F. Montanari, G. Modena, and G. Scorrano, *Chem. Commun.*, 3 (1969).

Experimental Section

Preparation of Oxygen-18 Enriched Para-Substituted Phenyl Methyl Sulfoxides.—Unenriched *p*-methoxy-, *p*-methyl-, unsubstituted, *p*-chloro-, and *p*-nitrophenyl methyl sulfoxides were prepared by treatment of the corresponding thiophenols with dimethyl sulfate in alkaline solution,[29] followed by oxidation of the sulfides to the sulfoxides using hydrogen peroxide in acetic acid. The sulfoxides were distilled under reduced pressure or recrystallized until their physical constants agreed with those given in the literature. All samples were determined to be at least 99.5% pure by glc and nmr analyses.

The above sulfoxides were prepared in oxygen-18 enriched form by hydrogen chloride catalyzed exchange with water-^{18}O in dioxane solution. A 5-g sample of the unenriched sulfoxide was dissolved in 150 ml of dioxane, and 20 ml of 1.2 *N* hydrochloric acid containing 1.54% oxygen-18 in the water was added. The solution was heated in a 75 ± 0.2° oil bath for 4 hr for the *p*-methoxy and *p*-methyl compounds, and for 20 hr for the *p*-nitro, *p*-chloro, and unsubstituted compounds. The reaction mixture was poured into 100 ml of cold chloroform. The water layer was separated and the chloroform layer was washed with 20 ml of water, with 5% sodium hydroxide, and then with water again. The chloroform solution was dried over sodium sulfate the solvent was removed, and the residue was distilled under reduced pressure or recrystallized from methanol. The purities of the recovered sulfoxides were over 99% as shown by glc analyses or nmr spectroscopy. The oxygen-18 contents were determined to be 1.38, 1.43, 1.54, 1.25, and 1.11 excess atom per cent for the *p*-methoxy-, *p*-methyl-, unsubstituted, *p*-chloro-, and *p*-nitrophenyl compounds, respectively. For the *p*-methoxy compound the excess atom per cent value given is corrected (experimental excess times 2) for dilution by the methoxy oxygen. For the *p*-nitro compound, it seemed possible that the nitro group oxygens might undergo exchange. Fry and Lusser[30] found no oxygen-18 exchange for a group of aromatic nitro compounds under a variety of conditions, but no sulfoxide-substituted nitro compounds were included in their study. Accordingly, the overall oxygen-18 enrichment of the recovered *p*-nitrophenyl methyl sulfoxide was determined, the sulfoxide was reduced to the nitro-substituted sulfide by the procedure of Landini, Montanari, Hogeveen, and Maccagnani,[26] and the oxygen-18 enrichment (now of the nitro group only) was determined again. A small amount of oxygen-18 enrichment (about 5% of the sulfoxide oxygen enrichment in the longest time experiments) was found in the nitro group, and appropriate dilution (experimental excess times 3) and nitro group oxygen enrichment corrections were made.

Oxygen-18 Analyses.—Oxygen-18 analyses were carried out by the method of Rittenberg and Ponticorvo[31] as modified by Anbar and Guttmann[32] and in this laboratory. Samples of about 20 mg of the compounds to be analyzed were pyrolyzed with about 100 mg of a mixture of mercuric cyanide and mercuric chloride in sealed tubes at 500° for 7 hr. The tubes were opened in a vacuum system, and the carbon dioxide was distilled twice, utilizing 5,6-benzoquinoline to remove the hydrogen chloride and other acidic gases formed in the pyrolysis. The purified carbon dioxide was analyzed for oxygen-18 in a mass spectrometer by recording the intensities of the *m/e* 44 and 46 peaks. The oxygen-18 content of the carbon dioxide is given by the formula

$$\text{atom \% oxygen-18} = \frac{R}{2 + R} \times 100$$

where R is the 46/44 *m/e* ratio. To correct for day-to-day instrumental variations in the operation of the mass spectrometer, a standard sample of tank carbon dioxide (taken to be 0.204 atom % oxygen-18, the normal abundance ratio) was analyzed prior to each set of analyses, and all samples were normalized to the 0.204 value. These correction factors were seldom very large, being in the range of 1.022–1.041. For each case, the normal abundance atom per cent, 0.204, was substracted from the measured atom per cent value to give the excess atom per cent.

Preliminary Experiments.—In preliminary experiments solutions of about 0.6 mmol of *p*-methoxyphenyl methyl sulfoxide-^{18}O in 3 ml of dioxane were brought to temperature in a constant-temperature bath, and 0.4 ml portions of various aqueous acid solutions were added. After 24 hr in the constant-temperature bath, the mixtures were poured into cold chloroform. The water layers which separated were removed by pipette, and the chloroform solutions were washed with alkali and water. The chloroform solutions were dried over sodium sulfate and the solvent was removed. The residues were kept in a vacuum desiccator. The purities of the recovered sulfoxides were determined by gas chromatography and nmr spectroscopy, and in all cases were over 99%. The results of the oxygen-18 analyses in these preliminary experiments are listed in Table II.

Kinetic Experiments.—The procedure for the kinetic experiments was substantially the same as that used for the preliminary experiments, except that the amounts of the various -substrates, solvents, and reagents were increased by a factor of ten, and aliquots were removed from the reaction solution when it had reached bath temperature (zero time sample) and at various appropriate times after that. These aliquots were worked up and analyzed as described above. Representative per cent excess oxygen-18 analytical data as a function of time for the determination of the rate of hydrochloric acid catalyzed exchange between water and *p*-nitrophenyl methyl sulfoxide-^{18}O are as follows: 0.948%, 0 time; 0.873%, 0.5 hr; 0.868%, 1 hr; 0.810%, 2 hr; 0.612%, 5 hr; 0.372%, 10 hr. Individual points were generally reproducible to ±0.005 in excess atom per cent.

Treatment of Kinetic Data.—The first order rate expression for a simple exchange reaction is given[33] by

$$-\ln (1 - F) = k_{ex}t$$

where k_{ex} is the observed first-order rate constant for exchange. F is defined as the fraction of exchange and is calculated from the equation

$$F = \frac{(^{18}O_0) - (^{18}O_t)}{(^{18}O_0) - (^{18}O_\infty)}$$

where $(^{18}O_0)$ = atom fraction in sulfoxide at time zero, $(^{18}O_t)$ = atom fraction in sulfoxide at time t, and $(^{18}O_\infty)$ = atom fraction in sulfoxide at infinite time.

The values for the oxygen-18 contents at infinite time were calculated as the percentages of total oxygen-18 to total exchangeable oxygen in the system (not including the dioxane, methoxy, or nitro oxygens). For all cases, the calculated values were used as the infinite time values. Since the nitro group oxygen-18 exchange was so much slower than that of the sulfoxide oxygen, for the purposes of these short time calculations it was assumed that the excess oxygen-18 in the nitro group did not decrease during the reaction.

Plots of $(1 - F)$ *vs.* time were linear up to 60–70% reaction in all cases, with relatively little scatter of the points. The rate constants for the various reactions were calculated from the slopes of the lines in these plots, using the method of least squares. These rate constants are summarized in Tables III and IV.

Registry No.—Hydrogen chloride, 7647-01-0; oxygen-18, 14797-71-8; water, 7732-18-5.

(29) H. Gilman and M. J. Beaber, *J. Amer. Chem. Soc.*, **47**, 1449 (1925).
(30) A. Fry and M. Lusser, *J. Org. Chem.*, **31**, 3422 (1966).
(31) D. Rittenberg and L. Ponticorvo, *J. Appl. Rad. Isotopes*, **1**, 208 (1956).
(32) M. Anbar and S. Guttmann, *ibid.*, **5**, 233 (1959).
(33) A. Frost and R. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1963, Chapter 8.

N-Monoalkylation of Sulfonamides

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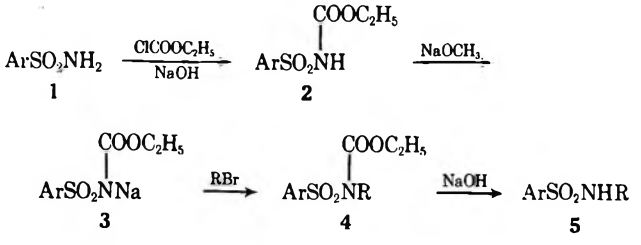
The present paper describes a reliable two-stage process for preparing N-monoalkyl sulfonamides **5** from the corresponding alkyl bromide without going through the alkylamine. The method calls for alkylation of the sodio derivative **3** of sulfonyl carbamate **2**, followed by mild saponification and decarboxylation of the resulting ethyl *N*-(arylsulfonyl)carbamate (**4**) to give **5**.

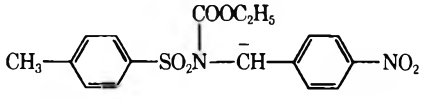
This work started when a need arose for a practical source of *N*-(3-bromallyl)benzenesulfonamide.[1b] Attempts to prepare 3-bromallylamine failed, so that we could not combine benzenesulfonyl chloride with the amine in the usual way. We then considered the alternate way of alkylating benzenesulfonamide directly with 1,3-dibromopropene. Use of the sodio derivative of benzenesulfonamide, even in excess, gave only the dialkylation product, *N*,*N*-di(3-bromallyl)benzenesulfonamide.[2] The silver salt with 1,3-dibromopropene also gave no sign of the desired monoalkyl compound. With direct alkylation showing little promise, we sought a way of blocking one of the sulfonamide position, and this approach led eventually to sequence **1**–**5** (Scheme I).

SCHEME I



1 **2** **3** **4** **5**

The generality of this method was tested with several bromides. Tables I and II summarize the results, which show that a variety of alkyl bromides can be converted to *N*-monoalkyl sulfonamides in a straightforward way, with the complication of mixtures avoided altogether. Arylsulfonamides combine smoothly with ethyl chloroformate to give the necessary blocked intermediates, the ethyl *N*-(arylsulfonyl)carbamates. Although we did not try the reaction, there seems to be no reason to expect difficulty with alkylsulfonamides. Alkylations **3** to **4** were conducted in various solvents, under various conditions, with yields of alkylation product **4** ranging from 27 to 88%. The only compound that failed to yield a product was trimethylbromoethylammonium bromide. The saponification–decarboxylation step **4** to **5** occurred smoothly to give the monoalkyl product **5** in feasible yield (*cf.* Table II). The exceptions were ethyl *N*-(*p*-nitrobenzyl)-*N*-(*p*-toluenesulfonyl)carbamate, which gave 38% of monoalkyl sulfonamide, and ethyl *N*-(*p*-phenylphenacyl)-*N*-(*p*-toluenesulfonyl)carbamate, which gave only a trace of product. Only with these two carbamates was a deep color observed during the saponification step **4** to **5**. Possibly formation of the corresponding carbanions, *e.g.*, **6**, complicated the procedure.



6

Experimental Section

General.—Temperatures are uncorrected. The infrared absorption data were obtained from double-beam instruments, with wavenumbers calibrated against polystyrene. Most curves were obtained with the compounds in chloroform or carbon tetrachloride solutions, some from mineral oil mulls. Nuclear magnetic resonance curves were obtained at 60 MHz, with chemical shifts reported in parts per million downfield from tetramethylsilane. Analyses for elements were performed by Galbraith Laboratories, Knoxville, Tenn., Spang Microanalytical Laboratory, Ann Arbor, Mich., and Scandinavian Microanalytical Laboratory, Herlev, Denmark. Thin layer chromatography made use of silica gel layers from Gelman Instrument Co. (type SG) or from Eastman Kodak Co. (type $K_{301}R$ or Chromogram Sheet 6060), with fluorescence or iodine vapor for bringing out the spots. Volatile solvents were removed routinely in a rotary evaporatory under water pump pressures and at temperatures just above room temperature.

Ethyl *N*-(Arylsulfonyl)carbamate (2).—Ethyl *N*-(benzenesulfonyl)carbamate, precipitated by acidifying the alkaline mixture in which it was formed from ethyl chloroformate and benzenesulfonamide,[3] was obtained in 69% yield. The melting point was 107–109° before and after crystallization from methanol (lit.[3] mp 108–110°).

Anal. Calcd for $C_9H_{11}NO_4S$: C, 47.16; H, 4.80. Found: C, 47.20; H, 4.68.

This carbamate (as in **2**) shows ir absorptions ($CHCl_3$) at 1155 and 1350 (SO_2N), 1750 (C=O), and 3390 cm^{-1} (NH); nmr ($CDCl_3$) δ 1.15 (t, 3, J = 8.0 Hz, CH_2CH_3), 4.15 (q, 2, J = 8.0 Hz, OCH_2CH_3), and 7.8 ppm (m, 6, NH plus aromatic H's).

Ethyl *N*-(*p*-toluenesulfonyl)carbamate, prepared from *p*-toluenesulfonamide essentially according to the directions given for the phenyl compound, was obtained as white crystals; mp 80–82° (lit.[4] 75–77°; 82–84°); ir ($CHCl_3$) 1160, 1350, 1750, and 3390 cm^{-1}.

Sodio Derivative of Ethyl *N*-(Arylsulfonyl)carbamate (3).[5]—The sodium salt was obtained as a white solid, mp 220–222°, in 59–75% yield by neutralizing the corresponding carbamate (30

(1) (a) To whom correspondence should be addressed at Boston University. (b) S. K. Dheer, unpublished work at Boston University. Dr. Dheer first worked out and used the general carbamate approach as described in this paper.

(2) *A priori*, mixtures of unchanged sulfonamide, monoalkylated sulfonamide, and dialkylated sulfonamide would always have to be contended with, the ratio of products being dependent on the relative rates of the first and the second alkylation [*cf.* D. Klamann, G. Hofbauer, and F. Drahowzal, *Monatsh. Chem.*, **83**, 870 (1952); Z. Földi, *Chem. Ber.*, **55**, 1535 (1922); M. de Montmollin and P. Matile, *Helv. Chim. Acta*, **12**, 870 (1929); D. H. Peacock and U. C. Dutta, *J. Chem. Soc.*, 1303 (1934)]. Preparation of monoalkyl compounds in this way may also be further complicated by the insolubility of certain monoalkylated sulfonamides in alkali, in which case separating the monoalkyl from the dialkyl sulfonamide becomes troublesome [see references in W. J. Gensler and J. C. Rockett, *J. Amer. Chem. Soc.*, **77**, 3262 (1955)].

(3) F. J. Marshall and M. V. Sigal, Jr., *J. Org. Chem.*, **23**, 927 (1958).

(4) E. S. Levchenko, E. S. Kozlov, and A. V. Kirsanov, *Chem. Abstr.*, **56**, 4654a (1962) [*Zh. Obshch. Khim.*, **31**, 2381 (1961)]; K. Lanyi and Zs. Szabo, *Chem. Abstr.*, **56**, 7194 (1962) [*Acta Chim. Acad. Sci. Hung.*, **29**, 85 (1961)].

(5) O. C. Billeter, *Chem. Ber.*, **37**, 690 (1904).

Table I

Ethyl *N*-(Alkyl)-*N*-(arylsulfonyl)carbamate (4) by Alkylating the Sodio Derivative of Ethyl *N*-(Arylsulfonyl)carbamate (3)

$$ArSO_2\overset{COOC_2H_5}{\underset{|}{N}}-Na \xrightarrow{RBr} ArSO_2\overset{COOC_2H_5}{\underset{|}{N}}-R$$

Alkyl bromide, g (mmol)	Sodio deriv, g (mmol)	Solvent (ml)	Time, hr; temp[n]	Yield[b] of product, %
$BrCH{=}CHCH_2Br$, 10 (50)	12.6 (50)[a]	CH_3OH plus H_2O	*c*	27[a]
p-$NO_2C_6H_4CH_2Br$, 0.18 (0.83)	0.25 (1.0)[a]	DMSO (3)	2¼; *ca.* RT[d]	85[a]
p-$C_6H_5C_6H_4\overset{O}{\overset{\|}{C}}CH_2Br$, 1.9 (6.9)	2.0 (8.0)[a]	DMSO	2⅓; RT[e]	62[a]
$C_2H_5OOCCH_2Br$, 0.52 (3.1)	1.0 (4.1)[a]	DMSO (8)	50; RT[f]	87[a]
$C_6H_5CH_2Cl$, 2.3 (18)	5.3 (20)[g]	DMSO (27)	20; RT[h]	58[g]
p-$BrC_6H_4CH_2Br$, 5.2 (21)	6.0 (23)[g]	DMSO (40)	6¼; RT[i]	80[g]
$C_6H_5CH{=}CHCH_2Br$, 2.0 (10)	2.9 (11)[g]	Acetone–water 9:1 (25)	16; RT[j]	~80[g]
$CH_3CH_2CH_2CH_2Br$, 0.68 (5)	1.5 (5.5)[g]	DMF (20)	16; RT[k]	~60[g]
$C_6H_5CH_2CH_2Br$, 1.9 (10)	2.9 (12)[g]	DMF (40)	18; RT[l]	88[g]
$(CH_3)_3\overset{+}{N}CH_2CH_2Br\ \overset{-}{Br}$, 2.46 (10)	2.92 (11)[g]	DMSO (30)	24; RT	0[m]

[a] Benzenesulfonyl derivative. [b] No special effort was made to determine optimal conditions. [c] After the reaction mixture in 250 ml of methanol had been stirred for 19 hr at room temperature, water (150 ml) was added and the temperature was held at the boiling point for 12 hr. Volatiles were removed *in vacuo* at 50°, and the residue was extracted with benzene. The carefully dried extract was freed of solvent, and the residue was chromatographed through neutral alumina with benzene as eluent. Solvent-free ethyl *N*-(3-bromoallyl)-*N*-(benzenesulfonyl)carbamate was obtained as a viscous water-white oil (4.7 g), homogeneous according to thin layer chromotography; $n^{24}D$ 1.5436; ir (CCl_4) 3075, 3050 (BrCH=CHR), 1737 (C=O), 1375, and 1175 cm^{-1}; nmr (CCl_4) δ 1.15 (t, 3, J = 6.0 Hz, CH_2CH_3), 4.10 (q, 2, J = 6.0 Hz, CH_2CH_3), 4.40 (q, 2, J = 6.0 Hz, CH_2N), 6.30 (m, 2, olefinic H's), and 7.70 ppm (m, 5, aromatic H's). *Anal.* Calcd for $C_{12}H_{14}BrNO_4S$: C, 41.38; H, 4.02. Found: C, 41.59; H, 4.02. [d] Adding 15 ml of water to the reaction mixture precipitated essentially pure ethyl *N*-(*p*-nitrobenzyl)-*N*-(benzenesulfonyl)carbamate, which melted at 110–112° before crystallization from aqueous methanol and at 111.5–112.5° after crystallization; ir ($CHCl_3$) 1730, 1520, 1375, 1350, and 1170 cm^{-1}; nmr ($CDCl_3$) δ 1.10 (t, 3, J = 7.0 Hz, CH_2CH_3), 4.10 (q, 2, J = 7.0 Hz, CH_2CH_3), 5.10 (s, 2, NCH_2), 7.4–8.2 (m, 9, aromatic H's). *Anal.* Calcd for $C_{16}H_{16}N_2O_6S$: C, 52.74; H, 4.43. Found: C, 52.54; H, 4.32. The same product was obtained in 66% yield when the reaction solvent was boiling aqueous ethanol. [e] Dilution of the reaction mixture (protected from air) with 125 ml of water gave a sticky solid, which after crystallization from 95% ethanol appeared as yellow crystals of ethyl *N*-(*p*-phenylphenacyl)-*N*-(benzenesulfonyl)carbamate (1.8 g), mp 145–147°. The same product was obtained in 45% yield when the alkylation was performed with hot aqueous ethanol. Crystallization from aqueous acetone furnished analytically pure material; mp 150.5–152°; ir ($CHCl_3$) 1735, 1700, 1360, 1170 cm^{-1}. *Anal.* Calcd for $C_{23}H_{21}NO_5S$: C, 65.23; H, 5.00. Found: C, 65.41; H, 4.80. [f] Benzene extraction of the reaction mixture that had been diluted with water, followed by removal of solvent from the extract, left residual white ethyl *N*-(carbethoxymethyl)-*N*-(benzenesulfonyl)carbamate (0.86 g), which melted at 52.5–54.5° before and at 56.5–58° after crystallization from chloroform–petroleum ether (bp 30–60°); ir ($CHCl_3$) 1735, 1360, 1170 cm^{-1}; nmr ($CDCl_3$) δ 0.97–1.35 (m, 6, $2CH_3$), 3.9–4.5 (m, 4, $2OCH_2$), 4.55 (s, 2, NCH_2), 7.55–8.1 ppm (m, 5, aromatic H's). *Anal.* Calcd for $C_{13}H_{17}NO_6S$: C, 49.52; H, 5.43. Found: C, 49.70; H, 5.55. [g] *p*-Toluenesulfonyl derivative. [h] The reaction mixture (nitrogen atmosphere) was diluted with water and extracted with ether. The extract was rinsed with bicarbonate and with water, then dried and stripped of solvent. Refrigeration of the residue for several days gave an oil–solid mixture that was pressed on filter paper and washed with cold petroleum ether. The resulting ethyl *N*-benzyl-*N*-(*p*-toluenesulfonyl)carbamate (3.5 g, mp 52–55°) was recrystallized from petroleum ether to furnish white, crystalline product; mp 56–58°; ir ($CHCl_3$) 1725, 1355, 1168 cm^{-1}. *Anal.* Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74. Found: C, 61.52; H, 5.86. [i] The product, isolated by diluting the reaction mixture with water and extracting with ether, was crystallized from aqueous methanol to give ethyl *N*-(*p*-bromobenzyl)-*N*-(*p*-toluenesulfonyl)carbamate (80%); mp 84–85°; ir ($CHCl_3$) 1720, 1350, 1170 cm^{-1}; nmr ($CDCl_3$) δ 1.11 (t, 3, J = 7.0 Hz, CH_2CH_3), 2.38 (s, 3, $ArCH_3$), 4.09 (q, 2, J = 7.0 Hz, CH_2CH_3), 4.94 (s, 2, NCH_2), 7.1–7.7 ppm (m, 8, aromatic H's). *Anal.* Calcd for $C_{17}H_{18}BrNO_4S$: C, 49.53; H, 4.40. Found: C, 49.37; H, 4.24. [j] The crude, solvent-free product (2.9 g, 81%), obtained by ether extraction of the reaction mixture that had been diluted with water, consisted according to thin layer chromatography (R_f 0.43 with benzene solvent) essentially of a single product; actually, hydrolysis of this material gave *N*-cinnamyl-*p*-toluenesulfonamide in the same yield and quality as hydrolysis of the purified product. Column chromatography over Fisher alumina using first ligroin and then benzene afforded 0.9 g of colorless oily ethyl *N*-(cinnamyl)-*N*-toluenesulfonyl)carbamate showing a single thin layer chromatographic spot (R_f 0.43); $n^{25}D$ 1.5920; ir ($CHCl_3$) 1720, 1340, 1160 cm^{-1}; nmr ($CDCl_3$) δ 1.16 (t, 3, J = 7.0 Hz, CH_2CH_3), 2.37 (s, 3, $ArCH_3$), 4.12 (q, 2, J = 7.0 Hz, CH_2CH_3), 4.60 (d, 2, J = 6.0 Hz, NCH_2), 6.50 (m, 2, olefinic H's), 7.1–7.9 ppm (m, 9, aromatic H's). *Anal.* Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89. Found: C, 63.49; H, 6.06. [k] The solvent-free product isolated from its ether extract appeared as a near-colorless oil (1.0 g, 71%), $n^{25}D$ 1.5075, estimated by thin layer chromatography to be more than 80% pure. Column chromatography as in footnote *j* gave 0.38 g (26%) of colorless oily ethyl *N*-butyl-*N*-(*p*-toluenesulfonyl)carbamate, homogeneous according to thin layer chromatography (R_f 0.35); $n^{25}D$ 1.5082; ir ($CHCl_3$) 1720, 1345, 1170 cm^{-1}; nmr ($CDCl_3$) δ 0.97 (d, J = 6 Hz, $CH_2CH_2CH_3$), 1.20 (d, J = 7 Hz, OCH_2CH_3), 1.6 (m, $CH_2CH_2CH_3$), 2.40 (s, 3, $ArCH_3$), 3.7–4.3 (m, 4, NCH_2 plus OCH_2), 7.25 and 7.77 ppm (two d's, J = 9 Hz, aromatic H's). The δ 0.97–1.6 ppm signals integrate to a total of 10 protons. *Anal.* Calcd for $C_{14}H_{21}NO_4S$: C, 56.16; H, 7.07. Found: C, 56.14; H, 7.17. [l] The crude product obtained as described in footnote *j* emerged as an oil, which after standing for a day afforded pure, white crystals of ethyl *N*-(phenethyl)-*N*-(*p*-toluenesulfonyl)carbamate (3.8 g); mp 77–78°; ir ($CHCl_3$) 1720, 1345, 1160 cm^{-1}; nmr ($CDCl_3$) δ 1.15 (t, 3, J = 7.0 Hz, CH_2CH_3), 2.40 (s, 3, $ArCH_3$), 3.00 (deformed t, 2, J = 8.0 Hz, (NCH_2), 4.05 (m, 4, $ArCH_2$ plus OCH_2), 7.3 (m, C_6H_5), 7.73 ppm (d, J = 8 Hz, $CH_3C_6H_4$). The last two signals correspond to a total of 9 protons. *Anal.* Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09. Found: C, 62.35; H, 6.31. [m] The starting trimethyl(bromoethyl)ammonium bromide was recovered to an extent of 88%. The same process using aqueous ethanol as solvent and a 16-hr reflux period led to a 79% recovery of starting material. [n] RT = room temperature.

TABLE II

N-ALKYLARYLSULFONAMIDE (*cf.* 5) BY HYDROLYSIS AND DECARBOXYLATION OF ETHYL *N*-(ALKYL)ARYLCARBAMATE (*cf.* 4)

$$ArSO_2\overset{\displaystyle COOC_2H_5}{\underset{\displaystyle |}{N}}R \longrightarrow ArSO_2NHR$$

Carbamate (R), g (mmol)	NaOH [and solvent (ml)]	Time, hr; temp[k]	Yield of product, %[a]
BrCH=CHCH$_2$–,[b] 3.5 (10)	2.9 g [C_2H_5OH (400) + H_2O (200)]	21; RT[c]	93[b]
p-BrC$_6$H$_4$CH$_2$–,[d] 0.40 (1.0)	3% aq NaOH (10) [C_2H_5OH (15) + THF (5)]	15^1/$_2$; RT[e]	85
C$_6$H$_5$CH$_2$–,[d] 1.7 (5.2)	1% aq NaOH (100) [C_2H_5OH (200)]	17^1/$_2$; stir[f] RT	83
p-NO$_2$C$_6$H$_4$CH$_2$–,[b] 1.5 (4.1)	5% aq NaOH (40) [THF (15)]	20^1/$_2$; stir[g] RT	38[b]
C$_6$H$_5$CH=CHCH$_2$–,[d] 0.24 (0.69)	1% alc NaOH (15)	4; reflux[h]	78
CH$_3$CH$_2$CH$_2$CH$_2$–[d]	1% alc NaOH	4; reflux[i]	74
C$_6$H$_5$CH$_2$CH$_2$–[d]	1% alc NaOH	4; reflux[j]	76
p-C$_6$H$_5$C$_6$H$_4$COCH$_2$–[d]	1% alc NaOH	4; reflux	<1

[a] No special effort was made to find optimal conditions. [b] Refers to the benzenesulfonyl derivative. [c] Most of the alcohol solvent was removed under reduced pressure, and the aqueous residue was acidified with 5% hydrobromic acid. The ether extract from this acid mixture was washed with water and with bicarbonate solution, dried, and stripped of all volatiles. The residual water-white, viscous *N*-bromoallylbenzenesulfonamide (2.6 g) was homogeneous by thin layer chromatography (R_f 0.26 with benzene); n^{26}D 1.5712; ir (neat) 3300, 3075, 1625, 1325, 1165 cm^{-1}; nmr (CCl_4) δ 3.55 (q, 2, $J \cong 5$ Hz, CH_2N), 6.00 (m, 3, olefinic H's plus NH), 7.60 ppm (m, 5, aromatic H's). *Anal.* Calcd for $C_9H_{10}BrNO_2S$: C, 39.13; H, 3.62; N, 5.07. Found: C, 39.24; H, 3.54; N, 5.11. [d] Refers to the *p*-toluenesulfonyl derivative. [e] The reaction mixture, after acidification with 5% hydrochloric acid, was concentrated *in vacuo* at room temperature. Filtration afforded white crystals of analytically pure *N*-(*p*-bromobenzyl)-*p*-toluenesulfonamide; mp 115–117°; ir ($CHCl_3$) *ca.* 3500, 1330, 1160 cm^{-1}. *Anal.* Calcd for $C_{14}H_{14}BrNO_2S$: C, 49.42; H, 4.15. Found: C, 49.59; H, 4.36. [f] When alcohol was removed from the hydrolysis reaction mixture, the glistening white crystals of product were collected on the funnel (0.7 g, mp 109–111°). Acidification of the filtrate gave more of the same white material (0.4 g, mp 112–113°); ir ($CHCl_3$) 3360, 1332, 1160 cm^{-1}. *N*-Benzyl-*p*-toluenesulfonamide prepared from *p*-toluenesulfonyl chloride and benzylamine melted at 111–112°; the mixture melting point was 111–113°. [g] *N*-(*p*-Nitrobenzyl)-benzenesulfonamide, isolated as described in footnote *e*, showed mp 121.5–122.5°. In another preparation, crystallization of the product from aqueous methanol brought the melting point to 122–123.5°; ir ($CHCl_3$) 3390, 1520, 1348, and 1160 cm^{-1}. *Anal.* Calcd for $C_{13}H_{12}N_2O_4S$: C, 53.42; H, 4.14. Found: C, 53.28; H, 4.20. [h] The hydrolysis reaction mixture, diluted with 25 ml of water, was extracted thoroughly with benzene. The benzene solution was shaken with 5% aqueous sodium bicarbonate, 5% hydrochloric acid, and water, dried, and finally stripped of solvent. The residual white crystalline *N*-cinnamyl-*p*-toluenesulfonamide showed mp 110–111° [P. A. Briscoe, F. Challenger, and P. S. Duckworth, *J. Chem. Soc.*, 1755 (1956), and E. E. Schweizer, L. D. Smucker, and R. J. Votral, *J. Org. Chem.*, **31**, 467 (1966) report mp 108–109 and 110°]; ir ($CHCl_3$) 3500, 1330, 1160 cm^{-1}. [i] The isolation procedure followed footnote *h* except that ether was used for extraction instead of benzene. White *N*-butyl-*p*-toluenesulfonamide was obtained with mp 40–41°. A sample of the same material prepared from *p*-toluenesulfonyl chloride and butylamine and crystallized from aqueous methanol melted at 40–42° both before and after mixing with the hydrolysis product. [j] By following essentially the same procedure as given in footnote *i*, *N*-phenethyl-*p*-toluenesulfonamide was obtained as white needles, mp 65–66° [G. R. Proctor and R. H. Thomson, *J. Chem. Soc.*, 2302 (1957), and M. S. Kharasch and H. M. Priestley, *J. Amer. Chem. Soc.*, 61, 3425 (1939), report mp 66 and 67°]; ir ($CHCl_3$) *ca.* 3400, 1330, 1160 cm^{-1}. [k] RT = room temperature.

g, 0.13 mol) with sodium (3.0 g, 0.13 g-atom) dissolved in methanol (750 ml); ir 1175 and 1375 (SO_2N) and 1660 cm^{-1} (C=O).

Anal. Calcd for $C_9H_{10}NNaO_4S$: C, 43.03; H, 3.98. Found: C, 43.30; H, 4.09.

Crystallization raised the melting point to 221–223°. Adding hydrochloric acid to an aqueous solution of the sodium derivative regenerated ethyl *N*-(benzenesulfonyl)carbamate, mp 108.5–109.5°.

The sodio derivative of ethyl *N*-(*p*-toluenesulfonyl)carbamate was prepared in 95% yield in a manner analogous to that used with the phenyl compound.

Alkylation of Sodio Derivatives 3.—Generally the sodio derivative was stirred with the alkyl bromide (in slight molar deficiency) in solvents such as methanol, aqueous ethanol, and dimethyl sulfoxide for periods ranging from 2 hr to 2 days. In most of the preparations, water was added after the reaction period, and the product was collected by filtration or by extraction. Table I gives details.

***N*-Alkylarylsulfonamides (5).**—The carbamates **4** were hydrolyzed and decarboxylated by exposure to sodium hydroxide, generally with stirring. Acidification precipitated the monoalkyl sulfonamide **5**. Table II presents details.

1,3-Dibromopropene. A. By Allylic Bromination of 1-Bromopropene.—According to its gas–liquid chromatographic assay, the 1-bromopropene used here consisted of one part cis material and eight parts trans. A mixture of 1-bromopropene (100 g, 0.83 mol), *N*-bromosuccinimide (147 g, 0.83 mol) and benzoyl peroxide (0.61 g) in carbon tetrachloride (750 ml) was boiled and stirred for for 2 hr under a blanket of nitrogen. The cooled mixture was filtered, and the filtrate was fractionated through a short vacuum-jacketed Vigreux column. The product, 1,3-dibromopropene, weighed 105 g (64%), boiled at 62–69° (30 mm) [lit.[6] bp 60–66° (25 mm)], and showed two peaks in gas–liquid chromatography with retention times the same as those from the dehydration procedure.

B. From 1,3-Dibromo-2-hydroxypropane.—Phosphorus pentoxide (9.8 g, 0.069 mol) was added in small portions over a 3-hr period to 1,3-dibromo-2-hydroxypropane (10.0 g, 0.040 mol) in a moisture-protected flask. The mixture was stirred during the addition until, when most of the reagent was in, the increased viscosity made stirring impossible. After standing for 0.5 hr at room temperature, the mixture was warmed on the steam bath for 1 hr and then allowed to cool. Ice (250 g) was added followed by 5% aqueous sodium hydroxide until the mixture was basic. Extraction with ether gave a solution of the crude product, which was rinsed three times with water, twice with 2 *N* hydrochloric acid, several times with saturated aqueous bicarbonate, finally with water, and was then dried with sodium sulfate. Fractionation through a 6-in. Vigreux column gave 1.9 g (21%) of the desired 1,3-dibromopropene, n^{26}D 1.5600 (lit.[6] n^{25}D 1.552–1.557), bp 150–156° (lit.[7] bp 156°).

Anal. Calcd for $C_3H_4Br_2$ (cis and trans): C, 18.00; H, 2.00; Br, 80.00. Found: C, 18.02; H, 2.02; Br, 80.03.

The 1,3-dibromopropene, as a cis–trans mixture, showed two peaks of roughly equal area in gas–liquid chromatography; ir (CCl_4) 3070 and 3080 (RCH=CHR), 1620 cm^{-1} (RCH=CHBr); nmr (CCl_4) δ 3.95 (m, 2, CH_2Br), 6.40 ppm (m, 2, olefinic H's).

Dehydration of 1,3-dibromo-2-hydroxypropane with phosphorus oxybromide[7] instead of phosphorus pentoxide offered no advantage.

A higher fraction (2.1 g, 17%) proved to be 1,2,3-tribromopropane, n^{26}D 1.5800 (lit.[8] n^{18}D 1.584), bp 220° (lit[7] bp 220°), nmr (CCl_4) δ 3.85 (d, 4, J = 3 Hz, $2CH_2Br$), 4.30 ppm (quintet, 1, J = 3.0 Hz, CHBr), and was homogeneous according to gas–liquid chromatography.

Anal. Calcd for $C_3H_5Br_3$: C, 12.81; H, 1.78; Br, 85.41. Found: C, 12.84; H, 1.80; Br, 85.45.

1,3-Dibromopropene with the Sodio Derivative of Benzenesulfonamide.—A mixture of 1,3-dibromopropene (10 g, 0.050 mol), benzenesulfonamide (12 g, 0.075 mol), sodium hydroxide

(6) Compare A. T. Bottini, B. J. King, and J. M. Lucas, *J. Org. Chem.*, **27**, 3688 (1962), who utilize the procedure of F. L. Greenwood, M. D. Kellert, and J. Sedlak, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 108, for the allylic bromination of 2-heptene.

(7) J. v. Braun and M. Kuhn, *Chem. Ber.*, **58**, 2168 (1925). Stanley M. Klainer and Joseph Casella contributed to developing this preparation of 1,3-dibromopropene, which develops less tar and shows better reproducibility than the preferred phosphorus oxybromide method of Braun and Kuhn.

(8) I. M. Heilbron, Ed., "Dictionary of Organic Compounds," Vol. 3, Oxford University Press, New York, N. Y., 1934, p 809.

(2.0 g, 0.050 mol), water (400 ml), and 95% alcohol (700 ml) was stirred for 18 hr. After several separation steps, the only alkali-soluble material that could be identified was unchanged benzenesulfonamide (0.8 g). Other products included a trace of solid (40 mg) whose melting point (123–125°) and infrared absorption spectrum agreed with those of diphenyl sulfone; a trace of oil whose R_f value suggested its identity as unchanged 1,3-dibromopropene; 3.7 g (19%) of *N,N*-di(3-bromallyl)benzenesulfonamide with R_f (benzene) 0.58 and with n^{25}D 1.5801; and 3.1 g (15%) of *N,N*-di(3-bromallyl)benzenesulfonamide with R_f (benzene) 0.28 and with n^{22}D 1.5704. The absorption curves for the last two materials were essentially the same, both showing ir (neat) 3075, 1613, 1350, 1170 cm^{-1}; nmr (CCl_4) δ 3.82 (q, 4, J = 4 Hz, $2CH_2N$), 6.15 (m, 4, olefinic H's), and 7.60 ppm (m, 5, aromatic H's). A roughly 1:1 mixture of the last two materials was analyzed.

Anal. Calcd for $C_{12}H_{13}Br_2NO_2S$: C, 36.46; H, 3.29; Br, 40.51. Found: C, 36.42; H, 3.33; Br, 40.70.

1,3-Dibromopropene with the Silver Derivative of Benzenesulfonamide.—The silver salt was prepared[9,10] by adding silver nitrate (0.25 g, 1.5 mmol) in 2 ml of water to a stirred solution of benzenesulfonamide (0.2 g, 1.5 mmol) and sodium hydroxide (0.6 g) in 2 ml of water. The resulting brown-yellow silver derivative of benzenesulfonamide was collected, washed with 95% alcohol and ether, and dried in a desiccator. The derivative weighed 0.33 g and showed mp 220–230° dec.

A heterogeneous mixture of 1,3-dibromopropene (0.2 g, 1 mmol), the silver derivative (0.32 g, 1.2 mmol), and ether (45 ml) was stirred at room temperature for 16 hr. Processing the reaction mixture afforded no sign of *N*-(3-bromallyl)benzenesulfonamide. According to thin layer chromatographic evidence, the viscous oily product contained *N,N*-di(3-bromallyl)benzenesulfonamide. This was substantiated by recovery of the same material from column chromatography (neutral alumina) and comparing its nmr curve with the corresponding material obtained from the sodio derivative. The neat crude oil before separation showed an ir peak at 3200 cm^{-1}, an indication that a propargyl group might be present.

(9) A. Hantzsch and E. Voegelen, *Chem. Ber.*, **34**, 3142 (1901).
(10) J. Casella, unpublished work at Boston University.

Registry No.—2 (Ar = Ph), 32111-09-4; 2 (Ar = $C_6H_4CH_3$-*p*), 5577-13-9; 3 (Ar = Ph), 32111-11-8; 4 (Ar = Ph, R = CH_2CH=$CHBr$), 32111-12-9; 4 (Ar = Ph, R = $CH_2C_6H_4NO_2$-*p*), 32207-42-4; 4 (Ar = Ph, R = CH_2COC_6HPh-*p*), 32111-13-0; 4 Ar = Ph, R = CH_2COOEt), 32120-94-8; 4 (Ar = $C_6H_4CH_3$-*p*, R = CH_2Ph), 32120-95-9; 4 (Ar = $C_6H_4CH_3$-*p*, R = $CH_2C_6H_4Br$-*p*), 32120-96-0; 4 (Ar = $C_6H_4CH_3$-*p*, R = CH_2CH=$CHPh$), 32120-97-1; 4 (Ar = $C_6H_4CH_3$-*p*, R = Bu), 32120-98-2; 4 (Ar = $C_6H_4CH_3$-*p*, R = CH_2CH_2Ph), 32120-99-3; 5 (Ar = Ph, R = CH_2CH=$CHBr$), 32121-00-9; 5 (Ar = $C_6H_4CH_3$-*p*, R = $CH_2C_6H_4Br$-*p*), 10504-96-8; 5 (Ar = $C_6H_4CH_3$-*p*, R = CH_2Ph), 1576-37-0; 5 (Ar = Ph, R = $CH_2C_6H_4NO_2$-*p*), 32121-03-2; 5 (Ar = $C_6H_4CH_3$-*p*, R = C_2CH=$CHPh$), 32121-04-3; 5 (Ar = $C_6H_4CH_3$-*p*, R = CH_2CH_2Ph), 5450-75-9; *cis*-1,3-dibromopropene, 32121-06-5; *trans*-1,3-dibromopropene, 32121-07-6; 1,2,3-tribromopropane, 96-21-9; *N,N*-di(3-bromoallyl)benzenesulfonamide, 32111-14-1.

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Nucleosides. LXXI. 3′-Amino-3′-deoxyhexopyranosyl Nucleosides. VI. Reactions of Some Mesyloxy Nucleosides[1]

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The reactions of variously mesylated 1-(3-acetamido-3-deoxy-β-D-glucopyranosyl)uracils were studied in order to examine the behavior of their neighboring groups. Alkaline treatment of the 2′,4′,6′-trimesylate (**5**) afforded the 4′,6′-dimesylate of the 2,2′-anhydromanno nucleoside **6** which by further alkaline treatment gave 1-(3-acetamido-2,6-anhydro-3-deoxy-4-*O*-mesyl-β-D-mannosyl)uracil (**7**) and 1-(3-acetamido-2,6-anhydro-3-deoxy-β-D-talosyl)uracil (**8**). The nmr spectra of **7** and **8** were consistent with the bicyclo[2.2.2]octane system for their carbohydrate moieties. Treatment of 1-(3-acetamido-3-deoxy-2,4-di-*O*-mesyl-6-*O*-trityl-β-D-glucosyl)-uracil (**12**) with alkoxide gave the 2,2′-anhydro derivative **13** which was detritylated and then hydrolyzed in alkali to the 4′-mesylate of 3′-acetamidomannosyluracil (**16**). When nucleoside **12** is detritylated first and then treated with alkali, 1-(3-acetamido-3-deoxy-β-D-talopyranosyl)uracil (**19**) was formed which was converted to its crystalline triacetate **20** and hydrogenated to the 5,6-dihydro derivative **21**. The unexpected chemical shift for the 2′-acetoxy signal in the nmr spectrum of **21** relative to **20** was observed and assigned unequivocally by the syntheses and spectral comparison with the analogous 4′,6′-di-*O*-deuterioacetylated derivatives **25** and **26**. Attempts to prepare a 2,6′-anhydro nucleoside **31** from 1-(3-acetamido-2-*O*-acetyl-3-deoxy-β-D-glucopyranosyl)uracil (**29**) *via* its 4′,6′-dimesylate **30** was not successful. The 6′-mesylate **32** of **29** was displaced by nucleophiles (iodide or benzoate) to afford compounds **33**. Treatment of the 6′-iodo analog **33b** with silver fluoride in pyridine afforded 1-(3-acetamido-2-*O*-acetyl-3,6-dideoxy-β-D-*xylo*-hex-5-enopyranosyl)uracil (**34**).

Previous reports[2] from this laboratory dealt with the syntheses of 3′-deoxy-3′-aminohexopyranosyl nucleosides from uridine as part of a program designed toward the synthesis of analogs of certain nucleoside antibiotics[2e] containing amino sugar moieties. It was found[2d] that treatment of 1-(3-acetamido-3-deoxy-2-*O*-mesyl-4,6-*O*-benzylidene-β-D-glucosyl)uracil (**1**) with sodium methoxide gave the crystalline 2,2′-anhydromannosyl nucleoside **2** in high yield as the sole product rather than the oxazoline derivative **3**

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08748).

(2) (a) K. A. Watanabe and J. J. Fox, *Chem. Pharm. Bull.*, **12**, 975 (1964); (b) *J. Org. Chem.*, **31**, 211 (1966); (c) K. A. Watanabe, J. Beranek, H. A. Friedman, and J. J. Fox, *ibid.*, **30**, 2735 (1965); (d) ref 2b; (e) J. J. Fox, K. A. Watanabe, and A. Bloch, *Progr. Nucleic Acid Res. Mol. Biol.*, **5**, 251 (1966).

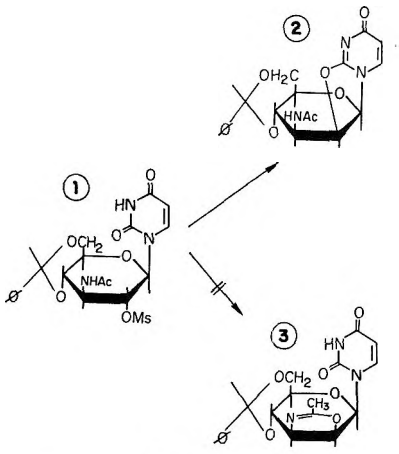

Figure 1.

(Figure 1). Thus, in spite of the known facility for oxazoline formation with other acetamido sugars vicinally substituted with sulfonyloxy groups, it is clear that (with uracil as the aglycon) the 2-carbonyl participated preferentially to the 3′-acetamido group in an intramolecular displacement reaction. The potential biological importance[2e] of amino sugar nucleoside derivatives warranted a study of the chemistry of variously mesylated 3′-acetamido-3′-deoxyhexosyluracils in order to examine the behavior of their neighboring groups (Figure 2).

Crystalline 1-(3-acetamido-3-deoxy-tri-*O*-mesyl-β-D-glucopyranosyl)uracil (**5**) was prepared by exhaustive mesylation of 3′-acetamidoglucosyluracil (**4**). This derivative (**5**) contains three leaving groups and several potential intramolecular nucleophiles. The behavior of this compound toward sodium ethoxide as well as that of mono- and di-O-mesylated nucleosides derived from **4** was investigated.

When treated with 1 equiv of sodium methoxide in anhydrous methanol, compound **5** was rapidly converted to 2,2′-anhydro-1-(3-acetamido-4,6-di-*O*-mesyl-β-D-mannosyl)uracil (**6**) with uv spectral characteristics (λ_{max}^{MeOH} 247 and 277 mμ) similar to those of **2**. Compound **6** was treated further with 2 equiv of anhydrous sodium ethoxide. After prolonged refluxing, approximately 1.2 equiv of alkoxide was consumed and five products were detected on tlc. After addition of water to the reaction mixture, only two products were detected by tlc. From this hydrolysate two crystalline products were isolated.

The structure of one of these crystalline products was established as **8** on the basis of the following data: the elemental analyses were consistent with **8**; nmr analyses showed the absence of mesyloxy substituents and the presence of only three replaceable protons suggestive of an anhydro-type structure. The uv spectrum was also similar to that for uracil nucleosides[3] and differed from those for anhydro nucleoside structures[4] involving a bridge between the aglycon and sugar moiety. The presence of a doublet at low field (NH, τ 2.31, J = 7.2 Hz) which disappears after addition of CD_3COOD showed that the 3′-acetamido group was not involved in a bridged structure. The configuration at C-2′ was readily established by the small H-1′–H-2′ coupling (anomeric signal, τ 4.02, $J_{1',2'} \cong 0$) diagnostic for the gauche relationship. Treatment of **8** with acetic anhydride in pyridine gave a crystalline mono-*O*-acetate (**9**) whose nmr spectrum showed a doublet for one proton at τ 4.80 ($J \cong 10.0$ Hz). This large coupling rules out C-2′ as the position of attachment of the acetoxy group since H-2′ is cis to both H-1′ and H-3′. Finally, since only *one* proton was shifted downfield upon O-acetylation of **8** to **9**, position 6 can be excluded as the site of acetylation. Therefore, the acetoxy group is linked to C-4′, and, consequently, the anhydro linkage in the sugar moiety must exist between the 2′ and 6′ positions. The large H-3′–H-4′ coupling of ~10.0 cps is indicative of a cis relationship for these protons in a dioxabicyclo[2.2.2]octane[5] system.

The structure of the second crystalline product was established as 1-(3-acetamido-2,6-anhydro-3-deoxy-4-*O*-mesyl-β-D-mannosyl)uracil (**7**) on the following evidence: the uv spectrum of **7** resembled uridine. The nmr spectrum showed that it contained one acetyl and one mesyl group and only two replaceable protons (τ 1.05 and −1.66) attributable to the acetamido and N-3 protons, respectively. The anomeric singlet at τ 4.15 and a narrow downfield singlet at τ 5.09 (integrated for one proton) suggested that the mesyloxy function was attached to C-4′ and that the anhydro bridge was formed between the 2′ and 6′ positions. In such a dioxabicyclo[2.2.2]octane system, H-3′ and H-4′ or H-4′ and H-5′ are no longer in trans-diaxial arrangement so that the H-4′ signal would become a singlet. However, the nmr data alone are not sufficient to establish the structure definitively since, if the chemical shifts of H-2′ and H-3′ were very close, both the H-1′ and H-4′ signals may become singlets even though the couplings between H-1′ and H-2′ or between H-3′ and H-4′ are large.[6]

When compound **7** was treated with sodium iodide in acetone followed by catalytic hydrogenation, starting material was recovered unchanged, whereas even under milder conditions the trimesylate **5** afforded the 6-deoxy derivative **10**. It is thus clear that the mesyloxy substituent in **7** is not on C-6′ and, since **7** was derived from intermediate **6**, the mesyloxy substituent is linked to C-4′. Compound **7** was also recovered unchanged after treatment with acetic anhydride in pyridine, which ruled out the possibility of free hydroxyl functions in this compound. These data establish the structure of **7**.

The overall conversion of the 2′,2-anhydro nucleoside **6** to the 2′,6′-anhydro derivatives **7** and **8** is readily explained by the alcoholysis or hydrolysis at C-2 of **6** to generate an intermediate 2′-hydroxy anion, which displaces the 6′-mesyloxy function by attack on the primary carbon atom to form a 2′,6′-anhydro linkage. Such an intramolecular displacement is eminently feasible if the intermediate structure containing the 2′-hydroxy anion adopts a boat (*B2*) conformation which would place the C-2′ substituent very close to C-6′. The conversion of **7** to **8** probably occurs by participation of the 3′-acetamido group *via* an oxazo-

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(4) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **30**, 476 (1965).

(5) J. S. Webb, R. W. Broschard, D. B. Cosulich, J. H. Mowat, and J. E. Lancaster, *J. Amer. Chem. Soc.*, **84**, 3183 (1962); K. Tori, Y. Takano, and K. Kitahonoki, *Chem. Ber.*, **97**, 2798 (1964); K. Somekawa, T. Matsuo, and S. Kumamotoi *Bull. Chem. Soc. Jap.*, **42**, 3499 (1969).

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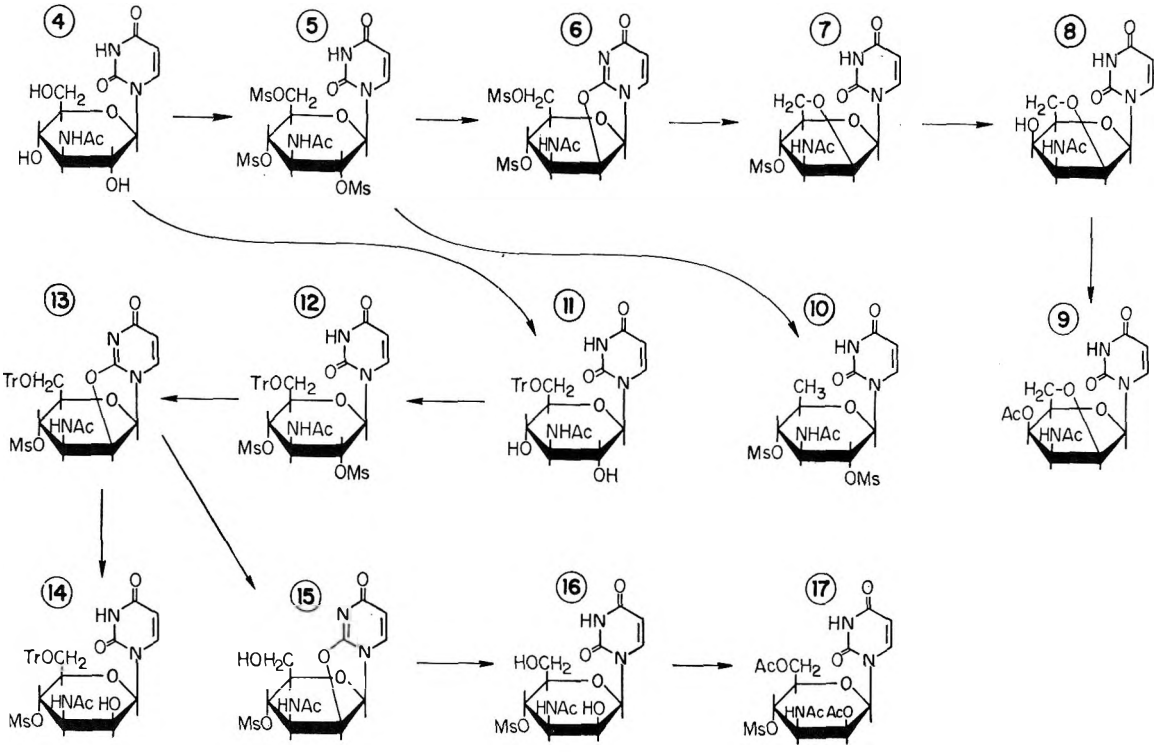

Figure 2.

line intermediate. The formation of **7** and **8** from **6** is somewhat akin to the conversion of 2′,3′-epoxylyxofuranosyluracils by sodium benzylate to 2′,5′-anhydro nucleosides previously reported from this laboratory.[7] The formation of a (2.2.2)bicyclic system is of interest. Only few examples of bicyclic [2.2.2] carbohydrates have been reported.[8-11]

It is noted that a 3′,6′-cyclic linkage with a nitrogen bridge was not detected among the products formed by reaction of **6** with sodium methoxide even though the formation of such a pyrrolidine derivative could be expected from an internal displacement of the C-6′ mesyloxy group by attack of acetamide nitrogen.[12] An examination of molecular models shows that a *B1* or *1C* conformation would be required for the pyrrolidine linkage to form. However, such conformations would not bring the acetamido nitrogen as close to C-6′ as does the *2B* conformation for the 2′-oxygen atom. The preferential formation of a 2′,6′-anhydro bridge may be due, therefore, mainly to the closer proximity of the 2′-hydroxy anion to C-6′.

Compound **8** was a very minor component formed in the overall reaction of **6** with sodium methoxide. When the reaction time was prolonged, the proportion of **8** was increased. This phenomenon is readily explained by intermediate **7** which slowly undergoes solvolysis[13] to the talo nucleoside **8** *via* an oxazoline derivative formed by anchimeric assistance of the 3′-acetamido group. When compound **5** was refluxed with 3 equiv of *aqueous* sodium hydroxide for 20 hr, compound **8** was isolated as the major product (*ca.* 30%) together with a small amount of **7**.

It was of interest to study the behavior of a di-*O*-mesyl derivative in which there is no leaving group at the 6′ position. For this purpose the 6′-*O*-trityl derivative **11** was prepared from **4**. After mesylation, the di-*O*-mesylate **12** was treated with 1 equiv of sodium methoxide in methanol. Crystalline 2,2′-anhydro nucleoside **13** was obtained which upon hydrolysis gave the mono-*O*-mesyl-*manno* nucleoside **14**. It is noted that, as in the reaction of **1** → **2** or **5** → **6**, the reaction of **12** with alkoxide also produced a 2,2′-anhydro linkage (compound **13**), showing again the preference of the 2-carbonyl over other potential intramolecular nucleophiles in the initial displacement. Detritylation of **14** gave 1-(3-acetamido-3-deoxy-4-*O*-mesyl-β-D-mannopyranosyl)uracil (**16**). The di-*O*-acetate **17** was prepared from **16** as a reference compound for nmr studies. Compound **16** was obtained alternatively from **13** by detritylation to **15** followed by hydrolysis. The nmr data of these compounds are listed in Table I.

Attempts to displace the 4-mesyloxy group of **13** in boiling methanolic sodium methoxide by anchimeric assistance of the 3′-acetamido function were unsuccessful and starting material was recovered unchanged. However, it was found (Figure 3) that after detritylation of **12** to **18**, displacement of both mesyloxy functions in alkali occurred with the formation of a nucleoside (**19**). This compound was purified and acetylated to its crystalline tetraacetate and characterized as the talo nucleoside (**20**). The conversion of **18** to **20** may have involved anchimeric assistance of the 6′-hydroxy anion, rather than the 3′-acetamido group, in displacement of the 4′-mesyloxy substituent.

(7) I. L. Doerr, J. F. Codington, and J. J. Fox, *J. Org. Chem.*, **30**, 467 (1965).

(8) L. N. Owen and P. A. Robins, *J. Chem. Soc.*, 326 (1949).

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(10) N. A. Hughes, *J. Chem. Soc. C*, 2263 (1969).

(11) A. Zabacova and J. Jary, *Collect. Czech. Chem. Commun.*, **29**, 2042 (1964).

(12) H. H. Baer and T. Neilson, *Can. J. Chem.*, **43**, 840 (1965), suggested the possible formation of a 3,6-pyrrolidine structure by reaction of methyl 3-acetamido-2,3-dideoxy-4,6-di-*O*-mesyl-β-D-glucoside with sodium acetate in refluxing methanol; however, their data did not permit definitive structural assignment.

(13) B. R. Baker and R. E. Schaub, *J. Amer. Chem. Soc.*, **77**, 5900 (1955).

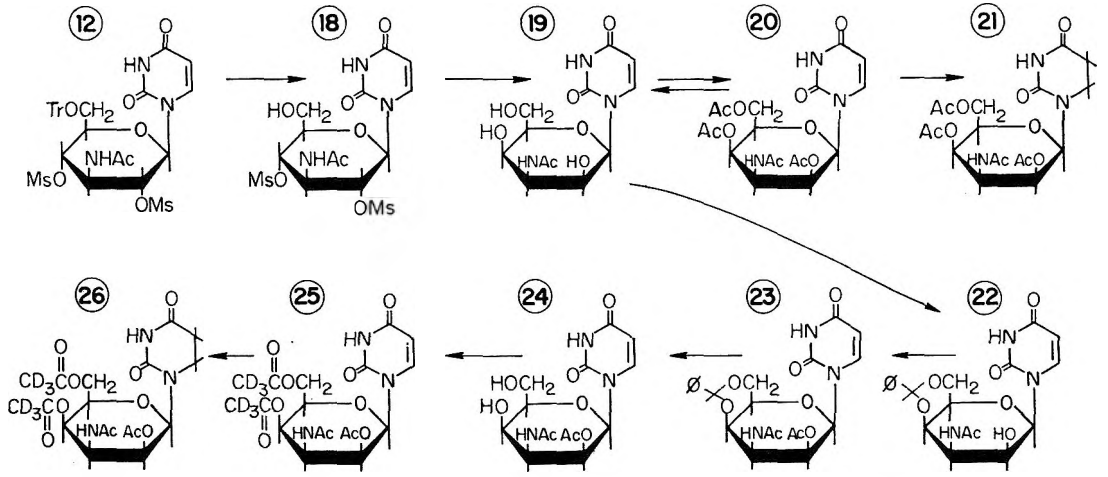

Figure 3.

TABLE I.—NUCLEAR MAGNETIC RESONANCE PARAMETERS FOR 1-(3-ACETAMIDO-3-DEOXY-β-D-HEXOSYL)URACILS[a]

	Chemical shifts, τ											Coupling constants, Hz			
Compd	H-1′	H-2′	H-3′	H-4′	H-5′	H-6′,6″	H-5	H-6	3′-NH	NAc	OAc	OMs	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$
4	4.56	———	6.2–6.5; 4(H)	———		6.58	4.27	2.38	2.09	8.11			9.0			
5	3.91		5.32			5.60	4.28	2.48	1.91	8.12		6.92, 6.85, 6.77	8.0			
7	4.15	5.85	5.61	5.09			4.36	2.10	1.05	8.04		6.70	~0			
8	4.02	———	5.4–6.3; 5(H)	———			4.22	2.04	2.31	8.05			~0		~0	
9	3.94	5.82	5.35	4.80	6.19	5.82	4.32	2.03	1.94	8.09	7.92		~0	1.5	10.0	2.0
10	4.00					8.76	4.25	2.39	1.67	8.10		6.90, 6.77	8.0			
11	4.54						4.28	2.46		8.13			8.0			
12	3.97						4.14	3.38	1.86	8.12		7.15, 6.89	~9.0			
14	4.12			5.37			4.22	2.40	2.00	8.12		7.08	~0		9.0	
17	3.81	4.83	5.25	5.17	5.7	5.7	4.33	2.52	1.80	8.15	7.95, 7.90	6.73	~0	~2.0	~9.0	
18	4.04	5.30		~5.3		~6.4	4.29	2.47	1.93	8.14		6.94, 6.80	8.5			
19	4.35		5.91	6.1		6.6	4.42	2.31	2.07	8.07			~0			
20	4.01	4.92	5.28	4.92	5.57	5.92	4.38	2.56		8.17	8.00, 7.97, 7.88		~1.0	3.5	3.5	4.0
21	4.33	4.95	5.37	4.95		5.93				8.18	8.01, 7.88 (2)		~1.5	3.5	3.5	4.0
22[b]	3.78	5.42	5.02				4.30	1.92	1.15	7.91			~1.0	4.0		
23	3.99	4.94	5.31				4.32	2.47	2.21	8.15	7.96		~1.0	3.5	3.5	
23[b]	3.57	4.02	4.67	——5.5–5.7——			4.18	2.09	1.07	8.23	8.01		~1.0	3.0	3.0	
24[b]	3.63	3.97	~4.9			5.62	4.38	2.10	~1.4	8.18	7.94		~1.0	3.5		
25	4.01	4.92	5.28	4.92	5.57	5.92	4.18	2.56	2.27	8.17	7.97		~1.5	3.5	3.5	4.0
26	4.33	4.95	5.28	4.95		5.93			2.32	8.18	7.88		~1.0	3.5	3.5	4.0
30	3.95	4.83	———	5.1–5.7; 4 (H)	———		4.26	2.40	1.97	8.17	8.08	6.83, 6.77	8.5	10.0		
32	4.17	5.01	———	5.3–6.7; 4 (H)	———		4.32	2.48	2.17	8.18	8.12	6.83	8.5	10.0		
33a	4.18	4.95	——5.7–6.4; 3 (H)——			5.47	4.30	2.47	~2.3	8.17	8.10		8.5	9.5		
33b	4.17	5.08	———	5.5–6.7; 4 (H)	———		4.25	2.58	2.15	8.20	8.12		8.5	9.5		
34	4.24	4.75	——5.6–6.4——			5.23	4.25	2.23	2.03	8.16	8.08		8.5	9.5		

[a] In DMSO unless specified othersie. [b] In pyridine.

Assignment of the talo configuration to **20** is based on the following data: this nucleoside differs in melting point, optical rotation, and ir spectrum from the known tetraacetylated derivatives of the corresponding gluco,[2a,b] manno,[14] and galacto[14] isomers. The nmr spectrum of **20** showed a very narrow doublet for the anomeric proton signal at τ 4.01 ($J_{1',2'} \cong 1.0$ Hz). The narrow signal at τ 4.92 integrated for two protons (H-2′, H-4′), indicating that the couplings between the sugar ring protons are very small. The sextet for the H-3′ signal at τ 5.28 collapsed by deuterioacetic acid treatment to a narrow triplet ($J_{2',3'} \cong 3.5$ cps). These data (Table I) are in good agreement with the talo configuration in which all the sugar ring protons are in a gauche relationship with their neighbors.

The nmr data for **20** do not rule out any one of the two chair conformations (*C1* or *1C*). However, an examination of a Courtauld molecular model of **20** showed that it was impossible to build a *1C* conformation for this compound due to steric hindrance by the three bulky axial substituents which this conformation requires. On the other hand, the *C1* conformational model showed no serious interactions between the bulky functional groups. The nmr data as well as the examination of Courtauld molecular models also rule out any boat conformation because in each of these one of the dihedral angles defined by H-1′–H-2′, H-2′–H-3′, or H-3′–H-4′ must approach 0° and should exhibit a large coupling. Such a large coupling is not shown by the nmr spectrum of **20**. The data described thus far would warrant the assignment of the talo configuration in the *C1* conformation (in DMSO) to **20**.

Previous nmr studies[14] of a host of pyrimidine nucleosides from this laboratory have shown that removal of the anisotropy of the 5,6 double bond by hydrogenation produced an effect on the chemical shift of the C-2′-acetoxy resonance. A generalization was developed from these studies which stated that, in the case of pyranosyl-pyrimidine nucleosides, when the C-2′-acetoxy group and the pyrimidine are in a cis relationship, the C-2′-acetoxy resonance will be shifted upfield by 0.21–0.23 ppm when the 5,6 double bond is hydrogenated. When a trans-diequatorial relationship obtains, a small but significant downfield shift of the C-2′-acetoxy signal occurs upon removal of the unsaturation. This approach was applied to the talo nucleoside **20**.

The nmr spectrum of **20** exhibited four acetyl signals in DMSO-d_6 at τ 8.17, 8.00, 7.97, and 7.88. The 5,6-dihydro derivative **21**, obtained by hydrogenation of **20** over Adams catalyst, exhibited acetyl signals at τ 8.18, 8.01, and 7.88 (the latter signal integrating for six protons). A diamagnetic shift expected for one of the acetoxy resonances in **21** on the basis of earlier studies[14] with nucleosides was not observed. Indeed, these compounds (**20** and **21**) comprise the first example in the pyrimidine nucleoside area of the failure to conform to the generalization on upfield 2′-acetoxy resonance shifts for nucleosides bearing a cis relationship between the aglycon and the 2′-acetoxy group.

It should be noted that the generalizations proposed[14] for pyrimidine nucleosides assumed *a priori* a chair conformation for the carbohydrate and a *substantial* population in the anti conformation (that is, the 5,6 double bond sits over the sugar ring). The failure of the pair **20** and **21** to obey these generalizations may be due to either of the following. (a) The population of conformers in the anti form may deviate substantially from the norm in which the plane of the uracil moiety lies perpendicular to the plane of the sugar ring and the 5,6 double bond "sits over" the sugar ring. Due to the nonbonded interactions inherent in the talo configuration, deformation of the chair and/or twisting the aglycone about the C-1′–N bond to a form more nearly adopted in, say, the 2,2′-anhydro derivative (~90° deflection) can be expected so that the C-2′-acetoxy substituent lies outside the cone of anisotropy produced by the 5,6 double bond. (b) The acetoxy resonance at τ 7.88 of **20** shifted diamagnetically to τ 8.01 in **21** while the two other acetoxy resonances at τ 8.00 and 7.97 gave paramagnetic shifts. In order to examine the latter possibility (b) it is necessary to assign the acetoxy resonances in **20** and **21** with certainty by a synthesis of 1-(4,6-di-*O*-deuterioacetyl-3-acetamido-di-*O*-acetyl-β-D-talopyranosyl)-uracil (**25**, see Figure 3). The acetyl signals for **25** appeared at τ 8.18 and 7.97 and (aside from the absence of C-4′ and C-6′ acetoxy resonances) the rest of the nmr spectrum was identical with that exhibited by the undeuterioacetylated isomer **20**. Hydrogenation of **25** over platinum catalyst proceeded very slowly and after 3 days only ~50% reduction occurred. The acetyl signals of this mixture (**25** and **26**) appeared at τ 8.18, 7.97, and 7.88, integrating approximately in a ratio of 2:1:1 protons respectively. Therefore, the acetyl signal at τ 8.18 is assigned to the *N*-acetyl group because the 2′ substituent should be most affected by the aglycon which is in cis relationship to it. Consequently, the 2′-acetoxy signal is at τ 7.97 in **20** and it is this signal which had moved *downfield* in **21** on removal of anisotropy by reduction of the 5,6 double bond. Thus possibility b is ruled out.

The possibility remains that a substantial population of conformers in **20** and **21** deviate from the anti conformation so that the C-2′ acetoxy group is outside of the positive region of the anisotropic cone produced by the 5,6 double bond. Frič, *et al.*,[15] have shown in ORD studies with pyrimidine nucleosides that the orientation of the 2′ position "exerts a strong influence on the magnitude of the amplitude of the Cotton effect but not in its sign." Emerson, *et al.*,[16] have shown that the effect of inversion of the 2′-hydroxyl group (ribosyl → arabinosyl) is to hold the pyrimidine ring in a more rigid conformation, thereby *increasing* the magnitude of the Cotton effect. The ORD data for the gluco (**27**), manno (**28**), and talo (**20**) nucleosides are given in Figure 4. Thus, while the molar amplitude of the Cotton effect of the manno nucleoside relative to the gluco isomer is increased, the talo isomer is considerably *lower*, contrary to what might be expected from the previous studies.[15,16] However, Emerson[16] has also shown that, as the uracil moiety in nucleosides departs from the anti conformation, the Cotton effect is reduced in amplitude. The ORD

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(15) I. Frič, J. Šmejkal, and J. Farkaš, *Tetrahedron Lett.*, 75 (1966).

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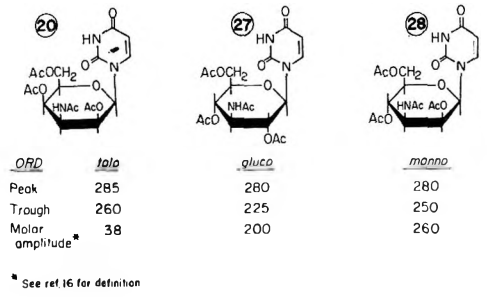

Figure 4.

data in Figure 4 are at least consistent with the hypothesis that the "failure" of **20** and **21** to obey the C-2 -acetoxy shift generalization of Cushley, *et al.*,[14] may be a result of altered conformer populations away from anti in these derivatives; hence ORD studies should accompany nmr studies in cases inconsistent with the acetoxy shift rules.[14]

It is noted that the formation of 2,6′- or 2,4′-anhydro nucleosides was not observed when the 2′,4′,6′-tri-*O*-mesylate (**5**, Figure 2) was treated with alkoxide and, instead, the 2,2′-anhydro derivative **6** was formed *preferentially* as the first step. The 2,2′-anhydro nucleoside **2** previously reported[2d] and those reported herein probably exist in the *C1* conformation. Recently, 2,3′-anhydro-1-(β-D-glycopyranosyl)pyrimidines were synthesized.[17,18] These latter structures probably adopt a *2B* (boat) conformation, though the *1C* conformation is possible but less likely. The hitherto unknown 2,4′-anhydro nucleoside structure would require a *B1* conformation whereas the 2,6′-anhydro isomer (also unknown) could probably take a *1C* or twist conformation.

Attempts to prepare (Figure 5) a 2,6′-anhydro nucleoside (*e.g.*, **31**, R′ = mesyl or H) from the 4′,6′-dimesylate **30** or the 6′-mesylate **32** were not successful. These latter compounds were synthesized readily by exhaustive or by selective mesylation of the known[2d] 1-(3-acetamido-2-*O*-acetyl-3-deoxy-β-D-glucopyranosyl) uracil (**29**). Treatment of the dimesylate **30** with lithium aluminum hydride in tetrahydrofuran (conditions by which the 2,4-dimesylate of methyl 3-benzamido-3,6-dideoxy-α-L-glucoside was converted into the 3,4-epiminogalactoside derivative)[18] caused complete loss of selective absorption in the ultraviolet, indicating that the 5,6 double bond of the aglycon was reduced. Therefore, this reaction was not studied further. Heating of **30** and **32** with potassium *tert*-butoxide in DMF gave intractable mixtures, although under identical conditions 1-(2-deoxy-3,4-di-*O*-mesyl-β-D-*erythro*-pentopyranosyl)uracil afforded a 2,3′-anhydro nucleoside.[17] Reaction of **32** with sodium benzoate in DMF did not afford a 2,6′-anhydro derivative but rather the crystalline 6′-benzoate **33a** in 80% yield. Similarly, treatment of **32** with sodium iodide in DMF afforded the 6′-iodo derivative **33b**. It may be postulated that in the course of reaction of **32** to **33** a 2,6′-anhydro derivative may have been an intermediate, but evidence for such a mechanism is lacking. Indeed, treatment of the 6′-iodo nucleoside **33b** with silver acetate in methanol (conditions which

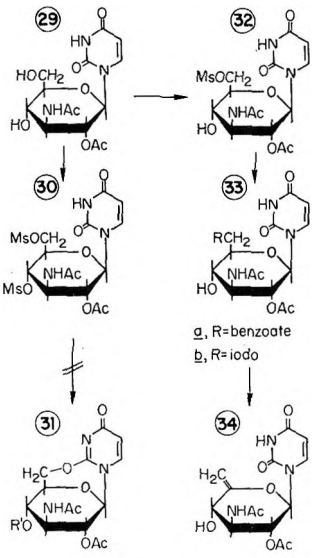

Figure 5.

convert a 5′-iodouridine into a 2,5′-anhydrouridine)[19] gave several products of which the major component was characterized as the 5′,6′-unsaturated derivative **34**. Crystalline **34** was synthesized in good yield from **33b** using silver fluoride in pyridine[20] as the reagent.

Experimental Section

Melting points were determined on a Thomas–Hoover apparatus and are not corrected. Elementary analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by Spang Microanalytical Laboratory, Ann Arbor, Mich. The nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as internal reference. Thin layer chromatography (tlc) was performed on silica gel GF_{254} (Merck) using the following solvent systems: solvent A, acetone–chloroform–water (5:1:1); B, *n*-butyl alcohol–water (84:16); C, chloroform–methanol (9:1). The uv spectra were determined on a Cary Model 15 spectrophotometer.

1-(3-Acetamido-3-deoxy-2,4,6-tri-*O*-mesyl-β-D-glucosyl)uracil (5).—Compound **4**[2a] (9.45 g, 0.03 mol) was dissolved in pyridine (190 ml) and cooled in an ice bath. Mesyl chloride (9.2 ml, 0.12 mol) was added to the stirred solution. The mixture was kept overnight at room temperature and evaporated to dryness. A small amount of pyridine was removed azeotropically with ethanol (100 ml) and the gummy residue was triturated twice with ethanol (50 ml). The ethanol-insoluble material was dissolved in hot water (30 ml) and diluted with hot ethanol (400 ml). The crystals which deposited after cooling the mixture were filtered and washed with 95% ethanol (20 ml). Amber-colored product (**5**, 8.5 g) was obtained in 57% yield: mp 165–168°; $[\alpha]_D$ +40° (c 0.75, H_2O); uv λ_{max}^{MeOH} 255 mμ (ε 10,900), λ_{min}^{MeOH} 226 mμ (ε 3000).

Anal. Calcd for $C_{15}H_{23}O_{13}N_3S_3$: C, 32.78; H, 4.22; N, 7.65; S, 17.50. Found: C, 32.76; H, 4.63; N, 7.59; S, 17.45.

Reaction of Compound 5 with Sodium Ethoxide, to 7 and 8.—A mixture of **5** (8.25 g, 0.015 mol) in ethanol (450 ml) and 0.48 *N* sodium ethoxide (33.5 ml) was refluxed for 30 min. A neutral, clear solution was obtained (uv λ_{max}^{EtOH} 248 and 227 mμ, λ_{min}^{EtOH} 233 mμ). A second mole of sodium ethoxide (0.48 *N*, 31 ml) was added and after 30 min under reflux temperature the reaction was neutral. Finally, sodium ethoxide (0.48 *N*, 12 ml) was added to the mixture and refluxing was continued for 1 hr. Sodium mesylate (3.4 g) precipitated on cooling and was removed by filtration. The filtrate contained five compounds as determined by tlc in solvent A. The filtrate was condensed to ~300 ml, then diluted with water (200 ml) and 1 *N* sodium hydroxide (15 ml). The mixture was warmed to 45–50° for 30

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min. Tlc examination showed that the solution contained two compounds. The mixture was neutralized to pH ~6.0–6.4 with 1 *N* acetic acid (20 ml). After evaporation of the solvent, the residue was dissolved in water (25 ml) and allowed to stand overnight at room temperature, after which colorless crystals (platelets) separated. After recrystallization from ethanol–water, 0.22 g of **8**, mp 260–261°, $[\alpha]_D$ −10° (*c* 0.11, pyridine), was obtained.

Anal. Calcd for $C_{12}H_{15}O_6N_3$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.48; H, 5.10; N, 14.08.

The filtrate of crude **8** (T.O.D.[21] = 91,000) was applied on a column of Dowex 50 (H^+) (500 g) and the column was washed with water (5.6 l.). The uv-absorbing fractions (T.O.D. = 45,400) were collected and concentrated to dryness. The residue (1.55 g) was dissolved in a small amount of water and precipitated by adding six volumes of ethanol. After two recrystallizations by the same procedure, colorless microcrystals of **7** were obtained, 350 mg, mp 175–176°.

Anal. Calcd for $C_{13}H_{17}O_8N_3S \cdot 0.5C_2H_5OH$: C, 42.20; H, 5.06; N, 10.54; S, 8.05. Found: C, 42.58; H, 5.16; N, 10.64; S, 8.13. (The sample contained ethanol as determined by nmr.)

1-(3-Acetamido-2,6-anhydro-3-deoxy-β-D-talopyranosyl)uracil (8).—Compound **5** (2.7 g, 0.0052 mol) was dissolved in a mixture of methanol (54 ml), water (27 ml), and 1 *N* sodium hydroxide (15.6 ml) and the mixture was refluxed for 48 hr. The mixture was evaporated to dryness and the residue was further dried azeotropically by distillation with ethanol. The residue was extracted with boiling ethanol (three 30-ml portions). Sodium mesylate (1.3 g) was obtained as ethanol-insoluble crystals. The ethanol extracts were combined and evaporated to dryness and the residue was crystallized from a small amount of water. Compound **8** separated as colorless crystals, 419 mg (29%), mp 260–261°. The nmr and ir spectra were identical with those of **8** obtained previously.

1-(3-Acetamido-4-*O*-acetyl-2,6-anhydro-3-deoxy-β-D-talosyl)uracil (9).—Acetic anhydride (2.4 ml) was added to a suspension of **8** (0.11 g) in dry pyridine (1.8 ml). The mixture was stirred overnight, after which it was treated with ethanol (2.5 ml). After evaporation of the mixture, the residue was triturated with ether (10 ml). A colorless powder, mp 163–165°, was obtained which was crystallized from ethanol–chloroform (0.1 g, mp 165–167°): $[\alpha]_D$ +15° (*c* 0.78, ethanol); uv λ_{max}^{MeOH} 261 mμ (ε 9200), λ_{min}^{MeOH} 228 mμ (ε 1400).

Anal. Calcd for $C_{14}H_{17}N_3O_7 \cdot H_2O$: C, 48.28; H, 5.17; N, 12.07. Found: C, 48.54; H, 4.91; N, 11.95.

1-(3-Acetamido-3,6-dideoxy-2,4-di-*O*-mesyl-β-D-glucosyl)uracil (10).—A mixture of **5** (0.55 g) and sodium iodide (1.5 g) in acetone (4.5 ml) in a sealed tube was heated on a steam bath for 25 min. After cooling, the precipitated sodium mesylate was filtered and washed with acetone (5 ml). The combined filtrate and washings were evaporated to dryness to a syrup which was then dissolved in 50% aqueous ethanol (20 ml) and hydrogenated at room temperature in the presence of 5% Pd/C catalyst (0.5 g). After consumption of 1 mol of hydrogen (3 hr), the catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in a mixture of ethanol and water and treated batchwise with Dowex 50 (H^+) and Dowex 1 (acetate) to remove sodium and iodide ions. After removal of the resins, the filtrate was evaporated to dryness and the residue was crystallized (0.3 g, mp 176–179° eff) from acetone–ether. Recrystallization of the precipitate from methanol–water gave an analytical sample: mp 188.5–191°; $[\alpha]_D$ +22° (*c* 0.7, H_2O); paper electrophoretic migration, +3.4 cm (borate buffer pH 9.2, 900 V, 3.5 hr).

Anal. Calcd for $C_{14}H_{21}O_{10}N_3S_2 \cdot H_2O$: C, 36.83; H, 4.86; N, 9.21; S, 14.05. Found: C, 36.86; H, 4.82; N, 9.28; S, 14.08.

The presence of one molecule of water of crystallization was shown by nmr spectroscopy.

1-(3-Acetamido-3-deoxy-6-*O*-trityl-β-D-glucopyranosyl)uracil (11).—A mixture of **4** (15.7 g) and trityl chloride (15.4 g) in pyridine (300 ml) was heated at 80° for 6 hr and allowed to remain at room temperature overnight. Another charge of trityl chloride (10.1 g) was added and the mixture was heated to 80° for 5 hr. The cooled mixture was poured into a stirred, ice–water mixture (2.5 l.). The precipitate was collected and triturated with a mixture of ethanol (60 ml) and ether (400 ml) in order to remove tritanol. The insoluble solid (mp 159–162°) was dissolved in acetone (1:1) and diluted with petroleum ether (bp 30–60°) (2 l.). After standing overnight, crystallization of **11** occurred (17.0 g): mp 165–168°; $[\alpha]_D$ +15° (*c* 0.74, MeOH); uv λ_{max}^{MeOH} 252 mμ (ε 11,000); λ_{min}^{MeOH} 239 mμ (ε, 7200). An analytical sample was prepared by recrystallization from ethanol, mp 165–168°.

Anal. Calcd for $C_{31}H_{31}N_3O_7 \cdot {}^2/_3C_2H_5OH$: C, 66.01; H, 5.99; N, 7.14. Found: C, 65.90; H, 5.87; N, 7.40.

1-(3-Acetamido-3-deoxy-2,4-di-*O*-mesyl-6-*O*-trityl-β-D-glucosyl)uracil (12).—Mesyl chloride (4.28 ml) was added to a stirred, ice-cold solution of **11** (9.46 g, 0.017 mol) in pyridine (95 ml). The reaction mixture was kept overnight at room temperature and then poured into an ice–water mixture (1.2 l.) with stirring. The amber-colored precipitate was filtered and washed with a small amount of water. The solid (10.1 g, mp 198–201°) was dissolved in pyridine and treated with charcoal. The hot filtrate was treated with a few drops of water and cooled. Colorless crystals of **12** (7.5 g) precipitated: mp 201–202°; $[\alpha]_D$ +61° (*c* 0.7, pyridine); uv λ_{max}^{MeOH} 257 mμ (ε 10,200), λ_{min}^{MeOH} 240 mμ (ε 7200).

Anal. Calcd for $C_{33}H_{35}O_{11}N_3S_2$: C, 55.52; H, 4.94; N, 5.89; S, 8.98. Found: C, 55.11; H, 5.16; N, 5.75; S, 8.85.

2,2′-Anhydro-1-(3-acetamido-3-deoxy-4-*O*-mesyl-6-*O*-trityl-β-D-mannosyl)uracil (13).—A mixture of **12** (14.3 g, 0.02 mol), methanol (1.2 l.), and 0.47 *N* sodium ethoxide (40 ml) was refluxed gently for 30 min and concentrated to ~70 ml. After dilution of the alcoholic solution with ethyl acetate (120 ml), the precipitate (sodium mesylate, 1.99 g) was removed by filtration. The filtrate was concentrated to a syrup, dissolved in ethanol, and poured into ice–water (700 ml). After filtration, the precipitate (12.9 g) was dissolved in chloroform (50 ml). Tlc (solvent B) showed one major spot accompanied by two small spots. The mixture was applied to an alumina column (500 g, neutral AG 7 grade). The column was washed with a mixture of chloroform and methanol (3:1). Eluted fractions were monitored by tlc and those containing the major spot were combined and evaporated to dryness. The residue was dissolved in chloroform (20 ml) and the solution was diluted with *n*-heptane. A white powder (7.8 g) precipitated, mp 161–164°. This product (**13**) exhibited a shoulder at ~250 mμ in its uv spectrum.

Anal. Calcd for $C_{32}H_{31}O_8N_3S$: C, 62.22; H, 5.06; N, 6.80; S, 5.19. Found: C, 61.93; H, 5.22; N, 6.54; S, 5.02.

1-(3-Acetamido-3-deoxy-4-*O*-mesyl-6-*O*-trityl-β-D-mannosyl)uracil (14).—Compound **13** (5.60 g) was stirred in a mixture of ethanol (400 ml), water (100 ml), and 1 *N* sodium hydroxide (8 ml) for 15 min at room temperature. During this period the uv spectrum of the mixture changed to a uridinelike absorption. The reaction mixture was neutralized with 1 *N* acetic acid (20 ml) to ~pH 6. After evaporation of the solvent, the residue was triturated with water (three 20-ml portions). The almost colorless solid (mp 159–162°) was dissolved in methanol and diluted with water from which product **14** precipitated: 4.3 g; mp 165–168°; uv λ_{max}^{MeOH} 258 mμ, λ_{min}^{MeOH} 242 mμ.

Anal. Calcd for $C_{32}H_{33}O_9N_3S$: C, 60.46; H, 5.23; N, 6.61; S, 5.04. Found: C, 59.98; H, 5.46; N, 6.33; S, 4.93.

2,2′-Anhydro-1-(3-acetamido-3-deoxy-4-*O*-mesyl-β-D-mannopyranosyl)uracil (15).—The trityl derivative (**13**, 2.15 g, 0.0035 mol) was dissolved in a mixture of ethanol (38 ml) and water (49 ml). The mixture was gently refluxed for 3.5 hr and evaporated to dryness. The residue was triturated with water (10 ml) and filtered from trityl alcohol (0.81 g). The filtrate was evaporated to dryness and the colorless residual solid was recrystallized from water to afford needles: mp 194–196°; $[\alpha]_D$ −17° (*c* 0.66, MeOH); uv λ_{max}^{MeOH} 248 and 227 mμ (ε 10,600 and 10,000), λ_{min}^{MeOH} 236 mμ (ε 9700). (For analyses, a small sample was recrystallized from methanol.)

Anal. Calcd for $C_{13}H_{17}O_8N_3S \cdot CH_3OH$: C, 41.26; H, 5.40; N, 10.31; S, 7.86. Found: C, 40.87; H, 5.52; N, 10.17; S, 7.95.

The aqueous mother liquor of recrystallization was adsorbed on a column of Dowex 50 (H^+) (6 ml) and washed with water (1500 ml). The eluate was concentrated to ~3 ml and the solution was kept at 4° for 3 days. Colorless needles (80 mg) separated, mp 190–191°. The ir spectrum of this crystalline material was identical with that of compound **16** prepared from **15**. (See below.)

1-(3-Acetamido-3-deoxy-4-*O*-mesyl-β-D-mannopyranosyl)uracil (16) from 15.—Compound **15** (440 mg) was dissolved in a mixture of dioxane (15 ml), water (15 ml), and 0.1 *N* sodium hydroxide (10 ml). The solution was kept at room temperature for 1 hr, after which it was neutralized with Dowex 50 (H^+) (3 ml). The resin was filtered and washed with water (200 ml). The combined

(21) Total optical density.

filtrate and washings were evaporated to ~1.5 ml and diluted with ethanol (1.5 ml). The mixture was kept at 4° overnight. Colorless needles (298 mg) separated: mp 193–195°; $[\alpha]_D$ +26° (*c* 0.73, H_2O); uv $\lambda_{max}^{H_2O}$ 260 mμ (ε 10,600), $\lambda_{min}^{H_2O}$ 228 mμ (ε, 2000).

Anal. Calcd for $C_{13}H_{19}O_9N_3S \cdot H_2O$: C, 37.95; H, 5.15; N, 10.21; S, 7.79. Found: C, 37.26; H, 5.30; N, 9.96; S, 7.72.

1-(3-Acetamido-2,6-di-*O*-acetyl-3-deoxy-4-*O*-mesyl-β-D-mannosyl)uracil (17).—Compound **16** (250 mg) was acetylated with acetic anhydride (2.5 ml) in pyridine (2 ml) overnight at room temperature. The clear solution was evaporated to dryness and traces of pyridine and acetic anhydride were removed by azeotropic distillation with ethanol. The residual colorless solid was crystallized from methanol–ethanol to yield compound **17**, 220 mg, mp 195°, $[\alpha]_D$ +34° (c 78, MeOH).

Anal. Calcd for $C_{17}H_{23}N_3O_{11}S$: C, 42.76; H, 4.86; N, 8.80; S, 6.71. Found: C, 42.75; H, 4.98; N, 9.06; S, 7.05.

1-(3-Acetamido-3-deoxy-2,4-di-*O*-mesyl-β-D-glucopyranosyl)uracil (18).—Compound **12** (7.13 g, 0.01 mol) was dissolved in warm acetic acid (80 ml). The solution was diluted with water (20 ml) and the mixture was heated on a steam bath for 45 min. After evaporation of the solvent, the residue was partitioned between water (80 ml) and ether (80 ml). The aqueous layer was separated and washed with ether (80 ml), and evaporated to dryness. The residue was crystallized from ethanol. Recrystallization from ethanol yielded pale yellow crystals, 3.21 g (70%), mp 160–161°, $[\alpha]_D$ +39° (*c* 0.82 pyridine).

Anal. Calcd for $C_{14}H_{21}O_{11}N_3S_2$: C, 35.67; H, 4.49; N, 8.91; S, 13.60. Found: C, 35.28; H, 4.61; N, 8.67; S, 13.42.

1-(3-Acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-β-D-talosyl)uracil (20).—Compound **18** (471 mg, 0.001 mol) was dissolved in a mixture of water (8 ml) and 1 *N* sodium hydroxide (1 ml). The mixture was refluxed for 10 min, at which time the reaction mixture became neutral. Another charge of 1 *N* sodium hydroxide (1 ml) was added and the mixture was refluxed for 30 min. The neutral mixture was evaporated to dryness. The residue was dried further by azeotropic distillation with toluene and acetylated with acetic anhydride (2 ml) and pyridine (2 ml) overnight. After evaporation of the solvent, the residue was mixed with chloroform (2 ml) and chromatographed over silica gel G column (10 g, 2.2 × 5 cm) using 10% methanol in chloroform. Compound **20** (187 mg) was obtained as colorless crystals after recrystallization from methanol, mp 186–189°, $[\alpha]_D$ +41° (c 0.96, pyridine).

Anal. Calcd for $C_{18}H_{23}O_{10}N_3$: C, 48.98; H, 5.22; N, 9.52. Found: C, 48.96; H, 5.14; N, 9.49.

1-(3-Acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-β-D-talosyl)-5,6-dihydrouracil (21).—A mixture of compound **20** (200 mg) and platinum oxide (100 mg) in methanol (50 ml) and acetic acid (1 ml) was reduced for 20 hr at room temperature. The catalyst was filtered and the filtrate was concentrated *in vacuo* to a residue which was crystallized from methanol, 172 mg, mp 153–154°, $[\alpha]_D$ 0 (*c* 1.0, MeOH).

Anal. Calcd for $C_{18}H_{25}O_{10}N_3$: C, 48.76; H, 5.64; N, 9.48. Found: C, 48.52; H, 5.81; N, 9.23.

1-(3-Acetamido-3-deoxy-β-D-talopyranosyl)uracil (19).—To the suspension of compound **20** (2.1 g) in methanol (55 ml) was added 1 *N* sodium methoxide (1 ml). A clear solution was obtained immediately. After 3 hr, the mixture was evaporated to dryness and the residue was dissolved in 20 ml of water and treated batchwise with Dowex 50 (H^+) (2 ml). The resin was filtered and washed with a small amount of water. The combined filtrate and washings were evaporated to a syrup which was homogeneous as determined by tlc (solvent B) and nmr spectroscopy, but which did not crystallize. The yield of this syrup (**19**) was quantitative (1.5 g).

1-(3-Acetamido-4,6-*O*-benzylidene-3-deoxy-β-D-talosyl)uracil (22).—Compound **19** (1.13 g) was mixed with ~1.5 g of zinc chloride (freshly fused and pulverized) and freshly distilled benzaldehyde (20 ml). The mixture was shaken for 16 hr and then poured into an ice–water mixture (200 ml). Ether (200 ml) was added to the suspension and the mixture was stirred vigorously for 20 min. The insoluble solid was removed by filtration and washed with ether. Purification from hot methanol gave a colorless powder (850 mg) which did not crystallize but which was homogeneous to tlc. The mother liquor contained a considerable amount of compound **19**, indicating that appreciable debenzylidenation had occurred. The nmr spectrum of the colorless powder was consistent with compound **22**.

1-(3-Acetamido-2-*O*-acetyl-4,6-di-*O*-benzylidene-3-deoxy-β-D-talosyl)uracil (23).—Compound **22** (850 mg) was acetylated with acetic anhydride (1 ml) in pyridine (5 ml) for 2 hr at room temperature. The solvent was removed by evaporation and traces of pyridine and acetic anhydride were removed by codistillation with toluene. The residue was dissolved in a small amount of methanol and the mixture was left overnight at room temperature. A small amount of insoluble material was removed and the filtrate was evaporated to dryness. The residue was triturated with a small amount of water and ether. A colorless powder (500 mg) was obtained which was homogeneous on tlc. The nmr spectrum of this product (see Table I) was consistent with compound **23**.

1-(3-Acetamido-2-*O*-acetyl-3-deoxy-4,6-di-*O*-deuterioacetyl-β-D-talosyl)uracil (25).—Compound **23** (500 mg) was dissolved in 80% acetic acid. After the solution was diluted with 5 ml of water, the mixture was heated on a steam bath for 45 min and then cooled to room temperature. The mixture was shaken in a hydrogen atmosphere in the presence of 5% palladium-on-charcoal catalyst (100 mg) for 30 min. After filtration from catalyst, the filtrate was evaporated to dryness. Traces of acetic acid were removed by azeotropic distillation with toluene. The residue (compound **24**) was dissolved in pyridine (3 ml) and treated with deuterioacetic anhydride (0.5 ml) at room temperature for 1 hr. The solvent was removed by distillation *in vacuo* and the residue was dissolved in a small amount of 10% methanol in chloroform and applied on a column of silica gel G (10 g, 6 × 2 cm). The column was eluted with 10% methanol in chloroform. Appropriate fractions were collected, concentrated to dryness, and crystallized from methanol. The yield of compound **25**, after two recrystallizations from methanol, was 184 mg, mp 186–189°, $[\alpha]_D$ +40° (*c* 0.7, pyridine).

Anal. Calcd for $C_{18}H_{17}D_6O_{10}N_3$: C, 48.32; H, and D, 6.49; N, 9.40. Found: C, 48.49; H and D, 6.27; N, 9.56.

1-(3-Acetamido-2-*O*-acetyl-3-deoxy-4,6-di-*O*-mesyl-β-D-glucosyl)uracil (30).—Compound **29**[2d] (2.5 g, 0.007 mol) was dissolved in pyridine (50 ml). Mesyl chloride (1.1 ml) was added dropwise to the stirred, ice-cold solution. The mixture was kept at 4° for 30 min, after which it remained at room temperature overnight. The solvent was evaporated to dryness and the residue was triturated with 35 ml of ice–water. Crystals separated (2.6 g, 76%) which were filtered and recrystallized from methanol to yield 2.04 g of **30**, mp 199–202° dec, $[\alpha]_D$ +24° (*c* 0.9, pyridine).

Anal. Calcd for $C_{16}H_{23}O_{12}N_3S_2$: C, 37.42; H, 4.51; N, 8.13; S, 12.49. Found: C, 37.34; H, 4.42; N, 8.07; S, 12.48.

1-(3-Acetamido-2-*O*-acetyl-3-deoxy-6-*O*-mesyl-β-D-glucosyl)uracil (32).—To a stirred, cold solution of compound **29** (2.5 g) in pyridine (100 ml) was added mesyl chloride (0.5 ml). After 30 min, ice was added and the mixture was stirred for 5 min. After evaporation of the mixture to dryness, the residue was triturated with ethanol. Product (compound **32**) crystallized, 2.33 g, mp 229–230° dec, $[\alpha]_D$ +16° (*c* 1.2, pyridine).

Anal. Calcd for $C_{15}H_{21}O_{10}N_3S$: C, 41.37; H, 4.86; N, 9.65. Found: C, 41.28; H, 4.87; N, 9.55.

1-(3-Acetamido-2-*O*-acetyl-6-*O*-benzoyl-3-deoxy-β-D-glucosyl)uracil (33a).—A mixture of compound **32** (225 mg) and dry sodium benzoate (144 mg) in DMF (10 ml) was refluxed for 30 min. After cooling, insoluble precipitate was filtered and the filtrate was evaporated to dryness. The residue was extracted with acetone and the acetone extracts were applied to two silica gel PF_{254} plates (20 × 20 cm, 2 mm thick). The plates were developed in a mixture of chloroform and methanol (4:1). The major band was scraped off and extracted with acetone. The acetone extracts were evaporated and the residue was dissolved in ethyl acetate. After removal of a small amount of insoluble material by filtration, the filtrate was concentrated *in vacuo* and the residue was crystallized from ethyl acetate–benzene. Colorless crystals, 207 mg (80%), were obtained which sintered at 143–145° but had no definite melting point, $[\alpha]_D$ +55° (*c* 0.8, pyridine).

Anal. Calcd for $C_{21}H_{23}O_9N_3$: C, 54.66; H, 5.02; N, 9.11. Found: C, 54.21; H, 5.08; N, 9.03.

1-(3-Acetamido-2-*O*-acetyl-3,6-dideoxy-6-iodo-β-D-glucosyl)uracil (33b).—A mixture of compound **32** (1.0 g) and sodium iodide (0.5 g) in DMF (40 ml) was refluxed for 30 min and then evaporated to dryness. The residue was chromatographed over a silica gel G (50 g) column using a chloroform–methanol (10:1) solvent system as the eluent. Appropriate fractions were collected and concentrated to dryness. The residue was crystal-

lized from a small amount of acetone, 530 mg (46%), mp 191–193°, $[\alpha]_D$ +7.2° (*c* 1.3, pyridine).

Anal. Calcd for $C_{14}H_{18}O_7N_3I$: C, 35.99; H, 3.88; N, 8.99. Found: C, 35.93; H, 3.87; N, 8.92.

(1-(3-Acetamido-2-*O*-acetyl-3,6-dideoxy-β-D-*xylo*-hex-5-enopyranosyl)uracil (**34**).—A mixture of compound **33b** (708 mg) and silver fluoride (1.83 g) in pyridine (20 ml) was shaken for 3 hr and filtered. The filtrate was evaporated to dryness and the residue was dissolved in methanol (100 ml). A small amount of insoluble material was removed by filtration. Hydrogen sulfide was bubbled into the methanol solution to precipitate silver ion. The dark mixture was filtered through a Celite bed and the filtrate was concentrated to dryness. The residue was dissolved in a small amount of methanol and applied to two silica gel PF_{254} plates (20 × 20 cm, 2 mm). The plates were developed with chloroform–methanol (4:1). The main band was removed and extracted with acetone–methanol (4:1) and concentrated to dryness. The residue was crystallized from acetone, 297 mg, mp 145–146°, $[\alpha]_D$ −63° (*c* 1.2, pyridine).

Anal. Calcd for $C_{14}H_{17}O_7N_3$: C, 49.56; H, 5.05; N, 12.38. Found: C, 49.40; H, 5.07; N, 12.32.

Registry No.—**4**, 4338-36-7; **5**, 32254-26-5; **7**, 32254-27-6; **8**, 32254-28-7; **9**, 32254-29-8; **10**, 32254-30-1; **11**, 32254-31-2; **12**, 32254-32-3; **13**, 32254-33-4; **14**, 32254-34-5; **15**, 32254-35-6; **16**, 32254-36-7; **17**, 32367-45-6; **18**, 32254-37-8; **19**, 32254-38-9; **20**, 32254-39-0; **21**, 32304-21-5; **22**, 32254-40-3; **23**, 32254-41-4; **24**, 32254-42-5; **25**, 32254-43-6; **26**, 32254-44-7; **30**, 32304-22-6; **32**, 32254-45-8; **33a**, 32254-46-9; **33b**, 32254-47-0; **34**, 32254-48-1.

Nucleosides. LXXIII. Ribosyl Analogs of Chloramphenicol[1]

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The synthesis of *p*-(5-dichloroacetamido-5-deoxy-β-D-ribofuranosyl)nitrobenzene (**20b**) and *p*-(β-D-ribofuranosyl)nitrobenzene 5-phosphate (**12**) from β-D-ribofuranosylbenzene (**6**) are described. Precursor **6** was obtained by condensation of diphenylcadmium with tri-*O*-benzoyl-D-ribofuranosyl chloride (**2**) and the β configuration of **6** was established by periodate and nmr studies. Acetylation and nitration of **6** afforded a mixture of the *o*- and *p*-nitro isomers **10a** and **10b** which was resolved after deacetylation to *o*- and *p*-(β-D-ribofuranosyl)-nitrobenzene (**11a** and **11b**). The para isomer **11b** was acetonated, phosphorylated, and deisopropylidenated to give the 5-phosphate **12**. Acetonation of **6** followed by mesylation, azidation, and reduction afforded the amine **16**. Dichloroacetylation of **16** followed by deisopropylidenation gave (5-dichloroacetamido-5-deoxy-β-D-ribofuranosyl)benzene (**18**) which was converted in two steps to the *o*- and *p*-nitro derivatives **20a** and **20b**.

It was reported[2] that the antibiotic chloramphenicol (a protein synthesis inhibitor) adopts a "curled" conformation (Figure 1) in solution and, as such, resembles the nucleotide, uridine 5′-phosphate. It has been suggested further that the mode of action of this antibiotic may be related to this conformation.[2,3] If this hypothesis is valid, one might expect that *p*-(5-dichloroacetamido-5-deoxy-β-D-ribosyl)nitrobenzene(**20b**) or *p*-(β-D-ribofuranosyl)nitrobenzene 5-phosphate (**12**) may also be inhibitors of protein synthesis. This paper deals with the synthesis of **12** and **20** as part of our program directed toward the preparation of nucleoside analogs of potential biochemical significance.

The glucopyranosylbenzene derivative (**1**, Figure 2) has been prepared by Hurd and Bonner[4] by condensation of poly-*O*-acetyl-α-D-glucosyl chloride with phenylmagnesium bromide. Zhdanov, *et al.*,[5] have prepared ribopyranosylbenzene analogously by using the corresponding ribopyranosyl chloride. The β configuration was assumed for **1**[6] solely by analogy of optical rotation data with a related derivative of the xylo series. With diphenylcadmium as the condensing agent, Hurd and Holysz[7] also obtained compound **1**, albeit in lower yield. Mertes, *et al.*,[8] reacted bis(2,6-dibenzyloxypyridyl-3)cadmium with tri-*O*-benzoyl-D-ribofuranosyl chloride (**2**) and obtained the corresponding 3-ribosylpyridine derivative. Attempts in our laboratory to apply the condensation of phenylmagnesium bromide with **2** in order to prepare **6** were unsuccessful. However, the use of diphenylcadmium with **2** in refluxing benzene solution afforded the "nucleoside" **3** in 20% yield. The major product of this reaction (**2** → **3**) was the sugar ketal **4** which, after saponification with methoxide, afforded the crystalline ketal **5**. Proof of the structure of **5** as 1,2-*O*-diphenylmethylidene-α-D-ribofuranose was obtained by elemental analyses, by nmr measurements, and by acid hydrolysis to benzophenone and ribose. Ketals analogous to **5** had been reported[7] from similar type reactions. Debenzoylation of **3** with sodium methoxide in methanol yielded the unblocked nucleoside **6**.

The β configuration for **3** and **6** was established as follows. Periodate oxidation of **6** afforded the dialdehyde **7**, which was reduced with sodium borohydride to the trialcohol **8**. Deacetylation of **1** followed by a similar oxidation and reduction afforded a trialcohol which was identical (melting point, mixture melting point, optical rotation) with compound **8** obtained from **3**. The nmr spectrum of **1** in pyridine-d_5 and of its deacetylated derivative in DMSO-d_6 all show large splittings for H-1–H-2 ($J \cong 10$ Hz) which establishes definitively the β configuration for **1** and, thereby, the β configuration for **3** and **6**.

Nitration of the tri-*O*-acetate **9** of **6** was accomplished

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08748). Paper LXXII: *Carbohyd. Research*, in press.

(2) O. Jardetzky, *J. Biol. Chem.*, **238**, 2498 (1963).

(3) N. S. Beard, S. A. Armentrout, and A. S. Weisberger, *Pharmacol. Rev.*, **21**, 213 (1969).

(4) C. D. Hurd and W. A. Bonner, *J. Amer. Chem. Soc.*, **67**, 1972 (1945).

(5) Yu. A. Zhdanov, G. A. Dorol'chenko, and L. A. Kubasskaya, *Dokl. Akad. Nauk SSSR*, **128**, 1185 (1959); *Chem. Abstr.*, **54**, 8644 (1960).

(6) W. A. Bonner and C. D. Hurd, *J. Amer. Chem. Soc.*, **73**, 4290 (1951).

(7) C. D. Hurd and R. P. Holysz, *ibid.*, **72**, 2005 (1950).

(8) M. P. Mertes, J. Zielinski, and C. Pillar, *J. Med. Chem.*, **10**, 320 (1967).

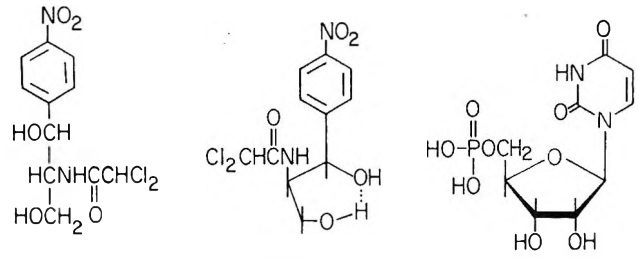

Figure 1.

The synthesis of the 5-dichloroacetamido-5-deoxy-β-D-ribosylnitrobenzenes (**20**) was achieved from **6** by the following route. Isopropylidenation of **6** to **13** followed by mesylation gave the 5-mesylate **14**, which was treated with sodium azide in DMF to afford the 5-azido derivative **15**. Reduction of the latter derivative with borohydride in refluxing 2-propanol[11] gave the 5-amino analog **16** which, after acylation, afforded the 5-dichloroacetamido derivative **17** as an analytically pure syrup in 65% overall yield from **6**. Deacetonation of **17** gave an almost quantitative

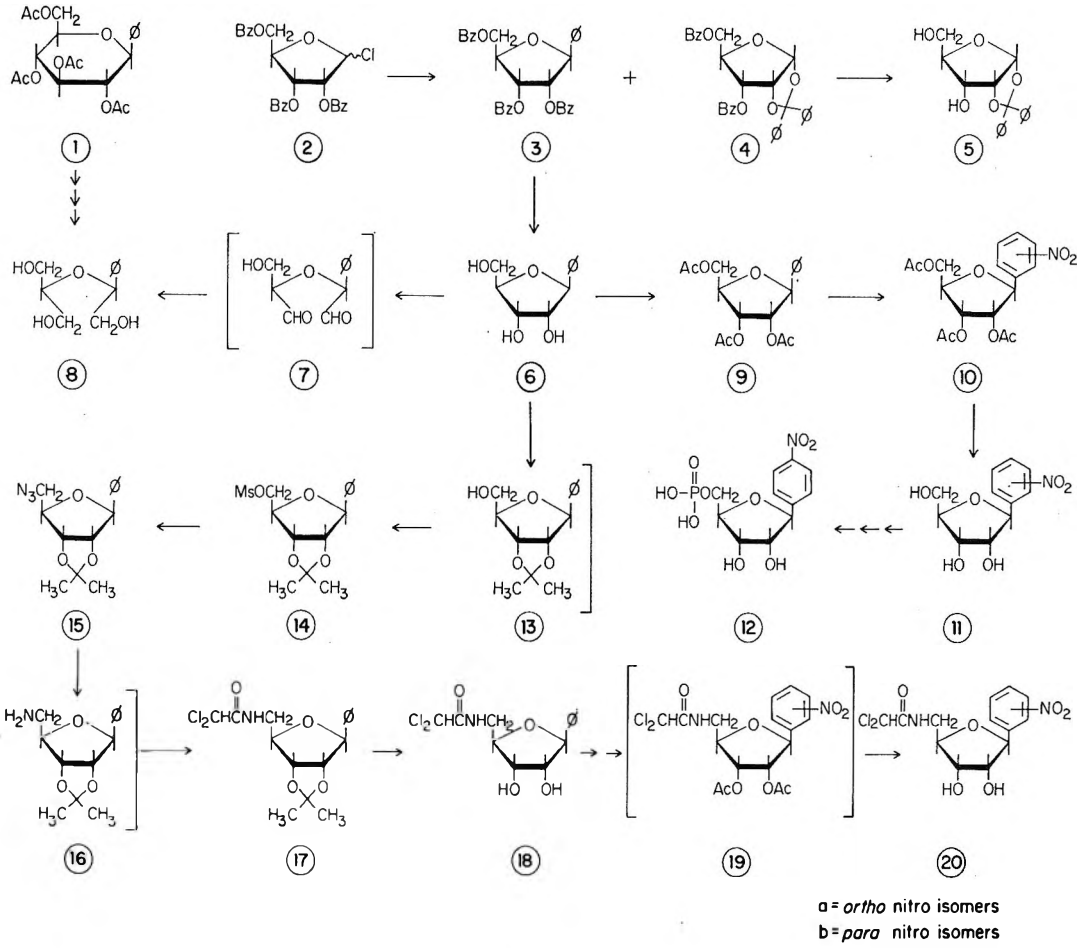

Figure 2.

in an acetic anhydride–cupric nitrate mixture[9] to give both the ortho and para isomers (**10**) in approximately equal amounts in a combined yield of 58%. Attempts to obtain separation of this mixture by tlc were unsuccessful. Even after deacetylation to **11**, the isomeric mixture exhibited similar migration properties on tlc in a variety of solvent systems. It was found that fractional crystallization of the mixture (**11**) could be achieved from ethyl acetate, whereby each crop was characterized by its ir and nmr spectrum. Isopropylidenation of the *p*-nitro isomer **11b** followed by phosphorylation with 2-cyanoethyl phosphate and dicyclohexylcarbodiimide[10] and removal of the protecting groups gave the "nucleotide" **12**, which was isolated as the calcium salt.

(9) J. M. Craig and W. A. Bonner, *J. Amer. Chem. Soc.*, **72**, 4808 (1950); A. Gerecs and M. Windholz, *Acta Chim. Acad. Sci. Hung.*, **13**, 231 (1957) [*Chem. Abstr.*, **52**, 11778 (1958)].

(10) P. T. Gilham and G. M. Tener, *Chem. Ind. (London)*, 542 (1959).

yield of crystalline **18**, which was acetylated and then nitrated with acetic anhydride–cupric nitrate reagent[9] to a mixture of ortho and para isomers in fair yield. Separation of these isomers was accomplished by use of thick layer chromatography on alumina. The dissimilar migratory properties of these isomers (**19**) are probably related to the susceptibility of the ortho isomer to intramolecular hydrogen bonding between the nitro and amido groups. Deacetylation of each of the isomers (**19**) was performed under mild conditions with triethylamine in methanol. Each of the isomers (**20**) was obtained in crystalline form.

A more direct route to **20b** was attempted from **11b**, which involved acetonation, mesylation, and displacement of the 5-mesylate with ammonia. Though this approach was satisfactory for the ortho series, the para 5-mesylate isomer underwent extensive

(11) H. Ohrui and S. Emoto, *Agr. Biol. Chem. (Tokyo)*, **32**, 1371 (1968).

decomposition in the presence of ammonia. This approach to **20b** was therefore abandoned.

The ribofuranosylnitrobenzenes described herein have been submitted to another laboratory for biochemical evaluation. The results of these studies, when completed, will be reported elsewhere.

Experimental Section

General Procedure.—Melting points were determined on a Thomas–Hoover apparatus (capillary method) and are uncorrected. The nmr spectra were measured on a Varian A-60 spectrometer using TMS as internal standard. Chemical shifts are reported in parts per million (δ) and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), or m (complex multiplet). Values given for coupling constants are first order. Thin layer chromatography was performed on silica gel GF_{254} (Merck); spots were detected by uv absorbance or by spraying with 20% v/v sulfuric acid–ethanol and heating. Column chromatography was performed[12] over silica gel G under positive pressure. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. All evaporations were carried out *in vacuo*.

β-D-Ribofuranosylbenzene (6) and **1,2-*O*-Diphenylmethylidene-α-D-ribofuranose** (5).—To a suspension of 36.7 g (0.200 mol) of finely powdered $CdCl_2$ (previously dried for 1 hr at 100°) in 1 l. of anhydrous tetrahydrofuran was added 133 ml of 3.13 *M* phenylmagnesium bromide in ether (Alfa Inorganics, Ventron). The gray suspension was heated to reflux and 300 ml of solvent were distilled off. To the resulting clear mixture was added a solution of 2,3,5-tri-*O*-benzoyl-D-ribosyl chloride (2) (from 0.2 mol of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose) in 500 ml of benzene. After addition of another 500 ml of benzene the solution was heated for 1 additional hr as 700 ml were distilled off. After cooling, the mixture was poured into 0.8 l. of an ice–water mixture and enough acetic acid was added to dissolve all precipitated solid (pH of aqueous layer was ~7.0). After separation, the aqueous layer was washed with more benzene and the organic extracts were washed with aqueous $NaHCO_3$ and H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue was dissolved in 1 l. of warm methanol containing 1 mmol of NaOMe. After complete reaction the solution was neutralized with Dowex AG 50 (H^+), filtered, and evaporated to dryness. The residue was partitioned between 500 ml each of water and ether and each layer was back-extracted again. The ether extracts were pooled and dried over Na_2SO_4. Evaporation to dryness and crystallization of the residue from benzene–petroleum ether (bp 30–60°) gave 35 g (55%) of crude **5**, which was recrystallized from the same solvent pair to give analytically pure material: mp 139–140°; nmr ($CDCl_3$) δ 7.20–7.60 (10, m, 2 C_6H_5), 5.84 (1, d, H-1), 4.53 (1, q, H-2), 4.15–3.50 (4, m, H-3, H-4, and H-5), 2.20 (2, s, OH's), $J_{1,2}$ = 4, $J_{2,3}$ = 4 Hz.

Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.82; H, 5.77.

The aqueous extract was evaporated to give a semicrystalline residue which crystallized from ethyl acetate–benzene to afford 7.8 g of crude **6**. Column chromatography of the mother liquor on 400 g of silica gel G (7.5:1, chloroform–methanol) afforded another 2.6 g of **6** (25% total yield). Recrystallization from ethyl acetate–benzene gave the pure product: mp 121–122°; nmr (DMSO-d_6) δ 7.40 (5, m, C_6H_5), 4.75–5.02 (3, m, OH's), 4.64 (1, d, H-1), 3.55–4.05 (5, m, H-2, H-3, H-4, and H-5), $J_{1,2}$ = 6.5 Hz.

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.45; H, 6.51.

2-[2-(1,3-Dihydroxy)propyloxy]-2-phenyl-2(*R*)-ethanol (8). **Method A, from 6.**—To a solution of 2.67 g (0.0147 mol) of **1** in 50 ml of water was added 3.45 g (0.0161 mol) of $NaIO_4$. The mixture was left at ambient temperature for 1 hr, then poured into 200 ml of absolute ethanol and stirred for 15 min at room temperature. After filtration from the white solid the solution was reduced in volume to 50 ml and added slowly to a stirred solution protected from light, containing sodium borohydride (3.06 g, 0.080 mol) dissolved in 70 ml of water. After stirring for 30 min the mixture was stored at 0–5° overnight. The pH was then adjusted to 7 with Dowex AG-50 (H^+) and the resin was removed by filtration. The aqueous solution was then evaporated to dryness and the residue (one major spot on tlc) was chromatographed on 100 g of silica gel G (4:1, chloroform–methanol). The fractions containing the product were evaporated to dryness and the residue was recrystallized from ethyl acetate. Compound **8** (1.59 g, 51%) was very hygroscopic and had to be filtered under a nitrogen atmosphere and stored over phosphorus pentoxide: mp 69–71°; $[\alpha]^{23}D$ +86 ± 1° (*c* 1.3, water); nmr (DMSO-d_6) δ 7.31 (5, s, C_6H_5), 4.36–5.40 (4, m, 3 OH's and anomeric), 3.40–3.70 (7, m).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.05; H, 7.49.

Method B, from 1.—Tetra-*O*-acetyl-β-D-glucopyranosylbenzene (6.70 g, 0.0164 mol) was deblocked with 300 ml of methanol containing 100 mg of sodium methoxide. The mixture was neutralized with Dowex AG 50 (H^+), filtered, and evaporated to dryness. The syrupy glucopyranosylbenzene was then subjected to cleavage by metaperiodate (2 equiv) and borohydride reduction in a manner similar to that described in method A. Purification by column chromatography and recrystallization of the product from ethyl acetate gave compound **8** (2.41 g, 69%) identical in all respects with the product obtained by method A: mp and mmp 69–71°; $[\alpha]^{23}D$ +86 ± 1° (*c* 1.3, water).

***o*- and *p*-(β-D-Ribofuranosyl)nitrobenzene** (11a and 11b).—β-D-Ribofuranosylbenzene **6** (1.90 g, 0.0104 mol) in 20 ml of pyridine was treated with 2 ml of acetic anhydride and kept overnight at room temperature. Excess acetic anhydride was hydrolyzed by addition of a small amount of water and the mixture was evaporated to dryness. After partition (chloroform–sodium bicarbonate, then water) the organic phase was dried over sodium sulfate and evaporated. Tlc (10:1, benzene–ethyl acetate) of the syrup indicated the presence of only one component (R_f 0.2). The triacetate **9** was dissolved in 45 ml of acetic anhydride and 15 g of cupric nitrate trihydrate was added in three portions. The mixture was kept at 50° for 35 min. It was then rapidly cooled and poured into 120 ml of ice–water. It was extracted with 300 ml of benzene in two portions and the organic layer was washed with aqueous sodium bicarbonate and water and was finally dried over anhydrous sodium sulfate. After evaporation to dryness, the yellow syrupy residue (3.4 g) was chromatographed on 150 g of silica gel G (7:1 benzene–ethyl acetate). The major fractions were pooled and evaporated to give 2.3 g of syrup (~58%). This ortho–para mixture was deacetylated in methanol with sodium methoxide and the product was crystallized from ethyl acetate to give 1.14 g (48% based on **6**) of mixed *o*- and *p*-(β-D-ribofuranosyl)nitrobenzene (**11a** and **11b**) in four crops. Pure samples of each isomer were obtained using fractional crystallization from ethyl acetate by alternately seeding the concentrated mother liquor after the isolation of each pure fraction with crystals of the other isomer. Each crop was identified by its crystalline form and its ir spectrum.

The ortho isomer (**11a**, 0.225 g) was obtained as small spherical fibrous aggregates: mp 155–157°; nmr (DMSO-d_6) δ 7.30–8.30 (4, m, C_6H_4), 5.12 (1, d, H-1), 4.72–5.06 (3, m, OH's), 3.50–3.95 (5, m, H-2, H-3, H-4, and H-5), $J_{1,2}$ = 4.5 Hz; ir ν_{max}^{KBr} 790 (1:2 disubstituted), 1005 and 1015 (1:2 disubstituted), 1180 and 1200 (1:2 disubstituted), 1550 and 1575 cm^{-1} (NO_2).

Anal. Calcd for $C_{11}H_{13}NO_6$: C, 51.77; H, 5.13; N, 5.49. Found: C, 51.94; H, 5.09; N, 5.47.

The para isomer (**11b**, 0.524 g) crystallized from ethyl acetate as stout prisms: mp 151–153°; nmr (DMSO-d_6) δ 7.72 and 8.30 (4, 2d, C_6H_4), 4.85–5.25 (3, m, OH's), 4.79 (1, d, H-1), 3.55–4.05 (5, m, H-2, H-3, H-4, and H-5), $J_{1,2}$ = 7.0 Hz; ir ν_{max}^{KBr} 850 (1:4 disubstituted), 1180 (1:4 disubstituted), 1575 cm^{-1} (NO_2).

Anal. Calcd for $C_{11}H_{13}NO_6$: C, 51.77; H, 5.13; N, 5.49. Found: C, 51.94; H, 5.09; N, 5.47.

***p*-(β-D-Ribofuranosyl)nitrobenzene 5-(Calcium phosphate)** (12).—To a solution of **11b** (0.454 g, 0.0018 mol) in 40 ml of acetone were added two drops of concentrated sulfuric acid and 0.25 ml of dimethoxypropane. The mixture was left overnight and neutralized by shaking with anhydrous sodium carbonate. The suspension was filtered and the filtrate was evaporated to dryness. The residue was dissolved in chloroform, which was extracted with water and dried over sodium sulfate. The residue, in 4 ml of dry pyridine, was added to a solution of 2-cyanoethyl phosphate (0.54 g, 0.00356 mol) and dicyclohexylcarbodiimide (1.46 g, 0.00712 mol) in 25 ml of anhydrous pyridine. The mixture was left for 2 days at room temperature and treated with 3.5 ml of H_2O and filtered. The filtrate was evaporated under vacuum below 35° and the residue was dissolved in 100 ml of 70% acetic

(12) B. J. Hunt and W. Rigby, *Chem. Ind. (London)*, 1868 (1967).

acid and heated for 30 min at 100°. The mixture was evaporated to dryness; the residue was dissolved in 70 ml of H_2O; and the solution was filtered again. To the filtrate was added 10 ml of 6 *M* KOH and the solution was heated on a steam bath for 30–40 min. After cooling, it was passed through a short Dowex AG 50 (H^+) column, washed, and adjusted to pH 7.5–8 with NH_4OH. The solution was concentrated and chromatographed on six sheets of Whatman No. 3 MM with 5:2 ethanol–1 *M* ammonium formate. The aqueous eluates from the appropriate bands were pooled, evaporated to a small volume, and passed through a short Dowex AG 50 (Na^+) column. The solution was then evaporated to dryness to give 1.03 g of a white solid. Optical density measurements (based on **11**) indicated that the solid obtained was 40% pure **12** (as the Na salt in 60% yield) and was present together with a uv-nonabsorbing salt (possibly HCOONa). Paper chromatography (Whatman No. 1, 5:2 ethanol–0.5 *M* ammonium formate; R_f 0.35) and paper electrophoresis (Whatman No. 3 MM, 0.05 *M* ammonium bicarbonate, pH 5, R_{UMP} 0.91) indicated the presence of only one uv-absorbing component. The product was purified by precipitation as the sparingly soluble calcium salt of **12** (0.244 g).

Anal. Calcd for $C_{11}H_{12}NO_9PCa \cdot H_2O$: C, 33.76; H, 3.60; N, 3.58; P, 7.91; Ca, 10.24. Found: C, 33.69; H, 3.60; N, 3.58; P, 7.82; Ca, 10.12.

(2,3-Isopropylidene-5-dichloroacetamido-5-deoxy-β-D-ribofuranosyl)benzene (17).—Compound **6** (4.30 g, 0.0236 mol) in 100 ml of acetone was treated with three drops of concentrated H_2SO_4 and 2.5 ml of dimethoxypropane at room temperature overnight. Tlc (20:1, chloroform–methanol) showed complete conversion to product **13** (R_f 0.65). Excess sodium carbonate was added to the solution and the suspension was filtered. The solution was evaporated to a syrup that did not crystallize. This was dissolved in 30 ml of pyridine and 3.2 g (0.0028 mol) of mesyl chloride. Mesylation was completed within 2 hr at room temperature. The mixture was evaporated to dryness and partitioned between chloroform and water, and the organic layer was dried over Na_2SO_4 and evaporated to a syrup (**14**) (tlc, 10:1 benzene–ethyl acetate, R_f 0.4). This was dissolved in 50 ml of DMF, and finely powdered sodium azide (4.87 g, 0.0750 mol) was added in portions. The suspension was heated over a steam bath with frequent shaking. After 45 min tlc indicated complete conversion to compound **15** (10:1 benzene–ethyl acetate, R_f 0.7). The mixture was cooled, filtered, and evaporated and the residue was partitioned between chloroform and water. The organic layer was dried and evaporated to give **15** as a syrup. This was dissolved in 160 ml of 2-propanol and sodium borohydride (2.85 g, 0.075 mol) was added. The mixture was heated to reflux for a total of 22 hr, evaporated to dryness, and partitioned between dichloromethane and water (150 ml each). The organic layer was dried and evaporated to give **16** as an oil. Tlc of the product (20:1 chloroform–methanol, $R_f \cong 0.3$) revealed only small amounts of side products. The amine **16** was therefore used without further purification. It was dissolved in 50 ml of dry pyridine, chilled to 0°, and treated with dichloroacetic anhydride (6.0 g, 0.025 mol). The mixture was left for 2 hr at room temperature, treated with a small amount of methanol, and evaporated to dryness. The residue was partitioned between water and chloroform and the organic layer was decolorized with charcoal and dried over Na_2SO_4. After evaporation of the filtrate, the residue was chromatographed on 400 g of silica gel G (5:1 benzene–ethyl acetate). Appropriate fractions were collected and after evaporation to dryness compound **17** (5.60 g, 65% based on **6**) was obtained pure as a colorless syrup: nmr ($CDCl_3$) δ 7.33 (5, s, C_6H_5), 7.00 (1, t, NH), 5.94 (1, s, $CHCl_2$), 4.88 (1, m, H-1), 4.52 (2, m, H-2 and H-3), 4.02–4.30 (1, m, H-4), 3.65 (2, q, H-5).

Anal. Calcd for $C_{16}H_{19}NO_4Cl_2 \cdot {}^1/_2H_2O$: C, 52.05; H, 5.46; N, 3.79; Cl, 19.20. Found: C, 52.03; H, 5.40; N, 3.81, Cl, 19.25.

(5-Dichloroacetamido-5-deoxy-β-D-ribofuranosyl)benzene (18). Compound **17** (4.94 g, 0.0134 mol) was dissolved in 100 ml of 70% acetic acid and the solution was heated on the steam bath for 30 min. The mixture was evaporated to dryness and the residue was crystallized from ethyl acetate–ether to give 4.09 g of compound **18** (95%). Recrystallization from the same solvent pair gave the analytical sample (mp 109–111°) as long white needles: nmr (DMSO-d_6) δ 8.65 (1, t, NH), 7.31 (5, s, C_6H_5), 6.50 (1, s, $CHCl_2$), 5.00 (2, m, OH's), 4.60 (1, d, H-1), 3.30–3.95 (5, m, H-2, H-3, H-4, and H-5), $J_{1,2}$ = 6.0 Hz.

Anal. Calcd for $C_{13}H_{15}NO_4Cl_2$: C, 48.78; H, 4.72; N, 4.37; Cl, 22.12. Found: C, 48.68; H, 4.64; N, 4.36; Cl, 22.03.

***o*- and *p*-(5-Dichloroacetamido-5-deoxy-β-D-ribofuranosyl)-nitrobenzene (20a and 20b).**—Compound **18** (4.70 g, 0.016 mol) was acetylated in 30 ml of pyridine with 6.1 g (0.060 mol) of acetic anhydride. The mixture was worked up as for **9** and compound **19** (obtained as a syrup) was dissolved in 60 ml of acetic anhydride. It was nitrated with 20 g of cupric nitrate and worked up in the manner described above. The crude mixture of products was separated on 800 g of silica gel G (50:1, $CHCl_3$–MeOH) and appropriate fractions were collected and evaporated to give 2.90 g of a mixture of **20a** and **20b**. The two isomers were separated on ten plates (20 × 40 cm, 2 mm alumina HF_{254}, $CHCl_3$) where the ortho isomer migrated slightly ahead of the para isomer All bands were eluted with ethyl acetate and the appropriate eluates were pooled and evaporated to give 0.269 g of **19a** (ortho) and 0.581 g of **19b** (para) as syrups: nmr (**19a** in $CDCl_3$) δ 7.50–8.10 (4, m, C_6H_4), 7.08 (1, broad t, NH), 5.98 (1, s, $CHCl_2$), 5.57 (1, d, H-1), 4.90–5.40 (2, m, H-2 and H-3), 4.05–4.45 (1, m, H-4), 3.50–3.95 (2, m, H-5), 2.09 and 2.17 (6, 2 s, $2CH_3CO$–), $J_{1,2}$ = 3.5 Hz; nmr (**19b** in $CDCl_3$) δ 8.20 and 7.57 (4, 2 d, C_6H_4), 7.14 (1, broad t, NH), 6.00 (1, s, $CHCl_2$), 5.07 (3, broad s, H-1, H-2, and H-3), 4.30 (1, m, H-4), 3.80 (2, m, H-5), 2.13 (6, s, $2CH_3CO$–). All of **19a** obtained above was dissolved in 4 ml of methanol and treated with 0.2 ml of triethylamine. The mixture was left at room temperature for 16 hr and evaporated to dryness. The semicrystalline residue was recrystallized from ethanol to give 120 mg of analytically pure **20a**: mp 157–158°; nmr (DMSO-d_6) δ 8.69 (1, broad t, NH), 7.30–8.00 (4, m, C_6H_4), 6.50 (1, s, $CHCl_2$), 4.95–5.30 (3, m, H-1 and OH's), 3.40–4.00 (5, m, H-2, H-3, H-4, and H-5), $J_{1,2}$ = 4.0 Hz.

Anal. Calcd for $C_{13}H_{14}N_2O_6Cl_2$: C, 42.76; H, 3.86; N, 7.67; Cl, 19.41. Found: C, 42.85; H, 3.72; N, 7.66; Cl, 19.56.

All of **19b** obtained above was similarly deacetylated in 8 ml of methanol with 0.4 ml of triethylamine. After complete evaporation of the solvent, the syrupy residue was crystallized very slowly from ethanol. Recrystallization was repeated several times until **20b** separated as analytically pure white needles (221 mg). Compound **20b** showed no definite melting point but, after cooling, the melt resolidified and melted sharply at 131–133°: nmr (DMSO-d_6) δ 8.69 (1, broad t, NH), 8.20 and 7.63 (4, 2 d, C_6H_4), 6.50 (1, s, $CHCl_2$), 5.00–5.30 (2, m, OH's), 4.75 (1, d, H-1), 3.25–4.00 (5, m, H-2, H-3, H-4, and H-5), $J_{1,2}$ = 6.5 Hz.

Anal. Calcd for $C_{13}H_{14}N_2O_6Cl_2$: C, 42.76; H, 3.86; N, 7.67; Cl, 19.41. Found: C, 42.55; H, 3.77; N, 7.68; Cl, 19.48.

Registry No.—**5**, 32252-02-1; **6**, 32252-03-2; **8**, 32304-19-1; **11a**, 32252-04-3; **11b**, 32252-05-4; **12**, 32304-20-4; **17**, 32252-06-5; **18**, 32251-31-3; **19a**, 32251-32-4; **20a**, 32251-33-5; **20b**, 32251-34-6.

A Convenient Synthesis of Ketones from Certain Substituted Ethylenes. Procedure and Mechanism[1]

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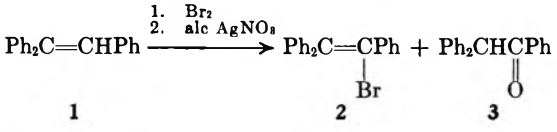
A novel method for the direct conversion of some substituted ethylenes to ketones is described. The ketone synthesis is shown to proceed with a concurrent rearrangement of the carbon skeleton. A mechanism, supported by isotopic labeling experiments, is postulated to account for the transformation.

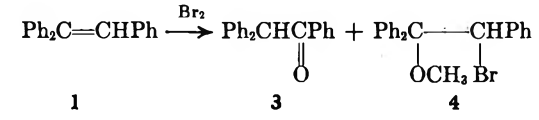
The addition of bromine to olefins is a well-known reaction frequently used as a qualitative test for unsaturation. The products of such additions are usually the corresponding dibromides. However, in at least two reported[4,5] instances ketones have been isolated as by-products.

In the first of these reports,[4] the bromination of triphenylethylene (1) in either chloroform or glacial acetic acid, followed by decomposition with alcoholic silver nitrate, has been reported to give triphenylethylene bromide (2) as well as variable quantities of phenyl benzhydryl ketone (3).

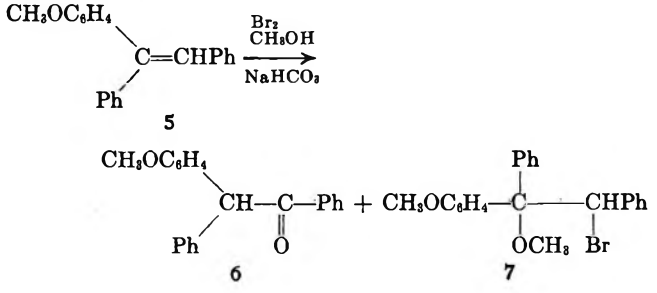


The same report described some of the experimental conditions which affect the nature and composition of the products.

A similar bromination of triphenylethylene, this time in methanol, was found[5] to give a mixture of phenyl benzhydryl ketone (3) and 2-bromo-1-methoxy-1,1,2-triphenylethane (4).



This report also describes the conversion of *cis*- and *trans*-1-(*p*-anisyl)-1,2-diphenylethylene (5) to 1-keto-2-(*p*-anisyl)-1,2-diphenylethane (6) and 1-(*p*-anisyl)-2-bromo-1-methoxy-1,2-diphenylethane (7). The bromo compounds 4 and 7 were found[5] to rearrange to ketones 3 and 6 when treated with alcoholic silver nitrate.



Despite these reports, to our best knowledge, a systematic study of the mechanism which can account for the ketone formation has never been undertaken. Furthermore, the potential synthetic utility of these reactions has not been fully explored. Consequently, we felt that it would be of considerable theoretical as well as practical interest to investigate the mechanism of these transformations and to establish a generally useful synthetic procedure for the direct conversion of certain substituted ethylenes to the corresponding ketones.

Our investigation consisted of three phases. First we directed our efforts toward the determination of the optimum experimental conditions for obtaining the maximum yield of ketones from the corresponding substituted ethylenes. We then tried to get some insight into the mechanism of the rearrangement by means of isotopic labeling and other techniques. Finally we sought to determine the scope of the procedure by preparing a number of substituted ethylenes and subjecting them to the same experimental conditions which were identified in the first part of our study as producing maximum yield of ketones.

For convenience each of these phases of our work will be discussed individually.

Results and Discussion

Maximizing the Yield of the Rearranged Products.— Since the rearrangement was first observed with triphenylethylene, most of our initial trials were conducted with this compound. The object was to discover the experimental conditions which would augment the yield of ketone, thus making it the main product instead of a by-product.

In this connection we conducted numerous experiments involving repetitive bromination reactions of triphenylethylene and other olefins, each time varying one of the experimental parameters and observing the effect that this variation had on the yield of the corresponding ketones.

The variables consisted of (1) the reaction temperature, (2) the reaction time, (3) the type of solvent used, (4) the nature of the decomposition reagent, (5) the solvent used in preparing the decomposing solution, (6) the contact time with the decomposition reagent, (7) the size of the run, and (8) the molar ratio of bromine to olefin. After each experiment the reaction mixtures were examined by thin layer chromatography and nmr and infrared spectroscopy. The components of the mixtures were whenever possible separated by column chromatography and identified.

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(1) (a) This paper was presented in part at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969; (b) support of this work by grants from the Research Corporation is gratefully acknowledged.

(2) To whom inquiries should be directed.

(3) Master of Arts in Teaching Chemistry Thesis, Chapman College, Nov 1968.

(4) S. Apelgot, A. Cheutin, S. Mars, and M. R. Berger, *Bull. Soc. Chim. Fr.*, **19**, 533 (1952).

(5) D. Y. Curtin and E. K. Meislich, *J. Amer. Chem. Soc.*, **74**, 5518 (1952).

Since this phase of our investigation involved several hundred trials it is both impossible and unnecessary to describe each experiment in detail. Instead we will enumerate and discuss only the most important of our findings which can be summarized as follows.

1. The formation of the ketones occurs in the work-up, since the infrared spectra of the brominated reaction mixtures show no carbonyl absorption band before decomposition and strong carbonyl absorption band right after decomposition. This explains why the ketone formation could not be prevented by excluding oxygen from the reaction as was attempted by Apelgot, *et al.*,[4] who erroneously sought an explanation for the ketone formation in the bromination reaction itself.

2. The elimination of hydrogen bromide gas in many instances competes with the ketone formation and gives rise to vinyl bromides which are unreactive toward silver nitrate or any of the other decomposition reagents tried. This observation provides the clue for the profound effect that the reaction temperature and time have on the nature and composition of the products. In general, lower temperatures and short reaction times favor the formation of ketones, whereas at high temperatures or long reaction times the principal products are vinyl bromides. This is because at low temperatures the initially formed dibromides are more stable; thus hydrogen bromide gas elimination is considerably slower and the bulk of the substrate remains in a form which is reactive toward silver nitrate. Similarly, the longer the reaction time the greater the proportion of the substrate which has been transformed into the unreactive vinyl bromide. This explanation is supported by the fact that the reactions of tetrasubstituted ethylenes, where hydrogen bromide gas elimination is not possible, are not affected by variations in the reaction temperature and time. Consequently such compounds are readily converted to ketones by our procedure, subject only to the limitations described in the last part of the discussion section.

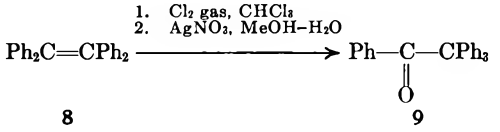
3. The presence of water is essential to the formation of the ketone. During several trials in which anhydrous alcoholic silver nitrate was used no ketones were formed. However, duplicate runs, under identical conditions except for the use of alcoholic silver nitrate containing at least 5% water, readily generated ketones. The role of water was further investigated by oxygen-18 labeling and will be discussed in detail in the next part of this section.

4. Several other reagents, such as solutions of mercuric and lead salts, activated alumina, silver hydroxide, or simply alcohol–water mixtures, were also found to promote the ketone formation; however, the conversion is much slower, the product mixtures are more complex, and the yields of ketone are generally much lower than those obtained when alcoholic silver nitrate is used.

In a few instances, silver carbonate precipitated on Celite, a mixture known as "Fetizon's Reagent,"[6] was found to be superior to alcoholic silver nitrate in bringing about the rearrangement to the ketone. A more detailed discussion of the reactions involving this reagent will be presented in the last part of this section.

(6) M. Fétizon and M. Golfier, *C. R. Acad. Sci., Ser. C*, **276**, 900 (1968).

5. The action of alcoholic silver nitrate on chlorinated substrates can also promote conversion to ketones. Although it is generally more convenient to work with bromine, with some compounds chlorine must be used. In the case of tetraphenylethylene (**8**) for example, which is unreactive toward bromine, we tried our procedure with chlorine, passing the gas through a chloroform solution of the olefin. Upon decomposition with alcoholic silver nitrate a nearly quantitative yield of phenyltrityl ketone (**9**) was obtained. This conversion is incidentally an example of the favorable special cases of tetrasubstituted ethylenes, previously discussed, where the competitive elimination of hydrogen halide gas cannot take place.



8 9

6. The necessary contact time with the alcoholic silver nitrate for ketone formation is proportional to the stability of the dihalide substrate. With very labile dihalides the rearrangement takes places within minutes. With relatively stable dihalides several hours of stirring with the decomposition solution may be necessary for complete precipitation of the silver halide salts. In most cases overnight contact is sufficient.

7. The choice of solvent for carrying out the bromination reaction and for making up the bromine solutions has an important bearing on the outcome of the reaction. Nucleophilic solvents are generally unsatisfactory and give rise to complex mixtures of products where one or both of the halogen atoms have been substituted by nucleophilic species from the solvent. This results in lowering the yields of ketones and making their isolation and characterization difficult. The solvent also must be such that the substrates retain high solubility in it, even at very low temperatures. Thus from the various solvents tested (ether, dioxane, hexane, carbon tetrachloride, various alcohols, glacial acetic acid, etc.) we have found chloroform to be generally the most suitable.

8. The molar ratio of bromine to olefins has no effect on the nature and composition of the products; however, a large excess of bromine necessitates inordinate amounts of silver nitrate solution and thus should be avoided.

9. The per cent yield of ketone is independent of the size of the run. Thus our procedure can be equally applied to large as to small scale preparations of ketones.

Summarizing the above findings the best conditions for ketone formation are as follows: Dry Ice temperature, the shortest possible reaction time, chloroform solvent for both the olefin and the bromine, decomposition of the brominated mixtures with methanolic silver nitrate containing 5–12% water (higher water content gives rise to unsatisfactory two-phase systems), and the allowance of sufficient time for complete precipitation of the silver halide salts.

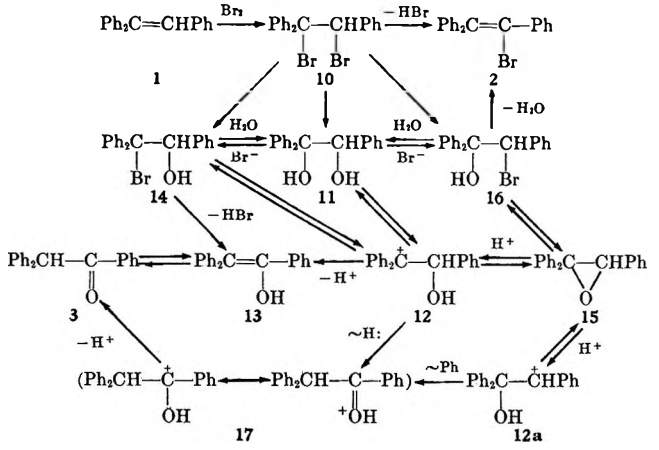
When the above procedure is followed, high and often quantitative yields of ketones are obtained from the corresponding olefins, subject only to the limitations discussed in the last part of this section.

Mechanistic Studies.—As before, the principal model for these studies was triphenylethylene. Some of the clues as to the mechanism of the ketone formation were provided by the experiments described in the previous part of this section. However, there still remained several theoretically plausible pathways by means of which the conversion could have taken place. Consequently we have proceeded to list the various mechanistic alternatives and to perform experiments which would allow us to differentiate among them.

The possibilities which have been ruled out by our experiments are summarized in Scheme I. One pos-

SCHEME I

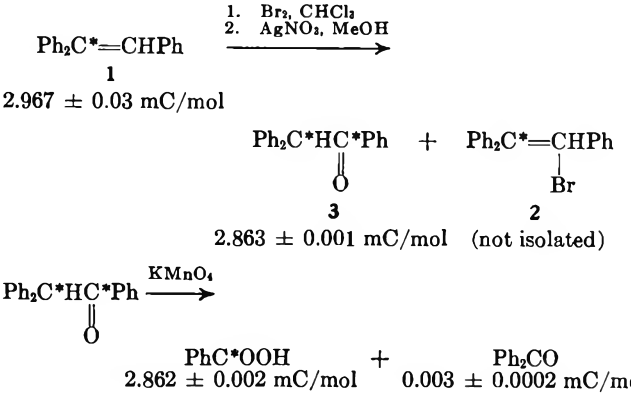
THEORETICALLY PLAUSIBLE MECHANISTIC PATHS FOR THE CONVERSION OF TRIPHENYLETHYLENE TO PHENYL BENZHYDRYL KETONE



sible sequence could involve the formation of the dibromide **10** from triphenylethylene (**1**) followed by direct or indirect hydrolysis of this compound to the glycol **11**, an identified[7] precursor of phenyl benzhydryl ketone (**3**) *via* the well-known pinacol rearrangement.[8]

This rearrangement can theoretically[9] take place in two ways: either through the carbonium ion **12** followed by a hydride shift or through the enol form **13**. The latter can also derive from the bromohydrin **14** by elimination of hydrogen bromide gas. The same bromohydrin **14** can also, theoretically, give rise to the carbonium ion **12** following the removal of the bromide by silver nitrate. The role of the carbonium ion **12a** can be safely neglected since its contribution to the pinacol rearrangement of **11** has been shown[7] to be insignificant.

To test for these possibilities we have subjected a sample of 1,1,2-triphenylethylene-*1*-^{14}C (**1**) to our bromination and silver nitrate decomposition procedure as outlined in the Experimental Section. After two crystallizations from methanol, an 88% yield of pure (mp 139–140°) phenyl benzhydryl ketone-^{14}C (**3**) was obtained. The ketone was subsequently oxidized to benzophenone and benzoic acid by the method of Bonner and Collins;[10] the fragments were assayed for radioactivity. These transformations can be illustrated by the following equations. (The double asterisk designates uncertainty as to the position of the label and not double labeling.)



Our radiochemical data, given above, showed that all of the label resided in the benzoic acid fraction. Thus the conversion of triphenylethylene to phenyl benzhydryl ketone by our method was found to proceed with 100% phenyl migration. This rules out the participation of either the carbonium ion **12** or the bromohydrin **14** as intermediates in the present rearrangement, since in each of those instances the carbon skeleton would have remained unrearranged. The same data also rule out the intervention of the enol form **13**. Nevertheless, since the enol form was shown as the ketone precursor when our procedure was cited by Fieser,[11] we have conducted an additional experiment for further confirmation. The bromination of triphenylethylene was carried out as usual except that this time the mixture was decomposed with methanolic silver nitrate prepared with 90% deuteriomethanol (CH_3OD) and 10% D_2O.

The reaction afforded a 90% yield of pure (mp 139–140°) phenyl benzhydryl ketone. The integrated nmr spectrum of the product showed no incorporation of deuterium. Furthermore, when an authentic sample of the deuterated ketone $Ph_2CDCOPh$ (99.5% deuterium) was subjected to our experimental conditions and examined by nmr all of the original label had been retained. Since the enol form **13** of phenyl benzhydryl ketone undergoes deuterium exchange readily, we have concluded that it cannot be a precursor of phenyl benzhydryl ketone in the present case.

It has been known for some time[12] that triphenylethylene oxide (**15**) can under certain conditions revert to phenyl benzhydryl ketone. However, its involvement in the present rearrangement is highly unlikely for two reasons. First, under the fairly mild acidic conditions of our experiment this compound has been found[13] to give not phenyl benzhydryl ketone (**3**) but the glycol **11**. Second, for the ketone production to proceed *via* the epoxide in a manner consistent with our radiochemical findings, the ring opening must take place in such a way as to produce the carbonium ion **12a** exclusively. This is entirely unreasonable since the alternate carbonium ion **12** is the more stable of the two. Hence if the epoxide **15** was a precursor of the ketone one would have expected the integrity of the carbon skeleton to be preserved at least in part.

(7) C. J. Collins, *J. Amer. Chem. Soc.*, **77**, 5517 (1955). This paper contains all the pertinent earlier references.

(8) C. J. Collins, *Quart Rev. Chem. Soc.*, **14**, 357 (1960).

(9) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1962, p 602.

(10) W. A. Bonner and C. J. Collins, *J. Amer. Chem. Soc.*, **75**, 5378 (1953).

(11) M. Fieser and L. Fieser, "Reagents for Organic Synthesis," Vol. 2, Wiley-Interscience, New York, N. Y., 1969, pp 367, 368.

(12) R. Lagrave, *Ann. Chim.*, **8**, 363 (1927).

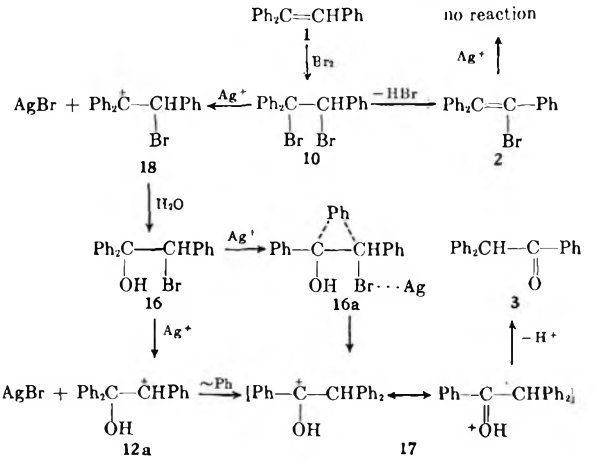
(13) J. F. Lane and D. R. Walters, *J. Amer. Chem. Soc.*, **73**, 4234 (1951).

Since our labeling experiments showed conclusively that a 100% rearrangement has taken place, we are forced to rule out this possibility.

In view of the above, only one reasonable mechanism remained which was consistent with our data; it is summarized in Scheme II. The proposed mecha-

SCHEME II

POSTULATED MECHANISM FOR THE CONVERSION OF TRIPHENYLETHYLENE TO PHENYL BENZHYDRYL KETONE



nism postulates the initial formation of the dibromide **10**, which then can either remain intact to undergo further transformations during the work-up or eliminate hydrogen bromide gas, irreversibly producing the vinyl bromide **2**, which is unreactive toward silver nitrate. The profound effect of the reaction temperature and time on this competition between the elimination of hydrogen bromide gas and the formation of the ketone has already been discussed and explained in the previous part of this section. This explanation is supported by the findings of Meisenheimer,[14] who has prepared the dibromide **10** and reported that it does in fact decompose on standing or heating to the vinyl bromide **2**. It is therefore the portion of the dibromide **10** which remains unchanged that undergoes nucleophilic substitution either with water or other nucleophiles, *e.g.*, methanol. The latter possibility will account for the reported[5] isolation of such products as 2-bromo-1-methoxy-1,1,2-triphenylethane described in the beginning of this paper.

In the absence of silver nitrate these substitutions as well as the subsequent reactions of that system are slow and cannot effectively compete with the hydrogen bromide gas elimination. Thus only minor yields of ketones are obtained from the process. On the other hand the interaction of the dibromide **10** with silver nitrate accelerates the reaction by facilitating removal of the bromide from the carbon bearing the two phenyl groups. This is most likely an SN1 process involving the initial formation of the rather stable carbonium ion **18**; however, our data do not permit differentiation between this and the alternate SN2 process. When water is the nucleophile the product of the above substitution is the bromohydrin **16**. The involvement of water as the oxygen source for the ketone formation was suggested by the fact that anhydrous decomposition reagents failed to produce the ketone. To obtain further confirmation we have conducted the bromination of triphenylethylene under the usual conditions except that the decomposition reagent consisted of a saturated silver nitrate solution made up with anhydrous methanol (95%) and oxygen-18 enriched water (5%). The isotopic enrichment of the water was 3 atom per cent. The phenyl benzhydryl ketone thus produced was examined by mass spectrometry.

The mass spectrum contained no molecular ion. However it showed two fragmentation peaks at masses 107 and 105 corresponding to the fragments $PhCH^{18}O$ and $PhCH^{16}O$, respectively. The ratio of these peaks was 1.5:1. To preclude the possibility of exchange after the ketone was formed, an authentic sample was subjected to the same reaction conditions and the mass spectrum of the recovered material was examined. This spectrum showed a peak ratio of mass 107 to mass 105 of 0.5:1, most likely due to the double carbon-13 isotope.

The data thus indicated a net incorporation of oxygen-18 from the water to the ketone of 1%.

Since the isotopic enrichment of the water was 3 atom %, two-thirds of the label remained unaccounted for. We can offer only one explanation for this discrepancy: it may be due to a combination of a kinetic isotope effect and preliminary oxygen exchange between the water and the nitrate ions of the decomposing solution. Such exchanges under acidic conditions are sometimes known[15] to occur.

Continuing with our postulated mechanism we propose further that the initially formed bromohydrin **16** undergoes semipinacolic dehydrobromination catalyzed by silver ions and accompanied by phenyl migration. This may theoretically be a one-step process *via* the transition state **16a** or a two-step process involving the formation of carbonium ion **12a** followed by phenyl migration. Our data do not permit differentiation between these two possibilities. However, for reasons already stated the intervention of **12a** is highly unlikely. In either case the product is the protonated ketone **17** which reverts to phenyl benzhydryl ketone (**3**) by a proton transfer.

This type of rearrangement of halohydrins to ketones is well known.[13,16] Furthermore, the transformation of the bromohydrin **16** to phenyl benzhydryl ketone under a variety of conditions has already been reported by Lane and Walters.[13] Finally, Bonner and Collins[17] have radiochemically demonstrated that the ketone formation takes place with complete phenyl migration. As a further confirmation an authentic sample of the bromohydrin **16** was synthesized and subjected to our experimental conditions, following a procedure identical with the bromination and decomposition of the triphenylethylene samples. A quantitative yield of phenyl benzhydryl ketone was obtained from the above reaction.

It is evident from the preceding discussion that the mechanism we have postulated is not only consistent with our own data but also strongly supported by the

(14) J. Meisenheimer, *Justus Liebigs Ann. Chem.*, **456**, 126 (1927).

(15) R. Klein and R. A. Friedel, *J. Amer. Chem. Soc.*, **72**, 3810 (1950).

(16) (a) D. Y. Curtin and E. K. Meilich, *ibid.*, **74**, 5905 (1952). (b) For a complete discussion see G. W. Wheland, "Advanced Organic Chemistry," Wiley, New York, N. Y., 1960, Chapter 12.

(17) W. A. Bonner and C. J. Collins, *J. Amer. Chem. Soc.*, **75**, 5379 (1953).

findings of other investigators. We therefore believe it to be the correct mechanism for the transformation of substituted ethylenes to ketones by our previously described procedure.

Establishing the Scope of the Procedure.—In the last part of our work, we sought to test the generality of our method of olefin conversion to ketones and to examine its relative merits from the point of view of synthesis. To this end a number of substituted ethylenes were prepared by action of appropriate Grignard reagents on ketones or esters, followed by dehydration of the resulting tertiary alcohols or by the Wittig reaction.[18] The olefins obtained in this manner were then subjected to our bromination and decomposition procedure as described at the end of the first part of this section. A number of commercial products as well as samples supplied by private sources were also tested.

The results of these experiments are summarized in Table I, which shows the principal carbonyl compounds obtained in each case and the approximate yields. The list was meant to be representative of the various types of substituted ethylenes rather than exhaustive. The data obtained from the reactions of these compounds permit us to make certain generalizations regarding the usefulness of our procedure for converting substituted ethylenes to carbonyl compounds.

We can generally conclude that our method will work best with highly substituted ethylenes providing that at least some of the substituents are aromatic. The presence of such substituents on the ethylenic carbons stabilizes the incipient carbonium ions, thus resulting in the formation of dihalides which are quite reactive toward silver nitrate. Thus the yields of ketones decrease as the proportion of alkyl substituents increases and the procedure fails completely with systems that have only aliphatic substituents. With such compounds a modified procedure employing somewhat more drastic conditions was tried. It consisted of brominating the olefins at room temperature in either chloroform or carbon tetrachloride followed by decomposition with silver carbonate–Celite reagent.[6]

After stirring for several hours either at room temperature or under reflux, low yields of ketones were obtained. The product mixtures were, however, complex, containing the brominated compounds, some starting material, and variable quantities of substitution products such as cyclic carbonates. We are now in the process of evaluating further the potential uses of the silver carbonate–Celite reagent, attempting to discover conditions which will minimize the yields of undesirable products.

With either procedure, if the substituents on the ethylenic carbon atoms are not all the same, mixtures of ketonic products may of course result. The composition of these mixtures will then depend on the relative migration tendencies of the substituents and the stereochemical requirements of the molecules. The separation of the various components in these mixtures proved to be difficult and hence was not pursued. Consequently, in all such cases, only the principal component was identified and listed in Table I. The stated yield, however, is the total yield of the ketonic products.

(18) A. Maercker, *Org. React.*, **14**, 270 (1965).

It is noteworthy, from the point of view of synthesis, that often when low yields of ketones were obtained, a substantial portion of the reaction mixture was unchanged starting material. Thus, at least in some instances, it is possible to augment the yield of ketones by recycling. Other important features of our process are the extremely mild conditions and the very short reaction time. These make it possible to achieve conversion of certain olefins to ketones even when other sensitive groups are present in the same molecule.

Taking into account the various limitations which we have outlined above, it can be concluded that our process can be conveniently applied to a large number of substituted ethylenes, converting them directly to ketones in high yields.

Although our initial studies were confined to simple compounds, further studies are now in progress, exploring the reactions of more complex systems such as mono- and polycyclic olefins. We are also investigating the potential application of this rearrangement to the synthesis and degradation of natural products.

Experimental Section[19]

I. Isotopically Labeled Compounds[20] and Experiments. Radioactivity Assays.—Radioactivity levels of the various carbon-14 labeled compounds were determined by dry combustion of the samples to carbon dioxide which was collected in an ionization chamber and assayed in the usual way,[21] using a Cary Model 31 vibrating-reed electrometer.

All determinations were performed in triplicate, the reported values being the average of these determinations.

1,1,2-Triphenylethylene-*1*-^{14}C (1).—This compound was prepared by the reaction of benzylmagnesium chloride with carbonyl-labeled benzophenone,[22] followed by the formic acid dehydration of the resulting 1,1,2-triphenylethanol-*1*-^{14}C. The procedure used was essentially that of Adkins and Zartman.[23] After chromatography on an alumina column and several recrystallizations from ethanol an analytically pure (mp 71–72°) sample of 1,2,2-triphenylethylene-*1*-^{14}C (specific activity 2.967 ± 0.03 mCi/mol) was obtained. The identity of the sample was established by comparing its infrared spectrum with that of an authentic sample.

Phenyl Benzhydryl Ketone-^{14}C (3).—A sample of 1,1,2-triphenylethylene-*1*-^{14}C (2 g, *ca.* 0.00782 mol, specific activity 2.967 ± 0.03 mCi/mol, mp 71–72°) was converted to phenyl benzhydryl ketone-^{14}C by the application of method B as outlined in the next part of this section. The crude product (1.92 g, 90%, mp 136–138°) was purified by successive crystallizations from ethanol. Thus 1.87 g (88%) of pure (mp 139–140°) phenyl benzhydryl ketone-^{14}C (specific activity 2.863 ± 0.001 mCi/mol) was obtained. The infrared spectrum of this product matched that of an authentic sample.

Oxidative Degradation of Phenyl Benzhydryl Ketone-^{14}C.—A sample of the above phenyl benzhydryl ketone-^{14}C (1.77 g, 0.00614 mol, specific activity 2.863 ± 0.001 mCi/mol) was oxidized to benzoic acid and benzophenone using potassium permanganate dissolved in aqueous acetone, adapting the procedure of Bonner and Collines.[10] Yields of the oxidation products were

(19) Melting points were taken on a Thomas–Hoover "Uni-Melt" apparatus and are uncorrected. Nmr spectra were recorded on a Varian A-60A or T-60 spectrometer, with tetramethylsilane as an internal standard. Infrared spectral data were recorded on Beckman IR-8 or Perkin-Elmer 457 spectrometers. Vpc analysis of liquid samples was performed with a Varian Aerograph 90-P chromatograph. Mass spectra were obtained with a consolidated CEC 110 high resolution mass spectrometer at Union Oil Research Center, Brea, Calif.

(20) All isotopically labeled compounds were synthesized by Dr. Frederic J. Kakis at Oak Ridge National Laboratory, Oak Ridge, Tenn., under a Research Participation Fellowship. Radioactivity determinations were also performed during that period.

(21) V. A. Raaen and G. A. Ropp, *Justus Liebigs Ann. Chem.*, **25**, 174 (1953).

(22) From Oak Ridge National Laboratory.

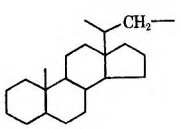
(23) H. Adkins and W. Zartman, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 606.

TABLE I

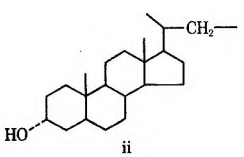
SUBSTITUTED ETHYLENES TESTED AND THEIR MAIN REARRANGEMENT PRODUCTS

	Alkene				Principal carbonyl product					
No	R_1	R_2	R_3	R_4	R_1'	R_2'	R_3'	R_4'	Yield, %[a]	Method[b]
1	Ph	Ph	Ph	Ph	Ph	Ph	Ph	Ph	94	A
2	Ph	Ph	Me	Ph	Ph	Me	Ph	Ph	88	A
3	Ph	Ph	Me	H	Ph	Me	Ph	H	85	B
4	Ph	Ph	*n*-Octyl	H	Ph	Ph	*n*-Octyl	H	87	B
5	Ph	Ph	Ph	H	Ph	Ph	Ph	H	96	B
6	*p*-MePh	*p*-MePh	*p*-MePh	H	*p*-MePh	*p*-MePh	*p*-MePh	H	95	B
7	*p*-CH_3OPh	*p*-CH_3OPh	*p*-CH_3OPh	H	*p*-CH_3OPh	*p*-CH_3OPh	*p*-CH_3OPh	H	94	B
8[c]	Ph	*p*-CH_3OPh	*o*-MePh	H	Ph	*p*-CH_3OPh	*o*-MePh	H	85	B
9[c]	Ph	3,4-Me_2Ph	3,4-Me_2Ph	H	3,4-Me_2Ph	3,4-Me_2Ph	Ph	H	82	B
10[c]	Ph	1-Naphtyl	Ph	H	1-Naphtyl	Ph	Ph	H	60	B
11[c]	Ph	2,4-Me_2Ph	2,4-Me_2Ph	H	2,4-Me_2Ph	Ph	2,4-Me_2Ph	H	78	B
12[c]	Ph	2,5-Me_2Ph	*p*-MePh	H	2,5-Me_2Ph	Ph	*p*-MePh	H	72	B
13[c]	Ph	2,5-Me_2Ph	*o*-MePh	H	2,5-Me_2Ph	Ph	*o*-MePh	H	70	B
14[c]	Ph	2,4-Me_2Ph	*o*-MePh	H	2,4-Me_2Ph	Ph	*o*-MePh	H	68	B
15[c]	Ph	H	*p*-CH_3OPh	*p*-MePh	*p*-MePh	Ph	*p*-CH_3OPh	H	86	B
16[c]	Ph	2,5-Me_2Ph	Ph	H	2,5-Me_2Ph	Ph	Ph	H	85	B
17[c]	Ph	3,4-Me_2Ph	Ph	H	3,4-Me_2Ph	Ph	Ph	H	82	B
18[c]	Ph	2,4-Me_2Ph	Ph	H	2,4-Me_2Ph	Ph	Ph	H	78	B
19[c]	Ph	*p*-MePh	Ph	H	Ph	Ph	*p*-MePh	H	86	B
20[c]	Ph	*m*-MePh	Ph	H	Ph	Ph	*m*-MePh	H	76	B
21	*p*-MePh	*p*-MePh	Ph	H	*p*-MePh	*p*-MePh	Ph	H	95	B
22[c]	Ph	*o*-MePh	Ph	H	*o*-MePh	Ph	Ph	H	76	B
23[c]	$Ph(CH_2)_3$–	Ph	Ph	H	H	Ph	Ph	$Ph(CH_2)_3$–	62	B
24[c]	Ph	*p*-ClPh	Ph	H	*p*-ClPh	Ph	Ph	H	45	B
25[c]	Ph	*p*-ClPh	3,4-Me_2Ph	H	*p*-ClPh	Ph	3,4-Me_2Ph	H	42	B
26[c]	*p*-Biphenyl	Ph	Ph	H	Ph	Ph	*p*-Biphenyl	H	84	B
27[c]	*p*-CH_3OPh	*p*-CH_3OPh	Steroid[e]	H	*p*-CH_3OPh	*p*-CH_3OPh	Steroid[e]	H	78	B
28	*p*-CH_3OPh	*p*-CH_3OPh	Steroid[f]	H	*p*-CH_3OPh	*p*-CH_3OPh	Steroid[f]	H	72	B
29[d]	*p*-CH_3OPh	*p*-CH_3OPh	H	H	*p*-CH_3OPh	*p*-CH_3OPh	H	H	62	B + C
30[d]	Ph	H	Me	H	H	Ph	Me	H	82	C
31[d]	Me	Me	Me	Me	Me	Me	Me	Me	58	C′
32[d]	Me	Me	Me	H	Me	Me	Me	H	38	C′
33[d]	Ph	Me	H	H	Ph	Me	H	H	55	C′
34[d]	Ph	Me	H	H	Me	Ph	H	H	60	B + C
35[d]	Me	Me	Et	H	Me	Me	Et	H	15	C′
36[d]	Me	H	Et	H	Et	Me	Me	H	10	C′
37[d]	1-Methylcyclohexene				1-Methylcyclohexanone					

[a] Often estimated from spectral and chromatographic data. In the event of mixtures the stated yield is the total yield of carbonyl compounds in the mixture. [b] See Experimental Section. [c] A mixture of threo and erythro or cis and trans isomers. [d] Procedure B failed with these compounds. [e] See structure i. [f] See structure ii.



i



ii

quantitative. The benzoic acid was purified by recrystallization from water followed by sublimation, mp 122.4–123.2°.

The benzophenone product was converted in the usual way into its 2,4-dinitrophenylhydrazone, which was purified by successive recrystallizations from ethyl acetate, mp 240.6–241.6°.

Radioactivity assays of these products showed that the benzoic acid fraction had retained all of the label (specific activity 2.862 ± 0.002 mCi/mol), whereas the benzophenone fraction was for all practical purposes nonradioactive (specific activity 0.003 ± 0.0002 mCi/mol).

Thus it was radiochemically demonstrated that the conversion of 1,1,2-triphenylethylene-1-^{14}C to phenyl benzhydryl ketone-^{14}C by method B was accompanied by 100% phenyl migration.

Chain Deuterium Labeled Phenyl Benzhydryl Ketone.—A sample of pure (mp 139–140°) phenyl benzhydryl ketone was dissolved in reagent grade toluene and treated under reflux with successive portions of pure (99.8%) D_2O made basic by the addition of lithium metal. A specially constructed pressure addition funnel, equipped with a two-way stopcock and an outlet, permitted the withdrawal of the exchanged portions of D_2O.

The incorporation of deuterium in the sample was followed by nmr by observing the gradual disappearance of the singlet proton peak at δ 6 ppm, relative to TMS (δ 0 ppm). In this fashion a sample of $Ph_2CDCOPh$ (99.5%) was obtained. The deuterated sample was subjected to the reaction conditions described in the next part of this section, under method B, after which it was reisolated and its nmr spectrum reexamined. It was found that all of the original deuterium label had been retained.

Rearrangement of Triphenylethylene in a Deuterated Medium.—A sample (1.0 g, 0.0039 mol) of pure (mp 71–72°) triphenylethylene was subjected to the experimental conditions described in the next part of this section under method B, except that the decomposing reagent consisted of a saturated solution of silver nitrate made up with D_2O (10% by volume) and CH_3OD (90% by

volume). The yield of crude (mp 132–134°) phenylbenzhydryl ketone was quantitative. After two recrystallizations from methanol, 0.96 g (90%) of the pure ketone (mp 139–140°) was obtained. The integrated nmr spectrum of the pure product showed that no deuterium had been incorporated into the ketone under these conditions.

Rearrangement of Triphenylethylene to Phenyl Benzhydryl Ketone in the Presence of Oxygen-18.—The object of this experiment was to determine whether oxygen-18 label from the water in the silver nitrate reagent is incorporated into the rearrangement product, phenyl benzhydryl ketone. The ketone, however, could conceivably undergo isotopic exchange after it is formed. To minimize this possibility, and in view of the fact that the yield was not important in this case, a procedure was sought which would, in the shortest possible reaction time, give a reasonable amount of relatively pure product. The conditions were worked out during several preliminary trials with unlabeled reagents.

Thus triphenylethylene (1 g, 0.0039 mol, mp 71–72°) was dissolved in spectral grade chloroform (25 ml) and cooled in a Dry Ice–isopropyl alcohol bath. The mixture was stirred magnetically and treated with a 5% solution of bromine in chloroform (4.1 ml) in a flask fitted with a drying tube.

Subsequently a saturated silver nitrate solution (35 ml), prepared with anhydrous methanol (95% by volume) and oxygen-18 enriched (3 atom %) water (5% by volume), was added to the reaction mixture and the stirring continued for 15 min. To remove the silver salts and achieve rapid drying three successive suction filtrations through layers of anhydrous magnesium and sodium sulfates were performed.

After removal of the solvents by rotatory evaporation a white solid was obtained which was purified by dissolving it in boiling ethanol, filtering the hot solution to remove insoluble impurities, and cooling at zero degrees overnight. The resulting crystals were collected by suction filtration and dried under vacuum over phosphorus pentoxide (0.31 g, 52%, mp 133–135°).

A sample of this product, identified by its infrared spectrum as phenyl benzhydryl ketone, was without further purification (for fear that it might undergo isotopic exchange) submitted for mass spectrometric analysis.

The mass spectrum showed two fragmentation peaks at masses 107 and 105 corresponding to the fragments $PhCH^{18}O$ and $PhCH^{16}O$ respectively. The ratio of these peaks was 1.5:1. However, when an authentic sample of phenyl benzhydryl ketone was subjected to the above reaction conditions and the mass spectrum of the recovered material was examined it showed a ratio of the same peaks of 0.5:1. Thus the net incorporation of oxygen-18 from the water to the ketone was found to be of the order of 1%.

II. Unlabeled Compounds and Experiments. Synthesis and Rearrangement of 2-Bromo-1,1,2-triphenylethanol.—An authentic sample of 2-bromo-1,1,2-triphenylethanol was prepared by the method of Lane and Walters,[13] and purified by filtration through decolorizing charcoal and recrystallization from hexane.

A sample (0.91 g) of the purified material (mp 123–124°) was then dissolved in chloroform (25 ml) and subjected to the conditions of method B described below. This resulted in the isolation of a quantitative yield (0.69 g, 98%) of crude (mp 133–135°) phenyl benzhydryl ketone. After one recrystallization from ether, 0.61 g (92%) of pure (mp 139–140°) phenyl benzhydryl ketone was obtained.

Substituted Ethylenes.—A complete list of the substituted ethylenes used in our study appears in Table I. Compounds 1 and 30–37 are commercial samples obtained from various sources and used without further purification. Compounds 2–4 and 27–28 were privately supplied.[24] All the other compounds were prepared by standard Grignard reactions of appropriate aryl- or alkylmagnesium halides with substituted benzophenones, deoxybenzoins, or esters. Some of the resulting tertiary alcohols underwent spontaneous dehydration during the work-up, generating the corresponding substituted ethylenes. The remainder were dehyrated by means of formic acid containing some *p*-toluenesulfonic acid. A few compounds were prepared by the Wittig reaction.[18]

This process in most cases gave mixtures of either cis and trans or threo and erythro isomers.

The separation of these isomers proved to be difficult and time consuming and was therefore abandoned. Instead the mixtures were directly subjected to the rearrangement methods described below.

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Rearrangement of Substituted Ethylenes to Aldehydes or Ketones.—The following methods for converting substituted ethylenes to carbonyl compounds have resulted from numerous preliminary trials during which the conditions which would produce the maximum yield of the desired products were carefully worked out. The nature and scope of these experiments has been explored in the Discussion section but space limitations preclude a detailed description. Method A is recommended for compounds, which for steric reasons react too slowly or not at all with bromine. Method B is the most generally applicable method. Methods C and C′ were used with some success in those cases where the previous methods failed and are still in the development stage.

Method A. Phenyl Trityl Ketone from Tetraphenylethylene.—A chlorine cylinder was connected successively to an empty trap, a reaction flask, another empty trap, a trap containing water, and two traps containing a saturated solution of potassium carbonate. The reaction flask was equipped with a magnetic stirrer, a pressure addition funnel, and gas inlet tube with a fritted glass tip. Commercial grade (mp 220–223°) tetraphenylethylene (3.3. g, *ca.* 0.01 mol) was dissolved in chloroform (250 ml) and introduced to the reaction flask which was immersed in an ice bath. While the mixture was stirred chlorine gas was allowed to flow through at a slow rate until the solution had acquired a distinct yellow color. The flow of gas was then discontinued and the stirred mixture was treated all at once with a saturated silver nitrate solution (350 ml) made up with methanol (90% by volume) and water (10% by volume). The mixture was stirred at room temperature overnight, after which the inorganic salts were filtered off and washed with chloroform, and the washings and the filtrate were combined. An excess of water was then added to the filtrate and the chloroform layer was separated, washed several times with water, and dried over anhydrous magnesium and sodium sulfates. Upon removal of the solvents a viscous oil was obtained (3.27 g, 94%) which crystallized spontaneously.

The product was identified by its infrared and nmr spectra as phenyl trityl ketone.

After two recrystallizations from ethanol a pure (mp 183–184°) product (3 g, 86%) was obtained. Compound 2, Table I, was similarly treated.

Method B. Phenyl Benzhydryl Ketone from Triphenylethylene.—A sample (0.8832 g) of pure (mp 71-72°) triphenylethylene was dissolved in chloroform (25 ml) and cooled in a Dry Ice–isopropyl alcohol bath. The stirred reactants were then treated rapidly (*ca.* 1 min) with a bromine solution (5% Br_2 and 95% $CHCl_3$ by volume) until the first appearance of a permanent amber color.

Approximately 5 ml of the bromine solution was required. The mixture was then decomposed at *once* by the addition of a saturated silver nitrate solution (50 ml) made up with methanol (90% by volume) and water (10% by volume). After a work-up procedure identical with that given in method A, a quantitative yield of crude phenyl benzhydryl ketone was obtained. After two recrystallizations from methanol a pure (mp 138–139°) sample (0.8834 g, 94%) of phenyl benzhydryl ketone was obtained. Compounds 3–28, in Table I, were similarly treated with the results shown therein.

Method C. 2-Phenylpropionaldehyde from *trans*-1-Phenyl-1-propene.—A commercial[25] sample (1 ml, *ca.* 0.0076 mol) of *trans*-1-phenyl-1-propene was dissolved in chloroform (50 ml). The solution was stirred magnetically at room temperature and treated rapidly with bromine (*ca.* 0.5 ml) until the first appearance of a permanent amber color. The mixture was then immediately decomposed by the addition of silver carbonate–Celite reagent[6] (6 g). The heterogeneous mixture was stirred at room temperature for 2 days, during which the silver carbonate reagent became progressively darker. The phases were separated by filtration and the solid phase was washed several times with chloroform, combining the washings with the filtrate. After removal of the solvent by fractional distillation a residual oil (0.835 g, 82%) remained which was identified by its infrared and nmr spectra as 2-phenylpropionaldehyde. Compounds 30, 34, and 37, Table I, were similarly treated except that in the case of compound 34 the starting solution was the end product of an unsuccessful attempt to promote the rearrangement by method B.

Method C′. Methyl Isopropyl Ketone from 2-Methyl-2-butene.—A commercial[26] sample of 2-methyl-2-butene (1 ml, *ca.*

(25) Fluka Chemical Co., Geneva, Switzerland.

(26) Prolabo Chemical Co., Paris, France.

0.0094 mol) dissolved in CCl_4 (50 ml) was brominated and decomposed as in method C. The heterogeneous mixture was then refluxed for 2 days, after which the supernatant liquid was examined by infrared, nmr, and gas chromatography. Comparison of these spectra with the corresponding spectra of an authentic sample revealed that the only carbonyl compound produced was methyl isopropyl ketone. The yield of the ketone (38%) was determined by integration of the gas chromatographic peaks. Compounds 31, 33, and 35–36, Table I, were similarly treated, with the results stated therein.

Registry No.—Phenyl trityl ketone, 466-37-5; tetraphenylethylene, 632-51-9; phenyl benzhydryl ketone, 1733-63-7; triphenylethylene, 58-72-0; 2-phenylpropionaldehyde, 93-53-8; *trans*-1-phenyl-1-propene, 873-66-5; methyl isopropyl ketone, 563-80-4; 2-methyl-2-butene, 513-35-9.

Acknowledgment.—We are indebted to Dr. Lloyd Snyder for taking the mass spectra, to Dr. C. J. Collins, B. Benjamin, and V. Raaen for their help in the synthesis and assay of the isotopically labeled compounds, and to Professor M. Fétizon for supplying us with some of the samples and reagents.

Notes

Synthesis of *dl*-Muscone from Exaltone (Cyclopentadecanone)

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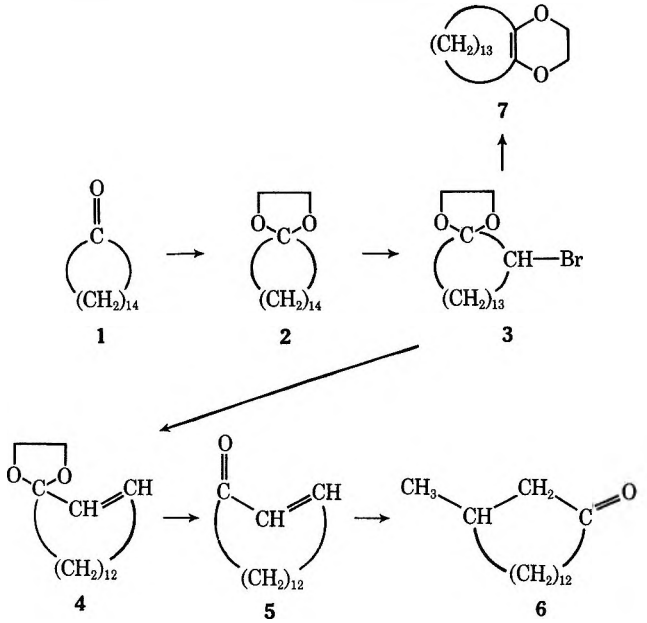
Muscone (6) and exaltone (1) are two similar compounds. The difference is that the former is a natural product;[1] the latter lacks a β-methyl group. Though there is a plethora of publications[2] for the synthesis of 6 from various starting materials, only Ruzicka and Stoll[3] have described the preparation of 6 from 1 in poor yield, The present paper reports an alternate five-step synthesis of *dl*-muscone (6) from exaltone (1) in an overall yield of 60%.



Treatment of 1 with ethylene glycol and *p*-toluenesulfonic acid monohydrate[4] in benzene afforded ketal 2 (98%) which was brominated with phenyltrimethylammonium tribromide[4,5] in tetrahydrofuran for 2 hr at 0° to give 2-bromo ketal 3 (≈100%). Though the treatment of 3 with potassium *tert*-butoxide in either *tert*-butyl alcohol or dimethyl sulfoxide[6] gave only dioxin 7, dehydrobromination of 3 with 1,5-diazabicyclo[4.3.0]non-5-ene[7,8] at 110° for 64 hr furnished the α,β-unsaturated ketal 4 (70%). Mild acid hydrolysis of 4 gave cyclopentadecenone (5) (100%) which on treatment with methyl Grignard in the presence of cuprous chloride and ether[2,9] was smoothly converted to *dl*-muscone (6) (81%).

Experimental Section

Melting points are uncorrected. Gas–liquid chromatography (glc) analyses were performed on an F & M 810 instrument using 5% Carbowax 20M and 5% silicone SE-30 coated on Anakrom ABS (80–100 mesh) packed in stainless steel columns (25 ft × 0.25 in.). The following spectrometers were used: infrared, Beckman IR-5A or Beckman IR-4; nuclear magnetic resonance, Varian HA-100 (CCl_4, TMS as internal standard); mass spectra, CEC Model 21-103 C, and AEI MS 9 for high-resolution spectra. Major mass spectral fragmentation peaks were recorded in decreasing order of intensity except for the molecular ion $(M)^+$ peak which is listed first. Five per cent deactivated silicic acid made by adding 5 ml of water to 95 g of silicic acid (Grace, 100–200 mesh) was used for column chromatography. Anhydrous magnesium sulfate was used as drying agent. Exaltone was purchased from Firmenich, New York, N. Y.

Ethylene Ketal of Cyclopentadecanone (2).—A mixture of 1 (50 g, 0.22 mol), *p*-toluenesulfonic acid monohydrate (4.2 g, 0.022 mol), freshly distilled ethylene glycol (444 ml), and anhydrous benzene (2.7 l.) was refluxed with constant removal of water. After 14 hr of reflux, 14 ml of water was collected. The mixture was cooled, the ethylene glycol layer was separated, and the benzene layer was washed successively with saturated sodium bicarbonate solution and sodium chloride solution and

(1) Muscone is the principal constituent (1%) of musk pod obtained from the male deer *Moschus moschiferus*.

(2) B. D. Mookherjee, R. Trenkle, and R. R. Patel. *J. Org. Chem.*, **36**, 3266 (1971), and references cited therein.

(3) L. Ruzicka and M. Stoll, *Helv. Chim. Acta*, **17**, 1308 (1934).

(4) W. S. Johnson, J. D. Bass, and K. L. Williamson, *Tetrahedron*, **19**, 861 (1963).

(5) A. Marquet, M. Dvolaitzky, H. Kagan, L. M. C. Quannes, and J. Jacques, *Bull. Soc. Chim. Fr.*, 1822 (1961).

(6) P. E. Eaton, *J. Amer. Chem. Soc.*, **84**, 2344 (1962).

(7) H. H. Wasserman, D. D. Ketih, and J. Nadelson, *ibid.*, **91**, 1264 (1969).

(8) H. Oediger, H. Kabbe, F. Muller, and K. Either, *Chem. Ber.*, **99**, 2012 (1966).

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dried. Removal of solvent gave 60.9 g (100%) of **2** which solidified on standing, mp 29.5–30°. Glc (silicone SE-30) showed one major peak (98.4%, **2**) and one minor peak (1.6%, **1**): ir of **2** (neat) 3.4, 3.5, 6.83, 7.2, 7.29, 7.39, 8.0, 8.29, 8.42, 8.6, 8.99, 9.1, 9.25, 9.35, 9.55, 10.55, 10.9, 12.1, 12.7, 14.1 μ; nmr δ 1.32 and 1.5 [two s, 28, $-(CH_2)_{14}-$], 3.89 (s, 4, $-OCH_2CH_2O-$); mass spectrum *m/e* 268 $(M)^+$, 99, 225, 155, 55, 84, 41.

Anal. Calcd for $C_{17}H_{32}O_2$: *m/e* 268.2402. Found: *m/e* 268.2403.

Ethylene Ketal of 2-Bromocyclopentadecanone (3).—To a cold (0°) stirred solution of **2** (60.9 g, 0.228 mol, from the above experiment) in anhydrous tetrahydrofuran (1.5 l.) was added rapidly phenyl trimethylammonium tribromide (85.7 g, 0.228 mol). An orange color was developed which gradually disappeared after 1 hr. The stirring was continued for an additional 1 hr at 0°. The mass was poured into saturated sodium bicarbonate solution (600 ml) and was stirred for 30 min. Most of the tetrahydrofuran was removed under reduced pressure without heating. The aqueous layer was extracted with ether. The ethereal solution was washed with saturated sodium chloride solution and dried. Removal of solvent gave 83 g (107%) of crude bromide **3**. Glc (silicone SE-30) showed a major peak and a minor peak due to **1** and **2**, respectively. Bromide **3** did not elute from the glc column: ir of **3** (crude) 5.89 (C=O of regenerated **1**) and 9.5 μ (–COC– of ketal **3**); nmr δ 1.1–2.1 (broad m with s at 1.32 and a shoulder at 1.3), 2.66 (small t), 3.42 (small t), 3.68 (small t), 3.8–4.36 (m, –CHBr and $-OCH_2CH_2O-$), 4.5–4.7 (small m); mass spectrum *m/e* 346 $(M)^+$ and 348 $(M + 2)^+$.

Anal. Calcd for $C_{17}H_{31}O_2Br$: *m/e* 346.1507. Found: *m/e* 346.1508.

Ethylene Ketal of 2-Cyclopentadecen-1-one (4.)—A 2.5-l. flask equipped with stirrer, reflux condenser, thermometer, and a nitrogen inlet tube was charged with crude bromide **3** (83 g, 0.2 mol, from the previous experiment) and 1,5-diazabicyclo[4.3.0]non-5-ene (89.28 g, 0.72 mol). The mixture was heated at 110° for 64 hr, cooled, and poured into water. The aqueous mixture was extracted with ether. The combined ether extracts were washed successively with water and saturated sodium chloride solution and dried. Removal of solvent gave 56.5 g of crude oil which was chromatographed on deactivated silicic acid (600 g); 10–20% ether in hexane (1.5 l. per fraction) eluted 47.1 g (74.6%) of **4**. Glc (Carbowax 20M) analysis showed one major peak (88%, **4**) and two minor peaks due to **1** (5%) and **2** (7%): ir of **4** (neat) 3.45, 3.5, 6.0, 6.85, 6.9, 7.2, 7.3, 7.4, 7.65, 7.79, 7.99, 8.49, 8.9, 9.5, 10.25, 10.55, 12.4, 13.4, and 13.85 μ; nmr δ 1.1–2.3 (major s at 1.3, and broad m at 1.7 and 2.1, 24, $-CH_2-$), 3.9 (s, 4, $-OCH_2CH_2O-$), 5.1–6.0 (d at 5.3, 1 and m at 5.7, 1, –CH=CHCOO); mass spectrum *m/e* 266 $(M)^+$, 125, 99, 55, 41.

Anal. Calcd for $C_{17}H_{30}O_2$: *m/e* 266.2247. Found: *m/e* 266.251.

2-Cyclopentadecen-1-one (5).—A solution of **4** (46.1 g, 0.17 mol, from the previous experiment) and *p*-toluenesulfonic acid monohydrate (6.65 g, 0.035 mol) in water (100 ml) and acetone (50 ml) was stirred for 16 hr at room temperature. Most of the acetone was removed under reduced pressure, and the residue was poured into water. The aqueous mixture was extracted with ether. The ether extracts were washed successively with water and saturated sodium chloride solution and dried. Removal of solvent under reduced pressure yielded 38.5 g (100%) of crude **5**. Glc analysis (silicone SE-30) showed one major peak (74%, **5**) and one minor peak (26%, **1**): ir of **5** (neat) 3.4, 3.5, 5.82, 5.9, 5.99, 6.15, 6.77, 6.82, 6.9, 7.2, 7.4, 7.8, 8.25, 8.75, 8.85, 9.25, 9.55, 10.2 μ; nmr δ 1.1–2.0 (m, 20 with a s at 1.3, $-CH_2-$), 2.1–2.54 (m, 4, $-CH_2COC{=}CCH_2$), 6.08–7.0 (d, at 6.16, 1 and m at 6.8, 1, –CH=CHCO); mass spectrum *m/e* 222 $(M)^+$ 41, 55, 81, 67, 68.

Anal. Calcd for $C_{15}H_{26}O$: *m/e* 222.1983. Found: *m/e* 222.1986.

***dl*-Muscone (6).**—A solution of **5** (37.5 g, 0.169 mol, from the previous experiment) in anhydrous ether was added slowly over a period of 1 hr to a stirred mixture of methylmagnesium bromide (62 ml, 0.185 mol) and cuprous chloride (11.16 g) in anhydrous ether (750 ml) at 10°. After the addition was completed, the reaction mixture assumed a dark grayish-green color and stirring was continued for 2 hr at 10°. Cold aqueous 10% hydrochloric acid (200 ml) was added slowly, and the organic phase was separated. The aqueous layer was extracted with ether. The combined ethereal solutions were washed successively with saturated sodium bicarbonate solution, water, and saturated sodium chloride solution (50 ml) and dried. Removal of solvent under reduced pressure gave 40.2 g of crude oil which was chromatographed on deactivated silicic acid (600 g): 5% and 7.5% ether in hexane (1 l. per fraction) eluted 32.2 g (81.1%; an overall 61.5% from exaltone **2**) of muscone (**6**). Glc analysis (Carbowax 20M and silicone SE-30) showed one peak. This material was further distilled to obtain 27 g of **6**: bp 100–101° (0.09 mm); ir of **6** (neat) 3.41, 3.5, 5.84, 6.82, 7.09, 7.29, 7.8, 8.35, 8.85, 9.2, 9.45, 9.8, and 14.0 μ; nmr δ 0.92 (d, J = 6 Hz, 3, CH_3CH-), 1.1–2.0 (m, 23, with s at 1.3), 2.1–2.5 (m, 4, $-CH_2COCH_2$); mass spectrum *m/e* 238 $(M)^+$, 41, 55, 85, 69, 71, 43.

(All these spectral data were superimposable with those of natural muscone and also with synthetic *dl*-muscone made from 1,9-cyclohexadecadiene.[2])

Anal. Calcd for $C_{16}H_{30}O$: *m/e* 238.2296. Found: *m/e* 238.2298.

Reaction of 3 with Potassium *tert*-Butoxide.—A mixture of **3** (1.15 g, 0.0033 mol), potassium *tert*-butoxide (1.11 g, 0.01 mol), and anhydrous *tert*-butyl alcohol (20 ml) was refluxed for 20 hr. Most of the solvent was removed under reduced pressure, water (20 ml) was added, and the mixture was extracted with ether. The combined ether extracts were washed with saturated sodium chloride solution and dried. Evaporation of solvent under reduced pressure gave 0.8 g of yellow oil. Glc (Carbowax 20M) gave one major peak due to **7**: ir (neat) 3.42, 3.5, 5.92, 6.9, 7.4, 7.82, 8.09, 8.3, 8.6, 8.7, 9.02, 9.32, 9.85, 10.8, and 11.15 μ; nmr δ 1.2–1.8 (m, 22, with s at 1.35, $-CH_2-$), 2.04 (m, 4, $-CH_2C{=}CCH_2$), 3.98 (s, 4, $-OCH_2CH_2O-$); mass spectrum *m/e* 266 $(M)^+$, 99 (base peak).

A solution of **3** (1.15 g) and potassium *tert*-butoxide (1.11 g) in dimethyl sulfoxide (20 ml) was refluxed for 10 hr. After usual work-up, a crude oil (1 g) was obtained. Glc showed a major peak due to **7**.

Anal. Calcd for $C_{17}H_{30}O_2$: *m/e* 266.2295. Found: *m/e* 266.2248.

Registry No.—**1**, 502-72-7; **2**, 184-41-8; **3**, 32247-06-6; **4**, 32247-07-7; **5**, 32247-08-8; **6**, 956-82-1; **7**, 32304-18-0.

Acknowledgment.—The authors express their gratitude to Dr. W. I. Taylor for his constant encouragement during this work. We also gratefully acknowledge Professor H. H. Wasserman for providing us with the detailed procedure of dehydrobromination with diazabicyclononene. We also thank Mr. H. Bondarovich for high resolution mass spectral analyses and Mr. M. Jacobs for nmr analyses.

Transannular Ring Closure by Reduction of Cyclooctane-1,5-diones. Synthesis of a Bisnoradamantan-1-ol

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A reasonable approach to the synthesis of the series of theoretically interesting bridgehead olefins **3**[1] appeared to be double bond formation from the glycols **2**, by one of a number of known reactions.[2–4] More-

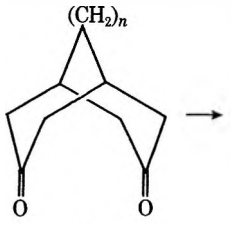
(1) For a recent example of a polycyclic molecule with a similar "strained" double bond, see N. M. Weinshenker and F. D. Greene, *J. Amer. Chem. Soc.*, **90**, 506 (1968).

(2) E. J. Corey, F. A. Carey, and R. A. E. Winter, *ibid.*, **87**, 934 (1965).

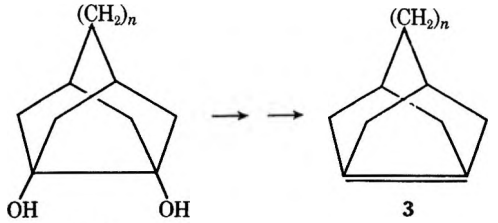
(3) J. N. Hines, M. J. Peagram, G. H. Whitham, and M. Wright, *Chem. Commun.*, 1593 (1968).

(4) F. W. Eastwood, K. J. Harrington, J. S. Josan, and J. L. Pura, *Tetrahedron Lett.*, 5223 (1970).

over, the facility of 1,5-transannular reactions in cyclooctane rings[5] and instances of intramolecular pinacol formation on reduction of diketones[6] suggested that the required diols (2) might be synthesized from the bridged cyclooctane-1,5-diones (1).



1



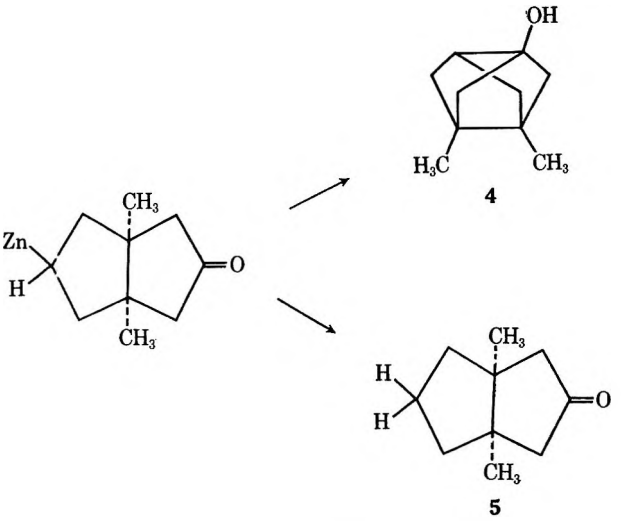
2 3

As a model system we first examined the reduction of cyclooctane-1,5-dione[7] itself. Reaction of the diketone with Zn–HCl in acetic anhydride[8] led to the isolation of a crystalline diacetate. Treatment with sodium methoxide in methanol liberated the bicyclic diol,[9] homogeneous by glc, in 60% overall yield after recrystallization from hexane, mp 61.5–62.0.° Alternatively the diol could be obtained directly and in essentially quantitative yield by reduction of the diketone with zinc amalgam in aqueous hydrochloric acid.[11]

Similarly, in the bridged system, reduction of bicyclo[3.3.1]nonane-3,7-dione (1, $n = 1$)[12] gave tricyclo[3.3.1.0^{3,7}]nonane-3,7-diol (2, $n = 1$), mp 301–303°.[13]

In contrast, in the $n = 0$ series the readily available 1,5-dimethylbicyclo[3.3.0]octane-3,7-dione[14] on reduction in acetic anhydride did not give the corresponding tricyclic diol. Instead, after deacetylation and purification by chromatography followed by sublimation,[15] a mono alcohol (*m/e* 152, correct analysis for $C_{10}H_{16}O$) was obtained in 50% yield, mp 108–109°. Its nmr spectrum ($CDCl_3$) showed δ 1.10 (s, 6 H), 1.2–1.9 (m, 8 H), 2.10 (t, $J = 3$ cps, 1 H) and one exchangeable proton, consistent with its formulation as 3,7-dimethyltricyclo[3.3.0.0^{3,7}]octan-1-ol (**4**). However, when the reduction was carried out in aqueous solution, **4** was only a minor product (10% yield); the major one was 1,5-dimethylbicyclo[3.3.0]octane, the hydrocarbon formed by "normal" Clemmensen reduction of the diketone.[16]

A mechanism for the formation of **4**, which also rationalizes the dependence of its yield on the solvent, is shown below. In the absence of appreciable interaction between the carbonyl groups in the diketone, due to the $n = 0$ bridge, Clemmensen reduction is expected to occur. A postulated intermediate in the reduction is the organozinc compound shown below.[6] It could undergo intramolecular addition to the remaining carbonyl to give **4** or it could be protonated to give **5**. Which course the reaction takes would depend on the availability of protons from the solvent. Clearly the path leading to **5** would be favored in aqueous solution; and **5** is found, as expected, to undergo reduction to the observed bicyclic hydrocarbon in the aqueous reaction.



Not only is **4** of interest on account of the unusual mechanism by which it is formed, it is the first molecule with a bisnoradamantane skeleton in which the bridgehead carbonium ion can be studied.[17] The geometry of this ion should be particularly unfavorable; in fact, Bingham and Schleyer have calculated that acetolysis of even the triflate to produce the bridgehead carbonium ion should have a rate constant on the order of 10^{-11} sec^{-1} at 200°.[18] Our preliminary results on the solvolysis of the tosylate indicate that the reaction appears to be accelerated by fission of the bond between C-2 and C-3, which both circumvents the bridgehead ion and relieves strain present in the bisnoradamantane skeleton.[19] Another manifestation of the strain present in this system is the transformation of **4** to **5** by potassium *tert*-butoxide in refluxing *tert*-butyl alcohol.[20]

(5) Review: A. C. Cope, M. M. Martin, and M. A. McKervey, *Quart. Rev., Chem. Soc.*, **20**, 119 (1966).

(6) Review: J. G. St. C. Buchanan and P. D. Woodgate, *ibid.*, **23**, 522 (1969).

(7) G. I. Glover, R. B. Smith, and H. Rapoport, *J. Amer. Chem. Soc.*, **87**, 2003 (1965).

(8) T. J. Curphey, C. W. Amelotti, T. P. Layloff, R. L. McCartney, and J. H. Williams, *ibid.*, **91**, 2817 (1969).

(9) The expected cis ring fusion was documented by the formation of the cyclic acetal of benzaldehyde, which on reaction with *n*-butyllithium[1] in ether gave $\Delta^{1,5}$-bicyclo[3.3.0]octene.[10]

(10) (a) L. A. Paquette and R. W. Hauser, *J. Amer. Chem. Soc.*, **91**, 3870 (1969); (b) E. J. Corey and E. Block, *J. Org. Chem.*, **34**, 1233 (1969); (c) E. Block, Ph.D. Thesis, Harvard University, 1967.

(11) E. Wenkert and J. E. Yoder, *J. Org. Chem.*, **35**, 2986 (1970).

(12) A. R. Gagneux and R. Meier, *Tetrahedron Lett.*, 1365 (1969).

(13) While this work was in progress, the preparation of this diol (reported mp 297–298°) by transannular ring closure on photoreduction of the diketone was reported by T. Mori, K. H. Kimoto, and H. Nozaki, *ibid.*, 2419 (1970).

(14) U. Weiss and J. M. Edwards, *ibid.*, 4885 (1968).

(15) From the crude product 1,5-dimethylbicyclo[3.3.0]octan-3-one (**5**) was also isolated in 10% yield.

(16) The hydrocarbon is not produced from **4**, which is stable under the reaction conditions.

(17) Solvolysis of 2-chloro- and a derivative of 2-hydroxybisnoradamantane has been studied: (a) P. K. Freeman, R. B. Kinnel, and J. D. Ziebarth, *Tetrahedron Lett.*, 1059 (1970); (b) R. R. Sauers and B. R. Sickles, *ibid.*, 1067 (1970).

(18) R. C. Bingham and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **93**, 3189 (1971).

(19) W. T. Borden and C. Schmidt, unpublished results. We are also studying the solvolysis of a derivative of the unsubstituted bisnoradamantan-1-ol.

(20) Similar facile reketonizations are observed in other strained systems: (a) cyclopropanols, C. H. DePuy, *Accounts Chem. Res.*, **1**, 33 (1968); (b) bird cage alcohols, R. Howe and S. Winstein, *J. Amer. Chem. Soc.*, **87**, 915 (1965); T. Fukunaga, *ibid.*, **87**, 917 (1965); (c) strained cyclobutanols, K. B. Wiberg, J. E. Hiatt, and K. Hsieh, *ibid.*, **92**, 544 (1970).

A study of the stereochemistry of this reaction has been reported separately.[21]

Experimental Section

All nmr spectra were run on a Varian A-60 instrument using $CDCl_3$ as solvent. Melting points were taken in sealed capillaries and are uncorrected. All reactions were carried out under an atmosphere of nitrogen.

General Procedure for Zn–HCl Reductions.—Acetic anhydride (40 ml) was saturated with HCl at −5 to −10° and 1 g of diketone was added; 10 g of activated zinc dust[22] was added slowly in portions over 3 hr with vigorous mechanical stirring so that the temperature of the reaction mixture remained below −5°. If the temperature was allowed to rise higher than this, the reaction became uncontrollable and the temperature rose rapidly to 40–50°. On completion of the addition the mixture was stirred for 2 hr longer at −5° and then filtered quickly through a prechilled funnel to remove the zinc residue, which was washed with cold acetic anhydride.

The diacetate was isolated by diluting the filtrate with 40 ml of water and adding solid Na_2CO_3 until the pH was neutral. The solution was extracted with three 100-ml portions of CH_2Cl_2, and the combined organic layers were washed with two 100-ml portions of water and dried over $MgSO_4$. Evaporation of solvents under reduced pressure gave the crude product.

This was converted to the free alcohol by stirring in 15 ml of methanol, 2 *N* in $NaOCH_3$, for 1 hr at room temperature. The solution was neutralized with excess Amberlite IR 120 (pyridinium form[23]), and the solution was decanted from the resin, which was washed with two 20-ml portions of methanol. Removal of the methanol under reduced pressure gave the crude alcohol, which was purified by chromatography, recrystallization, or sublimation.

Alternatively the alcohol could be isolated directly by adding the acetic anhydride filtrate to 200 ml of cold methanol and leaving the solution overnight. The solvents were removed under reduced pressure, and the oily residue was taken up in CH_2Cl_2 and washed with two 50-ml portions of H_2O, two 50-ml portions of 10% $NaHCO_3$, and 50 ml of H_2O. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to give the crude alcohol.

Reactions using zinc amalgam in aqueous solution were carried out using the procedure of Wenkert and Yoder.[11]

Bicyclo[3.3.0]octane-1,5-diol.—The diol showed a symmetrical multiplet centered at δ 1.8 (12 H) and two exchangeable protons. An analytical sample, mp 61.5–62.0°, was obtained by recrystallization from hexane, mass spectrum *m/e* 142.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.61; H, 9.78.

$\Delta^{1,5}$-Bicyclo[3.3.0]octene.[10]—The benzaldehyde acetal of bicyclo[3.3.0]octane-1,5-diol was prepared by refluxing a solution of 426 mg (3 mmol) of the diol and 318 mg (3 mmol) of benzaldehyde in 15 ml of benzene with a catalytic amount (20 mg) of *p*-toluenesulfonic acid for 3 hr. The cooled solution was stirred with solid K_2CO_3 and the solvents were evaporated. The residue was chromatographed over 10 g of neutral alumina to remove trace amounts of unreacted starting material. Elution with hexane gave 620 mg (90% yield) of a straw-colored liquid, nmr δ 1–2.5 (m, 12 H), 5.80 (s, 1 H), and 7.4 (m, 5 H).

To a solution of 230 mg (1 mmol) of the benzaldehyde acetal in 20 ml of ether at 0° was added 1.6 ml of 1.3 *M* *n*-butyllithium in pentane (2.1 mmol). The solution was stirred for 24 hr at 0° and then 2 ml of H_2O was added. The organic layer was separated, the water was washed with two 2-ml portions of ether, and the combined ether washings were washed with 2 ml of H_2O and 2 ml of brine. After drying over $MgSO_4$, most of the solvent was removed by distillation through a 25-cm Vigreux column. Then 1 ml of CH_2Cl_2 was added, the stillhead was attached directly to the pot, and the distillation was continued until no more solvent was collected at a pot temperature of 80°. The pot was allowed to cool to room temperature and the distillation was continued under vacuum (water aspirator ≈15 mm) while cooling the receiver in liquid nitrogen. The pot was briefly heated to 60° before the distillation was discontinued; 170 mg of volatile material was collected and analyzed by nmr, which showed three singlets, one for CH_2Cl_2, one for cyclohexane (present in the commercial *n*-butyllithium solution), and one at δ 2.18 from the $\Delta^{1,5}$-bicyclo[3.3.0]octenes.[10b] A pure sample of this material was isolated by glc and had an ir spectrum identical with that reported by Block.[10c]

Tricyclo[3.3.1.0^{3,7}]nonane-3,7-diol (2, *n* = 1).—Prepared by the general procedure described above, the crude diol was stirred with ether and filtered to give a granular solid, mp 301–303° (lit. 297–298°), mass spectrum *m/e* 154.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.05; H, 9.19.

3,7-Dimethyltricyclo[3.3.0.0^{3,7}]octan-1-ol (4).—The crude alcohol obtained by the general procedure described above was purified by chromatography on silica gel (25 g/g). Elution with 7:3 pentane–ether removed the ketone 5 from the column. The alcohol 4 eluted with 1:1 pentane–ether. Sublimation at 55–60° (15 mm) gave a 50% yield of pure alcohol, mp 108–109°, mass spectrum *m/e* 152.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.15; H, 10.68.

Tosylate of 4.—To a solution of 1.0 g (6.5 mmol) of the alcohol in 5 ml of dry pyridine at 0° was added 1.4 g (7.2 mmol) of tosyl chloride in 5 ml of pyridine. The solution was stirred for 16 hr, after which 0.5 ml of H_2O was added and the solution was stirred for an additional hour. Most of the pyridine was removed under reduced pressure, and the residue was taken up in CH_2Cl_2 and washed with 15 ml of 1 *M* HCl, 15 ml of H_2O, and 15 ml of 10% $NaHCO_3$. The CH_2Cl_2 was evaporated under reduced pressure to give 1.6 g (80% yield) of spectroscopically pure tosylate. Recrystallization from pentane afforded an analytical sample, mp 75.5–76.5°.

Anal. Calcd for $C_{17}H_{22}O_3S$: C, 66.65; H, 7.24; S, 10.46. Found: C, 66.57; H, 7.15; S, 10.54.

1,5-Dimethylbicyclo[3.3.0]octan-3-one (5).—A solution of 152 mg (1 mmol) of 4 and 168 mg (1.5 mmol) of potassium *t*-butyl alcohol was refluxed for 4 hr. After cooling it was diluted with 7 ml of H_2O, neutralized with 1 *M* HCl, and extracted with three 20-ml portions of ether. The ether extracts were washed with two 10-ml portions of water and with saturated brine, and dried over $MgSO_4$. Evaporation of the solvent gave 130 mg (85%) of the ketone 5 (ir 1740 cm^{-1}), pure by nmr [δ 1.06 (s, 6 H), 1.73 (s, 6 H), and 2.20 (d, 4 H)]. An analytical sample was prepared by sublimation.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.65: H, 10.45.

Registry No.—2 (*n* = 1), 29898-26-8; 4, 32139-02-9; 4 tosylate, 32256-06-7; 5, 32139-03-0; bicyclo[3.3.0]-octane-1,5-diol, 32139-04-1.

Acknowledgment.—We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Research Corporation for partial support of this work. We also wish to thank Messrs. Richard Weinberg and Conrad Schmidt for some experimental assistance.

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

(22) S. Yamamura and Y. Hirata, *J. Chem. Soc. C*, 2887 (1968).

(23) Prepared by washing the resin with 10% aqueous pyridine followed by distilled water and then methanol.

Synthesis of 1-Methyladamantano[1,2-*b*]pyrrolidine, a Novel Heterocyclic System

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Received May 24, 1971

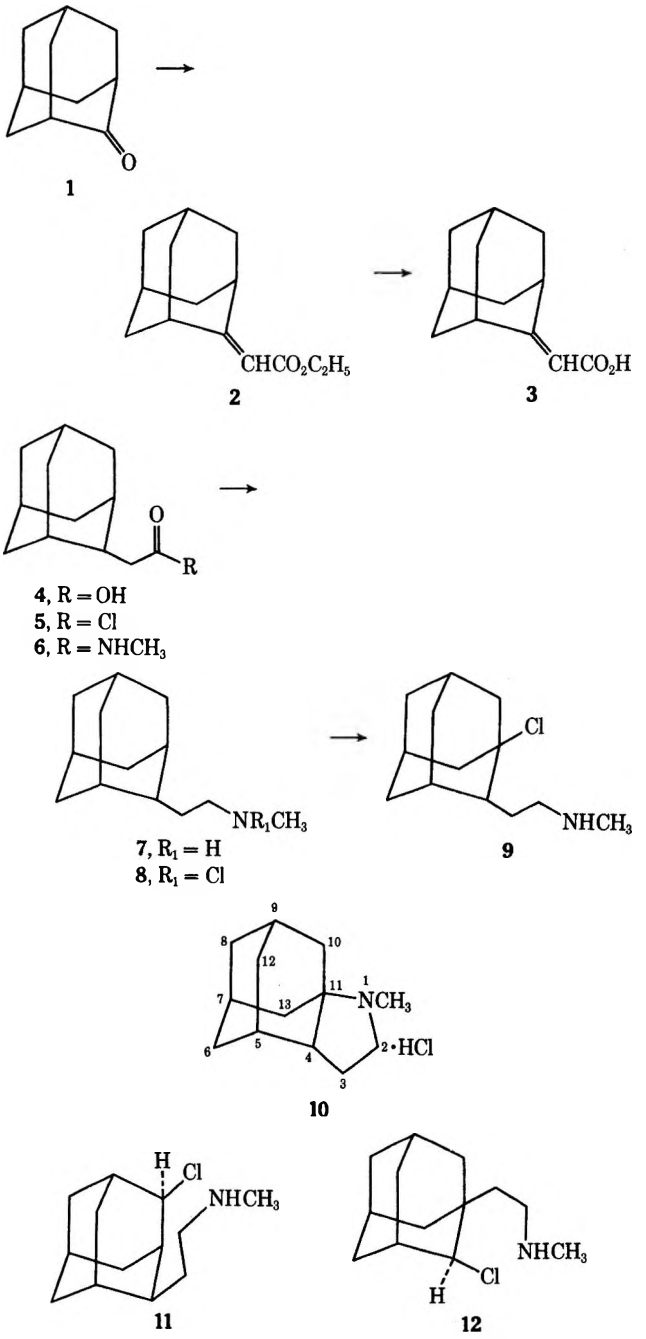
The interesting chemistry of adamantane[1] and the biological activity of aminoadamantane and its de-

(1) R. C. Fort, Jr., and P. v. R. Schleyer, *Chem. Rev.*, **64**, 277 (1964).

rivatives[2] have stimulated an interest in the syntheses of 1,2-disubstituted adamantanes.[3] The recent report on the syntheses of compounds containing heterocyclic ring systems fused onto the 1 and 2 positions of adamantane[4] prompts us to report our synthesis of 1-methyladamantano[1,2-*b*]pyrrolidine (**10**), a novel heterocyclic system.

The successful route to the synthesis is based on the reaction sequence shown in Scheme I. The reaction

SCHEME I



of 2-adamantanone with triethyl phosphonoacetate and sodium hydride gave Δ^2,α-adamantaneacetic acid ethyl ester (**2**). It was determined that, by using 1.5 equiv of triethyl phosphonoacetate to 1 equiv of 2-adamantanone and allowing the reaction to proceed at 45°, a nearly quantitative yield of **2** could be realized. Base hydrolysis of **2** furnished Δ^2,α-adamantaneacetic acid (**3**) in 98% yield. Catalytic hydrogenation of **3** over palladium on charcoal gave a quantitative yield of 2-adamantaneacetic acid (**4**). Compound **4** was converted to its acid chloride **5** by reaction with thionyl chloride. Treatment of **5** with 40% aqueous monomethylamine furnished an 86% yield of *N*-methyl-2-adamantaneacetamide (**6**). Reduction of **6** with lithium aluminum hydride in tetrahydrofuran gave a 90% yield of *N*-methyl-2-adamantaneethylamine (**7**). Treatment of **7** with aqueous sodium hypochlorite solution[5] yielded the desired *N*-chloroamine **8**.

The *N*-chloroamine **8** was then subjected to Hofmann–Loeffler–Freytag reaction. The reaction is customarily run in strong sulfuric acid or sulfuric acid–acetic acid mixtures, with heat or ultraviolet light used to initiate the free-radical reaction.[6] The use of strong acid and heat, in our case, led to the formation of 2-adamantanone.[7] However, photolysis of **8** in the sulfuric acid–acetic acid mixture, using a low-pressure mercury lamp at 25° for 1 hr, gave a good yield (85%) of a single product (tlc). It has been assigned structure **9**: nmr τ 6.05–6.30 (br, 1, NH), 7.44–7.58 (m, 2-$CH_2N<$), 7.75–7.87 (d, 3, CH_3NH), 7.87–8.09 (2, CH_2), 8.09–8.5 (s, 14 H). The alternate isomeric structure **11** is ruled out, since the characteristic upfield absorption (doublet at τ 8.5–8.7) of the hydrogen on the carbon bearing the chlorine in compounds of type **12**[8] is absent in our product. The much greater stability of the tertiary adamantane radical, together with the preferential formation of six-atom cyclic transition states, generally noted in Hofmann–Loeffler–Freytag reactions,[9] would explain the exclusive formation of **9**.

The cyclization of **9** presented considerable difficulties. Compound **9** was found to be particularly resistant to solvolytic displacement under a variety of reaction conditions. Clearly, no "back-side" attack is possible at the tertiary center through the cage compound. Even the aluminum halide catalyzed substitution reaction conditions involving the bridgehead "carbonium ion," so generally successful in the adamantane field,[1] failed. The cyclization was finally achieved in 34% yield by heating at 290° for 10 min. The structure of **10** is supported by microanalysis and the spectral data: ir 3.70–4.4 μ (>NH^+); nmr τ −2.17 to −1.50 (br, 1, N^+H), 5.83–6.42 (m, 2, $CH_2N<$), 6.90–7.30 (m, 2, CH_2), 7.35–7.45 (d, 3, >N^+H-CH_3), 7.65–8.5 (m, 14 H); mass spectrum *m/e* 191 (M^+ − HCl).

(2) (a) W. L. Davies, R. R. Grunert, R. F. Haff, J. W. McGrahen, E. N. Newmager, M. Paulshock, J. C. Watts, T. R. Wood, E. C. Hermann, and C. E. Hoffmann, *Science*, **144**, 862 (1964); (b) K. Gerzon, D. J. Tobias, Sr., E. R. Holmes, R. E. Rathbun, and R. W. Kattaw, *J. Med. Chem.*, **10**, 603 (1967), and earlier papers; (c) G. Tsatsas, E. Costakis, S. Casadio, B. Lumachi, and E. Marazzi-Uberti, *Ann. Pharm. Fr.*, **27**, 364 (1969); (d) A. Pedrazzoli, L. Dall'asta, V. Guzzon, and E. Ferrero, *Farmaco. Ed. Sci.*, **25**, 822 (1970).

(3) (a) W. H. W. Lunn, W. D. Podmore, and S. S. Szinai, *J. Chem. Soc. C*, 1657 (1968); (b) M. A. McKervey, *Chem. Ind. (London)*, 1791 (1967).

(4) C. K. Chakrabarti, S. S. Szinai, and A. Todd, *J. Chem. Soc. C*, 1303 (1970).

(5) J. F. Kerwin, M. E. Wolff, F. F. Owings, B. B. Lewis, B. Blank, A. Magnani, C. Karash, and V. Georgian, *J. Org. Chem.*, **27**, 3628 (1962).

(6) M. E. Wolff, *Chem. Rev.*, **63**, 55 (1963).

(7) H. W. Geluk and J. L. M. A. Schlatmann, *Tetrahedron*, **24**, 5361 (1968).

(8) For the synthesis of this compound, see ref 3 and Netherlands Patent 6,714,362 (1966), to Lilly Industries Ltd.

(9) (a) P. Kovacic, M. A. Lowery, and K. W. Field, *Chem. Rev.*, **70**, 639 (1970); (b) R. S. Neale, *Synthesis*, 1 (1971).

Experimental Section

Melting points were determined on a Thomas-Hoover "Uni-Melting" apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 21 spectrometer in Nujol. Nmr spectra were obtained on a Varian A-60 spectrometer in $CDCl_3$, with $(CH_3)_4Si$ as the internal standard. Mass spectra were determined on an AEI-MS-902 mass spectrometer.

Δ^2,α-Adamantaneacetic Acid (3).—To a well-stirred suspension of 21.8 g (0.45 mol) of sodium hydride (NaH) in 300 ml of dry 1,2-dimethoxyethane (DME), 100.9 g (0.45 mol) of triethyl phosphonoacetate was added slowly at 20°. After stirring for 2 hr at room temperature, a solution of 45.0 g (0.3 mol) of **1** in 450 ml of dry DME was added rapidly. The reaction mixture was maintained at 45° for 2 hr and then stirred overnight at room temperature. The mixture was concentrated, diluted with water, and extracted with ether. The ether extract was washed with water, dried ($MgSO_4$), and concentrated to give 65.5 g (99%) of **2** as a thick yellow liquid, ir 5.83 (C=O), 6.08 μ (conjugated C=C).

The crude ester **2** was hydrolyzed by refluxing with 300 ml of 5 *N* alcoholic KOH for 4 hr. The basic solution was cooled, acidified with 5 *N* HCl, and extracted with $CHCl_3$. The $CHCl_3$ solution was dried ($MgSO_4$) and evaporated *in vacuo* to give 56.6 g (98%) of **3** as brownish-white powder. Crystallization from dilute acetone gave an analytical sample: mp 136–138°; ir 3.70–4.00 (bonded OH), 5.90 (C=O), 6.10 μ (conjugated C=C); nmr τ 4.38 (s, 1, vinyl H), 5.83–6.05 (br, 1, OH), 7.37–7.66 (br, 2, CH adjacent to C=C), 7.83–8.25 (s, 12 H).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.19; H, 8.49.

2-Adamantaneacetic Acid (4).—A solution of 9.6 g (0.05 mol) of **3** in C_2H_5OH containing 1 equiv of 5 *N* NaOH was hydrogenated over 5% Pd/C. After acidification, the solvent was removed *in vacuo* and the residue was extracted with $CHCl_3$, dried ($MgSO_4$), and evaporated *in vacuo* to give 9.5 g (94%) of white solid, mp 118–120°. Recrystallization from pentane gave an analytical sample as white crystals: mp 118–120°; ir 3.70–4.00 (bonded OH), 5.92 μ (C=O); nmr τ 5.34 (s, 1, OH), 7.55 (br, 2, CH_2), 8.07–8.38 (s, 15H).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.05; H, 9.32.

***N*-Methyl-2-adamantaneacetamide (6).**—The reaction of 8.9 g (0.046 mol) of **4** with thionyl chloride gave 9.4 (97%) of the acid chloride **5**, ir 5.50 μ (C=O). It was dissolved in 50 ml of dry tetrahydrofuran (THF) and added dropwise to 10 ml of 40% aqueous solution of monomethylamine. The THF was evaporated *in vacuo*, and the residue was extracted with $CHCl_3$, dried ($MgSO_4$), and concentrated to give 7.9 g (86%) of **6** as a white solid, mp 142–149°. Crystallization from CH_3CN gave an analytical sample as white needles: mp 147–150°; ir 3.05–3.25 (NH), 6.02–6.12 μ (C=O); nmr τ 4.00–4.30 (br, 1, NH), 7.14–7.22 (d, 2, CH_2), 7.70 (br, 3, NCH_3), 8.05–8.40 (s, 15H).

Anal. Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.21; H, 10.15; N, 6.76.

***N*-Methyl-2-adamantaneethylamine (7).**—To a well-stirred suspension of 3.0 g of lithium aluminum hydride in 100 ml of dry THF cooled in ice, a solution of 7.4 g (0.36 mol) of **6** in 100 ml of dry THF was added dropwise. The reaction mixture was then refluxed overnight. Working up the reaction yielded 6.5 g (90%) of **7** as an oil: ir 3.00 μ (NH); nmr τ 4.30–4.55 (NH), 7.16–7.55, 8.08–8.45. The hydrochloride of **7** was crystallized from CH_3CN to give an analytical sample, mp >270°, ir 3.30–4.10 μ (NH_2^+ and CH).

Anal. Calcd for $C_{13}H_{23}N \cdot HCl$: C, 67.99; H, 10.53; N, 6.10. Found: C, 68.11; H, 10.81; N, 6.02.

1-Chloro-*N*-methyl-2-adamantaneethylamine (9).—A solution of 15.4 g (0.08 mol) of **7** in CH_2Cl_2 was stirred at room temperature with 200 ml of 5% NaOCl for 2 hr. The aqueous layer was removed, 200 ml of fresh NaOCl was added, and the mixture was stirred overnight at room temperature. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated *in vacuo* to give 16.4 g (90%) of **8** as an oil. Compound **8** was dissolved in 190 ml of acid solution (16.7 ml of 95–98% H_2SO_4, 4.3 ml of H_2O, and 160 ml of CH_3CO_2H) and photolyzed at 25° in a Hanovia photochemical reactor with a low-pressure mercury lamp. After 1 hr exposure, the reaction mixture gave a negative halogen test with KI solution. After cooling, the solution was made basic with 10% NaOH, extracted with $CHCl_3$, washed with water, dried ($MgSO_4$), and evaporated *in vacuo* to give 15.5 g (85%) of **9** as a yellow oil: ir 2.85–3.20 μ (NH); nmr τ 6.05–6.30 (br, 1, NH), 7.44–7.58 (m, 2, $CH_2N<$), 7.75–7.87 (d, 3, CH_3NH), 7.87–8.5 (br, 2, CH_2), 8.09–8.5 (s, 14 H). The hydrochloride of **9** was crystallized from CH_3CN to give an analytical sample, mp >270°.

Anal. Calcd for $C_{13}H_{22}NCl \cdot HCl$: C, 59.10; H, 8.77; N, 5.31. Found: C, 59.23; H, 8.92; N, 5.13.

1-Methyladamantano[1,2-*b*]pyrrolidine (10).—Compound **9** (4.5 g, 0.02 mol) was heated under nitrogen at 290° (previously heated oil bath) for 10 min. After cooling, the residue, ir 3.70–4.4 μ (N^+H-), was triturated with 10% NaOH. The oil that formed was extracted with $CHCl_3$, washed with water, dried ($MgSO_4$), and evaporated to give 3.2 g of residue. It was dissolved in 20 ml of acetic anhydride and stirred overnight at room temperature. The excess acetic anhydride was removed *in vacuo* and the residue was partitioned between $CHCl_3$ and 5 *N* HCl. The aqueous layer was separated, basified, extracted with $CHCl_3$, dried ($MgSO_4$), and evaporated *in vacuo* to give 1.3 g (34%) of **10** as a pale yellow oil. The hydrochloride of **10** was crystallized from dioxane to give white crystals: mp 231–236°; ir 3.70–4.44 μ ($>N^+H-$); nmr τ −2.17 to −1.50 (br, 1, N^+H), 5.83–6.42 (m, 2, $CH_2N<$), 6.90–7.30 (m, 2, CH_2), 7.35–7.45 (d, 3, $>N^+HCH_3$), 7.65–8.5 (m, 14 H); mass spectrum *m/e* 191 (M^+ − HCl).

Anal. Calcd for $C_{13}H_{21}N \cdot HCl$: C, 68.55; H, 9.74; N, 6.15; Cl, 15.57. Found: C, 68.30; H, 9.61; N, 6.18; Cl, 15.38.

Registry No.—**3**, 25220-07-9; **4**, 26082-22-4; **6**, 32132-60-8; **7** HCl, 32132-61-9; **9** HCl, 32132-63-1; **10**, 32139-10-9.

Reevaluation of α-Alkyl Substituent Kinetic Effects on Acid- and Base-Catalyzed Enolization

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Recently published work indicates that a controversy still exists regarding the exact nature of the influence exerted by α-alkyl groups on the rates of enolization of carbonyl compounds. According to Warkentin, *et al.*,[1] "the usual effect of an α-alkyl substituent is to accelerate acid-catalyzed enolization and to retard base-catalyzed enolization relative to the corresponding rates for unsubstituted ketone." This statement appears to be well authenticated for the case of base-catalyzed enolization[1,2] but appears to be less definite for acid-catalyzed enolization.[3] The above generalization arises essentially from studies of the preferential enolization rates of ketones containing two reaction sites, which of course constitutes a slightly different problem from that encountered in the comparative studies of alkyl- and nonalkyl-substituted ketones. Actually this generalization is in contradiction with results obtained for phenyl alkyl ketones[4] and dialkyl

(1) (a) J. Warkentin and O. S. Tee, *J. Amer. Chem. Soc.*, **88**, 5540 (1966); (b) J. Warkentin and C. Barnett, *ibid.*, **90**, 4629 (1968).

(2) (a) D. P. Evans and J. J. Gordon, *J. Chem. Soc.*, 1434 (1938); (b) C. F. Cullis and M. S. Hasmi, *ibid.*, 2512 (1956); (c) C. Rappe, *Acta Chem. Scand.*, **20**, 2236 (1966).

(3) (a) H. M. E. Cardwell and A. E. H. Kilner, *J. Chem. Soc.*, 2430 (1951); H. M. Dawson and R. Wheatley, *ibid.*, 2048 (1910); H. M. Dawson and H. Ark, *ibid.*, 1740 (1911); (b) C. Rappe and W. H. Sachs, *J. Org. Chem.*, **32**, 3700 (1967), and references cited therein.

(4) D. P. Evans, *J. Chem. Soc.*, 785 (1936).

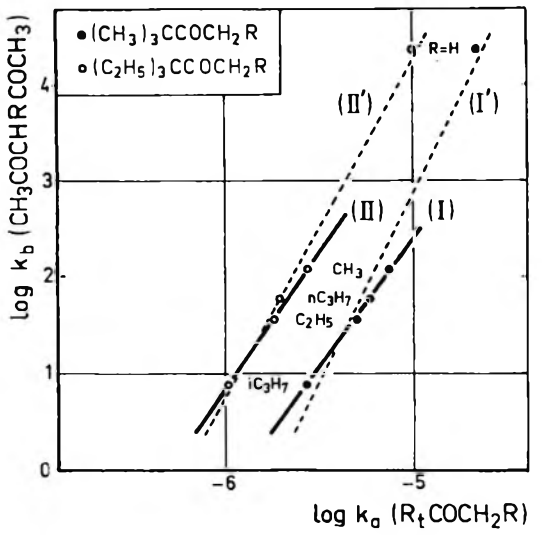

Figure 1.—Similar α-alkyl effects on acid- (k_a) and base- (k_b) catalyzed rate constants: with R = H (I'), $\log k_b = 22.7 + 3.96 \log k_a$ ($r = 0.983$); (II'), $\log k_b = 22.2 + 3.57 \log k_a$ ($r = 0.995$); without R = H (I), $\log k_b = 16.0 + 2.71 \log k_a$ ($r = 0.997$); (II), $\log k_b = 18.0 + 2.86 \log k_a$ ($r = 0.998$).

ketones[5,6] possessing a single enolization site, as well as with the results of the variation of the overall enolization rate of some dialkyl ketones with two different enolization sites.[7] Bothner-By and Sun,[8] on their part, maintain that α-alkyl substitution diminishes the acid-catalyzed reaction rate.

Our study of the acid-catalyzed enolization of R_tCOCH_2R (R_t = Me_3C or Et_3C) and of the base-catalyzed enolization of the diketone $CH_3COCHRCOCH_3$ allows a new approach to the latter problem. The results of these experiments are shown in Table I.

TABLE I

ACID- (MONOKETONES[a]) AND BASE- (β-DIKETONES[b]) CATALYZED ENOLIZATION RATE CONSTANTS

Compd R	$-10^5 k_a$ (R_tCOCH_2R), sec^{-1} — R_t = Me_3C[c]	R_t = Et_3C	k_b (CH_3CO-$CHRCOCH_3$), M^{-1} sec^{-1}
H	2.10	0.97	2.4×10^4 [d]
Me	0.72	0.27	130
Et	0.49	0.18	38
n-Pr	0.59	0.20	63
i-Pr	0.26	0.10	8

[a] Measurements were done at 25° in the following mixture: AcOH–H_2O (75% v/v), [HBr] = 0.5 M. Reproducibility ±5%. [b] At 25°, aqueous solution, catalysis OH^-, ionic strength 0.1. Reproducibility ±10%. [c] See ref 6. [d] 4×10^4 M^{-1} sec^{-1} has also been measured; see M. Eigen, *Pure Appl. Chem.*, **6**, 97 (1963); M. Ahrens, M. Eigen, W. Kruse, and G. Maass, *Ber. Bunsenges. Phys. Chem.*, **74**, 380 (1970).

When the logarithms of the acid-catalyzed enolization rate constants, k_a, for a ketone with a given alkyl substituent R, are plotted against the logarithms of the base-catalyzed enolization rate constants k_b, for the β-diketones with the same alkyl substituent, straight lines are obtained (Figure 1). As is shown by the following diagram, the same correlations can be made between the rate constants found in the present study and those found in the literature for substituted alkyl phenyl ketones.[2a,4]

$$\log k_a\,(Me_3CCOCH_2R) \xleftrightarrow{\text{slope} = 2.71,\ r = 0.997\ R \neq H} \log k_b\,(CH_3COCHRCOCH_3)$$

$$\text{slope} = 1.05,\ r = 0.994 \qquad \text{slope} = 2.88,\ r = 0.997$$

$$\log k_a\,(C_6H_5COCH_2R) \xleftrightarrow{\text{slope} = 1.10,\ r = 0.996,\ R \neq H} \log k_b\,(C_6H_5COCH_2R)$$

It should be noted that the decrease in the rate constant observed in the presence of an α-alkyl substituent seems to be a general trend both for base- and acid-catalyzed reactions. *Furthermore, the decrease in the rate constant as a function of R ($R \neq H$), is of the same magnitude both for acid and basic catalysis in the case of monoketones.*

These findings are somewhat surprising when one considers that it is generally admitted that the transition state for enolization under basic conditions is intermediate between the ketone and the enolate anion, whereas under acidic conditions the transition state is intermediate between the hydroxycarbonium ion and the enol.[9] The effects of structure and solvent on the rate of enolization have been explained on the basis of the charge distribution and structure in these transition states.[10] It seems doubtful that a given alkyl group would have the same effect, either polar or hyperconjugative, on transition states of opposite charges and differing structures. We will presently investigate our results supposing that (a) *dominant isosteric* influence of the R groups acts on the transition states of both acid- and base-catalyzed enolization, or (b) the substituents influence *primarily* the common ground state and have relatively little effect on the energy levels of the transition states.

In order to evaluate these hypotheses, it was necessary to have more information about the enol equilibrium constant. Such data are available from the studies carried out under acidic conditions at very low bromine concentrations.[6,11] Under these conditions, the successive steps of enolization and bromination have comparable rates. The well-known mechanism for this reaction can be represented as

$$\text{CHC(=O)—} + HA \underset{}{\overset{K_C}{\rightleftharpoons}} \text{CHC(}^{+}\text{OH)—} + A^- \underset{k_{-1}}{\overset{k_1'}{\rightleftharpoons}}$$

$$\text{C(OH)=C} + HA \xrightarrow[k_{Br_2}]{Br_2} \text{CBrC(=O)—} + HBr$$

(9) On the basis of experiments concerning kinetic isotopic substitution effects and the influence of catalysts (Brønsted correlations), it is accepted that the transition state is close to the enolate anion for the enolization of acetone ($\beta \cong 0.8$) by weak bases, midway between the ketone and the enolate anion for OH^-, and midway between the hydroxy carbonium ion and the enol for acid catalysis: C. G. Swain and A. S. Rosenberg, *J. Amer. Chem. Soc.*, **83**, 2154 (1961). This latter affirmation has been confirmed by a study of the solvent isotope effect on the conversion of 2-hydroxypropene into acetone under acidic conditions ($\alpha \cong 0.5$): J. E. Dubois and J. Toullec, *Chem. Commun.*, 478 (1969).

(10) The opposite effect of substituents on acid-catalyzed enolization ($\rho < 0$) and base-catalyzed enolization ($\rho > 0$) of aryl-substituted acetophenones and phenyl benzyl ketones is considered as one of the best pieces of evidence in favor of opposite charges in the transition states for acid and basic catalysis: A. Fischer, J. Packer, and J. Vaughan, *J. Chem. Soc.*, 3318 (1962); 226 (1963); D. P. Evans, V. G. Morgan, and H. B. Watson, *ibid.*, 1167 (1935); J. R. Jones, R. E. Marks, and S. C. Subba Rao, *Trans. Faraday Soc.*, **63**, 111, 993 (1967); H. J. Den Hertog and J. Koojman, *J. Catal.*, **6**, 347 (1966); S. Mishra, P. L. Nayak, and M. K. Rout, *J. Indian Chem. Soc.*, **46**, 645 (1969); D. N. Nanda, P. L. Nayak, and M. K. Pont, *Indian J. Chem.*, **7**, 469 (1969).

(11) J. E. Dubois and J. Toullec, *J. Chim. Phys.*, **65**, 2166 (1968).

(5) D. P. Evans and J. R. Young, *J. Chem. Soc.*, 1314 (1954).

(6) J. E. Dubois and J. Toullec, *Chem. Commun.*, 292 (1969).

(7) For an example, see P. D. Bartlett and C. H. Stauffer, *J. Amer. Chem. Soc.*, **57**, 2580 (1935).

(8) A. A. Bothner-By and C. Sun, *J. Org. Chem.*, **32**, 492 (1967).

If a quasistationary state is assumed for the enol, the rate equation may be written as

$$-\frac{d[Br_2]}{dt} = \frac{[Br_2]}{\frac{1}{k_{II}[C]} + \frac{1}{k_a[C]}[Br_2]} \quad (I)$$

$$k_a = K_C k_1'[HA] \quad (II)$$

$$k_{II} = K_E k_{Br_2} = (K_C k_1'/k_{-1})k_{Br_2} \quad (III)$$

with the keto–enol equilbrium constant represented by K_E.

This being so, we have posited that, by analogy with the reactivity of α- and β-alkyl vinyl ethers,[12] the bromination rate constant k_{Br_2} is insensitive to variations in the structures studied.[13] In this case, the variations in the experimental bromination rate constant k_{II} follow those of the enol equilibrium constant K_E. It is extremely interesting in such conditions to look for a linear free-energy relation between k_{II} and k_a. Figure 2 indicates a very satisfying one with *unit slope* for ketones with *the same degree of* α *substitution*.

This highly significant direct correlation could be explained by assuming that the steric structural effects (hypothesis a) arise from the change in hybridization of the carbon α acting in the *same* manner on the energy of the transition state and on that of the enol; the unit slope observed for the alkyl-substituted ketones (R $\neq$ H) would then mean that the transition state is near the enol structure, *i.e.*, the hybridization change is almost completed. Unfortunatly, such a conclusion cannot be drawn if one considers the proton is equally bonded to the hydroxycarbonium ion and the base and, therefore, not fully transferred.[9]

Steric effects for acid and base catalysis could also arise from interactions between the alkyl substituent and the base removing the proton in the slow step. *Such specific steric effects* on the transition state do not explain the parallelism between the rate constants and equilibrium constants for acid-catalyzed enolization.

On the other hand, the hypothesis that structural effects (R $\neq$ H) play a dominant role before the slow step in the reaction mechanism seems sufficient to explain the unit slope correlation between log k_a and log K_E. These effects can be determinant for the magnitude of the K_C stability (*cf.* eq II and III). However, this explanation as such cannot really account for the parallel substituent effects on the acid- and base-catalyzed reaction rates, except when the K_C variations *primarily* depend on the *ketone stability*. Interpretation b explaining these structural parallel effects then agrees with the unit slope rate–equilibrium relationship.

Such an analysis is still not fully satisfactory, since it implies a weak structural influence on the stability of the conjugated acid of the ketone, neglecting in particular solvation variations.[14] Moreover, it is highly probable[14a] that the population of conformers favorable to elimination is one of the major factors in determining the enolization rate. We are currently examining this aspect which could confirm our hypothesis regarding a dominant effect of alkyl groups before the slow step (conformational preequilibria).[15]

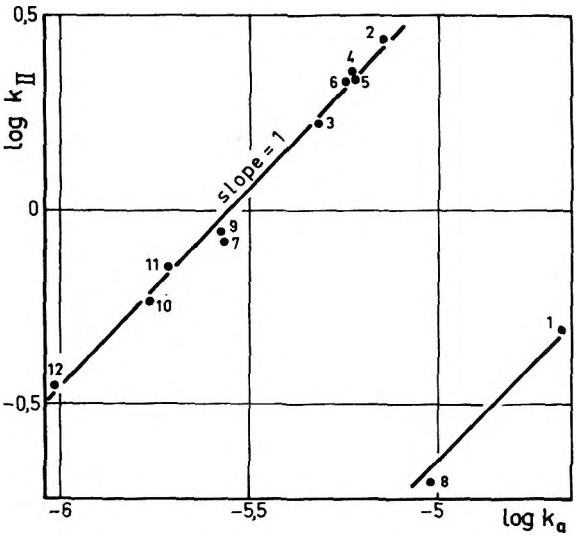

Figure 2.—Parallel structural effects on the bromination rate constants of R_tCOCH_2R (acid-catalyzed rate constant for enolization k_a, and apparent rate constant $k_{II} = K_E k_{Br_2}$, for the bromination of the enol): **1**, R_t = Me_3C, R = H; **2**, Me_3C, Me; **3**, Me_3C, Et; **4**, Me_3C, *n*-Pr; **5**, Me_3C, *n*-Bu; **6**, Me_3C, *n*-pentyl; **7**, Me_3C, *i*-Pr; **8**, Et_3C, H; **9**, Et_3C, Me, **10**, Et_3C, Et; **11**, Et_3C, *n*-Pr; **12**, Et_3C, *i*-Pr.

Experimental Section

Solvents and Reagents.—The monoketones, which were synthesized as part of a general study of hindered ketones,[16] have been the object of a systematic study by ir[17] and uv[18] spectroscopy. Analysis by vpc has shown them to be consistently better than 99% pure. The β-diketones were commercially available compounds (K & K Laboratories) and were also purified by vpc to better than 99% purity. Their physical constants, ir spectra (Perkin-Elmer 225), and nmr spectra (Jeol JNM-C-60HL) were in accordance with those reported in the literature.

For the acid-catalyzed enolization of the monoketones, the solvent (0.5 *N* HBr in 75% v/v aqueous acetic acid) was prepared as follows: 25 ml of 2 *N* HBr (prepared from Merck "suprapur") was mixed with 75 ml of pure acetic acid (Merck "pro analysi," 99–100%) and the volume was brought to 100 ml by the addition of water distilled from $KMnO_4$. For the base-catalyzed enolization of the β-diketones, the solvent used was a 0.1 *N* solution of $NaClO_4$ in deionized water, the desired pH being obtained by the addition of 1 *N* NaOH.

Kinetic Measurements.—The acid-catalyzed rate constants, k_a, were obtained by the automated couloamperometric technique[19] which allows rapid changes in very low bromine concentrations to be followed. With this technique the ketone is always in large excess (*ca.* 10^{-2} *M*) with respect to the initial bromine concentration (10^{-4} to 10^{-6} *M* depending on the ketone). The two constants k_a and k_{II} are calculated from the experimental data using an integrated form of the rate expression I.[6,11]

The base-catalyzed rate constants, k_b, were obtained by a chemical relaxation technique using a Messanlagen Studiengesellschaft (Göttingen, Germany) temperature-jump transient spectrometer (Type SBA7, Ser. No. 2–30). The calculation of the constant k_b from the experimental data has been described by Eigen in the case of the 2,4-pentanedione.[20]

(12) J. E. Dubois, J. Toullec, and G. Barbier, *Tetrahedron Lett.*, 4485 (1970).

(13) Supplementary evidence in favor of this supposition will be found in a later paper.

(14) The vapor-phase keto–enol equilibrium constant of α-alkyl keto esters shows the same dependency on the basic enolization rate constant k_b [J. B. Conant and A. F. Thompson, *J. Amer. Chem. Soc.*, **54**, 4039 (1932)], thus indicating that structural effects do not depend on the solvation of the various species.

(15) J. Toullec and J. E. Dubois, to be submitted for publication.

(16) J. E. Dubois, M. Chastrette, and E. Schunk, *Bull. Soc. Chim. Fr.*, 2011 (1967); J. E. Dubois, B. Leheup, F. Hennequin, and P. Bauer, *ibid.*, 1150 (1967); J. E. Dubois, G. Schutz, and J. M. Normant, *ibid.*, 3578 (1966).

(17) J. E. Dubois, A. Massat, and Ph. Guillaume, *J. Mol. Struct.*, **4**, 403 (1969); unpublished work.

(18) J. E. Dubois and A. Barbi, *J. Chim. Phys.*, **65**, 376 (1968); unpublished work.

(19) J. E. Dubois, P. Alcais, and G. Barbier, *J. Electroanal. Chem.*, **8**, 359 (1964).

(20) M. Eigen, *Pure Appl. Chem.*, **6**, 97 (1963); M. Ahrens, M. Eigen, W. Kruse, and G. Maass, *Ber. Bunsenges. Phys. Chem.*, **74**, 380 (1970).

Registry No.—1, 75-97-8; 2, 564-04-5; 3, 5405-79-8; 4, 19078-97-8; 5, 5340-64-7; 6, 22921-92-2; 7, 14705-50-7; 8, 17535-47-6; 9, 17535-48-7; 10, 17535-49-8; 11, 18295-58-4; 12, 31938-27-9; $CH_3COCH_2COCH_3$, 123-54-6; $CH_3COCH(CH_3)COCH_3$, 815-57-6; $CH_3COCH(Et)COCH_3$, 1540-34-7; $CH_3COCH(n\text{-}Pr)COCH_3$, 1540-35-8; $CH_3COCH(i\text{-}Pr)COCH_3$, 1540-3-81.

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Photodimerization of 4-Thiapyrone

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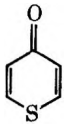
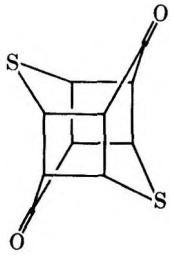
The photodimerization of unsaturated six-membered ring ketones which bear a heteroatom has been studied extensively. The structure of these photodimers depends upon the fragments of a polyene system which participate in a photoreaction. [2 + 2] cycloaddition products are obtained from 2-coumarins,[1] 2,3-dihydro-2,6-dimethyl-4-pyrone,[2] 2-pyrone,[3] and 2,6-diphenyl-4-thiapyrone;[4] [4 + 4] cycloaddition products from 4,6-dimethyl-2-pyrone[3] and 2-pyridones;[5] [2 + 2 + 2 + 2] cycloaddition products from 2,6-dimethyl-4-pyrone[6] and 2,6-dimethyl-4-thiapyrone.[7]

The present study is an attempt to extend these observations to 4-thiapyrone (I). The result on the photodimerization of I is reported here.

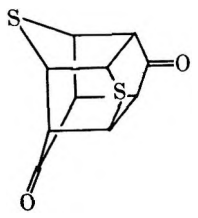
The irradiation of a 1% acetonitrile solution of I under nitrogen in a quartz tube with a medium-pressure lamp gave a photodimer, 3,9-dithiapentacyclo[6.4.-$0.0^{2,7}.0^{4,11}.0^{5,10}$]dodecane-6,12-dione (II). The structure of II was determined from the following spectral data. An examination of its nmr spectrum showed a multiplet at δ 3.45–3.70 assigned to the four α-carbonyl protons and a second multiplet at δ 4.55–4.80 ascribed to the four α-sulfide protons. There was no absorption attributable to an olefinic proton. The photoproduct no longer showed uv absorption characteristic of an unsaturated ketone. The infrared spectrum of the photoproduct has a strong carbonyl absorption at 1710 cm^{-1} and lacks other significant absorption in the 1650–1750-cm^{-1} region. The mass spectrum of the photoproduct displays a parent peak at m/e 224, which suggests that the photoproduct is a dimer of I. Moreover, the molecular weight determined by vapor pressure osmometry was 212, which was consistent with a dimeric species. From these results the alternative structures III and IV, in addition to II, could be written for this photodimer. Of these, III can be eliminated since there was no ir absorption of the carbonyl group in the five-membered ring (1745 cm^{-1}).[8] In the mass spectrum of the photodimer, the presence of a peak at m/e 112 corresponding to the ion of 4-thiapyrone, $(C_5H_4SO)^+$, and the absence of peaks at m/e 116 and 108 corresponding to the ions of 1,4-dithiacyclohexadiene, $(C_4H_4S_2)^+$, and 1,4-benzoquinone, $(C_6H_4O_2)^+$, respectively, suggest that the photodimer is assigned to the "head-to-tail" structure (II). Moreover, this assignment is confirmed from the fact that in addition to the peak of monomer I, an intense peak at m/e 86 was observed which may arise from I by expulsion of acetylene,[9] while the fragments at m/e 82, 80, and 54 were not observed, which could be expected from 1,4-benzoquinone ion.[10] These results indicate that the photoproduct has the structure II.



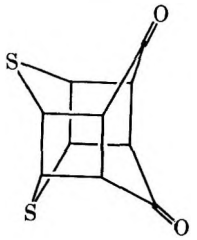
I



II



III



IV

While the irradiation of I in dioxane (2% solution) gave II in 2% yield, II was obtained in very low yield (<1%) from the irradiation of a 2% methanol solution of I. The 10% acetonitrile solution of I did not increase the yield of II. The photoreaction of I sensitized by benzophenone resulted in formation of II in 2% yield. This result suggests that the photodimerization of I proceeds *via* the excited triplet state of I.

The photodimerization of I leads exclusively to the head-to-tail [2 + 2 + 2 + 2] cycloadduct in striking contrast to 2,6-diphenyl-4-thiapyrone[4] and in close analogy with 2,6-dimethyl- and 2,6-diethyl-4-pyrone[6,11] and 2,6-dimethyl-4-thiapyrone.[7] The presence of the phenyl group in the thiapyrone could increase the steric barrier to [2 + 2 + 2 + 2] cycloaddition. At the same time this could affect the nature of the excitation

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(5) E. C. Taylor and R. O. Kan, *J. Amer. Chem. Soc.*, **85**, 776 (1963); L. A. Paquette and G. Slomp, *ibid.*, **85**, 765 (1963).

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(9) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco Calif., 1967, p 208.

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step and/or the reaction of the excited state with a ground-state molecule.

Experimental Section

Melting points are uncorrected. The infrared spectra were recorded on a JASCO DS-402G spectrophotometer; the ultraviolet spectra were obtained with a Hitachi 124 spectrophotometer; the nmr spectra were measured with a JEOLCO C-60HL spectrometer using tetramethylsilane as an internal standard; the mass spectrum was recorded on a Hitachi RMU-6E spectrometer; the molecular weight was determined by a Hitachi 115 molecular weight measuring apparatus.

4-Thiapyrone (I).—4-Thiapyrone was prepared by the method of Arndt and Bekir,[12] which gave a colorless needle after recrystallization from carbon tetrachloride, mp 110° (lit.[12] 110°). The uv and nmr spectra are consistent with the reported spectra.[13,14]

Direct Irradiation of I.—A solution of 2 g of I in 200 ml of acetonitrile was irradiated for 50 hr with a 100-W medium pressure mercury arc through a quartz filter. Purified nitrogen was passed through the solution during irradiation. After removal of solvent under vacuum the residual solid was chromatographed on a silica gel with benzene–chloroform eluent to yield 40 mg of II. After isolation of II 95% of I was recovered. II, a colorless solid, was recrystallized from acetone: mp 248° dec; uv $\lambda_{max}^{CH_3CN}$ 307 nm (ϵ *ca.* 100); ir (KBr) 1710 cm^{-1} ($\nu_{C=O}$); nmr (DMSO-d_6) δ 3.45–3.70 (m, 4 H) and 4.55–4.80 (m, 4 H); the principal peaks of mass spectrum at *m/e* (rel intensity) 224 (48.5), 149 (23.5), 137 (16.0), 113 (60.0), 112 (100.0), 86 (44.0), 84 (61.7), 58 (37.8), and 57 (22.7).

Anal. Calcd for $C_{10}H_8O_2S_2$: C, 53.55; H, 3.59; O, 14.27; S, 28.59. Found: C, 53.45; H, 3.71; O, 14.40; S, 28.38.

Photosensitized Reaction of I.—A 200-ml benzene solution of 2 g of I and 1 g of benzophenone was irradiated for 50 hr with a 100-W medium-pressure mercury lamp filtered by a Pyrex glass. After similar work-up described above, 42 mg of II was isolated.

Registry No.—I, 1003-41-4; II, 32538-05-9.

Acknowledgments.—The authors are grateful to Professor K. Teramura for his interest in this work.

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Rearrangement of the Grignard Reagent from 5-Chloro-1-pentene-5,5-d_2[1]

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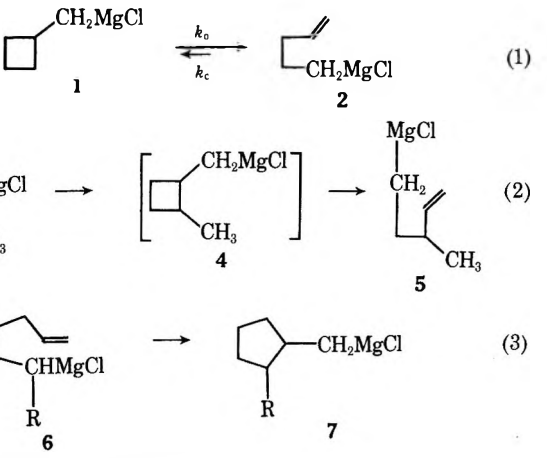
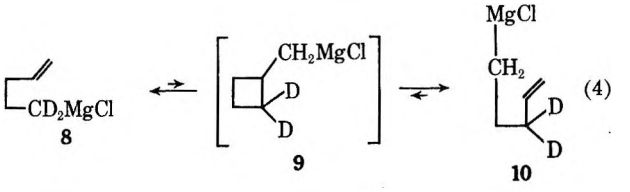
In previous work, it has been shown that the Grignard reagent **1** from cyclobutylmethyl chloride undergoes a ring-cleavage rearrangement to **2**.[2] In addition, rearrangement of Grignard reagent **3** to **5** was observed, the cyclized reagent **4** being proposed as an intermediate.[2a] In the latter case, the reaction most probably has as its driving force the conversion of a secondary Grignard reagent into a more stable primary one. Ring closure to a five-membered ring has also been



observed[3] (eq 3). It thus appeared desirable to demonstrate directly the reversibility implied in eq 1.

A Grignard reagent was prepared from 5-chloro-1-pentene-5,5-d_2 in tetrahydrofuran. The original solution lacked the high-field nmr signal of hydrogens α to a magnesium. However, after heating for several hours at 140°, a high-field triplet from **10** appeared. From the rate of appearance of the α-proton signal, the rate of approach to equilibrium was determined.



After correction for Grignard reagent destroyed by reaction with the solvent (see Experimental Section), approximate rate constants of 3×10^{-6} sec^{-1} at 140° and 3.5×10^{-5} sec^{-1} at 160° were determined. If possible secondary isotope effects on the rates and equilibria are ignored, the rate of ring closure equals the rate of approach to equilibrium: each act of ring closure would produce a molecule of **9**, which on cleavage, has an equal probability of yielding isomer **8** or **10**.

1-Pentene, isolated from hydrolysis of a solution heated for several half-lives, was examined by nmr. Integration showed that about 40% of the 1-pentene had the deuterium distribution corresponding to **10**.

Extrapolation of rate constants for the *cleavage* of the cyclobutylmethyl Grignard reagent (see Experimental Section) yields a value of 7.5×10^{-3} sec^{-1} at 140°. With the ring closure rate, an equilibrium constant of 2.5×10^3 is derived for eq 1. In principle, it should be possible to derive ΔH for eq 1 from the temperature dependence of this equilibrium constant, and hence an estimate of the strain energy of the cyclobutane ring. Because of the competing reaction with solvent, the present kinetics are insufficiently precise to allow this approach. However, by an alternative approach, ΔG and an estimate of ΔS[4] for eq 1 may be combined to yield $\Delta H = -2.1$ kcal/mol.

(1) This research was supported in part by a grant from the Petroleum Research Fund, administered by the American Chemical Society.

(2) (a) E. A. Hill, H. G. Richey, Jr., and T. C. Rees, *J. Org. Chem.*, **28**, 2161 (1963); (b) E. A. Hill and J. A. Davidson, *J. Amer. Chem. Soc.*, **86**, 4663 (1964).

(3) H. G. Richey, Jr., and T. C. Rees, *Tetrahedron Lett.*, 4297 (1966); E. A. Hill, R. J. Theissen, R. A. Doughty, and R. Miller, *J. Org. Chem.*, **34**, 3681 (1969).

(4) This estimate, 10.6 eu at 140°, uses the gas-phase entropy change of the model reaction methylcyclobutane ⇆ 1-pentene. The entropy of methylcyclobutane was obtained by adjustments from the published value for cyclobutane: G. W. Rathjens, Jr., N. K. Freeman, W. D. Gwinn, and K. S. Pitzer, *J. Amer. Chem. Soc.*, **75**, 5634 (1953). The authors may be consulted for further details.

Taken with an estimate of 21.7 kcal/mol[5] for the bond cleavage process

$$\begin{array}{l} RCH_2 \\ | \\ RCHCH_2MgX \end{array} \rightleftharpoons RCH_2MgX + RCH{=}CH_2$$

a ring strain of 24 kcal is derived. A value of 23 kcal is obtained from data at 160°.[6]

The estimates of ring strain obtained are in approximate agreement with the heat of combustion value of 26.2 kcal/mol.[7] The discrepancy, amounting to a factor of 10 to 40 in equilibrium or rate constants, could be the summation of errors from various sources in the kinetics and the estimation procedures, or it may represent the limits of applicability of the thermochemical approach to solution reactions. It could also result from some additional stabilization of the four-membered ring in the cyclobutylmethyl Grignard reagent, or from the incidence of a new, higher activation energy mechanism at the higher temperatures.[8] In any event, the current results provide a clear example of the quantitative influence of the thermochemical strain energy of a cyclobutane ring on the equilibrium constant for a chemical reaction.

Experimental Section

Nmr spectra were obtained on a Varian Associates HA-100 nmr spectrometer. Boiling points are uncorrected.

Cyclobutylmethylmagnesium chloride in tetrahydrofuran was prepared as described previously.[2b] Samples in nmr tubes were heated for appropriate times, and the extent of rearrangement was determined by integration of the signals at δ −0.35 and −0.66 ppm, corresponding to Grignard reagents 1 and 2, respectively.[2b] Rate constants obtained were 2.55×10^{-6} sec^{-1} at 59.6°; 2.76×10^{-5} sec^{-1} at 80.2°, and 2.18×10^{-4} sec^{-1} at 99.9°. Derived activation parameters were $\Delta H^{\pm} = 26.55 \pm 0.2$ kcal/mol and $\Delta S^{\pm} = -4.6 \pm 0.5$ eu.

4-Penten-1-ol-*1,1-d*$_2$ was prepared by reduction of methyl 4-pentenoate with lithium aluminum deuteride in diethyl ether, bp 137–140° (lit.[9] bp 141–141.5°° for isotopically normal compound).

5-Chloro-1-pentene-*5,5-d*$_2$ was prepared from the alcohol with thionyl chloride and tri-*n*-butylamine in ether by a procedure similar to one described previously:[2b] bp 98–103° (lit.[9] bp 103–104° for isotopically normal compound). The nmr spectrum showed no detectable absorption (<0.5%) at δ 3.5 ppm, where the α hydrogens of the isotopically normal compound absorb.

Grignard Reagent from 5-Chloro-1-pentene-*5,5-d*$_2$.—A Grignard reagent was prepared from 0.679 g of the chloride and 0.21 g of magnesium in 3 ml of tetrahydrofuran, and sealed in nmr tubes. After heating for several hours at 140°, a triplet signal, J = 8 Hz, appeared at δ −0.66 ppm. Poorly defined changes occurred in the olefinic absorption, and a new signal appeared at δ 6.45 ppm, attributable to ethylene formed from attack on the solvent.[10] At long reaction times, the α-hydrogen absorption reached a maximum of about 60% of one hydrogen (relative to the olefinic protons) and then decreased in size, while the ethylene absorption continued to increase. By using the appearance of ethylene as a measure of the amount of Grignard reagent destroyed by reaction with solvent, the spectra obtained for shorter reaction times were corrected for the loss of total organometallic. The rate of loss appeared to be about 20–30% of the rearrangement rate. The best rate measurements were made using a similar sample of concentration 0.92 *M* supplied by H. G. Richey, Jr., and T. C. Rees.

A sample which had been heated for four half-lives was hydrolyzed with water. The volatile materials were transferred from the residue under vacuum and gas chromatographed. The collected 1-pentene, the only detected reaction product, was analyzed by nmr. Integration yielded the following: δ 0.92 (t, 1.8, $J \cong 7.1$ Hz, CH_3 and CHD_2), 1.4 (q, 2, $J \cong 7.2$ Hz, CH_2), 2.02 (q, 1.2, $J \cong 7.2$ Hz, allylic CH_2), 4.95 (m, 2, $=CH_2$), and 5.7 ppm (m, 1, $=CH$).

Registry No.—1, 32251-57-3; 2, 30090-51-8; 8, 32251-59-5; 10, 32251-60-8.

Acknowledgment.—We are grateful to H. G. Richey, Jr., and T. C. Rees of the Pennsylvania State University for communication of their earlier results, and for the gift of a sample of deuterated Grignard reagent used for kinetics studies.

(5) S. W. Benson, F. R. Cruickshank, D. M. Golden, G. R. Haugen, H. E. O Neal, A. S. Rodgers, R. Shaw, and R. Walsh, *Chem. Rev.*, **69**, 279 (1969).

(6) It might be more valid to use only one-half of the rate of ring opening in calculating an equilibrium constant, since the observed ring cleavage is the sum of cleavages of two ring bonds. Such a treatment would lower the strain energy estimated by about 0.5 kcal/mol.

(7) S. Kaarsemaker and J. Coops, *Recl. Trav. Chim. Pays-Bas*, **71**, 261 (1952).

(8) The latter is consistent with preliminary results of T. C. Rees (Ph.D. thesis, Pennsylvania State University, communicated to us by Professor H. G. Richey, Jr.) in which no reaction was found after 170 hr at 110°.

(9) A. Juvala, *Chem. Ber.*, **63**, 1989 (1930).

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9-Anthroxy. A Protecting Group Removable by Singlet Oxygen Oxidation

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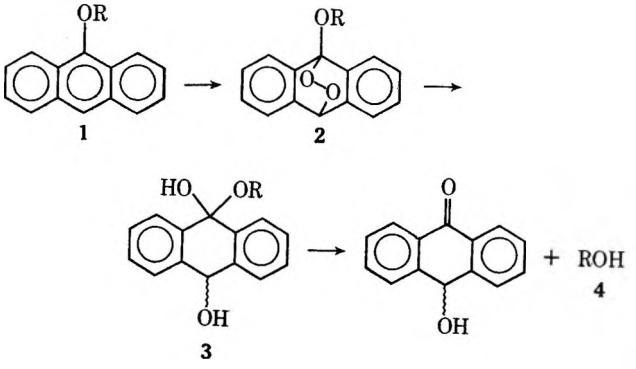
Aromatic ethers have not often[1,2] been used as protecting groups because of problems associated with attachment and removal by making and breaking the aromatic carbon–oxygen bond. We recently reported[3] that 9-anthroxy alkyl ethers 1 are useful protecting groups which can be readily cleaved at the aromatic carbon–oxygen bond by a sequence using low temperature (−30°) singlet oxygen oxidation[4] to an anthracenyl peroxide[5] (2) followed by mild catalytic reduction[6] of the weak oxygen–oxygen single bond. The initial reduction product is presumably the hemiketal **3**, which spontaneously eliminates the alcohol **4**. We report here some experimental details for cleaving 9-anthroxy ethers and a new method for synthesizing them.



(1) J. F. W. McOmie in "Advances in Organic Chemistry—Methods and Results," Vol. 3, Interscience, New York, N. Y., 1963, p 191.

(2) For a listing of protecting groups devised after McOmie's review see W. Theilheimer, "Synthetic Methods," subject indexes to Vol. 24, 23, and 20.

(3) W. E. Barnett and Larry L. Needham, *Chem. Commun.*, 1383 (1970).

(4) R. W. Murray and M. L. Kaplan, *J. Amer. Chem. Soc.*, **91**, 5358 (1969).

(5) W. Bergmann and M. J. McLean, *Chem. Rev.*, **28**, 367 (1941).

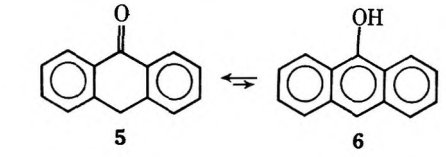
(6) C. Dufraisse and J. Houpillart, *C. R. Acad. Sci.*, **205**, 740 (1937).

In order for a protecting group to be generally useful it should be easily attached, it should survive reactions used for transforming other parts of the molecule, and it should be easily removed, preferably by some highly specific reaction. In this context, the singlet oxygen method for cleaving an aromatic ether is notable for its mildness. In a more general sense though, it is important because it has introduced a new kind of reagent for removing protecting groups. Thus in addition to protecting groups removable under acidic, basic, reductive,[1,2] and photochemical[7-10] conditions, we have a group removable under highly specific, and highly selective, oxidative conditions.[11] The result of singlet oxygen oxidation is to generate a labile peroxide which can be cleaved by a variety of reactions[12] to produce the alcohol **4** or a derivative thereof.

Singlet oxygen can be generated in a variety of ways. The removal scheme we use employs triphenyl phosphite[4] to generate singlet oxygen. This method is convenient and has the advantage that stoichiometry can be controlled better than by most other methods, but the triphenyl phosphate formed is a nuisance to separate from relatively nonpolar alcohols such as 1-hexadecanol. Hexadecanol and triphenyl phosphate have remarkably similar R_f values in several solvent sysems. Although the boiling points differ widely, we have preferred, for small-scale work, a chemical separation rather than distillation. In such a case, mild base-catalyzed hydrolysis can be employed to free the alcohol from phosphate ester. Obviously this difficulty can be corrected by modification of the phosphite for generating singlet oxygen, thus allowing the phosphite method to be used without the hydrolysis step. This would be necessary for 9-anthroxy cleavage in the presence of other esters whose hydrolysis is undersirable. In the case of water-soluble alcohols, no difficulty is experienced as shown by the isolation of butane-1,4-diol from its 9-anthroxy ether. The by-product triphenyl phosphate is easily separated by virtue of its water insolubility.

By choosing 9-anthroxy as the aromatic ether protecting group we were able to develop a mild method of regenerating the protected alcohol. We were, however, still faced with the problem of synthesizing these ethers. The usual way to construct aromatic–aliphatic ethers is by the Williamson synthesis. With a few special exceptions,[3] this turns out to be an effective method for attaching the 9-anthroxy group. The alcohol to be protected is changed into its tosylate, which is in turn converted into the 9-anthroxy ether by displacement with the phenolate ion from anthrone.[3] Obviously this method involves attachment by making the alkyl carbon–oxygen bond. It is desirable, however, to have a method for attaching the goup *via* the aromatic carbon–oxygen bond, a method which would be useful in cases where tosylate displacement is ineffective. It was noted that, although the 9-anthroxy group is stable to a variety of reaction conditions, in very strong acid[13] it will undergo hydrolysis to anthrone and an alcohol. We hoped to employ the reverse of this reaction as a method of synthesizing 9-anthroxy ethers *via* aromatic carbon–oxygen bond formation. However, using *p*-toluenesulfonic acid as catalyst we have been unable to force this reaction completely in the direction of ether formation. Prolonged refluxing of equimolar amounts of an alcohol and anthrone in benzene or toluene under conditions where water could be removed by azeotropic distillation gives mixtures containing starting materials as well as the desired ether.

Although these results were not fully understood, it was speculated that the difficulty might involve the unfavorable anthrone–9-anthrol, **5**–**6**, equilibrium. A way of eliminating this probem would be to O-methylate anthrone and to use the resulting methyl ether, **7**, in acid-catalyzed exchange reactions with other higher boiling alcohols. In practice this works well. Equimolar amounts of 9-methoxyanthracene[14] and of the alcohol to be protected, **8**, are refluxed in benzene con-



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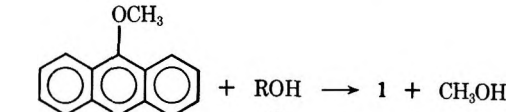


7 8

taining a catalytic amount of tosyl acid. The condensate is collected in a Dean–Stark trap containing calcium chloride to trap some of the methanol. The trap is drained periodically over a period of 24–63 hr until almost all of the benzene and methanol have been removed from the system. Primary alcohols give excellent yields of ethers, **1**, by this method. Secondary alcohols react only partially. Some examples are shown in Table I.

TABLE I
9-ANTHROXY ETHERS FROM 9-METHOXYANTHRACENE

9-Anthroxy ether	Decrease[a] in 9-methoxyanthracene, %	Reflux time, hr	Yield of ether,[b] %
1′-Hexadecanyl	Quantitative	62	83
1′-Dodecanyl	Quantitative	21	90
1′-Octanyl	Quantitative	22	91
4′-Hydroxy-1′-butanyl	Quantitative	62	85
2′-Octanyl	63	62[c]	
Cyclohexanyl	66	63[c]	
3′-Cholesteryl	45	63[c]	

[a] Measured by nmr. [b] After chromatography. [c] Longer times do not result in a further decrease of 9-methoxyanthracene.

Experimental Section

Nmr spectra were taken on a Varian HA-100 spectrometer. Melting points were taken on a Thomas–Hoover capillary tube melting point apparatus and are uncorrected. Except where indicated, all infrared spectra were taken in $CHCl_3$ solution on a Perkin-Elmer Model 257 spectrometer. They were calibrated at 1603 cm^{-1} with a polystyrene film.

(7) J. A. Barltrap and P. Schofield, *J. Chem. Soc.*, 4758 (1965).
(8) D. H. R. Barton, Y. L. Chow, A. Cox, and G. W. Kirby, *ibid.*, 3571 (1965).
(9) J. W. Chamberlin, *J. Org. Chem.*, **31**, 1658 (1966).
(10) A. J. Kirby and A. G. Varvoglis, *Chem. Commun.*, 406 (1967).
(11) Oxidation has been used as a secondary step in removing a protecting group. In strongly basic media, allyl ethers are isomerized to enol ethers which can becleaved by acid or by oxidation: R. Grigg and C. D. Warren, *J. Chem. Soc.*, 2205 (1965).
(12) W. E. Barnett and L. L. Needham, results to be published.
(13) E. deB. Barnett, J. W. Cook, and M. A. Matthews, *J. Chem. Soc.*, **123**, 1994 (1923).
(14) J. S. Meek, P. A. Monroe, and C. J. Bouboulis, *J. Org. Chem.*, **28**, 2572 (1963).

Methyl tosylate was prepared according to an "Organic Syntheses" procedure;[15] an 88% yield of crude tosylate was obtained.

9-Methoxyanthracene was prepared from crude methyl tosylate according to the method of Barnett, *et al.*,[13] total yield 60%, mp 93–94° (lit.[13] mp 94°).

9-Hexadecyloxyanthracene.—A mixture of 2.08 g (0.010 mol) of 9-methoxyanthracene, 2.42 g (0.010 mol) of hexadecanol, and 0.020 g of *p*-toluenesulfonic acid in 50 ml of benzene was refluxed for 62 hr. Throughout this period, a Dean–Stark trap containing approximately 10 g of $CaCl_2$ was attached. Periodically, benzene was removed so that the final volume was about 10 ml. The mixture was then cooled and diluted to 75 ml with ether. This solution was washed with 5 ml of 2 *N* NaOH and 5 ml of water. The organic layer was dried ($MgSO_4$), filtered, and evaporated to give 3.92 g (96%) of a crystalline solid. Nmr analysis showed this material to be greater than 90% pure hexadecyloxy ether. The material was recrystallized from EtOAc–hexane (5 ml–20 ml) to give 2.31 g of white powder, mp 58–59.5°. The mother liquors were evaporated to dryness and triturated with 5 ml of pentane. On cooling (−5°) white crystals precipitated but some dark material coprecipitated. The pentane was removed and the residue was dissolved in 20 ml of warm hexane. This homogeneous solution was filtered through 10 g of activity I Woelm alumina, using additional hexane. The first three 50-ml fractions gave white crystalline residues weighing 0.982, 0.084, and 0.012 g, respectively. The total yield of ether isolated was thus 3.37 g (83%). Elution with 50 ml of ether gave 0.213 g of a red oil which was not further investigated. Pure hexadecyloxy ether gave the following nmr ($DCCl_3$): δ 5.60 (t, 2 H), 7.34–8.30 (m, 9 H), 0.87–2.09 (m, 31 H).

Anal. Calcd for $C_{30}H_{42}O$: C, 86.07; H, 10.11. Found: C, 86.21; H, 10.11.

9-Dodecyloxyanthracene.—A procedure and apparatus similar to that used for the preparation of the hexadecyl ether were used. A benzene solution of 1.86 g (0.010 mol) of dodecanol, 2.08 g (0.010 mol) of 9-methoxyanthracene, and 0.020 g of *p*-toluenesulfonic acid was refluxed for 21 hr *with periodic removal of benzene*. After the usual work-up with base and water, the reaction mixture was dried over Na_2SO_4 and filtered, and the solvent was removed *in vacuo*. The crude yield was 3.53 g. Nmr analysis showed nearly quantitative formation of the dodecanyl ether. The crystalline material was dissolved in the minimum amount of warm hexane and filtered through a column containing 10 g of alumina. Additional hexane was added so that three 50-ml fractions were collected. The respective weights were 2.98, 0.55, and 0.08 g. The first fraction was recrystallized from a small amount of pentane: yield 2.68 g; mp 48–49°; nmr ($DCCl_3$) δ 7.6–8.34 (m, 9 H), 4.17 (t, 2 H), 0.90–2.10 (m, 23 H).

Anal. Calcd for $C_{26}H_{34}O$: C, 86.13; H, 9.45. Found: C, 86.31; H, 9.65.

9-Dodecycloxyanthracene.—The amounts of reagents used were the same as in the preceding experiment. The reflux time was 44 hr and *no benzene* was drained from the Dean–Stark trap. The work-up was as usual; the crude yield was 3.52 g. The nmr spectrum, however, showed only about a 50% decrease in the intensity of the methoxy singlet.

9-(4-Hydroxybutoxy)anthracene.—A mixture of 6.28 g (0.0302 mol) of 9-methoxyanthracene, 54.3 g (0.604 mol) of 1,4-butanediol, and 0.090 g of *p*-toluenesulfonic acid in benzene (120 ml) was refluxed for 62 hr with periodic draining of the Dean–Stark trap, which contained *ca.* 10 g of $CaCl_2$. After cooling, benzene (50 ml) was added along with 2 *N* NaOH (20 ml). After separating the layers, the organic layer was washed twice with water (50 ml) in order to rid the product of unreacted diol. The organic layer was dried (Na_2SO_4) and filtered, and the solvent was removed *in vacuo*. The product (7.116 g) was dissolved in the minimum amount of methylene chloride. This solution was then preadsorbed onto 3 g of basic alumina (activity I). The preadsorbed material was added to alumina (30 g), and the product was eluted with light petroleum containing increasing amounts of ether. The 9-(4-hydroxybutoxy)anthracene was collected in fractions varying in ether percentage from 15 to 100. The total yield was 6.77 g (84.5%), mp 77–81°. A 100% ether fraction was recrystallized from an ethyl acetate–hexane mixture: mp 81–82°; nmr ($DCCl_3$) δ 7.20–8.31 (m, 9 H), 4.18 (t, 2 H), 3.78 (t, 2 H), 1.85–2.20 (m, 4 H).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.25; H, 6.81.

Cleavage of the Hexadecanyl Ether.—A solution of triphenyl phosphite (3.1 g, 0.010 mol) in methylene chloride (100 ml) was ozonized for 45 min at the rate of 100 mmol/min. After purging the blue solution with nitrogen, a heterogeneous mixture of the 9-hexadecyloxyanthracene (2.09 g, 0.005 mol) in methylene chloride (50 ml) at approximately −78° was added to the ozonolysis flask. The reaction temperature was allowed to rise slowly until it reached 25°. Methylene chloride was removed *in vacuo*. The residue was dissolved in ethyl acetate (125 ml) and 0.52 g of 10% Pd/C was added. The hydrogenation was carried out at a pressure of 43.8–43.4 psi for 30 min. The hydrogenated turquoise solution was then filtered through 3 g of Celite. The Celite was washed repeatedly with ethyl acetate. The filtrate was concentrated *in vacuo* to give a crude yield of crystalline material, 5.2 g. The nmr of this material showed no $-OCH_2-$ triplet in the ether region (4–4.1 ppm), but there was a triplet at 3.6 ppm where the triplet in an authentic sample of hexadecanol is located. An attempt was made to separate the hexadecanol from triphenyl phosphate *via* column chromatography. However, an efficient separation was not possible.

In another run the crude Pd reduction product (from 0.003 mol of 9-decyloxyanthracene) was treated with 6 equiv of KOH in 100 ml of methanol in order to hydrolyze the triphenyl phosphate. The reaction mixture was stirred magnetically overnight at room temperature. The methanol was removed *in vacuo* and water (200 ml) was added. This basic mixture was extracted twice with ether (100 ml). The combined ether layers were dried (Na_2SO_4), and the ether was evaporated *in vacuo*. Nmr analysis of the yellowish material indicated that the products were hexadecanol and a small amount of aromatic material. This material was then treated with hot hexane (10 ml) and filtered with suction. The insoluble material was washed twice with hot hexane (5 ml). The hexane layers were combined and the solvent was removed *in vacuo*. The yield was 0.63 g (87%) of beige crystalline material. Spectral data were almost identical with those of authentic hexadecanol. In order to purify this material further, it was dissolved in warm hexane (20 ml) and filtered through neutral alumina (5 g). Fractions (40 ml) of hexane and varying amounts of ether (from 0 to 36%) were taken. These five fractions weighed 0.48 g (68%). The nmr spectrum and the melting point were identical with those of hexadecanol.

Cleavage of 9-(4-Hydroxybutoxy)anthracene Ether.—The apparatus used was similar to that used previously. However, this time the procedure was slightly different. Methylene chloride (100 ml) was ozonized at −78° until the solvent was saturated with ozone (detected by blue coloring of CH_2Cl_2). The cold triphenyl phosphite in methylene chloride was added until the blue color disappeared. The ozonolysis was repeated until the appearance of a blue coloration again; then more of the triphenyl phosphite was added. This continual ozonolysis and addition was repeated until all the triphenyl phosphite (3.10 g, 0.010 mol) had been added. After purging with nitrogen, the 9-(4-hydroxybutoxy)anthracene (1.33 g, 0.005 mol) was added in a methylene chloride solution. The yellow solution was then allowed to warm to room temperature. The methylene chloride was removed *in vacuo* and the yellow residue was dissolved in ethyl acetate (100 ml). It was transferred to a Paar hydrogenation bottle and 0.52 g of 10% Pd/C was added as a slurry with ethyl acetate to the bottle. After hydrogenation for 30 min and filtration through Celite, the solvent was evaporated *in vacuo*. In order to extract the water-soluble diol, distilled water (200 ml) was added. After filtering through a Büchner suction filter, the water was evaporated to a volume of about 70 ml. This aqueous solution was cooled at 5°. The contents again were filtered and the water was evaporated *in vacuo*, yield 0.31 g. Nmr analysis indicated that the product still contained some water and that the per cent yield of diol was 47.

Registry No.—9-Hexadecyloxyanthracene, 30253-18-0; 9-dodecyloxyanthracene, 31734-34-6; 9-(4-hydroxybutoxy)anthracene, 31734-35-7.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the office of General Research at the University of Georgia for support of this research (PRF 3321-A1).

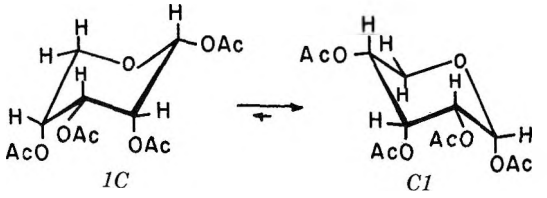
(15) "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 146.

Additions and Corrections

Vol. 36, 1971

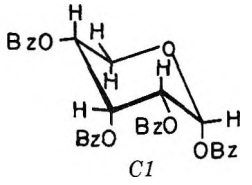
P. L. Durette and D. Horton: Conformational Studies on Pyranoid Sugar Derivatives. The Conformational Equilibria of the D-Aldopentopyranose Tetraacetates and Tetrabenzoates.

Page 2659. The formulas for α-D-*ribo* (1) should be as follows.



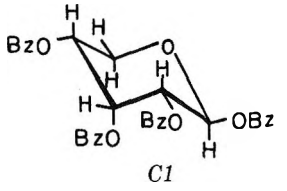
1C *C1*

Page 2660. The formula for the *C1* conformation of α-D-*ribo* (9) should be as follows.



C1

The formula for the *C1* conformation of β-D-*ribo* (10) should be as follows.



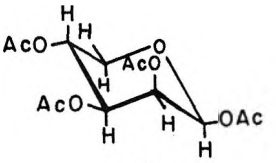
C1

Page 2661. Column 2, lines 4 and 5. The sentence "The values reported are considered accurate to ±0.1 Hz," should be deleted.

Page 2664. Table X, lines 3 and 4. The equilibrium data for α-D-*arabino* (3) and β-D-*arabino* (4) should read as follows.

	% *C1*	% *1C*	*K* = *C1*/*1C*
α-D-*arabino*	21	79	0.26
β-D-*arabino*	4	96	0.04

Page 2665. The formula for the *C1* conformation of β-D-lyxopyranose tetraacetate (8) should be as follows.

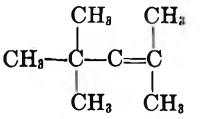


C1

L. de Vries: An Aminocyanoketenime, Aminomalononitrile, and Aminocyanoimidazole from Diisobutene, Hydrogen Cyanide, and Hydrogen Fluoride. Preparation of Novel Diaminoethylenes and Diiminoethanes.

Page 3444. The unnumbered figure in the middle of the first column is part of footnote 6.

Page 3445. In Scheme II the left-hand structure should be



Page 3445. Structure **13** in footnote 17 should have the positive charge associated with the central nitrogen atom not the R group.

Page 3447. Column 2, line 9. "*N-tert*-octyl-*tert*-octylmalononitrile" should read *N-tert*-octylamino-*tert*-octylmalononitrile.

Author Index TO VOLUME 36, 1971

Subject Index TO VOLUME 36, 1971[1]

(1) The index was prepared by Dr. James A. Waters of the Laboratory of Chemistry, NIAMD, National Insiitutes of Health, Bethesda, Md.

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Dr. Robert A. Moss
Rutgers State University
New Brunswick, N.J.
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Sidney W. Fox and Dr. Kaoru Harada, University of Miami; Dr. Gottfried Krampitz, University of Bonn; and Dr. George Mueller, University of Concepcion, Chile
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Ralph G. Pearson
Northwestern University
Evanston, Ill.
September 28, 1970 **50¢**

Reaction mechanisms in both organic and inorganic chemistry have been so extensively and successfully studied in past years that in the 1960's it seemed impossible that any revolutionary advance could occur in this field. Yet chemists' recent realization of the importance of orbital symmetry effects in chemical reactions must be considered in the major breakthrough category. **92870**

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Bruce F. Greek, C&EN
February 22, 1971 **50¢**

Another price-capacity-construction cycle under way. The ethylene cost-supply situation will interest management, engineering, and technical staff people alike. Taking the U.S. ethylene industry as a whole, future supply seems to rank above other concerns now as company research men and other planners revise their views for the next five years. **22271**

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Howard J. Sanders, C&EN
May 19, 1969 & June 2, 1969 **75¢**

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Alan R. Katritzky
University of East Anglia
England
April 13, 1970 **50¢**

The article examines some of the recent advances in heterocyclic chemistry—a field important to understanding biochemical mechanisms, natural-product chemistry, dyes, pharmaceuticals, and polymers. **41370**

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University of Lund, Sweden
Norman L. Weinberg
Hooker Chemical
Niagara Falls, N.Y. **50¢**
January 25, 1971

A useful tool for synthetic organic chemists. Industry in general is making a very close reappraisal of electrochemical processing. Perhaps it is overly optimistic to expect electrolytic processes for the production of the most common organic chemicals, but such methods should certainly be of great interest to manufacturers of fine chemicals. **12571**

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Michael Heylin, C&EN
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Aaron M. Altschul
U. S. Department of Agriculture
Washington, D.C.
Nov. 24, 1969 **50¢**

Worldwide, the overriding problem is poverty, thus economic problems must be solved in addition to improving natural foodstuffs and developing new ones. **11249**

Free Radical Pathology

William A. Pryor
Louisiana State University
Baton Rouge
June 7, 1971 **50¢**

Efforts have intensified in recent years to understand the mechanisms of aging at a molecular level and, as part of the program, a great deal of research has been done on the free radical theory of aging and the role of radical inhibitors such as vitamin E in the cell. **06771**

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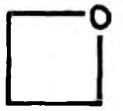

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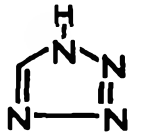

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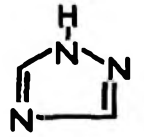

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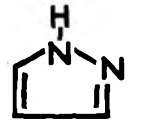

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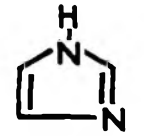

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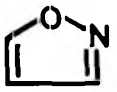

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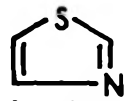

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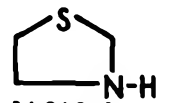

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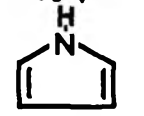

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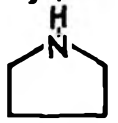

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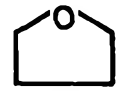

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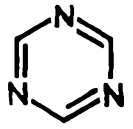

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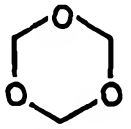

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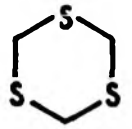

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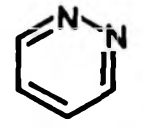

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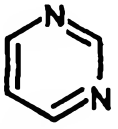

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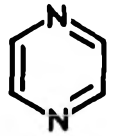

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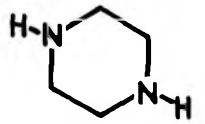

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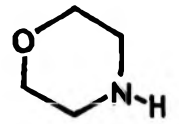

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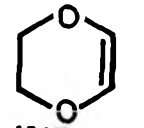

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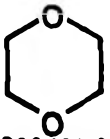

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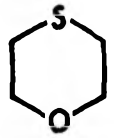

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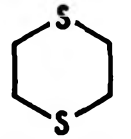

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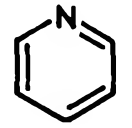
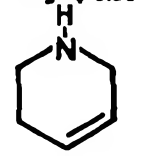
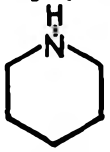


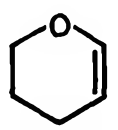
P5750-6
500g-$3.55



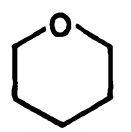
13,475-9
100g-$8.65



10,409-4
500g-$8.00



D10,620-8
100g-$3.00



T1440-0
100g-$7.80

P700-2
5g-$3.35

H1660-4
25g-$15.60

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