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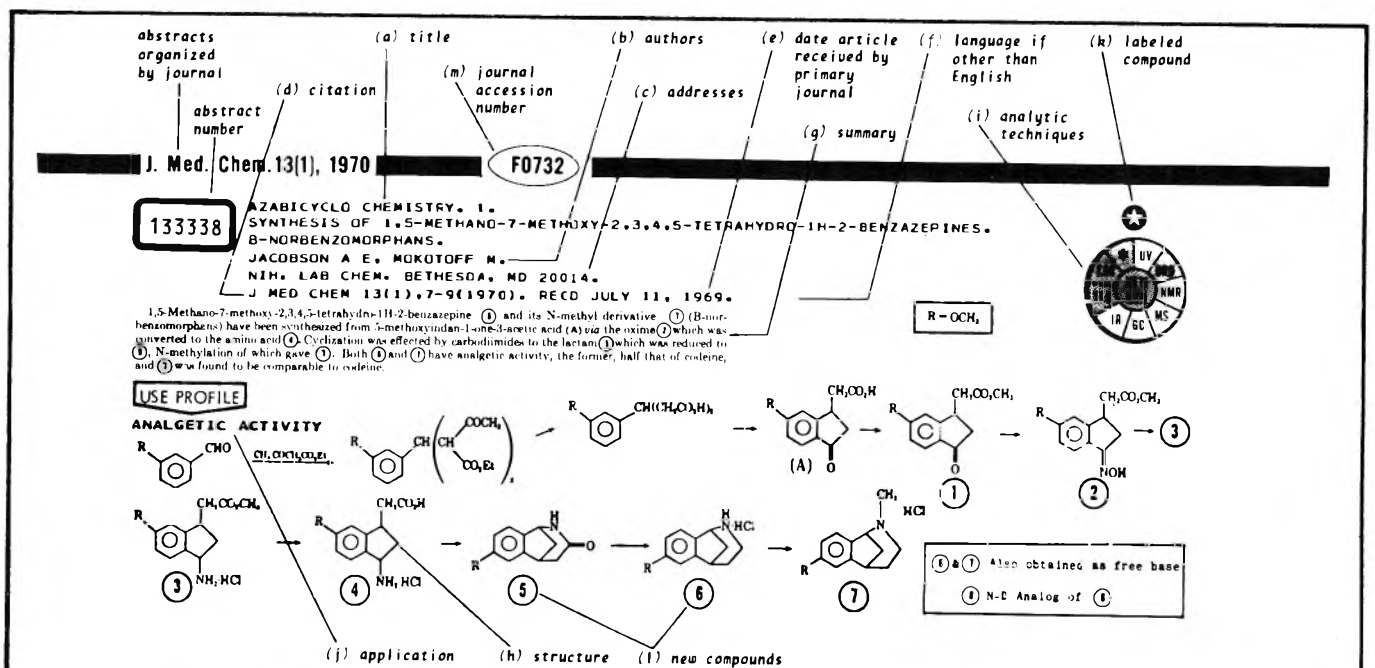

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(In nmr descriptions, s = singlet, d = doublet, t = triplet, m = multiplet.)

"The ethereal extract was dried ($MgSO_4$), concentrated, and distilled giving 10.23 g (65%) of the acetoxy ketone 12: bp 82–83° (2.9 mm); n_D^{25} 1.4266 [lit.[6] bp 80–82° (3 mm); n_D^{25} 1.4261]; d_4^{25} 0.823; $[\alpha]_D^{25}$ 0.0° (c 6, CH_3OH); uv max (95% EtOH) 275 mμ (ε 21); ir (CCl_4) 1725 (C=O), 1740 cm^{-1} (ester C=O); nmr (CCl_4) δ 3.98 (t, 2, J = 6 Hz, CH_2OAc), 2.43 (t, 2, J = 6 Hz, CH_2CO), 2.07 (s, 3), 1.97 (s, 3), and 1.6 (m, 4); mass spectrum (70 eV) m/e (rel intensity) 158 (5), 143 (5), 115 (6), 100 (50), 99 (11), 98 (100), 85 (10)."

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Reactions of 2-Acyl-1,3-indandiones with o-Phenylenediamines

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Received October 24, 1969

The condensation of 2-acyl-1,3-indandiones with various *o*-phenylenediamines gave benz[*b*]indeno[1,2-*e*][1,4]-diazepin-12(5H)-ones (**2a–s**) in good yields. In some cases, depending upon the reaction conditions, the intermediate noncyclic 1:1 adducts, 2-[1-(*o*-aminophenylimino)alkyl]-1,3-indandiones (**1a–d**), or the 1:2 adduct, 2,2′-[*o*-phenylenebis(nitrilomethylidyne)]di-1,3-indandione (**3**), were obtained. The reactions of the carbonyl group of several benzindenodiazepinones **2** with hydroxylamine and with various hydrazines were investigated.

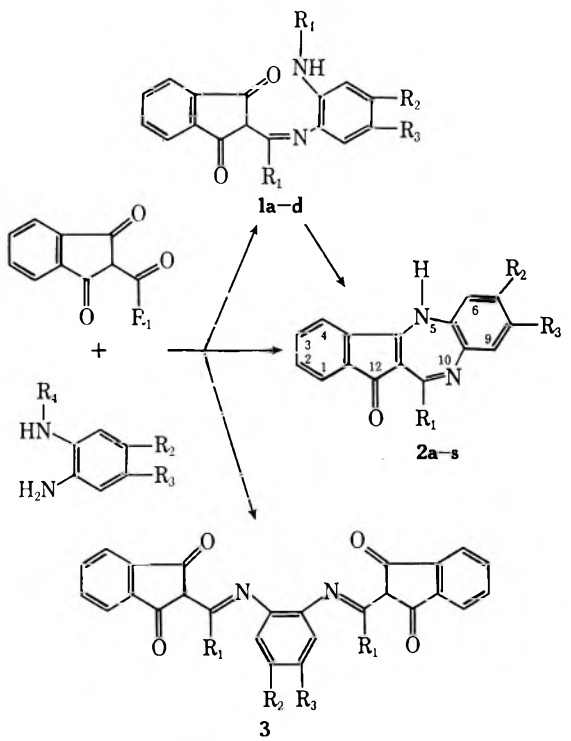
In a previous paper[1] in this field, we described the reactions of 2-acyl-1,3-indandiones with aliphatic diamines. Now we report the reactions of 2-acyl-1,3-indandiones with a variety of *o*-phenylenediamines with the emphasis on a new class of compounds, the benz[*b*]indeno[1,2-*e*][1,4]diazepin-12(5H)-ones (**2a–s**, Scheme I).

The cyclization of open-chain β-diketones with *o*-phenylenediamine to give 2,4-disubstituted 1,5-benzodiazepines has been studied extensively,[2–4] but prior to our work there has been no report on the cyclization of 2-acyl-1,3-indandiones with *o*-phenylenediamine. Two somewhat related reactions are described in the literature, namely, the condensation of 1-chloroindene-2-carboxaldehyde and of 1-oxo-2-indanglyoxylic acid with *o*-phenylenediamine to give respectively 5,12-dihydrobenz[*b*]indeno[1,2-*e*][1,4]diazepine[5] and the corresponding 11-carboxylic acid.[6]

In our study we found that addition of 2-acyl-1,3-indandiones to refluxing ethanolic solutions of *o*-phenylenediamines, in the presence of an acidic catalyst, usually formic acid, gave benz[*b*]indeno[1,2-*e*]-[1,4]diazepin-12(5H)-ones (**2a–s**) in very good yields.

Only in four cases, the intermediate noncyclic 1:1 adducts, 2-[1-(*o*-aminophenylimino)alkyl]-1,3-indandiones (**1a–d**), were isolated. The indandiones **1a** ($R_1 = R_2 = R_3 = R_4 = H$) and **1b** ($R_1 = CH_3$; $R_2 = R_3 = R_4 = H$) were obtained by adding the appropriate 2-acyl-1,3-indandione to *o*-phenylenediamine at or below room temperature. The indandiones **1c** ($R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = C_6H_5$) and **1d** ($R_1 = C_6H_5$; $R_2 = R_3 = H$; $R_4 = C_6H_5$) were formed when N-phenyl-*o*-phenylenediamine was used in refluxing ethanol. When **1a** and **1b** were heated to reflux in dry ethanol or were treated with hydrochloric or perchloric acid in the cold, the corresponding ring-closed compounds **2a** ($R_1 = R_2 = R_3 = H$) and **2b** ($R_1 = CH_3$; $R_2 = R_3 = H$) were obtained. With the above acids the salts of **2a** and **2b** were formed. Several attempts to ring-close **1c** and **1d** were unsuccessful, even when concentrated sulfuric acid or polyphosphoric acid was used.

SCHEME I[a]



[a] For R_1, R_2, R_3, and R_4 see Tables I–III and Experimental Section.

(1) W. A. Mosher and S. Piesch, *J. Org. Chem.*, **35**, 1026 (1970).
(2) J. Thiele and G. Steimming, *Chem. Ber.*, **40**, 955 (1907).
(3) C. A. Haley and P. Maitland, *J. Chem. Soc.*, 3159 (1951).
(4) J. A. Barltrop, C. G. Richards, D. M. Russel, and G. Ryback, *J. Chem. Soc.*, 1132 (1959).
(5) M. Weissenfels, H. Schurig, and G. Hübsam, *Chem. Ber.*, **100**, 584 (1967).
(6) J. N. Chatterjea and K. Prasad, *J. Indian Chem. Soc.*, **34**, 377 (1957).

TABLE I

11-SUBSTITUTED BENZ[*b*]INDENO[1,2-*e*][1,4]DIAZEPIN-12(5H)-ONES (**2**, $R_2 = R_3 = H$)

Compd	R_1	Method	Reaction time	Yield, %	Mp, °C	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
2b	CH_3[a]	A	5 hr	86	299–300[b]	$C_{17}H_{12}N_2O$	78.44	4.65	10.76	78.03	4.82	10.73
2c	C_2H_5	B	20 hr	60	244[b]	$C_{18}H_{14}N_2O$	78.81	5.15	10.21	78.69	5.27	10.06
2d	$CH(CH_3)_2$	B	20 hr	75	202–203[c]	$C_{19}H_{16}N_2O$	79.16	5.55	9.64	79.30	5.68	9.64
2e	$CH_2CH(CH_3)_2$[d]	B	48 hr	60	204–205	$C_{20}H_{18}N_2O$	79.44	6.00	9.27	79.32	5.80	9.13
2f	$CH(C_6H_5)_2$	B	9 days	55	190–192[c]	$C_{29}H_{20}N_2O$	84.44	4.89	6.79	84.42	4.98	6.79
2g	C_6H_5	A	20 hr	65	>300[e]	$C_{22}H_{14}N_2O$	82.00	4.36	8.69	81.85	4.45	8.64
2h	C_6H_4-*p*-Cl	A	15 hr	35	>300[e]	$C_{22}H_{13}ClN_2O$	74.05	3.66	7.85	74.20	3.81	7.74

[a] Perchlorate, mp 300° dec. [b] Recrystn solvent: dioxane. [c] Recrystn solvent: ethanol. [d] Perchlorate, mp 279° dec. [e] Recrystn solvent: ethanol–dimethylformamide.

TABLE II

7 (OR 8),11-DISUBSTITUTED BENZ[*b*]INDENO[1,2-*e*][1,4]DIAZEPIN-12(5H)-ONES (**2**)

Compd	R_1	R_2 or R_3	Method	Reaction time	Yield, %	Mp, °C	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
2i	CH_3	CH_3[a]	A	10 hr	75	285 dec[b]	$C_{18}H_{14}N_2O$	78.81	5.15	10.21	78.93	5.31	9.96
2j	C_6H_5	CH_3[a]	A	10 hr	65	276–286[b]	$C_{23}H_{16}N_2O$	82.12	4.80	8.33	82.00	4.85	8.39
2k	CH_3	Cl[c,d]	A	12 hr	80	298–300 dec[b]	$C_{17}H_{11}ClN_2O$	69.27	3.78	9.51	69.55	3.99	9.32
2l	$CH_2CH(CH_3)_2$	Cl[c]	B	36 hr	75	200[e]	$C_{20}H_{17}ClN_2O$	69.01	6.06	7.32	68.95	6.24	7.51
2m	$CH(C_6H_5)_2$	NO_2[c]	B	10 days	45	>300[b]	$C_{29}H_{19}N_3O_3$	76.20	4.16	9.17	76.44	4.16	9.11
2n	C_6H_5	Cl[c]	A	36 hr	70	298–300 dec[b]	$C_{22}H_{13}ClN_2O$	74.05	3.66	9.94	74.02	3.82	9.88
2o	C_6H_5	NO_2[c]	B	24 hr	60	>300[b]	$C_{22}H_{13}N_3O_3$	72.33	3.59	11.50	72.11	3.74	11.69

[a] A mixture of 7 and 8 isomers is probably formed. [b] Recrystn solvent: ethanol–dimethylformamide. [c] A single isomer (7 or 8) is formed. [d] Perchlorate, mp 300. [e] Recrystn solvent: ethanol.

TABLE III

7,8,11-TRISUBSTITUTED BENZ[*b*]INDENO[1,2-*e*][1,4]DIAZEPIN-12(5H)-ONES (**2**)

Compd	R_1	$R_2 = R_3$	Method	Reaction time	Yield, %	Mp, °C	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
2p	CH_3	CH_3	A	10 hr	75	284–286 dec[a]	$C_{19}H_{16}N_2O$	79.16	5.55	9.64	79.00	5.74	9.63
2q	C_6H_5	CH_3	A	10 hr	75	>300[b]	$C_{24}H_{18}N_2O$	82.26	5.18	8.00	82.48	5.16	8.41
2r	CH_3	Cl	A	10 hr	70	>300[b]	$C_{17}H_{10}Cl_2N_2O$	62.02	3.06	8.54	61.99	3.40	8.34
2s	$CH(C_6H_5)_2$	Cl	B	3 days	70	260–261[b]	$C_{29}H_{18}Cl_2N_2O$	72.35	3.77	5.82	72.24	4.13	5.71

[a] Recrystn solvent: dimethylformamide. [b] Recrystn solvent: ethanol–dimethylformamide.

Reverse addition of the reactants, *o*-phenylenediamine to 2-formyl-1,3-indandione, gave the 1:2 adduct, 2,2′-[*o*-phenylenebis(nitrilomethylidyne)]di-1,3-indandione (**3**, $R_1 = R_2 = R_3 = H$). Attempts to ring-close **3** failed.

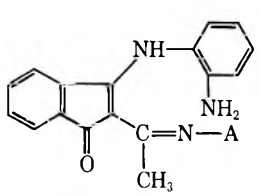
The structures of these compounds are based upon the elemental analyses and are consistent with the infrared spectra. The benzindenodiazepinones (**2a–s**) are red crystalline compounds. Their melting points and elemental analyses are summarized in Tables I–III. In neutral alcoholic solution these compounds show absorption bands between 300 mμ (ε 14,000–35,000) and 430 mμ (ε 3500–6000). In acidic solution the absorption bands are shifted bathochromically [325 mμ (ε 20,000–35,000) and 640–675 mμ (ε 400–750)]. The infrared spectra show absorption peaks at *ca.* 3300, at 1675–1640, and at *ca.* 1600 cm^{-1}.

Treatment of compounds **2a–s** with concentrated hydrochloric or perchloric acid gave the corresponding salts, which have a characteristic intense blue color and a metallic luster. Anhydrous hydrazine reacted with **2b** (Scheme II) in ethanolic solution, splitting off *o*-phenylenediamine and yielding the known hydrazone of the 3-methylindeno[1,2-*c*]pyrazol-4(1H)-one[7] (**4**).

Treatment of **2b** and **2g** with 1,1-dimethylhydrazine in dioxane gave respectively the 11-methyl- and 11-phenyl-12-(2,2-dimethylhydrazino)benz[*b*]indeno[1,2-*e*][1,4]diazepin-12(5H)-ols (**5a** and **5b**). When phenylhydrazine was used in place of 1,1-dimethylhydrazine in the reaction with **2b**, 11-methyl-12-(2-phenylhydrazino)benz[*b*]indeno[1,2-*e*][1,4]diazepin-12(5H)-ol (**5c**) was formed.[8] Treatment of **2b**, **2e**, and **2g** with hydroxylamine in dimethylformamide yielded respectively the 11-methyl-, 11-isobutyl- and 11-phenyl-12-hydroxyaminobenz[*b*]indeno[1,2-*e*][1,4]diazepin-12-(5H)-ols (**6a–c**).[8] All attempts to dehydrate compounds **5** or **6** to the corresponding hydrazones or oximes failed. Reaction of **5** or **6** with ethanolic hydrochloric acid gave the characteristic blue salts **7**. Treatment of these salts with aqueous ammonia yielded the benzindenodiazepinones **2**. These benzindenodiazepinones were also obtained when compounds **5** and **6** were heated for several minutes in refluxing 95% ethanol.

(7) R. A. Braun and W. A. Mosher, *J. Amer. Chem. Soc.*, **80**, 4919 (1958).

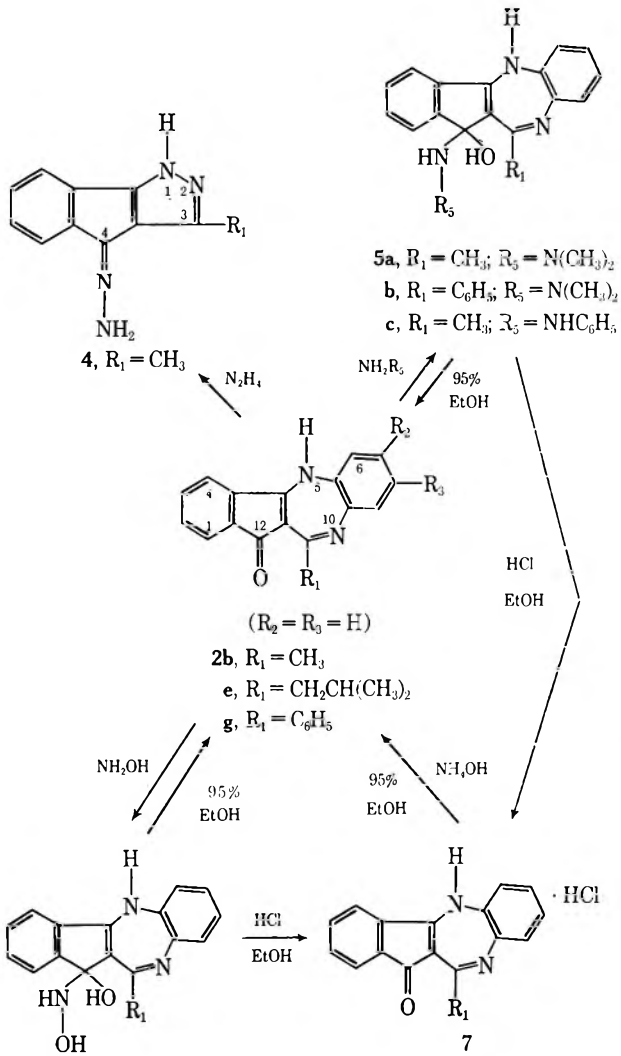
(8) Referee II has suggested that the diazepine ring of compounds **2** may open in the reaction with substituted hydrazines and with hydroxylamine to give the isomeric structure.



A = NHR, NR_2, or OH

The mass spectral fragmentation patterns of products **5c** and **6a** are very similar to that of the starting material **2b**, after the loss of the phenylhydrazine and of hydroxylamine, respectively. These results support the structures given to compounds **5** and **6**.

SCHEME II



Experimental Section[9]

2-Acyl-1,3-indandiones.—2-Formyl-1,3-indandione was prepared as described in ref 1 from triethyl orthoformate, acetic anhydride, and 1,3-indandione. All the other 2-acyl-1,3-indandiones were prepared according to known methods[10,11] from dimethyl phthalate and the appropriate methyl ketones in the presence of sodium amide[12] instead of sodium methoxide. It was found that sodium amide generally gives better yields than sodium methoxide. For example, in the preparation of 2-(*p*-chlorobenzoyl)-1,3-indandione, 70% yields were obtained using sodium amide (the reported[11] yield using sodium methoxide is only 5%).

2-[(*o*-Aminophenylimino)methyl]-1,3-indandione (**1a**, $R_1 = R_2 = R_3 = R_4 = H$).—A solution of 2-formyl-1,3-indandione (5 g) in ethanol (100 ml) was added dropwise over a period of 5 min to a stirred, cold solution of an excess of *o*-phenylenediamine (3 g) in acetic acid (2 ml) and ethanol (50 ml). The yellow precipitate was collected by filtration and washed with cold ethanol to give an 80% yield of **1a**, as fine yellow needles of mp 197° dec.

Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.85; H, 4.63; N, 10.43.

A solution of **1a** in dry ethanol, refluxed for 10 min, yielded **2a**, as red needles. Treatment of **1a** with cold perchloric acid gave the characteristic blue salt of the ring-closed compound **2a**.

2-[1-(*o*-Aminophenylimino)ethyl]-1,3-indandione (**1b**, $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$).—2-Acetyl-1,3-indandione was allowed to react with *o*-phenylenediamine as described above for **1a** (reaction time 20 min) to give fine yellow needles of **1b**, contaminated with a small amount of the ring-closed compound **2b**.

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07. Found: C, 73.73; H, 5.38.

The perchlorate of the ring-closed compound **2b** was obtained as blue crystals by treatment of **1b** with cold perchloric acid. Upon refluxing **1b** in dry ethanol **2b** was formed as red needles.

2-[1-(*o*-Anilinophenylimino)ethyl]1,3-indandione (**1c**, $R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = C_6H_5$).—2-Acetyl-1,3-indandione was allowed to react with N-phenyl-*o*-phenylenediamine as described in method A (reaction time 7 hr) to give an 80% yield of **1c**, as deep yellow needles of mp 218° (dioxane or 1-propanol).

Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.94; H, 5.12, O, 9.03. Found: C, 78.21; H, 5.29; O, 9.20.

2-[(*o*-Anilinophenylimino)benzyl]-1,3-indandione (**1d**, $R_1 = C_6H_5$; $R_2 = R_3 = H$; $R_4 = C_6H_5$) was prepared from 2-benzoyl-1,3-indandione and N-phenyl-*o*-phenylenediamine as described in method B (reaction time 24 hr). A 60% yield of **1d**, as brownish yellow needles of mp 185° (1-propanol), was obtained. The 1-propanol solution fluoresces deep red under ultraviolet light.

Anal. Calcd for $C_{28}H_{20}N_2O_2$: C, 80.77; H, 4.84; O, 7.66. Found: C, 80.83; H, 5.13; O, 8.73.

Compounds **1c** and **1d** failed to give the perchlorates of the corresponding ring-closed compounds by treatment with perchloric acid.

Benz[*b*]indeno[1,2-*e*][1,4]-diazepin-12(5H)-one (**2a**, $R_1 = R_2 = R_3 = H$).—A solution of 2-formyl-1,3-indandione (10 g, 57 mmol) in ethanol (200 ml) was added dropwise over a 3-hr period to a refluxing solution of formic acid (2 ml) and *o*-phenylenediamine (10 g, 100 mmol) in ethanol (200 ml). The mixture was refluxed for 1 additional hr and then filtered rapidly through a sintered-glass funnel. The insoluble yellow material was shown to be compound **3** ($R_1 = R_2 = R_3 = H$), formed as a by-product. The deep red filtrate was concentrated to 100 ml by distillation and the residue allowed to stand at room temperature. The dark red solid was collected and recrystallized from dioxane or ethanol to give a 60% yield of **2a**, as deep red needles of mp 287° dec: λ_{max}, mμ (ε), in neutral alcoholic solution 300 (14,000), 328 (12,000), 342 (10,000), 413 (7500), and 435 (6000); in acidic solution, 325 (20,000), 350 (11,000), 570 (1000), 618 (1000), 675 (650); ir 3300, 1675–1650, 1600–1525 cm^{-1}.

Anal. Calcd for $C_{16}H_{10}N_2O$: C, 78.03; H, 4.09; N, 11.38. Found: C, 77.83; H, 4.20; N, 11.41.

Treatment of the mother liquor of **2a** with concentrated hydrochloric acid gave the corresponding hydrochloride as blue crystals of mp 268°.

Anal. Calcd for $C_{16}H_{10}N_2O \cdot HCl$: C, 67.97; H, 3.92; N, 9.91; Cl, 12.54. Found: C, 68.06; H, 3.93; N, 9.82; Cl, 12.39.

Mono-, Di-, and Trisubstituted Benz[*b*]indeno[1,2-*e*][1,4]diazepin-12(5H)-ones (2b–s). Method A.—A solution of the appropriate 2-acyl-1,3-indandione (90 mmol) in ethanol (200 ml, or more if necessary to obtain a solution) was added dropwise over a 2-hr period to a refluxing and stirred solution of the appropriate *o*-phenylenediamine (90 mmol) in a mixture of formic acid (2.5 ml) and ethanol (1000 ml). The mixture was refluxed for the time indicated in Tables I–III. The product was then collected by filtration at room temperature, washed with cold methanol, and recrystallized from suitable solvents (see Tables I–III) to give red needles (except **2p**, red plates, and **2r**, violet-red prisms). Compound **2h**: λ_{max}, mμ (ε), in neutral alcoholic solution, 325 (25,000), 340 (18,000), 390 (5000), 410 (3500); in acidic solution, 335 (35,000), 540 (1100), 640 (500); ir 3400, 1640, and 1600 cm^{-1}. Compound **2r**: λ_{max}, mμ (ε), in neutral alcoholic solution, 310 (35,000), 340 (12,000), 390 (5500), and 410 (4000); in acidic solution, 325 (30,000), 540 (850), 585 (850), and 640 (750); ir 3300, 1650, and 1590–1550 cm^{-1}.

An additional amount of product (about 5% of the yield given in Tables I–III) was obtained, as the hydrochlorides or perchlorates, by adding 20 ml of the appropriate concentrated acid

(9) Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. The infrared spectra were recorded with a Perkin-Elmer Infracord Model 137 (Nujol), and the electron spectra were recorded with a Perkin-Elmer 202 instrument. Mass spectra were taken with a CEC 21/110B mass spectrometer. Elemental analyses were performed by Dr. A. Bernhardt, Mikroanalytisches Laboratorium, Max Planck Institut für Kohlenforschung, Mülheim (Ruhr), West Germany.

(10) L. B. Kilgore, J. H. Ford, and C. W. Wolfe, *Ind. Eng. Chem.*, **34**, 494 (1942).

(11) R. L. Horton and K. C. Murdock, *J. Org. Chem.*, **25**, 838 (1960).

(12) L. Gattermann, "Die Praxis des Organischen Chemikers," 38th ed, Walter de Gruyter and Co., Berlin, 1958, p 220.

to the mother liquors and precipitating the blue salts by addition of ether.

Method B.—The appropriate 2-acyl-1,3-indandione and the appropriate *o*-phenylenediamine were condensed as described in method A except that, after the reaction time indicated in Tables I–III, the mixture was concentrated to 150 ml and allowed to stand for 2 days. The solid was collected by filtration, washed twice with methanol (25 ml), and recrystallized from a suitable solvent (see Tables I–III) to give red needles (except **2f**, red plates). Compound **2c**: λ_{max}, mμ (ϵ), in neutral alcoholic solution, 400 (6000); in acidic solution, 550 (680), 590 (630), and 650 (400); ir 3300, 1645, and 1580–1550 cm^{-1}. Treatment of the mother liquor with concentrated hydrochloric or perchloric acid gave an additional amount of product, as the corresponding salt of intense blue color.

2,2′-[*o*-Phenylenebis(nitrilomethylidyne)]di-1,3-indandione (3, $R_1 = R_2 = R_3 = H$).—A solution of *o*-phenylenediamine (2.5 g) and formic acid (0.5 ml) in ethanol (50 ml) was added dropwise over a period of 15 min to a refluxing solution of 2-formyl-1,3-indandione (5 g) in ethanol (100 ml). The mixture was then cooled to room temperature and the precipitate was collected by filtration. A 90% yield of **3**, as bright yellow plates of mp >300° (dimethylformamide), was obtained.

Anal. Calcd for $C_{26}H_{16}N_2O_4$: C, 74.28; H, 3.84; N, 6.66. Found: C, 74.27; H, 3.73; N, 6.75.

Compound **3** failed to cyclize by treatment with perchloric, sulfuric, or polyphosphoric acid.

Reactions of 2b and 2g with Hydrazines.—The general procedure used was as follows. The appropriate anhydrous substituted hydrazine (75 mmol) was added to a stirred, cold solution or suspension of the appropriate benzindenodiazepinone **2** (50 mmol) in anhydrous dioxane (100 ml), followed by the addition of anhydrous formic acid (0.5 ml). Agitation was continued for about 5 hr. Then the reaction mixture was evaporated to dryness under reduced pressure at room temperature and the residue was recrystallized from a suitable solvent.

12-(2,2-Dimethylhydrazino)-11-methylbenz[*b*]indeno[1,2-*e*][1,4]diazepin-12(5H)-ol (5a) was obtained in 60% yield, as yellow-red plates of mp 172° (anhydrous ethanol or dioxane–hexane) by reaction of **2b** with 1,1-dimethylhydrazine.

Anal. Calcd for $C_{19}H_{20}N_4O$: C, 71.23; H, 6.25; N, 17.49. Found: C, 71.22; H, 6.33; N, 17.31.

12-(2,2-Dimethylhydrazino)-11-phenylbenz[*b*]indeno[1,2-*e*][1,4]diazepin-12(5H)-ol (5b) was obtained in 40% yield as yellow needles of mp 210–212° (dioxane–hexane) by reaction of **2g** with 1,1-dimethylhydrazine.

Anal. Calcd for $C_{24}H_{22}N_4O$: C, 75.37; H, 5.80; N, 14.65. Found: C, 75.05; H, 5.90; N, 14.19.

11-Methyl-12-(2-phenylhydrazino)benz[*b*]indeno[1,2-*e*][1,4]diazepin-12(5H)-ol (5c) was obtained in 40% yield as yellow plates of mp 165–168° (ethanol) by reaction of **2b** with phenylhydrazine. In the mass spectrum of **5c**, there was molecular ion peak at *m/e* 368 with abundant fragment peaks at *m/e* 353, 260, 245, 231, 219, 190, 132, 115, 108, 92, and 77. The mass spectrum of the starting material **2b** revealed a molecular ion peak at *m/e* 260 with abundant fragment peaks at *m/e* 245, 231, 219, 190, 130, 115, 108, 102, and 77.

Anal. Calcd for $C_{23}H_{20}N_4O$: C, 75.18; H, 5.21; N, 15.25. Found: C, 75.27; H, 5.53; N, 14.72.

3-Methylindeno[1,2-*c*]pyrazol-4(1H)-one 4-Hydrazone (4).—When anhydrous hydrazine in ethanol was used, in place of the above substituted hydrazine in dioxane, in the reaction with **2b**, yellow crystals of mp 250–255° were obtained. The identity of this compound with an authentic sample of 3-methylindeno[1,2-*c*]pyrazol-4(1H)-one 4-hydrazone, obtained from 2-acetyl-1,3-indandione and hydrazine,[7] was established by mixture melting point determinations and by comparison of the ir spectra.

Reactions of 2b, 2e, and 2g with Hydroxylamine.—The following general procedure was used. A mixture of hydroxylamine hydrochloride (55 mmol) and sodium acetate (55 mmol) was added in one portion to a stirred, cold solution of the appropriate benzindenodiazepinone **2** (50 mmol) in dimethylformamide (100 ml). The agitation was continued until the solution turned dull yellow. Then the reaction mixture was poured into 600 ml of vigorously stirred ice–water. (The reverse procedure, *i.e.*, addition of water to the reaction mixture, caused decomposition of the product giving the starting material.) The yellow precipitate was collected by filtration, washed with ice–water, dried over P_2O_5, and recrystallized from anhydrous solvents.

12-Hydroxyamino-11-methylbenz[*b*]indeno[1,2-*e*][1,4]diazepin-12(5H)-ol (6a) was obtained in 90% yield as yellow plates of mp 205° dec (dioxane–hexane or ethanol) by reaction of **2b** with hydroxylamine for 5 hr. The mass spectrum of **6a** revealed a molecular ion peak at *m/e* 293 with abundant fragment peaks at *m/e* 278, 260, 245, 231, 219, 190, 160, 133, 130, 115, 108, 102, 92, and 77. The mass spectrum of the starting material **2b** is reported above (see compound **5c**).

Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.62; H, 5.16; N, 14.33. Found: C, 69.28; H, 5.40; N, 14.43.

12-Hydroxyamino-11-isobutylbenz[*b*]indeno[1,2-*e*][1,4]diazepin-12(5H)-ol (6b) was obtained in 75% yield as brownish yellow plates of mp 215° dec (ethanol) by treating **2e** with hydroxylamine for 10 hr.

Anal. Calcd for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.75; H, 6.23; N, 12.46.

12-Hydroxyamino-11-phenylbenz[*b*]indeno[1,2-*e*][1,4]diazepin-12(5H)-ol (6c) was obtained in 55% yield as deep yellow crystals of mp 223° (ethanol or dioxane–hexane) by reaction of **2g** with hydroxylamine for 10 hr.

Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.12; H, 4.96; N, 12.37.

Miscellaneous Reactions of Compounds 5 and 6.—These compounds reduced silver nitrate solution in the cold. When refluxed for a few minutes in 95% ethanol they gave the corresponding benzindenodiazepinones **2** and when treated with hydrochloric acid in ethanol solution produced the blue hydrochlorides **7**. Treatment of these salts with aqueous alcoholic solutions of ammonia gave the corresponding bases **2**.

Registry No.—**1a**, 24472-20-6; **1b**, 24515-43-3; **1c**, 24472-21-7; **1d**, 24472-22-8; **2a**, 24472-23-9; **2a** (HCl), 24472-24-0; **2b**, 24472-25-1; **2b** ($HClO_4$), 24467-34-3; **2c**, 24472-26-2; **2d**, 24472-27-3; **2e**, 24472-28-4; **2e** ($HClO_4$), 24523-21-5; **2f**, 24472-29-5; **2g**, 24472-30-8; **2b**, 24472-31-9; **2i** (7 isomer), 24472-32-0; **2i** (8 isomer), 24472-49-9; **2j** (7 isomer), 24472-34-2; **2j** (8 isomer), 24472-50-2; **2p**, 24472-35-3; **2q**, 24472-36-4; **2r**, 24472-37-5; **2s**, 24472-38-6; **3a**, 24472-39-7; **4**, 24472-40-0; **5a**, 24472-41-1; **5b**, 24472-42-2; **5c**, 24472-43-3; **6a**, 24472-46-6; **6b**, 24472-47-7; **6c**, 24472-48-8.

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Stereochemistry of Nucleophilic Displacements by Amines on Activated Vinyl Halides

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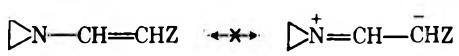
Displacements by ethylenimine on several activated vinylic chlorides (ClC=CZ, where Z = CO_2Et, SO_2Ar, CN, and PhCO) proceed with retention of configuration.

Nucleophilic substitution reactions on vinyl halides activated by electron-withdrawing groups generally proceed readily and with retention of geometric configuration.[1-6] However, like displacements by amines

$$XCH{=}CHZ + N: \longrightarrow NCH{=}CHZ + X:$$

X = halogen; Z = CO_2Et, CN, SO_2Ar, PhCO

were reported to proceed nonstereospecifically, *i.e.*, only one product isomer being obtained from both *cis* and *trans* substrates.[2,5e,6c,d] Recently, it was shown that activated *cis*-enamines readily isomerize to the more thermodynamically stable *trans* structures either by thermal[7a,b] or acid-catalyzed processes.[7c] These isomerizations were precluded by use of ethylenimine (**1**),[7a,8] presumably because the ring strain effect minimized contribution in the product from zwitterionic resonance form **2**, which, by lowering the bond order, would have facilitated a thermal isomerization. Also, owing to lower basicity, the adductfro m ethylenimine is less subject to an acid-catalyzed isomerization.



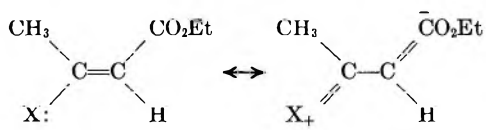
2

In a brief communication,[8] the preliminary results of the reactions of **1** with β-chloroacrylic esters and analogous sulfones were presented. To establish the generality of stereospecific displacements by **1**, four additional systems were studied, and the results are summarized in Table I. The reactions were carried out in benzene and in absolute ethanol, at 0–25°. The configurational assignments were made on the basis of the α- and β-vinyl proton coupling constants.[9] For the β-substituted crotonate system, where there was no β-vinyl hydrogen, assignments were based on the chemical shift of the β-methyl group, which is known to absorb at lower field when *cis* to the ester group.[10]

When ethyl *cis*-β-chloroacrylate was treated with diethylamine, ethyl *trans*-β-(diethylamino) acrylate was isolated. However, reaction with **1** gave exclusively ethyl *cis*-β-(ethylenimino)acrylate. Treatment of ethyl *trans*-β-chloroacrylate with **1** gave only *trans*-substitution product. Comparison of these data with those obtained from the addition of **1** to ethyl propiolate (Table II) excluded an elimination–addition sequence, and, therefore, a substitution mechanism (involving a dipolar adduct) is proposed for these reactions.

Likewise, ethyl *cis*- and *trans*-β-chlorocrotonates[6a,11] reacted with **1** in a stereospecific manner. Comparison of these data with those in Table II for the addition of **1** to ethyl tetrolate precludes an elimination–addition mechanism.

Incidentally, with the β-aminocrotonates, the *cis* isomer being the more thermodynamically stable[7a,12] accounts for why only *cis*-β-aminocrotonates were isolated from displacement by simple secondary amines on both the *cis* and *trans* substrates[6c,d,12] In fact, other electron-releasing (resonancewise) substituents (*e.g.*, chloro and ethylthio) *trans* to the carbethoxy substituent generally constitute the more stable configuration of the corresponding substituted crotonates.[6a] The greater stability of these *cis* crotonates is accountable by a contribution from form **3**, like resonance interaction being less with the geometrical isomers because of steric inhibition to coplanarity; support for this concept is provided by dipole moment studies.[7c]



3

The reactions of *cis*- (**4a**) and *trans*-1-chloro-2-(*p*-tolylsulfonyl)ethene (**4b**) with **1** proceed with complete retention of configuration. An elimination–addition mechanism for **4a** deserves consideration in view of the *trans* stereoselectivity for addition of the amine to the ethynyl sulfone (Table II). However, Modena, *et al.*,[5e] have shown through rate studies that amines react with β-halovinyl sulfones by a direct substitution mechanism, and such characteristics of the elimination–addition

(1) (a) S. Patai and Z. Rappoport, "The Chemistry of Alkenes," Interscience Publishers, Inc., New York, N. Y., 1964, p 525 ff; (b) Z. Rappoport, *Advan. Phys. Org. Chem.*, **7**, 1 (1969).

(2) F. Scotti and E. J. Frazza, *J. Org. Chem.*, **29**, 1800 (1964).

(3) (a) D. Landini and F. Montanari, *Chem. Commun.*, 180 (1967); (b) A. N. Nesmeyanov, M. I. Rybinskaya, and T. G. Kelekhsaeva, *Zh. Org. Khim.*, **4**, 921 (1967); (c) F. Montanari, D. Landini, and B. Cavalchi, *J. Chem., Soc. C*, 1204 (1969).

(4) (a) S. I. Miller and P. K. Yonan, *J. Amer. Chem. Soc.*, **79**, 5937 (1967); (b) G. Marchese, G. Modena and F. Naso, *Tetrahedron*, **24**, 663 (1968).

(5) (a) L. Maioli and G. Modena, *Gazz. Chim. Ital.*, **89**, 854 (1959); (b) G. Modena and P. E. Todesco, *ibid.*, 866 (1959); (c) G. Modena, P. E. Todesco, and S. Tonti, *ibid.*, **89**, 878 (1959); (d) F. Montanari, *Boll. Sci. Fac. Chim. Ind. Bologna*, **16**, 31 (1958); (e) S. Ghersetti; G. Lugli, G. Melloni, G. Modena, P. E. Todesco, and P. Vivarelli, *J. Chem. Soc.*, 2227 (1965).

(6) (a) D. E. Jones, R. O. Morris, C. A. Vernon, and R. F. M. White, *ibid.*, 2349 (1960); (b) W. E. Truce and J. S. Pizey, *J. Org. Chem.*, **30**, 4355 (1965); (c) R. Vessiere, *Bull. Soc. Chim. Fr.*, 1645 (1959); (d) J. S. Pizey and W. E. Truce, *J. Chem. Soc.*, 865 (1964).

(7) (a) W. E. Truce and D. G. Brady, *J. Org. Chem.*, **31**, 3543 (1966); (b) Y. Shvo and H. Shanan-Atidi, *J. Amer. Chem. Soc.*, **91**, 6683, 6689 (1969); Y. Shvo and I. Belsky, *Tetrahedron*, **25**, 4649 (1969); (c) R. Huisgen, K. Herbig, A. Siegel, and H. Huber, *Chem. Ber.*, **99**, 2526, 2546 (1966).

(8) W. E. Truce, J. E. Parr, and M. L. Gorbaty, *Chem. Ind.* (London), 660 (1967).

(9) L. N. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy to Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, pp 85–87.

(10) (a) R. Morris C. A. Vernon, and R. F. M. White, *Proc. Chem. Soc. London*, **303** (1958); (b) L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 2886 (1960).

(11) *cis* and *trans* refers to the positions of the methyl and carbethoxy groups.

(12) A. Sanchez, M. T. Aldave, and U. Scheidegger, *J. Chem. Soc., C*, 2570 (1968).

TABLE I

STEREOCHEMISTRY OF THE REACTION OF ETHYLENIMINE WITH ClC(R)=CHZ

Substrate			Product		
R	Z	Configuration	% *cis*[a]	% *trans*[a]	Bp (mm) [mp], °C
H	CO_2Et	*cis*	100[b]	0	41 (0.2)
H	CO_2Et	*trans*	0[b]	100	82 (1.0)
CH_3	CO_2Et	*cis*	100	0	86 (6.0)
CH_3	CO_2Et	*trans*	0	100	97–98 (9.0)
H	Ts	*cis* (**4a**)	100[b]	0	[88–89]
H	Ts	*trans* (**4b**)	0[b]	100	[68–70]
H	CN	>97% *cis* (**5a**)	>97	<3	78–79 (11.0)
H	CN	*trans* (**5b**)	0	100	86 (9.0)
H	COPh[c]	*cis* (**6a**)	85 (**8a**)	15 (**8b**)	Oil
H	COPh[c]	*trans* (**6b**)	0	100	Oil
H	*p*-$NO_2C_6H_4$	*cis*	No reaction		
H	*p*-$NO_2C_6H_4$	*trans*	No reaction		

[a] Determined from nmr analysis of crude and purified products. [b] Reference 8. [c] Reactions carried out only in benzene.

TABLE II

ADDITIONS OF ETHYLENIMINE TO ZC≡CR

Substrate			Product[a]	
R	Z	Solvent	% *cis*	% *trans*
H	CO_2Et[b]	Benzene	10	90
		Ethanol	56	44
CH_3	CO_2Et	Benzene	90	10[b,c]
		Ethanol	64	36[b,c]
H	$SO_2C_7H_7$[b]	Benzene	≥95	≤5
		Ethanol	100	0
H	CN	Benzene	93	7
		Ethanol	95	5
H	COPh	Benzene	36	64
		Ethanol	23	77
H	*p*-$NO_2C_6H_4$	Benzene	No reaction	
		Ethanol	No reaction	

[a] Determined by nmr analysis of the crude mixture. [b] Reference 7a. [c] Vessiere, *et al.* [*C. R. Acad. Sci. Paris, Ser. C*, 267, 426 (1968)] report 86% *cis* and 14% *trans* in benzene and 60% *cis* and 40% *trans* in ethanol.

mechanism as were observed in the displacement reactions by amines were claimed to be due to small amounts of alkoxide ion generated by the amine–alcohol equilibrium

$$R_2NH + R'OH \rightleftharpoons R_2\overset{+}{N}H_2 + RO^-$$

It is highly unlikely that **1** could participate in such an equilibrium owing to its low basicity (pK_b = 6.1),[13] and consequently, reaction of **1** with **4a** as well as with **4b** is postulated to proceed by a direct substitution pathway.

Besides carbethoxy and arylsulfonyl, a third activating group employed was cyano as in *cis*- and *trans*-chloroacrylonitriles.[14] The *cis* isomer (**5a**), containing 2-3% *trans* isomer (**5b**) was used as such, while **5b** was obtained pure. The results of the reactions of **1** with **5a** and **5b** are summarized in Table I. Although the *cis* product contained approximately 2-3% *trans* product, there can be no doubt that the reaction is stereospecific, because no more of the *trans* product was found than there was *trans* substrate. The results of the addition of **1** to propiolonitrile are included in Table II. Here again an elimination–addition[15] pathway cannot be excluded for the *cis* isomer based only on these results, but is considered unlikely owing to the basicity of **1**.

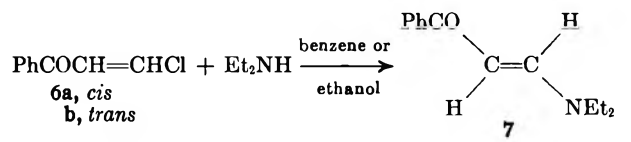
(13) G. J. Buist and H. S. Lucas, *J. Amer. Chem. Soc.*, **79**, 6157 (1957).

(14) A. N. Kurtz, W. E. Billups, R. B. Greenlee, H. F. Hamil, and W. T. Pace, *J. Org. Chem.*, **30**, 3141 (1965).

(15) W. E. Truce and M. M. Boudakian, *J. Amer. Chem. Soc.*, **78**, 2748 (1956).

Until recently *cis* isomers of β-halovinyl ketones were unknown.[16] Montanari,[3a,c] and Nesmeyanov[3b] successfully prepared aryl *cis*-β-chlorovinyl ketones, and showed that displacements by thiolate[3a,c] and azide[3b] proceeded with retention of configuration.

When either phenyl *cis*- or *trans*-β-chlorovinyl ketone[3a] was allowed to react with diethylamine, only phenyl *trans*-β-(diethylamino)vinyl ketone (**7**) was

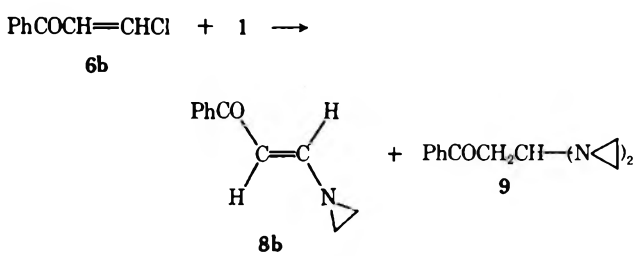


6a, *cis*
b, *trans*

7

obtained. The results of the reaction of **6a** and **6b** with **1** in benzene are summarized in Table I; those of the additions of **1** to phenyl ethynyl ketone are summarized in Table II. The product of the reaction of **1** with **6b** in absolute ethanol was an amorphous yellow solid, believed to be polymeric material, which was not characterized.

When **6b** was allowed to react with 2 equiv (stoichiometric amount) of **1**, there was obtained an oil of which 95% was phenyl *trans*-β-(ethylenimino)vinyl ketone (**8b**) and 5% β,β-di(ethylenimino)propiophenone



8b

9

(**9**). The latter no doubt arises from the addition of **1** to **8**, since **9** is also formed when excess **1** is added to phenyl ethynyl ketone. Other cases where **1** adds to activated olefins are the additions to substituted acrylonitriles[17] and to 1,2-bis(*p*-tolylsulfonyl)ethene.[18]

(16) In our attempts to prepare methyl *cis*-β-chlorovinyl ketone, *cis*-β-chloroacrylic acid was treated with 2 equiv of methyllithium according to the procedure of C. Tegner, *Acta Chem. Scand.*, **6**, 782 (1952). However, only starting material could be recovered. Undoubtedly, the lithium salt of *cis*-β-chloroacrylic acid was so insoluble in ether that further reaction with methyllithium was not realized.

(17) L. H. Chance, D. J. Daigele, and G. L. Drake, Jr., *J. Chem. Eng. Data*, **13**, 442 (1968); H. Bestian, *Justus Liebigs Ann. Chem.*, **566**, 210 (1950).

(18) J. S. Meek and J. S. Fowler, *J. Org. Chem.*, **33**, 985 (1968).

TABLE III

CHEMICAL SHIFTS OF THE α PROTONS OF *Trans* YC(R)=CHZ

Registry no.	Z	R	Y	$\delta_{H\alpha}$[a]	Δδ	J_{HH}[b]	Solvent
1883-81-4	CO_2Et	H	▷N	5.25		13.0	$CDCl_3$
13894-28-5			Et_2N	4.43	0.82	13.0	CCl_4
15358-63-1	CO_2Et	CH_3	▷N	5.20			$CDCl_3$
6288-65-9			Et_2N	4.64	0.56		$CDCl_3$
			Piperidino	4.67	0.53		CCl_4
23220-69-1	CN	H	▷N	4.71		14.0	CCl_4
			Piperidino[c]	3.90	0.81	14.0	$CDCl_3$
			Morpholino[d]	3.93	0.78	14.0	$CDCl_3$
			Pyrrolidino[d]	3.64	1.07	13.5	$CDCl_3$
16491-06-8	$SO_2C_7H_7$	H	▷N	5.58		13.0	$CDCl_3$
			Et_2N[e]	4.90	0.68	14.0	$CDCl_3$
			Me_2N[e]	4.90		14.0	$CDCl_3$
	PhCO	H	▷N	6.40		13.0	$CDCl_3$
			Et_2N	5.74	0.66	12.9	$CDCl_3$

[a] δ (parts per million) from tetramethylsilane. [b] Coupling constants are given in cycles per second. [c] Reference 6. [d] T. Sasaki, T. Yoshioka, and K. Shoji, *J. Chem. Soc., C*, 1086 (1969). [e] Reference 7a.

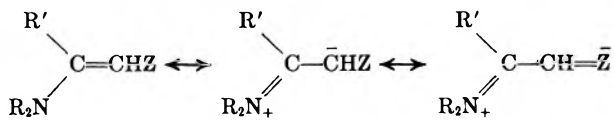
The reaction of 2 equiv of **1** with **6a** in benzene led to an oil which consisted of 71% phenyl *cis*-β-(ethylenimino)vinyl ketone (**8a**) and 14% **8b**, in ratio of 85:15, and 14% **9**. Use of 1 equiv of **1** with **6a** gave a mixture of 57% **8a** and 9.5% **8b** (in a ratio of 85:15) and 22.1% **6a** and 11.4% **6b** (ratio of 66:34).

The reaction of **1** with **6a** appears to be at least largely stereospecific. The fact that some **6b** was observed when a deficiency of amine was used indicated that **6a** was being isomerized, probably through acid catalysis. One equivalent of hydrogen chloride, and thus presumably 1 equiv of amine hydrochloride, was formed for every equivalent of substitution product formed. The conjugate acid of **1** should be acidic enough ($pK_a \cong 8.0$) to provide the acid catalyst. It is known that **6a** is extremely sensitive to acid, and will isomerize in its presence.[3] The data in Table II rule out an elimination–addition sequence.

A final system, which was studied briefly, was the pair, *cis*- and *trans*-*p*-nitro-β-bromostyrene, which failed to react with **1** or diethylamine in either benzene or absolute ethanol, at room temperature or at reflux.

The preceding data have demonstrated the stereospecificity of displacements by **1** on activated vinyl halides and point to the probability that displacements by other amines also proceed with initial retention of configuration, the nonstereospecificity of amine displacements reported by others being due to a facile postisomerization of the initially formed substitution product.

Two mechanisms were proposed for the postisomerization of activated enamines derived from simple amines,[7] the basis of both being a greater contribution to the ground state from a zwitterionic resonance form in enamines derived from simple amines than from those derived from **1**. There is ample evidence to support the concept of the zwitterionic character of the ground states of activated enamines;[19–22,7c] however, no data were available for the ethylenimino derivatives. Hence, it was desirable to determine at least qualitatively, if there is greater zwitterionic character in the ground state of activated enamines from simple amines than in those from **1**. Such contribution would be



expected to produce a pronounced shielding effect on the α proton in the nmr spectrum, causing an upfield shift of the signal.[23] Thus, the chemical shifts of the α protons in a series of β-enamino compounds of the same configuration should offer an estimate of the importance of zwitterionic character in the ground state. It can be seen from the data in Table III that there is a considerable upfield shift of the α protons of enamines derived from simple amines relative to those derived from **1**, supporting the hypothesis of greater zwitterionic character in the ground state of the former. Furthermore, ethyl *cis*-β-(diethylamino)crotonate [λ_{max} 289 mμ (log ε 4.57)] showed a bathochromic shift of 33 mμ relative to ethyl *cis*-β-(ethylenimino)crotonate [λ_{max} 256 mμ (log ε 4.79)].

Experimental Section[24]

Starting Materials.—Ethylenimine was supplied by the Dow Chemical Co., was stored over caustic soda pellets, and was used without further purification. Distilled commercial grade absolute ethanol and spectrophotometric grade benzene were used. Other reagents were obtained through the usual chemical supply companies, and were used without further purification. *cis*- and *trans*-1-chloro-2-(*p*-tolylsulfonyl)ethene,[25,26] phenyl *trans*-

(19) H. W. Duerbeck, *Z. Anal. Chem.*, **235**, 43 (1968).
(20) J. Dabrowski, *Spectrochim. Acta*, **19**, 475 (1963).
(21) A. Shidlovskaya, Y. Syrkin, and N. Kochetkov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 254 (1956).
(22) R. Huisgen and K. Herbig, *Justus Liebigs Ann. Chem.*, **688**, 98 (1965).
(23) N. F. Firrell and P. W. Hickmott, *J. Chem. Soc., B*, 293 (1969); K. Nagarajan and S. Rajappa, *Tetrahedron Lett.*, 2203 (1969).
(24) All microanalyses were carried out by Dr. C. S. Yeh and staff of the Purdue Chemistry Microanalytical Laboratory. All melting points and boiling points are uncorrected. All nmr spectra were run on a Varian A-60 or A-60A with the spectrometer operating at 60 MHz and using tetramethylsilane as an internal standard. Vpc analyses were performed on a Perkin-Elmer Model 154 vapor fractometer at 125–130° on column "O."
(25) L. Maioli and G. Modena, *Boll. Sci. Fac. Chim. Ind. Bologna*, **16**, 86 (1958); *Chem. Abstr.*, **53**, 7080b (1959).
(26) F. Montanari, *Gazz. Chim. Ital.*, **86**, 406 (1956).

β-chlorovinyl ketone,[27] *cis*- and *trans*-*p*-nitro-β-bromostyrene,[4b] phenyl ethynyl ketone,[28] and ethyl tetrolate[29] were prepared by known procedures.

Ethyl *cis*-β-Chloroacrylate.—Esterification of *cis*-β-chloroacrylic acid[14] with ethanol and catalytic sulfuric acid gave a 65% yield of pure product: bp 71–73° (27 mm); nmr (CCl_4) δ 1.30 (t, 3 H, J = 7.0 cps), 4.19 (q, 2 H, J = 7.0 cps), 6.08 (d, 1 H, J = 8.5 cps, α-vinyl proton) 6.62, ppm (d, 1 H, J = 8.5 cps, β-vinyl proton).

Ethyl *trans*-β-Chloroacrylate.—This was prepared in 41% yield as above by esterification of *trans*-β-chloroacrylic acid.[14] The product boiled at 50–51° (22 mm): nmr (CCl_4) δ 1.25 (t, 3 H, J = 7.0 cps), 4.08 (q, 2 H, J = 7.0 cps), 6.09 (d, 1 H, J = 13.0 cps, α-vinyl proton), 7.19 ppm (d, 1 H, J = 13.0 cps, β-vinyl proton).

Ethyl *cis* and *trans*-β-Chlorocrotonate.—These were prepared by the method of Jones, *et al.*[6a] The isomers were separated by fractionation on a spinning-band column to afford vpc pure *cis* ester, bp 48–50° (11.0 mm) [lit.[6a] bp 68–69° (10 mm)], and *trans* ester, bp 62–63° (11.0 mm) [lit.[6a] bp 68–69° (10 mm)], which contained a 10% impurity. The *trans* ester was obtained pure by collection from an Aerograph Autoprep Model A-700, using a 4 ft × 3/8 in. SF 96 column at 128°: nmr (CCl_4) of *cis* ester δ 1.27 (t, 3 H, J = 7.0 cps), 2.56 (d, 3 H, J = 1.5 cps, $CH_3C{=}C$), 4.13 (q, 2 H, J = 7.0 cps), 6.00 ppm (m, 1 H, $CH_3C{=}CH$); nmr (CCl_4) of *trans* ester δ 1.27 (t, 3 H, J = 7.0 cps), 2.24 (d, 3 H, J = 1.5 cps, $CH_3C{=}C$), 4.14 (q, 2 H, J = 7.0 cps), 5.93 ppm (m, 1 H, $CH_3C{=}CH$).

***cis* and *trans*-β-Chloroacrylonitriles.**—These were prepared by pyrolysis of 2,3-dichloropropionitrile according to the method of Kurtz, *et al.*[14] The crude pyrolysate was distilled, bp 28–48° (20 mm), and the distillate was redistilled at atmospheric pressure to give two main cuts, bp 87–139°, which contained α-chloroacrylonitrile and *trans*-β-chloroacrylonitrile, and bp 143–146°, which was 97% pure *cis*-β-chloroacrylonitrile (lit.[2] bp 145°). The first cut was redistilled on a spinning-band column to give pure *trans* isomer: bp 114°; mp 45–46° (lit.[2] bp 118° mp 45°); nmr (CCl_4) of *cis* isomer δ 5.82 (d, 1 H, J = 7.8 cps, α-vinyl proton), 6.95 ppm (d, 1 H, J = 7.8 cps); nmr (CCl_4) of *trans* isomer δ 5.79 (d, 1 H, J = 13.0 cps, α-vinyl proton), 7.15 ppm (d, 1 H, J = 13.0 cps).

Phenyl *cis*-β-Chlorovinyl Ketone.—This was prepared by the method of Montanari.[3a,c] The crude material contained 3–5% starting material, 10–20% *trans* isomer, and product. A portion of this material, 2.3 g, was chromatographed on silica gel (30 cm × 3.5 cm) using a 2:1:1 solution of *n*-hexane–ethyl acetate–petroleum either (bp 30–60) as eluent.[3c] Twenty-milliliter fractions were taken, and fractions 15, 16, and 17, 0.85, g, were combined and shown by nmr to be >98% phenyl *cis*-β-chlorovinyl ketone and <2% starting material: nmr (CCl_4) δ 6.68 (d, 1 H, J = 8.0 cps, α-vinyl proton), 6.98 (d, 1 H, J = 8.0 cps, β-vinyl proton), 7.42 (m, 3 H, aromatic protons), 7.87 (m, 2 H, aromatic protons). *This compound is a lachrymator and vesicant and should be handled with extreme care.*

Propiolonitrile.—A mixture of 3.0 g (0.043 mol) of propiolamide[30] and 10.0 g (0.071 mol) of phosphorus pentoxide were ground and well mixed under a nitrogen stream, and the mixture was transferred to a 100-ml flask equipped with a distillation head. The mixture was heated to 200° and the distillate was collected to give 1.4 g (65%) of propiolonitrile, bp 40–42° (lit.[30] bp 42°).

General Procedure for the Reaction of Ethylenimine with Activated Vinylic Halides.—To a stirred solution of the halide in about half the solvent, in a flame-dried flask under nitrogen at 0° was added dropwise the solution of ethylenimine (two- to threefold excess) in the remaining solvent. The mixture was stirred at 0°, then at room temperature. The reaction mixtures in benzene were filtered and the solvent was removed *in vacuo*. Those in ethanol were worked up by removing the solvent *in vacuo* and treating the residue with ether and water to remove the amine hydrochloride. The crude material was analyzed by nmr and purified by distillation or recrystallization, and the pure product was analyzed by nmr.

Ethyl *cis*-β-(Ethylenimino)acrylate.—The procedure outlined above was used with 1.00 g (0.0075 mol) of ethyl *cis*-β-chloroacrylate, 1.24 g (0.029 mol) of 1, and 50.0 ml of benzene. After stirring for 4 hr at 25° and work-up, the crude material was distilled to give 0.46 g (44%) of product: bp 40–41° (0.2 mm); nmr ($CDCl_3$) δ 1.23 (t, 3 H, J = 7.0 cps), 2.08 (s, 4 H, ethylenimino protons), 4.09 (q, 2 H, J = 7.0 cps), 5.01 (d, 1 H, J = 9.0 cps, α-vinyl proton), 6.54 ppm (d, 1 H, J = 9.0 cps). When absolute ethanol was used, 0.40 g (38%) of the same product was isolated. The spectral data were identical with those reported earlier.[7a]

Ethyl *trans*-β-(Ethylenimino)acrylate.—Ethyl *trans*-β-chloroacrylate (1.00 g, 0.0075 mol) was treated as above with 0.832 g (0.0193 mol) of 1 using 50 ml of benzene. After stirring 4.5 hr and work-up, 0.70 g of liquid, shown to be 47% product (32% yield), was isolated. This was distilled to give pure product: bp 82° (7.0 mm); nmr ($CDCl_3$) δ 1.25 (t, 3 H, J = 7.0 cps), 1.95 (s, 4 H, ethylenimino protons), 4.08 (q, 2 H, J = 7.0 cps), 5.25 (d, 1 H, J = 13.0 cps, α-vinyl proton), 7.40 ppm (d, 1 H, J = 13.0 cps). The reaction in ethanol was stirred at room temperature for 22 hr to give a 75% yield of product. The spectral data were identical with those reported earlier.[7a]

Ethyl *trans*-β-(Diethylamino)acrylate.—This was prepared from 0.75 g (0.0056 mol) of ethyl *cis*-β-chloroacrylate, 1.64 g (0.22 mol) of diethylamine, and 20 ml of absolute ethanol. After stirring for 7 hr, and work-up, 0.75 g (79%) of product was isolated: bp 82° (1.0 mm) [lit.[31] bp 90–91° (0.15 mm)]; nmr (CCl_4) δ 1.20 (overlapping triplets, 9 H), 3.21 (q, 4 H, J = 7.0 cps, CH_3CH_2N), 4.02 (q, 2 H, J = 7.0 cps, CH_3CH_2O), 4.43 (d, 1 H, J = 13.0, α-vinyl proton), 7.30 ppm (d, 1 H, J = 13.0 cps).

Ethyl *cis*-β-(Ethylenimino)crotonate.—The general procedure was followed, using 2.00 g (0.013 mol) of ethyl *cis*-β-chlorocrotonate, 0.295 ml (0.058 mol) of 1, and 20 ml of benzene. The mixture was stirred for 3 days at room temperature. Work-up gave 1.5 g of liquid, 81% of which was product (59% yield). This was distilled to give pure product: bp 86° (6.0 mm); nmr ($CDCl_3$) δ 1.23 (t, 3 H, J = 7.0 cps), 1.96 (s, 4 H, ethylenimino protons), 2.28 (s, 3 H, $CH_3C{=}C$), 4.09 (q, 2 H, J = 7.0 cps), 5.20 ppm (s, 1 H, C=CH).

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03; mol wt, 155.2. Found: C, 61.67; H, 8.58; N, 8.87; mol wt, 158.

When the reaction was carried out in ethanol, a 71% yield was obtained.

Ethyl *trans*-β-(Ethylenimino)crotonate.—The general procedure was followed using 0.85 g (0.0058 mol) of ethyl *trans*-β-chlorocrotonate and 0.75 ml (0.014 mol) of 1 in 15 ml of benzene. The flask was stoppered and stored at 0–3° for 3 days. The reaction was monitored by vpc which showed only *trans* substrate and *trans* product. Work-up gave 0.70 g (79%) of product: bp 97–98° (9.0 mm); nmr ($CDCl_3$) δ 1.26 (t, 3 H, J = 7.5 cps), 1.93 (s, 3 H, $CH_3C{=}C$), 2.15 (s, 4 H, ethylenimino protons), 4.15 (q, 2 H, J = 7.5 cps), 5.15 ppm (s, 1 H, C=CH).

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.75; H, 8.40; N, 9.07.

When the reaction was carried out in ethanol, 61% product was obtained.

Ethyl *cis*-β-(Diethylamino)crotonate.—This was prepared from 0.55 g (0.0037 mol) of ethyl *cis*-β-chlorocrotonate and 1.02 g (0.015 mol) of diethylamine in 15 ml of benzene. The flask was stoppered and allowed to stand for 2 weeks at room temperature. Work-up gave 0.40 g of material, 87% of which was product. Distillation gave the pure product: bp 123–124 (6.0 mm) [lit.[32] bp 120–121 (2.5 mm)]; nmr ($CDCl_3$) δ 1.16 (overlapping triplets, 9 H), 2.46 (s, 3 H, $CH_3C{=}C$), 3.30 (q, 4 H, CH_3CH_2N), 4.23 (q, 2 H, CH_3CH_2O), 4.64 ppm (s, 1 H, C=CH).

***cis*-1-Ethylenimino-2-(*p*-tolylsulfonyl)ethene.**—This was prepared from 1.5 g (0.0070 mol) of 4a, 2.0 (0.038 mol) of 1, and 50 ml of benzene. After stirring 4 hr at room temperature, the solvent was removed *in vacuo* and the solid was recrystallized from benzene–hexane to give product: mp 88–89° (lit.[7a] mp 88–89°); nmr ($CDCl_3$) δ 2.25 (s, 4 H, ethylenimino protons), 2.50 (s, 3 H, $CH_3C_6H_4$), 5.57 (d, 1 H, J = 9.0 cps, α-vinyl proton), 6.55 (d, 1 H, J = 9.0 cps), 7.30 (s, 2 H, J = 9.0 cps, aromatic protons), 7.90 ppm (d, 2 H, J = 9.0 cps). The same product was obtained in ethanol.

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trans-1-Ethylenimino-2-(*p*-tolylsulfonyl)ethene.—This was prepared, as above, from 1.0 g (0.0046 mol) of **4b**, 2.0 ml (0.038 mol) of 1, and 50 ml of benzene. After 4 hr, the solvent was removed *in vacuo* to give an oil which eventually crystallized, mp 68–70°. A large portion (70%) of starting material was recovered: nmr (CCl_4) δ 1.86 (s, 4 H, ethylenimino protons), 2.50 (s, 3 H, $CH_3C_6H_4$), 5.58 (d, 1 H, J = 13.0 cps, α-vinyl proton), 7.5 ppm (m, 5 H, β-vinyl proton and aromatic protons). The reaction in ethanol gave the same product. The nmr spectrum was completely consistent with the assigned structure.

Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.86; N, 6.27; S, 14.36; mol wt, 223. Found: C, 58.94; H, 5.95; N, 6.17; S, 14.24; mol wt, 225.

cis-β-(Ethylenimino)acrylonitrile.—The general procedure was followed using 0.80 g (0.0092 mol) of **5a**, 1.91 ml (0.037 mol) of 1, and 30 ml of benzene. After stirring at room temperature for 8 hr and work-up, 0.80 g (92%) of crude product was obtained. Distillation gave pure product: bp 78–79° (11.0 mm); nmr (CCl_4) δ 2.12 (s, 4 H, ethylenimino protons), 4.54 (d, 1 H, J = 8.5 cps, α-vinyl proton), 6.75 (d, 1 H, J = 8.5 cps).

Anal. Calcd for $C_5H_6N_2$: C, 63.80; H, 6.42; N, 29.77; mol wt, 94. Found: C, 63.72; H, 6.40; N, 29.98; mol wt, 98.

An 81% yield was obtained in ethanol. This material became an amorphous mass on standing under nitrogen in a sealed ampoule.

trans-β-(Ethylenimino)acrylonitrile.—The above procedure was followed using 0.90 g (0.010 mol) of **5b**, 2.15 ml (0.042 mol) of 1, and 25 ml of benzene. After stirring for 9 hr and work-up, 0.80 g (82%) of crude product was obtained. Distillation afforded pure product: bp 86–86.5° (9.0 mm); nmr (CCl_4) δ 1.98 (s, 4 H, ethylenimino protons), 4.71 (d, 1 H, J = 14.0 cps, α-vinyl proton), 7.10 ppm (d, 1 H, J = 14.0 cps).

Anal. Calcd for $C_5H_6N_2$: C, 63.80; H, 6.42; N, 29.77; mol wt, 94. Found: C, 63.97; H, 6.40; N, 30.00; mol wt, 98.

A 71% yield was obtained in ethanol. This material polymerized on standing under nitrogen in a sealed ampoule.

Phenyl *trans*-β-(Diethylamino)vinyl Ketone.—This was prepared from 1.66 g (0.010 mol) of **6b**, 1.46 g (0.020 mol) of diethylamine, and 30 ml of benzene. Work-up afforded 1.50 g (74%) of crude material which was recrystallized from pentane to give pure product: mp 52–54° (lit.[33] mp 53–54°); nmr ($CDCl_3$) δ 1.15 (t, 6 H, J = 7.5 cps), 3.23 (q, 4 H, J = 7.5 cps), 5.74 (d, 1 H, J = 12.9 cps, α-vinyl proton), 7.32 (m, 3 H, aromatic protons), 7.80 ppm (m, 3 H, aromatic and β-vinyl protons). The same product was obtained in 94% yield in ethanol, and also by addition of diethylamine to phenyl ethynyl ketone in benzene and ethanol.

Reaction of Phenyl *trans*-β-Chlorovinyl Ketone (6b) with Ethylenimine in Benzene.—The general procedure was followed, using 1.66 g (0.010 mol) of **6b**, 1.10 ml (0.021 mol) of 1, and 22 ml of benzene. After 3 hr, the mixture was filtered and the solvent was removed *in vacuo*. The residue was dissolved in ether, washed with water, and dried ($MgSO_4$); the ether was removed *in vacuo* to give 1.40 g (81%) of **8b** contaminated with approximately 5% **9**. Attempted purification by distillation and chromatography of a portion of this material led to decomposition. The remainder became a thick viscous oil which solidified to an amorphous black mass on standing at room temperature over a period of 3 days. A satisfactory analysis could not be obtained: nmr ($CDCl_3$) of **8b** δ 1.97 (s, 4 H, ethylenimino protons), 6.40 (d, 1 H, J = 13.0 cps, α-vinyl proton), 7.40 (m, 3 H, aromatic protons), 7.68 (d, 1 H, J = 13.0 cps), 7.85 ppm (m, 2 H, aromatic protons); nmr ($CDCl_3$) of **9** δ 1.45 (broad singlet, 8 H, ethylenimino protons), 2.38 (t, 1 H, J = 5.9 cps, CH_2CH), 3.32 (d, 2 H, J = 5.9 cps, CH_2CH), 7.3 (m, 3 H, aromatic protons), 7.9 ppm (m, 2 H, aromatic protons).

Reaction of Phenyl *cis*-β-Chlorovinyl Ketone (6a) with Ethylenimine in Benzene. (a) Stoichiometric Amounts.—The procedure above was followed using 0.20 g (0.0012 mol) of **6a**, 0.124 ml (0.0024 mol) of 1, and 20 ml of benzene. After 3.5 hr the mixture was filtered and the solvent was removed *in vacuo* to give 0.15 g of liquid whose nmr spectrum showed it to be a mixture of 72% **8a**, 14% **8b**, in ratio of 82:18, and 14% **9**: nmr (CCl_4) of **8a** δ 2.02 (s, 4 H, ethylenimino protons), 6.09 (d, 1 H, J = 9.0 cps, α-vinyl proton), 6.67 (d, 1 H, J = 9.0 cps), 7.33 (m, 3 H, aromatic protons), 7.84 ppm (m, 2 H, aromatic protons). Further purification was not attempted.

(b) Deficiency of 1.—The general procedure above was followed with 0.22 g (0.0013 mol) of **6a**, 0.0685 ml (0.0013 mol) of 1, and 20 ml of benzene. Work-up as before gave 0.15 g of material whose nmr showed it was a mixture of 57% **8a**, 9.5% **8b** in ratio of 86:14, 22.1% **6a** and 11.4% **6b**, and no **9**.

Reaction of *cis*- and *trans*-*p*-Nitro-β-Bromostyrene with Amines.—The reactions were carried out as above, with diethylamine and 1, in both benzene and ethanol at room temperature and at reflux for 4 hr, but work-up gave starting materials in >95% recovery.

Addition of Ethylenimine to Activated Acetylenes.—The general procedure of Truce and Brady[7a] was followed. The reactions were run in both benzene and ethanol and the results are summarized in Table II.

(a) To Ethyl Tetrolate.—Ethyl tetrolate (0.50 g, 0.0045 mol) was treated with 0.30 ml (0.0058 mol) of 1 in 10 ml of benzene. After standing 200 hr at room temperature, the solvent was removed *in vacuo* to give 62% adducts (Table II). In ethanol, after 80 hr a quantitative yield of adducts was obtained.

(b) To Propiolonitrile.—The above procedure was used with 0.70 g (0.014 mol) of propiolonitrile, 1.07 ml (0.020 mol) of 1, and 25 ml of benzene. After 7 hr 0.85 g (66%) of adducts was obtained. In ethanol, after 2.5 hr, a 77.5% yield of adducts was obtained.

(c) To Phenyl Ethynyl Ketone.—The above procedure was followed with 1.30 g (0.010 mol) of phenyl ethynyl ketone, 0.40 ml (0.0077 mol) of 1, and 10 ml of benzene. After 4 hr the solvent was removed *in vacuo* to give 1.50 g of material, 26% of which was starting material and 74% was a mixture of adducts (Table II). This became a thick dark oil on standing at room temperature. When 0.78 ml (0.015 mol) of 1 was used, 1.60 g of material was obtained which was a mixture of 28% **8a**, 44% **8b**, in a ratio of 38:62, and 28% **9**.

Registry No.—**7**, 23674-58-0; **8b**, 24627-31-4; ethyl *cis*-β-(ethylenimino)crotonate, 24627-32-5; *cis*-β-(ethylenimino)acrylonitrile, 24599-16-4.

Acknowledgment.—This investigation was supported by the National Science Foundation under Grant GP-05175, and the Public Health Service Research Grant No. CA-04536-11 from the National Cancer Institute.

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Radical Reaction of Isocyanide with Thiol

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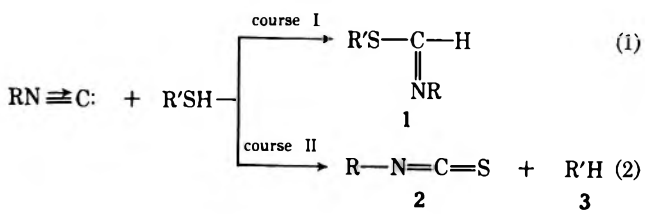
The reaction of an isocyanide with a thiol proceeds in two courses. Course I is regarded as α,α additions of the thiyl group and hydrogen to the isocyanide carbon atom to produce a thioformimidate (1). Course II forms an isothiocyanate (2) from the isocyanide and an alkane (3) from the alkyl group of the thiol. First, experimental results supporting the radical chain mechanism involving the thiyl radical are given. Radical reactions of primary and aromatic thiols take course I, whereas those of α-toluenethiol as well as tertiary thiols take course II. The reaction with a secondary thiol takes both courses. The copper-catalyzed reaction, however, takes course I predominantly, regardless of the nature of the thiol alkyl group.

We have reported a set of reactions of isocyanide, which are the insertions of the isocyanide carbon atom into the nitrogen–hydrogen bond of amine,[1] the oxygen–hydrogen bond of alcohol,[2] the sulfur–hydrogen bond of thiol,[3] the phosphorus–hydrogen bond of phosphine,[4] and the silicon–hydrogen bond of silanes.[5] All these reactions are catalyzed by copper compounds and produce the corresponding derivatives of formimidic acid in high yields.

Among these reactions, the isocyanide–thiol reaction differs from the others; *i.e.*, the isocyanide–thiol reaction is also induced by a radical initiator. This paper describes the radical reaction of an isocyanide with a thiol which involves an intermediate imidoyl radical. It is of interest to note that the imidoyl radical is isoelectronic with vinyl and acyl radicals of σ character.

$[\dot{C}{=}N\sim]$	$[\dot{C}{=}C<]$	$[\dot{C}{=}O]$
imidoyl radical	vinyl radical	acyl radical

The reaction of isocyanide with thiol proceeds in two courses. Course I (eq 1) is regarded as α,α additions of the thiyl group and hydrogen to the isocyanide carbon atom carrying lone-pair electrons, which produces a thioformimidate (**1**). In course II (eq 2), an isothiocyanate (**2**) and an alkane (**3**) are formed. The course of the reaction is determined by the nature of the thiol alkyl group; *i.e.*, primary and aromatic thiols take course I exclusively, whereas α-toluenethiol as well as tertiary thiols take course II. The reaction with secondary thiols proceeds along both courses.



(i) (2)

In the present studies, experimental evidence to support the radical chain mechanism is given. The difference between the radical reaction of an isocyanide with a thiol and the copper-catalyzed one is also mentioned. So far as we know, the present study is the first to describe useful reactions of isocyanides *via* radical chain mechanism.

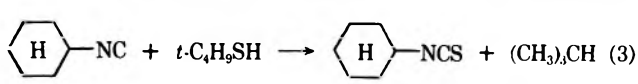
Results and Discussion

Support for a Radical Chain Mechanism.—When a mixture of thiol and isocyanide is heated without any added catalyst, a reaction occurs between them. This reaction can be shown to be a radical chain reaction by the following results: (i) the reaction is accelerated by radical initiators, such as azobisisobutyronitrile (AIBN), and by ultraviolet irradiation and (ii) the reaction is suppressed by radical inhibitors such as hydroquinone (HQ), *t*-butylcatechol, and *p*-benzoquinone (*p*-BQ).

Table I illustrates the radical-initiated reaction of an isocyanide with a thiol. The reactions of primary and aromatic thiols induced by radical initiators proceed *via* course I. Copper-catalyzed reactions of these combinations take the same course. The isocyanide–secondary thiol reactions, both copper-catalyzed and photoinduced ones, give the products of the two courses. The course of the reactions of α-toluenethiol and tertiary thiols, however, is determined by the nature of catalyst; *i.e.*, those induced by radical initiators take course II, whereas those catalyzed by a copper compound take course I.

The mechanism of a radical-initiated reaction of an isocyanide with a thiol obviously differs from that of copper-catalyzed one. The copper-catalyzed reaction of cyclohexyl isocyanide (**5**) with 2-propanethiol (**12**) is not affected by the addition of hydroquinone. On the other hand, the radical-initiated reaction of an isocyanide with a thiol is suppressed by the so-called radical inhibitors, as will be described in the following parts of this paper. The difference in the products (Table I, runs 3 and 4) also distinguished the radical-initiated reaction from the copper-catalyzed one.

The effects of radical initiators and inhibitors upon the reaction of **5** with 2-methyl-2-propanethiol (**11**) giving cyclohexyl isothiocyanate (**13**) and isobutane are shown in Figure 1. The progress of reaction was followed



(3)

by the glpc determination of **13** at several times of reaction. The reaction of an equimolar mixture (neat) of **5** and **11** at 60° under nitrogen is shown by curve a, in which a small amount of oxygen due to incomplete exclusion of air may cause the radical reaction. The addition of AIBN (1 mol %) much enhanced the reaction

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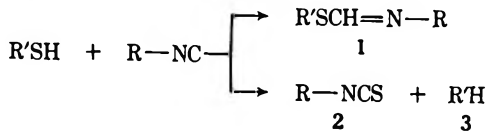
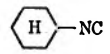
TABLE I

RADICAL AND CUPRIC OXIDE CATALYZED REACTIONS OF THIOLS WITH ISOCYANIDES



No.	R-NC (mmol)	R'SH (mmol)	Additive (mmol)	Reaction Temp, °C	Reaction Time, hr	Product yield, %[a] 1	2	3
1	*t*-C_4H_9NC (4) (5.0)	C_2H_5SH (7) (5.0)	AIBN (0.01)	35	4.0	60	0	0
2	4 (5.0)	C_6H_5SH (8) (5.0)	AIBN (0.01)	80	2.0	82	0	0
3	4 (12.0)	$C_6H_5CH_2SH$ (9) (10.0)	AIBN (0.02)	100	0.2	0	93	96
4	4 (12.0)	9 (10.0)	CuO (0.1)	100	2.0	91	0	0
5	 (5) (5.0)	*sec*-C_4H_9SH (10) (5.0)	*b*	0	0.1	83	11	N.d.[c]
6	C_6H_5NC (6) (6.0)	*t*-C_4H_9SH (11) (20.0)	AIBN (0.05)	75	0.2	0	97	N.d.[c]
7	5 (5.0)	11 (7.0)	CuO (0.1) and *p*-BQ (0.5)	90	3.0	64	6	N.d.[c]

[a] Determined by glpc. [b] Irradiated by uv in 2 ml of diethyl ether under nitrogen [c] N.d., not determined.

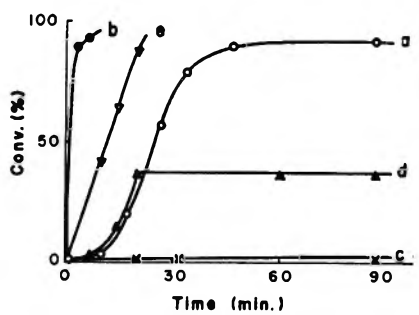


Figure 1.—Reaction of cyclohexyl isocyanide with 2-methyl-2-propanethiol. Effects of radical initiator and inhibitor: (a) without added catalyst at 60°, (b) with 1 mol % of AIBN at 60°, (c) with 5 mol % of hydroquinone at 60°, (d) with addition of 2 mol % of hydroquinone after 20 min at 60°, (e) irradiated in diethyl ether at 0°.

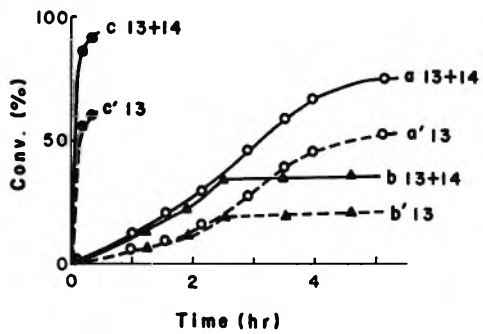
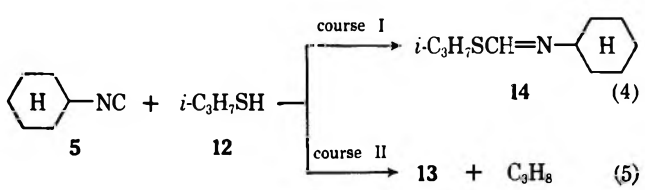


Figure 2.—Reaction of cyclohexyl isocyanide with 2-propanethiol: (a and a') without added catalyst at 100°, (b and b') with addition of 2 mol % of hydroquinone after 2.5 hr at 100°, (c and c') with 0.5 mol % of AIBN at 70°.

(curve b), whereas the addition of hydroquinone suppressed it (curve c). The addition of hydroquinone at a halfway point (at 20 min) to the reaction system without any added catalyst interrupted the reaction completely (curve d). In addition, the reaction was accelerated by uv irradiation. A mixture of **5**, **11**, and diethyl ether (solvent) in a Pyrex tube was irradiated at 0° under nitrogen (curve e). Here, no reaction was observed at all in the dark at 0° in diethyl ether solvent.

In the combination of isocyanide and secondary thiol, two modes of reaction, courses I and II, take place. The reaction of **5** with 2-propanethiol (**12**) was carried out under various conditions (Figure 2). The total



yield of the two products, **13** and **14**, and the yield of **13** at several times of reaction without any added catalyst at 100° are shown by curves a and a', respectively. The addition of 2 mol % of hydroquinone at a time of 2.5 hr interrupted both courses of reaction (curves b and b'). The reaction was accelerated by AIBN (reaction at 70°, curves c and c'). It is quite significant that

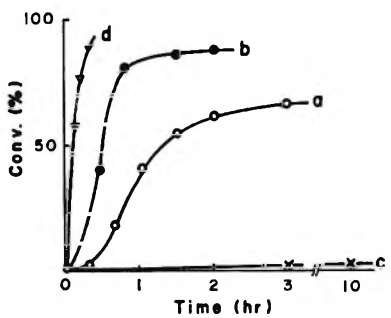
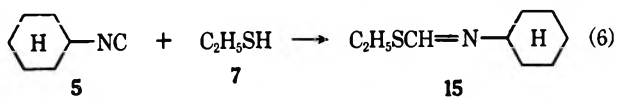


Figure 3.—Reaction of cyclohexyl isocyanide with ethanethiol: (a) without added catalyst at 40°, (b) with 0.1 mol % of AIBN at 40°, (c) with 10 mol % of *p*-BQ at 40°, (d) irradiated in diethyl ether at 0°.

the ratio of the final yields of the two products, **13**/**14**, was 3/2 in each of these three reactions. Furthermore, 1 mol % of *t*-butylcatechol was enough to inhibit the reaction completely.

The reaction with a primary thiol proceeds through course I. In Figure 3, the acceleration by AIBN (curve b) and by uv irradiation (curve d), as well as the inhibition by *p*-benzoquinone, are demonstrated in the reaction of **5** with ethanethiol (**7**).



These several findings are taken to support a radical chain mechanism, which may be explained by the scheme (reactions 7–9) involving thiyl radical **16**. The thiyl radical **16** is first formed from the thiol by a

$$R'SH \longrightarrow \underset{\mathbf{16}}{R'S\cdot} \xrightarrow{R-N\equiv C:} \underset{\mathbf{17}}{[R'-\overset{\beta}{S}-\dot{C}=N-R]} \quad (7)$$

$$\mathbf{17} + R'SH \xrightarrow[k_a]{\text{H abstraction}} \underset{\mathbf{1}}{R'-SCH=N-R} + \underset{\mathbf{16}}{R'S\cdot} \quad (8)$$

$$\mathbf{17} \xrightarrow[k_d]{\beta\text{ scission}} \underset{\mathbf{2}}{R-N=C=S} + \underset{\mathbf{18}}{R'\cdot} \xrightarrow{R'SH} \underset{\mathbf{3}}{R'H} + \underset{\mathbf{16}}{R'S\cdot} \quad (9)$$

radical initiator or by irradiation, and then attacks the isocyanide to produce the intermediate imidoyl radical **17**. The imidoyl radical **17** may undergo two reactions, *i.e.*, hydrogen abstraction from thiol (eq 8) and β scission (eq 9). The hydrogen abstraction gives thioformimidate **1** and **16**. On the other hand, the β scission at the alkyl– (or benzyl–) sulfur bond leads to isothiocyanate **2** and alkyl (or benzyl) radical **18**. The second hydrogen abstraction of **18** from thiol produces hydrocarbon **3** and **16**. These two reactions are competitive ones. The relative degrees of participation of the two reactions are determined by the stability of R′–S bond of **17** and the steric hindrance to the approach of a thiol to **17** in the H abstraction (eq 8). Preference of β scission in the case of a tertiary thiol is ascribed to these two factors. In the reaction of α-toluenethiol, the stability of the resultant benzyl radical may predominate in the determination of the direction of reaction. On the other hand, when R′ is less stable as a radical and the steric hindrance is less significant, **17** prefers to abstract hydrogen from the thiol (eq 8). The reactions with primary and aromatic thiols take this course.

The case of secondary thiol is between these two extremes. The reaction of **5** with **12** gives the two products **13** and **14**. On the basis of the above equations (8 and 9), the molar ratio of the two products is expressed by eq 10 where k_a is the rate constant of hydrogen abstraction of **17** from the thiol and k_d is the rate constant of β scission of **17**.

$$\frac{\mathbf{14}}{\mathbf{13}} = \frac{k_a}{k_d}[R'SH] \quad (10)$$

In accord with eq 10, the molar ratio of **14**/**13** was gradually decreased as the reaction proceeds to decrease the concentration of **12** (Figure 2).

In addition, a series of experiments was conducted in which the initial concentration of **12** was varied. The ratios of **14**/**13** at a low conversion (below 10%) were found to vary linearly with the concentration of **12** as shown in Figure 4.

In the above scheme, both courses involve thiyl radical as the common chain carrier. The coupling of two thiyl radicals constitutes the chain termination, which produces the corresponding disulfide. A small amount of dialkyl disulfide was actually detected in the reaction mixture. For instance, 3.5×10^{-5} mol of di-*t*-butyl disulfide was detected by glpc in the mixture of the **5**–**11** reaction (Figure 1, curve a). Assuming that di-*t*-butyl disulfide is formed only by the termination reaction, the chain length is calculated to be 140.

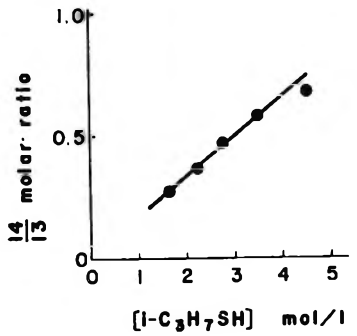


Figure 4.—Dependency of the molar ratio of **14**/**13** on the concentration of 2-propanethiol.

In the intermediate imidoyl radical **17**, the R–N bond is located at another β position (β_2), which may possibly be involved in a β-scission reaction especially when R is

$$\underset{\mathbf{17}}{[R'-\overset{\beta_1}{S}-\dot{C}=N-\overset{\beta_2}{R}]}$$

a good leaving group as a free radical. The isocyanide–thiol reaction, however, does not involve β_2 scission at the R–N bond; *i.e.*, in the first two reactions of Table I using *t*-butyl isocyanide (**4**), no product derived from the β_2 scission of **17** was detected. This is quite different from the radical reaction of isocyanide with trialkylstannane, which involves scission at β_2 position (eq 11).[6]

$$R'_3Sn\cdot + R-N\equiv C: \longrightarrow [R'_3-\overset{\beta_1}{Sn}-\dot{C}=N-\overset{\beta_2}{R}] \xrightarrow{\beta_2\text{ scission}} R'_3SnCN + R\cdot \quad (11)$$

Experimental Section

Materials.—All thiols were commercial samples of pure grade, which were purified by rectification under nitrogen prior to use. Isocyanides were prepared from the corresponding formamides according to Ugi's procedure.[7]

Reactions of Cyclohexyl Isocyanide (5) with 2-Methyl-2-propanethiol (11) (Figure 1).—Curve a reaction: A mixture of 0.90 g (10 mmol) of **11** and 1.08 g (10 mmol) of **4** was heated at 60° in a nitrogen atmosphere without added catalyst. The progress of the reaction was followed by glpc determination of **13** at several times of reaction (column, silicon DC 550 and PEG 20000). Curve b reaction: A ternary mixture of 0.90 g (10 mmol) of **11**, 1.08 g (10 mmol) of **5**, and 17 mg (0.1 mol) of AIBN was heated at 60°. Curve c reaction: As a radical inhibitor, 55 mg (0.5 mmol) of hydroquinone was added at the beginning of the curve a reaction. Curve d reaction: After the reaction proceeded for 20 min under the same conditions as those of the curve a reaction, 22 mg (0.2 mmol) of hydroquinone was added to the reaction system. Curve e reaction: A solution of 0.45 g (5 mmol) of **11**, 0.54 g (5 mmol) of **5**, and 2 ml of diethyl ether (solvent) in a Pyrex test tube cooled in an ice bath was irradiated using a high-pressure mercury lamp under nitrogen atmosphere.

Reactions of Cyclohexyl Isocyanide (5) with 2-Propanethiol (12), Ethanethiol (7), and 2-Butanethiol (10).—The time-conversion curve of the reactions of **5** with **12** (Figure 2) and **5** with **7** (Figure 3) were made by the same procedures as the above. The structures of **14** and **15** were established already.[3] *sec*-Butyl N-cyclohexylthioformimidate was produced in the **5**–**10** reaction: bp 99–100° (4 mm), $n^{25}D$ 1.5012.

(6) T. Saegusa, S. Kobayashi, Y. Ito, and N. Yasuda, *J. Amer. Chem. Soc.*, **90**, 4182 (1968).

(7) I. Ugi and R. Meyr, *Chem. Ber.*, **93**, 239 (1960).

Anal. Calcd for $C_{11}H_{21}NS$: C, 66.27; H, 10.62; N, 7.03. Found: C, 66.03; H, 10.51; N, 7.11.

Nmr and ir ($\nu_{C=N}$ at 1595 cm^{-1}) spectra supported its structure.

Reaction of *t*-Butyl Isocyanide (4) with Benzenethiol (8).—A mixture of 0.55 g (5 mmol) of **8** and 0.42 g (5 mmol) of **4** was heated in the presence of 1.7 mg (0.01 mmol) of AIBN at 80° for 2 hr. Distillation gave 0.65 g (67%) of phenyl N-*t*-butylthiothioformimidate: bp 99–101° (3 mm), $n^{25}D$ 1.5514.

Anal. Calcd for $C_{11}N_{15}NS$: C, 68.34; H, 7.82. Found: C, 68.22; H, 7.95.

The structure was further confirmed by nmr and ir ($\nu_{C=N}$ at 1597 cm^{-1}) spectra.

Reaction of *t*-Butyl Isocyanide (4) with Ethanethiol (7).—Similarly, the **4–7** reaction by AIBN was carried out at 35° for 4 hr, which gave ethyl N-*t*-butylthioformimidate: bp 75–76° (70 mm), $n^{25}D$ 1.4654.

Anal. Calcd for $C_7H_{15}NS$: C, 57.90; H, 10.34. Found: C, 57.60; H, 10.20.

Dependency of the Molar Ratio of 14/13 on the Concentration of 2-Propanethiol (12).—A series of five reactions was carried out, in which the initial concentration of 2-propanethiol was varied. A typical run was as follows. A mixture of 0.43 g (5.6 mmol) of **12** and 1.34 g (12.4 mmol) of **5** (concentration of **12**, 2.8 mol/l.) was heated without radical initiator at 100° for 20 min. The total conversion for **12** was 8% and the molar ratio of **14/13** was determined to be 0.48 by glpc analysis.

Reactions of *t*-Butyl Isocyanide (4) with α-Toluenethiol (9).—The radical reaction of **4** with **9** by AIBN at 80° gave 93% *t*-butyl isothiocyanate and 96% toluene.

To a mixture of 1.24 g (10 mmol) of **9** and 1.00 g (12 mmol) of **4** was added 8.0 mg (0.1 mmol) of cupric oxide as a catalyst. The reaction system soon became homogeneous at room temperature. When the reaction mixture was heated at 100° for 2.0 hr, 91% of **9** disappeared. Benzyl N-*t*-butylthioformimidate was isolated by preparative glpc, $n^{25}D$ 1.5435.

Anal. Calcd for $C_{12}H_{17}NS$: C, 69.51; H, 8.26; N, 6.76. Found: C, 69.78; H, 8.37; N, 6.52.

Reaction of Cyclohexyl Isocyanide (5) with 2-Methyl-2-propanethiol (11) in the Presence of Cupric Oxide and *p*-Benzoquinone.—A mixture of 0.63 g (7 mmol) of **11**, 0.54 g (5 mmol) of **5**, 8 mg (0.1 mmol) of cupric oxide, and 55 mg (0.5 mmol) of *p*-benzoquinone was refluxed at 90° for 3 hr. By glpc analysis of the reaction mixture, *t*-butyl N-cyclohexylthioformimidate[3] (64%) and **13** (6%) were formed.

Registry No.—*sec*-Butyl N-cyclohexylthioformimidate, 24058-23-9; phenyl N-*t*-butylthioformimidate, 24058-24-0; ethyl-N-*t*-butylthioformimidate, 24058-25-1; benzyl N-*t*-butylthioformimidate, 24058-26-2; **4**, 630-18-2; **5**, 931-53-3; **6**, 100-47-0; **7**, 75-08-1; **8**, 108-98-5; **9**, 100-53-8; **10**, 513-53-1; **11**, 75-66-1.

Peroxide–Metal Ion Oxidations. II. A Convenient Synthesis of Imides

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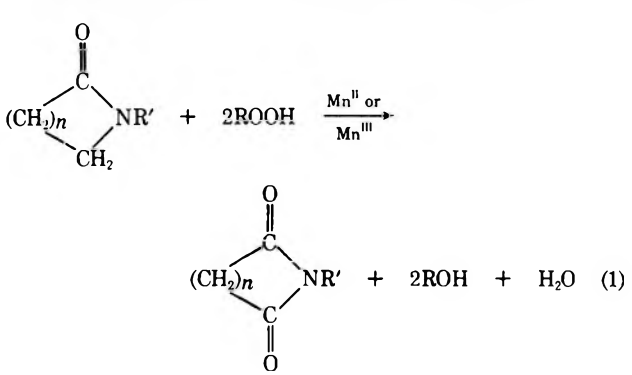
A novel and highly selective oxidation of lactams and N-alkylamides to the corresponding imides has been developed. The oxidant consists of a hydroperoxide or a peroxy acid in combination with a catalytic amount of a manganese(II) or -(III) salt. The extremely mild reaction represents the first convenient method for synthesizing many imides, including adipimide, a polymer intermediate which had previously been preparable only in low yields. The synthetic scope of the oxidation and its limitations are discussed.

A convenient synthesis of imides has been developed, using a novel and particularly mild oxidation procedure.[1] Lactams or N-alkylamides treated with a hydroperoxide or a peroxy acid in the presence of a metal ion catalyst such as manganese(II) produced the corresponding imides in excellent yield. The oxidation has proved to be quite general, proceeding under mild conditions to provide imides, many of which have previously been preparable only in poor yields. The general reaction and apparent stoichiometry are indicated below.



Metal ion interactions with hydroperoxides and peroxy acids are well known[2,3] and have been used to synthetic advantage in the past. Kharasch, Kochi, and their respective groups prepared 2-alken-1-yl esters and unsymmetrical peroxides by copper(I)-catalyzed treatment of olefins with peroxy esters and hydroperoxides, respectively.[4] More recently, primary amines have been converted to oximes,[5] tertiary amines to amine oxides,[6] and sulfides to sulfoxides and sulfones[7] by peroxide–metal ion oxidants. These latter reactions are characterized by oxidative transformations at the heteroatom.

The oxidation of amides to imides, a two-electron transformation at the position adjacent to the heteroatom, has been accomplished in low yield by autoxidation[8] and by treatment with ruthenium tetroxide[9] and persulfates.[10] The procedure which we describe offers several advantages, the most significant being ease of operation, high selectivity, and generally satisfactory

(1) For a preliminary report on the oxidation system, see A. R. Doumaux, Jr., J. E. McKeon, and D. J. Trecker, *J. Amer. Chem. Soc.*, **91**, 3992 (1969).

(2) A. G. Davies, "Organic Peroxides," Butterworth and Co. (Publishers) Ltd., London, 1961, Chapters 12 and 13.

(3) E. G. E. Hawkins, "Organic Peroxides, Their Formation and Reactions," D. Van Nostrand Co., Inc., Princeton, N. J., 1961, Chapters 1, 3, and 7.

(4) M. S. Kharasch and A. Fono, *J. Org. Chem.*, **24**, 606 (1959), and references therein. J. K. Kochi, *J. Amer. Chem. Soc.*, **83**, 3162 (1961); **84**, 774, 2121, 3271 (1962).

(5) L. Jarkovsky and J. Pasek, *Chem. Prum.*, **16**, 591 (1966); Belgium Patent 668,811 (1966).

(6) U. S. Patent 3,274,252 (1966); L. Kuhnen, *Chem. Ber.*, **99**, 3384 (1966); M. N. Sheng and J. G. Zajacek, *J. Org. Chem.*, **33**, 588 (1968).

(7) L. Kuhnen, *Angew. Chem. Int. Ed. Engl.*, **5**, 893 (1966).

(8) A. Rieche and W. Schön, *Chem. Ber.*, **99**, 3238 (1966); M. V. Lock and B. F. Sagar, *J. Chem. Soc., B*, 690 (1966); B. F. Sagar, *ibid.*, 428, 1047 (1967).

(9) British Patent 900,107 (1962).

(10) H. L. Needles and R. E. Whitfield, *J. Org. Chem.*, **31**, 341 (1966).

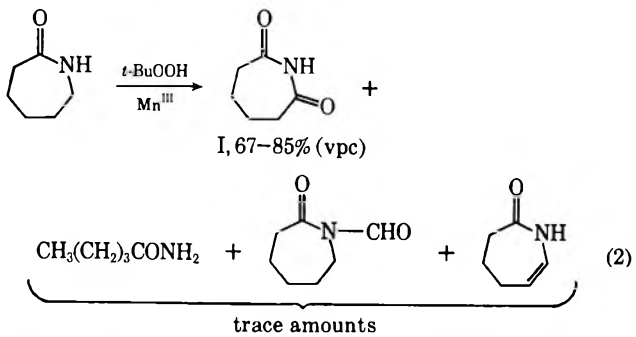
TABLE I

t-BUTYL HYDROPEROXIDE OXIDATION OF ϵ-CAPROLACTAM

Catalyst	*t*-BuOOH/ lactam mole ratio	*t*-BuOOH/ metal mole ratio	Reaction time, hr	% conversion of Lactam	% conversion of *t*-BuOOH	% yield of imide based on Lactam	% yield of imide based on *t*-BuOOH
Cobalt(II) naphthenate	1.03	182	64	21.8	50.8	23.7	10.9
Cobalt(II) naphthenate	1.13	200	136	21.2	100.0	44.6	16.7
$Mn(acac)_2$	1.13	200	136	38.7	56.1	44.5	54.2
$Mn(acac)_3$	1.13	200	136	28.6	54.6	78.0	72.1
$Mn(acac)_3$	1.03	182	64	20.6	28.1	80.5	89.0
$Mn(acac)_3$	1.13	357	144	23.9	31.0	76.8	52.2
$Mn(acac)_3$	2.03	355	96	18.5	67.8	84.5	48.9

yields. A typical procedure consists of simply mixing the lactam and a twofold molar excess of hydroperoxide, adding a trace of manganese(III) acetylacetonate, and stirring at room temperature for several days. When a peroxy acid is used as the oxidant, it is added dropwise to a stirred solution of lactam and the metal ion catalyst in ethyl acetate at 0–10°.

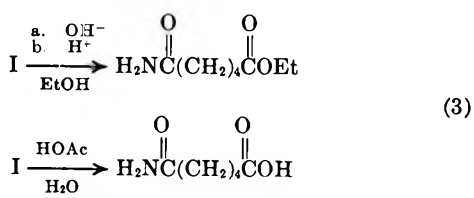
Oxidation of ϵ-Caprolactam.—*t*-Butyl hydroperoxide–manganese(III) treatment of ϵ-caprolactam provided a useful synthesis of adipimide (I). Adipimide has been prepared previously in low yields by other routes[11] and is a compound of interest as a polymer intermediate.[12] Several coproducts formed in lesser amounts were also identified (eq 2). Table I records the conversions and



(2)

yields achieved under a variety of reaction conditions. Most of the transition metal ions studied provided some reactivity, but manganese(II) or (III) was clearly the catalyst of choice.

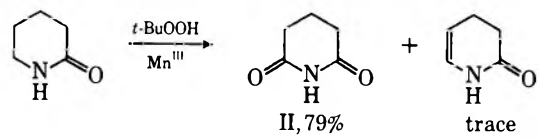
Much shorter reaction times were possible when peracetic acid was used as the oxidant. With manganous dichloride as the catalyst, 33–38% isolated yields of adipimide were obtained after 32 hr at 0°. Vpc analyses indicated yields approaching 60%, but isolation difficulties amplified by the reactivity of I resulted in diminished actual yields. Adipimide was found to be extremely susceptible to ring opening from nucleophilic reagents, forming adipamic acid derivatives with ease (see Experimental Section). This was found to be especially true in the presence of acetic acid (formed



(3)

when peracetic acid was used as the oxidant), adipamic acid being formed in high yield (eq 3).

2-Piperidone and Derivatives.—Both hydroperoxides and peroxy acids reacted smoothly with 2-piperidone, giving rise to glutarimide (II) with high selectivity.



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Isolated yields of 54–72% were routinely achieved from peracetic acid treatment. The effectiveness of various metal ion catalysts is recorded in Table II.

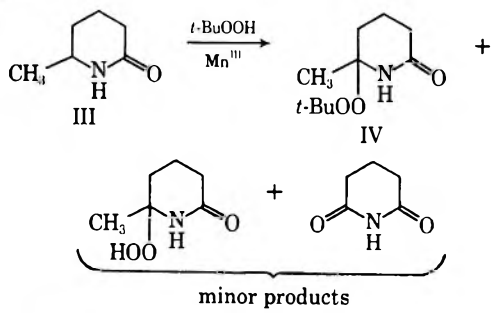
TABLE II

EFFECT OF METAL ION CATALYSTS[a] ON THE PERACETIC ACID OXIDATION OF 2-PIPERIDONE[b]

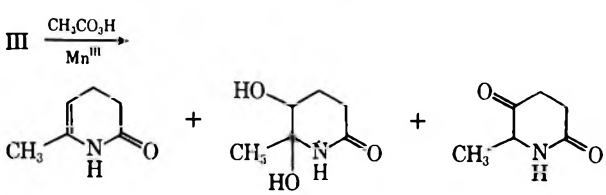
Metal salt[c]	% conversion into II based on 2-piperidone
None	5.0
$Mn(acac)_3$	72.0
$Mn(OAc)_2$	59.8
$MnCl_2$	78.3
$Fe(acac)_3$	23.1
$Co(acac)_3$	35.2
$CoCl_2$	26.3
$Co(acac)_2$	53.1

[a] $VO(acac)_2$, $Cr(acac)_3$, $Cu(O_2CC_6H_5)_2$, $Zn(acac)_2$, $Zr(acac)_4$, $Mo(CO)_6$, $RuCl_3$, $RhCl_3$, $PdCl_2$, $(NH_4)_2WO_4$, NH_4ReO_4, $OsCl_3$, $IrCl_3$, $IrCl_4$, H_2PtCl_6, $HgCl_2$ $Tl(OAc)_3$, $Pb(OAc)_2$, and $Ce(acac)_3$. $Ni(acac)_2$ caused an explosion. The concentration of peracetic acid was too high. All reactions using peracetic acid should be tested for peroxide concentration during the reaction. [b] 0.1 *M* 2-piperidone; 0.2 *M* in peracetic acid; reaction in ethyl acetate at room temperature. [c] 10^{-3} *M* in metal salt.

Of considerable interest was the reaction of 6-methyl-2-piperidone (III) with *t*-butyl hydroperoxide. With



(5)

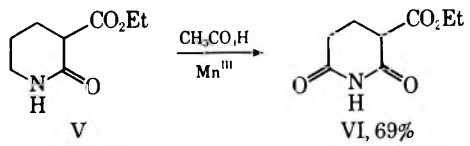


(11) E. N. Zil'berman, *Zh. Obshch. Khim.*, **25**, 2127 (1955); **30**, 596(1960). H. K. Hall, Jr., and A. K. Schneider, *J. Amer. Chem. Soc.*, **80**, 6409 (1958). N. Tokura, R. Tada, and K. Yokoyama, *Bull. Chem. Soc. Jap.*, **34**, 1812 (1961).

(12) U. S. Patent 3,033,831 (1962); Netherlands Patent 6,516,904 (1966); O. Wichterle, J. Stehlíček, T. Kodaira, and J. Šebenda, *Polym. Lett.*, **5**, 931 (1967).

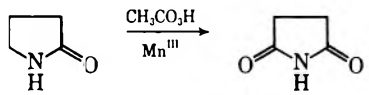
only one available carbon–hydrogen bond at the reactive site, oxidation proceeded to give the stable 6-*t*-butylperoxy derivative (IV) as the major product. A considerably more complex reaction occurred with peracetic acid, giving rise to numerous products of secondary oxidation, including 6-methyl-3,4-dihydro-2-pyridone and 6-methyl-5,6-dihydroxy-2-piperidone.

The remarkable selectivity of the peroxide–manganese ion system was illustrated convincingly with 3-carbethoxy-2-piperidone (V), a compound with three distinct reactive sites. As before, oxidation proceeded solely at the nitrogen-adjacent methylene group to give VI as the only isclable product.



(6)

2-Pyrrolidone and Derivatives.—Near-quantitative yields based on consumed 2-pyrrolidone, were achieved for the *t*-butyl hydroperoxide preparation of succinimide (VII). However, a very sluggish reaction rate—92 hr was required to convert 11% of the lactam—made peroxy acid treatment the preferred synthetic route. Reaction with peracetic acid–manganese(III) provided a 64% isolable yield of VII in a 16-hr reaction period. Replacement of the amide hydrogen with a methyl group (VIII) did not impede the oxidation, with attack



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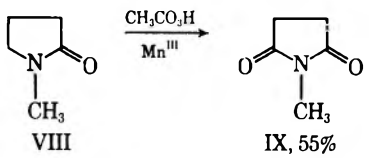
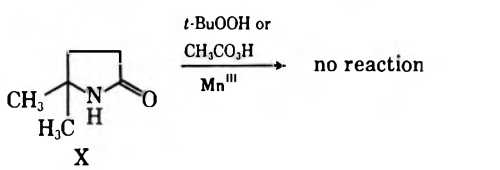


(8)

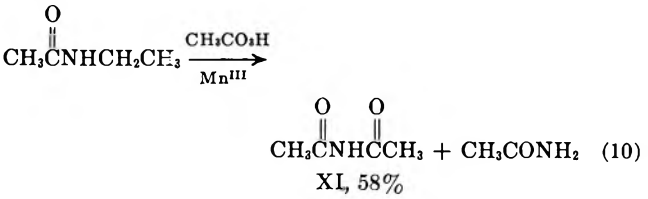


(9)

still occurring at the methylene group adjacent to the amide nitrogen (eq 8). A control experiment showed that succinimide was inert to further oxidation under normal reaction conditions. Starting material was recovered quantitatively.

Monomethyl substitution at the 5 position provided the 5-*t*-butylperoxy product from treatment with *t*-butyl hydroperoxide. Here, however, unlike IV, the unsymmetrical peroxide was unstable and product isolation in pure form was not possible. 5,5-Dimethyl substitution (X) rendered the lactam completely inert to both hydroperoxide and peroxyacid oxidation. The next lower lactam homolog, β-propiolactam, examined as its N-phenyl derivative, was also unreactive to oxidation with peracetic acid.

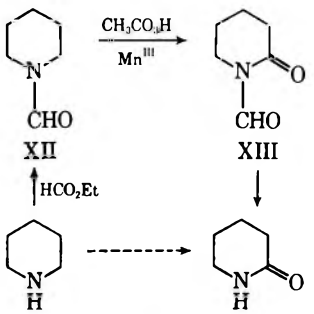
Oxidation of N-Alkylamides.—Linear N-alkylamides possessing a methylene adjacent to the amide nitrogen responded readily to peracetic acid–manganese(III) oxidation but reacted sluggishly when treated with hydroperoxide and manganese; competing reactions



(10)

occurred instead. Peracetic acid oxidized N-ethylacetamide to diacetamide (XI) and a small amount of acetamide. Similar reaction with *t*-butyl hydroperoxide gave rise to a host of products.

Ring-containing amides and compounds disubstituted at the nitrogen-adjacent position were found to be generally inert. Thus, N-acetylpiperidine, N-acetylpyrrolidine, N-cyclohexylbenzamide, and N-cyclohexylacetamide were recovered unreacted from normal oxidation treatment. An exception was N-formylpiperidine (XII), which was converted into N-formyl-2-piperidone (XIII). The ease of reversible N-formyl-



(11)

ation in such systems suggests that this route may be useful for converting cyclic amines into lactams.

Discussion

Regarding mechanism, several pathways are consonant with the observed results. A detailed study of the oxidation mechanism is underway, and the results will be presented in a subsequent publication. However, several observations bear mention at this time. First, the high degree of selectivity at the nitrogen-adjacent site makes it clear that the oxidation may not involve strictly free radicals[13a]—this in spite of the fact that conventional transition metal ion (*e.g.*, Co^{II}, Mn^{II}) interactions with hydroperoxides and peroxyacids are known to produce such species.[2,3] This apparent inconsistency may be resolved if one postulates the formation of a metal ion–carbonyl or –nitrogen complex which precedes oxidation and establishes a template that controls the direction of subsequent attack. Amide–transition metal complexes have been well documented.[13b] Bonding between the amide and the metal ion appears to occur through the carbonyl oxygen.[13b] Finally, the isolation of IV from the hydroperoxide treatment of III suggests that such

(13) (a) Radical abstraction has been observed at *both* the nitrogen-adjacent and the carbonyl-adjacent methylenes of lactams: G. I. Nikishin and R. I. Mustafaev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1832 (1964); D. Elad and J. Sinnreich, *Chem. Ind.* (London), 768 (1965). (b) W. E. Bull, S. K. Madan, and J. E. Willis, *Inorg. Chem.*, **2**, 303 (1963); S. K. Madan and H. H. Denk, *J. Inorg. Nucl. Chem.*, **29**, 1669 (1967); R. J. Niedzielski and G. Znider, *Can. J. Chem.*, **43**, 2618 (1965); Y. Saito, H. Iwasaki, Y. Wawata, and A. Masuko, *Chem. Abstr.*, **67**, 371143 (1967).

peroxides (and perhaps the corresponding peroxy esters) are intermediates, albeit unstable ones, in the oxidation sequence of the corresponding unsubstituted lactams.

Experimental Section

General Procedure. Hydroperoxide Oxidation.—The lactam was dissolved in up to a twofold molar excess of *t*-butyl hydroperoxide (Matheson Coleman and Bell, 69–70% assay in *t*-butyl alcohol) and then treated with a manganese salt (usually 0.5–1.0% of the lactam). The resulting solution was stirred magnetically at room temperature for 3–6 days. At the end of that time the unreacted hydroperoxide was determined by conventional iodide/thiosulfate analysis.[14]

General Procedure. Peroxy Acid Oxidation.—The lactam and manganese salt (0.5–1.0% of the lactam) were dissolved in ethyl acetate (with added acetic acid if necessary to obtain homogeneity) and placed in a reaction flask equipped with dropping funnel, condenser, thermometer, magnetic stirrer, and external brine-cooled jacket. A twofold molar excess of peracetic acid (Union Carbide Corp., 25% assay in ethyl acetate) was then added at a rate sufficient to maintain a reaction temperature of 0–10°. After addition was complete, stirring was continued, generally overnight, or until an iodide test for peracid was negative.[14]

Oxidation of ε-Caprolactam.—In a typical hydroperoxide oxidation, ε-caprolactam (213 g, 1.89 mol), manganic acetylacetonate (3.8 g, 1.1×10^{-2} mol), and 69.1% by weight *t*-butyl hydroperoxide (500 g, containing 3.84 mol of hydroperoxide) were stirred together at room temperature for 96 hr. Analysis of caprolactam and adipimide (I) was carried out by vpc, employing a 10-ft 5% Carbowax 20M on Chromosorb G column at 170° and dibutyl adipate as an internal standard. Work-up consisted of filtration to remove a dark precipitate, presumably spent catalyst, and then *in vacuo* distillation. After removal of the unreacted hydroperoxide and *t*-butyl alcohol, several large fractions were taken (bp 85–90° at 0.025 mm) which contained caprolactam, I, and five minor coproducts. Separation of I was accomplished by continuously extracting the distillate in a Soxhlet extractor with refluxing 35–37° boiling petroleum ether. Essentially pure I was recovered from the thimble after extracting a 124-g sample for 113 hr. The material melted at 100–101° and was spectroscopically (ir, nmr) identical with an authentic sample.[11]

In a typical peroxy acid oxidation, ε-caprolactam (282.5 g, 2.5 mol) and manganese chloride (*ca.* 10^{-5} mol in 10 ml of ethyl acetate) in ethyl acetate (200 ml) were treated dropwise with peracetic acid (1500 g of 25%, 4.9 mol), with the temperature being maintained at 0–10°. After stirring overnight, the reaction mixture was filtered and the filtrate was evaporated *in vacuo* to a red oil. Trituration with isopropyl alcohol and subsequent cooling gave I as a white crystalline solid (120 g, 0.94 mol, 37.6% yield).

Several minor coproducts obtained from a forerun distillation fraction (bp 65–68° at 0.1 mm) of a large-scale synthesis run (H_2O_2) were isolated by preparative-scale vpc (12 ft × 1/4 in. Al, 5% Carbowax 20M on Chromosorb G, DMCS-treated and acid washed, 175°). Valeramide was identified by comparison of melting point and spectra (ir, nmr) with those of an authentic sample. N-Formyl-ε-caprolactam was similarly compared with an independently synthesized sample.[15] Also identified was 1-[H]-7-oxo-4,5-dihydroazepine: ir (neat) 3125 (NH) and 1665 cm^{-1} (C=O); uv (MeOH) λ_{max} 236 mμ (ϵ_{max} 6240); nmr ($CDCl_3$) δ 1.91 (m, 2, ring CH_2), 2.21 (m, 2, $-C=CHCH_2-$), 2.57 (m, 2, $-CH_2CO-$), 4.98 (m, 1, $-C=CHCH_2-$), 5.76 (m, 1, $-NHCH=CH$), and 8.15 (s, 1, NH).

Anal. Calcd for C_6H_9ON: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.03; H, 8.49; N, 12.32.

Ring Opening of Adipimide.—Adipimide (1.0 g) was stirred into a solution of sodium hydroxide (2.0 g) in absolute ethanol (50 ml). The precipitate formed (10–15 min) was collected by filtration and washed with *n*-heptane: ir (KBr) 3230 (NH_2), 1645 (CO), 1572 and 1422 cm^{-1} (CO_2^-). Esterification was accomplished by treatment with gaseous HCl in absolute alcohol. After removal of the precipitated NaCl by filtration, the solution was evaporated to dryness. The crystals which remained were washed with acetone, and the acetone wash was evaporated to dryness. Thus obtained, the product was washed with *n*-hexane and collected by filtration: mp 74°; nmr (CD_3COCD_3) δ 1.22 (t, 3, CH_3CH_2), 1.63 (m, 4, $-CH_2-$), 2.27 (m, 4, CH_2CO), 4.14 (q, 2, CH_2CH_3), 6.2 (s, 2, NH_2); ir (KBr) 3260 (NH), 1720 (ester CO), 1668 (amide CO), 1638 cm^{-1}.

Anal. Calcd for $C_8H_{15}O_3N$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.28; H, 8.56; N, 8.01.

Oxidation of 2-Piperidone.—A solution of 2-piperidone (95 g, 0.96 mol), manganic acetylacetonate (1.0 g), and 68.8% *t*-butyl hydroperoxide (200 g, containing 1.53 mol of hydroperoxide) was stirred for 96 hr. Analysis by vpc (12 ft × 1/4 in. Al, 5% Carbowax 20M on Chromosorb G, 175°), employing dibutyl adipate as an internal standard, showed unreacted valerolactam (0.582 mol, 39.4% conversion), II (0.299 mol, 79.2% based on consumed lactam), and a small amount of 3,4-dihydro-2-pyridone. Fractional distillation provided II (bp 72.5–73 at 0.1 mm), which after several washings with 35–37° boiling petroleum ether, melted at 145–146°[16] and was spectroscopically (ir, nmr) identical with an authentic sample. 3,4-Dihydro-2-pyridone was isolated by careful redistillation of early fractions: bp 72.5–73° at 0.1 mm; mp 27°; ir 3215 (NH), 1682 (amide C=O), 1635 cm^{-1} (C=C); nmr ($CDCl_3$) δ 2.42 (m, 4, ring $-CH_2-$), 5.11 (m, 1, $-C=CHCH_2$), 6.17 (q, 1, J = 7.5 Hz, J' = 5 Hz, $HNCH=C$), 8.83 (s, 1, NH).

Anal. Calcd for C_5H_7ON: C, 61.83; H, 7.26; N, 14.43; parent mass, 97. Found: C, 61.55; H, 7.49; N, 14.50; parent mass, 97.

By the general procedure described above, peracetic acid (64 g, 25%, 0.2 mol) treatment of 2-piperidone (9.9 g, 0.1 mol) and manganic acetylacetonate in ethyl acetate (50 ml) provided II (in 72% yield), recovered by solvent evaporation and recrystallization from ethanol.

Oxidation of 6-Methyl-2-piperidone with *t*-Butyl Hydroperoxide.—A solution of 6-methyl-2-piperidone (28.25 g, 0.25 mol), *t*-butyl hydroperoxide (74.25 g, 0.50 mol), and manganic acetylacetonate (0.5 g, 1.4×10^{-3} mol) was stirred at room temperature for 144 hr. The reaction mixture was then filtered, and the filtrate was evaporated *in vacuo* to give a pale yellow solid. Three recrystallizations from isopropyl alcohol–hexane provided material (9.0 g) which melted at 118.6–121.6°: nmr ($CDCl_3$) δ 1.20 (s, 9, CH_3C), 1.48 (s, 3, CH_3C), 1.78 (m, 4, $-CH_2-$), 2.30 (m, 2, CH_2CO), 6.65 (s, 1, NH); ir (KBr) 3450, 3200, 2980, 1650 (C=O), 1465, 1450, 1410, 1280, 1217, 1194, 1135, 1107, 966, 923, 891, 876 (OO), 833 cm^{-1}. The structure was thus identified as 6-methyl-6-*t*-butylperoxy-2-piperidone (IV).

Anal. Calcd for $C_{10}H_{19}O_3N$: C, 59.67; H, 9.52; N, 6.96. Found: C, 59.65; H, 9.54; N, 7.00.

The insoluble brown residue from which the original reaction material was filtered was slurried with chloroform, filtered, and then dissolved in boiling isopropyl alcohol and refiltered while hot. Cooling afforded a white crystalline solid (1.1 g) which, when recrystallized from isopropyl alcohol, melted (dec) at 142.7°: ir (KBr) 3450 (OH), 3200 (NH), 1650 cm^{-1} (NHCO); nmr (pyridine-d_5) δ 1.66 (s, 3, CH_3C), 2.0–1.3 (m, 4, CH_2), 2.35 (m, 2, CH_2CO). The structure was thus identified as 6-methyl-6-hydroperoxy-2-piperidone.

Anal. Calcd for $C_6H_{11}O_3N$: C, 49.64; H, 7.64; N, 9.65. Found: C, 49.87; H, 7.83; N, 9.41.

Oxidation of 6-Methyl-2-piperidone with Peracetic Acid.—Peracetic acid (64.0 g, 25%, 0.2 mol) was added dropwise to a solution of 6-methyl-2-piperidone (11.3 g, 0.1 mol), manganic acetylacetonate (50 mg), ethyl acetate (50 ml), and acetic acid (50 ml). After stirring for 3 days (−10°) the solution was filtered giving a white crystalline product, 6-methyl-5,6-dihydroxy-2-piperidone: mp 131–133° (recrystallization from acetonitrile raised the melting point to 138.5–142°); nmr (D_2O) δ 1.80 (s, 3, CH_3-), 2.23 (m, 2, CH_2), 2.70 (m, 2, CH_2CO), 4.1 (m, 1, CHO) (the multiplets at 4.1 and 2.33 were coupled as shown by a spin-decoupling experiment); ir (KBr) 3200 (broad, NH, OH), 1660, 1645 (amide C=O), 1087 cm^{-1} (CO).

Anal. Calcd for $C_6H_{11}O_3N$: C, 49.64; H, 7.64; N, 9.65. Found: C, 49.80; H, 7.74; N, 9.94.

The filtrate was evaporated under reduced pressure to a red oil, then distilled *in vacuo* into two fractions. Fraction 1, bp 125–130° at 2 mm, was identified as a mixture of 6-methyl-4,5-

(14) C. D. Wagner, R. H. Smith, and E. D. Peters, *Anal. Chem.*, **19**, 976 (1947).

(15) E. Hanvig and K. Rieckhoff, *Pharmazie*, **19**, 571 (1964).

(16) I. M. Heilbron, "Dictionary of Organic Compounds," Vol. 3, Oxford University Press, New York, N. Y., 1965, p 1532.

dihydro-2-pyridone and glutarimide. Purification of 6-methyl-4,5-dihydro-2-pyridone was accomplished by preparative vpc (1/4 in. × 12 ft Al, 5% Versamide on Chromosorb G, DMCS treated, acid washed, 175°, 120 cc/mm He, retention time 11.2 min): mp 113–115°; nmr ($CDCl_3$) δ 1.81 (s, 3, CH_3C=), 2.34 (m, 4, $-CH_2-$), 4.78 (m, 1, $-CH$=C–), 8.5 (broad singlet, 1, NH); ir (KBr) 3150 (NH), 1670 (amide CO), 1239, 1179, 918, 813, 762, 663 cm^{-1}.

Anal. Calcd for C_6H_9ON: C, 64.84; H, 8.13; N, 12.60. Found: C, 64.80; H, 8.46; N, 12.80.

Fraction 2, bp 130–160° at 2 mm, was recrystallized from isopropyl alcohol–*n*-hexane: mp 143–145°; nmr ($CDCl_3$) δ 1.40 (d, 3, CH_3CH), 2.67 (s, 4, CH_2CO), 3.98 (q, 1, $CHCH_3$), 7.76 (broad singlet, 1, NH); ir (KBr) 3200 (NH), 1725 (C=O), 1670 cm^{-1} (amide C=O).

Anal. Calcd for $C_6H_9O_2N$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.79; H, 6.97; N, 10.79.

This compound was identified as 6-methyl-5-oxo-2-piperidone.

Oxidation of 3-Carbethoxy-2-piperidone.—Peracetic acid (32 g, 25%, 0.1 mol), 3-carbethoxy-2-piperidone (8.55 g, 0.05 mol), and manganic acetylacetonate (50 mg) were allowed to react in the usual manner. Evaporation under vacuum afforded VI as a white solid (6.4 g, 69% yield) which, after two recrystallizations from ethanol, had mp 74–76°; ir (KBr) 3100 (hydrogen bonded NH), 1745 (ester C=O), 1708 (sh), 1690 cm^{-1} (imide C=O); nmr ($CDCl_3$), δ 1.29 (t, 3, CH_3CH_2-), 2.24 (m, 2, $-CH_2-CH-$), 2.66 (m, 2, CH_2CO), 3.6 (t, 1, $-CHCH_2$), 4.27 (q, 2, CH_2CH_3).

Anal. Calcd for $C_8H_{11}O_4N$: C, 51.88; H, 5.99; N, 7.56. Found: C, 51.60; H, 5.81; N, 7.32.

Oxidation of 2-Pyrrolidone.—Peracetic acid (64 g, 25%, 0.2 mol) treatment of 2-pyrrolidone (8.5 g, 0.1 mol) and manganic acetylacetonate (50 mg) in ethyl acetate (50 ml) was carried out in the usual manner. Filtration and evaporation provided succinimide (5.7 g, 63.7% yield) as a white crystalline material whose melting point (124°, ethanol recrystallization) and infrared spectrum were identical with those of an authentic sample.

Oxidation of N-Methyl-2-pyrrolidone.—Peracetic acid (64 g, 25%, 0.2 mol), N-methyl-2-pyrrolidone (9.9 g, 0.1 mol), and manganic acetylacetonate (50 mg) in ethyl acetate (50 ml) were allowed to react in the usual manner. Work-up afforded N-methylsuccinimide (6.25 g, 55.3% yield), mp 64°.[17] The structure was verified by infrared comparison with an authentic sample.

Oxidation of N-Ethylacetamide.—A solution of N-ethylacetamide (8.7 g, 0.1 mol) and manganic acetylacetonate (50 mg) in ethyl acetate (50 ml) was treated with peracetic acid (64 g, 25%, 0.2 mol) in the usual manner. Filtration and evaporation provided an oil which, upon distillation, yielded a small amount of acetamide and diacetamide: 5.9 g (58.4%); bp 80–90° at 1.4 mm; mp 75.5–77°;[18] nmr ($CDCl_3$) δ 2.32 (s, 6, CH_3C), 9.73 (s, 1, NH). Spectral (ir, nmr) comparisons with an authentic sample verified the structure as that of diacetamide. A mixture melting point was undepressed.

Oxidation of N-Formylpiperidine.—N-Formylpiperidine (11.3 g, 0.1 mol) and manganous chloride (5×10^{-3} mol) in ethyl acetate (50 ml) were treated with peracetic acid (120, 25%, 0.4 mol) in the usual manner. Fractional distillation gave a mixture of starting material and N-formyl-2-piperidone (bp 80–82° at 3 mm). Preparative-scale vpc (6 ft × 1/4 in. Al, 20% Tergitol N-P44 on Chromosorb W, 170°) provided pure N-formyl-2-piperidone: nmr ($CDCl_3$) δ 1.87 (m, 4, CH_2), 2.56 (m, 2, CH_2C=O), 3.60 (m, 2, $-CH_2N$), 10.43 (s, 1, CHO); ir (neat) 1720 (CHO), 1690 cm^{-1} ($-NHCO-$).

Anal. Calcd for $C_6H_9O_2N$: C, 56.68; H, 7.14. Found: C, 56.28; H, 7.28.

Registry No.—1-[H]-7-Oxo-4,5-dihydroazepine, 2228-76-4; adipamic acid ethyl ester, 1190-69-8; 3,4-dihydro-2-pyridone, 24058-44-4; 6-methyl-6-hydroperoxy-2-piperidone, 24058-46-6; 6-methyl-5,6-dihydro-2-piperidone, 24058-47-7; 6-methyl-4,5-dihydro-2-pyridone, 24058-29-5; 6-methyl-5-oxo-2-piperidone, 24058-30-8; N-formyl-2-piperidone, 24058-32-0; $Mn(acac)_2$, 14024-58-9; $Mn(acac)_3$, 14284-89-0; IV, 24058-45-5; VI, 24058-31-9.

(17) A. Labruto, *Gazz. Chim. Ital.*, **63**, 266 (1933).
(18) I. M. Heilbron, *ibid.*, **63**, 845 (1933).

Fluoro Olefins. III. The Synthesis of β-Substituted 1-Chloroperfluoro Olefins[1]

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The reaction of polyfluorinated ketones with chlorofluoromethylenetriphenylphosphorane, $(C_6H_5)_3P$=CFCl, generated *in situ* from sodium dichlorofluoroacetate and triphenylphosphine, provides a general, one-step route to β-substituted 1-chloroperfluoro olefins. The β substituent can either be an aryl or alkyl group. The reaction of this ylide with several typical aldehydes and ketones was also briefly studied. The proposed mechanism for the formation of the chlorofluoromethylene ylide involves the decomposition of an intermediate phosphobetaine salt. An alternate route to the chlorofluoromethylene ylide, *via* reaction of dichlorofluoromethane with potassium *t*-butoxide and triphenylphosphine, is also presented.

Earlier reported preparations of 1-chlorofluoro olefins generally required several steps, involving Grignard reagents and zinc dehalogenations.[3-7] Reaction of the chlorofluoromethylene ylide with a carbonyl moiety offers a simple, one-step route to these olefins. Particularly, reaction with polyfluorinated ketones offers a facile synthesis of β-substituted 1-chloroperfluoro olefins.

At present, two reports other than our own[1c] have appeared in the literature which describe the chlorofluoromethylene ylide route to 1-chlorofluoro olefins. Speziale and Ratts[8] prepared 1,1-diphenyl-2-fluoroethylene *via* the following sequence.[9] The chlorofluoromethylene ylide was generated from dichlorofluoromethane, potassium *t*-butoxide, and triphenyl-

$$(C_6H_5)_3P{=}CFCl + (C_6H_5)_2C{=}O \longrightarrow (C_6H_5)_2C{=}CFCl + (C_6H_5)_3PO$$

(1) (a) Presented in part: Abstracts, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, p 2k. (b) Taken in part from the Doctoral Dissertation of H. C. Krutzsch, The University of Iowa, Aug 1968. (c) Preliminary report: *Tetrahedron Lett.*, 71 (1968). (d) Part II: *J. Org. Chem.*, **33**, 1854 (1968).
(2) National Institutes of Health Predoctoral Fellow, 1965–1968.
(3) S. G. Cohen, H. T. Wolosinski, and P. J. Scheuer, *J. Amer. Chem. Soc.*, **72**, 3952 (1950).
(4) P. Tarrant and D. A. Walker, *ibid.*, **76**, 1624 (1954).
(5) S. Dixon, *J. Org. Chem.*, **21**, 400 (1956).
(6) E. D. Bergmann, *et al.*, *J. Amer. Chem. Soc.*, **79**, 4174 (1957).
(7) T. Ando, *et al.*, *Bull. Chem. Soc. Jap.*, **40**, 1275 (1967).
(8) A. J. Speziale and K. W. Ratts, *J. Amer. Chem. Soc.*, **84**, 854 (1962).
(9) We have been unable to substantiate this earlier report. In our experiments, benzophenone did not react with the fluorochloro ylide. Professor Ando[10] has also informed us that his group was also unsuccessful in duplicating this report.
(10) Professor T. Ando, private communication. We are indebted to Professor Ando for communicating some of his unpublished data to us.

TABLE I

PHYSICAL PROPERTIES OF β-SUBSTITUTED 1-CHLOROPERFLUORO OLEFINS

AR(R)	R_f	Isomer[a]	Bp, °C (mm)	$n^{20}D$	$\nu_{C=CFCl}$, μ	Cyclohexane, λ_{max}, mμ (ε)	Ethanol, λ_{max}, mμ (ε)
C_6H_5	CF_3	A	75 (40)	1.4558	5.97	221 (5,730)	221 (5,380)
		B	77 (40)	1.4636	6.01	227 (8,350)	227 (7,790)
C_6H_5	C_2F_5	A	75 (30)	1.4334	6.02	222 (5,350)	222 (4,750)
		B	77 (30)	1.4401	6.04	223 (7,460)	223 (6,500)
C_6H_5	n-C_3F_7	A	83 (25)	1.4181	6.01	222 (4,800)	222 (4,730)
		B	85 (25)	1.4243	6.05	223 (7,300)	223 (6,400)
p-ClC_6H_4	CF_3	A	94 (20)	1.4788	5.98	226 (10,300)	225 (9,150)
		B	97 (20)	1.4874	6.02	231 (11,600)	231 (10,900)
p-$CH_3OC_6H_4$	CF_3	A	104 (15)	1.4736	5.98	246 (5,400)	246 (5,160)
		B	107 (15)	1.4846	6.02	252 (7,360)	251 (6,420)
p-FC_6H_4	CF_3	A	84 (40)	1.4435	5.97	222 (5,130)	223 (4,690)
		B	86 (40)	1.4508	6.02	228 (7,370)	228 (6,980)
p-$CH_3C_6H_4$	CF_3	A	90 (25)	1.4606	5.98	228 (6,050)	230 (5,340)
		B	93 (25)	1.4697	6.02	233 (8,940)	231 (8,550)
C_6H_5	CF_2Cl[b]	A	78 (15)	1.4895	5.98	223 (5,940)	223 (5,460)
		B	78 (15)	1.4941	6.03	227 (7,580)	227 (7,280)
C_6H_{11}	CF_3	A	76 (35)	1.4181	6.00		
		B	76 (35)	1.4204	6.01		
n-C_4H_9	CF_3[b]	A	114 (739)	1.3753	5.94		
		B	114 (739)	1.3775	5.95		
$C_6H_5CH_2$	CF_3	A + B[c] (50/50)	81 (20)	1.4647	5.95		

[a] A = $\frac{AR(R)}{R_f}>C=C<\frac{Cl}{F}$, B = $\frac{AR(R)}{R_f}>C=C<\frac{F}{Cl}$. Registry numbers in descending order are 19302-03-5, 19302-02-4, 24165-18-2, 24165-19-3, 24165-20-6, 24165-21-7, 19302-07-9, 19302-06-8, 19302-11-5, 19302-10-4, 19302-05-7, 19302-04-6, 19302-09-1, 19302-08-0, 24165-29-5, 24164-51-0, 24164-52-1, 24299-52-9, 24164-53-2, 24164-54-3, 16205-21-3 (A), 16205-22-4 (B). [b] Isomers were not separable by distillation. [c] Isomers were inseparable by distillation or preparative glpc.

TABLE II

β-SUBSTITUTED 1-CHLOROPERFLUORO OLEFINS

AR(R)	R_f	Yield, %[a]	A/B ratio[b]	C, % Calcd	C, % Found	H, % Calcd	H, % Found	Cl, % Calcd	Cl, % Found	F, % Calcd	F, % Found
C_6H_5	CF_3	56	53/47	48.10	47.99	2.23	2.21	16.04	15.81	33.85	33.90
C_6H_5	C_2F_5	42	59/41	43.70	43.98	1.82	1.63	12.94	13.02	41.50	41.66
C_6H_5	n-C_3F_7	41	60/40	40.65	40.39	1.54	1.39	10.93	11.06	46.80	48.74
p-ClC_6H_4	CF_3	53	55/45	41.75	42.06	1.55	1.59	27.40	27.60	29.40	30.22
p-$CH_3OC_6H_4$	CF_3	67	52/48	47.25	47.54	2.75	3.01	13.93	13.69	29.85	30.09
p-FC_6H_4	CF_3	27	55/45	44.50	44.77	1.65	1.61	14.65	15.42	39.20	39.63
p-$CH_3C_6H_4$	CF_3	48	53/47	50.30	50.18	2.94	2.91	14.90	15.40	31.85	32.67
$C_6H_5CH_2$	CF_3	37	50/50	50.43	50.58	2.94	2.86	14.90	15.42	31.85	32.15
C_6H_{11}	CF_3	70	42/58	47.00	47.25	4.78	4.88	15.40	15.30	32.90	33.09
n-C_4H_9	CF_3	34	48/52	41.20	41.33	4.41	4.54	17.36	17.23	37.15	37.10
C_6H_5	CF_2Cl	29[c]	52/48	44.80	44.50	2.07	2.22				

[a] Glpc yield was based on starting ketone. [b] This was the *cis/trans* ratio afforded from the olefination reaction. A and B are the same as in Table I. [c] This olefin was prepared from the chlorofluoromethylenetriphenylphosphorane ylide generated from potassium *t*-butoxide, dichlorofluoromethane, and triphenylphosphine.

phosphine. Ando and coworkers[11] have prepared this ylide by the reaction of methyl dichlorofluoroacetate with triphenylphosphine and sodium methoxide in petroleum ether.

Results and Discussion

Chlorofluoromethylenetriphenylphosphorane, generated from sodium dichlorofluoroacetate and triphenylphosphine, reacted with polyfluorinated ketones to afford the corresponding *cis–trans* β-substituted 1-chloroperfluoro olefins in yields of 34–70%. The polyfluorinated ketones were prepared by reaction of the appropriate Grignard reagent with a polyfluorinated acid.[12] Reaction of the chlorofluoromethylene ylide with several typical nonfluorinated aldehydes and ketones afforded the corresponding chlorofluoro olefins in yields of 9 to 49%.

$$(C_6H_5)_3P + CFCl_2CO_2Na \longrightarrow (C_6H_5)_3P{=}CFCl + NaCl + CO_2$$

$$(C_6H_5)_3P{=}CFCl + AR(R)COR_f \longrightarrow AR(R)C(R_f){=}CFCl + (C_6H_5)_3PO$$

On a small-scale basis these reactions were carried out by simply heating a triglyme solution of the carbonyl compound, triphenylphosphine, and sodium dichlorofluoroacetate at 80 to 90° for a period of several hours. For preparative-scale reactions, a solution of sodium dichlorofluoroacetate in triglyme was added dropwise to a mixture of triphenylphosphine and carbonyl compound in triglyme at 80–90°. This procedure prevented a rapid uncontrollable evolution of carbon dioxide. The results of these reactions, in-

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TABLE III

MISCELLANEOUS β-CHLOROFLUORO OLEFINS

Chlorofluoro olefin	Yield, %[a]	Bp, °C (mm)[b]	A/B ratio[c]	C, % Calcd	C, % Found	H, % Calcd	H, % Found	Cl, % Calcd	Cl, % Found	F, % Calcd	F, % Found
$C_6H_5CH=CFCl$[d]	49	63 (16)	56/44	61.30	61.19	3.83	4.10	22.70	22.40	12.15	12.29
n-$C_4H_9CH=CFCl$[e]	25	108 (738)	61/39	52.75	52.83	7.33	7.36	26.00	25.74	13.92	14.21
$CH_2(CH_2)_3C=CFCl$[f]	9	59 (75)		53.50	53.43	5.95	6.08	26.40	26.11	14.11	14.42
$CH_2(CH_2)_3C=CFCl$	23[g]										
$(C_6H_5)_2C=CFCl$	0										

[a] Glpc yield was based on starting ketone. [b] Boiling point of *cis–trans* mixture obtained from ylide reaction. [c] This was the *cis/trans* ratio of product afforded from the olefination reaction; A = $\frac{AR(R)}{H}>C=C<\frac{Cl}{F}$, B = $\frac{AR(R)}{H}>C=C<\frac{F}{Cl}$. [d] $n^{20}D$ 1.5410 (*cis–trans* mixture), $\nu_{C=CFCl}$, 5.98 μ (*cis–trans* mixture). Registry numbers are 16205-22-4 (A), 16629-98-4 (B). [e] $n^{20}D$ 1.4090 (*cis–trans* mixture), $\nu_{C=CFCl}$, 5.93 (*cis–trans* mixture). Registry numbers are 24164-59-8 (A), 24164-60-1 (B). [f] $n^{20}D$ 1.4456, $\nu_{C=CFCl}$, 5.87 μ. Registry number is 24164-76-9. [g] Tributylphosphine was used in place of triphenylphosphine.

cluding some of the physical properties of these olefins are summarized on Tables I–III.

Concentration studies demonstrated that for best results a mole ratio of 1.5:1.5:1.0 of triphenylphosphine, sodium dichlorofluoroacetate, and carbonyl compound, respectively, should be used. The *cis–trans* olefin was isolated by flash distillation of the reaction mixture into a Dry Ice cooled receiver. Careful distillation on a spinning-band column and/or preparative glpc yielded pure *cis* and *trans* olefin. *cis–trans* isomer assignments for the olefins were based on J_{F,CF_3} or $J_{H,F}$.

To determine the effect solvent had on reaction yields and *cis/trans* ratios, a variety of dipolar aprotic solvents was studied, using trifluoroacetophenone as a model ketone. The results are summarized in Table IV. As the results of this table illustrate, the *cis/trans*

TABLE IV

EFFECT OF SOLVENTS ON THE REACTION OF TRIFLUOROACETOPHENONE WITH TRIPHENYLPHOSPHINE AND SODIUM DICHLOROFLUOROACETATE AT 90°

Solvent	Time, min[a]	Yield, % Carbon dioxide	Yield, % Olefin[b]	A/B ratio[c]
Dimethylformamide	21	100	20	55/45
N-Methyl-2-pyrrolidone	23	77	20	54/46
Monoglyme	281	88	27	54/46
Diglyme	135	88	54	55/45
Triglyme	90	86	56	53/47
Dimethyl sulfoxide[d]				

[a] Time required for the maximum amount of carbon dioxide to be evolved. [b] Glpc yield based on starting ketone. [c] This was the *cis/trans* ratio of product afforded from the olefination reaction; A = $\frac{C_6H_5}{CF_3}>C=C<\frac{Cl}{F}$, B = $\frac{C_6H_5}{CF_3}>C=C<\frac{F}{Cl}$. [d] Rapid evolution of dimethyl sulfide precluded any further measurements.

isomer ratios are not affected by a change in solvent.[13] When dimethyl sulfoxide was used as the solvent for the reaction, a competing side reaction took place, which produced dimethyl sulfide [isolated as its mercuric chloride adduct, $2(CH_3)_2S$–$3HgCl_2$[14]]. Heating a solution of sodium dichlorofluoroacetate in dimethyl sulfoxide also caused evolution of dimethyl sulfide.

Several workers have claimed that addition of lithium ion or iodide ion to a Wittig reaction mixture has a noticeable effect on the *cis/trans* ratio of the product.[15–17] However, others have disputed this claim.[18,19] In this work the product *cis/trans* ratio was not significantly affected when the reaction with trifluoroacetophenone was carried out in the presence of lithium ion (as $CFCl_2CO_2Li$) or in the presence of iodide ion (as NaI); the isomer ratio in the presence of lithium ion was 51/49, and in the presence of iodide ion was 54/46.

However, an increase in the size of the perfluoroalkyl group did affect the *cis/trans* isomer ratio. When trifluoroacetophenone was allowed to react with the chlorofluoromethylene ylide, 53% of the product was the isomer bearing the phenyl and chlorine groups *cis*, and with pentafluoropropiophenone the percentage of the corresponding isomer increased to 59%. The substitution of an aliphatic group for an aromatic group also had an effect on the *cis/trans* isomer ratio, but in the opposite direction. When a cyclohexyl group was substituted for a phenyl group, the percentage of the corresponding isomer decreased to 42%. A butyl or a benzyl group had less effect in this respect. *para* substituents on the aromatic ring had little effect on the product *cis/trans* isomer ratio. When an aldehyde was allowed to react with the chlorofluoromethylene ylide, the less sterically favored isomer was formed in greater amounts. For example, 56% of the chlorofluoro olefin from the reaction of benzaldehyde with the chlorofluoromethylene ylide was the olefin bearing the phenyl and chlorine groups *cis*. With valeraldehyde, the percentage of the corresponding isomer was 61%. This anomaly is rationalized by assuming hydrogen bonding between the aldehydic proton and the ylide fluorine in the betaine-forming step, thus producing more of the betaine that yields the less sterically favored *cis* isomer upon decomposition into chlorofluoro olefin and triphenylphosphine oxide. Ando and coworkers have also carried out the reaction of benzaldehyde with the chlorofluoromethylene ylide. Their

(13) Although we have found no solvent effects in the reaction of the fluorochloro ylide generated *via* sodium dichlorofluoroacetate, Ando and coworkers[10] have found that, when the ylide is generated from methyl dichlorofluoroacetate, the *cis/trans* product ratios do vary with the polarity of the solvent.

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TABLE V

COMPARISON OF DECARBOXYLATION[a] AND BASE PLUS HALOFORM[b] METHODS OF YLIDE GENERATION

Starting ketone	Decarboxy[c] yield, %	Base[c] yield, %	Decarboxy[d] A/B ratio	Base[d] A/B ratio
Benzaldehyde	49	39	56/44	56/44
Trifluoroacetophenone	56	31	53/47	52/48
Cyclopentanone	9	27		
Cyclopentanone[e]	23	0		
Benzophenone	0	0		

[a] Decarboxylation method: $(C_6H_5)_3P + CFCl_2CO_2Na \longrightarrow (C_6H_5)_3P{=}CFCl + CO_2 + NaCl$. [b] Base + haloform method: $(C_6H_5)_3P + CHFCl_2 + t\text{-BuOK} \longrightarrow (C_6H_5)_3P{=}CFCl + t\text{-BuOH} + KCl$. [c] Glpc yield based on starting ketone. [d] This was the *cis/trans* ratio of product afforded from the olefination reaction, A = $\frac{C_6H_5}{CF_3(H)}{>}C{=}C{<}^{Cl}_{F}$, B = $\frac{C_6H_5}{CF_3(H)}{>}C{=}C{<}^{F}_{Cl}$. [e] Tri-*n*-octylphosphine substituted for triphenylphosphine.

results indicated that 56% of the chlorofluoro olefin from the reaction was the isomer bearing the phenyl and chlorine groups *trans*, just the opposite of our results. We are unable at present to account for this disparity between our results and theirs.

The reaction of dichlorofluoromethane with potassium *t*-butoxide and triphenylphosphine as an alternate route to the chlorofluoromethylene ylide was also investigated. Briefly, the procedure used was to add dichlorofluoromethane to a slurry of potassium *t*-butoxide and triphenylphosphine in heptane at 0°. Then the desired carbonyl compound was added. The ratio of reactants was formally the same as that used in the decarboxylation method of ylide generation previously described. The resulting mixture was stirred for several hours at room temperature, then subjected to product separation. Product yields and isomer ratios were determined by glpc analysis. The results obtained from this method of ylide generation are compared with the decarboxylation method of ylide generation in Table V. The results in this table illustrate that reaction temperature and changes in solvent have no influence on the *cis/trans* ratio of product. These data also demonstrate that the decarboxylation method used in conjunction with aldehydes and reactive (polyfluorinated) ketones generally enables somewhat higher yields of olefins. With unreactive ketones, such as cyclopentanone, the reactivity and stability of the intermediate ylide become more important. At the higher reaction temperature of the decarboxylation method of ylide generation, most of the ylide decomposes before reaction with the unreactive carbonyl species. At the lower temperature of the haloform and base method of ylide generation, however, the ylide is more stable, and hence reaction even with an unreactive carbonyl compound gives a higher yield of olefin. Although the ylide (from sodium dichlorofluoroacetate) decomposes at the higher temperature, rapid cooling and addition of a reactive carbonyl component showed that a reasonable amount of ylide still remained, since a 36% yield of product was obtained when trifluoroacetophenone was added to the reaction mixture of triphenylphosphine and sodium dichlorofluoroacetate in triglyme after carbon dioxide evolution had ceased. When tri-*n*-butylphosphine was substituted for triphenylphosphine, a more reactive chlorofluoromethylene ylide was formed. For example, a 25% yield of chlorofluoro olefin was obtained with cyclopentanone when tri-*n*-butylphosphine was substituted for triphenylphosphine in the decarboxylation method of ylide generation. However, this alkyl ylide is much less stable. When cyclopentanone was added to the reaction mixture of *tri-n*-butylphosphine and sodium dichlorofluoroacetate in triglyme (85°) after all carbon dioxide evolution, no chlorofluoroolefin was obtained. Similarly, no chlorofluoro olefin was obtained when cyclopentanone was added to the reaction mixture of dichlorofluoromethane, potassium *t*-butoxide, and tri-*n*-butylphosphine in heptane (0°). Benzophenone failed to react under either method of chlorofluoromethylene ylide generation.[9] By increasing the ratio of chlorofluoromethylene ylide precursor (triphenylphosphine, potassium *t*-butoxide, and dichlorofluoromethane) to carbonyl compound from 1.5 to 3 to 1 in the haloform plus base method of ylide generation, the yield of chlorofluoro olefin from trifluoroacetophenone increased from 31 to 55%. Thus, the utility of the cheaper haloform method can be increased by employing a large excess of the fluorochloromethylene ylide.

The identification of the chlorofluoro olefins was based primarily on elemental analysis and infrared, ultraviolet, and proton and fluorine nmr spectroscopy. The infrared spectra of the chlorofluoro olefins always exhibited a strong >C=CFCl absorption between 5.97 and 6.05 μ. The position at which the >C=CFCl absorption occurred in any pair of *cis–trans* isomers differed by 0.05 μ or less.

The ultraviolet spectra of the β-aryl substituted 1-chloroperfluoro olefins exhibited a decrease in extinction coefficient between cyclohexane and ethanol. The $\pi \rightarrow \pi^*$ primary absorption band in the *para*-substituted 2-phenyl-1-chloroperfluoro olefins showed an increasing wavelength value in the following order: p-CH_3O > p-CH_3 > p-H > p-F. In the homologous 2-phenyl-1-chloroperfluoropropene, butene, and pentene series, the value of the absorption maxima and extinction coefficient decreased with increasing perfluoroalkyl group size in the order $CF_3 > C_2F_5 > n\text{-}C_3F_7$. Apparently, the larger the perfluoroalkyl group, the more the phenyl ring was twisted out of conjugation with the double bond, lowering both the wavelength and the extinction coefficient.

In any given pair of *cis–trans* isomers, both the absorption maxima and the extinction coefficient were larger in the isomer bearing the aryl and chlorine groups in a *trans* configuration than in the isomer bearing the aryl and chlorine groups *cis*. This effect could be rationalized in terms of steric crowding between the aromatic ring and the chlorine atom. When the phenyl and chlorine groups occupied *cis* positions, the phenyl ring was twisted out of conjugation to a greater extent with the double bond than when the phenyl and chlorine groups occupied *trans* positions.

The fluorine nmr data were also consistent for the assigned structures of the β-substituted 1-chloroperfluoro olefins, and were used to assign the configurations of the *cis* and *trans* isomers on the basis of the F,CF_3 or F,CF_2X coupling constants across the double bond (see Table VI). The *trans* F,CF_3 or F,CF_2X (X = CF_3, C_2F_5, or Cl) coupling constants ranged from 7 to 13 cps. Both Stone[20] and Swalen[21] have reported coupling constants of 21–24 and 9–12 cps for the respective *cis* and *trans* F,CF_3 coupling constants in α-substituted perfluoropropenes.

TABLE VI

FLUORINE NMR[a] SPECTRAL DATA OF β-SUBSTITUTED 1-CHLOROPERFLUORO OLEFINS

$AR(R)C(CF_2X)_1{=}_2CFCl$

AR(R)	X	Isomer[b]	$J_{1,2}$	ϕ_1	ϕ_2
C_6H_5	F	A	24	64.1	59.0
		B	13	61.7	59.0
p-ClC_6H_4	F	A	24	62.8	59.0
		B	13	60.5	59.2
p-$CH_3OC_6H_4$	F	A4	24	64.2	59.4
		B	13	62.4	59.3
p-FC_6H_4[c]	F	A	24	63.2	59.1
		B	13	61.5	59.3
p-$CH_3C_6H_4$	F	A	24	64.3	59.4
		B	13	62.2	59.2
C_6H_{11}	F	A	26	64.6	57.3
		B	12	64.5	59.7
n-C_4H_9	F	A	21	65.8	61.1
		B	12	68.0	60.2
C_6H_5	Cl	A	31	63.3	46.1
		B	12	63.4	46.2
C_6H_5	CF_3	A	27	60.9	108.8
		B	7	52.8	109.5
C_6H_5	C_2F_5	A	28	58.7	105.2
		B	8	51.9	106.3

[a] The chemical shift values are expressed in ϕ (parts per million) values upfield from CCl_3F and the coupling constant values are in cycles per second. [b] A = $\frac{AR(R)}{XF_2C}{>}C{=}C{<}\frac{Cl}{F}$, B = $\frac{AR(R)}{XF_2C}{>}C{=}C{<}\frac{F}{Cl}$. [c] Isomer A or B: aromatic F = +110.0ϕ.

Mechanism for Chlorofluoromethylene Ylide Formation from Sodium Dichlorofluoroacetate and Triphenylphosphine.—Several plausible mechanisms can be envisioned to explain the formation of the chlorofluoromethylene ylide from triphenylphosphine and sodium dichlorofluoroacetate. One possibility involves prior decomposition of sodium dichlorofluoroacetate to form chlorofluorocarbene, which then reacts with triphenylphosphine to form the chlorofluoromethylene ylide. In another possibility, sodium dichlorofluoroacetate reacts with triphenylphosphine to form a phosphobetaine salt, such as $(C_6H_5)_3P^+CFClCO_2^-$, before losing carbon dioxide to form the chlorofluoromethylene ylide. When sodium dichlorofluoroacetate was allowed to decarboxylate in the presence of tetramethylene, a 37% yield of the corresponding chlorofluorocyclopropane adduct was produced. When a similar decarboxylation was carried out in the presence of equimolar amounts of triphenylphosphine and tetramethylethylene, no cyclopropane adduct was formed. Either triphenylphosphine is a better trapping agent for the chlorofluorocarbene, or triphenylphosphine reacts with the fluorochloroacetate to form the phosphobetaine salt discussed above. To evaluate this former possibility, the chlorofluoromethylene ylide was generated *via* the reaction of dichlorofluoromethane with potassium *t*-butoxide in the presence of equimolar amounts of tetramethylethylene and triphenylphosphine. Subsequently, trifluoroacetophenone was added to the reaction mixture. After work-up, glpc analysis showed a 14% yield of the cyclopropane adduct and a 19% yield of $C_6H_5C(CF_3){=}CFCl$. These results indicate that triphenylphosphine and tetramethylethylene are of comparable ability as trapping agents for the chlorofluorocarbene. Consequently, the absence of cyclopropane formation, when sodium dichlorofluoroacetate was decarboxylated in the presence of equivalent amounts of triphenylphosphine and tetramethylethylene, lends support to the phosphobetaine salt $(C_6H_5)_3P^+CFClCO_2^-$ as the precursor to the chlorofluoromethylene ylide in the decarboxylation method of ylide generation. Evidence for the formation of similar phosphobetaine salts has been observed by Denney[22] in the corresponding hydrocarbon analogs, $(C_6H_5)_3P^+(CH_2)_nCO_2^-$, n = 2, 3. These salts could not be isolated in the case where n was equal to 1. Similarly, the analogous fluorinated salt, $(C_6H_5)_3P^+CFClCO_2^-$, could not be isolated.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer using a neat film of sample, and calibrated *vs.* a 0.07-mm polystyrene film. Ultraviolet spectra were obtained on a Beckman DK-2A recording spectrophotometer, using both cyclohexane and ethanol as solvents. Proton nmr spectra were obtained on a Varian A-60 spectrometer and are reported in δ values downfield from an internal standard of tetramethylsilane. Fluorine nmr spectra were obtained on a Varian HA-100 spectrometer at 94.1 Mcps and are reported in ϕ values upfield from an internal standard of trichlorofluoromethane. Glpc analyses were obtained on an F & M Model 720 dual column gas chromatograph using helium as a carrier gas. Product yields were determined from comparison of the relative areas under peaks to areas due to external standards of the same compounds. Column A was a 6 ft × 0.25 in. i.d. copper column packed with 10% w/w silicone rubber supported on 100–120 mesh Gas-Chrom P. Column B was a 6 ft × 0.25 in. i.d. copper column packed with 10% w/w Carbowax 20M supported on 80–100 mesh Chromosorb P. Column C was a 10 ft × 0.50 in. i.d. copper column packed with 20% w/w DC-QF-1 fluorosilicone rubber supported on 80–100 mesh Chromosorb P. Carbon and hydrogen analyses were obtained in this laboratory, and fluorine and chlorine analyses were carried out by Schwarzkopf Analytical Laboratories in Woodside, N. Y.

Sodium Dichlorofluoroacetate.—Sodium dichlorofluoroacetate was prepared by the careful neutralization of 80 g (0.54 mol) of dichlorofluoroacetic acid in 150 ml of ether with 29 g (0.27 mol) of anhydrous sodium carbonate, with subsequent removal of the ether and water under reduced pressure, then heating overnight at reduced pressure (*ca.* 4 mm or lower) at 50°. Lithium dichlorofluoroacetate was prepared in a similar manner.

Polyfluorinated Ketones.—The polyfluorinated ketones used in this study were prepared by the method of Dishart and Levine.[12] A good example of this type of synthesis is described elsewhere.[23]

General Method for the Synthesis of 1-Chlorofluoro Olefins.—The reaction apparatus employed consisted of a three-necked

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round-bottomed flask equipped with a magnetic stirrer, a nitrogen inlet tube, and a reflux condenser equipped with a nitrogen outlet leading to a mercury bubbler and a Dry Ice cooled trap. For small-scale reactions, the pressure-equalized dropping funnel was deleted from the apparatus.

A typical preparative-scale reaction using the synthesis of 2-(*p*-chlorophenyl)-1-chloroperfluoropropene, *p*-$ClC_6H_4C(CF_3)$=CFCl, as an example proceeded as follows. Into a 500-ml three-necked flask, equipped in the manner previously described, were placed 100 ml of triglyme, 80 g (0.3 mol) of triphenylphosphine, and 4.16 g (0.2 mol) of *p*-chlorotrifluoroacetophenone. The reaction mixture was heated to 90° and approximately one-quarter of a solution of 51 g (0.3 mol) of sodium dichlorofluoroacetate in 70 ml of triglyme was added to the reaction mixture. Once the reaction mixture had turned to a dark red or black color, the remaining three-quarters of the solution was added dropwise and the resulting mixture was allowed to stir overnight at 90°. The reaction mixture was then subjected to flash distillation. The distillate was poured into 400 ml of water and the resulting mixture extracted twice with 200-ml portions of ether. The combined ether extracts were washed five times with 200-ml portions of water, dried over anhydrous magnesium sulfate, and diluted to 250 ml with ether. Product yield determined by glpc analysis of the solution on column A indicated a 53% yield of olefin, based on starting ketone, and the absence of starting ketone. If any starting ketone was present it could be readily removed by stirring the ether extract over 100 ml of an aqueous 10% sodium hydroxide solution. The *cis/trans* ratio of product was determined on column B. The configurations of both isomers were determined by the fluorine nmr spectra (see Results and Discussion). Concentration of the ether solution, followed by distillation at reduced pressure yielded 21.5 g (42%) of pure *cis–trans* olefin, bp 88° (15 mm). Pure *cis* and *trans* olefin were obtained by distillation of the *cis–trans* isomer mixture through a 24-in. Nester–Faust Teflon spinning-band column with a reflux ratio of 25:1. Since the lower boiling isomer was still contaminated with about 4% higher boiling isomer after distillation, it was further purified by preparative glpc using column C.

Solvent Study.—The apparatus and general experimental procedure were the same as previously described. A 50-ml three-necked flask was substituted for the 500-ml three-necked flask, and all the reagents were placed in the flask. The reactants were triphenylphosphine, sodium dichlorofluoroacetate, and trifluoroacetophenone in a molar ratio of 1.5:1.5:1, respectively. The rate of decarboxylation and the total amount of carbon dioxide evolved were obtained by collection of the liberated carbon dioxide over water previously saturated with carbon dioxide.

Reaction of Triphenylphosphine, Sodium Dichlorofluoroacetate, and Tetramethylethylene in Triglyme at 70°.—A mixture consisting of 6.4 g (0.037 mol) of sodium dichlorofluoroacetate, 9.8 g (0.037 mol) of triphenylphosphine, and 3.1 g (0.037 mol) of tetramethylethylene in 20 ml of triglyme was heated at 70° until carbon dioxide evolution had ceased. Flash distillation of the volatile material into a Dry Ice cooled receiver, followed by glpc analysis of the distillate on column A showed the absence of any cyclopropane derivative. From the reaction, 3.0 g (97%) of the tetramethylethylene was recovered.

A control reaction consisting of a solution of 25 g (0.3 mol) of tetramethylethylene and 34 g (0.2 mol) of sodium dichlorofluoroacetate in 100 ml of triglyme heated overnight at 70° gave the corresponding chlorofluorocyclopropane adduct in a 37% yield. The proton nmr spectrum of the compound showed a doublet at δ 1.13 (J_{F,CF_3} = 2.0 cps).[24]

Anal. Calcd for $C_7H_{12}ClF$: C, 55.81; H, 7.97. Found: C, 55.74; H, 7.69.

A third reaction was carried out consisting of 50 ml of dry diethyl ether, 9.8 g (0.037 mol) of triphenylphosphine, 4.3 g (0.037 mol) of potassium *t*-butoxide, and 3.4 g (0.040 mol) of tetramethylethylene. The resulting mixture was cooled in an ice bath and 5.0 g (0.040 mol) of dichlorofluoromethane was added. Then 4.0 g (0.025 mole) of trifluoroacetophenone was added. Flash distillation of the volatile material into a Dry Ice cooled receiver, followed by glpc analysis of the distillate on column A showed a 14% yield of the cyclopropane adduct and a 19% yield of $C_6H_5C(CF_3)$=CFCl.

Preparation of the Chlorofluoromethylene Ylide *via* Triphenylphosphine, Dichlorofluoromethane, and Potassium *t*-Butoxide.—The reaction apparatus employed consisted of a 100-ml three-necked round-bottomed flask equipped with a nitrogen inlet, magnetic stirrer, rubber septum, and a Dry Ice condenser fitted with an inlet near the bottom for the introduction of condensable gases and an outlet at the top leading to a mercury bubbler, and a Dry Ice cooled trap.

Into the reaction apparatus were placed 65 ml of heptane, 4.3 g (0.038 mol) of potassium *t*-butoxide, and 9.8 g (0.037 mol) of triphenylphosphine. The resulting slurry was cooled in an ice bath, a slow flow of nitrogen started, and 5 g (0.040 mol) of dichlorofluoromethane was added *via* the gas inlet at the bottom of the Dry Ice condenser. When the gas came into contact with the Dry Ice cooled cold finger in the center of the condenser, it liquified and dripped into the reaction mixture in much the same fashion as a liquid added from a dropping funnel. As the dichlorofluoromethane was added, the color of the reaction mixture turned from yellow to orange to brown. Ten minutes after all of the dichlorofluoromethane was added, 4 g (0.025 mol) of trifluoroacetophenone was added. The resulting mixture was stirred overnight at room temperature, then flash distilled into a Dry Ice cooled receiver at a reduced pressure of 4 mm (or lower if possible) and an oil-bath temperature of 130°. Glpc analysis of the distillate on column A showed a 31% yield of $C_6H_5C(CF_3)$=CFCl. When the amount of solvent was increased to 100 ml, and the amounts of triphenylphosphine, potassium *t*-butoxide, and dichlorofluoromethane were doubled, the yield of $C_6H_5C(CF_3)$=CFCl was increased to 55%.

Acknowledgment.—This work was supported in part by the Public Health Service (GM 11809 and CA 10745).

(24) Reported for 1-chlorofluorotetramethylcyclopropane, doublet at δ 1.13 (J_{F,CH_3} = 2.0 cps): R. A. Moss and R. Gerstl, *Tetrahedron*, **23**, 2549 (1967).

Methanesulfenyl Chloride. VI. A Stereochemical Study of Certain Organosulfur Reactions[1]

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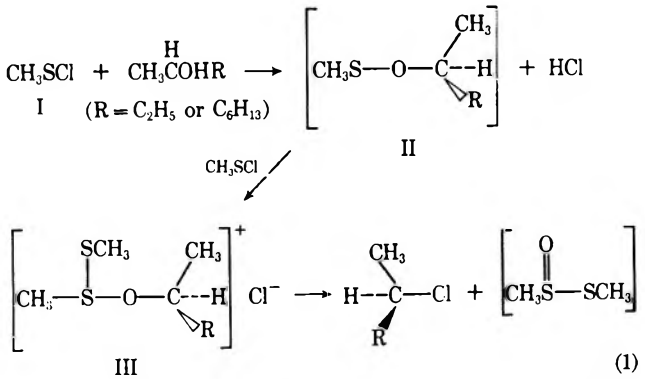
The reaction of methanesulfenyl chloride (I) with optically active 2-octanol or 2-butanol, and with the methyl xanthates, $CH_3SC(S)OR$, or methanesulfinate esters, $CH_3S(O)OR$, containing these optically active groups resulted in the formation of 2-octyl or 2-butyl chlorides of predominantly inverted configuration. The reaction of methylsulfur trichloride with the same optically active alcohols produced alkyl chlorides with a high degree of inversion. The alkyl chlorides formed when chlorine reacts with the 2-octyl or 2-butyl methanesulfinate esters showed a lower degree of inversion (greater racemization) than those formed in the other reaction. Evidence is presented that in the reaction of I with sulfinate esters, RS(O)OR′, electrophilic attack can occur at either the alkoxide or sulfoxide oxygen atoms or at the sulfur atom. When R′ is methyl, reaction appears to occur chiefly at the alkoxide oxygen but as R′ becomes more bulky attack at the alkoxide oxygen is inhibited and the predominant reaction is at the sulfur atom.

In previous papers from this laboratory we reported that methyl chloride is formed when methanesulfenyl chloride, CH_3SCl (I), reacts with S-alkyl O-methylxanthate[2] or with methanol,[3,4] when methylsulfur trichloride reacts with methanol,[5] and when chlorine reacts with methyl methanesulfinate.[6] It seemed of interest to reexamine these reactions using optically active 2-octanol and 2-butanol, and optically active compounds containing octyl and butyl groups, to determine if the results would shed light on the mechanism by which the alkyl halide is formed.

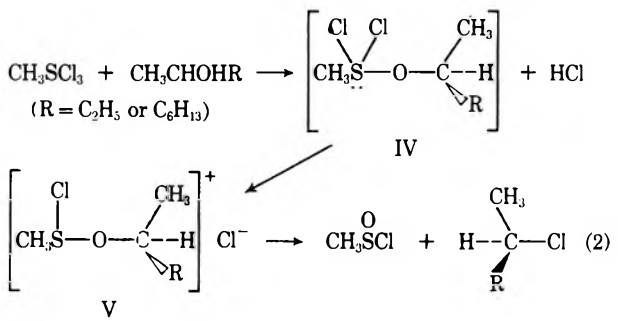
In most cases the reactions took place with predominant inversion of the optically active groups, suggesting typical nucleophilic displacement at carbon by chloride ion in the product-forming step. A higher degree of racemization in some cases can be explained in terms of inductive effects which weaken the carbon–oxygen bond and facilitate the separation of a carbonium ion.

The reaction of methanesulfenyl chloride (I) with methanol was reported earlier to yield a complex mixture of six different organic compounds, the formation of which has been explained by a sequence of reactions,[4] the correctness of which has been supported by additional work in our laboratory. On the basis of the previously postulated reaction steps and the inverted configuration of the alkyl chlorides isolated (2-butyl, 89–95%, and 2-octyl, 55–72%), the formation of alkyl chlorides in the reaction of I with 2-butanol and 2-octanol appears chiefly to proceed as shown in eq 1.



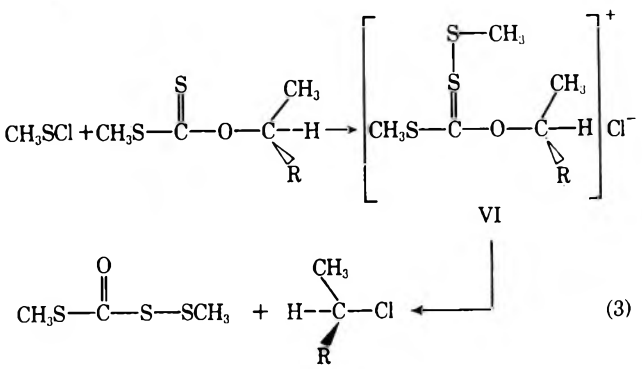
(1)

The alcoholysis of methylsulfur trichloride to produce methanesulfinyl chloride and alkyl chlorides[5] produced the latter with high degrees of inversion (2-butyl, 92%, and 2-octyl, 61–73%). Following the previously proposed mechanistic pathway,[7] eq 2 shows how this reaction is believed to occur.



(2)

The reaction of I with S-methyl O-alkyl dithiocarbonates (xanthates) showed predominant inversion of the alkyl group but also gave some evidence for a solvent effect. The sequence of reactions previously postulated[3] and supported in the present study, together with the stereochemical explanation for the inversion (2-butyl, 66–81%, and 2-octyl, 57–89%) is shown in eq 3.



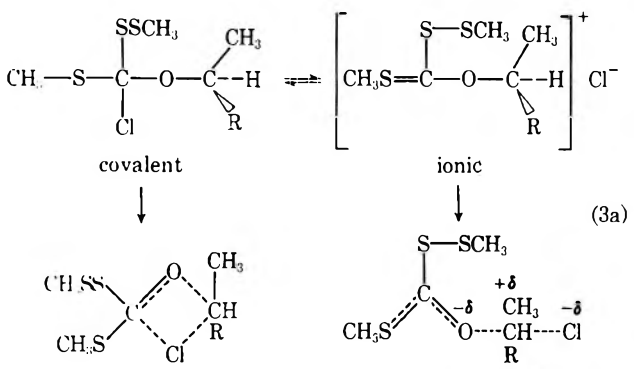
(3)

The degree of inversion appeared to be somewhat solvent dependent in the reaction of I with methyl 2-butylxanthate. When the reaction was carried out in carbon tetrachloride the 2-butyl chloride formed

(1) Taken from the M.S. and Ph.D. Theses of R. V. Norton, University of Maine, 1965 and 1967, and D. A. Koop, University of Maine, 1969 and 1962; M.S. Thesis of P. M. Cocanour, University of Maine, 1969.
(2) I. B. Douglass and W. J. Evers, *J. Org. Chem.*, **29**, 419 (1964).
(3) I. B. Douglass, *ibid.*, **24**, 2004 (1959).
(4) I. B. Douglass and D. A. Koop, *ibid.*, **27**, 1398 (1962).
(5) I. B. Douglass and D. R. Poole, *ibid.*, **22**, 536 (1957).
(6) I. B. Douglass, *ibid.*, **30**, 633 (1965).
(7) I. B. Douglass and R. V. Norton, *ibid.*, **33**, 2104 (1968).

showed 66–69% inversion. In dioxane the inversion was 80–81%. These results suggest that dioxane, the more polar solvent, has a stabilizing influence on the ionic intermediate VI retarding its tendency to dissociate into a carbonium ion and holding the ion intact until the 2-butyl group is removed in an S_N2 type of reaction.

Dr. Harold Kwart, in a private communication, has suggested that the different degrees of inversion obtained in nonionizing and polar solvents may be due to different transition states resulting from the covalent and ionic forms of intermediate VI (eq 3a). No such

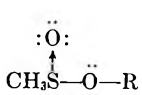


(3a)

solvent effect could be detected in the case of methyl 2-octylxanthate. Although the reaction was carried out in dioxane, ether, chloroform, and carbon tetrachloride using different solvent volumes and molar ratios of reactants, the variation in degree of inversion (50–89%) showed no significant pattern and seemed to result from some unidentified and uncontrolled factor.

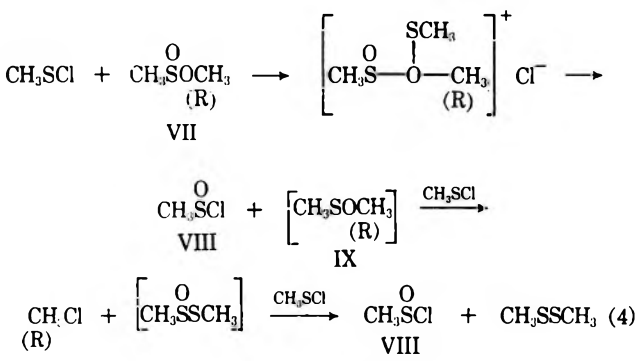
The reaction of I with alkyl methanesulfinates has special interest. The formation of methyl methanesulfinate, $CH_3S(O)OCH_3$ (VII), was reported earlier[4] to be part of the sequence of reactions taking place when I and methanol are brought together. In a previous paper[4] we reported that, when I and VII are caused to react in the absence of other reagents, the products include methyl chloride (26 mol %), methyl disulfide (29 mol %), methanesulfonyl chloride (17 mol %), methanesulfinyl chloride (23 mol %), and methyl methanethiolsulfonate, $CH_3SO_2SCH_3$ (5 mol %), with all products representing a total yield of 71%. In our previous paper we referred to the initial reaction as resulting in an "addition complex." We are now convinced that the "addition complex" may have several forms depending on where in the sulfinate ester molecule the initial attack by I occurs.

The sulfinate ester



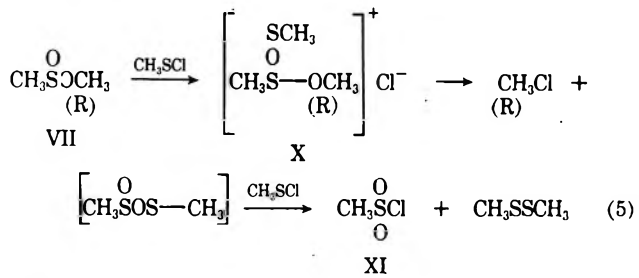
contains three types of unshared electron pairs, one type on the sulfur atom, another type on the sulfoxide oxygen atom, and a third type on the alkoxide oxygen. Since I is an electrophilic reagent it may be expected to attack the unshared pair most available.

If attack occurs on the alkoxide moiety, the reaction would proceed as shown in eq 4 with 2 mol of methanesulfinyl chloride (VIII) being formed as 3 mol of I are consumed in the reaction sequence. If attack occurs



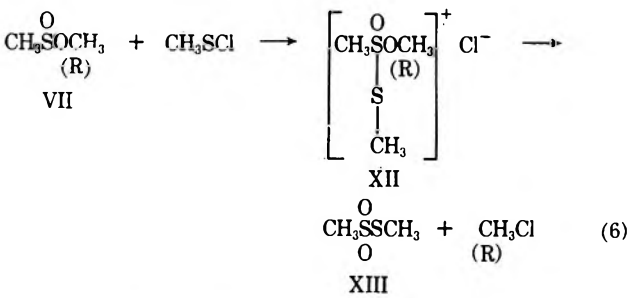
(4)

at the sulfoxide oxygen, however, the reaction might take place as shown in eq 5 with 1 mol of methanesulfonyl chloride (XI) being formed with simultaneous consumption of 2 mol of I.



(5)

If electrophilic attack by I occurred at the sulfur atom, the products would be methyl methanethiolsulfonate as shown in eq 6. When the reaction of I with



(6)

sulfinate esters was first studied[3] it was anticipated that electrophilic attack would occur primarily at the sulfur. The finding of a sulfonyl chloride instead of a thiolsulfonate, however, led us to believe that reaction occurred at an oxygen atom.

In the study referred to above[4] we observed that the reaction of various esters with different sulfenyl chlorides gave varying proportions of sulfinyl and sulfonyl chlorides. One of us[8] attempted, with only partial success because of the experimental problems involved, to demonstrate the steric influence of R and R′ groups of different sizes in the reaction of I with esters R′O-S(O)R. Table I shows the results obtained. The only conclusion which could be drawn was that with bulky groups there was greater tendency for the reaction to favor sulfonyl chloride formation and, presumably, sulfoxide attack.

More recently we have found that nuclear magnetic resonance (nmr) spectroscopy affords a convenient

(8) D. A. Koop, Ph.D. Thesis, University of Maine, 1962.

TABLE I

THE REACTION OF CH_3SCl WITH SULFINATE ESTERS RSOR' (molar ratio of CH_3SCl/ester = 2)

R	R'	Mol of RSO_2Cl formed	Mol of RSOOR' used	Molar ratio[a] of RSO_2Cl/ RS(O)OR'
Me	Me	0.04	0.12	0.3
Me	Et	0.03	0.11	0.3
Me	Pr	0.06	0.25	0.2
Et	Me	0.04	0.17	0.2
Et	Et	0.05	0.12	0.4
Et	Pr	0.08	0.17	0.5
2-Pr	Et	0.07	0.11	0.6
2-Pr	Pr	0.12	0.14	0.9

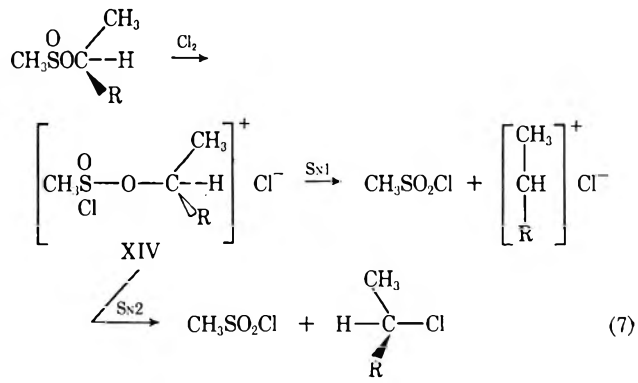
[a] The ratios listed are equivalent to the per cent of the ester which reacts by attack at the sulfoxide oxygen. The results are not entirely consistent with the more accurately determined values shown in Table II, partly as a result of the inherent difficulty of determining the sulfonyl chloride content in a mixture of disulfide, sulfinyl chloride, thiolsulfonate, alkyl halide, unreacted ester, and spontaneous decomposition products of methanesulfenyl chloride.

means for identifying individual components of complex mixtures of organosulfur compounds. The chemical shift for CH_3SOCl (VIII) is a sharp singlet at δ 3.37, that for CH_3SO_2Cl (XI) is at δ 3.61, that for $CH_3SO_2SCH_3$ is at δ 3.28, and that for $CH_3SO_2SCH_3$ is at δ 2.69 with no interference from other signals in the mixtures studied. Table II shows the results obtained when various alkyl methanesulfinates were treated with I. The molar ratio of products formed was obtained by integrating the relative δ responses of the different types of methyl groups in the nmr spectra of the crude reaction mixtures.

The nmr spectra used in obtaining the data for Table II clearly showed that CH_3SO_2Cl, CH_3SOCl, and $CH_3SO_2SCH_3$ are all formed. On the assumption that the mechanisms outlined in eq 4, 5, and 6 are correct, the results indicate that electrophilic attack by I occurs to varying degrees at all available electron pairs. As the group R in the ester $CH_3S(O)OR$ becomes more bulky, electrophilic attack at the alkoxide oxygen is inhibited. The available data do not indicate what factors influence preferential attack at the sulfoxide oxygen or at the sulfur. We can offer no explanation for the fact that in the case of the ethyl ester, attack at the sulfoxide oxygen is greatly favored.

Other stereochemical effects were observed in the reactions of I with 2-butyl methanesulfinate. In duplicate experiments the 2-butyl chloride formed was found to have 80% inversion, a value lower than that obtained when I reacts with 2-butanol. Although an examination of eq 1 and 4 would suggest that the 2-butyl chloride produced in each should have the same degree of rotation (intermediates II and IX are identical), it must be realized that the reaction of I with a sulfinate ester also involved eq 5 and 6. The 2-butyl chloride isolated, therefore, has been formed in three different ways and the observed rotation is a net effect.

The reaction of sulfinate esters with chlorine produced alkyl halides significantly lower in their degree of inversion than any of the reactions described above, 54–56% in the case of 2-butyl and 19–37% in the case of 2-octyl. The postulated course of the reaction is shown in eq 7.



The relatively high degree of racemization suggests that inductive forces in the ionic intermediate XIV facilitate the separation of a carbonium ion which, on combining with chloride ion, formed racemized alkyl halide.

Without clearer evidence for the existence of the postulated ionic intermediates which decompose in the alkyl chloride-forming steps, one is not justified in attempting a full explanation for the differences in degree of inversion observed in the different reactions. If one compares the structures of III, V, X, and XIV, however, interesting structural differences appear. All the structures are alike except for different atoms or groups attached to the common sulfur atom of the CH_3–S–O–C chain (III, SCH_3; V, Cl; X, O-SCH_3; XIV, O and Cl). If one assumes that these intermediates actually exist and react to form the alkyl halides, one is tempted to compare their structures for indications of inductive forces which could account for carbonium ion separation and racemization of the alkyl chloride. The experimental results do not show any consistent and outstanding differences in racemization of alkyl chlorides formed from III, V, and X. In the case of XIV, however, the presence of both oxygen and chlorine atoms on the sulfur, each held by a semipolar bond, leads one to expect an unusually strong inductive force which might weaken the oxygen–carbon bond facilitating carbonium ion separation. The high degree of racemization found in both the butyl chloride (44–46% racemized) and octyl chloride (63–81% racemized) is consistent with this view.

Experimental Section

All boiling points are uncorrected. Microanalyses were performed by the Schwartzkopf Microanalytical Laboratory, Woodside, N. Y. Optical rotations were determined in the early part of the study by means of an antiquated Franz Schmidt and Haensch polarimeter using a 1-dm D. C. Rudolph and Son's water-jacketed micropolarimeter cell at 25 ± 0.1°. In repeating part of the 2-octyl work and in all of the 2-butyl study, a precision polarimeter, PEPOL 60 manufactured by Bellingham and Stanley Ltd. of London, England, was employed. No serious disagreement between the values obtained with the two instruments was observed.

The resolution of 2-octanol was accomplished using the procedure developed by Kenyon.[9] After fractional crystallization of the brucine salt of 2-octyl hydrogen phthalate from acetone, the fractions were hydrolyzed and the recovered 2-octanol was distilled. In this manner (*S*)-(+)-2-octanol having $[\alpha]^{25}D$ +9.34 ± 0.18° (91% optical purity) and (*R*)-(−)-2-octanol having $[\alpha]^{25}D$ −9.21 ± 0.07° and $[\alpha]^{25}D$ −9.42 ± 0.05° (90

(9) H. Gilman and A. H. Blatt, Ed., "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1932, p 418.

TABLE II

REACTION OF CH_3SCl WITH ALKYL METHANESULFINATES, $CH_3S(O)OR$
(0.10 mol of ester, 0.02 mol of CH_3SCl)

Sulfinate ester $CH_3S(O)OR$	Products,[a] mol % CH_3SOCl eq 4	CH_3SO_2Cl eq 5	$CH_3SO_2SCH_3$ eq 6	% of attack[b] by CH_3SCl at Alkoxide oxygen eq 4	Sulfoxide oxygen eq 5	Sulfur sulfur eq 6
Methyl	58.1	13.9	28.0	41.0	19.6	39.4
	63.5	13.5	23.0	46.5	19.8	33.7
Ethyl	42.5	36.0	21.8	26.8	45.5	27.7
	42.7	34.8	22.5	27.3	44.1	28.6
	40.5	38.1	21.4	25.3	47.8	26.9
2-Propyl	17.8	28.9	53.3	9.8	31.7	58.5
	15.4	30.8	53.8	8.3	33.3	58.4
2-Butyl	6.5	35.0	58.5	3.4	36.2	60.4
	5.7	34.1	60.2	2.9	35.1	62.0
2-Octyl	0	40.0	60.0	0	40.0	60.0
	0	38.2	61.8	0	38.2	61.8

[a] The molar ratios of these three compounds were obtained by integrating the nmr spectra of crude reaction mixtures obtained on a Varian A-60 analytical spectrometer at ambient probe temperature. [b] Assuming that the moles of ester reacting at the alkoxide oxygen are equal to 0.5 of the moles of sulfinyl chloride formed (eq 4), at the sulfoxide oxygen are equal to the moles of sulfonyl chloride formed (eq 5), and at the sulfur atom are equal to the moles of thiolsulfonate formed (eq 6), the per cent reacting in each way can be calculated from the mole per cents of products as follows.

$$\% \text{ attack} = \frac{100 \times \text{mol \% of } (0.5CH_3SOCl \text{ or } CH_3SO_2Cl \text{ or } CH_3SO_2SCH_3)}{\text{mol \% of } (0.5CH_3SOCl + CH_3SO_2Cl + CH_3SO_2SCH_3)}$$

and 92% optical purity, respectively, based on a maximum rotation of $[\alpha]^{25}D \pm 10.3°$)[10] were obtained.

The preparation of (*S*)-(+)-2-butanol was carried out by the procedure of Brown.[11,12] After purification by preparative gas chromatogaphy using a Varian Aerograph Model 700 Autoprep, 2-butanol was obtained having $[\alpha]^{25}D$ +11.24° (83% optically pure) and $[\alpha]^{25}D$ 9.37° (69% optically pure) compared with $[\alpha]^{25}D \pm 13.51°$.[13]

Methanesulfenyl chloride[3] and methylsulfur trichloride[14] were prepared by methods previously described. Methanesulfinyl chloride was prepared in 88% yield by the modification of previous methods recently described.[7]

(*S*)-2-Octyl methanesulfinate was prepared by allowing 2-octanol (4.95 g, 0.038 mol, $[\alpha]^{25}D$ +9.21 ± 0.07°) to react with freshly distilled methanesulfinyl chloride (4.36 g, 0.0043 mol) at −30° under an atmosphere of dry nitrogen. After a stirring period of 1 hr at the reduced temperature the solution was allowed to stand at room temperature for several hours and then was distilled through a 9-in. Vigreux column. The resulting ester, obtained in 84% yield, boiled at 72° (0.75 mm) and had $n^{25}D$ 1.4443 and $[\alpha]^{25}D$ −31.04 ± 0.37°. It was assumed to have the same optical purity as the 2-octanol used (90%).

Anal. Calcd for $C_9H_{20}O_2S$: C, 56.29; H, 10.50; S, 16.70. Found: C, 56.48; H, 10.50; S, 16.21.

(*S*)-(+)-2-Butyl methanesulfinate was prepared in an analogous manner. Starting with 0.1 mol each of alcohol and sulfinyl chloride the product was obtained in 74% yield, boiled at 56° (11 mm), and had $n^{25}D$ 1.4214 and $[\alpha]^{25}D$ +17.87.

Anal. Calcd for $C_5H_{12}O_2S$: C, 43.19; H, 8.70; S, 23.06. Found: C, 43.54; H, 8.71; S, 23.33.

The S-methyl O-alkyl xanthates were prepared by adding sodium hydride (10.00 g, 0.262 mol) to a solution of the optically active alcohol (0.23 mol) in 50 ml of anhydrous ether contained in a three-neck flask equipped with stirrer, reflux condenser, and nitrogen-flushing system at such a rate as to maintain boiling. After 1 hr, carbon disulfide (35.2 g, 0.25 mol) was added at such a rate that the reaction could be controlled and stirring was continued an additional hour. Methyl iodide (35.2 g, 0.25 mol) was then cautiously added and gentle refluxing continued for 10 hr, following which the mixture was added to 50 ml of water. Separation of the ethereal layer, drying, and distillation at reduced pressure yielded the following product: O-(*S*)-(+)-2-butyl S-methyl dithiocarbonate, prepared from 2-butanol of 83% optical purity (81% yield), boiled at 78° (11 mm) and had $n^{25}D$ 1.5124 and $[\alpha]^{25}D$ +5.6.

Anal. Calcd for $C_6H_{12}OS_2$: C, 43.87; H, 7.36; S, 39.03. Found: C, 43.74; H, 7.55; S, 39.25.

O-(*S*)-(+)-2-Octanol S-methyl dithiocarbonate, prepared from 2-octanol of 91% optical purity (89% yield), boiled at 102° (0.4 mm) and had $n^{25}D$ 1.5065, d^{24}_4 0.988, $[\alpha]^{25}D$ −6.75.

Anal. Calcd for $C_{10}H_{20}OS_2$: C, 54.50; H, 9.15; S, 29.09. Found: C, 55.04; H, 9.20; S, 29.24.

Neither of the two compounds showed any infrared absorption in the carbonyl region and thus were free from any S,S-dialkyl isomers.

Reaction of I with Sulfinate Esters.—The reactions reported in Table II were carried out by mixing 0.01 mol of the ester to be tested with 0.02 mol of I in a test tube held at the temperature of solid carbon dioxide. Each mixture was then allowed to warm to room temperature and a small portion was diluted to a 10% concentration with spectral grade carbon tetrachloride containing 1% of tetramethylsilane. The nmr spectra of the diluted samples were determined without delay. The spectra showed proton δ signals for the alkyl halides and methyl disulfide but these signals did not interfere with those for the critical products: CH_3SOCl, δ 3.37 ppm; CH_3SO_2Cl, δ 3.61 ppm; $CH_3SO_2SCH_3$, δ 3.28 ppm; $CH_3SO_2SCH_3$, δ 2.69 ppm.

Procedure for Obtaining Optically Active Alkyl Chlorides (Table III).—In carrying out reactions with I, the optically active compound was placed in a three-necked 25-ml flask equipped with a Teflon stirrer assembly, a nitrogen-flushing system, and a septum adapter. After cooling of the stirring liquid to −20° or lower, freshly prepared I was added in one portion through the septum adapter and the mixture was stirred for 15 min.

The reactions with methylsulfur trichloride were carried out by slowly adding the alcohols to well-stirred slurries of freshly prepared methylsulfur trichloride in 25 ml of methylene chloride at approximately −30°. After the solid disappeared the reaction mixture was kept at 0° for several hours.

In the chorination experiments the optically active sulfinate esters were treated with chlorine at −50° in the absence of solvent under a nitrogen atmosphere.

The 2-octyl chloride samples were isolated by chromatographing the crude reaction mixtures on a column of Mallinckrodt 250 mesh silica gel with hexane as the initial developer, using 50 g of adsorbent per 1.5 g of reaction mixture. The 2-octyl chloride was eluted in the first 100 ml of hexane. After removal of the solvent, the residual 2-octyl chloride was identified by comparing its ir and pmr spectra with those of authentic samples.

The 2-butyl chloride was recovered by heating the crude reaction mixtures, with continued stirring to 75°, while flushing with a stream of dry nitrogen and collecting all volatile material driven off in a liquid nitrogen trap. After the volatile product was washed with water, and dried, the 2-butyl chloride was isolated by preparative gas chromatography using a Varian-Aerograph Model 700 Autoprep with 20 ft × 3/8 in. stainless steel

(10) N. Kornblum, L. Fishbein, and R. A. Smiley, *J. Amer. Chem. Soc.*, **77**, 6261 (1955).
(11) H. C. Brown and G. Zweifel, *ibid.*, **83**, 486 (1961).
(12) H. C. Brown, in *Org. React.* **13**, (1963).
(13) P. J. Leroux and H. S. Lucas, *J. Amer. Chem. Soc.*, **73**, 41 (1951).
(14) I. B. Douglass, K. R. Brower, and F. T. Martin, *ibid.*, **74**, 5770 (1952).

TABLE III

STERIC COURSE OF VARIOUS ORGANOSULFUR REACTIONS

Optically active reagent	% optical purity	Reactant	Molar ratio, reagent/ reactant	% yield, alkyl chloride	% optical purity	% inversion
S-Methyl O-(*S*)-(+)-2-octylxanthate	91	CH_3SCl	1:1	51	63	69
S-Methyl O-(*S*)-(+)-2-octylxanthate	81	CH_3SCl	4:3	26	46	57
(*R*)-(−)-2-Octanol	92	CH_3SCl	1:2	20	51	55
(*S*)-(+)-2-Octanol	91	CH_3SCl	5:4	17	66	72
(*R*)-(−)-2-Octanol	92	CH_3SCl_3	1:1	26	67	73
(*S*)-(+)-2-Octanol	91	CH_3SCl_3	1:1	31	55	61
(*S*)-(+)-2-Octyl methanesulfinate (*RS*)	91	Cl_2	1:1.3	56	17	19
(*R*)-(−)-2-Octyl methanesulfinate (*RS*)	90	Cl_2	1:1.2	43	33	37
S-Methyl O-(*S*)-(+)-2-butylxanthate (6 g, 10 ml of CCl_4)	82.2	CH_3SCl in 10 ml of CCl_4	2:3	40	54	66
S-Methyl O-(*S*)-(+)-2-butylxanthate (6 g, 10 ml of CCl_4)	82.2	CH_3SCl in 10 ml of CCl_4	2:3	35	56	69
S-Methyl O-(*S*)-(+)-2-butylxanthate (6 g, 10 ml of dioxane)	82.2	CH_3SCl in 10 ml of dioxane	2:3	20	67	81
S-Methyl O-(*S*)-(+)-2-butylxanthate (6 g, 10 ml of dioxane)	82.2	CH_3SCl in 10 ml of dioxane	2:3	20	66	80
(*S*)-(+)-2-Butanol	68.0	CH_3SCl	1:3	32	60	89
(*S*)-(+)-2-Butanol	82.2	CH_3SCl	1:3		78	95
(*S*)-(+)-2-Butyl methanesulfinate (*RS*)	68	CH_3SCl	1:1	2	54	80
(*S*)-(+)-2-Butyl methanesulfinate (*RS*)	68	CH_3SCl	1:1	5	54	80
(*S*)-(+)-2-Butanol	68	CH_3SCl_3	3:4	9	62	92
(*S*)-(+)-2-Butanol	68	CH_3SCl_3	3:4	48	63	92
(*S*)-(+)-2-Butyl methanesulfinate (*RS*)	68	Cl_2	1:1		38	56
(*S*)-(+)-2-Butyl methanesulfinate (*RS*)	68	Cl_2	1:1		37	54

column packed with 30% SE-30 on Chromosorb P and operated at 130° with a helium carrier flow rate of 150 ml/min. The exit tip was modified by fastening to it a hypodermic needle which was inserted through the septum of a sealed trap cooled in liquid nitrogen. This arrangement made it possible to collect the low-boiling 2-butyl chloride with minimal loss.

The stoichiometry of the various reactions has been discussed previously[2,4,6] and all expected products were identified in the present study. Because of the problems involved in recovering pure alkyl chlorides for polarometric analysis, the yield data reported in Table III represent only the pure material isolated rather than the maximum amount formed in the reaction. In some cases when enough alkyl chloride had been separated to determine the optical rotation no further attempt was made to isolate additional product.

Determining the Degree of Inversion.—Values for the optically pure reference compounds used in this study were as follows: 2-butanol, $[\alpha]^{25}D$ 13.51°;[13] 2-octanol, $[\alpha]^{25}D$ 10.3°;[10] 2-butyl chloride, $[\alpha]^{25}D$ 33.8°[15]; and 2-octyl chloride, $[\alpha]^{25}D$ 41.2°, the latter obtained by extrapolating data reported by Gerrard and Hudson.[16] This value for 2-octyl chloride is somewhat lower than the average of values which could be obtained by extrapolating more recent data,[17] but there is sufficient uncertainty in the actual value to make the difference insignificant.

The optical purity of the alcohols used as starting materials was determined by dividing their observed specific rotations by the values for optically pure material given above. The xanthate and methanesulfinate intermediates were assumed to have the same optical purity as the alcohols from which they were prepared. It was also assumed that the optical purity of the original alcohol set an upper limit on the optical purity of the alkyl chloride produced. Thus, multiplication of the specific rotation of optically pure 2-butyl or 2-octyl chloride by the fractional purity of the alcohol from which it was derived gave a maximum specific rotation which the chloride might have. The degree of inversion was then determined as the ratio of the observed rotation to the calculated theoretical maximum value.

Registry No.—I, 5813-48-9; (*S*)-2-octyl methanesulfinate, 24694-99-3; (*S*)-(+)-2-butyl methanesulfinate, 24694-94-8; O-(*S*)-(+)-2-butyl S-methyl dithiocarbonate, 24694-95-9; O-(*S*)-(+)-2-octanol S-methyl dithiocarbonate, 24694-96-0; (*R*)-(−)-2-octanol, 5978-70-1; (*S*)-(+)-2-octanol, 6169-06-8; (*S*)-(+)-2-octyl, methanesulfinate, 24694-99-3; (*R*)-(−)-2-octyl methanesulfinate, 24695-00-9; S-methyl O-(*S*)-(+)-2-butylxanthate, 24694-95-9; (*S*)-(+)-2-butanol, 4221-99-2; chlorine, 7782-50-5; CH_3SCl_3, 661-38-1.

Acknowledgment.—The early phase of this study was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society,

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but the major part was carried out under Grant APOO383 from the National Air Pollution Control Administration, Consumer Protection and Environmental Health Service, Public Health Service. The authors gratefully acknowledge the support given. The senior author also wishes to express his thanks to Dr. Harold Kwart for helpful suggestions during the preparation of the manuscript.

Chemistry of a Cumulated Double-Bond Compound. X. Reactions of Isocyanates and Carbodiimide with Acetylenic Compounds

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In the reaction of phenyl isocyanate with phenylacetylene in the presence of $Fe(CO)_5$, 4-benzylidene-1,3-diphenylhydantoin (**1a**) was obtained in 85% yield by the addition reaction and hydrogen shift. Oxidation of **1a** gave diphenylparabanic acid. The hydrogen transfer of acetylenic hydrogen was identified with phenylacetylene-1-*d*. The reaction of diphenylcarbodiimide with phenylacetylene in the presence of $Fe(CO)_5$ gave 4-benzylidene-1,3-diphenyl-2,5-bis(phenylimino)imidazolidine and 4-benzylidene-1,3-diphenyl-2-phenyliminoimidazolidin-5-one in 78 and 17% yields, respectively. 1,3,4-Triphenylpyrroline-2,5-dione and 1,3,4-triphenyl-5-phenyliminopyrrolin-2-one were obtained in 42 and 15% yields, respectively, in the reaction using phenyl isocyanate, diphenylacetylene, and $Fe(CO)_5$. In this reaction, hydantoin and imidazolidine were not obtained. Reaction mechanisms are discussed.

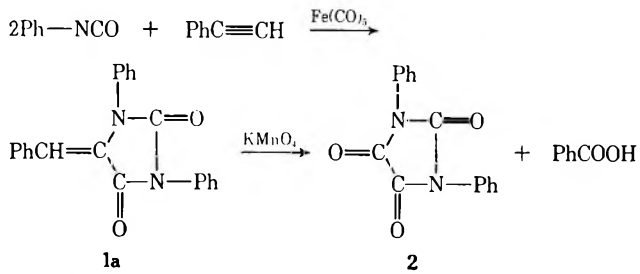
Cycloaddition reactions of heterocumulenes to olefins have been investigated in detail for a long time.[1] On the other hand, the reaction between heterocumulene and acetylenic compound has been dealt with in a few papers,[2-5] but there is no information regarding a reaction between isocyanate (or carbodiimide) and phenylacetylenes without the reaction between metal phenylacetylide and aryl isocyanates.[6-8] It was recognized in our preliminary experiments that isocyanates and carbodiimides were unreactive to acetylenic compounds without a catalyst.

It is well known that acetylenic compounds[9] and heterocumulenes[10-14] form numerous organometallic complexes with metal carbonyls. Consequently, we can expect some reaction between heterocumulenes, such as isocyanates or carbodiimides, and acetylenic compounds in the presence of metal carbonyls *via* metal complex intermediate formation.

In this paper, reactions of isocyanates and carbodiimides with acetylenic compounds in the presence of iron carbonyls are studied and some interesting results are obtained.

Results and Discussion

Reactions with Phenylacetylene.—In the reaction of phenyl isocyanate with phenylacetylene in the presence of iron pentacarbonyl at 150–160°, 4-benzylidene-1,3-diphenylhydantoin (**1a**) was obtained in 85% yield. This product seemed to be formed with 2 mol of phenyl isocyanate and 1 mol of phenylacetylene by an addition reaction and hydrogen shift. The structure of **1a** was confirmed by ir, nmr, and mass spectra, and furthermore, by oxidation of **1a** which gave diphenylparabanic acid (**2**) and benzoic acid.



1a **2**

The ir spectrum of **1a** in a Nujol mull indicated peaks at 1775, 1725, and 1650 cm^{-1}. The former two peaks were assigned to C=O stretching vibration of –CO–NR–CO– group in a five-membered ring and the latter to a C=C stretching vibration. In the mass spectrum of **1a**, the molecular ion was found at *m/e* 340 (calcd for $C_{22}H_{16}N_2O_2$: 340), and the major fragment was found at 193 which corresponded to PhCH=C=NPh resulting from **1a** by losing the –CO–NR–CO– group (calcd for $C_{14}H_{11}N$: 193). The pattern of fragmentation well explained the structure of **1a**.

The hydantoin **1a** had been prepared through different processes,[6-8] and fair agreements between the observed and reported values were obtained by melting point and ir, nmr, and mass spectra.

The hydrogen transfer of the acetylenic hydrogen of phenylacetylene was identified by the following results. The reaction using phenylacetylene-1-*d* in place of phenylacetylene gave 4-(benzylidene-*α*-*d*)-1,3-diphenylhydantoin (**1'a**) in 60% yield. The melting point of **1'a** was identical with that of hydantoin **1a**, 200°; the mixture melting point of the hydantoin **1a** and **1'a** was not depressed. The ir spectrum of the hydantoin **1'a** was identical with that of hydantoin **1a**

(1) H. Ulrich, "Cycloaddition Reactions of Heterocumulenes," Academic Press Inc., New York, N. Y., 1967, pp 45, 135.
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(3) A. G. Hortmann, *J. Amer. Chem. Soc.*, **87**, 4972 (1965).
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TABLE I.—REACTION OF PHENYL ISOCYANATE WITH PHENYLACETYLENE

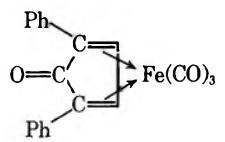
Expt no.	Reactant, mol			Solvent	Temp, °C	Time, hr	Yield, %					
	PhNCO	PhC≡CH	$Fe(CO)_5$				Hydantoin **1a**[a]	Complex **3**[b]	Isocyanurate **4**	Urea **5**[h]	Adduct **6**[a,i]	PhC≡CH[c]
1[d]	0.05	0.025	0.025		160	1.5	85			Trace	Trace	
2[e]	0.025	0.025	0.025		180	4	68	7	7	8	5	
3[e]	0.1	0.05	0.05	THF	67	6	33	Trace	20	34	Trace	50
4[e]	0.06	0.03	*f*	THF	67	6	11	4	69	16		
5[d]	0.05	0.025	*g*		180	6.5	41			24	15	40

[a] Based on PhNCO. [b] Based on PhC≡CH. [c] Unreacted. [d] PhC≡CH was added to the mixture of PhNCO and $Fe(CO)_5$. [e] PhNCO was added to the mixture of PhC≡CH and $Fe(CO)_5$. [f] $Fe_3(CO)_{12}$ (0.01 mol) was used in place of $Fe(CO)_5$. [g] Cu-C≡CPh (5 wt %) was used in place of $Fe(CO)_5$. [h] **5** is N,N′-diphenylurea. [i] **6** is the 3:1 adduct of PhNCO and PhC≡CH.

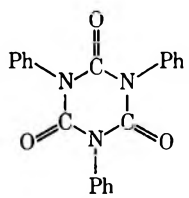
except for the absorption band of the C–D bond; the peak of C–D in-plane deformation of the hydantoin **1′a** appeared at 1250 cm^{-1}, compared with the peak of the hydantoin **1a** (1280 cm^{-1} for C–H). The mass spectrum of the hydantoin **1′a** showed the molecular ion at 341 (calcd for $C_{22}H_{15}DN_2O_2$: 341) and the major fragment corresponding to PhCD=C=NPh at 194 (calcd for $C_{14}H_{10}DN$: 194).

The results of the reaction of phenyl isocyanate and phenylacetylene with and without iron pentacarbonyl at several conditions are summarized in Table I.

In the case of addition of phenyl isocyanate to the mixture of phenylacetylene and iron pentacarbonyl, the yield of the hydantoin **1a** was relatively poor because of formation of stable iron complexes, *i.e.*, 2,5-diphenylcyclopentadienoneiron tricarbonyl (**3**). When the same reaction was carried out in tetrahydrofuran, triphenyl isocyanurate (**4**) was the major product and the yield of the hydantoin **1a** was decreased.



3



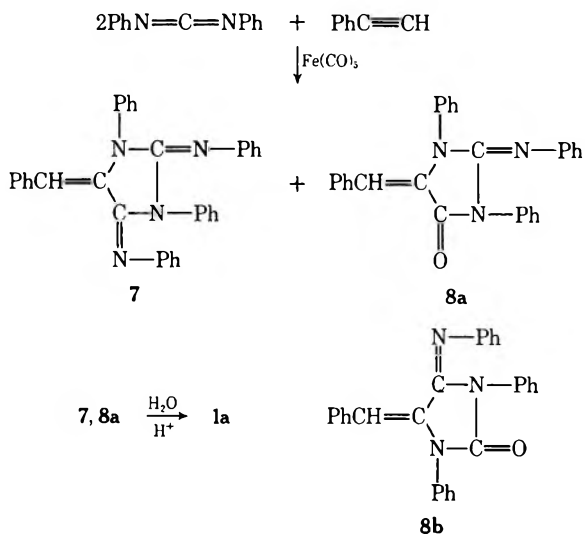
4

The reaction using triiron dodecacarbonyl in place of iron pentacarbonyl gave the hydantoin **1a** in poor yield.

A similar reaction was observed by using 5% (by weight) copper phenylacetylide in place of iron carbonyls; however, the 3:1 adduct **6** of phenyl isocyanate and phenylacetylene was obtained in 15% yield. We could not clarify the structure of the adduct **6**.

The results of the reaction using several isocyanates are shown in Table II. There was no significant difference in the reaction using phenyl isocyanate. *n*-Butyl isocyanate was less reactive and easily formed isocyanurate in 80% yield.

The reaction of diphenylcarbodiimide (2 mol) with phenylacetylene (1 mol) in the presence of iron pentacarbonyl (1 mol) was carried out at 180° for 5 hr, and 4-benzylidene-1,3-diphenyl-2,5-bis(phenylimino)imidazolidine (**7**) and 4-benzylidene-1,3-diphenyl-2-phenyliminoimidazolidin-5-one (**8a**) were obtained in 78 and 17% yields, respectively. The imidazolidines **7** and **8a** were hydrolyzed quantitatively to the hydantoin **1a**. The structure of the imidazolidine **7** was identified by ir and mass spectra and elemental analysis. For the structure of the imidazolidinone, two forms, **8a** and **8b**, were proposed from the infrared spectrum, 1750 (C=O), 1660 (C=N), and 1635 cm^{-1} (C=C). The mass spectrum showed the fragment at 208; this corresponded to $(PhN)_2C{=}NPh$ minus Ph for **8a**. Consequently, the structure of the product was identified as **8a**.



It seemed that the imidazolidine **8a** was formed from phenyl isocyanate, diphenylcarbodiimide, and phenylacetylene. Hence the equimolecular reaction of phenyl isocyanate, diphenylcarbodiimide, phenylacetylene, and iron pentacarbonyl was carried out at 190° for 2 hr. However, the imidazolidine **8a** was not obtained, and the hydantoin **1a**, the imidazolidine **7**, and 5-benzylidene-2,3,4,5-tetrahydro-3-phenyl-1H-1-benzodiazepine-2,4-dione (**11**) were obtained in 82, 67, and 12% yields, respectively.

The reaction mechanism was assumed as shown in Scheme I.

It seemed that the hydrido carbonyl acetylide complex played an important role as an intermediate in the formation of the hydantoins **1a–f** and the imidazolidine **7**. The "doubly σ-bonded" acetylene complex **12** was probably formed at first, and the complex **12** changed readily to the acetylide complex **13** owing to the polarization of the C–H bond of the acetylenic group. A similar conversion has previously been proposed by Meriwether[15] and Collman.[16] Acetylene–iron carbonyl complexes such as **12** had been isolated[17] and termed "doubly σ bonded."[16]

In the second step, R–NCX was inserted into the C–Fe bond of the complex **13**, and the complex **14** was

(15) L. S. Meriwether, M. F. Leto, E. C. Colthup, and G. W. Kennerly, *J. Org. Chem.*, **27**, 3930 (1962).
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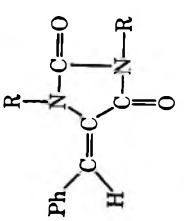
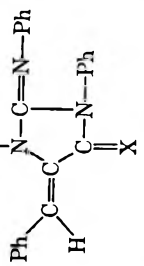
(17) Reference 9, pp 277, 284.

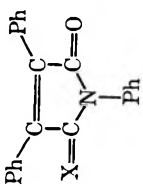
TABLE II.—CHARACTERIZATION DATA ON REACTION PRODUCTS



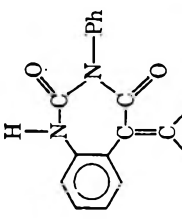
Hydantoin **1a–f**



Imidazolidine **7,8**



Pyrroline **9,10**

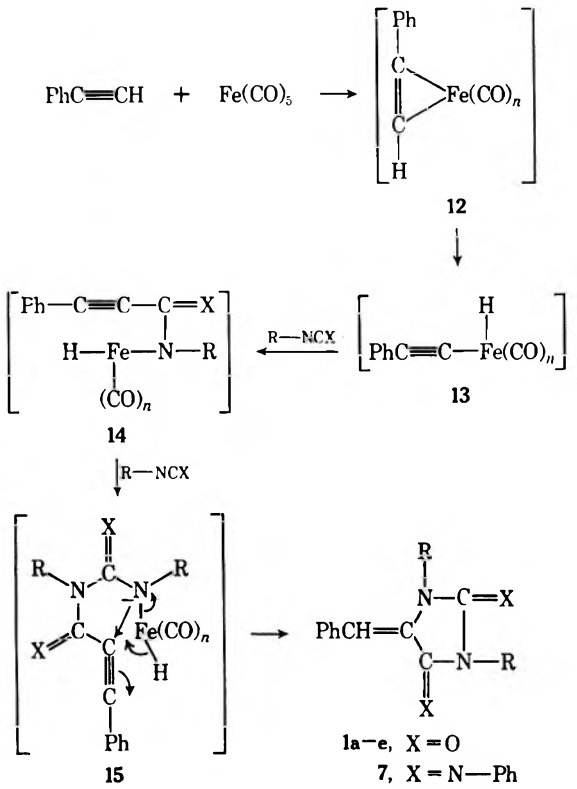


Benzodiazepinone **11**

Compd	X	R	Yield, %	Mp, °C	Ir, cm⁻¹ $\nu_{C=O}$	Ir, cm⁻¹ $\nu_{C=N}$	Ir, cm⁻¹ $\nu_{C=C}$	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Obsd, % C	Obsd, % H	Obsd, % N
1a		Phenyl	85	200	1775, 1725		1650	$C_{22}H_{16}O_2N_2$	77.63	4.74	8.23	77.94	4.78	8.01
1b		*o*-Chlorophenyl	67	147.5	1775, 1730		1650	$C_{22}H_{14}O_2N_2Cl_2$[a]	64.56	3.45	6.85	64.82	3.33	6.56
1c		*o*-Tolyl	38	221	1770, 1725		1650	$C_{24}H_{20}O_2N_2$	78.24	5.47	7.60	78.25	5.16	7.32
1d		*α*-Naphthyl	33	259–260	1770, 1730		1645	$C_{30}H_{20}O_2N_2$	81.80	4.58	6.30	81.27	4.41	6.20
1e		Cyclohexyl	48		1760, 1710		1650	$C_{22}H_{28}O_2N_2$	74.96	8.01	7.95	75.27	8.29	7.49
1f		*n*-Butyl	7		1760, 1710		1650	$C_{18}H_{24}O_2N_2$	71.97	8.05	9.33	71.83	7.92	9.10
7	N–Ph		78	145		1690, 1660	1635	$C_{34}H_{28}N_4$	83.24	5.34	11.42	83.12	5.29	11.51
8	O		17	195	1750	1660	1635	$C_{28}H_{21}ON_3$	80.94	5.09	10.11	81.37	5.00	10.04
9	O		42[b]	180–181	1770, 1710		1620	$C_{22}H_{15}O_2N$	81.21	4.65	4.31	81.47	4.64	4.40
10	N–Ph		48	157–158	1720	1635	1590	$C_{28}H_{20}ON_2$	83.97	5.03	7.00	83.98	5.03	6.79
11			12	215–216	1760, 1710	*c*	1645	$C_{22}H_{16}O_2N_2$	77.63	4.74	8.23	77.58	4.65	8.14

[a] Cl, %: calcd 17.33, obsd 17.31. [b] Pyrroline **10** was obtained in 15% yield. [c] NH stretching: 3300 cm⁻¹.

SCHEME I

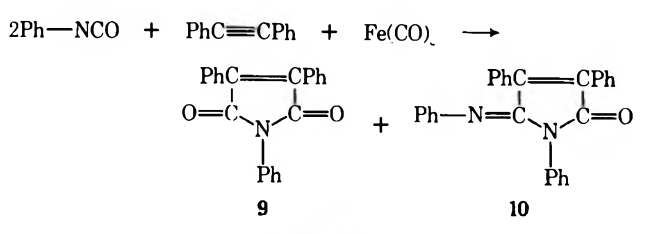


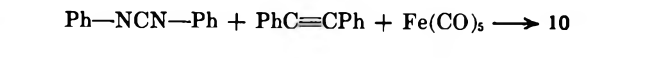
formed consequently. The insertion of an additional R–NCX into the complex **14** led to the complex **15**. The complex **15** was converted into the hydantoins **1a–f** and the imidazolidine **7** by hydrogen transfer and ring closure.

The reaction mechanism as shown above was supported by the result of the reaction between phenyl isocyanate and phenylacetylene with copper phenylacetylide catalyst, in which the hydantoin **1a** was obtained in high yield. There are several reports for the reaction between metal phenylacetylide (metal: Na,[6] $PbEt_3$,[7] $SnEt_3$[8]) and aryl isocyanate (Ar = phenyl, *α*-naphthyl) resulting in the formation of the hydantoin **1a**.

The reaction path to the imidazolidine **8a** could not be clarified from the results of this experiment.

Reactions with Diphenylacetylene.—In the reaction using diphenylacetylene in place of phenylacetylene, the 2:1 adduct with phenyl isocyanate or diphenylcarbodiimide, corresponding to the hydantoin **1** or the imidazolidine **7**, was not obtained. 1,3,4-Triphenylpyrroline-2,5-dione (**9**) and 1,3,4-triphenyl-5-phenyliminopyrrolin-2-one (**10**) were obtained in 42 and 15% yields, respectively, in the reaction using 2 mol of phenyl isocyanate, 1 mol of diphenylacetylene, and 1 mol of iron pentacarbonyl at 175° for 4 hr. The results are shown in Table II.

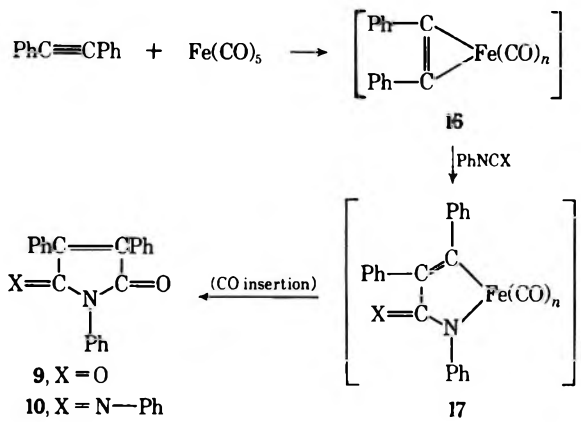




These products were formed by CO insertion and their structures were confirmed by ir and mass spectra and elemental analysis. It could be presumed that the pyrroline **10** may be constructed with diphenylacetylene, carbon monoxide, and diphenylcarbodiimide which was produced *in situ* from phenyl isocyanate under the catalysis of iron pentacarbonyl.[12] The pyrroline **10** was also obtained in 45% yield in the equimolecular reaction using diphenylcarbodiimide, diphenylacetylene, and iron pentacarbonyl at 185° for 2 hr. The pyrroline **10** was hydrolyzed quantitatively to the pyrroline **9** by acid.

The reaction mechanism to produce the pyrrolines **9** and **10** was assumed to proceed as shown in Scheme II.

SCHEME II



The "doubly σ-bonded" acetylene complex **16** was initially formed and was easily added to Ph–NCX across the N=C bond to form the complex **17**. The complex **17** was converted to the pyrrolines **9** and **10** by insertion of CO.

Experimental Section

All melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected.

Infrared spectra were taken with a Jasco IR-E spectrometer. Proton magnetic resonance spectra were taken with a Joel LNM-3H-60 spectrometer in CCl_4 with TMS as the internal standard. Mass spectra were taken with a Hitachi RMU-6E spectrometer.

All reactions were carried out under a nitrogen atmosphere in a 50-ml four-necked flask equipped with a mechanical stirrer, reflux condenser, dropping funnel, and nitrogen inlet. Chromatographic separations were carried out using activated alumina columns.

Materials.—Phenyl isocyanate, *n*-butyl isocyanate, α-naphthyl isocyanate, phenylacetylene, and iron pentacarbonyl were purchased from a commercial source. *o*-Chlorophenyl isocyanate, *o*-tolyl isocyanate, and cyclohexyl isocyanate were prepared from the corresponding amines and carbonyl chloride in the usual way.[18] Diphenylacetylene,[19] N,N′-diphenylcarbodiimide,[12] copper phenylacetylide,[20] and triiron dodecacarbonyl[21] were prepared according to previously outlined procedures. Phenylacetylene-1-*d*[15] was prepared in 88.8% isotopic purity by hydrolysis of the Grignard reagent of phenylacetylene with 99.7% deuterium oxide. Tetrahydrofuran was dried by refluxing on sodium wire in the presence of benzophenone.

4-Benzylidene-1,3-diphenylhydantoin (1a).—A mixture of phenyl isocyanate (0.05 mol) and iron pentacarbonyl (0.025 mol) was stirred at 150° for 40 min. Phenylacetylene (0.025 mol) was added dropwise to the mixture, and stirring was continued for 1.5 hr at 150–160°. After removal of carbon monoxide, the reaction mixture was extracted (benzene) and crystallized (benzene) to give 7.5 g of the yellow crystals **1a**. The product was chromatographed (benzene) and recrystallized (benzene) to give the hydantoin **1a** (white crystals): mp 200° (lit.[7] 193–194°); nmr (CCl_4) δ 7.65–6.70 (all protons); ir (Nujol mull) 1775 and 1725 (C=O), 1650 cm^{-1} (C=C); mass spectrum (70 eV) *m/e* 340 (M^+), 193 (PhCH=C=NPh).

The equimolecular reaction of phenyl isocyanate and phenylacetylene was carried out in a similar manner (*vide supra*). The products were chromatographed with benzene (fractions 1–3), benzene–ethyl ether (1:1) (fraction 4), and ethyl ether–ethanol (1:1) (fraction 5). From the first fraction, 0.3 g of π-2,5-diphenylcyclopentadieneiron tricarbonyl (**3**) was obtained and recrystallized (benzene–ethanol), mp 222° dec; the melting point of the mixture of compound **3** and the authentic sample[22] was not depressed. From the second fraction, 2.9 g of the hydantoin **1a** was obtained. From the third fraction, 0.2 g of triphenyl isocyanurate (**4**) was obtained and recrystallized (benzene), mp 294°; no depression of melting point was observed for the mixture with the authentic sample.[23] From the fourth fraction, 0.2 g of adduct **6** (white crystals) was isolated and recrystallized (benzene): mp 165°; ir (Nujol mull) 1775 and 1730 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* 459 (M^+), 368 (M − N–C_6H_5), 340 (M − C_6H_5NCO), 249 (M − $C_6H_5NCONC_6H_5$).

Anal. Calcd for $C_{29}H_{21}N_3O_3$: C, 75.80; H, 4.61; N, 9.15. Found: C, 75.50; H, 4.49; N, 9.05.

From the fifth fraction, 0.2 g of N,N′-diphenylurea (**5**) was obtained and recrystallized (ethanol), mp 239°; no depression of melting point was observed for the mixture with the authentic sample.[24]

4-Benzylidene 1,3-Disubstituted Hydantoins (1b–f).—Reactions between isocyanate (0.05 mol), iron pentacarbonyl (0.025 mol), and phenylacetylene (0.025 mol) were carried out at 150–180° for 3 hr in a similar manner (*vide supra*). Isocyanates used were *o*-chlorophenyl, *o*-tolyl, α-naphthyl, cyclohexyl, and *n*-butyl isocyanates. After similar treatments, the following products were obtained by recrystallization or distillation (Table II).

4-Benzylidene-1,3-di-*o*-chlorophenylhydantoin (**1b**): white crystals; mp 147.5°; mass spectrum (70 eV) *m/e* 192 (C_6H_4N=C=CHPh), 227 and 229 (ClC_6H_4N=C=CHPh), 373 and 375 (M − Cl), 408 and 410 (M^+).

4-Benzylidene-1,3-di-*o*-tolylhydantoin (**1c**): white crystals; mp 221°; mass spectrum 368 (M^+), 291 (M − C_6H_5), 277 (M − C_7H_7), 207 (C_6H_5CH=C=$NC_6H_4CH_3$).

4-Benzylidene-1,3-di-α-naphthylhydantoin (**1d**): white crystals; mp 259–260° (lit.[7] 254–256°); mass spectrum 440 (M^+), 363 (M − C_6H_5), 243 (C_6H_5CH=C=$NC_{10}H_7$).

4-Benzylidene-1,3-dicyclohexylhydantoin (**1e**): orange oil; bp 180° (3 mm); mass spectrum 352 (M^+), 270 (M − C_6H_{10}), 199 (C_6H_5CH=C=NC_6H_{11}), 188 (M − $2C_6H_{10}$).

4-Benzylidene-1,3-di-*n*-butylhydantoin (**1f**): orange oil; bp 148° (0.3 mm); mass spectrum 300 (M^+), 243 (M − C_4H_9), 186 (M − $2C_4H_9$), 173 (C_6H_5CH=C=NC_4H_9). In the reaction of *n*-butyl isocyanate, 4.0 g of tri-*n*-butyl isocyanurate was obtained as a by-product in 80% yield, ir 1690 cm^{-1} (C=O); the ir spectrum was identical with that of the authentic sample.

4-Benzylidene-1,3-diphenyl-2,5-bis(phenylimino)imidazolidine (7) and 4-Benzylidene-1,3-diphenyl-2-phenyliminoimidazolidin-5-one (8a).—The reaction using N,N′-diphenylcarbodiimide (0.0366 mol), iron pentacarbonyl (0.0183 mol), and phenylacetylene (0.0183 mol) was carried out in a similar manner as above at 150–180° for 5 hr. The products were extracted (benzene), chromatographed (benzene), and recrystallized (benzene–hexane) to give following compounds.

Imidazolidine **7**: yellow crystals; 7.0 g; mp 145°; mass spectrum 490 (M^+), 296 (M − C_6H_5N=C=NC_6H_5), 193 (C_6H_5-CH=C=NC_6H_5).

Imidazolidine **8a**: yellowish orange crystals; 1.3 g; mp 195°; mass spectrum 415 (M^+), 338 (M − C_6H_5), 296 (M − C_6H_5-NCO), 208 [C_6H_5N=C(NC_6H_5)$_2$ − C_6H_5], 193 (C_6H_5CH=C=NC_6H_5).

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1,3,4-Triphenylpyrroline-2,5-dione (9) and 1,3,4-Triphenyl-5-phenyliminopyrrolin-2-one (10).—The reaction using phenyl isocyanate (0.05 mol), diphenylacetylene (0.025 mol), and iron pentacarbonyl (0.025 mol) was carried out in a similar manner as above at 175° for 4 hr, and the products were extracted (benzene) and chromatographed (benzene, fractions 1–5; ethanol, fraction 6). From the first fraction, 0.1 g of π-tetraphenylcyclobutadieneiron tricarbonyl, $Fe(CO)_3(PhC_2Ph)_2$ (mp 238° dec), and 0.7 g of the binuclear iron carbonyl complex, $Fe_2(CO)_6$–$(PhC_2Ph)_2$ (mp 205° dec), were obtained and recrystallized (benzene–ethanol); no depressions of melting points were observed for each mixture with authentic samples.[22] From the second fraction, 0.2 g of 2,3,4,5-tetraphenyl-2,4-cyclopentadien-1-one (mp 220°) was obtained and recrystallized (benzene); no depression of the melting point was observed for the mixture with the authentic sample.[25] From the third fraction, the pyrroline **9** was obtained and recrystallized (benzene–ethanol): yellow needles; 3.3 g; mp 180–181° (lit.[26] 178–179°); mass spectrum (70 eV) *m/e* 325 (M^+), 297 (M − CO), 206 (M − C_6H_5NCO). From the fourth fraction, the pyrroline **10** was obtained and recrystallized (ethanol): orange crystals; 1.5 g; mp 157–158°; mass spectrum (70 eV) *m/e* 400 (M^+), 372 (M − CO), 295 (372 − C_6H_5), 281 (M − C_6H_5NCO), 194 ($C_6H_6N{=}C{=}NC_6H_5$). From the fifth and sixth fractions, 0.1 g of the cyanurate **4** (mp 294°) and 1.0 g of the urea **5** (mp 239°) were obtained; no depression of melting points were observed for the mixture with the authentic samples.[23,24]

The pyrroline **10** was also obtained in 48% yield in the reaction using N,N′-diphenylcarbodiimide (0.0073 mol), diphenylacetylene (0.0073 mol), and iron pentacarbonyl (0.0073 mol) at 185° for 2 hr.

4-(Benzylidene-α-*d*)-1,3-diphenylhydantoin (1′a).—The hydantoin **1′a** was prepared from phenylacetylene-1-*d* in a similar manner to that used to prepare the hydantoin **1a**: white crystals, 60% yield, mp 200°.

Equimolecular Reaction of Phenyl Isocyanate, Diphenylcarbodiimide, Phenylacetylene, and Iron Pentacarbonyl.—A mixture of diphenylcarbodiimide (0.01 mol), phenyl isocyanate (0.01 mol), and iron pentacarbonyl (0.01 mol) was heated to 140° for 30 min. Phenylacetylene was added dropwise to the mixture, and stirring was continued for 2 hr at 140–190°. The products were extracted (benzene), concentrated, and chromatographed (benzene). From the first and second fractions, 1.7 g (67%) of the imidazolidine **7** and 1.4 g (82%) of the hydantoin **1a** were obtained, respectively. From the third fraction, 0.2 g (12%) of the benzodiazepinone **11** was obtained and recrystallized (benzene–ethanol): yellow crystals; mp 215–216° (lit.[6] 202–203°); mass spectrum (70 eV) *m/e* 340 (M^+), 220 (M − PhNCO), 192 [M − CON(Ph)CO].

Acid Hydrolysis of the Imidazolidines 7 and 8a and the Pyrroline 10.—Either **7**, **8a**, or **10** (0.5 g) was dissolved in a mixture of 20 ml of ethanol and 10 ml of water, and concentrated hydrochloric acid (10 ml) was added. After refluxing for 10 min on a steam bath, the reaction mixture was cooled, extracted (ethyl ether), dried ($MgSO_4$), concentrated, and recrystallized (benzene) giving **1a** (from **7** and **8a**) or **9** (from **10**). Hydrolyses were quantitative.

Oxidation of the Hydantoin 1a.—Powdered potassium permanganate (1.3 g) was added over 1 hr to the hydantoin **1a** (1.5 g) dissolved in pyridine (20 ml)–water (2 ml) with vigorous stirring; the temperature was held at 18–20°. Water (10 ml) in limited amounts was added to the reaction mixture with stirring, and stirring was continued for 30 min. The solution was made acid to congo red with dilute sulfuric acid and decolorized by sodium hydrogen sulfite. The precipitate was washed with water (30 ml) and ethyl ether (30 ml) and crystallized (benzene–hexane), giving 1.0 g (85%) of white needles of parabanic acid **2**: mp 210° (lit.[27] 206–207°); ir 1785 and 1740 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* 266 (M^+), 119 (C_6H_5NCO).

Anal. Calcd for $C_{15}H_{10}N_2O_2$: C, 67.66; H, 3.79; N, 10.52. Found: C, 67.67; H, 3.79; N, 10.46.

The filtrate was made acid with concentrated hydrochloric acid and extracted with two 100-ml portions of ether. The ethereal extract was dried ($MgSO_4$) and concentrated. Benzoic acid (0.2 g) was obtained by crystallization of the residue with hexane: 37% yield; mp 124°; no depression of melting point was observed for the mixture with the authentic sample.

Registry No.—**1a**, 4514-33-4; **1b**, 24707-10-6; **1c**, 24707-11-7; **1d**, 17858-25-2; **1e**, 24707-13-9; **1f**, 24704-22-1; **2**, 6488-59-1; **7**, 24707-15-1; **8a**, 24707-16-2; **9**, 5191-53-7; **10**, 24707-18-4; **11**, 4514-34-5.

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Mass Spectra of Tetraza-3,6-disilacyclohexanes and Silylhydrazines

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The mass spectra of some silylhydrazines and tetraaza-3,6-disilacyclohexanes are presented. Silicon-containing fragments are the most abundant. Characteristic fragmentation modes are the direct and stepwise loss of free radicals and neutral molecules from the molecular and fragment ions. Hydrogen transfer and skeletal rearrangement processes are observed. Evidence for rearrangements of doubly charged ions has been obtained. Two different types of metastable ions are detected which support many fragmentation modes. High-resolution data are in agreement with the proposed fragmentation processes.

Although the interest in organosilicon chemistry has been steadily increasing in recent years, only a limited amount of information is available concerning the mass spectral fragmentation of organosilicon compounds.[2–7] The mass spectra of trimethylsilyl ethers, amines, and sulfides, derivatives of acids,[8–10] and siloxanes[11–13] have been reported.

The information available in literature on the be-

(1) (a) The National Chemical Laboratory, Poona; (b) Department of Chemistry, Indian Institute of Technology, Kanpur.

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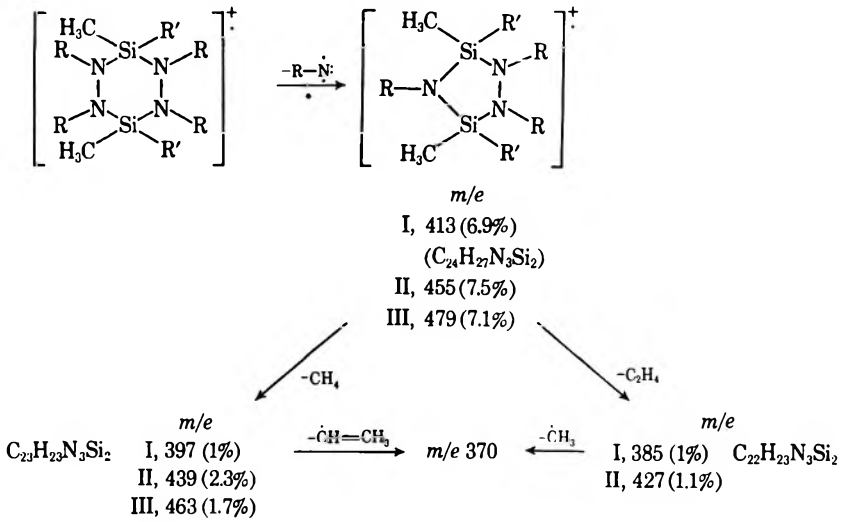
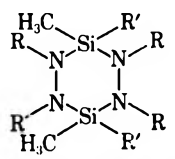
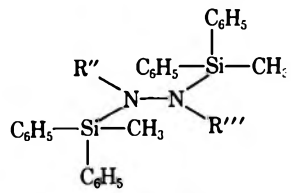
CHART I



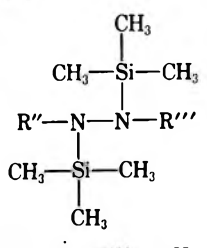
havior of Si–N bond under electron impact is scanty.[14,15] It has been reported that, in the mass spectra of silazanes, the molecular ion was observed as a minor peak, the base peak being the M − 15 ion formed by the loss of a methyl radical. The subsequent fragmentation modes reported are the expulsion of neutral molecules such as methane, ammonia, formaldehyde, and hydrogen chloride. In the present studies, we have examined the mass spectra of a few silicon–nitrogen compounds such as silylhydrazines and tetraaza-3,6-disilacyclohexanes. The tetraaza-3,6-disilacyclohexanes include 1,2,4,5-tetraphenyl-3,6-dimethyl-3,6-divinyl-1,2,4,5-tetraaza-3,6-disilacyclohexane (I), 1,2,4,5-tetra(*m*-tolyl)-3,6-dimethyl-3,6-divinyl-1,2,4,5-tetraaza-3,6-disilacyclohexane (II), and 1,2,4,5-(*m*-anisyl)-3,3,6,6-tetramethyl-1,2,4,5-tetraaza-3,6-disilacyclohexane (III). The silylhydrazines that we have studied are



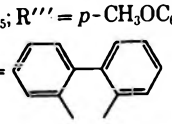
I, R = C_6H_5; R′ = CH_2=CH
II, R = *m*-$CH_3C_6H_4$; R′ = CH_2=CH
III, R = *m*-$CH_3OC_6H_4$; R′ = CH_3



IV, R″ = C_6H_5; R‴ = C_6H_5
V, R″ = C_6H_5; R‴ = *p*-$CH_3C_6H_4$
VI, R″ = C_6H_5; R‴ = *p*-$CH_3OC_6H_4$



VIII, R″ = R‴ = C_6H_5



VII, R″, R‴ =

N,N′-diphenyl-N,N′-bis(diphenylmethylsilyl)hydrazine (IV), N-phenyl-N′-(*p*-tolyl)-N,N′-bis(diphenylmethylsilyl)hydrazine (V), N-phenyl-N′-(*p*-anisyl)-N,N′-bis(diphenylmethylsilyl)hydrazine (VI), N,N′-bis(diphenylmethylsilyl)dibenzodihydropyridazine (VII), and N,N′-diphenyl-N,N′-bis(trimethylsilyl)-hydrazine (VIII).

Results and Discussion

The mass spectra of the three tetraaza-3,6-disilacyclohexanes (I–III) are shown in Figure 1. Like the mass spectra of cyclosilzanes reported recently,[15] the molecular ion is significant and is the base peak in the spectra of these compounds. Fragments corresponding to direct and/or successive loss of methyl, vinyl, and phenyl radicals are negligible. The loss of phenylnitrene R–N: from a molecular ion is a very significant metastable-supported fragmentation mode. The resulting odd-electron ion then appears to eliminate neutral molecules such as methane and ethylene and finally stabilize by expulsion of vinyl and methyl radicals. High-resolution data obtained on peaks at *m/e* 413, 397, 385, and 370 in the spectrum of compound I support this (Chart I).

From the ion abundances alone it is difficult to establish whether the initial ionization takes place by the loss of a bonding or nonbonding electron.[16] The observed elimination of phenylnitrene can be reasonably explained by assuming that the initial ionization is taking place by the loss of a bonding electron of the Si–N bond, the charge remaining on the silicon atom because of the large difference between the electronegativity of silicon and nitrogen. This is followed by a homolytic cleavage of the N–N bond resulting in the elimination of phenylnitrene. Djerassi, *et al.*,[17,18] have reported the formation of nitrogen entities with electron sextet as preferred intermediates and product ions in the mass spectra of oximes and N,N-dimethylhydrazones.

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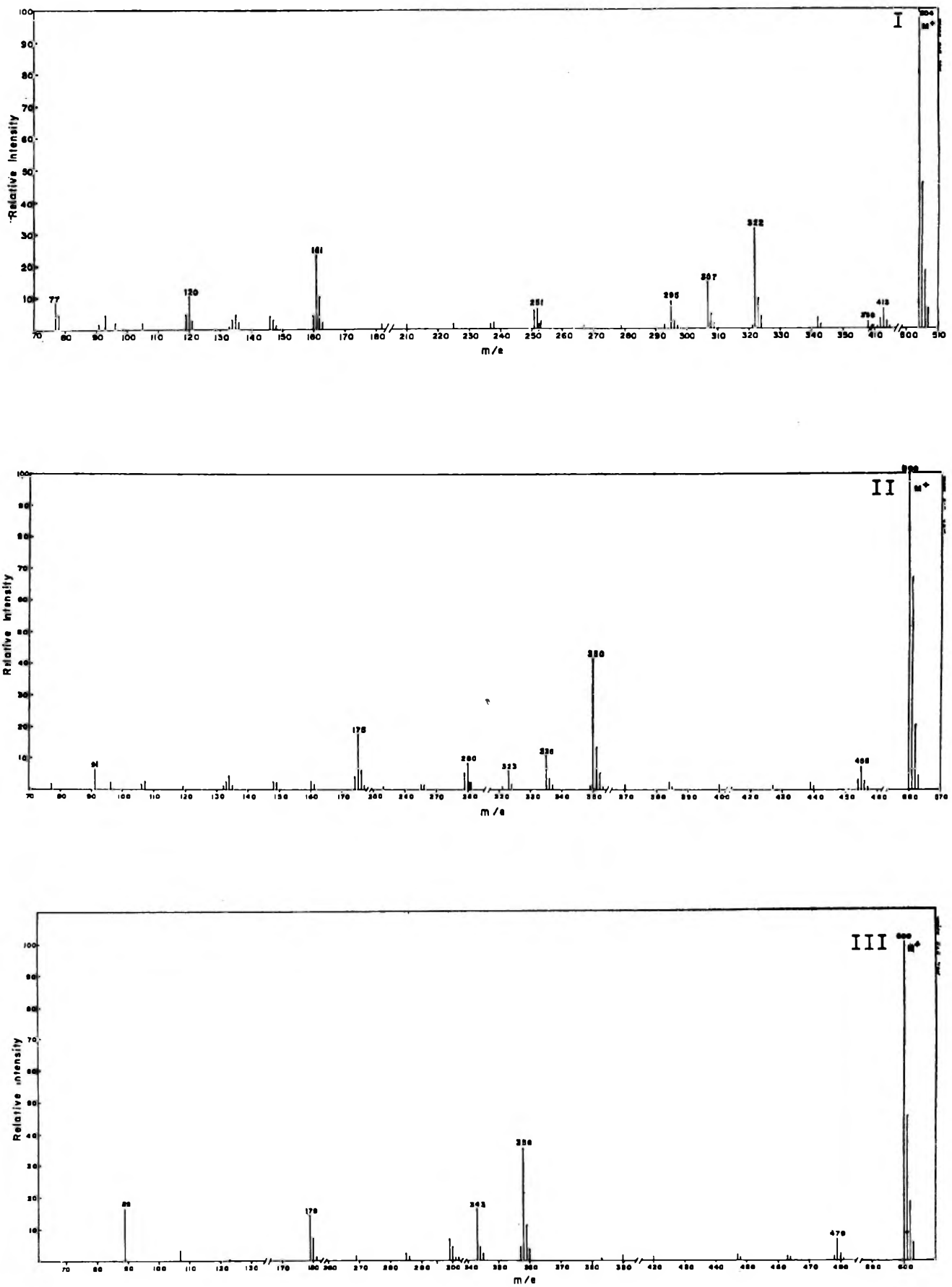
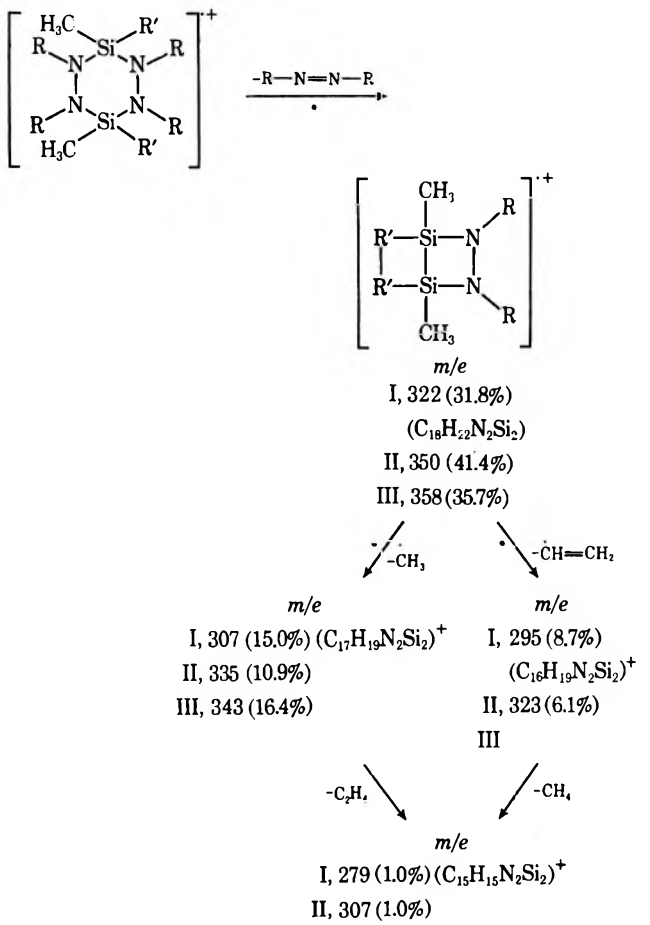


Figure 1.—Mass spectra of 1,2,4,5-tetraphenyl-3,6-dimethyl-3,6-divinyl-1,2,4,5-tetraaza-3,6-disilacyclohexane, (I) 1,2,4,5-tetra(*m*-tolyl)-3,6-dimethyl-3,6-divinyl-1,2,4,5-tetraaza-3,6-disilacyclohexane (II), and 1,2,4,5-tetra(*m*-anisyl)-3,3,6,6-tetramethyl-1,2,4,5-tetraaza-3,6-disilacyclohexane (III).

Photolytic[19] and thermal[20] elimination of phenylnitrene is well known. The elimination of phenylnitrene under electron impact appears to be a novel type of fragmentation mode.

Another fragmentation mode supported by an appropriate metastable peak is the loss of a neutral molecule (RN=NR) from the molecular ion which results in the formation of an odd-electron fragment ion. This fragmentation mode resembles the loss of tolane from the M − 15 ion in the mass spectrum of 1,1,4,4-tetramethyl-2,3,5,6-tetraphenyl 1,4-disilin.[21] It is pertinent to observe that the loss of neutral molecules such as RN=NR was also observed in the thermal decompositions of tetraaza-3,6-disilacyclohexanes.[22] Further fragmentation is dominated by the expulsion of free radicals (methyl and vinyl) which leads to the formation of stable even-electron ions. These even-electron ions, in turn, appear to lose neutral molecules such as ethylene or methane. Evidence in support of these fragmentation processes was obtained from accurate mass measurements.



In the mass spectra of benzene[23] and 9,10-diphenylanthracene,[24] doubly and triply charged ions have been reported to undergo metastable supported rearrangements. The metastable peak at *m/e* 411.6 (calcd 411.4) in the spectrum of I has been rationalized by assuming the decomposition of the doubly charged molecular ion into two singly charged ions as shown.

$$M^{2+} \xrightarrow{*} [M - (C_6H_5N{=}NC_6H_5)]^+ + [C_6H_5N{=}NC_6H_5]^+$$

m/e 322 *m/e* 182

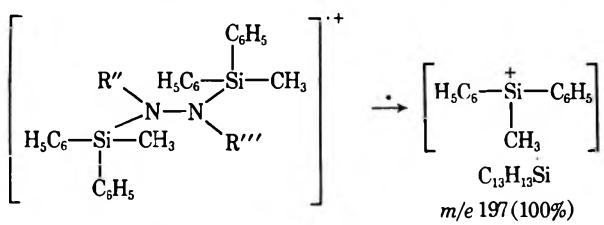
I, mol wt 504

Doubly charged ions have been observed which correspond to the molecular and the M − (RN=NR) ions. These doubly charged ions with integral masses were identified from their isotopic peaks observed at *m/e* 252.5 and 161.5. High-resolution data also support the elemental compositions assigned to them. This observation can be explained by assuming that the doubly charged molecular ion undergoes the following ion decomposition reaction

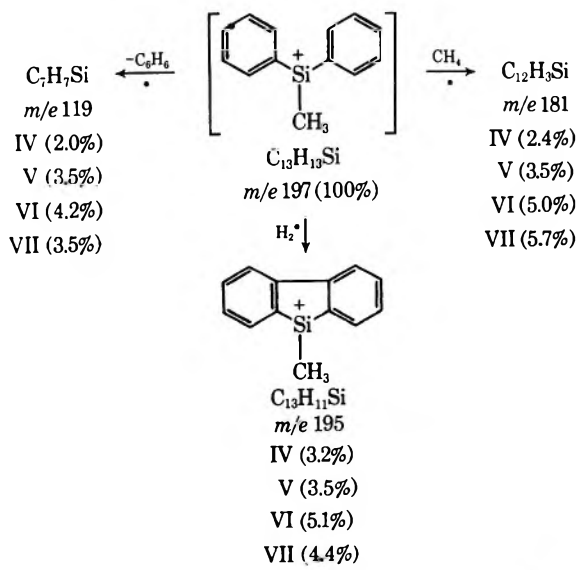
$$M^{2+} \longrightarrow [M - (RN{=}NR)]^{2+} + RN{=}NR$$

It appears that this fragmentation mode operates in both the singly and doubly charged molecular ions and takes place in a single step.

Figure 2 shows the mass spectra of the compounds IV, V, and VI. It is reasonable to assume that in these compounds, also, the initial ionization takes place by the loss of a bonding electron. This seems to trigger the fragmentation process leading to the formation of the base peak at *m/e* 197. The M − 197 ion is, however, a minor peak.

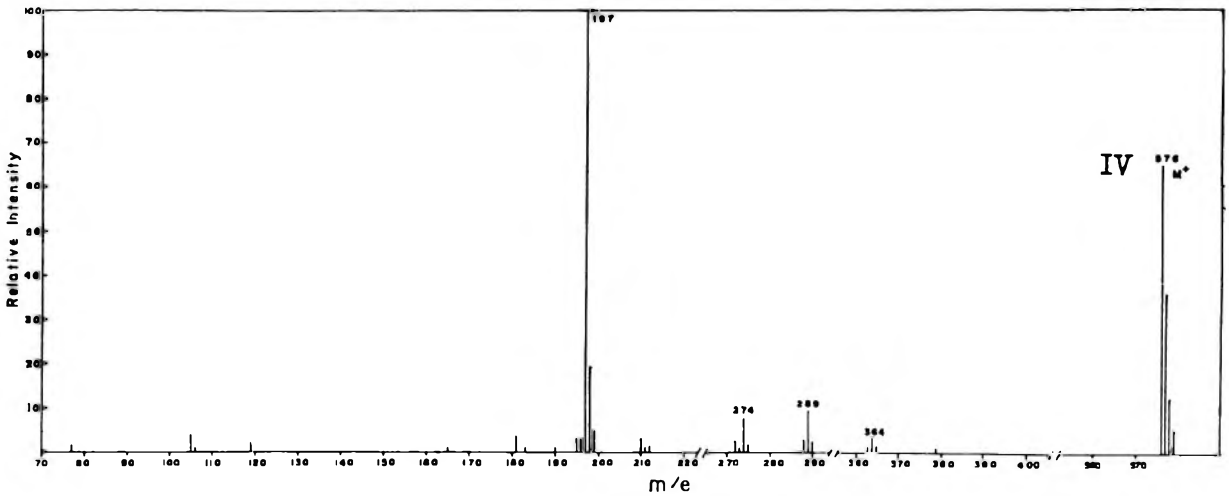


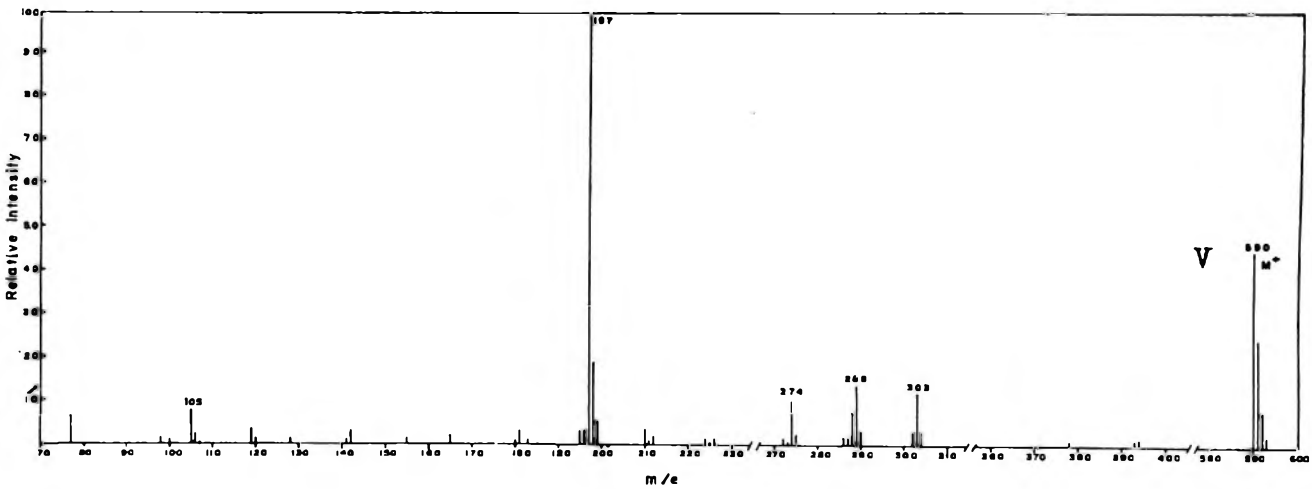
The loss of neutral molecules such as H_2, CH_4, and C_6H_6 allows easy degradation paths for the even-electron fragment *m/e* (197). This gives rise to daughter ions *m/e* 195, 181, and 119. Compositions of these ions are confirmed from high resolution data.



Loss of two hydrogen atoms in one step by the "ortho coupling" has been shown in the spectra of triphenylphosphine, triphenylarsine, triphenylstibine, diphenyl-

(19) J. S. Splitter and M. Calvin, *Tetrahedron Lett.*, 1445 (1968).
(20) F. P. Lossing, *Ann. N. Y. Acad. Sci.*, **67**, 499 (1957).
(21) F. Johnson, R. S. Gohlke, and W. A. Nasutavicus, *J. Organometal. Chem.*, **3**, 233 (1965).
(22) V. Kalyanaraman and M. V. George, unpublished results.
(23) W. Higgins and K. R. Jennings, *Chem. Commun.*, 99 (1965).
(24) K. R. Jennings and A. F. Whitings, *ibid.*, 820 (1967).





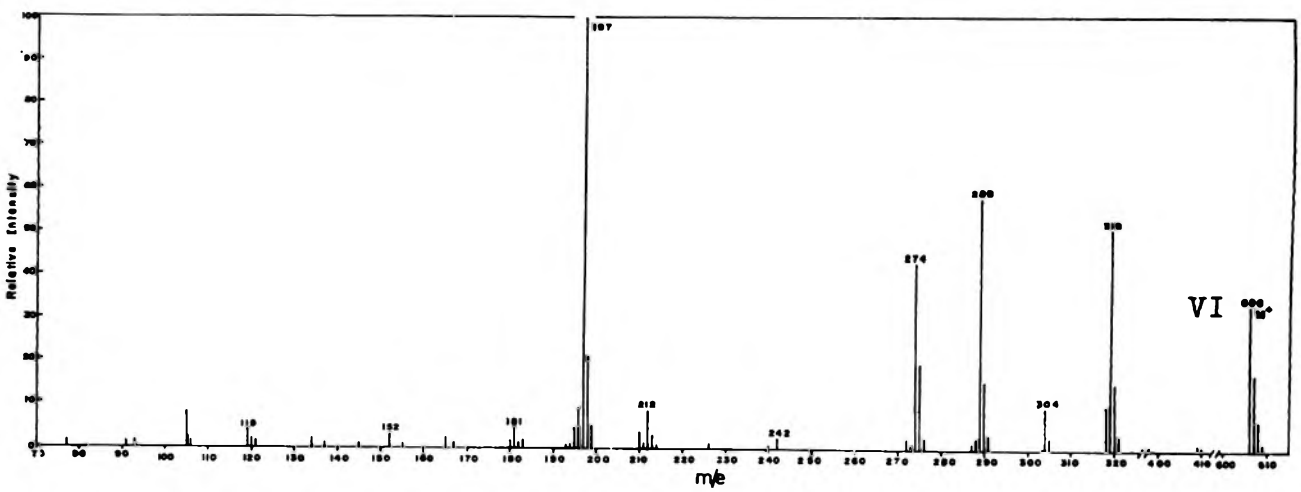
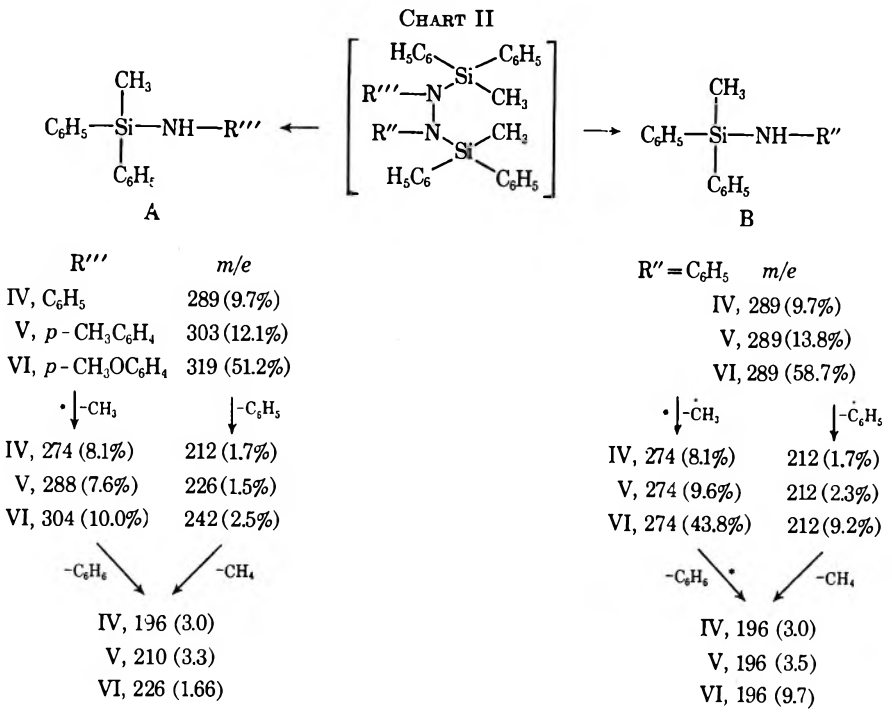


Figure 2.—Mass spectra of N,N′-diphenyl-N,N′-bis-(diphenylmethylsilyl)hydrazine (IV), N-phenyl-N′-(*p*-tolyl)-N,N′-bis(diphenylmethylsilyl)hydrazine (V), and N-phenyl-N′-(*p*-anisyl)-N,N′-bis(diphenylmethylsilyl)hydrazine (VI).

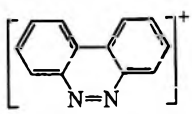
CHART II



methane,[25] and diphenylamine.[26] Elimination of methyl and phenyl radicals from the molecular ion is insignificant. However, the loss of a methyl group is preferred to the loss of a phenyl group attached to a silicon atom.

Simple cleavage of N–N bond in silyhydrazines is not very significant in the spectra of compounds IV to VII. However, cleavage of the N–N bond takes place with hydrogen transfer which results in the formation of odd-electron fragmentation, A and B. Other precursors of these rearrangement ions could not be identified in the absence of appropriate metastable peaks. In compound VIII this rearrangement is not very significant, since the simple cleavage of the N–N bond seems to be preferred over the rearrangement. In the absence of sufficient deuteration data it is difficult to propose any satisfactory mechanism for these rearrangements (see Chart II).

The spectrum of VII is slightly different from those of IV, V, and VI. One of the differences is the stepwise loss of two fragments with mass 197. The driving force for this fragmentation seems to be the formation of a stable aromatic system.

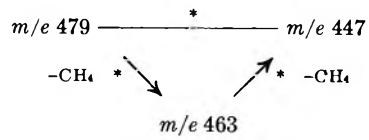


m/e 180 (2.5%) $C_{12}H_8N_2$

The characteristic peak observed at *m/e* 289 in the spectra of IV, V, and VI is absent in the spectrum of VII which indicates that the hydrogen rearrangement process is not operating to a significant extent. No rearrangement involving the transfer of alkyl and aryl groups has been observed. The rigidity of the molecule compared with IV, V, and VI may be responsible for the absence of these fragmentation modes in VII.

(25) D. E. Bublitz and A. W. Baker, *J. Organometal. Chem.*, **9**, 383 (1967).
(26) K. G. Das, P. T. Funke, and A. K. Bose, *J. Amer. Chem. Soc.*, **86**, 3728 (1964).

The observed values of apparent mass of the metastable ions agreed with calculated values to ±0.2 mass unit. The metastable peaks were sharp when neutral molecules and radicals were eliminated, and diffuse and broad when silicon-containing fragments were lost. Some metastable peaks observed in the spectra of III, IV, and V can be expalined by two-step fragmentation processes, since the fragments lost are not present as single structural units in the parent ion. For example, in compound III it is obvious that the M − (R–N:) ion (*m/e* 479) does not contain any single structural entity



with 32 mass units. Hence, this should involve successive loss of two molecules of methane. Metastable peaks are observed for all these decompositions.

Experimental Section

The mass spectra of compounds I–VIII were recorded on a CEC 21-110B mass spectrometer. The samples were introduced through the direct inlet probe and the ion source was operated between 150 and 200°, the ionizing current was 40 μA, and the ionizing voltage was 70 eV. The accurate masses of fragments ions were determined by high-resolution mass spectrometry at a resolution of 6000.

The tetraaza-3,6-disilacyclohexanes (I–III) and silylhydrazines (IV–VIII) were prepared according to reported procedures.[27–29]

In the bar spectra of the compounds reported in Figures 1 and 2, intensities of the peaks >1% of the base peak are only reported. The asterisks indicate the observed metastable transitions.

Registry No.—I, 17082-85-8; II, 17082-87-0; III, 17082-89-2; IV, 5994-98-9; V, 15951-44-7; VI, 15951-45-8; VII, 15951-51-6; VIII, 5994-95-6.

(27) S. S. Dua and M. V. George, *J. Organometal. Chem.*, **10**, 219 (1967).
(28) S. S. Dua and M. V. George, *ibid.*, **9**, 413 (1967).
(29) M. V. George, P. B. Talukdar, and H. Gilman, *ibid.*, **5**, 397 (1966).

Amination of Cycloalkanes with Trichloramine–Aluminum Chloride[1a]

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The nature of the reaction between cycloalkanes and trichloramine–aluminum chloride was investigated. Amination of methylcyclopentane afforded 1-amino-1-methylcyclopentane; *cis*- and *trans*-decalins gave *cis*-9-aminodecalin; and hydrindan provided *cis*-8-aminohydrindan. The reaction with cyclohexane produced temperature-dependent products. At low temperatures cyclohexylamine was formed, while at higher temperatures 1-amino-1-methylcyclopentane predominated. Cycloheptane underwent rearrangement with formation of 1-amino-1-methylcyclohexane. Cyclooctane, methylcycloheptane, and 1,3- and 1,4-dimethylcyclohexane produced a mixture of rearranged products consisting primarily of 1,3- and 1,4-dimethyl-1-aminocyclohexanes. Primary and secondary amines as well as aziridines and N-alkylaziridines were generated from cyclopentane. Relative rate data were obtained for secondary *vs.* tertiary alkanes. An important step in the mechanistic pathways for the various reaction categories appears to entail interaction of a carbonium ion with a nitrogen-containing nucleophile. Synthetic utility is demonstrated for the procedure.

Prior reports from this laboratory have shown that the trichloramine–aluminum chloride combination can effect direct amination of organic compounds. Treatment of monoalkylbenzenes gave products of unusual orientation, namely, *m*-alkylanilines.[4-6] Additional studies revealed that naphthalene,[7] biphenyl,[7] and dialkylbenzenes[8] also demonstrated this unusual substitution pattern. More recent investigations have dealt with the conversion of aryldialkylmethines to *t*-benzylamines in the presence of *t*-butyl bromide.[9,10] This observation led to studies of direct amination of alkanes,[11] alkyl halides,[12,13] and hydrocarbons in the bicyclic[13] and tricyclic[14,15] category. Each type of organic substrate proved amenable to amination, thus providing a new route to amines.

Heretofore, only one simple alicyclic substrate, methylcyclohexane, was subjected to this technique, producing 1-amino-1-methylcyclohexane.[11] The purpose of the present study was to investigate the scope and mechanistic aspects of the amination of cycloalkanes, together with a consideration of synthetic utility.

Results and Discussion

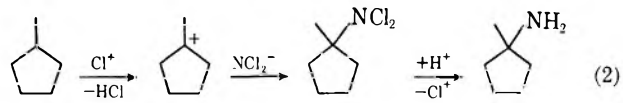
The reactions with trichloramine–aluminum chloride were generally carried out within the range of −20 to 18° with a trichloramine:aluminum chloride:alicyclic hydrocarbon:methylene chloride molar ratio of 0.1:0.2:0.5:2. The aminocycloalkanes could, in most cases, be separated from the minor reaction products by fractional distillation. Characterization of the major products was accomplished by comparison with authentic material, preparation of derivatives, and, in some cases, degradative techniques. Yields are based on an equimolar relationship between the basic, distilled product and trichloramine.

***t*-Alicyclic Hydrocarbons.**—These substrates gave the corresponding carbinamines as predominant reaction products. Their formation is consistent with the prior observation that *tertiary* centers are generally the preferred reaction sites.[11,12,14,15]

Methylcyclopentane.—When this hydrocarbon was aminated at 3° under standard conditions, a 61% yield of 1-amino-1-methylcyclopentane was obtained. The authentic compound was prepared by the Ritter reaction with 1-methylcyclopentanol.

Mechanistically, the result can be rationalized as shown in eq 1 and 2. Hydrogen chloride was evolved

$$Cl_3N + AlCl_3 \rightleftharpoons Cl^{\delta+}(AlCl_3NCl_2)^{\delta-} \quad (1)$$



(2)

throughout the reaction. Participation of chloronium type ion was invoked in a recent communication[16] dealing with another Lewis acid system. Alternatively, hydride abstraction might be effected by $^{+}CH_2Cl$ which may arise from the action of aluminum chloride on methylene chloride.[17] This possibility is considered unlikely since methyl chloride was formed only in trace amounts in the amination of methylcyclohexane. Other lines of supporting evidence for the proposed scheme are discussed elsewhere.[9-15]

Decalin.—Amination of *trans* (100%), *cis* (97%), and mixed (39% *trans*, 61% *cis*) decalins (Table I) provided the same major product, 9-aminodecalin, on the basis of physical properties and infrared spectra. Acetylation gave pure *cis*-N-9-decalylacetamide.[18] The

(1) (a) Paper XV of Chemistry of N-Halamines; presented in part at the Third Great Lakes Regional Meeting of the American Chemical Society, DeKalb, Ill., June 6, 1969. (b) From the Ph.D. Thesis of K. W. F., Case Western Reserve University, 1970.

(2) Address correspondence to this author at the Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wis. 53201.

(3) NSF–URP participant, Case Western Reserve University, summer 1966.

(4) P. Kovacic, C. T. Goralski, J. J. Hiller, Jr., J. A. Levisky, and R. M. Lange, *J. Amer. Chem. Soc.*, **87**, 1262 (1965).

(5) P. Kovacic, J. A. Levisky, and C. T. Goralski, *ibid.*, **88**, 100 (1966).

(6) P. Kovacic and J. A. Levisky, *ibid.*, **88**, 1000 (1966).

(7) P. Kovacic and A. E. Harrison, *J. Org. Chem.*, **32**, 207 (1967).

(8) P. Kovacic, K. W. Field, P. D. Roskos, and F. V. Scalzi, *ibid.*, **32**, 585 (1967).

(9) P. Kovacic and R. J. Hopper, *Tetrahedron*, **23**, 3977 (1967).

(10) P. Kovacic, J. F. Gormish, R. J. Hopper, and J. W. Knapczyk, *J. Org. Chem.*, **33**, 4515 (1968).

(11) P. Kovacic and S. S. Chaudhary, *Tetrahedron*, **23**, 3563 (1967).

(12) P. Kovacic and M. K. Lowery, *J. Org. Chem.*, **34**, 911 (1969).

(13) P. Kovacic, M. K. Lowery, and P. D. Roskos, *Tetrahedron*, **26**, 529 (1970).

(14) P. Kovacic and P. D. Roskos, *Tetrahedron Lett.*, 5833 (1968).

(15) P. Kovacic and P. D. Roskos, *J. Amer. Chem. Soc.*, **91**, 6457 (1969).

(16) W. Bracke, W. J. Cheng, J. M. Pearson, and M. Szwarc, *ibid.*, **91**, 203 (1969).

(17) *Cf.* K. M. Harmon, A. B. Harmon, and F. E. Cummings, *ibid.*, **83**, 3914 (1961).

(18) W. Hückel and M. Blohm, *Justus Liebigs Ann. Chem.*, **502**, 114 (1933).

stereochemistry indicated by the acetamide derivative was confirmed by comparison of the amine with authentic material obtained by Hofmann degradation of *cis*-9-decalincarboxamide. In all cases the recovered decalin consisted of the *trans* isomer only.

TABLE I
AMINATION OF DECALIN[a]

Decalin	Addition time,[b] min	Yield, % Crude base[c]	Yield, % *cis*-9-Aminodecalin[d]
trans[e]	53	55	41
cis[f,g]	60	49	31
Mixed[h]	67	47	35
Mixed[i-k]	120	8	6
Mixed[i,l,m]	100	42	17
Mixed[i,n]	75	68	50

[a] Temperature, 0–5°. [b] Followed by 0.5-hr stirring. [c] Distilled material. [d] The remaining base contained numerous unidentified components, all of which could be removed by distillation. [e] NCl_3:$AlCl_3$:decalin:CH_2Cl_2 = 0.1:0.2:0.35:2. [f] NCl_3:$AlCl_3$:decalin:CH_2Cl_2 = 0.1:0.2:0.4:2. [g] *cis* (97%), *trans* (3%). [h] *trans* (34%), *cis* (66%). [i] *cis* (61%), *trans* (39%). [j] Inverse addition; decalin was added to a mixture of trichloramine–aluminum chloride in methylene chloride solvent. [k] −1 to 1°. [l] Aluminum bromide was used in place of aluminum chloride; *t*-butyl bromide (0.036 mol) was added to the reaction mixture prior to the trichloramine. [m] 4–7°. [n] See Experimental Section, general procedure B.

Because of the specificity of the reaction and the synthetic advantage offered by this procedure over the circuitous literature routes, an investigation of reaction conditions was undertaken in order to optimize the yield. Earlier studies have revealed that the preferred method for amination of alkyl halides involves addition of the alkyl halide to the trichloramine–aluminum chloride mixture.[12] In an experiment in which the mode of addition was reversed the yield of crude base was drastically reduced (Table I, entry 4) perhaps resulting from destruction[19] of trichloramine by the generated hydrogen chloride. Use of the aluminum bromide–*t*-butyl bromide catalyst system[14,15] decreased the yield of desired material and increased the amount of by-product amine (Table I, entry 5). The stronger catalyst[20] might cases a deep-seated isomerization of the parent nucleus.[21] A modified work-up procedure[15] afforded the highest yields (50%). For increased efficiency, the methylene chloride solvent was removed by distillation during hydrolysis.

Hydrindan.—The specificity observed with decalin also pertained to hydrindan. Amination at 5–10° afforded *cis*-8-aminohydrindan in 70% yield. The authentic amine was synthesized by a Hofmann degradation procedure similar to the one used for *cis*-9-aminodecalin.

The stereospecificity observed on amination of the fused-ring substrates has precedence. Models show that *trans*-9-N,N-dichloroaminodecalin is more crowded than the *trans*-9-methyl analog. In the case of the 9-methyldecalins, it appears that the *cis* isomer is slightly favored at equilibrium.[22,23] The observed specificity may reflect the relief of axial–axial interactions in the *trans* compound. Furthermore, Bartlett and coworkers demonstrated that *cis*-decalin-9-carboxylic acid is thermodynamically favored in the isomerization of *trans*-decalin-9-carboxylic acid with fuming sulfuric acid.[24] Analogously, in 8-methylhydrindan the *cis* conformer is energetically preferred since only in the *cis* compound can the methyl group assume an equatorial position.[22] Christol and Solladie have shown that, under the conditions of the Ritter reaction, certain precursors undergo isomerization and then amination to give *cis*-8-aminohydrindan after hydrolysis of the initially formed formamide precursor.[25]

Secondary Alicyclic Hydrocarbons.—Many alicyclic compounds are extensively isomerized under Friedel–Crafts conditions.[21,26,27] Application of the standard reaction to substrates in this category affords alicyclic amines derived from rearranged hydrocarbons.

Cycloheptane.—Upon treatment at 5–10° with trichloramine–aluminum chloride, cycloheptane produced a 65% yield of 1-amino-1-methylcyclohexane. Lewis acids are known to convert cycloheptane to methylcyclohexane,[26] and in fact none of the excess starting material was found unchanged in the neutral portion of the amination mixture. The basic product was identified by comparison with authentic material.[11]

Eight-Carbon Alicyclics.—In the presence of aluminum chloride as catalyst, cyclooctane, methylcycloheptane, *cis*-1,3-dimethylcyclohexane, and 1,4-dimethylcyclohexane are rearranged to a mixture of dimethylcyclohexanes consisting mainly of the 1,3 and 1,4 isomers.[26,27] In our system the hydrocarbons underwent extensive isomerization, to the extent that in the recovered organic phase from the amination of cyclooctane or methylcycloheptane no unrearranged starting material was found.

The major product from each substrate was an inseparable mixture (glpc) of 1,3- and 1,4-dimethyl-1-aminocyclohexanes (Table II). The infrared spectra of the product mixtures were identical except for a few slight intensity differences. As an aid in identification, a Hofmann elimination was performed after conversion to the quaternary hydroxides, followed by ozonolysis of the resultant olefins. Analysis of the methylcyclo-

TABLE II
AMINATION OF C_8 CYCLOALKANES

Substrate	Temp, °C	Basic product, yield, % Crude[a]	Basic product, yield, % Purified[b]
Cyclooctane	5–10	70	50
Methylcycloheptane	0–3	72	50
cis-1,3-Dimethylcyclohexane	0–3	77	55
1,4-Dimethylcyclohexane	4–6	72	50

[a] Total base. [b] The major product is a mixture of 1,3- and 1,4-dimethyl-1-aminocyclohexanes.

(19) W. A. Noyes, *J. Amer. Chem. Soc.*, **42**, 2173 (1920).
(20) P. von R. Schleyer and M. M. Donaldson, *ibid.*, **82**, 4645 (1960).
(21) E. Wilson, *Chem. Rev.*, **21**, 129 (1937).
(22) N. L. Allinger, *J. Org. Chem.*, **21**, 915 (1956).
(23) A. Ross, P. A. S. Smith, and A. S. Dreiding, *ibid.*, **20**, 905 (1955).
(24) R. E. Pincock, E. Grigat, and P. D. Bartlett, *J. Amer Chem. Soc.*, **81**, 6332 (1959).
(25) H. Christol and G. Solladie, *Bull. Soc. Chim. Fr.*, 3193 (1966).
(26) M. B. Turova-Pollak, *Dokl. Akad. Nauk SSSR*, **60**, 807 (1948).
(27) G. Chiurdoglu, P. J. C. Fierens, and C. Henkart, *Bull. Soc. Chim. Belges*, **59**, 140 (1950).

hexanones revealed that the starting amine possessed the approximate isomeric composition of 71% 1,3 and 29% 1,4. For verification, the olefinic mixture was aromatized with palladium on carbon, producing *m*-xylene (73%) and *p*-xylene (27%). No cyclooctylamine or 1-amino-1-methylcycloheptane was detected in the base obtained from cyclooctane or methylcycloheptane, respectively.

Cyclododecane.—Amination of cyclododecane at 3–6° gave many products, presumably cyclohexane derivatives, which appear to arise from isomerization; no cyclododecane was recovered. Although identification of the product mixture was not carried out, it was shown that cyclododecylamine was not a component (glpc comparison with authentic material).

Cyclohexane.—The amination of cyclohexane was found to be quite sensitive to temperature changes and the addition of isomerization catalyst, *e.g.*, olefin (Table III). Cyclohexylamine was the predominant product

TABLE III

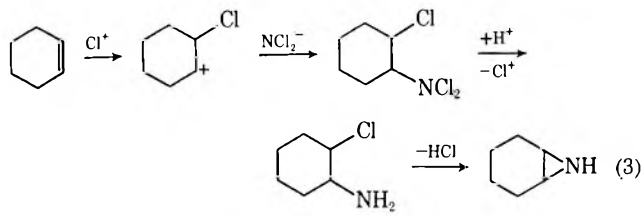
AMINATION OF CYCLOHEXANE[a]

Cyclohexene,[b] mol	Temp, °C	Products, % of total base: Cyclohexylamine	1-Amino-1-methylcyclopentane	7-Azabicyclo[4.1.0]heptane	Yield,[c] %
	−10	80	6		45
0.01	−10	78	16		53
d	10–15	6	90	4	54
0.01	10–15	Trace	98	1	46

[a] $NCl_3:AlCl_3:C_6H_{12}:CH_2Cl_2$ = 0.1:0.2:1:1. [b] Added before trichloramine. [c] Crude base. [d] $NCl_3:AlCl_3:C_6H_{12}:CH_2Cl_2$ = 0.1:0.2:0.5:2.

at low temperatures, even in the presence of cyclohexene. However, at higher temperatures, particularly with added promoter, 1-amino-1-methylcyclopentane is formed preferentially. Ipatieff and coworkers noted that the Lewis acid catalyzed isomerization of cyclohexane at 25°, with hydrogen bromide and cyclohexene as cocatalysts, gave only a 9% yield of methylcyclopentane.[28] It is our contention that 1-amino-1-methylcyclopentane predominates at 10–15° because amination selectively involves the tertiary center, thus siphoning off the *t*-alkane as it is formed. Since rearrangement is slow at −10°, nucleophilic attack at a secondary position of cyclohexane is favored. In some cases, 7-azabicyclo[4.1.0]heptane was formed in minor quantities. 1-Amino-1-methylcyclopentane was compared with authentic material obtained by independent synthesis. A literature method was used to prepare authentic cyclohexenimine.[29]

Mechanistically, the major products can be rationalized by the processes outlined in eq 1 and 2. An explanation for formation of the aziridine involves stepwise addition of trichloramine to cyclohexene (eq 3). The olefin was detected in the reaction mixture. The ring-closure step, believed to occur during work-up, exemplifies the Gabriel synthesis of aziridines.[30] Coleman and collaborators found that trichloramine will add



(3)

to cyclohexene in an uncatalyzed system, eventually giving rise to 2-chlorocyclohexylamine.[31]

Evidence that the N,N-dichloroamine serves as precursor to the end product (eq 2) was obtained from low-temperature amination of cyclohexane. With a modified work-up procedure, N,N-dichlorocyclohexylamine was isolated in 18% yield and identified by comparison with a sample of authentic material. Similarly, 1-N,N-dichloroaminoadamantane and N,N-dichloro-*t*-butylamine have been shown to be generated in amination of adamantane[14,15] and *t*-butyl chloride,[12] respectively.

In order to gain additional mechanistic insight, competitive aminations were performed with hydrindan–cyclohexane mixtures. Relative rate data were obtained with two different molar ratios of tertiary *vs.* secondary hydrocarbon. The value (1 *t*-H *vs.* 1-*sec*-H) for a 1:1 mixture was 1.5×10^3, while that for a 1:10 composition was 3×10^3, yielding an average figure of 2.25×10^3. From the data of Hughes, a value of 4.8×10^3 for the relative rate of the unimolecular hydrolysis of *t*-butyl chloride:isopropyl chloride in 80% aqueous ethanol can be calculated.[32] A comparison of the data is valid since solvolysis at a tertiary position incorporated in a cyclohexane ring proceeds at approximately the same rate as for the acyclic analog.[33] Corroboration is provided from the relative rates of solvolysis of 1-chloro-1-methylcyclohexane:*t*-butyl chloride and isopropyl chloride:cyclohexyl chloride,[33] together with Hughes' value for solvolysis of *t*-butyl chloride:isopropyl chloride. Computation furnishes a relative rate of about 2.6×10^3 for solvolysis of 1-chloro-1-methylcyclohexane:cyclohexyl chloride. Thus, good evidence is in hand for cation formation in the rate-determining step of amination.[10]

Several experiments[2] were carried out pertaining to reversibility during amination; *cf.* the Ritter reaction.[34] There was no positive evidence, since 1-amino-1-methylcyclopentane was not formed in systems containing N,N-dichlorocyclohexylamine, aluminum chloride, and cocatalysts, such as hydrogen chloride, *t*-butyl chloride, and trichloramine.

Cyclopentane.—With cyclopentane as substrate, several simultaneous reactions are occurring which give rise to various types of amines (Table IV). In keeping with earlier postulates,[11,12] plausible pathways for formation of the products are described. The cyclopentylamine route can be visualized as proceeding in the same manner as for eq 2. Two of the products, dicyclopentylamine and N-cyclopentyl-6-azabicyclo-

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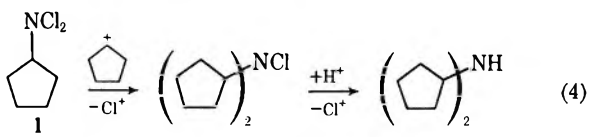
TABLE IV
AMINATION OF CYCLOPENTANE[a]

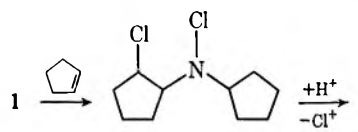
Substrate	Temp, °C	Products, % Cyclopentylamine	6-Azabicyclo[3.1.0]hexane	N-Cyclopentyl-6-azabicyclo[3.1.0]hexane	Dicyclopentylamine	Yield,[b] %
Cyclopentane	15–18	6	66	24	4	54
Cyclopentane	3–7	25	19	47	10	43
Cyclopentene	−10 to −15		9			23[c]
trans-1,2-Dichlorocyclopentane	−5–0		5			15[c]

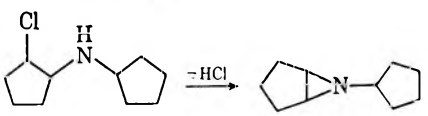
[a] See Experimental Section, general procedure C. [b] Crude base. [c] Contained many unidentified components.

[3.1.0]hexane are believed to arise as shown in eq 4 and 5. The presence of 6-azabicyclo[3.1.0]-



(4)





(5)

hexane can be rationalized on the basis of the steps outlined in eq 3. Cyclopentenimine is the major product at 15–18°, suggesting that addition of the nitrogenous nucleophile to 2-chlorocyclopentyl cation is involved. One would expect cyclopentene formation to increase with rise in temperature. Cyclopentenimine is also produced, in low yield, from *trans*-1,2-dichlorocyclopentane, one of the chlorinated hydrocarbons found in the neutral portion of the reaction mixtures from cyclopentane and cyclopentene. Imine formation with vicinal dichloride as a precursor has been observed previously.[12] The amination of cyclopentyl bromide gave similar results; however, the presence of cyclopentenimine was not determined.[12]

Synthetic Utility.—In relation to synthetic utility, the merits of certain examples from the present method become evident on comparison with literature procedures. Several uncomplicated syntheses are known which yield *trans*-9-aminodecalin;[34,35] however, no simple method is available for preparation of the *cis* isomer. Thus, treatment of decalin with trichloramine–aluminum chloride comprises the preferred route to *cis*-9-aminodecalin. Similarly, *cis*-8-aminohydrindan may be obtained in one step from hydrindan. Several alternative pathways are reported. The Ritter reaction on spiro[4.4]nonan-1-ol and $\Delta^{1,6}$-bicyclo[4.3.0]nonene give the desired material,[36] as does the Schmidt reaction with *cis*-8-hydrindancarboxylic acid.[25] The literature methods entail the use of precursors which must be synthesized. Amination of cyclopentane provides 6-azabicyclo[3.1.0]hexane or N-cyclopentyl-6-azabicyclo[3.1.0]hexane by simple fractional distillation. In comparison with this one-step procedure, a prior synthesis of 6-azabicyclo[3.1.0]hexane entailed four steps with an overall yield of 4%.[37,38] Aziridines unsubstituted on nitrogen may be obtained in several steps in high yield from iodine isocyanate and olefins.[39,40]

Application of the general procedure to tertiary alicyclic hydrocarbons which do not readily undergo acid-catalyzed isomerization seems to constitute a general method for effecting direct amination to the corresponding *t*-carbinamine. The Ritter reaction normally employes carbinol and alkene-type substrates.[41,42]

Experimental Section[43]

Materials.—Most reagents were used as received after their purity had been checked by glpc analysis. Methylene chloride was distilled from calcium hydride.

Analytical Procedures.—Infrared spectra were obtained with a Beckman IR-8 spectrophotometer on neat samples or Nujol mulls. Mass spectra were obtained on a Varian M-66 mass spectrometer. All spectra were taken on samples purified by glpc. Gas chromatography was carried out with an Aerograph Hi-Fi 1200 (column E), and a homemade unit (columns A–D): (A) 15 ft × 0.25 in., Carbowax 6000 (20%) on Chromosorb P (30–60 mesh; 5% NaOH); (B) 6 ft × 0.25 in., SE-52 (10%) on Chromosorb P (30–60 mesh); (C) 5 ft × 0.25 in., SE-30 (3%) on Var-A-Port 30 (100–120 mesh); (D) 11 ft × 0.25 in., Bentone-34 (5%) and dioctyl phthalate (5%) on firebrick (60–80 mesh); (E) 10 ft × 0.13 in., Carbowax 20M (10%) on Chromosorb P (60–80 mesh; 5% NaOH). Melting points (uncorrected) were determined on a Thomas–Hoover capillary melting point apparatus. Galbraith Laboratories, Knoxville, Tenn., performed the elemental analyses.

Preparation of Trichloramine Solution.—A published procedure (method B) was used with methylene chloride as solvent.[4] Positive halogen analysis was carried out as previously described.[4] *Caution:* Use the necessary precautions when working with N-halamines.[44] Trichloramine solution may be stored at −20° for 1 month without decomposition. Disposal can be effected by slowly adding to a cold dilute solution of sodium metabisulfite and stirring until the contents are colorless.[44]

Amination of Alicyclic Hydrocarbons. General Procedure A.—The apparatus consisted of a 500-ml, three-necked flask equipped with a mechanical stirrer, thermometer, condenser, and a funnel for below surface addition. A slow sweep of nitrogen was maintained throughout the reaction. After a mixture of the alicyclic hydrocarbon (0.5 mol) and methylene chloride (2 mol) was cooled to 0°, aluminum chloride (0.2 mol) was added in one portion, producing a heterogeneous system. A cold solution of trichloramine (0.1 mol) in methylene chloride was added dropwise during 1 hr at the desired temperature. After 30 min, the

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contents were stirred into a mixture of ice (400 g) and 75 ml of concentrated hydrochloric acid. The organic layer was separated and treated twice with 100-ml portions of dilute hydrochloric acid. The aqueous fractions were combined, extracted with ether, and treated with cold 50% sodium hydroxide. The amine was extracted with ether and dried. Removal of solvent by rotary evaporation was followed by distillation, usually through a Bantamware Minilab apparatus at reduced pressure. In some cases further purification was accomplished by means of a 25-plate spinning-band column. *cis*-9-Aminodecalin and N-cyclopentyl-6-azabicyclo[3.1.0]hexane were isolated in purity greater than 99% by this procedure.

Water-Insoluble Amine Hydrochlorides. General Procedure B.—Procedure A was modified in the work-up. After completion of the trichloramine addition and subsequent stirring, 75 ml of concentrated hydrochloric acid and 100 ml of water were added, solvent was removed by distillation, and the mixture was heated to 95° during 1 hr. Procedure A was followed for the remainder of the work-up.

Water-Soluble Amines. General Procedure C.—The aqueous layer obtained as in procedure A was concentrated by rotary evaporation to a viscous, dark liquid. The amine was liberated by treatment with 50% sodium hydroxide solution.

Competitive Aminations.—Procedure A was followed at approximately −20°. Molar ratios of trichloramine:aluminum chloride:cyclohexane:hydrindan of 1:2:5:5 and 1:2:50:5 were used. Glpc analysis (column A) with cyclopentylamine as an internal standard afforded the product ratios.

Isolation of N,N-Dichlorocyclohexylamine.—Cyclohexane (54 ml, 0.5 mol) and methylene chloride (128 ml) were placed in the standard vessel and cooled to −20°. After aluminum chloride (0.2 mol) was added in one portion, 122 ml of trichloramine solution (0.08 mol) was added dropwise between −20 and −15°. The mixture was stirred for 5 min and then quenched in ice with vigorous stirring. The organic portion was washed once with distilled water and dried. Removal of unchanged trichloramine and solvent afforded a yellow liquid which gave three fractions on distillation. The second one, bp 66° (4 mm), was shown to be N,N-dichlorocyclohexylamine (18%) by comparison of the infrared spectrum with that of authentic material.

Product Identification.—The amines were identified by comparison with authentic materials (glpc retention times and infrared spectra), either obtained commercially or by synthesis.

1-Amino-1-methylcyclopentane.—Data for this compound and its derivatives are given from the present work, Ritter product,[45] literature, respectively: yield (%) 61, 40, 30;[46] bp [°C (mm)] 35–38 (20–25), 33–38 (23), 138 (760);[46] hydrochloride mp (°C dec) 268, 268, 269–270;[47] benzamide mp (°C) 122, 122, 122–123.[46]

***cis*-9-Aminodecalin.**—Data for this compound and its derivatives are presented from present work, authentic, literature,[18] respectively: bp [°C (mm)] 74 (1.5), 70 (2), 82 (7); hydrochloride mp (°C, subl) *ca.* 315–320, ..., ...; formate mp (°C dec) 162–163, ..., 165; acetamide mp (°C) 126–126.5, 127, 127; $n^{24.5}$D 1.4949, ..., ...

Anal. Calcd for *cis*-9-aminodecalin hydrochloride ($C_{10}H_{20}NCl$): C, 63.31; H, 10.63; Cl, 18.69; N, 7.38. Found: C, 63.47; H, 10.68; Cl, 18.53; N, 7.35.

***cis*-8-Aminohydrindane.**—Data for this compound and its derivatives are given from present work, authentic, literature, respectively: yield (%) 70, ..., 34;[25] bp [°C (mm)] 80–82 (18), 79–80 (18), 83–84 (20);[25] mp (°C) 41–42, 42, 11;[36] acetamide mp (°C) 88–89, 88–89, 88.[35]

***cis*-9-Aminodecalin. a. 9-Decalincarboxylic Acid.**—The desired material was obtained by an available method.[48] The infrared spectrum indicated that the acid (66% yield) was largely *trans* (10.29 μ) with some *cis* isomer (11.26 μ).[24]

b. *cis*-9-Decalincarboxylic Acid.—The 9-decalincarboxylic acid isomers (15 g) were mixed with 34 g of 88% formic acid, and the resulting paste was added in small portions with stirring during 30 min at 5° to a mixture of fuming sulfuric acid (135 g, 30%) and sulfuric acid (281 g, 98%).[24] After 5 g of 88% formic acid was added dropwise, the reaction mixture was stirred for 1 hr. The mixture was quenched in ice with vigorous stirring and the organic product was taken up in ether and purified as in part a. The recovered acid, 14.9 g, displayed an infrared spectrum with strong absorption at 11.26 μ and a smaller band at 10.29 μ indicating isomerization from predominantly *trans* to mainly *cis*.

c. *cis*-9-Decalincarbonyl Chloride.—The crude *cis* acid was treated with thionyl chloride to produce the crude acid chloride (99% yield) contaminated with some *trans*-9-decalincarbonyl chloride.[49]

d. *cis*-9-Decalincarboxamide.—The amide was prepared from the acid chloride by reaction with ammonia gas. The crude yield was greater than theoretical because *trans*-9-decalincarbonyl chloride does not react under these conditions.[50] The infrared spectrum confirmed the presence of the impurity. Recrystallization from hexane–benzene gave 5.6 g of white needles, mp 126.5–127° (lit.[50] mp 129.7–130.5°). A second crop (6.3 g) was isolated from the mother liquor giving an 80% overall yield of *cis*-amide from the acid chloride.

e. *cis*-9-Aminodecalin.—A solution of 5.15 g (0.028 mol) of *cis*-amide in 40 ml of methanol was mixed with a solution prepared from 1.5 g (0.067 mol) of sodium and 48 ml of methanol.[51] Bromine (4.55 g, 0.028 mol) was added dropwise with magnetic stirring. The yellow solution was heated over steam for 20 min, and then made acidic with glacial acetic acid. After the methanol was removed by distillation, the urethan was thoroughly mixed with 23.4 g of calcium oxide and 15 ml of water. The mixture was heated to about 95° to distil the amine, then 15 ml of water was added and distillation was repeated. The distillates were combined, made acidic with concentrated hydrochloric acid, and extracted with ether. The amine was liberated by treatment with 50% sodium hydroxide solution, extracted with ether, and dried. Evaporation of the ether gave 3.4 g (79%) of pure *cis*-9-aminodecalin according to glpc analysis (column A).

Hydrindan.—In a 1-l. stainless steel autoclave was placed 500 g of indene and about 170 g of Raney nickel in 100 ml of absolute ethanol. After agitation for 48 hr at 210° in the presence of hydrogen (136 atm), the catalyst was removed by filtration and the solvent by distillation. Rectification of the residue gave (1) 230.4 g, bp 163–165°, of hydrindan (67.3%), indan (30.3%), and unknown (2.4%); (2) 85 g, bp 165–170°, of hydrindan (31%) and indan (69%); (3) 65 g, bp 170–175°, of hydrindan (8%) and indan (92%). Glpc collection (column D) of the products was used in identification. The hydrindan parent ion was observed at 124 amu (10 eV). Indan was characterized by infrared comparison with a published spectrum.[52] Purification was effected by sulfonation. A mixture of 219 g of fraction 1 and 440 ml of 98% sulfuric acid was heated at 65° with a water bath. After 25 min the layers were separated, and the organic portion was washed twice with dilute sodium hydroxide solution and twice with distilled water. After drying, distillation gave 115 g of product (hydrindan 96%, and unknown, 4%), hydrindan, bp 167°, n^{25}D 1.4705 (lit.[35] *cis*, bp 167.8°, n^{20}D 1.4720; *trans*, bp 161°, n^{20}D 1.4636).

***cis*-8-Aminohydrindan. a. 5-Hydrindanol.**—A stainless steel autoclave was charged with 5-indanol (100 g) and Raney nickel (50 g) in 200 ml of absolute ethanol. The agitated contents were subjected to 123 atm of hydrogen pressure for 72 hr at 170°. Distillation gave 5-hydrindanol (70%), bp 112° (11 mm) [lit.[53] bp 119–120° (22 mm)].

b. *cis*-8-Hydrindancarboxylic Acid.—A known pathway was followed.[53] Hydrindanol (65 g) and 97% formic acid (84.4 g) were added dropwise over a 4-hr period at 9–14° to sulfuric acid (553 g). The crude acid (64%) was isolated after an additional 1.5 hr of stirring at 18°.

c. *cis*-8-Hydrindancarbonyl Chloride.—The acid chloride (73%) was obtained by interaction of the acid with thionyl chloride.

d. *cis*-8-Hydrindancarboxamide.—The amide was derived from the acid chloride by treatment in ether solution with anhydrous ammonia gas. The product was recrystallized from hexane, mp 109–110° (lit.[53] mp 110–111°).

e. *cis*-8-Aminohydrindan.—The procedure for *cis*-9-aminodecalin was used giving the desired amine in 46% yield.

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Anal. Calcd for $C_9H_{17}N$: C, 77.75; H, 12.22; N, 10.06. Found: C, 77.45; H, 12.38; N, 10.16.

The acetamide derivative (acetic anhydride reagent), mp 88–89°, was crystallized three times from acetone–water (lit.[35] mp 88°, stereochemistry not determined, apparently *cis*).

Identification of Dimethylcyclohexylamines.—Characterization was carried out on the major product from amination of cyclooctane.

a. N,N-Dimethyldimethylcyclohexylamines.—The literature procedure[54] involving 90% formic acid and 37% formaldehyde gave the desired material, bp 54–57° (1.5 mm), in 85% yield (essentially pure by glpc analysis, column A).

b. N,N,N-Trimethyldimethylcyclohexyl Ammonium Iodides.—Treatment of the product from procedure a with methyl iodide afforded the quaternary ammonium iodides in 71% yield,[55] mp 203.5–204°.

c. N,N,N-Trimethyldimethylcyclohexyl Ammonium Hydroxides.[55]—Silver oxide (23.2 g, 0.1 mol) was added to a mixture of 75 ml of distilled water and 14.85 g (0.05 mol) of the quaternary ammonium iodides at 2°. After being stirred for 3 hr at 2–5°, the liquid mixture was freed of excess silver salts by filtration and concentrated by rotary evaporation at 4 mm (water bath at 35°).

d. Pyrolysis of N,N,N-Trimethyldimethylcyclohexyl Ammonium Hydroxides.[55]—The dark red product from procedure c was transferred to a 50 ml flask attached to an Ace Glass Mini-Lab distillation apparatus equipped with two traps, first, Dry Ice–acetone, and next, liquid nitrogen. The base was decomposed under nitrogen by slowly heating with an oil bath while maintaining a pressure of 20–25 mm. Reaction appeared to occur at 73°, and by 90° all the contents of the pot had distilled.

The material in the traps and receiver was combined. The organic layer was separated from the aqueous phase, and then washed with distilled water. The aqueous portions were combined, extracted with ether, and the ether extract added to the organic fraction which was dried. The olefin (52% from the amine) was subjected to glpc analysis (columns B and C) which revealed only one major peak. The infrared spectrum showed strong absorption at 1651 cm^{-1}, characteristic of a double bond exocyclic to a cyclohexane ring.[56]

e. Dehydrogenation of Product d.—A 100-ml stainless steel autoclave was charged with 15 g of benzene, 0.5 g of the olefin, and 0.25 g of 10% palladium on charcoal and shaken for 16.5 hr at 175°. Glpc analysis (column D) revealed the indicated mixture, starting material (16.5%), *p*-xylene (22.4%), and *m*-xylene (61.3%). The xylenes were identified by comparison with authentic material. In a control experiment in which *p*-xylene was subjected to identical conditions, no *m*-xylene was formed; *p*-xylene was the only compound present other than solvent.

f. Ozonolysis of Product d.[57]—The olefin (2 g) in 3.4 ml of dry pyridine and 30 ml of methylene chloride was ozonized at −72° for 45 min (Welsbach Model T-23). After standing for 6 hr the solution was washed with hydrochloric acid and then with distilled water. Glpc analysis of the dried product revealed two components, 3-methylcyclohexanone (71%) and 4-methylcyclohexanone (29%). The ketones were identified by comparison with authentic materials (retention times in glpc analysis, column A).

7-Azabicyclo[4.1.0]heptane. a. (±)-*trans*-2-Chlorocyclohexanol.—A literature method was used.[58] Treatment of cyclohexene with excess hypochlorous acid gave, after distillation, a colorless liquid (63%), bp 85–88° (20 mm), $n^{25.5}D$ 1.4864 (lit.[58] bp 88–90° (20 mm)).

b. (±)-*trans*-2-Aminocyclohexanol.—The procedure outlined by Wilson and Read was followed,[59] with the exception that the amino alcohol was isolated by sublimation (at 60°), white needles, mp 66.5–67.6° (lit.[59] mp 65°).

c. 7-Azabicyclo[4.1.0]heptane.—The method of Paris and Fanta[29] gave a colorless liquid, bp 150° (lit.[29] bp 149–150°). The infrared spectra of this product and the amination product were in agreement with the published spectrum.[29]

N,N-Dichlorocyclohexylamine.—A published procedure was used.[12] Distillation of the crude product afforded N,N-dichlorocyclohexylamine (67%), bp 65° (3.7 mm), $n^{26}D$ 1.5064 [lit.[60] bp 89–90° (17 mm)]. Infrared analysis showed NCl absorption at 690 cm^{-1},[61] but no NH stretching or deformation. The product contained 99.9% of the theoretical amount of positive chlorine according to iodometric titration.

6-Azabicyclo[3.1.0]hexane. a. (±)-*trans*-2-Chlorocyclopentanol.—The method of Coleman and Johnstone was followed.[58] Cyclopentene with excess hypochlorous acid gave a colorless liquid (49%), bp 89° (25 mm), $n^{25}D$ 1.4805 [lit.[37] bp 75–85° (15 mm), $n^{23}D$ 1.4795].

b. 1,2-Epoxycyclopentane.—Application of a literature procedure[62] to product a gave a 67% yield of colorless liquid, bp 100–102°, $n^{24.5}D$ 1.4340 (lit.[37] bp 99–102°, $n^{23}D$ 1.4330).

c. (±)-*trans*-2-Aminocyclopentanol Hydrochloride.—1,2-Epoxycyclopentane (7.5 g) was shaken in a stainless steel autoclave with 100 ml of concentrated ammonium hydroxide for 2 hr at 70–80°. The amino alcohol was liberated by the addition of sodium hydroxide pellets and extracted with ether. After removal of ether, the amino alcohol was dissolved in dilute hydrochloric acid and vacuum distilled to dryness, giving tan crystals (50%), mp 180° (lit.[37] mp 193–194°).

d. 6-Azabicyclo[3.1.0]hexane.—The method of Fanta was followed.[38] The hydrochloride afforded the imine (52%) (glpc analysis, column E), bp 123°, $n^{23.5}D$ 1.4698 (lit.[38] bp 122–123°, $n^{22}D$ 1.4700).

Registry No.—Trichloramine, 10025-85-1; aluminum chloride, 7446-70-0; decalin (*cis*), 493-01-6; cyclohexane, 110-82-7; cyclopentane, 287-92-3; *cis*-9-aminodecalin (HCl), 24302-24-7; *cis*-9-aminodecalin (acetamide), 24302-25-8; decalin (*trans*), 493-02-7.

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Aromatic Oxygenation with Benzoyl Peroxide–Iodine[1]

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A study was made of the direct synthesis of aryl benzoates from benzoyl peroxide–aromatic–iodine at 90°. After investigation of several reaction parameters, a standard procedure was adopted with toluene as substrate. Quantitative data were obtained for toluene, chlorobenzene, and anisole. The orientations and relative rates indicate that the substitution mechanism is similar to that previously established for the peroxide–cupric chloride reaction. Rates of peroxide disappearance were determined under various conditions. A chain sequence seems to be operative with halogen but not with benzoyl peroxide. The method appears to possess synthetic capability.

The literature describes various approaches to investigation of the peroxide–iodine system. In 1945, Perret and Perrot[5] reported the formation of aryl benzoates from reaction of benzoyl peroxide with aromatic substrates in the presence of iodine. For example, toluene afforded tolyl benzoates in 64% yield, accompanied by small quantities of *o*- and *p*-iodotoluene. In a similar manner, benzoyloxylation of several arenes was subsequently effected by other investigators.[6–8] With only the two reactants, benzoyl peroxide and iodine in carbon tetrachloride, Hammond and Soffer[9] were able to isolate iodobenzene in high yield. The preparative value of this technique[10] was subsequently improved,[11] extended[12a] to other aryl iodides, and enlarged in relation to the peroxide component.[12b] Alkyl iodides have been prepared[11,13] in an analogous fashion, *e.g.*, 1-iodooctane from pelargonyl peroxide. An investigation[11] of the benzoyl peroxide–iodine reaction in a variety of solvents revealed that aromatic compounds exerted a deleterious effect on iodobenzene production. Thus, benzoate esters were generated in a competing process when anisole, benzene, and chlorobenzene served as the media. The lack of requisite quantitative information in the existing literature for aromatic oxygenation with the peroxide–iodine combination precluded any meaningful mechanistic interpretation.[13a]

Previous reports[14–19] from this laboratory have presented a method for the oxygenation of aromatic compounds involving an appropriate peroxide and cupric chloride. With diisopropyl peroxydicarbonate, toluene afforded tolyl isopropyl carbonates in 85% yield,[15] and benzoyl peroxide gave tolyl benzoates in 40% yield.[16] A study[19] of the effect of variation in the catalyst demonstrated that iodine was relatively ineffective in the toluene–diisopropyl peroxydicarbonate–acetonitrile system.

Our main concern was to elucidate the mechanism of aromatic oxygenation with benzoyl peroxide–iodine. Investigation of a number of reaction variables was carried out, including several aromatic substrates. Quantitative data were obtained for the orientations and relative rates. Attention was also given to the synthetic utility.

Results and Discussion

After exploration of several reaction variables,[3] a standard procedure was adopted entailing benzoyloxylation for 20 hr at 90° with a toluene:peroxide:iodine ratio of 12.6:1:0.21, the same relative concentrations employed by Perret and Perrot.[5] Under these homogeneous conditions, tolyl benzoates were formed in 60% yield (based on peroxide), 50:20:30 *ortho:meta:para;* benzoic acid was formed in 78% yield and carbon dioxide in 37% yield; small amounts of benzene, bibenzyl, biphenyl, methylbiphenyl, phenyl benzoate, iodobenzene, *o*- and *p*-iodotoluenes, and benzyl iodide were also formed. The material balance based on carbon dioxide units was 175%, and the amount of iodine consumed was 62%. The earlier workers[5] reported no specific orientation data.

The findings from alteration in the catalyst:peroxide ratio are set forth in Table I. The yield of ester declined[5] when the ratio was less than 0.21 and, at higher values, remained essentially constant or perhaps passed through a maximum. Low ratios favored products derived from breakdown of benzoyloxy radicals, indicating that iodine exerts the net effect of countering decarboxylation. The figure 0.13 represents 62% of the iodine employed in the standard procedure, which is the amount consumed in the reaction. It is obvious that this level of iodine must be augmented for maximum efficiency in oxygenation. Hammond[8] noted in a similar study that the quantity of ester passed through a maximum during decomposition of the peroxide in benzene containing iodine.

Variation in the toluene:peroxide ratio (Table II)

(1) Paper XII of a series on aromatic oxygenation.

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TABLE I

VARIATION IN THE CATALYST:PEROXIDE RATIO[a]

Catalyst: peroxide, M	Products, %[b] Tolyl benzoates Yield	o	m	p	Benzoic acid	By-products[c]	CO_2
1.00[d]	57	49	11	40	89	1	13
0.525	63	46	18	36	89	2	10
0.210	60	50	20	30	78	5	37
0.130	35	53	19	28	76	12	46
0.084	16	54	16	30	78	21	100
0.040[e]	6	58	15	27	90	28	

[a] Toluene:peroxide = 12.6:1, 90 ± 2°, 20 hr. [b] See Experimental Section for yield basis. [c] Biphenyl, bibenzyl, and methylbiphenyl. [d] Heterogeneous. [e] Iodine color disappeared after 1 hr.

TABLE II

VARIATION IN THE TOLUENE:PEROXIDE RATIO[a]

Toluene: peroxide, M	Products, %[b] Tolyl benzoates Yield	o	m	p	Benzoic acid	By-products[c]
25.5	62	52	17	31	96	7
19.1	63	50	19	31	91	6
12.6	60	50	20	30	78	5
9.55	62	46	22	32	96	1

[a] Peroxide:iodine = 1:0.21, 90 ± 2°, 20 hr. [b] See Experimental Section for yield basis. [c] Biphenyl, bibenzyl, and methylbiphenyl.

elicited little change in yield of the ester product. With large quantities of toluene reactant, a slight increase was observed in hydrocarbon by-products. The ratio could not be lowered below 9.55 owing to insolubility of the peroxide. Unfortunately, the presence of solvents such as acetonitrile, *o*-dichlorobenzene, or nitromethane, produced a dramatic decrease in yield.[3]

Quite significant information was obtained from a study of the rate of peroxide disappearance at 85° with and without iodine. In the presence of iodine, peroxide decomposition displayed good first-order dependence[3] with a rate of 1.6×10^{-3} min^{-1}. First-order dependence, with a rate of 1.7×10^{-3} min^{-1}, also pertained when the halogen was omitted. Hence, little or no difference in rate under the two sets of conditions was detected. These values compare favorably with that ($k = 1.55 \times 10^{-3}$ min^{-1} at 79°) previously reported for breakdown of the peroxide in benzene both in the presence and absence of iodine.[8] Iodine is reported to produce a slight decrease in rate (carbon dioxide evolution) for the decomposition of acetyl peroxide in carbon tetrachloride.[20] The use of iodine as a radical trap, *e.g.*, in preventing the induced decomposition of peroxides, has been well documented.[9,21]

The organic chemistry of iodine is complicated by its versatility—the ready involvement in radical reactions, the variety of oxidation states, its ability to form complexes, and the behavior of possible by-products, such as hydrogen iodide. In light of the present findings, and by analogy with related systems, the salient features of a plausible mechanism are presented (eq 1–4).

$$Bz_2O_2 \longrightarrow 2BzO\cdot \quad (1)$$

$$BzO\cdot + I_2 \rightleftharpoons BzOI + I\cdot \quad (2)$$

$$C_6H_6 + BzO\cdot \longrightarrow \underset{1}{[C_6H_6OBz]\cdot} \xrightarrow{I\cdot} C_6H_5OBz + HI \quad (3)$$

$$BzOI + HI \longrightarrow BzOH + I_2 \quad (4)$$

Thermal homolysis of benzoyl peroxide (eq 1) is followed by combination of benzoyloxy radicals with iodine (eq 2) to produce benzoyl hypoiodite and iodine atoms, in accord with the observations of Hammond and Soffer.[9] One might expect this to be a reversible process,[5] considering that iodine atoms abstract iodine from alkyl iodides.[22a] Furthermore, other acyl derivatives of iodine have been reported, such as $I(OCOR)_3$,[13] and may be present. Equation 3 illustrates aromatic attack entailing the benzoyloxy radicals with subsequent rearomatization by iodine atoms to afford the aryl ester and hydrogen iodide. This pathway is analogous in some respects to that proposed for the peroxide–cupric chloride reactions;[14–19] the basic similarity in the substitution process is supported by an essentially identical orientation from toluene (*ortho*:*meta*:*para* = 56:18:26 with cupric chloride).[16] Although abstraction of alkane hydrogen by iodine atoms is not a facile process,[22a] the favorable energetics of rearomatization should be taken into account. It is noteworthy that hydrogen transfer between benzyloxy radicals and iodine appears to be exothermic.[23] During oxygenation, iodine could be regenerated subsequently by radical recombination[22b] or by metathesis of benzoyl hypoiodite and hydrogen iodide[24] (eq 4), similar to the interaction of benzoyl hypochlorite with hydrogen chloride.[25,26] A reviewer suggested that hydrogen iodide might combine with benzoyl peroxide. Whereas a chain process nicely accounts for the tenfold rate increase in peroxide disappearance with copper salt catalysis,[14] it is clear from the decomposition kinetics that such a sequence involving benzoyl peroxide is not occurring in the present case. At the same time, since a relatively small amount of iodine will suffice, a chain reaction with halogen as a link appears to be operative.

Several alternatives for removal of hydrogen from the cyclohexadienyl radical deserve consideration. It is possible that abstraction is effected by molecular iodine (or benzoyl hypoiodite) as illustrated in eq 5. This

$$1 \xrightarrow{I_2} C_6H_5OBz + HI + I\cdot \quad (5)$$

possibility resembles the peroxide–cupric chloride process wherein oxidative rearomatization produces esters, hydrogen chloride, and cuprous chloride.[14] Unlike the copper-catalyzed system, however, iodine atoms are ineffective in inducing peroxide decomposition. Since evidence exists that benzoyloxy radicals transform the σ complex in the last step of aromatic

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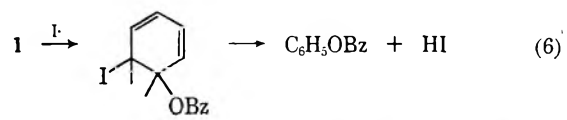
substitution by phenyl radicals,[27] the same pathway may be involved to a minor extent in oxygenation. Also, atomic iodine may add to **1** with subsequent loss of hydrogen iodide (eq 6) in an overall scheme which



(6)

amounts to substitution by addition–elimination.[28] Addition of benzoyl hypoiodite to the alkene functionality has been recorded.[5] In any event, a catalyst characterized by efficient oxidizing power is evidently present since this type of component appears to be necessary for smooth operation.[14,17,19]

The by-products are typical of processes arising from decomposition of benzoyl peroxide.[27,29] Decarboxylation of benzoyloxy radicals gives phenyl radicals which may dimerize to give biphenyl, or react with toluene by substitution or hydrogen abstraction. Benzyl radicals produced by the latter process account for benzyl iodide and bibenzyl. The small extent of side-chain participation is not surprising since benzoyloxy radicals are known to display a much lower propensity for hydrogen abstraction than do *t*-butoxy radicals.[30] Phenyl benzoate is believed to be the result of a cage effect.[31]

Benzoyl hypoiodite presumably serves as the precursor[9,32] of iodobenzene in a manner similar to the formation of chlorobenzene from the corresponding hypochlorite.[25] By analogy with the orientation observed in aromatic halogenation[24] by benzoyl peroxide–lithium chloride and by the Hunsdiecker reagent,[32] we believe that the *o*- and *p*-iodotoluenes arise *via* a pathway involving an electrophile[12b] derived from benzoyl hypoiodite. Perhaps a Lewis acid, *e.g.*, I_2 or HI, is exerting a catalytic effect.[12b] In a control experiment in the absence of peroxide, aryl iodides were not produced.

Relative rate data for a few of the aromatic substrates are presented in Table III. The minor amounts of phenyl benzoate formed from the peroxide in a side reaction have a negligible effect on the validity of the results. The figure for $k_{toluene}/k_{benzene}$, 3.3, is very close to the values recorded for the cupric chloride promoted

TABLE III

RELATIVE RATES WITH BENZOYL PEROXIDE–IODINE[a,b]

ArH	ArH: C_6H_6, *M*	Temp, °C	$[ArO_2CC_6H_5]$: $[C_6H_5O_2$-$CC_6H_5]$	Rel rate[c]
Toluene	0.836	88	2.46	2.94 ± 0.01[d]
Toluene	0.250	84	0.935	3.74 ± 0.15[d]
Anisole	0.820	89	5.07	6.19 ± 0.05[e]
Anisole	0.250	87	3.64	14.5 ± 0.10[e]

[a] Relative to benzene. [b] Total aromatic:peroxide:iodine = 51–28:1:0.21, 20 hr; see Experimental Section. [c] Each value is the average of two or more runs in close agreement. [d] Average for all toluene runs, 3.34 ± 0.4. [e] Average for all anisole runs, 10.3 ± 4.

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reactions (2.5 for benzoyl peroxide[16] and 3.8 for peroxydicarbonate[17]), which emphasizes the mechanistic parallel.

With diisopropyl peroxydicarbonate–toluene in acetonitrile, iodine was found to be an inefficient catalyst for oxygenation.[19] Table IV summarizes the results

TABLE IV

OXYGENATION OF TOLUENE WITH DIISOPROPYL PEROXYDICARBONATE[a]

ArH, mol	I_2, mol	Tolyl isopropyl carbonates: Yield, %	*o*	*m*	*p*
17.3	0.3	7[b]	48	30	22
17.7	0.21	36	58	17	25
12.6	0.21	36	58	17	25

[a] Peroxide, 1 mol, 60°. [b] Acetonitrile solvent, 150 ml; see ref 19.

from further investigations of oxygenation with this system, which were obtained at 60° because of thermal instability of the peroxide. Under neat conditions, ester production was increased to 36% with essentially the same orientation as observed for cupric chloride (*ortho*:*meta*:*para* = 57:15:28).[14] However, the yield is appreciably greater with benzoyl peroxide, presumably owing to the relative rates of decarboxylation of the isopropoxycarboxy and benzoyloxy radicals under these conditions. It is mechanistically pertinent that the orientations resulting from the two peroxides are similar. At 60° in the presence of iodine, the rate of decomposition of the peroxydicarbonate in toluene[3] was 5.73×10^{-3} min^{-1} compared[14] with 6.45×10^{-3} min^{-1} for the uncatalyzed case at 50° and 6.6×10^{-2} min^{-1} in the presence of cupric chloride.

A number of other aromatic substrates possessing a range of activities were scrutinized with benzoyl peroxide (Table V). Benzene afforded phenyl benzoate in

TABLE V

OXYGENATION OF AROMATIC COMPOUNDS WITH BENZOYL PEROXIDE–IODINE[a]

Aromatic	Products, %[b]: Aryl benzoates: Yield	*o*	*m*	*p*	Benzoic acid
Benzene	62				115
Chlorobenzene	25	47	21	32	49
Anisole	87	47	<1	53	95
m-Dimethoxybenzene	54[c,d]		2,4		122

[a] Aromatic:peroxide:iodine = 12.6:1:0.21, 90 ± 2°, 20 hr. [b] See Experimental Section for yield basis. [c] 2,4-Dimethoxyphenol; the nmr spectrum was in accord with this structure. [d] 72% of the unchanged *m*-dimethoxybenzene was recovered by distillation.

62% yield while chlorobenzene produced only modest amounts of an isomeric mixture of esters (for comparison, *ortho*:*meta*:*para* = 54:13:33 from peroxydicarbonate–cupric chloride[15] and, for benzoyl peroxide–cupric chloride[33] at 60°, 52:16:32). The indicated yield order, from the present work and earlier studies,[5] anisole > toluene > chlorobenzene > nitrobenzene, correlates nicely with the electrophilic character of carboxy radicals.[16] We observed the same type of relationship in the studies with diisopropyl peroxydicarbonate–cupric chloride.[15] Thus, further support is

(33) M. E. Kurz and M. Pellegrini, unpublished work; we are grateful to Dr. Kurz for making available these data.

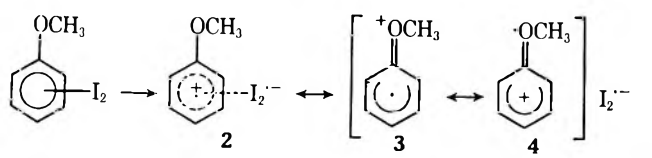
provided for the proposed reaction scheme. Observations concerning the preparation of iodobenzene from benzoyl peroxide–iodine in various solvents are relevant.[11] There was essentially an inverse relationship between iodobenzene formation and susceptibility of the aromatic solvent to electrophilic attack (oxygenation was observed as a competing reaction). For example, in chlorobenzene the competing process was claimed to provide 2- and 4-chlorophenyl benzoates in equal amounts. Oldham and Ubbelohde also commented that solvents such as toluene or xylene appear to react with iodine acyls.[13]

With anisole–benzoyl peroxide–cupric chloride,[16] it was found that the yield of anisyl benzoates decreased from 75 to 56% with an increase in temperature from 60 to 80°, which was attributed to an increased rate of decarboxylation of the benzoyloxy radical at the higher temperature. However, iodine as catalyst at 90° produced anisyl benzoates in 87% yield, in part because of the effect of the halogen in reducing the extent of decarboxylation. In addition to the favorable reactivity of the aromatic substrate, the high yield may also reflect stabilization of benzoyloxy radicals by complexing with the ether oxygen (*cf.* the interaction proposed with bromobenzene[34]).

The orientations present an even more vivid comparison. Oxygenation both in the neat system (*ortho*:*para* = 65–82:35–18)[35] and in the presence of cupric chloride (*ortho*:*meta*:*para* = 68:<1:32)[16] affords high *ortho*:*para* ratios, just as in the case of diisopropyl peroxydicarbonate–cupric chloride (*ortho*:*meta*:*para* = 63:<1:36).[17] The *ortho*:*para* ratio from benzoyl peroxide–iodine, however, was found to be considerably smaller, *i.e.*, slightly less than one (Table V). In independent work entailing a similar system, equal amounts of the *ortho* and *para* isomers were reported.[11] The relative rate data (6–15) for anisole *vs.* benzene (Table III) are close to that (10.4, *cf.*[33] 10.3) observed with copper salt catalysis (compare with 24.9 for peroxydicarbonate–cupric chloride).[14] The decomposition of benzoyl peroxide at 87° in anisole with iodine present displayed good first-order dependence,[3] rate of 2.3×10^{-3} min^{-1}, which is negligibly different from the value of 4.98×10^{-3} min^{-1} for decomposition at 80° in the absence of catalyst.[35] In addition there is good correspondence to the data obtained in toluene.

Several interpretations of the anomalous isomer distribution can be advanced. Within the framework of the working hypothesis, it is possible to visualize participation of a bulky attacking species, thus making for reduced entry at the *ortho* position. Since anisole is quite prone to substitution, a somewhat less active radical moiety, such as $C_6H_5C(=O)—O^{\delta\cdot}\cdots I^{\delta}$ or $C_6H_5CO_2\cdot\cdots I_2$, but with an enhanced steric factor, might be able to effect oxygenation. One should bear in mind that appreciable variation in isomer distributions for radical oxygenation can result from changes[14,19] in catalyst, solvent, time–temperature, or concentration

Alternatively, a charge-transfer phenomenon might be involved. Studies[36,37] of iodine–aromatic complexes indicate that the stability increases with increasing electron donation by the substituent. Also, findings concerning the influence of solvents led to the conclusion that **2** contributes to stabilization of the complex.[38]



2 **3** **4**

However, substituent effects[36] suggest that resonance participation is not pronounced. The canonical form **3** which should be favored over **4** energetically, might possibly interact with a benzoyloxy radical followed by loss of a proton.

One other aromatic ether, *m*-dimethoxybenzene, was explored. The crude ester, which was not isolated, provided 2,4-dimethoxyphenol[39] (54% overall yield) on hydrolysis.

A number of the prior investigators who observed aromatic oxygenation under related conditions commented on the mechanistic aspects. By analogy to the behavior of olefins, Perret and Perrot[5] proposed initial addition of benzoyl hypoiodite to the aromatic nucleus. Rearomatization was then accomplished by liberation of hydrogen iodide. Hammond[8] hypothesized that the ester is derived from benzoyl hypoiodite and aromatic substrate in an iodine-catalyzed reaction which is nonradical in nature. In benzoyloxylation of chlorobenzene by silver bromide dibenzoate, an electrophilic pathway involving $C_6H_5CO_2{}^+[Ag(O_2CC_6H_5)Br]^-$ was suggested.[40] However, it is evident from the $k_{chlorobenzene}/k_{benzene}$ data (0.34 for the Bryce-Smith and Clarke reagent[40]) that the process is decidedly more akin to free-radical oxygenation[15] (0.46) than to nitration (0.03). Hence, a "complexed" $C_6H_5CO_2\cdot$ species appears to be a more likely participant.

Finally, a brief discussion of synthetic utility[14,15] would be appropriate. In general, the peroxydicarbonate–cupric chloride combination affords somewhat higher yields of oxygenated product. However, the present procedure, which represents an improvement over the earlier method,[5] employs the more readily available benzoyl peroxide.

Experimental Section[41]

Materials.—Benzoyl peroxide (98%, Eastman) and iodine (Fisher, resublimed) were used as obtained. The solvents and aromatic reagents, of high purity by glpc analysis, were used directly. We are grateful to the Pittsburgh Plate Glass Co. for generous samples of diisopropyl peroxydicarbonate.

Aromatic Oxygenation. General Procedure.—The aromatic reactant (0.942 mol) was placed in a three-neck flask equipped with a stirrer, thermometer–gas inlet, and condenser. The flask was immersed in a constant-temperature bath and allowed to equilibrate at 90° (60° for diisopropyl peroxydicarbonate). Iodine (4 g, 0.0157 mol) was added, followed by benzoyl peroxide (17.92 g, 0.074 mol), causing a momentary temperature drop to 85°. After 20 hr, the mixture was quenched by pouring over ice (200 g), and the layers were separated. As noted in certain cases, the amount of iodine remaining was determined by removal of an aliquot from the reaction mixture. The organic layer from the reaction mixture was washed with sodium thiosulfate solu-

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(38) S. U. Choi and B. Y. Lee, *Daehan Hwahak Hwoejee*, **9**, 161 (1965); *Chem. Abstr.*, **65**, 3078 (1966).
(39) P. Kovacic and M. E. Kurz, *J. Org. Chem.*, **31**, 2011 (1966).
(40) D. Bryce-Smith and P. Clarke, *J. Chem. Soc.*, 2264 (1956).
(41) Boiling points and melting points are uncorrected.

tion (150 ml), saturated sodium carbonate (two 150-ml portions), and water and then dried over sodium sulfate.

A portion of the reaction mixture was concentrated by removal of most of the aromatic substrate under reduced pressure. After the products were separated and collected by glpc, the retention times and infrared spectra were compared with those of authentic samples. In this manner, the benzoate esters, biphenyl, bibenzyl, methylbiphenyl, iodotoluene, and the chlorobiphenyls were identified. The more volatile products, benzene, iodobenzene, and benzyl iodide, were characterized on the basis of the glpc retention time and peak enhancement with authentic material.

The combined aqueous extract, excluding the sodium thiosulfate wash, was acidified with concentrated hydrochloric acid (75 ml)–ice (50 g). The crude benzoic acid was collected, washed with cold water, and air-dried. Extraction of the filtrate with ether, followed by solvent removal, afforded additional crude benzoic acid which was combined with the first crop. In general, the acid was not further purified.

In the case of *m*-dimethoxybenzene, the reaction mixture was refluxed with 5% ethanolic potassium hydroxide (150 ml) under nitrogen for 2 hr. After removal of most of the ethanol *in vacuo*, the remaining semisolid material was washed with water (150 ml), and the layers were then separated. The organic portion was washed again with 10% sodium hydroxide (150 ml), and the combined aqueous extract was acidified with concentrated hydrochloric acid–ice. The mixture was then extracted with ether (two 150-ml portions), and the ethereal solution was washed with 10% sodium bicarbonate (two 100-ml portions). After removal of most of the ether *in vacuo*, distillation of the residue afforded 5.2 g (54%) of the phenolic product (pure by glpc, column 2), bp 86–90° (1.2 mm), along with 0.33 g (4%) of residue. The *p*-nitrobenzoate derivative melted at 127–128° (lit.[42] mp 129°). Acidification of the basic extracts of the original reaction mixture yielded 9.21 g (122%) of crude benzoic acid. In a similar manner, 1.2 g of benzoic acid was obtained after hydrolysis of the ester by acidification of the bicarbonate extracts.

Where noted, the additives were introduced into the standard reaction mixture before the iodine and benzoyl peroxide.

Authentic Materials.—Most of the products were commercially available. The benzoate esters were prepared by adaptation of a technique described for aryl isopropyl carbonate esters.[43]

Competitive Oxygenation.—After the aromatic reactants were equilibrated in the constant temperature bath, iodine and benzoyl peroxide were added as in the general procedure. The molar ratio of total aromatic:peroxide:iodine was 51–28:1:0.21, with a reaction time of 20 hr following peroxide addition. Duplicate runs were performed in each competition with excellent agreement.

Kinetic Studies. General Procedure.—A few modifications of the general procedure for oxygenation were made. The quantities of the reactants were doubled, and the temperature was maintained at 85°. Aliquots (10 ml) were removed at intervals and quenched with ice. After the usual work-up procedure, iodometric analyses were performed with 0.1 *N* sodium thiosulfate. Control experiments indicated that the peroxide was unaffected by the standard work-up procedure.

Analytical Procedures. A. Gas Chromatography.—A homemade unit and a Varian Model 1800 gas chromatograph were employed: block temperature, 250°; injector temperature, 280°; bridge current, 195 mA; sample size, 5–30 μl, with the appropriate attenuations for the home-made unit; the block temperature, 250°; injector temperature, 270°; bridge current, 150 mA; sample size, 5–20 μl, with the appropriate attenuations for the Varian unit. Two columns were used: (1) 6 ft × 0.25 in., 15% silicone grease (SE-52) on acid-washed Chromosorb P (30–60 mesh), He flow 60 ml/min; and (2) 10 ft by 0.25 in., 5% Apiezon L on acid-washed Chromosorb P (30–60 mesh), He flow 60 ml/min.

B. For Product Yields.—The benzoate esters and aromatic by-products were analyzed as previously described[15] by the method of internal standards, *m*-di(isopropoxycarboxy)benzene except for anisole, in which case α-naphthyl isopropyl carbonate was employed. Glpc column 1 at 150–200° was used for all of the analyses. The yields are based on 1 mol/mol of peroxide.

C. For Isomer Distributions.—A portion of the reaction mixture was concentrated by removal of the residual aromatic substrate under reduced pressure. The *meta*–*para* glpc peak was then collected and subjected to infrared analysis (Beckman IR-8). The molar ratio of the isomers was ascertained by comparing the respective intensity ratios with plots of intensity *vs.* mole ratio for known mixtures of the two isomers.

D. For Carbon Dioxide.—The indicated modifications were applied to the general procedure. A slow flow of nitrogen was maintained throughout the reaction, and the exit gases were passed through a preweighed Ascarite trap. In some cases, where gas evolution was exceptionally vigorous, a cold trap (Dry Ice–acetone) was inserted between the condenser exit and the Ascarite. The difference in weight of the vessel plus contents before and after reaction gave the amount of carbon dioxide evolved.

E. For Competitive Oxygenation.—Glpc column 1 was used in all of the experiments.

F. For Peroxides.—Iodometric methods were taken from the literature.[44,45]

Registry No.—Benzoyl peroxide, 94-36-0; iodine, 7553-56-2; toluene, 108-88-3; chlorobenzene, 108-90-7; anisole, 100-66-3.

Acknowledgment.—We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Science Foundation for support of this work.

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Electrochemical Studies of the Reactivity of Superoxide Ion with Several Alkyl Halides in Dimethyl Sulfoxide

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Stable solutions of tetraethylammonium superoxide can be prepared in aprotic solvents by electrochemical generation. This has provided a basis for a chronopotentiometric study of the kinetics for the nucleophilic displacement by superoxide of halide from alkyl halides to give peroxide radicals. The reaction is first order in superoxide and occurs with 1:1 stoichiometry. The pseudo-first-order rate constants at 28° for a series of butyl chlorides in dimethyl sulfoxide follow: *n*-butyl chloride, 3.2×10^{-1} sec^{-1}; *sec*-butyl chloride, 0.6×10^{-1} sec^{-1}; and *t*-butyl chloride, 0.4×10^{-1} sec^{-1}. The rates of reaction for the butyl bromides and iodides are too rapid for quantitative evaluation of their rate constants.

The reactions of the superoxide ion with organic compounds have not been studied extensively. Although both the sodium and potassium salts are commercially available, their low solubility in organic solvents has limited investigations of their reactions.[1] Russell and coworkers have suggested that superoxide is an intermediate in the oxidation of hydrocarbons in basic dimethyl sulfoxide.[2]

The studies that have been made of superoxide reactions have employed the solid salts in suspensions. Schmidt and Bipp[3] have treated potassium superoxide as an ether suspension with benzoyl chloride to give dibenzoyl peroxide, and with triphenylmethyl chloride to yield ditriphenylmethyl peroxide. These workers did not observe a reaction with simple aliphatic alkyl halides.

Le Berre and Berguer, who have studied the organic reactions of superoxides in detail, made similar observations.[4] They investigated the reactions of suspensions of potassium and sodium superoxides in tetrahydrofuran and benzene with various organic materials. Their results indicate that the superoxide does not act as a radical, but either as a mild reductant or as a very weak nucleophile. In terms of nucleophilicity, the solid superoxides react with triphenylmethyl chloride, but not with other alkyl halides under these conditions. After nucleophilic attack, the resulting peroxide radical reactions were postulated to depend upon substrate and reaction conditions.

The electrochemical behavior of oxygen and the superoxide ion in nonaqueous solvents has been studied extensively.[5-9] The results establish that the tetraalkylammonium superoxides are soluble and stable in a variety of aprotic organic solvents.[8,9] The present paper summarizes the results of a preliminary investigation of the reactions of tetraethylammonium superoxide in dimethyl sulfoxide with alkyl halides. The study illustrates the use of electrochemistry to study reactions of organic species not readily accessible by more conventional techniques. The results indicate that superoxide, under these conditions, behaves as a nucleophile rather than as a radical. Its nucleophilicity is stronger than previously reported.

Experimental Section

Materials.—Baker Analyzed reagent grade dimethyl sulfoxide (DMSO) was used without further purification. Acetonitrile, Mallinckrodt, was purified by a modification of Mann's procedure.[10] The alkyl halides, *t*-butyl hydroperoxide, and lithium chloride were obtained from Matheson Coleman and Bell and were used without purification. Tetraethylammonium perchlorate (TEAP), Distillation Products, was recrystallized three times from water and dried at 100°. Tetrabutylammonium bromide, Distillation Products, was recrystallized from ethyl acetate.

Equipment.—All electrochemical measurements were made using a solid-state potentiostat–amperostat[11] with a Sargent Model SR strip chart recorder and a Moseley Model 7030-A X–Y recorder. Standard two-compartment electrochemical cells with a three-electrode configuration were used. For controlled potential electrolysis experiments a large gold foil served as the working electrode. The chronopotentiometric and cyclic voltammetric studies utilized a gold billet sealed in a polyethylene tube (gold inlay electrode) as the working electrode. The area of this electrode was determined by reduction of ferricyanide ion in water. An aqueous Ag|AgCl reference electrode was used which has been previously described;[7] its potential was 0.000 V *vs.* sce. The reference electrode was isolated from the bulk of the solution by a fine frit and a large platinum gauze served as the isolated auxiliary electrode. A Sargent thermomitor was used to regulate the temperature of the water bath at 28.0 ± 0.5° for the kinetic studies. An Aerograph A90-P3 gas chromatograph was used to detect *t*-butyl hydroperoxide with two columns, 6% didecylphthalate on firebrick and 10% XE-60 on Chromosorb P. Columns of Teflon tubing (5 ft) (Penntube Plastics Corp.) were used and the injection port of the chromatograph was lined with Teflon to prevent decomposition of hydroperoxides.

Results and Discussion

Previous investigations[9] have shown that solutions of superoxide in DMSO (0.1 *F* TEAP), formed by the electrochemical reduction of oxygen, decay less than 3%/hour. Such stability indicates that this solvent is suitable for studies of the reactivity of superoxide.

Figure 1 illustrates cyclic voltammograms obtained for a solution of DMSO (0.1 *F* TEAP) saturated with oxygen, both in the absence and presence of *sec*-butyl chloride. (With cyclic voltammetry the peak current is proportional to the concentration of the electroactive species.) In the absence of the alkyl halide, the ratio of

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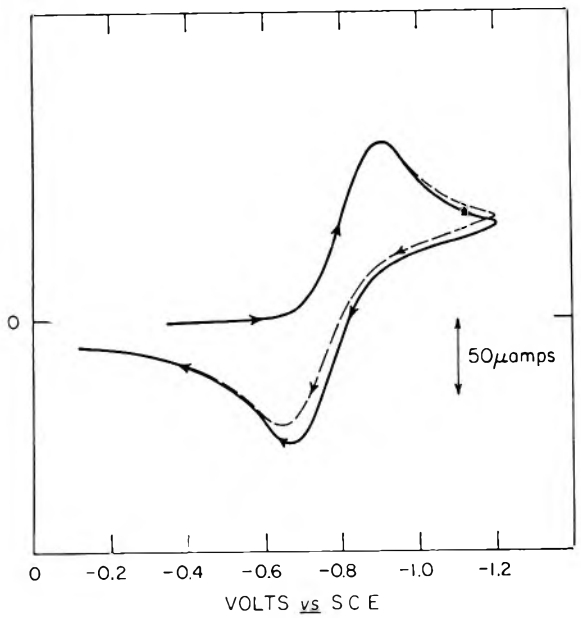

Figure 1.—Cyclic voltammetry of oxygen in DMSO (0.1 *F* TEAP) at a gold billet electrode; sweep rate, 0.1 V sec^{-1}; – – –, voltammogram taken in the presence of 0.10 *F* *sec*-butyl chloride.

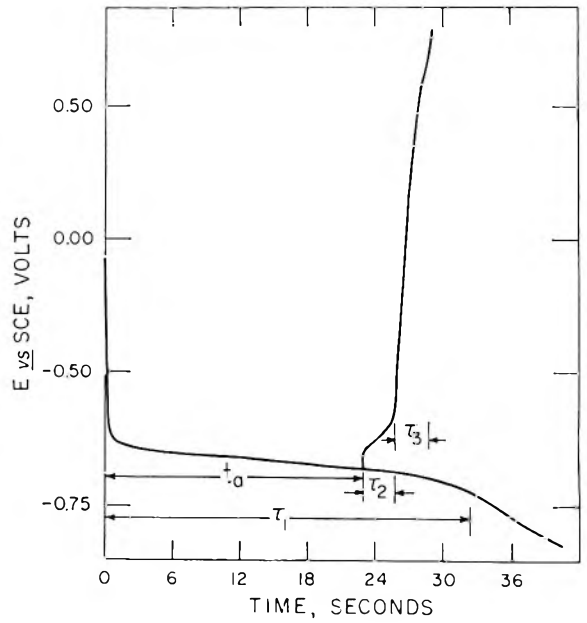

Figure 2.—Chronopotentiogram of oxygen in DMSO (0.1 *F* TEAP), in the presence of 0.10 *F* *sec*-butyl chloride at a gold billet electrode; *i*, 40 μA.

the anodic peak current to the cathodic peak current is 1; *i.e.*, the superoxide formed during the cathodic sweep does not react but can all be reoxidized when the potential sweep is reversed. In the presence of *sec*-butyl chloride the anodic peak current is reduced in height, which indicates that some of the superoxide has been consumed by reaction with the alkyl chloride. By comparing the ratio of i_p (anodic)/i_p (cathodic) for the oxygen redox system in the presence of a variety of alkyl halides, the primary halides are found to react faster than secondary species which react faster than tertiary halides; furthermore, iodides react faster than bromides. These results imply that the reaction of superoxide with alkyl halides is a nucleophilic displacement reaction. Although cyclic voltammetry can be used to determine the kinetics of reactions, it does not appear to offer any advantages over chronopotentiometry for this system.

In chronopotentiometry the transition time, τ, is proportional to the concentration of electroactive species

$$\tau^{1/2} = \frac{\pi^{1/2} nFD^{1/2} AC}{2i} \quad (1)$$

where n is the number of electrons transferred, F the faraday constant, A the electrode area, C the concentration of electroactive species, and i the current. The use of chronopotentiometry permits the concentration of superoxide to be monitored in the reaction with alkyl halides. The diffusion coefficient, D, for superoxide in this media has been reported previously.[9]

To determine the stoichiometry of the superoxide–alkyl halide reaction a solution of superoxide was prepared by reducing oxygen at −1.10 V *vs.* sce; the solution was then degassed with prepurified nitrogen, *t*-butyl bromide was added in small amounts, the solution was stirred briefly, and a chronopotentiogram was recorded to measure the superoxide concentration. (*t*-Butyl bromide was chosen because it appears to react instantaneously with superoxide as determined by cyclic voltammetry.) A plot of moles of superoxide consumed (calculated from the chronopotentiometric data) *vs.* moles of *t*-butyl bromide added yielded a straight line with a slope of one. This indicates that the superoxide and alkyl halide react with a 1:1 stoichiometry. Similar experiments in acetonitrile (0.1 *F* TEAP) indicate that both *n*-butyl bromide and *t*-butyl bromide consume about 3.5 mol of superoxide/mol of added alkyl bromide.

Figure 2 shows a typical chronopotentiogram of oxygen in DMSO (0.1 *F* TEAP) in the presence of *sec*-butyl chloride. For a chemically reversible, diffusion-controlled redox system, the ratio of the reverse transition time, τ_2, to the time, t_a, in which reduction has occurred, is equal to 1/3, provided $t_a \leq \tau_1$, the transition time for the reduction. In the absence of the alkyl halide, the ratio is 1/3 for oxygen in this solution. The ratio τ_2/t_a is reduced, however, in the presence of the halide. Hence, the extent of the decrease in this ratio is a measure of the rate of reaction with superoxide.

In Figure 2, τ_3 characterizes the amount of chloride ion formed in the reaction of superoxide with *sec*-butyl chloride. The anodic behavior of halide ions at a gold electrode in acetonitrile has been studied previously.[12] Chronopotentiograms of DMSO (0.1 *F* TEAP) solutions of lithium chloride and tetrabutylammonium bromide exhibit $E_{1/4}$ values which are approximately the same, respectively, as the $E_{0.22}$ values observed in reverse chronopotentiograms of oxygen in the presence of an alkyl chloride and an alkyl bromide. Furthermore, the ratio of $(\tau_2 + \tau_3)/t_a$ is equal to 1/3. This indicates that the only reaction of superoxide is one in which free halide is formed.

Testa and Reinmuth have described a method for obtaining kinetic parameters for homogeneous reactions between a substrate and a material generated chronopotentiometrically.[13] Their method involves measurement of the ratio of τ_2/t_a for various values of t_a and i. Using this ratio in an analytical function, values of kt_a

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can be determined. Then, a plot of kt_a *vs.* t_a yields a straight line with a slope equal to k.

DMSO (0.1 *F* TEAP) solutions of *n*-butyl, *sec*-butyl, and *t*-butyl chloride have been prepared with each 0.10 *F* in alkyl halide. A series of reverse chronopotentiograms have been recorded for each solution at 28.0 ± 0.5° for various values of t_a. The current density also has been varied over a minimum range of five for each solution; in the case of *t*-butyl chloride, the range of current density has been ten. In all cases, the ratio of τ_2/t_a is a function only of t_a and is independent of current density. This independence of current density indicates that the reaction is first order in the electroactive species; *i.e.*, superoxide.[13] The pseudo-first-order rate constants, k, for the reaction

$$RCl + O_2^- \longrightarrow RO_2\cdot + Cl^- \qquad (2)$$

are, for *n*-butyl chloride, 3.2×10^{-1} sec^{-1}; *sec*-butyl chloride, 0.6×10^{-1} sec^{-1}; and *t*-butyl chloride, 0.4×10^{-1} sec^{-1}. The rate of the reactions with any of the butyl bromides or butyl iodides is too rapid to measure by this method; *i.e.*, $\tau_2 = 0$.

Attempts have been made to detect hydroperoxide as an eventual product of the reaction to substantiate the belief that the initial product of the reaction is a peroxide radical. The latter would abstract a hydrogen atom from the solvent or the electrolyte to form a hydroperoxide. Large-scale electrolyses have been performed in which solutions of DMSO (0.1 *F* TEAP)–*t*-butyl bromide are kept saturated with oxygen while several hundred coulombs are allowed to pass through the solution. Samples then have been injected into a gas chromatograph and a material exhibiting the same retention time as that of an authentic sample of *t*-butyl hydroperoxide has been detected with two different columns. On this basis, some hydroperoxide is concluded to be formed from the superoxide–alkyl halide reaction. *t*-Butyl hydroperoxide also has been detected by gas chromatography in acetonitrile and acetone in similar experiments.

Summary and Conclusions

The data indicate that tetraethylammonium superoxide reacts with alkyl halide by a nucleophilic displacement of the halide to give peroxide radicals as the initial product. The reaction is first order with respect to superoxide, and occurs with 1:1 stoichiometry. Furthermore, *n*-butyl chloride reacts faster than *sec*-butyl chloride, which is faster than *t*-butyl chloride; alkyl chlorides react slower than bromides and iodides.

The results differ from those reported by Schmidt and Bipp[3] and by Le Berre and Berguer[4] who did not observe reactions for suspensions of potassium and sodium superoxide with alkyl halides. This difference probably is related to the fact that alkali and alkaline earth salts have a large effect on the reactivity of superoxide with water[5] and on its electrochemistry.[6] The greater reactivity of the tetraethylammonium salt implies that it may be of synthetic utility. A preparative procedure for the synthesis of tetramethylammonium superoxide is available.[14]

Registry No.—Superoxide ion, 12185-08-9; *n*-butyl chloride, 109-69-3; *sec*-butyl chloride, 78-86-4; *t*-butyl chloride, 507-20-0.

Acknowledgment.—This work was supported by the National Science Foundation under Grant No. GP-11608.

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Stable Carbonium Ions. XCIV.[1] Diprotonated Ketocarboxylic Acids and Keto Esters and Their Cleavage to Protonated Ketooxocarbonium Ions in Fluorosulfuric Acid–Antimony Pentafluoride Solution

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Protonation of a series of keto acids has been studied in FSO_3H–SbF_5–SO_2 solution. O-Diprotonation was observed at low temperature. Two isomeric species were found for protonated acetylvaleric acid and 3- and 4-benzoylbenzoic acids. At higher temperatures acetylbutyric, acetylvaleric, and 2-acetylbenzoic acids underwent dehydration to give the corresponding ketooxocarbonium ions. No cleavage reaction was observed for protonated levulinic acid and 3-acetyl-, 4-acetyl-, 3-benzoyl-, and 4-benzoylbenzoic acids even when solutions were heated up to +50°. Protonated pyruvic acid underwent dehydration and decarbonylation to give the methyloxocarbonium ion. Methyl and ethyl acetoacetates in FSO_3H–SbF_5–SO_2 solution are diprotonated. *t*-Butyl acetoacetate cleaves without observation of the protonated ester to diprotonated acetoacetic acid and the trimethylcarbonium ion.

Our recent investigations of protonated ketones,[3] carboxylic acids,[4] and dicarboxylic acids[5] lead us now to study the protonation of a series of aliphatic and aromatic keto acids in the super acid system, FSO_3H–SbF_5–SO_2. No nuclear magnetic resonance study of protonated keto acids has been reported in the literature, although a number of investigations of protonated carboxylic acids are known.[6–10]

(1) Part XCIII: G. A. Olah and A. T. Ku, *J. Org. Chem.*, **34**, 331 (1969).

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(3) G. A. Olah, M. Calin, and D. H. O'Brien, *J. Amer. Chem. Soc.*, **89**, 3586 (1967); G. A. Olah and M. Calin, *ibid.*, **90**, 938 (1968).

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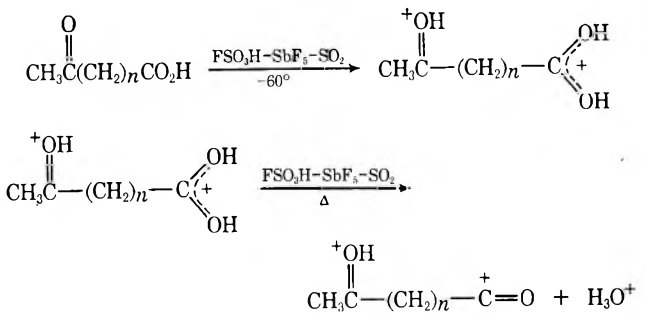
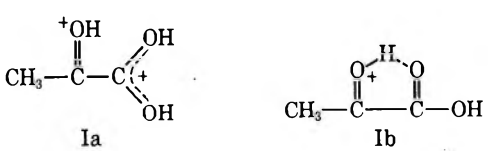
Results and Discussion

In the super acid system, FSO_3H–SbF_5–SO_2 ("magic acid"), all keto acids studied are completely diprotonated at −60°. When raising the temperature, we are able to observe in certain cases cleavage to the protonated ketooxocarbonium ions.



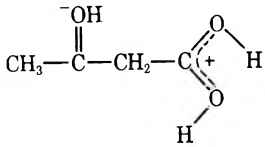
The following keto acids were studied in FSO_3H–SbF_5–SO_2 solution: pyruvic, acetoacetic, levulinic, acetylbutyric, and acetylvaleric acids as well as 2-acetyl-, 3-acetyl-, 4-acetyl-, 2-benzoyl-, 3-benzoyl-, and 4-benzoyl-benzoic acids. The pmr chemical shifts and coupling constants of diprotonated keto acids are summarized in Table I.

Protonated pyruvic acid was generated from the sodium salt of pyruvic acid in FSO_3H–SbF_5 solution diluted with SO_2. The pmr spectrum showed the OH protons as a broad resonance at δ 15.0 at −90°. This indicates that the OH protons are exchanging with the solvent acid system, the resonance of which was also broad. The methyl protons which showed no observable coupling appear as a singlet at δ 3.75 which is more deshielded than that of protonated acetone (δ 3.45)[3] and protonated acetic acid (δ 3.18).[4] The highly deshielded singlet methyl absorption at δ 3.75, close to that found for diprotonated 2,4-butanedione (δ 3.90),[11] indicates that pyruvic acid is also diprotonated as shown in Ia. The pmr spectrum of pyruvic acid also displays another small peak at δ 2.90 which is assigned to the methyl protons of the monoprotonated species Ib.



Ia Ib

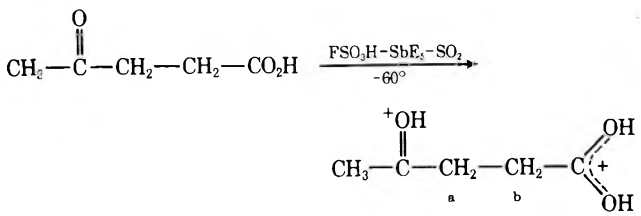
Protonated acetoacetic acid was generated by cleavage of *t*-butyl acetoacetate in 1:1 *M* FSO_3H–SbF_5 solution diluted with SO_2. The pmr spectrum of protonated acetoacetic acid at −80° showed the proton on the keto oxygen, C=OH^+, at δ 16.8 which is at a much lower field than that of protonated aliphatic ketones.[3] This broad resonance could not be resolved even at temperatures as low as −100°. The other two singlet absorptions of equal area at δ 14.10 and 14.27 are assigned to the OH protons of the protonated carboxyl group. As in the case of protonated aliphatic carboxylic acids,[4,5] the hydroxyl protons are in nonequivalent environments. This is interpreted, as in the case of protonated carboxylic acids,[4,5] as a consequence of structure II being the predominant species.



II

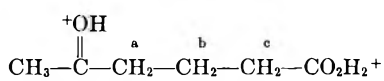
The methyl and methylene protons of protonated acetoacetic acid appeared at δ 3.67 and 5.53, respectively. These absorptions, although somewhat broad, showed no couplings. A small additional peak at δ 9.66 was also observed for protonated acetoacetic acid in FSO_3H–SbF_5–SO_2, even though the precursor, *t*-butyl acetoacetate, had been distilled several times. No assignment of this peak is made at the present time.

Levulinic acid (acetylpropionic acid) is also diprotonated in FSO_3H–SbF_5–SO_2 solution at −60°. It gives a well-resolved pmr spectrum with three singlet



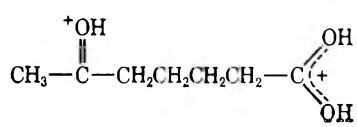
absorptions at δ 15.5, 13.4, and 13.18 for the hydroxyl protons. The lowest field singlet is due to the proton on the keto oxygen, and no coupling with the α protons was observed. The two singlets of equal area at a higher field in the hydroxy region are asigned to the protons on the carboxylic acid oxygens. The reason for the nonequivalence of the two hydroxyl groups is the same as that described for protonated acetoacetic acid. The pmr spectrum of protonated levulinic acid shows the methyl singlet at δ 3.45 and the two methylene triplets a and b at δ 4.25 and 3.85, respectively. Table I summarizes the chemical shifts and coupling constants.

Protonated acetylbutyric acid at −60° shows the $HO\overset{+}{=}C<$ proton as a singlet at δ 15.1 and the $CO_2H_2^+$



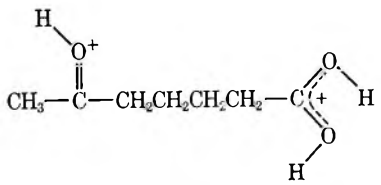
protons as two singlets of equal area at δ 13.1 and 12.9. These two singlets coalesced at −30°. The methyl protons appear as a singlet at δ 3.45. The methylene (a) appears as a triplet at δ 4.1, the methylene (b) as a multiplet centered at δ 2.85, and the methylene (c) as a triplet at δ 3.5. At low temperature, −60°, the C–H protons show broadening and the coupling constants between the methylene protons were evaluated from a spectrum recorded at −30°.

Protonated acetylvaleric acid at −60° shows the $HO\overset{+}{=}C<$ singlet at δ 14.5 and two $CO_2H_2^+$ singlets at

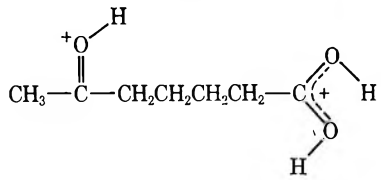


(11) G. A. Olah and M. Calin, *J. Amer. Chem. Soc.*, **90**, 4672 (1968).

δ 12.7 and 12.4 (equal area ratio) indicating that acetylvaleric acid is also diprotonated. No coupling was observed between the $HO{=}C<$ proton and the α-alkyl protons. Hence the structure of the diprotonated species could not be assigned (IIIa or IIIb). The nmr spectrum shows another small peak in the $HO{=}C<$ region (about $^1/_{20}$th the intensity of that at δ 14.5) at δ 14.2 which could possibly be due to another form of the diprotonated acetylvaleric acid (IIIa or IIIb). Since



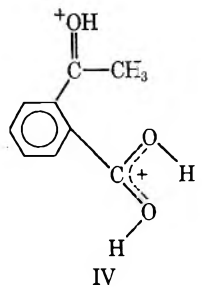
IIIa



IIIb

the intensity of this peak is so low, no further study could be made. The chemical shifts of the alkyl protons are summarized in Table I.

The nmr spectrum of **protonated 2-acetylbenzoic acid** (Table I) in FSO_3H–SbF_5–SO_2 solution[12] at $-60°$ shows two broad low-field absorption peaks at δ 13.53 and 14.73, in the OH region. The higher field OH peak could be resolved into two singlets at δ 13.43 and 13.97 at $-90°$. This indicates, as in the case of protonted simple carboxylic acids, that the two OH protons of the protonated carboxyl group are nonequivalent, as in structure IV. No coupling of the $HO{=}C<$ proton



IV

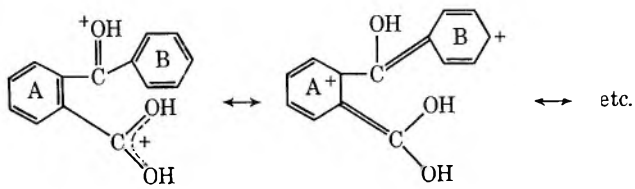
with either methyl or ring protons could be observed. Hence the orientation of the proton on the acetyl oxygen could not be established.

It has been shown that protonated benzoic acid[4,5] gives only a singlet for the OH proton. This is explained to be due to a low barrier of rotation about the C—O bonds. Protonated benzoic acid would be expected to have less double-bond character associated with the C—O bonds than the protonated simple aliphatic carboxylic acids, owing to resonance interaction with the phenyl ring. It is expected that a strong electron-withdrawing group on the ring of protonated benzoic acid would tend to prevent to some extent such resonance interaction. This would make the C—O bond of the carboxyl group more resemble a double bond than in protonated benzoic acid itself. This indeed is in accordance with our observations.

4-Acetylbenzoic acid in FSO_3H–SbF_5–SO_2 is also diprotonated. The pmr spectrum shows two OH singlets with an area ratio of 1:2 at δ 14.8 and 13.1. The higher field OH resonance is due to the OH of the protonated carboxyl group and the lower field OH is due to the proton on acetyl oxygen. The OH resonance of the carboxyl group could not be resolved even at a temperature as low as $-100°$. This is due to the fact that the inductive effect of the $HO{=}C<$ group is decreased as the separation of the two functional groups is increased. The aromatic protons gave an AB quartet centered at δ 8.86. The chemical shifts are summarized in Table I.

Protonated 3-acetylbenzoic acid shows two singlet resonance at δ 14.3 and 12.7 with a relative area ratio of 1:2. Again, the lower field OH resonance is assigned to the proton on the acetyl oxygen; the higher field OH resonance is due to the proton on the carboxyl group oxygen. These resonances are less deshielded than that of diprotonated 2- and 4-acetylbenzoic acid since the $HO{=}C<$ and $-CO_2H_2$ groups of protonated 3-acetylbenzoic acid are not directly conjugated. The resonance of the OH protons of the carboxyl group is a singlet even at a temperature as low as $-100°$. Table I summarizes the chemical shifts.

2-Benzoylbenzoic acid is diprotonated in FSO_3H–SbF_5 diluted with SO_2. The pmr spectrum shows two low-field singlets in the OH region at δ 13.3 and 12.9 for the proton on benzoyl oxygen and the carboxyl group, respectively. The chemical shift of the proton on benzoyl oxygen appears at a higher field than that of protonated 2-acetylbenzoic acid (δ 14.7). The resonance at δ 13.3 is a singlet even at a temperature as low as $-100°$. This is believed to be due to a low barrier to rotation about the C—OH bonds of the protonated carboxyl group. It is evident that the resonance interaction of the A ring and the protonated carboxyl group is still substantial. The positive charge of $HO{=}C<$ is substantially deceased by the resonance interaction with ring B, as shown above. The electron-withdrawing ability of the protonated benzoyl group $C_6H_5C(=OH)$– is not strong enough to prevent the resonance interaction of ring A and the carboxyl group.

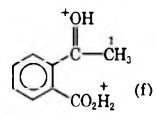
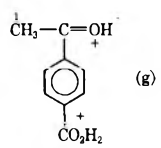
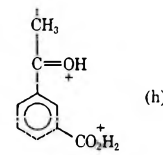
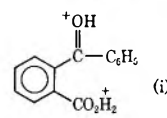
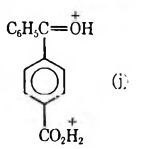
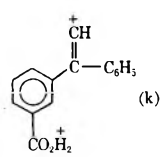


The pmr spectrum of **protonated 4-benzoylbenzoic acid** shows two absorption peaks for the proton on the benzoyl oxygen in a relative ratio of 60:40 indicating, as in the case of protonated ketones,[3] that two isomeric

(12) A 4:1 *M* FSO_3H–SbF_5 solution was used for all benzoic acid derivatives. This solution was used in preference to the 1:1 *M* acid since, in the latter solution, spectra were less well resolved particularly at higher temperature. The spectra obtained in both acids were in other respects identical.

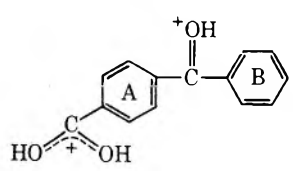
TABLE I

NMR CHEMICAL SHIFTS (IN PARTS PER MILLION)[a] AND COUPLING CONSTANTS (IN HERTZ) OF PROTONATED KETO ACIDS IN FSO_3H–SbF_5 SOLUTION

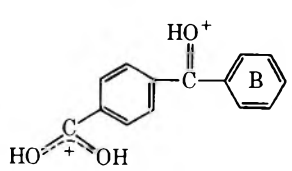
Keto acids	Temp, °C	^{+}OH ‖ –C–	$CO_2H_2^+$	H_1	H_2	H_3	H_4	H_5	Aromatic H
$CH_3\overset{1}{C}(^{+}OH)—CO_2H_2^+$ (a)	−90	15.0	15.0	3.75 2.90					
$CH_3\overset{1}{C}(^{+}OH)\overset{2}{C}H_2CO_2H_2^+$ (b)	−80	16.8	14.1 14.3	3.67	5.53				
$CH_3—\overset{1}{C}(^{+}OH)\overset{2}{C}H_2\overset{3}{C}H_2CO_2H_2^+$ (c)	−60	15.5	13.4 13.2	3.45	4.25 (t, 6.0)[b]	3.85 (t, 6.0)			
$CH_3—\overset{1}{C}(^{+}OH)\overset{2}{C}H_2\overset{4}{C}H_2\overset{3}{C}H_2CO_2H_2^+$ (d)	−60	15.1	13.1 12.9	3.45	4.1 (t, 7.0)	3.5 (t, 7.0)	2.85 (m)		
$CH_3—\overset{1}{C}(^{+}OH)—\overset{2}{C}H_2\overset{5}{C}H_2\overset{4}{C}H_2\overset{3}{C}H_2CO_2H_2^+$ (e)	−60	14.5 14.20	12.5 12.6	3.25	3.70 (m)	3.30 (m)	2.10 (m)	2.10	
 (f)	−90	14.9	13.4 13.9	3.75					8.26–9.20
 (g)	−60	14.8	13.1	3.75					8.86
 (h)	−60	14.3	12.7	3.63					8.13–9.46
 (i)	−60	13.3	12.9						7.83–9.13
 (j)	−60	13.4 13.1	12.95						7.90–9.00
 (k)	−60	13.2 13.0	12.7						7.90–9.30

[a] Referred to external TMS. [b] Multiplicity: t = triplet; q, quartet; m = multiplet.

species (V and VI) are present. The assignment of the two isomers could not be made, because no coupling



V



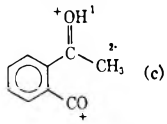
VI

was observed between this OH proton and ring protons. Only a singlet is observed for the OH protons of the protonated carboxyl group. As in the case of protonated 2-benzoylbenzoic acid, the resonance interaction of ring A with the protonated carboxyl group is still great.

3-Benzoylbenzoic acid in FSO_3H–SbF_5–SO_2 solution is also diprotonated. The pmr spectrum of protonated 3-benzoylbenzoic acid shows two singlets with relative

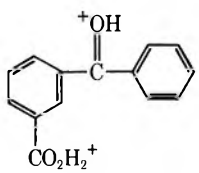
TABLE II

NMR CHEMICAL SHIFTS (IN PARTS PER MILLION)[a] AND COUPLING CONSTANTS (IN HERTZ) OF KETOOXOCARBONIUM IONS

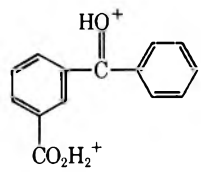
Ketooxocarbonium ions	Temp, °C	H_1	H_2	H_3	H_4	H_5	H_6	Ar H
$CH_3-\overset{+}{C}(OH)-CH_2CH_2CH_2CO^+$ (a)	−40	15.5	3.55	4.20 (m)	4.70 (t, 8)[b]	3.10 (m)		
$CH_3-\overset{+}{C}(OH_3)-CH_2CH_2CH_2CH_2CO^+$ (b)	−20	14.80	3.30	3.90 (m)	4.50 (t, 7.0)	2.50 (m)	2.20 (m)	
 (c)	−60		3.85					8.73–9.30

[a] Referred to external TMS. [b] Multiplicity: t = triplet; m = multiplet.

ratio of 40:60 for the proton on the benzoyl oxygen, indicating that two isomeric species (VII and VIII) are



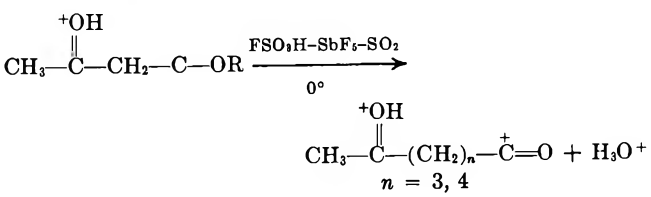
VII



VIII

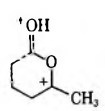
present. Assignment of the two isomers could not be made based on the present data. As in the case of protonated 2- and 4-benzoylbenzoic acid, the protons of the protonated carboxyl group appear only as a singlet at δ 12.7 which could not be resolved even at −100°. Table I summarizes the chemical shifts.

Cleavage of Diprotonated Keto Acids to Protonated Ketooxocarbonium Ions.—The mode of cleavage of diprotonated aliphatic keto acids is dependent on the distance between the keto and carboxyl groups. **Acetylbutyric and acetylvaleric acids** undergo complete dehydration at 0° to give the corresponding protonated ketooxocarbonium ions and an equimolar amount of H_3O^+.



An increase of deshielding is observed for all the protons of protonated ketooxocarbonium ions. The largest deshielding is observed in the methylene protons next to the carbonium carbon.[13] The chemical shifts and coupling constants of the protonated oxocarbonium ions are summarized in Table II.

(13) The possibility that the ions formed might be protonated cyclic ions, such as

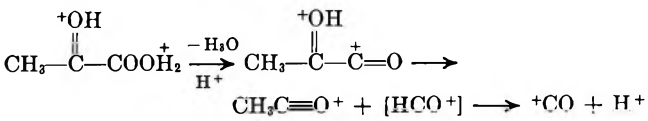


is ruled out based on this observation. In the cyclic ion one would expect that the methylene and the methyl protons originally next to the protonated keto group would be deshielded substantially.

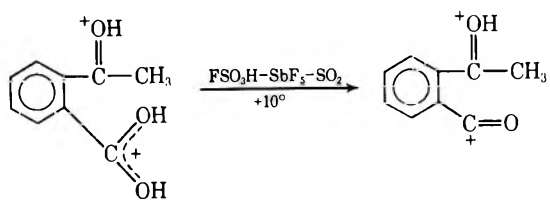
Diprotonated **levulinic acid** is very stable. No cleavage was observed even when the solution was heated to a temperature as high as +60°.

The cleavage reaction of diprotonated **acetoacetic acid** takes place slowly at 0° and gives a complex and yet unidentified mixture of products.

Protonated **pyruvic acid** undergoes cleavage at −20° to give the methyloxocarbonium ion (singlet at δ 4.05). The cleavage reaction can be rationalized in the following way.



Protonated **2-acetylbenzoic acid** undergoes dehydration at +10° to give 2-acetylphenyloxocarbonium ion. The proton on the acetyl oxygen is not observed, probably exchanging with the acid solvent system. The formation of the oxocarbonium ion is evident from the increase of the H_3O^+ peak which appears at δ 10.25 and the increased deshielding of the phenyl ring protons of the oxocarbonium ion. The chemical shifts are summarized in Table II.



Protonated **2-benzoylbenzoic acid** undergoes dehydration and acylation at room temperature to give diprotonated anthraquinone which gave an nmr spectrum identical with that obtained from the authentic material.

Protonated **3-** and **4-acetylbenzoic acid** and **3-** and **4-benzoylbenzyic acid** are very stable. No indication for the formation of the ketooxocarbonium ion was observed even when the solution was heated to +60°.

Protonated alkyl acetoacetates.—Methyl, ethyl, and *t*-butyl acetoacetates) were examined in FSO_3H–SbF_5–SO_2 solution. At −80° two low-field peaks in the hydroxyl region were observed for both protonated

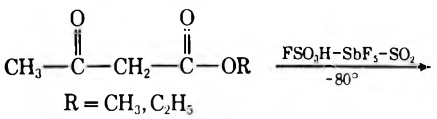
TABLE III

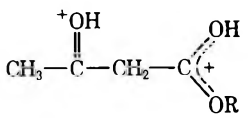
NMR CHEMICAL SHIFTS (IN PARTS PER MILLION),[a] AND COUPLING CONSTANTS (IN HERTZ) OF PROTONATED KETO ESTERS OF CARBOXYLIC ACIDS IN FSO_3H–SbF_5–SO_2 SOLUTION AT −60°

Acetoacetates	H_1	H_2	H_3	H_4	H_5	H_6	H_7
$^{+}OH\ ^{+}OH$ (1, 2) $CH_3CCH_2COCH_3$ (a) (3, 4, 5)	16.7[b]	14.2	3.66	5.43	5.05		
$^{+}OH\ ^{+}OH$ (1, 2) $CH_3CCH_2COCH_2CH_3$ (b) (3, 4, 5, 6)	16.3[b]	13.7	3.63	5.35	5.50 (q, 7.0)[c]	1.93 (t, 7.0)	

[a] Referred to external TMS. [b] Observed below −80°. [c] Multiplicity: q, = quartet; t, = triplet.

methyl and ethyl acetoacetates, indicating that the acetoacetates studied were diprotonated on the two carbonyl oxygens. At temperatures higher than −80°, the proton on acetyl oxygen could not be observed, and





the peak for the acid system is also broad, indicating an occurrence of proton exchange. No coupling was observed between the hydroxyl protons with either the acetyl or methylene protons; hence the orientation of the OH protons could not be established. Chemical shifts and coupling constants of the protonated acetoacetates are given in Table III.

Protonated *t*-butyl acetoacetate could not be observed even when solutions of *t*-butyl acetoacetate in FSO_3H–SbF_5–SO_2 were prepared and examined at −80°. The pmr spectra obtained corresponded only to protonated acetoacetic acid (see previous discussion) and *t*-butyl cation (singlet at $\delta \leq 2$).

Experimental Section

Materials.—With the exception of acetylvaleric acid and 4-acetylbenzoic, 3-acetylbenzoic, and 3-benzoylbenzoic acids, all the keto acids were commercially available materials and used without further purification.

Acetylvaleric acid was prepared by the oxidation of 2-methylcyclohexanone with chromic trioxide in dilute sulfuric acid solution.[14]

m- and *p*-acetylbenzoic acid were prepared by the hydrolysis of the corresponding cyanoacetophenone,[15] which in turn was prepared by means of the Sandmeyer reaction[16,17] from the corresponding aminoacetophenone. *m*-Benzoylbenzoic acid was prepared by the reaction of benzoic anhydride and benzoyl chloride in the presence of zinc chloride at high temperature.[18]

Spectra.—A Varian Associates Model A-56/60A nmr spectrometer with variable-temperature probe was used for all spectra.

Preparation of Protonated Keto Acids.—Samples of protonated keto acids were prepared by dissolving approximately 1.5 ml of FSO_3H–SbF_5 (1:1 *M* solution) in an equal volume of sulfur dioxide and cooling to −78°. The keto acids (approximately 0.2 ml) were dissolved in 1 ml of sulfur dioxide, cooled to −78°, and with vigorous agitation slowly added to the FSO_3H–SbF_5 acid solution. The acid solution was always in large excess as indicated by the large acid peak at about δ 10.9 to 12.0.

Registry No.—Table I—a, 24621-23-6; b, 24621-24-7; c, 24621-25-8; d, 24621-26-9; e, 24621-27-0; f, 24621-28-1; g, 24621-29-2; h, 24621-30-5; i, 24621-31-6; j, 24621-32-7; k, 24621-33-8; Table II—a, 24621-34-9; b, 24621-35-0; c, 24605-68-3; Table III—a, 24621-36-1; b, 19220-71-4.

Acknowledgment.—Support of this work by a grant from the National Institutes of Health is gratefully acknowledged.

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(15) W. K. Detweiler and E. D. Amstuts, *J. Amer. Chem. Soc.*, **72**, 2882 (1950).

(16) H. Rupe and K. V. Majewski, *Ber.*, **33**, 3408 (1900); A. I. Vogel, "Practical Organic Chemistry," 3rd ed, 1962, p 607.

(17) F. Ahrens, *Ber.*, **20**, 2955 (1887).

(18) O. Dohner, *Ann.*, **210**, 278 (1881).

Dye-Sensitized Photochemical Autoxidation of Aliphatic Amines in Nonaqueous Media

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The reactions involved in photosensitized autoxidation of mono-, di-, and tributylamine in organic solvents have been identified by examination of the reaction products. The predominant initial oxidation process is dehydrogenation in each case. Subsequent major reactions include (1) hydrolysis of imines to lower alkylated amines and aldehyde, (2) β-oxidation of N-alkylidene groups to give hydroperoxides which lead to formamides or α-ketoaldehyde derivatives, and (3) addition of hydroperoxide to intermediate imines followed by base-catalyzed rearrangement to amides. Several other reactions have also been established. The reactions of hydrogen peroxide with these amines in the dark take similar courses to a minor extent, N-oxidation being the major result.

Dye-sensitized photochemical autoxidation is of great interest as a possible technique for chemical utilization of the energy of visible light. Our own attention has focussed on sensitized autoxidation of nitrogen compounds and particularly on alkylamines, substrates which have received considerable study since Gaffron's original work in 1927[1] and which in recent years have become of practical importance in amine-activated photopolymerization processes.[2]

The extensive literature on both anaerobic photoreduction of dyes by amines and dye-sensitized autoxidation of amines was very helpful in our approach to this field, but it was evident that the published work fails to provide a basic understanding of the processes involved or indeed a consistent description of the phenomena to be observed. The major part of the published experimental work on autoxidation consists of measurements of the rate of oxygen absorption under illumination. Such data show the relative reactivities of different substrates, and general agreement has been reached that in water or in ethanol amines obey the reactivity order, tertiary > secondary ≫ primary.[3,4] Surprisingly, there has been no comment on the observation of Gaffron that the order is primary, secondary ≫ tertiary in acetone or pyridine. Oxygen-uptake measurements have also led to conclusions regarding the ultimate oxygen–amine stoichiometry which, however, has commonly appeared to vary with the solvent and with the experimenter.[3-5] From such work have come two basic, but conflicting, oversimplifications which have long influenced thinking in this area: Weil's recovery of trimethylamine oxide in fair yield after autoxidation of trimethylamine in water[3] has been taken as evidence for a general mode of reaction, while Schenck has stated that aliphatic amines are attacked cleanly at α-methylene groups to introduce one hydroperoxide structure at each available position.[5] In work which we shall not report in detail,[6] we have also attempted to measure the rates of oxygen uptake by amines in various solvents while concurrently monitoring the composition of the reaction solution. This approach was abandoned for several reasons: (1) rates were meaningless because in no case did the concentration of the sensitizing dye remain even approximately constant, (2) dark, oxygen-absorbing reactions were obviously contributing to the observed rates, (3) in no case could oxygen absorption be brought to completion, and rarely were sharp rate changes evident, (4) product analyses showed no simple correlation with the amount of oxygen absorbed, and (5) the reaction product mixtures were extremely complex almost from the outset. Inasmuch as many of these experiments were carried out at concentrations close to those reported by others, we doubt that published data of this kind can have more than crude qualitative value at present.

We have attempted to reduce this very complex problem to practical dimensions by concentrating on identification of the autoxidation products derived from mono-, di-, and tri-*n*-butylamine and from this knowledge attempting to deduce the basic oxidation processes. In preliminary experiments, it was found that dye-sensitized autoxidation in aqueous solution caused stepwise dealkylation, $Bu_3N \rightarrow Bu_2NH \rightarrow BuNH_2$, and formation of butyraldehyde. We chose to avoid the occurrence of the hydrolytic steps which these results implied by conducting the autoxidation in organic solvents where, indeed, more interesting solvent interaction might be expected. These reactions have proven to be much more complex than anticipated and to proceed through initial stages not evident in earlier work. However, nearly all aspects find precedent in other amine-oxidation processes.

In most of this work, rose bengal has been used as the sensitizer with occasional recourse to ethyl eosin or hematoporphyrin base for greater solubility in methyl methacrylate. Our experience, partly described herein, together with the published literature has convinced us that the dyes which are effective sensitizers of amine autoxidation (*e.g.*, eosin, rose bengal, methylene blue, chlorophyll, riboflavin, etc.) act by a common mechanism although with different efficiencies. We are not concerned here with the details of the photoexcitation and dye-recycling processes or with a close analysis of the reaction rates.

Results and Discussion

Autoxidation of *n*-Butylamine.—Initial experiments disclosed that dye-sensitized autoxidation of *n*-butylamine (1) in acetonitrile, ethanol, or methyl methacrylate gave N-butylidenebutylamine (2) in high yield as the first observable product. Measured rates of disappearance of 1 and appearance of 2 are shown in

(1) H. Gaffron, *Chem. Ber.*, **60**, 2229 (1927).
(2) G. Oster and N.-L. Yang, *Chem. Rev.*, **68**, 125 (1968).
(3) L. Weil and J. Maher, *Arch. Biochem. Biophys.*, **29**, 241 (1950).
(4) W. R. Frissell, C. W. Chung, and C. G. Mackenzie, *J. Biol. Chem.*, **234**, 1297 (1959).
(5) G. O. Schenck, *Angew. Chem.*, **69**, 579 (1957).
(6) In collaboration with W. E. Mealmaker.

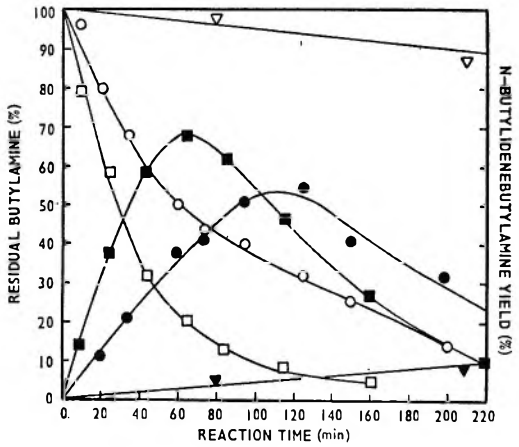


Figure 1.—Autoxidation of butylamine in various solvents (amine concn 0.02 *M*; sensitizer concn 1×10^{-4} *M*): ○ and ●, hematoporphyrin, methyl methacrylate; □ and ■, rose bengal, acetonitrile; ▽ and ▼, rose bengal, ethanol.

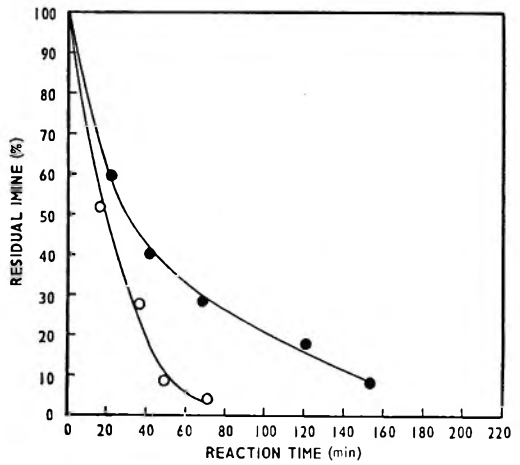


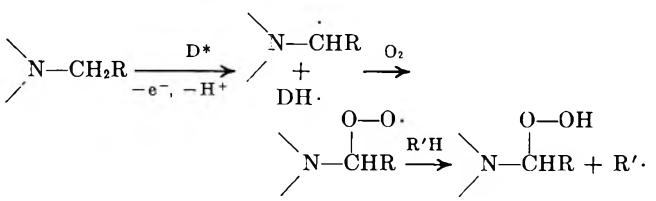
Figure 2.—Autoxidation of imines (imine concn 0.02 *M*; rose bengal concn 1.0×10^{-4} *M*): ○, N-butylidenebutylamine in acetonitrile; ●, N-isopropylidenebutylamine in acetone.

Figure 1. Further oxidation of **2** produced complex mixtures which presented difficult identification problems. When acetone was used as solvent, the primary amine was found to be nearly entirely present as N-isopropylidenebutylamine (**3**) from the outset.[7] This ketimine is closely analogous to **2**, and because the two alkyl moieties in **3** are distinguishable, we chose to examine its autoxidation products first. The rates of destruction of **2** and **3** are shown in Figure 2. The latter is slightly in error because of the presence of an unresolved minor amount of **2** formed by displacement of acetone from **3** by butyraldehyde, an observed oxidation product.

Autoxidation of **3** in acetone produced an astonishing variety of low-molecular-weight products by the time the ketimine had been completely destroyed, although about 80% of the material was lost as nonvolatile, probably polymeric tars. All of the appreciable glpc-detectable products were identified, however, and gave a fair picture of the reactions involved as well as the nature of the missing material. These identified products were butyraldehyde (**4**, *ca.* 0.1 mol/mol of **1**), N-butylformamide (**5**, 0.1 mol), N-butylacetamide (**6**, 0.02–0.04 mol), N-butylbutyramide (**7**, 0.005–0.02 mol), N,N′-dibutyloxamide (**8**, 0.005 mol), 2,2-dimethyl-6-propyl-4-piperidone (**9**, 0.03 mol), and N,N′-dibutylacetamidine (**10**, 0.01 mol). Fugitive intermediates also identified were **2** (0.1–0.2 mol maximum) and N,N′-dibutyl-1,2-propanediimine (**11**, 0.05 mol maximum). The yields of **6** and **7** nearly doubled as the oxidation product solution aged. Approximately 10 other products were present in smaller concentrations. It was significant, however, that the potential products, butyramide, N-formylbutyramide, dibutyramide, N-isopropylformamide, and N-isopropylbutyramide, could not be detected.

The observed products can be rationalized as indicated in the overall view of Scheme I. The reacting system probably contains several oxidizing species: excited dye, oxygen (ground state and excited singlet),[9,10] hydrogen peroxide[3] (possibly as $HO_2\cdot$ or $O_2\cdot^-$)[11,12] from reoxidation of the reduced dye by oxygen, and a variety of peroxy radicals, hydroperoxides, and peroxides. In some oxidation processes several of these may be equivalent. In others the reactions require specific oxidant types. Five significantly different oxidation processes (a–e) are discernible.

a. "Type I Photosensitized Oxygenation."—This classification has been given by Schenck[13] to hydroperoxide-forming reactions which proceed by hydrogen abstraction from the substrate, addition of oxygen to the substrate radical, and transfer of a hydrogen atom to the peroxy radical. His view[5] that sensitized autoxidation of amines is such a reaction has been widely accepted.[14] The capacity of excited dyes to



abstract hydrogen from amines (more precisely, a process of electron abstraction followed by release of a proton[17]) is well known from many anaerobic photoreduction studies.[18a] In the presence of oxygen, radicals thus produced could be expected to yield hydroperoxides in a reaction analogous to benzophenone-sensitized autoxidation of isopropyl alcohol.[18b] The semireduced dye might react with oxygen,[3] producing the hydroperoxy radical or be reoxidized by the peroxyamine radical, in which case no hydrogen peroxide-related species would appear. The latter would be in accord

(7) This easy reaction seems unappreciated.[8] Ir spectra show that, at concentrations below 0.4 *M*, less than 5% free amine is present after 2 hr. 2-Butylamino-2-hydroxypropane is insignificant at equilibrium.

(8) R. W. Layer, *Chem. Rev.*, **63**, 487 (1967).

(9) C. S. Foote and S. Wexler, *J. Amer. Chem. Soc.*, **86**, 3879, 3880 (1964).

(10) E. J. Corey and W. C. Taylor, *ibid.*, **86**, 3381 (1964).

(11) J. Weiss, *Trans. Faraday Soc.*, **34**, 451 (1938).

(12) L. Lindqvist, *Ark. Kemi*, **16**, 79 (1960).

(13) G. O. Schenck, *Ind. Eng. Chem.*, **55**, No. 6, 40 (1963).

(14) Recent demonstration of the quenching effect of tertiary amines toward singlet oxygen, without chemical reaction,[15] should restrain invocation of this species as the reagent in dye-sensitized amine autoxidation.[16]

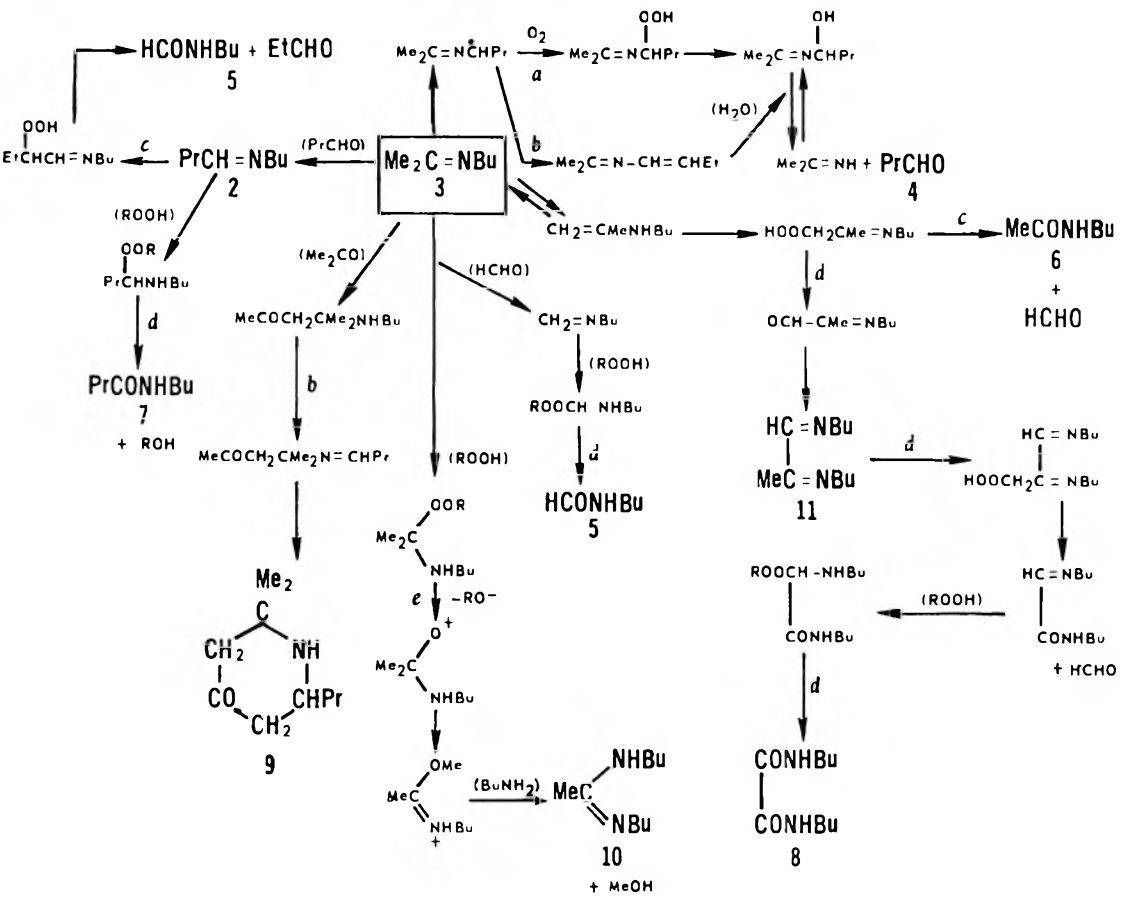
(15) C. Ouannès and T. Wilson, *J. Amer. Chem. Soc.*, **90**, 6527 (1968).

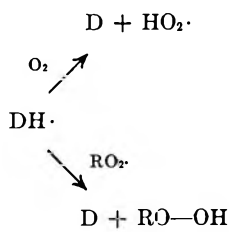
(16) K. Gollnick, *Advan. Photochem.*, **6**, 1 (1968).

(17) L. Horner in "Autoxidation and Antioxidants," Vol. I, W. O. Lundberg, Ed., Interscience Publishers, New York, N. Y., 1961, p 171.

(18) (a) H. Meier, "Die Photochemie der Organischen Farbstoffe," Springer Verlag, Berlin, 1963, p 91; (b) G. O. Schenck, H. D. Becker, K. H. Schulte-Elte, and C. H. Krauch, *Chem. Ber.*, **96**, 509 (1963).

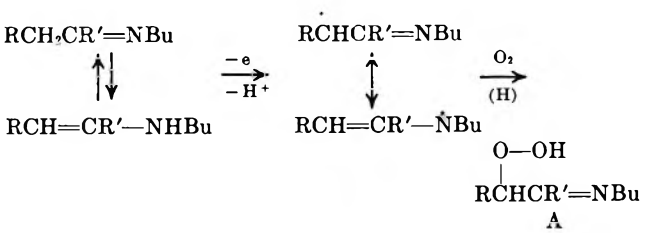
SCHEME I





with the fact that chain reactions have not been observed and also with our observation that dehalogenation of the sensitizers rose bengal and eosin does not occur, as could be expected if the semireduced dye had an appreciable lifetime.[19]

Radical attack on **3** may in this way give a hydroperoxide which might be degraded[20] to butyraldehyde (**4**) *via* a hemiaminal (Scheme I), although we are inclined to favor an alternate route (see b below). Abstraction of an electron from **3** or its tautomeric enamine[21] can also give a resonance-stabilized β radical



from which a β-hydroperoxide (A) will arise. As discussed below, an intermediate of type A is probably involved in the formation of **11**.

b. Dehydrogenation.—Oxidation of aliphatic amines by a variety of methods[22-26] has been shown to give imines and enamines. Such an oxidative process could be responsible for the conversion of **3** to **4**, an ambiguous case. Clear examples of dehydrogenation were later found with dibutylamine and tributylamine. Formation of **9** in the autoxidation of **3** is logically attributed to the steps shown in Scheme I. Dehydrogenation of the secondary amine formed by addition of acetone to **3**, followed by cyclization,[27] accounts for the formation of **9**.

A plausible reaction of **3**, or of an imine produced by amine dehydrogenation, is base-catalyzed addition of hydrogen peroxide or a hydroperoxide.[28] We suggest that this is the probable source of the α-peroxides which others have reported and which we require as intermediates in the formation of various product amides (see d below).

c. α,β Cleavage of Imines.—This process has become well recognized as a pathway of autoxidation of

(19) G. Oster, G. K. Oster, and G. Karg, *J. Phys. Chem.*, **66**, 2514 (1962).

(20) R. Hofmann, H. Hübner, G. Just, L. Krätzsch, A. K. Litkowez, W. Pritzkow, W. Rolle, and M. Wahren, *J. Prakt. Chem.*, [4] **37**, 102 (1968), show easy homolytic decomposition of hydroperoxides in basic solution. Reduction by **3** is an alternative demonstrated in the present work.

(21) B. Witkop and J. B. Patrick, *J. Amer. Chem. Soc.*, **73**, 2196 (1951).

(22) D. H. Rosenblatt, G. T. Davis, L. A. Hull, and G. D. Forberg, *J. Org. Chem.*, **33**, 1649 (1968).

(23) D. Buckley, S. Dunstan, and H. B. Henbest, *J. Chem. Soc.*, 4880, 4901 (1957).

(24) H. E. De La Mare, *J. Org. Chem.*, **25**, 2114 (1960).

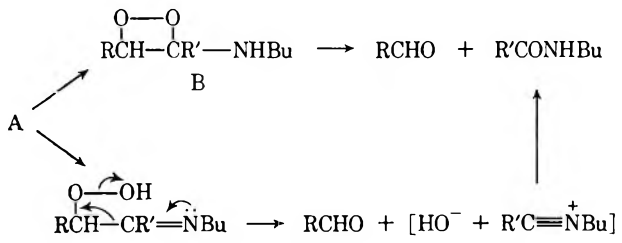
(25) M. Masui, H. Sayo, and Y. Tsuda, *J. Chem. Soc., B*, 973 (1968).

(26) (a) S. G. Cohen and R. J. Baumgarten, *J. Amer. Chem. Soc.*, **87**, 2996 (1965); (b) S. G. Cohen and R. J. Baumgarten, *ibid.*, **89**, 3471 (1967); (c) S. G. Cohen and H. M. Chao, *ibid.*, **90**, 165 (1968).

(27) (a) W. Heinz, *Justus Liebigs Ann. Chem.*, **189**, 214 (1877); (b) O. Antrick, *ibid.*, **227**, 365 (1885).

(28) E. Höft and A. Rieche, *Angew. Chem. Int. Ed. Engl.*, **4**, 524 (1965).

imines and enamines,[21,29a] although the details remain uncertain. Hydroperoxides of the type A might conceivably form transitory cyclic peroxides (B) which undergo carbonyl-forming scission, or a fragmentation process might be involved.[21,29b] In this way **3** gives rise to **6** and formaldehyde. Similarly, **2** will be



oxidized to **5** and propionaldehyde. The latter can reenter the degradation process, being converted to acetaldehyde and finally to formaldehyde as long as **3** remains. Recently singlet oxygen has been shown to be an excellent reagent for such enamine cleavage;[30] its involvement here provides a third possible mechanism.

d. Base-Catalyzed Peroxide-to-Carbonyl Elimination.—A well-documented mode of decomposition of hydroperoxides in alkaline media is the elimination reaction[31]

$$RR'CH{-}OOH \xrightarrow{-H^+} RR'C^-{-}OOH \longrightarrow RR'C{=}O + OH^-$$

N-Butylbutyramide (**7**) must be formed by such a process, following addition of a hydroperoxide to **2**.[32]

An intermediate hydroperoxide of type A provides a plausible mechanism for the early formation of **11**.

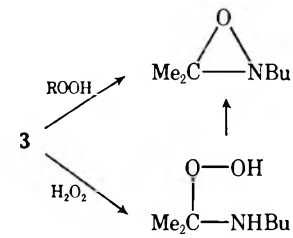
$$HO{-}OCH_2CMe{=}NBu \xrightarrow{(base)} O{=}CHCMe{=}NBu \xrightarrow{(3)} \mathbf{11} + Me_2CO$$

Such an oxidation product of an amine, imine, or enamine has not previously been reported to our knowledge. The bisimine **11** is, of course, susceptible to further oxidation. To some extent this could take the route shown in Scheme I which leads to the observed product **8**.

e. Heterolytic Peroxide Cleavage and Baeyer–Villiger Rearrangement.—The conversion of **3** to **10** depicted in Scheme I is analogous to a rearrangement observed as a side reaction in hydrogen peroxide oxidation of dibutylamine.[33]

Additional modes of oxidation of the ketimine could be postulated but were rejected as of no significance when the related potential products were shown not to be present in detectable amounts. (1) The ketimine apparently does not tautomerize significantly to the isomeric aldimine, since neither N-isopropylformamide nor N-isopropylbutyramide was found. (2) Further oxidation of the initial amide products to diacylamides cannot be appreciable;[34,35] neither N-formylbutyramide nor dibutyramide was detectable.

Other conceivable oxidation processes could be involved, but no conclusive evidence pro or con can be adduced. (1) 2-Butyl-3,3-dimethyloxazirane might be obtained by epoxidation of the ketimine.[28,36,37] This



product would probably not be stable in the basic reaction, mixture, however. Basic decomposition would give ammonia, acetone, and butyraldehyde; a radical oxidation process could lead to **6**.[37] The oxazirane was definitely not present in significant quantity in the final reaction mixture. (2) A nitrone might be a reasonable product to expect. Such compounds are prone to

$$(CH_3)_2C{=}N{-}C_4H_9 \xrightarrow{RCOOH} (CH_3)_2C{=}\overset{\uparrow}{N}{-}C_4H_9 \quad (O)$$

dimerize in alkaline media, however, which would lead to products of very low volatility.[38] In any case no glpc peak of substantial size was observed which could be attributed to this nitrone.

The formation of nonvolatile products from the bulk of the starting material is ascribed to base-catalyzed aldehyde and aldimine polymerization, aldehyde–amide condensation, oxidation of aldehyde to acid, and very possibly polymerization of oxazirane intermediates.[37]

Returning to the photosensitized autoxidation of butylamine itself, it is evident from the relationship in Figure 1 that this reaction must proceed predominantly by way of **2**. We see little doubt that this involves the dehydrogenation process (b above).[39] Conversion of

$$\underset{\mathbf{1}}{C_4H_9NH_2} \xrightarrow{-e} C_3H_7\dot{C}H_2\overset{+}{N}H_2 \xrightarrow{-H^+} C_3H_7\dot{C}H{-}NH_2 \longrightarrow C_3H_7CH{=}NH$$

$$C_3H_7CH{=}NH + \mathbf{1} \longrightarrow \underset{\mathbf{2}}{C_3H_7CH{=}NC_4H_9} + NH_3$$

the radical to the imine could be a disproportionation process[40] or proceed by a second electron and proton (or hydrogen atom) abstraction. The aldimine would be expected to react at once with starting amine.

Examination of the products from autoxidation of **2** in acetonitrile, ethanol, or methyl methacrylate[41] by glpc revealed no major differences, although only reactions in acetonitrile were studied in detail. In this

(29) (a) H. B. Henbest and P. Slade, *J. Chem. Soc.*, 1555 (1960); (b) E. Schmitz, A. Rieche, and A. Stark, *Chem. Ber.*, **101**, 1035 (1968).

(30) (a) C. S. Foote and J. W.-P. Lin, *Tetrahedron Lett.*, 3267 (1968); (b) J. E. Huber, *ibid.*, 3271 (1968).

(31) A. G. Davies, "Organic Peroxides," Butterworth and Co. (Publishers), Ltd., London, 1961, p 28.

(32) The influence of an α-amino group is uncertain. Decomposition by a radical process may compete, leading to an α-amino alcohol[20b] and to an aldehyde, or the base-catalyzed elimination may be slow as suggested by the gradual formation of **7**. [Compare W. H. Richardson and R. S. Smith, *J. Amer. Chem. Soc.*, **91**, 3610 (1969).] The enhanced acidity of a β proton in a β-peroxyimine such as A should favor elimination in competition with α,β cleavage.

(33) A. A. A. R. Sayigh, and H. Ulrick, *J. Chem. Soc.*, 3144 (1963).

(34) M. V. Lock and B. F. Sagar, *ibid.*, B, 690 (1966); B. F. Sagar, *ibid.*, 428, 1047 (1967).

(35) G. M. Burnett and K. M. Riches, *ibid.*, *B*, 1229 (1966).

(36) H. Krimm, *Chem. Ber.*, **91**, 1057 (1958).

(37) W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 5739 (1957).

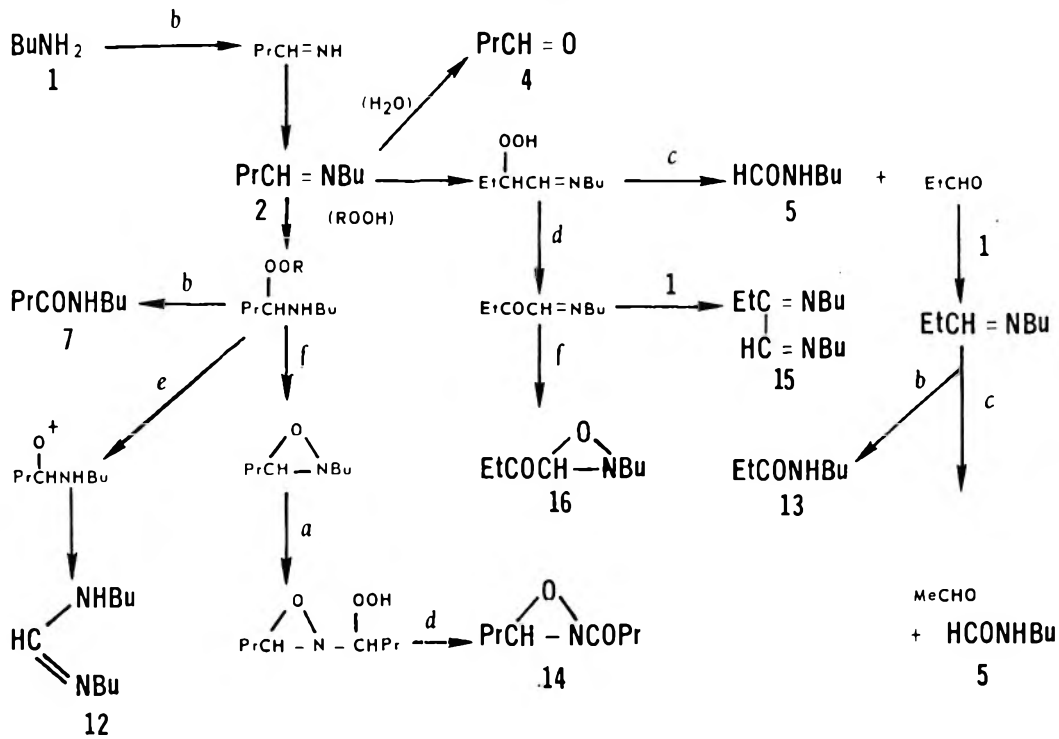
(38) R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and A. Todd, *J. Chem. Soc.*, 2094 (1959).

(39) Although dehydrogenation of **1** is not unequivocally demonstrated by the immediate appearance of **2**, this process is strongly indicated by the less debatable dehydrogenations seen with dibutylamine and tributylamine.

(40) D. Mackay and W. H. Waters, *J. Chem. Soc.*, *C*, 813 (1966).

(41) Methyl methacrylate reacts with **1** to give methyl 3-butylamino-2-methylpropionate, but this reaction is too slow to interfere significantly.

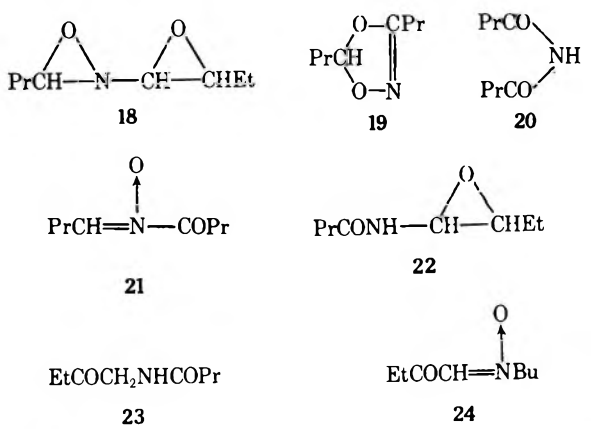
SCHEME II



solvent virtually identical product mixtures were obtained from **1**, distilled **2**, or **2** prepared *in situ* from equivalent amounts of **1** and **4**. The results were similar to those discussed above for **3** in acetone, and several of the same products were identified. However, in this case strong evidence of the involvement of oxazirane intermediates was found. Scheme II summarizes these results and indicates the occurrence of processes a–e as discussed above. The added oxazirane-forming oxidation is indicated as f. All of the oxidation processes of Scheme I have their counterparts here with the exception of the formation of **9**. However, this reaction, too, may have a parallel in the formation of a minor amount of 3,5-diethyl-4-propylpyridine (**17**) which was detected in the mass spectra of various partially resolved fractions (see below).

The major glpc-detectable products present after autoxidation of a 0.4 *M* solution of **1** in acetonitrile for 24 hr (essentially complete destruction of **1** and **2**) were **5**, a compound tentatively identified as 2-butyryl-3-propyloxazirane (**14**), and a mixture of N,N′-dibutylformamidine (**12**) and the acetamidine **10**. An intermediate product (**15**) was also observed to reach a maximum yield of about 15% when **1** was about half destroyed, but it was not detectable in the final mixture. Compound **15** was not isolated in sufficiently pure or stable form for satisfactory identification, but its glpc characteristics and other behavior were very similar to those of **11**, and it is eminently reasonable to identify it as N,N′-dibutyl-1,2-butanediimine.

In the course of experiments to identify **15**, a previously unseen compound (**16**) was discovered as a major component of the distilled concentrate containing **15**. Compound **16** was not a significant component of the autoxidation mixture and may have been formed in the distillation itself.[42] Its molecular weight was shown to be 157, most logically $C_8H_{15}NO_2$. The product **14**, which was more advantageously obtained as an autoxidation product of dibutylamine, proved to be isomeric with **16**. These compounds are believed to be oxazirane derivatives as indicated in Scheme II. Alternative formulations for the relatively volatile isomer **16** are **18** and **19**. Formation of **18** would require a dubious multistage oxidation, however. Rearrangement of **14**[43] might conceivably give **19** which cannot be ruled out with complete confidence. In any case, the formation of an oxazirane structure is required to explain the product, and this is the basic point to be made. Consequently, it is probable that 2-butyl-3-propyloxazirane (**25**) is also present. It may in fact account for an observed species, *m/e* 141, in the mass spectrum of crude **16**. (Loss of oxazirane oxygen, 157 → 141, might occur, but this is not a cleavage observed with 2-butyl-3,3-dimethyloxazirane.)



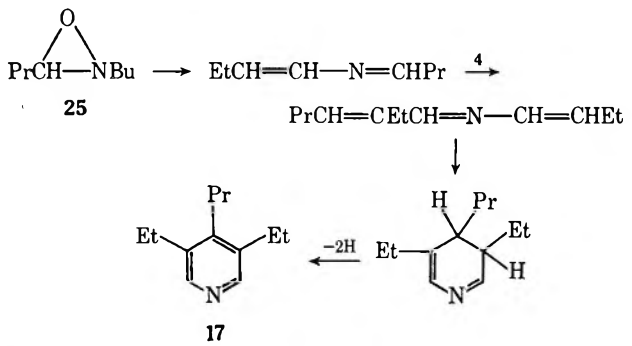
Assignment of the structure **14** to the less volatile $C_8H_{15}NO_2$ isomer rests on the following grounds. The glpc behavior is suggestive of an N,N-disubstituted

(42) A. Padwa, *J. Amer. Chem. Soc.*, **87**, 4365 (1965), has described a stable 3-acyloxazirane.

(43) E. Schmitz and S. Schramm, *Chem. Ber.*, **100**, 2593 (1967).

amide (**20**, **21**, **22**, and **23** would have much longer retention times). Such a product is a very likely one to be produced by autoxidation of **25** which is probably present during the reaction. The nitrone **24** remains a weak possibility.

In the course of a brief study of the properties of **25** prepared by an authentic procedure, it was found that heating at 150° caused the formation of **17**. This probably proceeds by way of an enimine.[37] The same



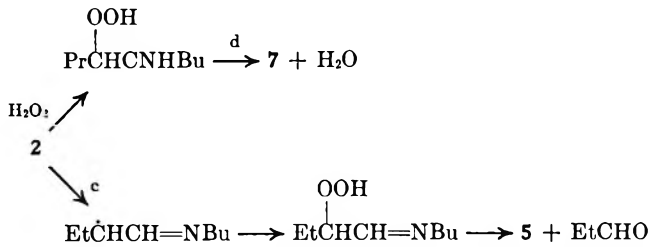
intermediates could well be formed in the autoxidation process[44] and are reflected in the occurrence of an *m/e* 177 species in the mass spectra of several product fractions having appropriate retention times.

The apparent absence of butyramide in the autoxidation product mixture from **1** provided further support for our persuasion that an α-hydroperoxy primary amine is not an important intermediate.

Oxidation of the Butylamines by Hydrogen Peroxide. —Hydrogen peroxide is probably produced during dye-sensitized autoxidation of amines in the cyclic regeneration of the dye from its semireduced form. Consequently it was significant to test its mode and rate of reaction with the usual substrates. Unsensitized reactions of **1**, dibutylamine (**26**), or tributylamine (**27**) with hydrogen peroxide in acetonitrile were found to occur readily at rates comparable to that of photosensitized autoxidation under our standard conditions. In each case the same oxidation products were formed as had been identified in the autoxidation studies. Product ratios were altered, however, and previously unobserved products of oxygenation at nitrogen reached substantial yields.

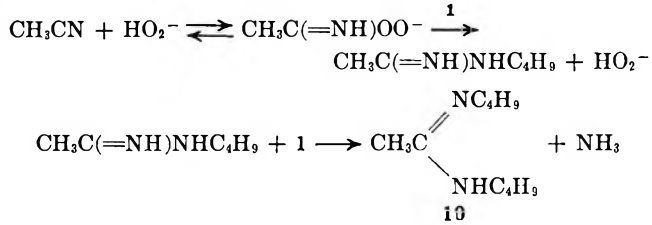
In acetonitrile the hydroperoxide anion tends to add to the nitrile group to give the peracetimidic acid anion, $CH_3C(=NH)OO^-$, which is recognized as a potent oxidant.[45] As the expected by-product of oxidations by this species or as the product of its reaction with additional hydrogen peroxide, acetamide was formed in substantial amount in each of these experiments.

The aldimine **2** was clearly the initial product obtained from **1**. It was found to react considerably faster than the primary amine with hydrogen peroxide, about $^1/_3$ being converted to **7** and **5** in a ratio of about 4:1. A smaller amount of **1** presumably was oxidized to N-butylhydroxylamine and this to butyraldoxime, an identified product. Oxygenation at the nitrogen atom is probably an appreciable reaction of peroxide in this system because of its high concentration. In autoxidation reactions, more reactive intermediate products may be efficient traps for the peroxide, as **2** proves to be. The dehydrogenation reaction leading to **2** demonstrates the capability of the peroxide to initiate concurrent dark free-radical reactions leading to the same products as observed in photosensitized autoxidation.[46] The ratio of **7** to **5** here is much higher than in autoxidation, reflecting the greater probability in this system of addition of peroxide to the imine structure compared to the radical process c.[47] The major part of



the substrate, as in autoxidation, was converted to nonvolatile products.

Interestingly, if the temperature was allowed to rise to about 60°, hydrogen peroxide reacted in a very different way with **1** in acetonitrile, producing **10** in about 80% yield. This seems best explained as hydroperoxide ion catalyzed addition of butylamine to the nitrile group.



It had been noted that in the autoxidation of **3** in acetone the reaction solution at no time contained an iodometrically detectable amount of peroxide, although autoxidations of the various substrates in other solvents commonly produced major amounts of titratable peroxide. Presumably the difference was owing to the ability of acetone to form hemiketal peroxides of much reduced oxidizing power. Hydrogen peroxide in acetone was sufficiently active to be measured satisfactorily by iodometry, but no reaction could be detected with **3** in the presence of a threefold excess of hydrogen peroxide in 24 hr. This system thus offered an excellent opportunity to test the possibility of dye-sensitized oxidation by peroxides, a type of process which may be involved in any of the sensitized autoxidation reactions. Such a reaction did occur under the usual photosensitization without added oxygen, and substantially the same product distribution as in autoxidation was obtained.

Reaction of **26** with hydrogen peroxide in acetonitrile gave a substantial yield of N,N-dibutylhydroxylamine (**28**) together with lesser amounts of **2** and its oxidation products. Oxidation at nitrogen was also an important reaction with **27**, giving tributylamine oxide in 43% yield. Accompanying dehydrogenation produced N-1-butenyldibutylamine (**29**) which in turn gave **4** and **26** in major amounts.

(44) A referee has pointed out that 1,4 cycloaddition of singlet oxygen to EtCH=CH—N=CHPr would provide an alternative source of the $C_8H_{15}NO_2$ compounds.

(45) G. B. Payne, *Tetrahedron*, **18**, 763 (1962).

(46) Weil[3] was able to show such participation of hydrogen peroxide during methylene blue-sensitized autoxidation of nicotine in water.

(47) C. Mentzer and Y. Burguer, *Bull. Soc. Chim. Fr.*, 218 (1952).

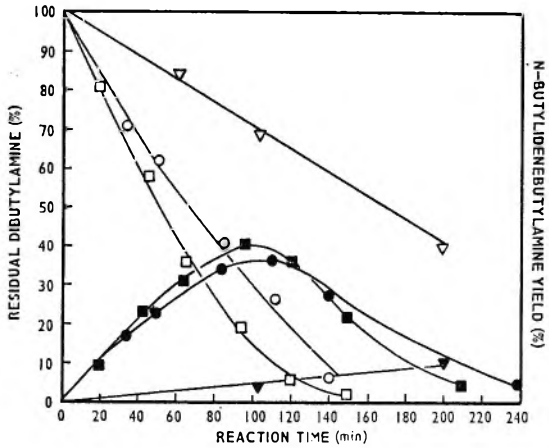


Figure 3.—Autoxidation of dibutylamine in various solvents (amine concn 0.02 *M*; sensitizer concn 1.0×10^{-4} *M*): ○ and ●, rose bengal, acetone; □ and ■, rose bengal, acetonitrile; ▽ and ▼, rose bengal acid, methyl methacrylate.

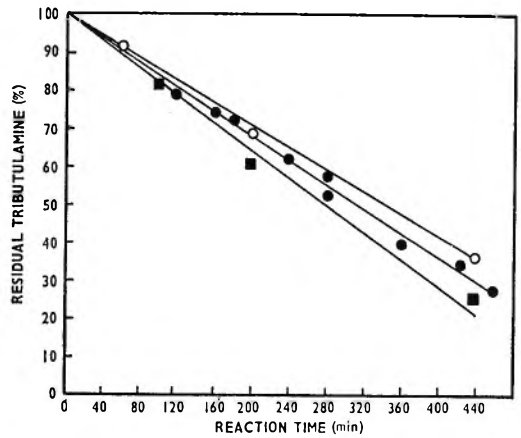


Figure 4.—Autoxidation of tributylamine in various solvents (amine concn 0.02 *M*; rose bengal concn 1.0×10^{-4} *M*): ○, acetone; ●, methyl methacrylate, absolute, ethanol, 95% ethanol; □, acetonitrile.

Autoxidation of Dibutylamine.—The rates of destruction of dibutylamine (**26**) by rose bengal-sensitized autoxidation in acetone, acetonitrile, and methyl methacrylate are shown in Figure 3 which also shows the concurrent formation of **2** as the predominant initial product. Examination of the oxidation product mixtures after substantial conversion disclosed the typical range and proportions of compounds obtained from **2** itself. In addition, N,N-dibutylformamide (**30**) was found in substantial amounts which depended on the solvent used. This amide must be an oxidation product of **29** which was never present at a detectable level, however. In principle, oxidation of **29** might

$$(C_4H_9)_2NH \underset{+2,\ -NH_3}{\overset{+C_3H_7CHO}{\rightleftharpoons}} (C_4H_9)_2NCH{=}CHC_2H_5 \xrightarrow{O_2} (C_4H_9)_2NCHO + C_2H_5CHO$$

26 **29** **30**

give rise to N,N-dibutylbutyramide as well, but this compound was not found.

Autoxidation in acetonitrile gave **30** in about 5% yield. However, in acetone a selective interaction increased the yield of this product to 23% without other significant changes being apparent. Possibly formation of an adduct, $Me_2C(OH)NBu_2$, partially protects the amine from attack until displacement of the acetone by **2** or **4** gives the easily oxidized enamine **29**. Infrared spectra did not give conclusive evidence for such an acetone adduct but did show that dehydration to N-isopropenyldibutylamine was not a significant reaction. Nevertheless, oxidation of this enamine would give N,N-dibutylacetamide, which appeared to be present in small amount.

The sluggish reaction in methyl methacrylate was primarily owing to the abnormal condition of the dye in this nonpolar solvent. The usual products were obtained, but as the oxidized solution aged in the dark, the yield of **30** increased substantially and, especially interestingly, the compound **14** increased from a very small amount to a 10–12% yield. These products may be slow to form because of the low polarity of the solvent or because of stabilization of peroxy radicals or hydroperoxides by addition to the methacrylate double bond.

Although dibutylhydroxylamine is a major product of the reaction of dibutylamine with hydrogen peroxide, it was not found in any autoxidation experiment.

Autoxidation of Tributylamine.—Sensitized autoxidation of **27** in acetone, acetonitrile, ethanol, or methyl methacrylate under standard conditions resulted in substantially equal rates of disappearance of the starting amine (Figure 4). The reactions in acetone and in acetonitrile gave very similar products. When the starting amine was 65–85% destroyed, about $^2/_3$ could be accounted for as an exceptionally clean mixture of identifiable compounds. The predominant product was **30** accompanied by substantial amounts of **4** and **26**. N-Butylidenebutylamine (**2**) and its principal derivatives, **5** and **7**, were minor constituents. In neither case could tributylamine oxide be detected.

Evidently two degradation paths compete in these reactions. The key intermediate leading to **30** must be **29** which cannot actually be observed. This undergoes oxidative cleavage of the α,β double bond to give the formamide and propionaldehyde. Two routes to **29** are available: dehydrogenation of the starting amine seems most reasonable as the principal route, following established precedent; α-oxidation may give rise to an α-hydroxy amine which can both lose water to give **29** and dissociate to **4** and **26**. As long as **26** remains, it will be

$$\begin{array}{l} \xrightarrow{-2H} Bu_2NCH{=}CHEt \longrightarrow Bu_2NCHO + EtCHO \\ \qquad\quad \mathbf{29} \qquad\qquad\quad \mathbf{30} \\ Bu_3N \quad \mathbf{27} \\ \xrightarrow{O_2} Bu_2NCHPr \rightleftharpoons Bu_2NH + PrCHO \\ \qquad\quad \mathbf{26} \qquad\quad \mathbf{4} \end{array}$$

$$\begin{array}{c} Bu_2NCH{=}CHEt \\ \mathbf{29} \\ \updownarrow -H_2O \\ Bu_2NCHPr \\ | \\ OH \end{array}$$

in equilibrium with **29** and can be converted to **30**. However, it will also be oxidized irreversibly to **2** and its derivatives. When the reaction was run in absolute ethanol, the product ratio **26**:**30** was greater, and a further increase resulted when 5% water was present. Presumably either water or ethanol reduces the small equilibrium concentration of **29**.

In methyl methacrylate, although the measured rate of loss of **27** was substantially the same as in acetone or acetonitrile, the reaction must take a new course leading

predominantly to non-glpc-detectable products. The yield of **30** was especially low, suggesting that the enamine might have been intercepted by the reactive solvent, but we find that **29** remains essentially unchanged in methyl methacrylate for several days at room temperature.

Experimental Section

Materials Used.—Rose bengal (disodium 3,4,5,6-tetrachloro-2′,4′,5′,7′-tetraiodofluorescein) and ethyl eosin (ethyl ester of 2′,4′,5′,7′-tetrabromofluorescein) were stain-grade dyes obtained from Allied Chemical and Dye Corp. Rose bengal acid was obtained by acidification of an aqueous solution of the sodium salt with sulfuric acid. Hematoporphyrin base was precipitated from an aqueous solution of the hydrochloride (Nutritional Biochemicals Corp.) by addition of sodium hydroxide. The butylamines and benzaldehyde (Eastman Kodak Co.) were redistilled before use and were essentially pure by glpc.

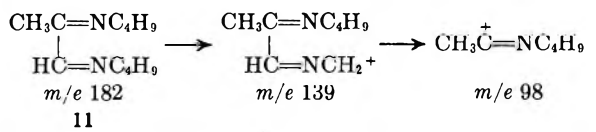
Glpc Techniques.—A flame ionization detector provided sufficient sensitivity for satisfactory observation of compounds at concentrations of 10^{-6} *M*. Usually the solvent was used as an internal standard with sufficient reproducibility. Chromatographic sensitivities were established for all of the principal components which could be identified. Otherwise it was assumed that the signal strength was proportional to the carbon content of the effluent gas stream. Identification of the reaction products was based on direct comparison by glpc with known materials when these were available or could be synthesized readily. Retention time agreement on two types of glpc columns was usually considered adequate proof of identity. A stationary phase of 4:1 polyethylene glycol–KOH was preferred for resolution of the amines as well as practically all products of reasonable volatility. For less volatile compounds and for comparison on a nonpolar column, silicone gum rubber was employed. Occasionally a column containing nonylphenoxypolyethoxyethanol–KOH was used; this had similar characteristics to the KOH–polyethylene glycol column. Similar $^1/_4$-in. columns were used with a thermal conductivity detector for analysis of product concentrates in a glpc–mass spectrometer combination.

We have found that the reaction products undergo further changes in dark storage after the photosensitized autoxidation reaction has stopped. Not only are unstable materials observed to disappear, but the concentrations of some products increase for a few days. This is presumably owing to slow breakdown of peroxides present. It might be considered that the compounds observed in glpc analysis are not present as such in the product mixture but are artifacts produced by pyrolysis in the gas chromatograph inlet from such peroxides and from polymeric material. Indeed, it is likely that such effects do occur and are responsible for some difficulties in using the glpc–mass spectrometer combination effectively. However, we are convinced that the reproducible retention times and clean peak shapes signify that our interpretation is proper; pyrolytic processes appear to have caused only high background signals.

Autoxidation Rate Measurements.—Appropriate solutions (50–70 ml) contained in 20 × 450 mm Pyrex glass tubes were irradiated with "Cool-White" fluorescent lamps while "breathing air" was continuously introduced at the bottom of the tubes through fritted disks at a rate ensuring active agitation and essential saturation of the solution (about 400 ml/min). A Dry Ice–acetone reflux condenser was used to minimize loss of solvent and reactants. The reaction mixtures were analyzed at appropriate intervals by glpc.

Autoxidation of N-Isopropylidenebutylamine (3) in Acetone.—Several runs were made at various concentrations and for various lengths of time without appreciable differences in the product distribution. Work-up varied for isolation of particular products. The overall results are summarized under Results and Discussion.

To recover a major but fugitive product, **11**, autoxidation of a 0.4 *M* solution of **3** was stopped after 4 hr when **11** was near its maximum concentration (5% yield). The solvent was evaporated and the residue extracted with petroleum ether, thus removing **11** from insoluble tar. Adsorption on a silica gel column and elution with ethyl ether gave an early fraction which appeared to be >90% **11** by glpc, and this material was moderately stable at −15°. Compound **11** had glpc characteristics suggestive of a strongly basic polyamine, and its ir spectrum exhibited a complex pattern in the 1500–1700-cm^{-1} region with very little –OH or –NH absorption. Mass spectrometric examination at low temperature and low voltage, with very short photoplate exposure to minimize fragmentation, failed to give a satisfactory spectrum. However, high resolution-peak matching under normal operating conditions identified two fragments as $C_8H_{15}N_2$ (calcd mass, 139.124; found, 139.125) and $C_6H_{12}N$ (calcd mass, 98.097; found, 98.097). These appeared to be derived from a parent compound of mass 182 (although this peak was very weak) formulated as **N,N′-dibutyl-1,2-propanediimine.** This identification of **11** was confirmed by glpc comparison with an authentic sample prepared by reaction of pyruvic aldehyde with excess butylamine.



11

To identify the products, 2,2-dimethyl-6-propyl-4-piperidone (**9**) and N,N′-dibutylacetamidine (**10**), a 0.4 *M* solution of **3** was autoxidized for 24 hr (about 90% destruction of **3** and **2**). Evaporation of the solvent left a gum which was extracted with petroleum ether. Nearly all **9** was found in the extract and **10** remained undissolved. Compound **9** was retained on a silica gel column after washing with petroleum ether which removed most of the other reaction products present in the extract. It was then eluted with ethyl ether and refined by further chromatography, yielding a product in which **9** was the only appreciable component (by glpc). Examination by ir suggested the presence of a propyl or butyl group and a carbonyl group (ν 1710 cm^{-1}, probably ketone). High resolution mass spectrometry at low temperature gave the empirical formula $C_{10}H_{19}NO$ (calcd mass, 169.147; found, 169.146). Fragments were also identified which helped suggest the 4-piperidone structure. This compound was synthesized as described later and proved to be identical with the autoxidation product **9**.

Compound **10** was extracted from the petroleum ether–insoluble gum with 0.5 *N* HCl under ethyl ether. The aqueous phase was then made strongly basic and extracted with ethyl ether. The solute recovered contained **10** with much larger amounts of **5** and **6**. Column chromatography on silica gel with ethyl ether elution removed much of the amide material leaving **10** on the column. Subsequent elution with methanol yielded a small amount of material in which the largest component was **10** with smaller, roughly equal amounts of **5**, **6**, and **9** present. It was suspected that **10** was either N,N′-dibutylformamidine or N,N′-dibutylacetamidine, and these compounds were prepared for glpc comparison by reaction of formamidine and acetamidine hydrochlorides, respectively, with butylamine in boiling ethanol followed by liberation of the free bases with aqueous KOH. The two amidines were not distinguishable on the KOH–polyethylene glycol column, but on the silicone column identity of the product **10** with the acetamidine was clear. For additional proof, the crude sample was hydrolyzed with aqueous methanolic KOH at 70° resulting in a substantial increase of the ratio of **6** to **5** in the solution.

At one point it appeared that autoxidation of **3** might be giving a product which was not resolvable from solvent acetone. This doubt was eliminated by carrying out a comparable autoxidation of *n*-octylamine in acetone. As with **1**, the ketimine was formed very quickly and was destroyed at about the same rate as **3**. Octanal and N-octylideneoctylamine were formed as expected, and as with **3** at least 75% of the octylamine was converted to nonvolatile, presumably polymeric material.

Autoxidation of Butylamine (1) in Acetonitrile.—The rate of destruction of **1** under standardized conditions is shown in Figure 1. When an identical run was interrupted after 85 min and the solution stored overnight in the dark, further 26% and 33% losses of residual **1** and **2** occurred during the dark period.

Autoxidation of **1** (0.4 *M*) in acetonitrile required 24–30 hr for essentially complete destruction of **1** and **2**. Glpc analysis showed the presence of compounds having the characteristics of **N,N′-dibutylformamidine** (**12**, approximately 0.06 mol per mol of **1**), **5** (0.05–0.06 mol), **4** (0.05 mol), **7** (0.025 mol), **13** (0.015 mol), **6** (0.01 mol), and **8** (0.005 mol). An additional major product (**14**, 6–8%) was unknown. An intermediate product (**15**) was also observed which reached a maximum yield of about 15% when **1** was half destroyed but was not detectable in the final

mixture. Several additional compounds were detectable in trace amounts. The product distribution did not change appreciably when the starting concentration of **1** was varied or if **2** was used either as freshly distilled material[48] or prepared *in situ* from **1** and **4**. In one run, exit gases were shown to contain ammonia trapped as NH_4Cl.

By interrupting the autoxidation of **2** (0.1 *M*) after 5 hr, when **15** was near maximum concentration, and evaporating the solvent, a product concentrate was obtained which contained **15** and a second substantial unknown product **16**, which seemed identical with 2-butyl-3-propyloxazirane (**25**) in glpc comparison on the silicone column. Both **15** and **16** were lost within 24-hr storage of the concentrate at −15°. Attempts to obtain their mass spectra through use of the glpc–mass spectrometer technique were unsuccessful with respect to **15**, but **16** was resolved sucessfully, and a satisfactory spectrum was obtained distinguishing this compound from **25**. The apparent molecular ion had *m/e* 157 and other masses observed were 141, 98, 84, 70, 60, 57, 41, 30, 29. The combined fresh product solutions from several concurrent runs were distilled rapidly through a short-path still at high vacuum. About 1/3 was collected below 150° (0.1 mm) and contained **15** (fraction 1); another third distilled at 150–200° (0.1–0.05 mm) and proved to be rich in **12** (fraction 2). Compound **16** was lost in the distillation, and **15** was still unstable in fraction 1. Attempts to resolve **15** from the fresh distillate by the glpc–mass spectrometer technique were unsuccessful, as were attempts at isolation by preparative glpc. Its properties were strikingly similar to those of **9**.

Experiments with **10** and **12** showed that, although these compounds are not resolvable on the KOH–polyethylene glycol column, the silicone column distinguishes between them when high concentrations are present. However, at low levels in autoxidation product mixtures their retention times are unreliable. Mass spectrometric examination of the distilled fraction 2 (above) gave no indication of the presence of either **10** or **12** although glpc had shown a high content of one or both. By mild hydrolysis of a sample of fraction 2 with aqueous KOH, the content of **5** was greatly increased while the amidine content decreased relative to other components, thus providing positive evidence for the presence of **12**.

Reaction of Amines with Hydrogen Peroxide in Acetonitrile. A. N-Butylidenebutylamine (2).—Hydrogen peroxide (98%) was dissolved in acetonitrile to give an 0.20 *M* solution. To this an equimolar amount of **2** was added at 25°. Analysis of the solution at intervals by glpc showed 39% loss of **2** in 2 hr and 50% loss in 8 hr, the reaction approaching a halt due to exhaustion of the peroxide. Residual **2** continued to decrease owing to slow disproportionation.[48] Glpc showed the major detectable product to be **7** (approximately 11% yield) with **5** about 3%. Butyraldehyde was also found in about 15% yield early in the reaction.

B. Butylamine (1).—Under the same conditions **1** was 30% destroyed in 24 hr, and no titratable peroxide remained. In another experiment the peroxide concentration was tripled (cooling required to hold the solution at 25°), resulting in 40% loss of **1**. A 13% yield of **2** was present after 12 hr when reaction had essentially stopped. The other principal detectable products were **5** (2.2%), **7** (1.8%), butyraldoxime[49] (1.9%), and PrCH=CEtCH=NBu (1.3%). Acetamide was also present in somewhat larger amount, but no amidine (**10** or **12**) was detected.

This experiment was repeated, but the temperature was allowed to rise to 50–60° during the initial mixing, leading to very different results. The predominant product was **N,N′-dibutylacetamidine (10)** (80% yield by peak area). Its identity was established by glpc isolation and high-resolution mass spectrometry which unequivocally gave the composition $C_{10}H_{22}N_2$ (calcd mass, 170.178; found, 170.178). It was then shown to be identical with an authentic sample by glpc and mass spectrometric comparison.

C. Dibutylamine (26).—Reaction of **26** (0.02 *M*) with hydrogen peroxide (98%, 0.62 *M*) in acetonitrile at room temperature essentially stopped at about 45% conversion in 90 min, when 2–3% yields of both **2** and **4** were present. The major detectable product proved to be N,N-dibutylhydroxylamine (**28**), approximately 12% yield. An unstable compound was also present (3% yield) in the fresh reaction mixture but was gone after 3 days. This had the glpc characteristics of **11**. Small amounts of N,N-dibutylformamide (**30**), **7**, and possibly **13** were present as well as considerable acetamide.

Identification of **28** was based on isolation by preparative glpc and comparison with an authentic sample by ir and mass spectrometry. The comparison sample was prepared by addition of an equivalent amount of 6% aqueous hydrogen peroxide to an equal volume of methanol containing **26**.[50] A distilled fraction boiling at 78–80° at 1.5 mm contained about 60% **28** plus substantial amounts of **30** and **7**. Mass spectrometric identification of **28** caused some problems because, instead of the molecular ion (*m/e* 145), the highst mass found was 143. This behavior was identical with both the experimental product and the comparison sample, for which the ir spectrum was adequate identification. Possibly the mass 143 represents the nitrone, PrCH=N-(O)Bu, produced by dehydrogenation in the mass spectrometer.

D. Tributylamine (27).—An acetonitrile solution containing **27** (0.02 *M*) and hydrogen peroxide (98%, 0.62 *M*) was stored at room temperature for 4 days. Glpc analysis then showed 81% loss of **27**, and **4** and **26** were present in yields of 33% and 30%, respectively, based on converted **27**. Small amounts (3–5% yields) were also found of **7** and N-butenyldibutylamine (**29**). The crude reaction mixture was evaporated to remove most of the acetonitrile and the residue was dissolved in ether. Mixing with water then extracted the tributylamine oxide present, and addition of aqueous picric acid to the water solution precipitated the amine oxide picrate, mp 108–110° (lit.[51] 100°), 43% yield.

For the comparison above and other purposes, **29** was prepared by gradual addition of **4** to a small excess of **26** in cold ether in the presence of anhydrous potassium carbonate.[52] After 3 hr anhydrous magnesium sulfate was added, and the solution was later distilled. A fraction boiling at 72° at 3 mm was at least 90% pure by glpc.

Autoxidation of Dibutylamine. A. In Acetonitrile.—Autoxidation of a 0.2 *M* acetonitrile solution of **26** under the usual conditions destroyed 35% of the amine in 11 hr. Approximately 20% of the amine lost was present as **2** at this point. The solution was evaporated and the residue was examined as follows. Glpc analysis showed **5** to be the major detectable product, with N,N-dibutylformamide (**30**), **7**, **13**, and **6** present in lesser amounts, decreasing in that order. Compounds **12** and **14** also appeared at low levels. The compound **14** was isolated satisfactorily in the glpc–mass spectrometer and found to have *m/e* 157 with fragment ions of masses 142, 129, 115, 100, 84, 72, 57 (doublet), 46, and 41. High resolution mass spectrometry of the total reaction product concentrate revealed the presence of two compounds with mass 157. One of these was **30** ($C_9H_{19}NO$: calcd mass, 157.147; found, 157.146); the other (**14**) had the composition $C_8H_{15}NO_2$ (calcd mass, 157.110; found, 157.111) and is believed to be **2-butyryl-3-propyloxazirane**.

The plausible oxidation product **28** would, if present, not be resolvable from **5** by the KOH–polyethylene glycol column nor from **30** by the silicone column. However, by isolation of the **5** peak using a KOH–polyethylene glycol column in the glpc–mass spectrometer combination it was shown that the characteristic *m/e* 143 fragment of **28** was absent.

As the product concentrate aged, a group of eight glpc peaks appeared which were shown by comparison with standards to be owing to the four possible aldehyde "dimers" from a mixture of **4** and propionaldehyde, together with the four aldimines derived by condensation of these dimers with **1**.

When the autoxidation was carried out in acetonitrile containing 5% water, there was very little difference in the reaction rate or the products. The yields of **2** and **4** were somewhat higher, however, 53 and 74%, respectively, at their maximum values.

B. In Acetone.—Changes in the concentrations of **26** and **2** during autoxidation under standard conditions are shown in Figure 3. The possibility that the glpc peak for **2** included appreciable **3** was rejected because of the presence of **4** throughout the run. Examination of the final solution (4-hr reaction) showed the predominant glpc observable product to be **30** (about 23% yield). Other amides present were **5** (8%

(48) The aldimine **2** disproportionates spontaneously to **1** and PrCH=CEtCH=NBu to the extent of 13% in 21 hr in 0.2 *M* solution. This is too slow to cause appreciable complication. In longer time, higher condensation products are formed, but only this "dimer" is observed in the autoxidation reactions.

(49) Butyraldoxime, when freshly prepared, gives two glpc peaks on the KOH–Carbowax column, but in the presence of amines it is rapidly converted to a single isomer

(50) W. R. Dunstan and E. Golding, *J. Chem. Soc.*, 1004 (1899).

(51) H. B. Henbest and M. J. W. Stratford, *ibid.*, 711 (1964).

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

yield), 6 (3%), 7 (1%), and 13 (1%). The presumed oxazirane derivative 14 amounted to about 3%, and other minor products normally derived from 2 were observed. The enamine 29 was not present in detectable amount. (A standard sample of 29 was easily resolved from the autoxidation products by the KOH–polyethylene glycol column.) A minor peak corresponding to N,N-dibutylacetamide could be seen when the silicone column was used, but this identification could not be confirmed because of inadequate resolution from 30 on the KOH–polyethylene glycol column.

The mass spectrum of the 30 peak after resolution on a silicone column contained no component of mass 143. This established the absence of 28 and of N-butyl-N-propylformamide which could conceivably have been an unresolvable product.

C. In Methyl Methacrylate.—For this reaction, rose bengal was used in the "acid" form (lactonized). In the presence of the amine (0.02 *M*) 63% of the normal dye absorbance developed. As reaction proceeded, partial dye precipitation occurred. Autoxidation products appeared much the same as in acetonitrile. When 60% of the starting amine was destroyed, 5, 7, and 30 were each present in about 6–7% yield. The yield of 16 was very low at this time but increased to 10–12% as the solution was held at 5° for 24 hr; 30 increased substantially, also.

Reaction of 26 with methyl methacrylate is too slow to interfere with the autoxidation process.

2,2-Dimethyl-6-propyl-4-piperidone (9).—A solution of 10.0 g of 2-amino-2-methyl-4-oxopentane acid oxalate,[53] 5.0 ml of butyraldehyde, and 20 ml of ethanol was heated at reflux for 20 hr.[54] After cooling, the mixture was filtered, and the salt was treated with excess KOH in ether–water. The ether phase was evaporated and the residue was examined by glpc. The predominant component was identical with 9 obtained in autoxidation of 3.

Reaction of 2-amino-2-methyl-4-oxopentane with butyraldehyde yielded a crude sample of **N-butylidene(2-amino-2-methyl-4-oxopentane)** which had glpc characteristics that would have made its resolution impossible in the autoxidation mixtures. It could have accompanied 11 as a fugitive intermediate. This aldimine was unstable at 25°, apparently "dimerizing" somewhat faster than 2.

Examination of 2-Butyl-3,3-dimethyloxazirane.—This oxazirane was prepared by the general method of Krimm.[36] It distilled cleanly at 43–45° at 10 mm and was essentially pure by nmr examination: nmr (CCl_4) δ 1.30 (s, 3, CH_3), 1.46 (s, 3, CH_3), 2.63 (m, 2, NCH_2Pr), 1.50 (m, 4, $CH_2CH_2CH_2CH_3$), 0.93 (t, 3, CH_2CH_3); mass spectrum *m/e* (relative intensity) 129 (1), 114 (2), 100 (1), 86 (5), 84 (2), 73 (2), 70 (2), 58 (8), 57 (4), 56 (6), 55 (2), 44 (100), 43 (38), 42 (10), 41 (9). The oxazirane gave a clean peak on the silicone column at 30–100° at the same retention time as 2, but it was shown by mass spectrometry that the oxazirane was not present in this peak after autoxidation of 3. On the KOH–polyethylene glycol column the oxazirane decomposes to several products, probably[37] including N-butyl-N-methylacetamide and 6; this behavior contraindicates its presence in autoxidation product mixtures.

The oxazirane was destroyed completely in an acetone solution containing an equivalent amount of 3 within 24 hr at 25°, but no products were formed which were detectable by glpc in the usual range of retention times. Presumably only polymeric imines and ammonia were formed.[37]

2-Butyl-3-propyloxazirane (25).—The product prepared by reaction of peracetic acid with 2 in CH_2Cl_2 according to the general procedure of Emmons[37] (bp 56° at 6 mm) was only about 50% pure by glpc and nmr analysis, containing a roughly equal amount of PrCH=CEtCHO. The somewhat different procedure of Krimm[36] gave essentially the same result. This low purity did not hamper establishment of the glpc characteristics of 25. Drastic decomposition occurred on the KOH–polyethylene glycol column at 65°, but on the silicone column 25 was stable to at least 150°.

Decomposition of crude 25 at 120° was >90% complete in 50 min and produced two unknown compounds, X and Y, as well as a small amount of 7. Subsequent heating for 45 min at 150° caused conversion of Y to another new substance, Z, and marked reduction of the butyraldehyde dimer. Distillation of the mixture yielded a fraction rich in X and Z from which both were isolated by preparative glpc using the Millipore Filter technique. The ir spectrum of X was consistent with a nitrone structure[55] PrCH=N(O)Bu: ir 1645 and 1632, strong doublet (C=N), 1085 and 1062 cm^{-1}, medium weak (possibly N→O). The only spectroscopically plausible alternative has appeared to be a disubstituted amide (*i.e.*, HCONBuPr), which would not be consistent with the glpc characteristics of X.

Spectroscopic evidence supported the postulated structure, **3,5-diethyl-4-propylpyridine** (17) for the product Z: ir 1602 (w), 1564 (m), 1417 (m, substituted pyridine nucleus), 902 cm^{-1} (m, isolated aromatic hydrogen);[56] mass spectrum *m/e* 177 (M^+), 176, 162, 149, 148, 134, 121, 106, 91, 77, 65, 53, 51, 44, 41.

Registry No.—1, 109-73-9; 2, 4853-56-9; 3, 6700-95-4; 26, 111-92-2; 27, 102-82-9.

Acknowledgment.—We are pleased to acknowledge the contributions of Mr. T. E. Mead, Dr. D. M. Desiderio, Jr., and Miss M. Yao who obtained and interpreted the mass spectrometry data.

(53) P. R. Haesler, *Org. Syn.*, **6**, 28 (1926).

(54) Adapted from ref 27.

(55) G. R. Delpierre and M. Lamehen, *Quart. Rev.* (London), 329 (1965).

(56) N. B. Colthup, L. H. Daly, and S. E. Wiberly, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N. Y., 1964, p 233.

Electrochemical Dealkylation of Aliphatic Tertiary and Secondary Amines

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Previous work has indicated that straight-chain aliphatic amines undergo dealkylation after anodic oxidation, either by hydrolysis of the enamine formed in a one-electron process, or by hydrolysis of the imminium salt formed in a two-electron process. In the present work, evidence is presented in favor of the enamine as the intermediate. In the earlier work, secondary amines were oxidized but dealkylation was not observed. This has been shown to be incorrect; the reaction of di-*n*-propylamine is very similar to that of tri-*n*-propylamine. It is suggested that electrolytic dealkylation of simple aliphatic amines is a general reaction which can lead from tertiary to secondary and primary amine and finally to ammonia and elemental nitrogen.

Accounts of detailed examinations of the anodic oxidation of primary and tertiary aliphatic amines have been published previously.[1,2] Straight-chain primary amines were found to undergo scission of the carbon–nitrogen bond which resulted in formation of ammonia, elemental nitrogen, protons, and an aldehyde having the same number of carbon atoms as the amine taken. Condensation products which would be expected from a mixture of primary amine and aldehyde were found. Two reaction schemes were suggested. One involved a two-electron formation of an iminium ion which hydrolyzed; the other involved decomposition of the initially formed ion radical.

Tertiary amines were found to undergo dealkylation to the corresponding secondary amine and the appropriate aldehyde. The reaction scheme proposed is outlined in eq 1–6, using tri-*n*-propylamine as the example. This reaction scheme led to predictions of product identities and yields which were in reasonable agreement with experimental results, provided that it was assumed that the secondary amine produced also underwent anodic oxidation. The reaction scheme consists of an initial electron transfer followed by proton loss to form the neutral radical **2**, which could either lose an electron to form the imminium salt **3**, or disproportionate to form the enamine **4**. Either of these would be expected to hydrolyze to give the products that are found. Furthermore, the stoichiometry is the same for either type of reaction; accordingly, on the basis of the information available, no distinction could be made between these two schemes.

$$(C_3H_7)_3N \xrightarrow{-e^-} \underset{\mathbf{1}}{(C_3H_7)_3\dot{N}^+} \quad (1)$$

$$\mathbf{1} \xrightarrow{-H^+} \underset{\mathbf{2}}{(C_3H_7)_2N{-}\dot{C}H{-}C_2H_5} \quad (2)$$

$$\mathbf{2} \xrightarrow{-e^-} \underset{\mathbf{3}}{(C_3H_7)_2N{-}\overset{+}{C}H{-}C_2H_5} \longleftrightarrow (C_3H_7)_2\overset{+}{N}{=}CHC_2H_5 \quad (3)$$

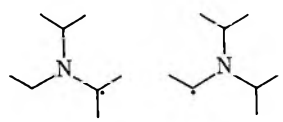
$$\mathbf{2} \longrightarrow (C_3H_7)_3N + \underset{\mathbf{4}}{(C_3H_7)_2NCH{=}CHCH_3} \quad (4)$$

$$\mathbf{3} + H_2O \longrightarrow (C_3H_7)_2NH + C_2H_5CHO + H^+ \quad (5)$$

$$\mathbf{4} + H_2O \longrightarrow (C_3H_7)_2NH + C_2H_5CHO \quad (6)$$

It was suggested, however, that, on examining the results obtained by oxidizing unsymmetrically substituted tertiary amines, a mechanism involving an enamine intermediate appeared to be plausible in certain cases. Reaction of benzyldimethylamine and dibenzylmethylamine resulted mainly in loss of the benzyl group rather than the methyl group. It would be predicted, on the basis of radical stability, that this would occur because of preferential loss of benzylic protons in step 2. Steps 3 and 5 would then follow. Oxidation of allyldiethylamine produced primarily diethylamine, indicating preferential loss of the allyl group. This also would be predicted on the same basis.

When this line of reasoning is extended to the cases of di-*i*-propylethylamine, dicyclohexylethylamine, or cyclohexyldiethylamine, incorrect predictions are obtained. One would expect that reactions analogous to steps 1 and 2 would produce, preferentially, radical **4** from diisopropylethylamine, rather than radical **5**.



4 **5**

However, this would logically lead to loss of an isopropyl group. In fact, loss of the ethyl group is strongly favored. Similarly, an ethyl group is lost in preference to the cyclohexyl group, contrary to predictions based upon radical stabilities. It may be noted that predictions based upon radical stabilities work out only in those cases which involve groups which would form especially stable radicals. This suggests that a different mechanism may be operating in the other cases. One possibility is that the enamine intermediate may be involved in the other cases. It may be noted that the one example studied which can neither form an enamine nor an especially stable radical, trimethylamine, apparently does not undergo simple dealkylation.

In the examinations of tertiary and primary amine oxidation, a degree of similarity was found in that reactions lead to cleavage of carbon–nitrogen bonds with formation of the less highly substituted amine or ammonia, and the appropriate aldehyde. It was noted, however, that no dealkylation was observed upon oxidation of dipropylamine. Apparently the reaction of secondary amines was significantly different from those of tertiary and primary amines.

The present work was undertaken in order to get a better understanding of the dealkylation process and to inquire into the anodic reactions of secondary aliphatic amines. As a result, we believe that it can be shown that the process of electrochemical dealkylation in straight-chain aliphatic amines is a very general one

(1) K. K. Barnes and C. K. Mann, *J. Org. Chem.*, **32**, 1474 (1967).
(2) P. J. Smith and C. K. Mann, *ibid.*, **34**, 1821 (1969).

leading, in principle, from a tertiary amine through the secondary and primary amines to ammonia and finally to nitrogen gas, together with appropriate aldehydes. We believe further that there is now convincing evidence for the involvement of the enamine as the intermediate in electrochemical dealkylation.

Results and Discussion

Dealkylation Mechanism.—In the earlier work,[2] it was demonstrated that dealkylation to aldehyde and amine occurs only in the presence of at least small amounts of water; accordingly, the hydrolyses in steps 5 and 6 were included. It may be noted that, while the stoichiometry is the same for either process, the actual mechanism of incorporation of water in the reactions that are summarized in steps 5 and 6 would be different. These reactions with deuterium oxide, rather than water, are outlined in steps 5a and 6a. They differ in

$$CH_3CH_2CH{=}\overset{+}{N}(C_3H_7)_2 + D_2O \longrightarrow [CH_3CH_2CH(OD)ND(C_3H_7)]^+ \longrightarrow CH_3CH_2CHO + (C_3H_7)_2ND + D^+ \quad (5a)$$

$$CH_3CH{=}CHN(C_3H_7)_2 + D_2O \longrightarrow CH_3CHDCH(OD)N(C_3H_7)_2 \longrightarrow CH_3CHDCHO + (C_3H_7)_2NH \quad (6a)$$

that aldehyde produced by reaction of enamine with D_2O would show deuterium at the α position, while that from the imminium salt would have hydrogen in that position.

To check this point, the oxidation of both tripropylamine and dipropylamine was carried out in a rigorously dried system to which a small amount of D_2O had been added. The aldehyde produced was recovered, purified, and examined by mass spectroscopy, nmr, and ir spectroscopy. In addition, the 2,4-dinitrophenylhydrazone was prepared. The mass spectrum of the aldehyde recovered from electrolysis of either amine with D_2O showed a molecular weight of 59, indicating inclusion of one deuterium. This aldehyde formed a 2,4-dinitrophenylhydrazone with a molecular weight of 239, also indicating monodeuteration. The nmr spectrum of the deuterated aldehyde exhibited a peak for the aldehyde proton at the chemical shift and in the intensity expected for propionaldehyde. Instead of the quartet and triplet shown by the ethyl group of propionaldehyde, very complex groups of peaks with 1.1-Hz splitting were observed, centered about the same chemical shifts exhibited by the methyl and methylene groups of propionaldehyde. This indicates that deuteration has occurred either at the 2 or the 3 position.

The infrared spectrum of the deuterated aldehyde contained peaks assigned to assymetric methyl stretch and carbon–hydrogen stretch of the aldehyde function which occurred at the same frequencies as did these peaks in the propionaldehyde spectrum. In propionaldehyde, the symmetric stretch vibrations for both methyl and methylene occur at the same frequency. For the deuterated compound, a peak at this frequency occurred, but it showed lower intensity relative to other peaks in the spectrum than was the case for propionaldehyde. The peaks for CH_2 assymetric stretch and for CH_2 wag, both present in the spectrum of propionaldehyde, are absent from the spectrum of the deuterated sample. All assigned frequencies fall within the expected ranges for the expected frequencies.[3] In addition, when compared with the vapor phase spectrum of propionaldehyde, for which assignments have been made,[4] the spectra correspond except that all peaks in the liquid phase spectra are shifted 10–30 cm^{-1} toward longer wavelengths relative to those in the vapor phase spectrum.

These data show that the aldehyde recovered from electrolyses made in the presence of D_2O is deuterated in the 2 position. If this is to be considered evidence in favor of a particular mechanism, there must be assurance that deuteration did not simply take place by exchange between D_2O and ordinary propionaldehyde. This reaction has been studied by Hine, *et al.*,[5] who demonstrated that aliphatic amines catalyze hydrogen–deuterium exchange in the aldehydes. They pointed out, however, that the exchange reaction is not an effective preparative route to the deuterated aldehyde. Attempts to prepare deuterated aldehyde by shaking the protreated compound with a concentrated solution of amine in D_2O gave only about a 33% yield. Our examination shows that the monodeuterated aldehyde is formed in the electrolysis virtually to the exclusion of ordinary aldehyde, indicating that some mechanism other than H–D exchange is operating. Our reaction 6a does, in fact, resemble the reaction actually used by Hine, *et al.*, to produce the deuterated aldehyde that they used as starting material.

While the possibility of H–D exchange during electrolysis is precluded, there could be a question about exchange during the separation procedure which includes a distillation. This was checked by performing the separation, starting with propionaldehyde in acetonitrile with D_2O added. Mass spectroscopic examination showed no appreciable deuterium enrichment above the natural abundance. We therefore conclude that propionaldehyde-2-*d* is produced during the electrolysis of both tripropylamine and dipropylamine and that H–D exchange is not responsible for its formation.

In considering the dealkylation process, it must be noted that enamine and iminium ion should be in equilibrium as indicated in eq 7. Furthermore, it

$$\underset{\mathbf{4}}{(C_3H_7)_2NCH{=}CHCH_3} \overset{+H^+}{\rightleftharpoons} \underset{\mathbf{3}}{(C_3H_7)_2\overset{+}{N}{=}CHC_2H_5} \quad (7)$$

would be expected by analogy from cyclic tertiary amines[6] that the enamine would be a significantly stronger base than the corresponding saturated amine.

In our experiments, the solution initially contains the saturated amine which is gradually protonated. If an equilibrium were established involving tripropylamine, tripropylammonium ions, enamine **4**, and iminium ions **3**, it would be shifted toward a mixture of **3** and tripropylamine. If **3** were formed as a result of reactions 1–3 then there would be no opportunity for enamine to be formed, because the system contains no base stronger than the enamine. Since we do have evidence that the enamine is being dealkylated, it therefore follows that the iminium salt is not being

(3) C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press Inc., New York, N. Y., 1963.
(4) E. F. Worden, *Spectrochim. Acta*, **18**, 1121 (1962).
(5) J. Hine, J. G. Houston, J. H. Jensen, and J. Mulders, *J. Amer. Chem. Soc.*, **87**, 5050 (1965).
(6) R. Adams and J. E. Mahan, *ibid.*, **64**, 2588 (1942).

formed either by reaction 3 or 7. We suppose that this indicates that reaction 4 is much faster than reactions 2 and 3 and that reaction 6 is faster than reaction 7.

The recoveries of amines in the present and previously reported work were never quantitative; for example, for tripropylamine it amounted to 80–95% based upon nitrogen in the starting amine. Reaction solutions showed a uv absorption at 315 nm. When water concentration was held below 5 mM, it was noted that this uv band was more intense. The material responsible for the 315-nm band was isolated as a gum from the nonvolatile fraction of the reaction mixture by $CHCl_3$ extraction and thin layer chromatography. Taken from the reaction mixture without having been made basic, it showed a sharp and intense ir absorption at 1695 cm^{-1}. If the material was made basic during the isolation, this peak was shifted to 1660 cm^{-1}. It is characteristic of α,β-unsaturated tertiary amines to show a peak at around 1650 cm^{-1} which shifts 20–50 cm^{-1} toward higher frequencies when the salt is prepared.[7] This behavior has been attributed to a transformation of the type indicated in eq 8. Mass spectra of these samples showed groups of peaks with about 14 mass units separation between adjacent maxima which exhibited a regular diminution in intensity to merge with background noise above m/e of 310.

We are unable to specify the structure of the high-molecular-weight product, the presence of which was mentioned in the previous report.[2] We suggest that it is formed from the enamine, perhaps by condensation with aldehyde, and, in the presence of dipropylammonium ions in the latter stages of the reaction, is converted to the salt form. Presumably stabilized by the condensation against C–N scission, it is capable of undergoing the enamine–salt conversion analogous to those shown by cyclic amines.

It is of interest to note that several examples of enamine formation by chemical oxidation of aliphatic amines have been reported. Leonard and coworkers[8] studied the mercuric acetate oxidation of a wide variety of monocyclic, bicyclic, and tetracyclic tertiary amines. In general, the products showed α,β-unsaturation and, because they were cyclic compounds, they could be readily isolated and identified. Henbest and coworkers have reported the production of enamines by MnO_2,[9] benzoyl peroxide,[10] and quinone[11] oxidation of aliphatic secondary and tertiary amines. They were detected by forming colored condensation products with halogenated quinones.

Anodic Oxidation of Secondary Amines.—To investigate the differences in reactions of simple tertiary and secondary aliphatic amines, an examination of the behavior of di-*n*-propylamine was carried out. In addition to the experiments described above which show that aldehyde is produced and that an enamine intermediate is involved for both tertiary and secondary amine dealkylations, an examination of the reaction products was undertaken. The product mixture was shown to contain dipropylammonium and *n*-propylammonium ions and propionaldehyde. These compounds were identified by comparing their retention times, on two different glpc columns, each run at three different temperatures, with those of valid samples. In addition, nmr spectra of samples of the amine perchlorates were shown to be identical with those of valid samples. The uv spectrum of the 2,4-dinitrophenylhydrazone was identical with that shown in the Sadtler Laboratories collection, No. 1194, Vol 4. As mentioned above, the hydrazone from the deuterated aldehyde had a molecular weight of 239, to be expected for the derivative of monodeuterated propionaldehyde. Some quantitative results are presented in Table I. In addition to these, the products included components which show uv absorption at 226 nm and at 315 nm. That responsible for the 315-nm absorption is discussed above. It was formed in much larger concentrations in reactions carried out at +1.00 V than in those run at +1.40 V. We assume that this material reacts further at the higher potentials. The compound responsible for the 226-nm absorption was isolated and identified as 2-methyl-2-pentenalpropylamine. This compound was shown to be one of the products of oxidation of *n*-propylamine.[1] It is formed in much larger concentrations from reaction at +1.40 V than at +1.00 V.

TABLE I

PRODUCT ANALYSIS AFTER REACTION OF DI-*n*-PROPYLAMINE[a]

Potential[b]	n	% EtCHO[c]	% $Pr_2NH_2^+$[c]	% $PrNH_3^+$[c]
1.40	0.88, 0.90	25.4, 25.3	16.4, 16.9	49
1.00	0.83, 0.85	19.6, 19.0	9.9, 10.4	66

[a] Initial amine concentration = 17 mM in 0.10 M $NaClO_4$–MeCN, initial water concentration = 500 mM. [b] Volts *vs.* Ag–$AgNO_3$ (0.10 M). [c] Mole per cent of starting amine.

The results described here indicate that the reaction of dipropylamine in the presence of small concentrations of water is fundamentally similar to that of tripropylamine. The reaction causes dealkylation to form primary amine, propionaldehyde, and protons. The enamine is involved in a hydrolytic dealkylation step as it is in the reaction of tripropylamine. Therefore, it is possible in principle to perform an electrochemical degradation, starting with a simple tertiary aliphatic amine and proceeding stepwise through the secondary amine, the primary amine, and ammonia to elemental nitrogen together with the aldehydes and protons formed in each of the steps. In practice, the formation of unreactive protonated amine greatly reduces the yield in each successive step. Starting with tripropylamine in acetonitrile, together with enough water to assure that the dealkylation steps analogous to reaction 6 can occur, only a very small yield of *n*-propylamine and no ammonia can be detected in the product mixture.

Experimental Section

Reagents.—The amines used were Eastman White Label, used as received after glpc examination showed them to have no apparent significant amounts of impurities. The solvent and supporting electrolyte were prepared as described previously.[2]

Procedures.—The electrolysis apparatus and procedures were similar to those previously described.[2] Electrolyses were carried out in H-type cells at perforated cylindrical platinum anodes. Taking the geometrical area of only the exterior of the anode as

(7) N. J. Leonard and V. W. Gash, *J. Amer. Chem. Soc.*, **76**, 2781 (1954).
(8) N. J. Leonard and coworkers, *ibid.*, **80**, 371 (1958), and preceeding papers.
(9) H. B. Henbest and A. Thomas, *J. Chem. Soc.*, 3032 1957.
(10) D. Buckley, S. Dunstan, and H. B. Henbest, *ibid.*, 4880 1957.
(11) H. B. Henbest and P. Slade, *ibid.*, 1558 1960.

a measure of the effective electrode area, current density at the outset of a typical experiment amounted to 9.8 mA/cm². This decreased continuously during the experiment to a constant value of 9 μA/cm². Product analyses for Pr_2NH, $PrNH_2$, and EtCHO were performed by glpc using Dowfax 9N9 with NaOH and also Carbowax 20M as liquid phases. These were repeated at 75, 100, and 150°.

Identification of Propionaldehyde-2-*d*.—A 150-ml MeCN solution, 0.25 *M* in $NaClO_4$, 230 m*M* in D_2O, and 50 m*M* in dipropylamine, was electrolyzed at a Pt anode at +1.00 V *vs.* Ag–$AgNO_3$ (0.10 *M*). The product mixture was distilled through a spinning-band column, the first 12 ml of distillate being taken at 72–74°. This fraction was redistilled with the separation efficiency monitored by glpc. A 2-ml cut contained most of the aldehyde; it was further fractionated by glpc, using a Carbowax 20M column at 100°. The aldehyde fraction was trapped and taken up in $CDCl_3$ for nmr and ir examination. A sample of propionaldehyde in MeCN was subjected to the same separation to ascertain that the separation procedure was not causing exchange. There was indication that some of the aldehyde was lost because of condensation at various stages.

The mass spectra were obtained by distilling some of the concentrated solution produced from the spinning-band column into the spectrometer inlet system while the fraction was maintained below ice temperature. It was ascertained, using a sample of propionaldehyde in MeCN of the appropriate concentration, that the molecular ion of the aldehyde is observed by this procedure. However, the solvent peaks obscure the fragmentation pattern of the aldehyde.

Preparation of 2-Methyl-2-pentenalpropylamine.—A sample of this product was prepared to provide a comparison with the electrolytically generated material by the procedure previously described.[1]

Registry No.—Di-*n*-propylamine, 142-84-7.

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Mechanism of the Ferricyanide-Catalyzed Chemiluminescence of Luminol

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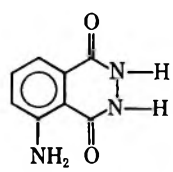
A study of the mechanism of the potassium ferricyanide chemiluminescent oxidation of luminol (5-amino-2,3-dihydro-1,4-phthalazinedione) is reported. An important feature of the proposed mechanism is the one-electron oxidation of the luminol dianion by ferricyanide to 5-aminophthalazine-1,4-semidione. The semidione intermediate may react with oxygen to produce electronically excited 3-aminophthalic acid and nitrogen. Alternatively, the semidione may be further oxidized by ferricyanide in a nonluminescent reaction.

In chemiluminescent systems, the rate of formation of the excited state is given by

$$d[x]/dt = i/\phi \quad (1)$$

where x is the luminescing molecule, ϕ the quantum yield for fluorescence of x, and i the intensity of emitted light. Thus, in systems where ϕ does not change during the reaction, the intensity is a measure of the rate of reaction. We have used this relationship to study the mechanism of the potassium ferricyanide oxidation of luminol (5-amino-2,3-dihydro-1,4-phthalazinedione, **1**) in aqueous base.



1

The chemiluminescence of luminol has been the subject of numerous investigations.[1] The mechanism of the reaction in aqueous dimethyl sulfoxide has been studied by White.[2] The role of ferricyanide as a catalyst has been explored;[3] however, the exact mechanism of its action has not been elucidated.

We studied the kinetics of the reaction in order to clarify the role of ferricyanide in this oxidation. The chemiluminescence with ferricyanide as a catalyst has generally been studied in the presence of hydrogen peroxide. In order to simplity analysis of the kinetics we have studied the reaction in the absence of peroxide.

Experimental Section

Materials.—Commercially available luminol was used without further purification. When the sodium salt of luminol,[4] which had been recrystallized from water, was used, the results were unchanged. All other reagents were of analytical grade and were not further purified. All solutions used were freshly prepared.

Light Intensity Measurements.—The reaction vessel was a test tube (15 × 150 mm) placed in a light-tight compartment provided with a shutter opening to an RCA IP21 phototube. The output voltage from the phototube was displayed on a Varian recorder as a function of time. The apparatus was calibrated with a standard luminol reaction by the method of Lee and Seliger[5] so that the intensity was reported in photons second^{-1}.

A solution of luminol (3.0 ml) in aqueous sodium hydroxide was placed in the test tube, and the reaction was initiated by injection of a potassium ferricyanide solution (0.3 ml). A stream of air was bubbled continuously through the reacting solution. This air stream ensured that the solution was kept saturated with oxygen and that mixing of the reactants was rapid. The rate of mixing appears to be fast compared to intensity decay; changing the rate of air flow into the solution did not alter the initial intensity of emitted light.

A Y-shaped reaction vessel equipped with a vacuum stopcock was used to measure intensity as a function of pressure. The luminol solution (3.0 ml) was placed in one arm of the vessel, and the ferricyanide solution (0.3 ml) in the other. The solutions were degassed, and air was introduced at known pressure. The vessel was placed in a light-tight box, and the reaction was

(1) E. H. White, "Light and Life," W. D. McElroy and B. Glass, Ed., Johns Hopkins Press, Baltimore, Md., 1961, p 183.

(2) E. H. White, O. Zafiriou, H. M. Kagi, and J. H. M. Hill, *J. Amer. Chem. Soc.*, **86**, 940 (1964); E. H. White and M. M. Bursey, *ibid.*, **86**, 941 (1964).

(3) F. H. Stross and G. K. Branch, *J. Org. Chem.*, **3**, 385 (1938).

(4) E. H. Huntress, L. N. Stanley, and A. S. Parker, *J. Chem. Educ.*, **11**, 241 (1934).

(5) J. Lee, A. S. Westley, J. F. Ferguson, III, and H. H. Seliger, in "Bioluminescence in Progress," F. H. Johnson and Y. Haneda, Ed., Princeton University Press, Princeton, N. J., 1966, p 35.

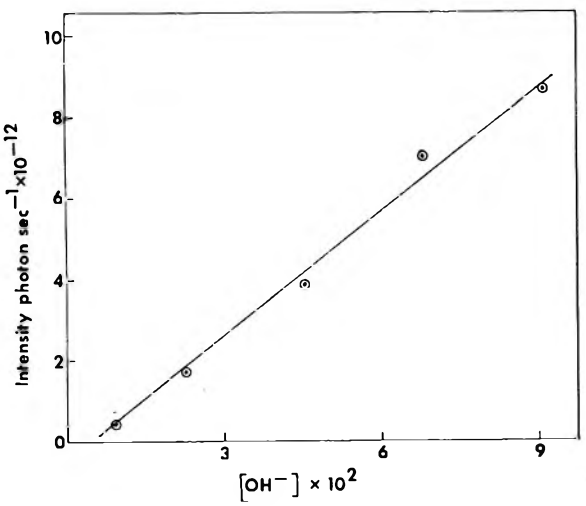


Figure 1.—Initial intensity as a function of base concentration: initial concentration of luminol and $K_3Fe(CN)_6$, 5.14×10^{-4} ml^{-1}; no $K_4Fe(CN)_6$ added initially.

initiated by a device that rocked the Y-tube back and forth, thus mixing the reactants. Emitted light was monitored with an RCA IP21 phototube.

Spectral Measurements.—The chemiluminescence spectra were measured in an Aminco–Bowman spectrophotofluorometer modified to permit injection of ferricyanide solution into the sample cell. The fluorescence spectra were measured on a Turner Associates Model 210 spectrophotofluorometer.

Results and Discussion

It has been established that 3-aminophthalic acid (**6**) is the emitting species when the reaction is carried out in aqueous dimethyl sulfoxide.[2] Similarly, we have compared the chemiluminescence spectra of the ferricyanide-catalyzed reaction with the fluorescence spectra of **6** in the presence of potassium ferricyanide. The spectra are identical, both exhibiting wavelengths of maximum emission at 450 mμ. These data lead us to conclude that **6** is also the emitting species in the ferricyanide-catalyzed chemiluminescence. The fluorescence maximum of **6** is shifted from 425 to 450 mμ by the addition of an equimolar amount of potassium ferricyanide. We have shown that equimolar amounts of potassium ferricyanide or potassium ferrocyanide do not quench the fluorescence of 3-aminophthalate under the reaction conditions.

The rate of formation of **6** should be proportional to the intensity of emitted light. With this relationship in mind, we have measured the effect of reactant concentration on intensity. The reactants in question are hydroxide ion, luminol, potassium ferricyanide, and oxygen. The effect of varying the concentration of a given reactant on intensity was measured while holding the concentration of all other reactants constant. In all cases, the initial intensity, i_0, was recorded as a function of concentration.

Figure 1 shows that the reaction is first order in hydroxide ion concentration over the pH range 12–13. In this pH range, complete formation of the monoanion of luminol ($pK_a = 6$)[6] is expected. If the monoanion were the reactive species, an effect of hydroxide ion on intensity would not be anticipated in this pH range. However, because such an effect is observed, we postulate that the dianion is the reactive species in this system. White[2] has postulated that the dianion is autoxidized directly in potassium *t*-butoxide–dimethyl sulfoxide solution. However, such an autoxidation would not be expected to be rapid in aqueous solution since the concentration of the dianion is much lower.

(6) A. K. Babko and L. I. Dufovenko, *Ukr. Khim. Zh.*, **29**, 479 (1963); *Chem. Abstr.*, **59**, 4594c (1963).

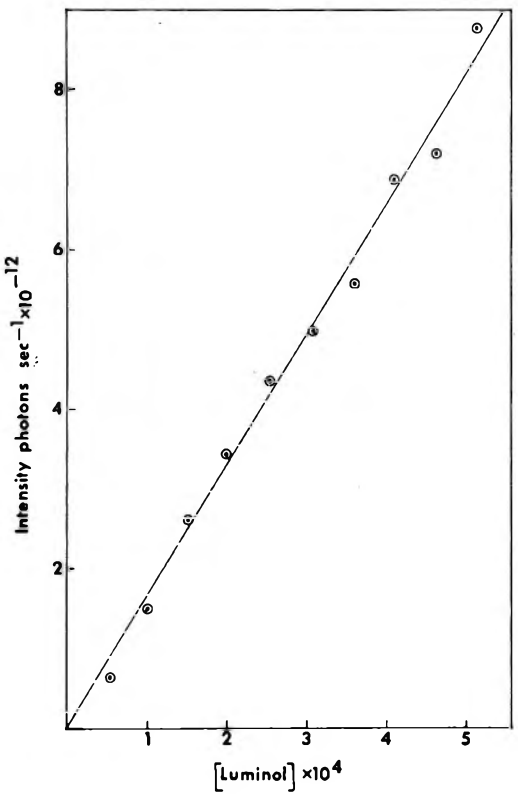


Figure 2.—Initial intensity as a function of luminol concentration: initial concentration of hydroxide, 9.1×10^{-2} ml^{-1}; of $K_3Fe(CN)_6$, 5.14×10^{-4} ml^{-1}; no $K_4Fe(CN)_6$ added initially.

The reaction is also first order in luminol concentration as shown in Figure 2.

The effect of potassium ferricyanide concentration on reaction rate is shown in Figure 3. The rate does not increase linearly with increasing ferricyanide but tends to level off at higher ferricyanide concentration.

Next, the effect of oxygen on the chemiluminescence was investigated. The light intensity was usually measured while bubbling a stream of air into the solution. When this air stream was replaced by a nitrogen stream, no light was emitted upon injection of ferricyanide solution. Furthermore, replacement of the nitrogen by air 10 min after injection of the ferricyanide gave no light. These results, along with those of Wilhelmsen, *et al.*,[7] show that oxygen is necessary for the production of light and that, in its absence, the luminol is consumed by ferricyanide in a nonluminescent reaction.

Figure 4 shows the effect of air pressure above the luminescing solution on intensity. Because air pressure is proportional to concentration of oxygen in solution, Figure 4 shows the dependence of reaction rate on oxygen concentration. The curve is similar to that obtained for the effect of ferricyanide concentration on intensity. The effect of oxygen on intensity cannot be due solely to quenching of fluorescence of aminophtha-

(7) P. C. Wilhelmsen, R. Lumry, and H. Eyring, in "The Luminescence of Biological Systems," F. H. Johnson, Ed., American Association for the Advancement of Science, Washington, D. C., 1955, p 75.

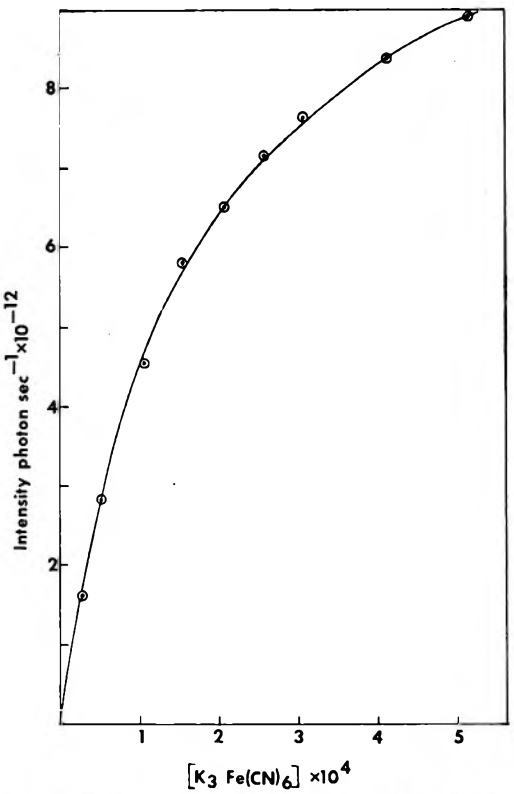
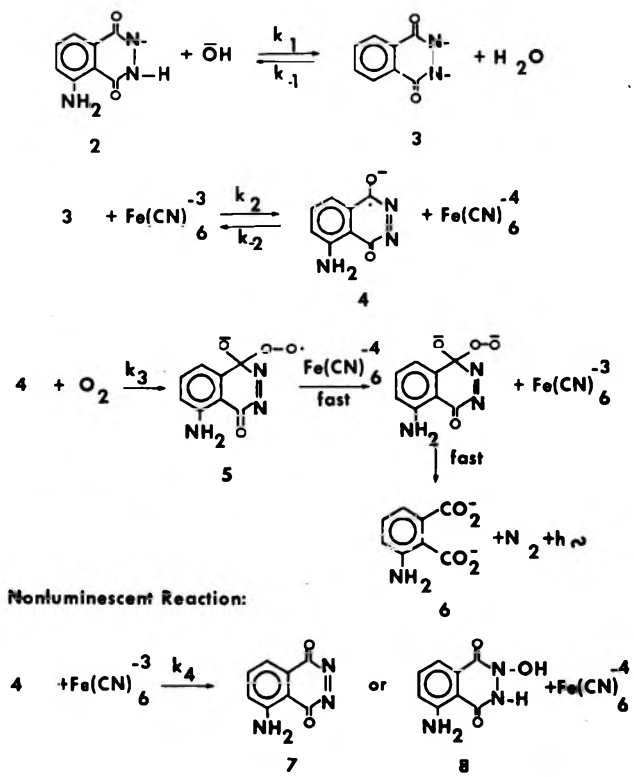


Figure 3.—Initial intensity as a function of $K_3Fe(CN)_6$ concentration: initial concentration of hydroxide, 9.1×10^{-2} ml^{-1}; of luminol, 5.14 ml^{-1}; no $K_4Fe(CN)_6$ added initially,

late by O_2. The fluorescence of 3-aminophthalate is decreased by only 10% in the presence of pure oxygen as compared with its fluorescence under nitrogen.

To explain the effect of reactant concentration, the mechanism outlined in Scheme I is proposed.

SCHEME I



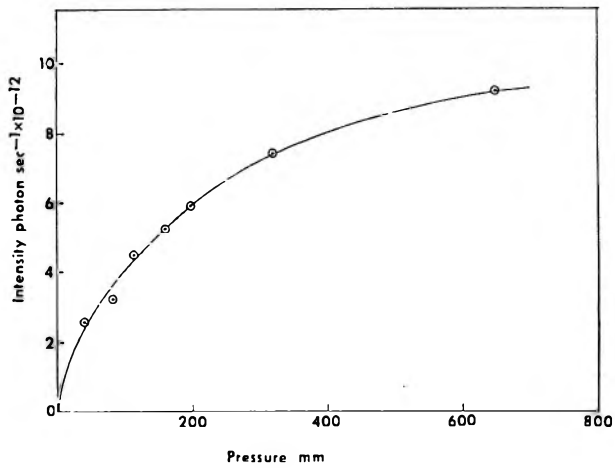
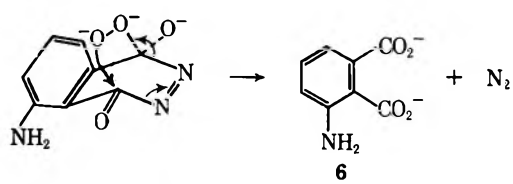


Figure 4.—Initial intensity as a function of initial pressure of air above solution: initial concentration of hydroxide, 9.1×10^{-2} ml^{-1}; of luminol and $K_3Fe(CN)_6$, 5.14×10^{-4} ml^{-1}; no $K_4Fe(CN)_6$ added initially.

The first step is simply the formation of the dianion **3** of luminol. The dianion is reversibly oxidized by ferricyanide to the semidione structure **4** shown in one of its resonance forms. The oxidation of **3** is written as reversible because addition of potassium ferrocyanide decreases the intensity of emitted light. Reversible one-electron transfers have been proposed for other ferricyanide oxidations.[8] Alternatively, a sequence can be written involving oxidation of **2** followed by removal of a proton by hydroxide to give the semidione.

The semidione reacts with oxygen to give the peroxy radical **5**. The peroxy radical is subsequently reduced in a fast step to give peroxy anion. We have depicted the reducing agent as ferrocyanide produced during the reaction. We feel that in the absence of any other obvious reducing agent, ferrocyanide is the most logical choice. The fact that ferricyanide is only 50% consumed during chemiluminescence supports this contention. Reduction of **5** by ferrocyanide must occur after the rate-determining step to explain the inhibitory effect of ferrocyanide ion.

The peroxy anion decomposes to electronically excited **6** with loss of nitrogen. A concerted decomposition of peroxy anion to give aminophthalate and nitrogen, as depicted, would be expected to be rapid with loss of nitrogen as the driving force. In the light-producing sequence proposed in Scheme I, the ferricyanide acts only as a catalyst and is not consumed. In this connection it should be noted that the potassium ferricyanide is not completely consumed during the chemiluminescence. A solution containing 2.82×10^{-4} *M* $K_3Fe(CN)_6$ and 2.82×10^{-4} *M* luminol initially, was found, by ultraviolet spectroscopy, to contain 1.24×10^{-4} *M* $K_3Fe(CN)_6$ at the termination of luminescence. However, both luminol and ferricyanide are destroyed



(8) C. G. Haynes, A. H. Turner, and W. A. Walters, *J. Chem. Soc.*, 2823 (1956).

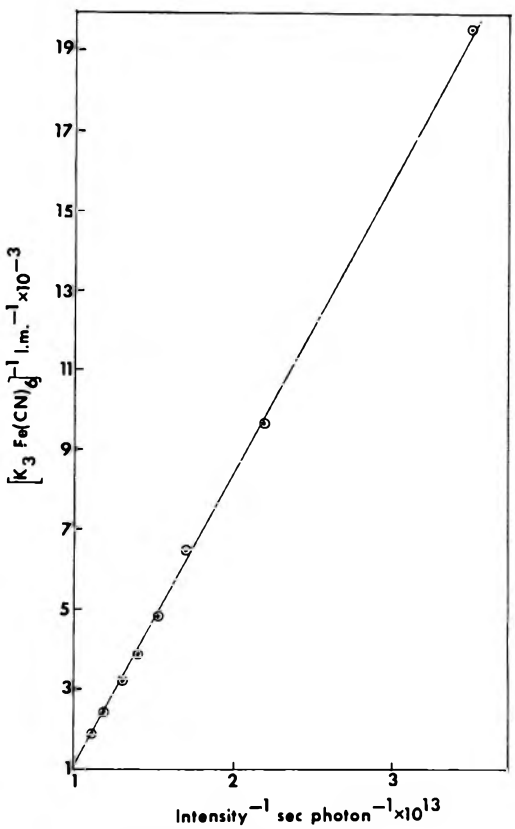


Figure 5.—Plot of reciprocal of initial intensity *vs.* reciprocal of $[K_3FeCN_6]$.

in a competing nonluminescent reaction. This nonluminescent reaction is the two-electron oxidation of luminol by ferricyanide. Although the product of the two-electron oxidation has not been isolated, it is most likely **7** or **8**. Both of these products would be extremely labile under the reaction conditions.[9]

Let us consider whether the proposed mechanism is consistent with the effects of concentration on intensity.

If a steady-state concentration of **4** is assumed,[10] the rate of product formation is given by

$$d[6]/dt = \frac{k_a[^-OH][2][Fe(CN)_6^{3-}]k_3[O_2]}{k_3[O_2] + k_{-2}[Fe(CN)_6^{4-}] + k_4[Fe(CN)_6^{3-}]} \quad (2)$$

where

$$k_a = k_1k_2/k_{-1}[H_2O]$$

From eq 1 and 2, an expression for intensity as a function of reactant concentration at any time is obtained (eq 3). This expression is consistent with the observed

$$i = \phi k_a \frac{[^-OH][2][Fe(CN)_6^{3-}]k_3[(O_2)]}{k_3[O_2] + k_{-2}[Fe(CN)_6^{4-}] + k_4[Fe(CN)_6^{3-}]} \quad (3)$$

first-order dependence of luminol and hydroxide ion. Equation 3 may be written in a more useful form.

$$\frac{1}{[Fe(CN)_6^{3-}]} + \frac{k_{-2}[Fe(CN)_6^{4-}]}{k_3[O_2][Fe(CN)_6^{3-}]} + \frac{k_4}{k_3[O_2]} = \frac{\phi k_a[^-OH][2]}{i} \quad (4)$$

(9) R. A. Clement, *J. Org. Chem.*, **25**, 1724 (1960); T. J. Kealy, *J. Amer. Chem. Soc.*, **84**, 966 (1962).

(10) A. A. Frost and R. G. Pearson "Kinetics and Mechanism," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1961, p 237.

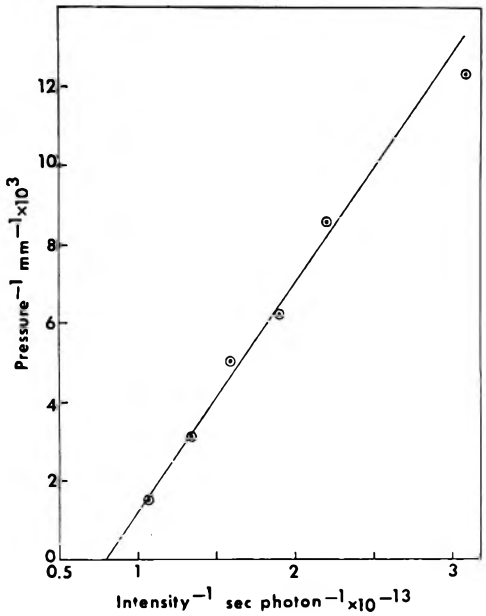


Figure 6.—Plot of reciprocal of initial intensity *vs.* reciprocal of initial pressure of air above solution.

If the initial intensity, i_0, is measured, and no ferrocyanide is added, the second term on the left-hand side of eq 4 drops out.

$$\frac{1}{[Fe(CN)_6^{3-}]} + \frac{k_4}{k_3[O_2]} = \frac{\phi k_a[^-OH][2]}{i_0} \quad (5)$$

A plot of $[K_3Fe(CN)_6]$ *vs.* i_0^{-1} should be linear with a slope equal to $\phi k_a[2][^-OH]$ and an intercept of $k_4/k_3 \cdot [O_2]$. Such a plot is shown in Figure 5; a least-squares treatment gives $\phi k_a = 1.6 \times 10^{21}$ l.^{3} photon mol^{-3} sec^{-1} and $k_4/k_3[O_2] = 6.5 \times 10^3$ l. mol^{-1}.

Substitution of $k_4/k_3[O_2]$ into eq 3 enables calculation of ϕk_a from the data in Figures 1 and 2. Such calculations yield $\phi k_a = 1.7 \times 10^{21}$ l.^{3} photon mol^{-3} sec^{-1} from Figure 1 and $\phi k_a = 1.5 \times 10^{21}$ l.^{3} photon mol^{-3} sec^{-1} from Figure 2.

A plot of $[O_2]^{-1}$ *vs.* reciprocal of initial intensity should also be linear when the concentrations of all other reactants are held constant. This linearity is demonstrated in Figure 6 as the reciprocal of air pressure over the solution plotted against i_0^{-1}.

When potassium ferrocyanide is added to the reaction initially, the second term on the left-hand side of eq 5 does not drop out. If the concentrations of all other reactants are held constant, a plot of added ferrocyanide *vs.* i_0^{-1} should permit evaluation of $k_2/k_3 \cdot [O_2]$. This plot, shown in Figure 7, gives $k_2/k_3[O_2] = 8.9 \times 10^3$ l. mol^{-1}.

A chain mechanism similar to that proposed for certain autoxidations may be envisioned.[11] In such a mechanism, the ferricyanide acts as an initiator, and the peroxy radical **5** is reduced in a chain-carrying step by the luminol dianion. If this mechanism were operative, the expression for intensity as a function of concentration would be

$$i = \frac{\phi k_a[^-OH][Fe(CN)_6^{3-}]k_3[O_2][2]}{k_{-2}[Fe(CN)_6^{4-}] + k_4[Fe(CN)_6^{3-}]} \quad (6)$$

This relationship, however, is inconsistent with the observed effect of oxygen concentration on intensity. A

(11) G. A. Russel, E. G. Janzen, A. G. Bemis, E. J. Geels, A. J. Moye, S. Mak, and E. T. Strom, "Selective Oxidation Processes," R. F. Gould, Ed., American Chemical Society, Washington, D.C., 1965, p 121.

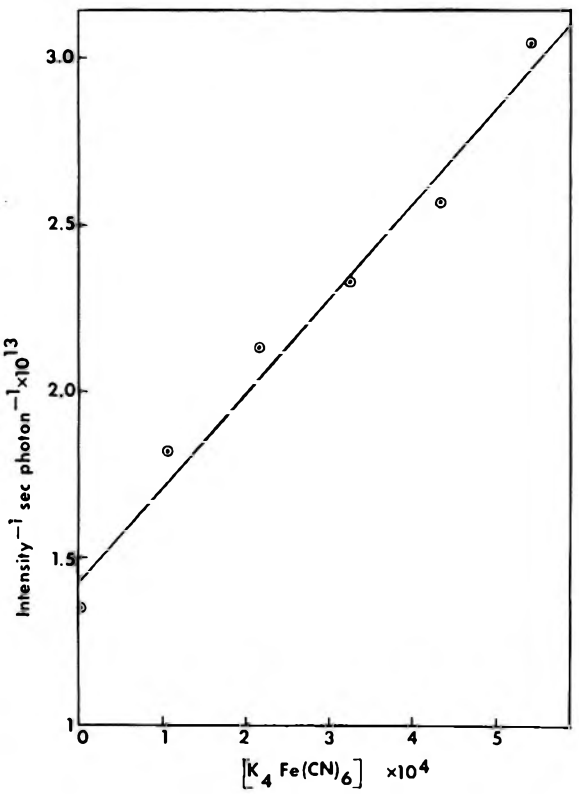


Figure 7.—Plot of concentration of $K_4Fe(CN)_6$ *vs.* reciprocal of initial intensity: initial concentration of hydroxide, 8.2×10^{-2} ml^{-1}; of luminol, 4.99×10^{-4} ml^{-1}; of $K_3Fe(CN)_6$, 5.06×10^{-4} ml^{-1}.

mechanism in which the nonluminescent reaction is the oxidative dimerization of luminol is ruled out because the reaction would not be first order in luminol.

A key feature of the reaction is competition of oxygen and ferricyanide for the semidione. Systems which provide a direct source of hydroperoxy radical for reaction with the semidione will enhance light production. Thus hydrogen peroxide increases the intensity and quantum yield. A solution 4.62×10^{-5} *M* in luminol, 5.14×10^{-4} *M* in $K_3Fe(CN)_6$, and 0.08 *M* in hydroxide has a quantum yield of 3.8×10^{-7}. A similar solution 8×10^{-3} *M* in hydrogen peroxide has a quantum yield of 3.25×10^{-6}. In the presence of oxygen, the semidione is consumed by further oxidation with ferricyanide.

This competition between reaction with oxygen and further oxidation is probably a general feature of all chemiluminescent reactions of luminol in which a one-electron oxidant is employed. The fact that chemiluminescence occurs at all is due to the stability of the semidione to further oxidation. In this connection, note that electron-donating substituents on the aromatic ring enhance luminescence. Such substituents would be expected to increase the stability of the semidione.[12]

Registry No.—Potassium ferricyanide, 13746-66-2; **1**, 521-31-3.

(12) E. H. White and M. M. Bursey, *J. Org. Chem.*, **31**, 1912 (1966). A referee has pointed out that electron-donating substituents also increase the fluorescence quantum yield of the phthalates.

Pyrolysis Studies. XIX.[1] Substituent Effect of 1-Aryl-3-buten-1-ols

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The unimolecular homogeneous thermolysis of nine 1-aryl-3-buten-1-ols has been studied in a seasoned, constant-volume, stainless steel reactor. Arrhenius parameters have been evaluated in the temperature range of 610–644°K. The small ρ value (−0.26) from a Hammett $\rho\sigma$ plot indicates a minor substituent effect for the *meta* and *para* isomers with apparently little or no charge development at the 1 position in the proposed concerted six-membered ring transition state. An *o*-methoxy substituent showed a marked proximity effect with an activation energy 4–7 kcal/mol lower and an entropy of activation of 6–9 eu, more negative than the other compounds studied.

β-Hydroxy olefins have been reported to pyrolyze to olefins and carbonyl compounds by a unimolecular homogeneous reaction, likely through a six-membered-ring transition state.[3,4] The influence of 3- and 4-phenyl and 1-alkyl substituents on the ease of thermolysis of 3-buten-1-ol has been reported by Smith and Yates.[5]

They found that π contribution increased the rate of pyrolysis at the 3 position more than at the 4 position and that the rate of pyrolysis followed the sequence tertiary > secondary > primary for alkyl substitution at the carbinol position. They presented a qualitative picture consisting of a positive charge forming at the 3 position and a slight negative charge developing at the 4 position in the transition state.

No direct study of π contribution has been reported at the carbinol position; only competitive[6,7] type reactions have been studied.

The gas-phase thermolysis of 1-aryl-3-buten-ols reported in this study, when compared with the result reported by Smith and Yates,[5] further substantiates the nature of this reaction and gives additional insight concerning the transition state.

Results

1-Aryl-3-buten-1-ols were pyrolyzed in a deactivated stainless steel reactor[8] over a temperature range of

(1) Part XVIII: K. K. Lum and G. G. Smith, *Int. J. Chem. Kinetics*, **1**, 401 (1969).

(2) (a) To whom all communications should be sent; (b) National Defense Education Act Predoctoral Fellow, 1968–1970.

(3) R. T. Arnold and G. Smolinsky, *J. Org. Chem.*, **25**, 129 (1960).

(4) G. G. Smith and R. Taylor, *Chem. Ind.* (London), **35**, 949 (1961).

(5) G. G. Smith and B. L. Yates, *J. Chem. Soc.*, 7242 (1965).

(6) A. Viola, E. J. Iorio K. K. Chen, G. M. Glover, U. Nayak, and P. J. Kocienski, *J. Amer. Chem. Soc.*, **89**, 3462 (1967).

(7) K. J. Voorhees, G. G. Smith, R. T. Arnold, D. G. Mikolasek, and R. R. Covington, *Tetrahedron Lett.*, 205 (1969).

(8) G. G. Smith and J. A. Kirby, *Analyst* (London), **94**, 242 (1969).

TABLE I

RATE CONSTANTS, TEMPERATURES, AND $1/T$ FOR THERMOLYSIS OF 1-ARYL-3-BUTEN-1-OLS

Compound	No. of runs	10^5k, sec^{-1}	Temp, °K	$1/T \times 10^3$
1-Phenyl-3-buten-1-ol	6	3 26	644.8	1.551
	3	1.82	630.9	1.558
	3	1.21	622.9	1.605
	4	0.877	615.4	1.625
	3	0.622	610.4	1.638
1-*p*-Methylphenyl-3-buten-1-ol	3	2.10	632.6	1.581
	3	1.53	625.5	1.599
	3	1.14	618.3	1.617
	3	0.738	609.7	1.640
1-*p*-Chlorophenyl-3-buten-1-ol	5	2.92	641.7	1.558
	3	1.84	632.0	1.582
	3	1.35	625.5	1.599
	3	0.943	618.0	1.618
	3	0.696	610.8	1.637
1-*p*-Methoxyphenyl-3-buten-1-ol	3	2.45	633.9	1.578
	5	1.48	623.5	1.604
	3	1.08	614.9	1.626
	3	0.737	607.6	1.646
1-*m*-Methoxyphenyl-3-buten-1-ol	3	2.00	631.9	1.583
	4	1.28	621.7	1.608
	3	0.787	612.9	1.632
	3	0.665	608.6	1.643
1-*m*-Methylphenyl-3-buten-1-ol	3	2.00	633.7	1.578
	3	1.26	622.5	1.606
	3	0.767	613.2	1.631
	3	0.629	608.1	1.645
1-*o*-Methylphenyl-3-buten-1-ol	3	2.29	632.2	1.582
	3	1.49	622.2	1.607
	3	1.16	615.5	1.625
1-*o*-Chlorophenyl-3-buten-1-ol	3	2.07	631.3	1.584
	3	1.20	621.7	1.609
	3	0.755	609.7	1.636
1-*o*-Methoxyphenyl-3-buten-1-ol	6	1.79	634.4	1.577
	6	1.10	622.5	1.607
	10	0.704	611.2	1.636

608–645°K, and the products, propene and substituted benzaldehydes, were identified. Table I lists the first-order rate constants which were obtained over 95% of the pyrolysis and the temperature of pyrolysis for these compounds. The stoichiometry was established by the ratio of P_0/P_∞ (1:1.99).

Reproducibility of the first-order rate constants was ±2%, and introduction of cyclohexene had no effect on the rate (3.24×10^{-2} compared with 3.18×10^{-2} with cyclohexene for 1-phenyl-3-buten-1-ol), thus demonstrating the absence of a radical chain reaction and the unimolecularity of the reaction. Variation of the sample size (0.10–0.25 ml) and initial pressure (80–200 mm) was made (for each compound) with no effect on the reproducibility.

An Arrhenius plot of each compound gave a straight line which is illustrated for 1-phenyl-3-buten-1-ol in Figure 1. The quality of the data is shown by the correlation coefficient of the linear regression of each Arrhenius plot (Table II).

Figure 2 is a Hammett $\rho\sigma$ plot resulting in a ρ of a −0.26 calculated using a linear repression analysis.

Discussion

As stated, the results from this study on the thermolysis of 1-aryl-3-buten-1-ols further substantiate the unimolecularity and homogeneity of this reaction and also supports a six-membered-ring transition state.[3-5,9] Furthermore, they demonstrate that a 1-phenyl substituent has twice the effect on the ease of thermolysis

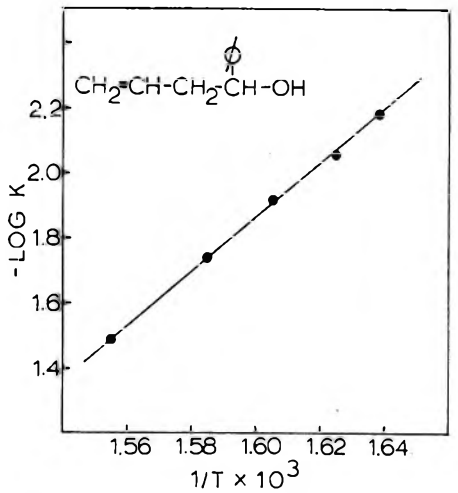


Figure 1.—Arrhenius plot of 1-phenyl-3-buten-1-ol thermolysis.

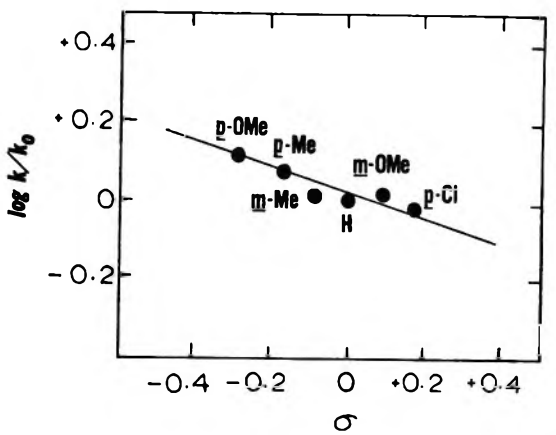


Figure 2.—Hammett plot of 1-aryl-3-buten-1-ols, $\rho = -0.26$.

TABLE II

ARRHENIUS PARAMETERS FOR 1-ARYL-3-BUTEN-1-OLS

Compound	E_a, kcal/mol	$\Delta S^\ddagger$, eu, at 619 °K	Log A	Correlation coefficient
1-Phenyl-3-buten-1-ol	36.2	−10.5	10.8	−0.999
1-*p*-Methylphenyl-3-buten-1-ol	34.9	−12.3	10.4	−0.999
1-*p*-Chlorophenyl-3-buten-1-ol	36.1	−10.8	10.7	−0.999
1-*p*-Methoxyphenyl-3-buten-1-ol	35.6	−10.9	10.7	−0.987
1-*m*-Methoxyphenyl-3-buten-1-ol	36.9	−9.3	11.0	−0.998
1-*m*-Methylphenyl-3-buten-1-ol	34.9	−12.5	10.4	−0.998
1-*o*-Methylphenyl-3-buten-1-ol	36.5	−9.8	11.0	−0.999
1-*o*-Chlorophenyl-3-buten-1-ol	38.4	−6.8	11.6	−0.998
1-*o*-Methoxyphenyl-3-buten-1-ol	31.4[a]	−18.4	9.1	−0.999

[a] Special care was taken to ensure that the reactor surfaces were completely deactivated.

(9) (a) R. T. Arnold and G. Smolinsky, *J. Amer. Chem. Soc.*, **82**, 4919 (1960); (b) R. T. Arnold and G. Metzger, *J. Org. Chem.*, **26**, 5185 (1961); (c) R. T. Arnold and G. Smolinsky, *J. Amer. Chem. Soc.*, **81**, 6443 (1959).

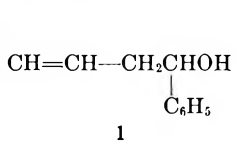
at 619°K as does a 3-phenyl substituent and 83 times the influence that was reported for a 4-phenyl substituent. This substituent also showed 7.5 times the influence of a methyl group at the carbinol position. Rate constants and relative rates are shown in Table III.

TABLE III
RATE CONSTANTS AND RELATIVE RATES FOR THE THERMOLYSIS OF β-HYDROXY OLEFINS

β-Hydroxy olefins	$10^2 k$ (sec^{-1}), at 619 °K	Rel rate
3-Buten-1-ol	0.053	4.4
4-Penten-2-ol	0.131	10.9
2-Methyl-4-penten-2-ol	0.280	23.3
1-Phenyl-3-buten-1-ol	1.0	83.0
3-Phenyl-3-buten-1-ol	0.5	41.5
4-Phenyl-3-buten-1-ol	0.012	1.0

At least two factors may contribute to the rate enhancement: (a) crowding in the ground state at the carbinol position which may cause steric acceleration; and (b) electronic stabilization of the transition state. Neither of these factors alone offers a completely satisfactory explanation.

Crowding in the ground state by a phenyl substituent would not be expected to be as large as by two methyl groups at the same position (E_s for phenyl is −0.90 and E_s for methyl is 0); yet 1-phenyl-3-buten-1-ol (1) pyrolyzes *four* times more readily than 2-methyl-4-penten-2-ol (2) which has two methyl groups attached at the carbinol position. The comparative rate constants for



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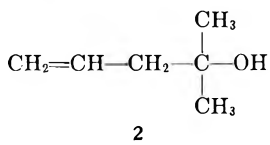

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thermolysis of 1-phenyl *vs.* a 1-methyl and 1,1-dimethyl substituents are shown in Table III.

The greater effect of phenyl over alkyl substituents at the carbinol position suggests that a charge develops at the carbinol carbon in the transition state. The extent of this charge, however, must be modest as the ρ value in the $\rho\sigma$ plot was small (−0.26), and the correlation was significantly better with σ than σ^+. A plot of Brown's and Okamoto's[10] σ^+ against log k/k_0 gave a slightly curved line with considerably more scattering than was observed for the regular Hammett plot. Steric effects are reported to be minor in the gas phase.[11] The acceleration in rate is more likely caused by a weakening of the C–C bond at the carbinol carbon by the attached phenyl substituent through a slight stabilization of the transition state. The most significant observation, however, is that gas-phase thermolysis of β-hydroxy olefins proceeds *via* a highly concerted electrocyclic process resulting in only minor substituent effect activity.

Energy of activation values reported in Table II range between 34.9 and 38.4 kcal/mol excepting that for 1-*o*-methoxyphenyl-3-buten-1-ol which is reported as 31.4 kcal/mol. The $\Delta S^{\pm}$ for this compound is also considerably more negative, (−18.4 eu). Since these values are significantly lower than the others, they were carefully reinvestigated several times, particularly to determine if the reactor surface was activated. (E_a values are lower for reactions showing heterogeneous reactivity.) After taking extensive deactivation and standardization precautions,[12] no change in the values of E_a and $\Delta S^{\pm}$ was detected.

The explanation for these marked differences is, of course, caused by a proximity effect peculiar to the alkyoxy group which is not found with either an *o*-chloro or *o*-methyl substituent. The entropy difference (degrees of freedom) between the ground state and activation complex is significantly more negative for the *o*-methoxy derivative than for other *ortho* derivatives or the *p*-methoxy compound. Perhaps the methoxy group is less free to rotate in the transition state than in the ground state, although the reason for this is not clearly understood. It is possible that an *o*-methoxy group raises the entropy of the ground state and also raises the ground-state energy. But it is more logical, however, that the *o*-methoxy group lowers the energy of the transition state, probably through a direct field effect between the *o*-methoxy group and the reacting group. A better understanding of this interesting proximity effect awaits future study.

Generally speaking, the results from this study seem to indicate that the thermolysis of β-hydroxy olefins proceeds through a highly concerted electrocyclic process with modest substituent effects. Since, however, a 1-aryl group has the most significant effect, the bond cleavage most important in controlling the activation energy is between C_1 and C_2 carbon atoms. In highly concerted electrocyclic reactions conjugation is known to be especially important.[13] The results for the 1-, 3-, and 4-phenyl-3-buten-1-ol study bear this out. When 3-buten-1-ol is substituted at the 4 position with a phenyl group, conjugation is lost during the reaction, and, therefore, a phenyl group at this position slows down the rate of thermolysis while it increases the rate at the other two positions as expected, based on the importance of conjugation to highly concerted electrocyclic reactions. The partial charge developing at the 1 position is stabilized by the developing C=O group as well as by the ring which helps to explain the small value (0.26).

Experimental Section

Synthesis of 1-Aryl-3-buten-1-ols.—All of the 1-aryl-3-buten-1-ols were prepared by the same procedure, beginning with the appropriate substituted benzaldehyde and allylmagnesium bromide. The synthesis of 1-phenyl-3-buten-1-ol is given as a typical case. Information concerning the synthesis of the other 1-aryl-3-buten-1-ols can be found in Table IV.

1-Phenyl-3-buten-1-ol.—Allyl bromide (40 g) dissolved in 50 ml of ether was added dropwise to magnesium ribbons (8.25 g) suspended in a 10 *M* (250 ml) excess of ether. Two hours later the reaction has subsided, and the mixture was cooled to −10°, and 32 g of benzaldehyde in 50 ml of ether was added dropwise. After addition of the benzaldehyde, stirring was continued for 1 hr at which time a saturated solution of ammonium chloride was added to hydrolyze the complex. The ether layer was separated from the aqueous layer and dried using magnesium sulfate. The aqueous layer was extracted with three 100-ml portions of ether. These portions were dried and combined with the first portion. The resulting solutions were filtered and the

(10) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).
(11) G. G. Smith, K. K. Lum, J. A. Kirby, and J. Pospisil, *J. Org. Chem.*, **34**, 2090 (1969).
(12) R. Taylor, G. G. Smith, and W. H. Wetzel, *J. Amer. Chem. Soc.*, **84**, 4817 (1962).
(13) A. Maccoll, and P. J. Thomas, *Progr. React. Kinet.*, **4**, 119 (1967).

Table IV
Physical Constants and Yields of 1-Aryl-3-buten-1-ols

Compound	Index of refraction, $n^{25}D$	Bp (mm), °C	Yield, %	Calcd, % C	Calcd, % H	Formula	Found,[a] % C	Found,[a] % H	Found,[a] % Cl
1-Phenyl-3-buten-1-ol (a)	1.5314[b]	71 (0.75)	41	81.04	8.10	$C_{10}H_{12}O$	81.16	7.92	
1-*p*-Methoxyphenyl-3-buten-1-ol (b)	1.5365	102–103 (0.35)	18	74.13	7.92	$C_{11}H_{14}O_2$	73.53	7.78	
1-*p*-Chlorophenyl-3-buten-1-ol (c)	1.5511	98.5–99 (0.30)	60	65.76	6.07	$C_{10}H_{11}OCl$	65.39	5.91	19.88[d]
1-*o*-Methylphenyl-3-buten-1-ol (d)	1.5313	74 (0.50)	19	81.44	8.70	$C_{11}H_{14}O$	81.24	8.70	
1-*p*-Methylphenyl-3-buten-1-ol (e)	1.5280	74–75 (0.42)	26	81.44	8.70	$C_{11}H_{14}O$	81.80	8.80	
1-*m*-Methylphenyl-3-buten-1-ol (f)	1.5272	79–80 (0.80)	31	81.44	8.70	$C_{11}H_{14}O$	81.88	8.57	
1-*m*-Methoxyphenyl-3-buten-1-ol (g)	1.5372	96–97 (0.30)	18	74.13	7.92	$C_{11}H_{14}O_2$	73.53	7.95	
1-*o*-Chlorophenyl-3-buten-1-ol[c] (h)		83 (0.38)	16	65.76	6.07	$C_{10}H_{11}OCl$	65.43	6.0	19.91[d]
1-*o*-Methoxyphenyl-3-buten-1-ol[c] (i)		96 (0.32)	20	74.13	7.92	$C_{11}H_{14}O_2$	74.52	8.06	

[a] The analytical work was done by M. H. W. Laboratories, Garden City, Mich. [b] Lit.[14] $n^{25}D$ 1.5305. [c] Solids at room temperature. [d] Calcd 19.42%.

excess ether removed by evaporation under vacuum. Distillation yielded 18.4 g of product: bp 71° (0.75 mm); yield 41%; $n^{25}D$ 1.5314 (lit. $n^{25}D$ 1.5305[14]); nmr δ 7.1, 5.1–6.0, 4.6, 2.3, 2.2; ir OH at 3400–3800 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}O$: C, 81.0; H, 8.1. Found: C, 81.16; H, 7.92.

Method of Pyrolysis.—The kinetics of pyrolysis were done using a carefully deactivated stainless steel static reactor[8] fitted with a null point gauge and an exterior pressure measuring system. A small sample (0.15–0.25 ml) of alcohol was injected, the reactor sealed, and the pressure followed with time. A pressure at time ∞ (reaction complete) was determined, and a plot of ln $(P_\infty - P_t)$ *vs.* time, where P_t is pressure at time t, was used to determine first-order rate constants. The furnace temperature was monitored to ±0.1° using an iron–constantan thermocouple which had previously been standardized against a Bureau of Standards calibrated platinum resistance thermometer.

Product Analysis.—The pyrolysis products from three or four 0.3-ml injections were collected in a Dry Ice–isopropyl alcohol trap attached directly to the exhaust value in the reaction vessel. To ensure that all products were retained in the trap, the trap was sealed and left in the Dry Ice–isopropyl alcohol slurry before removing from the vacuum line. Since the products from the pyrolysis of 1-aryl-3-buten-1-ols are propene and substituted benzaldehydes, a method was designed to separate the gas by distillation. The propene was distilled into a cold (−72°) mass spectrometer gas cell and analyzed from this directly by mass spectroscopy. The aldehydes were dissolved in deuteriochloroform containing an internal tetramethylsilane standard for nmr analysis.

The products, the stoichiometry, and excellent kinetic data conclusively demonstrated that the pyrolysis in a seasoned reactor of these β-hydroxy olefins followed first-order kinetics to greater than 99% of the reaction in the temperature range studied.

(14) M. Gaudeman, *Bull. Soc. Chim. Fr.*, **5**, 974 (1962).

Registry No.—Table IV—a, 936-58-3; b, 24165-60-4; c, 14506-33-3; d, 24165-62-6; e, 24165-63-7; f, 24165-64-8; g, 24165-65-9; h, 24165-66-0; i, 24165-67-1.

Acknowledgment.—We wish to thank the National Science Foundation, Grant GP 9251, the National Defense Education Act, and the Utah State University Research Council for generous support of this work. We are also indebted to Mr. George Eddington of Electrodynamic Laboratory at Utah State University for the maintenance of the kinetic equipment. Grateful acknowledgment is given to the National Bureau of Standards for the calibration of a platinum resistance thermometer and to the local chapter of Sigma Xi for a small research award to one of us (K. J. V.).

Redox Behavior of α-Tocopherol and Model Compounds. II. Ring Opening of 8a-Hydroxy-2,2,5,7,8-pentamethyl-6-chromanone

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Received October 31, 1969

Double-potential-step chronoamperometry has been used in the study of the kinetics and the mechanisms of the ring opening of 8a-hydroxy-2,2,5,7,8-pentamethyl-6-chromanone, a model of the hemiketal intermediate in the oxidation of α-tocopherol to α-tocopherylquinone. Working curves for the determination of the rate constants were obtained by a digital simulation technique. The system was observed to be both general acid and general base catalyzed. The mechanism proposed for general acid catalysis involves proton transfer from the acid to the oxygen in the 1 position followed by removal of a proton from the hydroxy group in the 8a position by the solvent, water. In the case of general base catalysis, the reaction proceeds by removal of the proton from the hydroxy group by the base and transfer of a proton from the solvent to the oxygen in the 1 position.

The widespread occurrence of chromanols and quinones in nature has led to extensive studies into their possible roles in biological processes.[1-3] The observance of the ready ease with which these compounds enter into redox reactions has led to several proposals relating oxidation–reduction processes to biological activities. Although elucidation of these biological processes must be provided ultimately by studies *in vivo*, the results of chemical studies *in vitro* can provide considerable information regarding intermediates, products, and rates of chemical processes.

(1) G. E. W. Wolstenholme and C. N. O'Connor, Ed., "Quinones in Electron Transport," Little, Brown and Co., Boston, Mass., 1960.

(2) R. A. Morton, Ed., "Biochemistry of Quinones," Academic Press, Inc., New York, N. Y., 1965.

(3) "International Symposium on Recent Advances in Research on Vitamins K and Quinones (Vitamins K, Ubiquinones or Coenzymes Q, Plastoquinones) in Honor of Professor Henrik Dam," in *Vitamins Hormones*, **24**, 291 (1966).

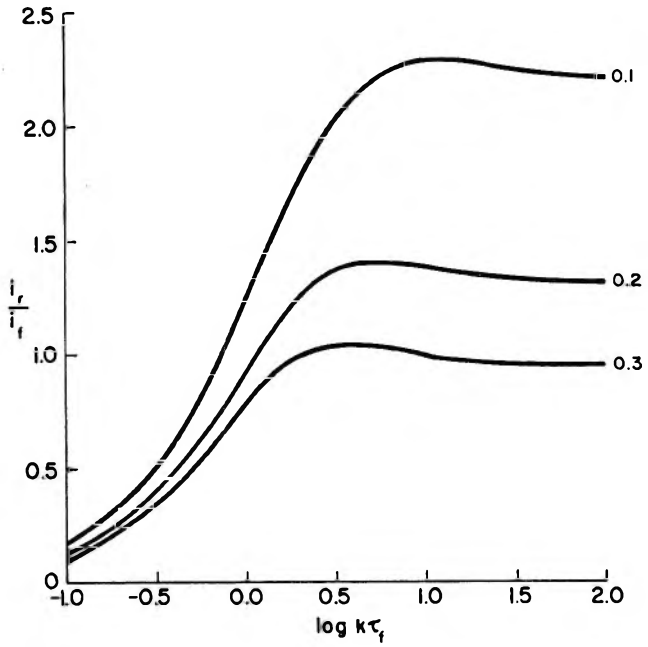
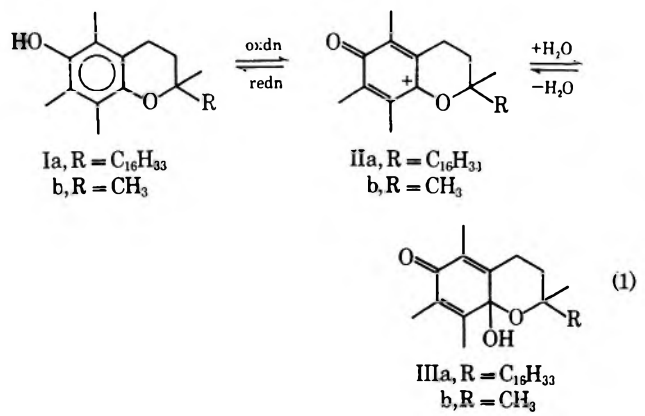


Figure 1.—Theoretical working curves for the double-potential-step chronoamperometric method: A → B + ne; B → C (k); C + ne ⇌ D. The ratios of τ_r/τ_f are indicated on the curves.

In an earlier report from this laboratory[4] it was shown that the predominant pathway for the electrochemical oxidation of α-tocopherol (Ia) and its model compound, 2,2,5,7,8-pentamethyl-6-hydroxychroman (Ib), was *via* a carbonium ion intermediate (eq 1). In the presence



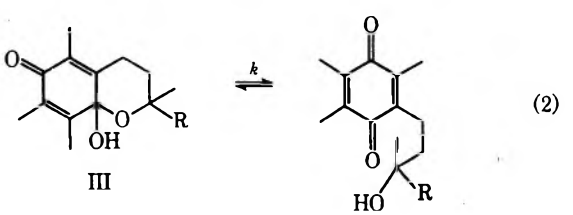
Ia, R = $C_{16}H_{33}$
b, R = CH_3

IIa, R = $C_{16}H_{33}$
b, R = CH_3

(1)

IIIa, R = $C_{16}H_{33}$
b, R = CH_3

of nucleophiles, such as water, the carbonium ion II was transformed rapidly into an electroinactive (but chemically reducible) chromanone III. Ring opening of this intermediate then yielded the corresponding quinone IV as the final product of the oxidation (eq 2).



III

IVa, R = $C_{16}H_{33}$
b, R = CH_3

(2)

(4) M. F. Marcus and M. D. Hawley, *Biochem. Biophys. Acta*, **201**, 1 (1970).

The present paper is principally concerned with the mechanism of this last reaction, the conversion of the chromanone into an electroactive quinone.

Experimental Section

Instrumentation.—The cyclic voltammetric and chronoamperometric studies were performed on a transistorized, three-electrode potentiostat–galvanostat described previously.[5] Readout in cyclic voltammetry and long-term chronoamperometry experiments was to a Moseley Model 7030A x–y recorder. For chronoamperometric studies of less than 5-sec duration, readout was to a Tektronix Model 564 oscilloscope equipped with 2A63 and 2B67 plug-ins. Oscilloscope traces were recorded on film using a Dumont Type 302 Polaroid camera. The signal source was a Hewlett–Packard Model 3300–3302 function generator.

Cells and Electrodes.—A planar gold button with a geometric area of 0.33 cm^2 was used as the working electrode in aqueous acetonitrile solutions. A saturated calomel and a platinum foil served as the reference and auxiliary electrodes, respectively. All solutions were deaerated with purified nitrogen to remove traces of oxygen.

Chemicals and Solutions.—2,2,5,7,8-Pentamethyl-6-hydroxychroman was prepared according to a published procedure.[6] The solvent composition was maintained at 25 vol % acetonitrile–75 vol % water. Reagent grade acetonitrile was used as received. Buffer solutions were prepared from reagent grade acids which were neutralized to the appropriate pH with carbonate-free sodium hydroxide. All measurements were made at 23.0 ± 0.1°.

Results

Development of a Working Model.—The calculations of the theoretical working curves for the double-potential-step chronoamperometric method were made by a digital simulation technique described by Feldberg.[7] It is assumed in the model that the oxidation of a chromanol is a two-electron, diffusion-controlled process which gives the corresponding carbonium ion. It is further assumed that the rate constant for the conversion of the carbonium ion to 8a-hydroxy-2,2,5,7,8-pentamethyl-6-chromanone (eq 1) is infinitely large in the presence of a large excess of water. This assumption is justified experimentally since the pseudo-first-order rate constant exceeds 100 sec^{-1} under our reaction conditions.[4]

The kinetically slow step which follows is the conversion of the electroinactive chromanone into an electroactive quinone (eq 2). After a forward electrolysis time, τ_f, the concentration of quinone is studied by stepping the potential cathodically. It is assumed in the model that the reduction of the quinone can be written as a two-electron process. Thus, while the model is compatible with the pathway which produces the corresponding hydroquinone as the reduction product,[4] the model is also compatible with a pathway which produces the recyclized chromanol I.[8] The reaction sequence is summarized in eq 3–5; the chronoamperometric working curves calculated for this sequence are shown in Figure 1.

$$A \longrightarrow B + 2e \quad (3)$$

$$B \xrightarrow{k} C \quad (4)$$

$$C + 2e \rightleftharpoons D \quad (5)$$

(5) J. G. Lawless and M. D. Hawley, *J. Electroanal. Chem.*, **21**, 365 (1969).

(6) L. I. Smith, H. E. Ungnade, H. H. Hoehn, and S. Wawzonek, *J. Org. Chem.*, **4**, 311 (1939).

(7) S. W. Feldberg in "Electroanalytical Chemistry—A Series of Advances," Vol. III, A. J. Bard, Ed., Marcel Dekker, Inc., New York, N. Y., 1969. A copy of the computer program is available upon request from the authors of this paper.

(8) V. D. Parker, *J. Amer. Chem. Soc.*, **91**, 5380 (1969).

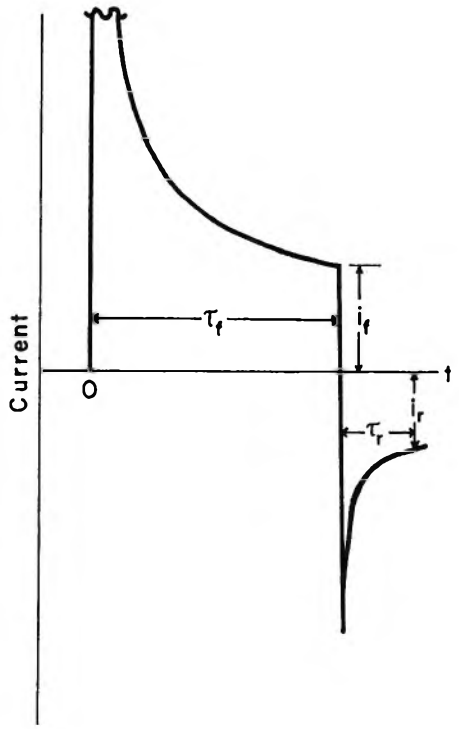


Figure 2.—Anodic–cathodic current–time curves for the model compound, 2,2,5,7,8-pentamethyl-6-hydroxychroman, showing the method of current and time measurements for the double-potential-step chronoamperometric technique. The ratio of τ_r/τ_f shown here is 0.3.

Tests of the Working Model.—Dimensionless working curves (Figure 1) were constructed for several different ratios of the reverse electrolysis time, τ_r, to the forward electrolysis time, τ_f. The method of measuring the forward and reverse currents and the forward and reverse electrolysis times is shown in Figure 2. Each of the working curves confirms the expectation that the ratio of the cathodic current, i_r, to the anodic current, i_f, approaches zero for very small values of $k\tau_f$; *i.e.*, the rate of ring opening of the electroinactive chromanone to produce the electroactive quinone is neglible for small values of $k\tau_f$. For large values of $k\tau_f$, the ratio of i_r/i_f approaches a limit of 2.21 when $\tau_r/\tau_f = 0.1$. This limiting value is predicted for a single redox couple when the anodic and cathodic processes are both diffusion controlled.[9] An experimental test of the model is shown in Figure 3. The linearity of the plot and its extrapolation to the origin confirm the validity of the theoretical model. The slope of the plot yields the rate constant directly.

Effect of pH and Buffer Concentration.—In general, the first-order rate constant for a reaction catalyzed by a single acid–base can be written as

$$k_{obsd} = k_o + k_H[H^+] + k_{OH}[OH^-] + k_{HA}[HA] + k_A[A^-] \quad (6)$$

In order to determine the values of the several catalytic constants, eq 6 can be rewritten in the form

$$k_{obsd} = a[A^-] + b \quad (7)$$

where

$$a = k_{HA}[HA]/[A^-] + k_A \quad (8)$$

and

$$b = k_o + k_H[H^+] + k_{OH}[OH^-] \quad (9)$$

(9) W. M. Smit and M. D. Wijnen, *Rec. Trav. Chim. Pays-Bas*, **79**, 5 (1960).

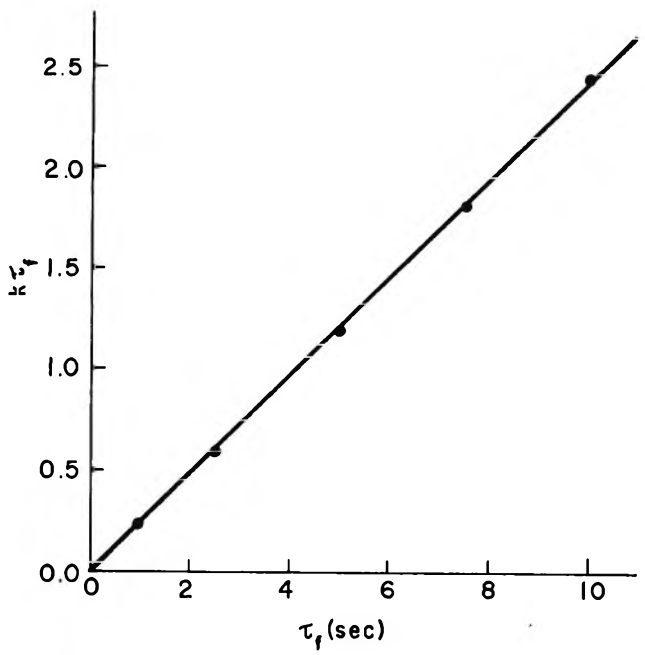


Figure 3.—Plot of $k_{obsd}\tau_f$ *vs.* τ_f for the rearrangement of 8a-hydroxy-2,2,5,7,8-pentamethyl-6-chromanone in 75 vol % water–25 vol % acetonitrile: pH 3.99, 0.5 *M* chloroacetic acid, 0.5 *M* sodium chloroacetate.

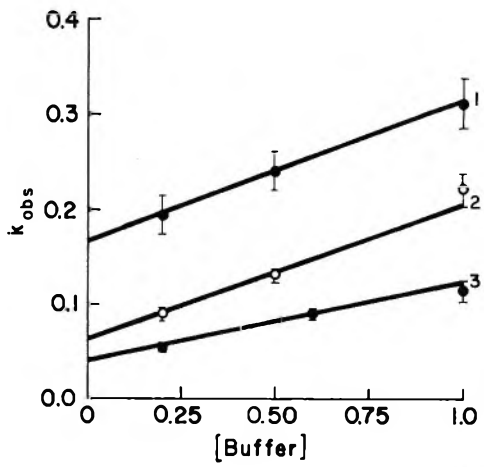


Figure 4.—Dependence of the rate constant for the ring opening of 8a-hydroxy-2,2,2,5,7,8-pentamethyl-6-chromanone on the analytical concentration of the acetic acid buffer and pH: (1) pH 6.24, 90% acetate; (2) pH 5.81, 80% acetate; and (3) pH 5.20, 50% acetate.

Thus, if a constant ratio of $[HA]/[A^-]$ is maintained, a plot of the observed rate constant, k_{obsd}, as a function of the concentration of the conjugate base, A^-, gives values for a and b. The catalytic constants k_{HA} and k_A are then determined either by the solution of the simultaneous equations (eq 8) or (preferably) by a plot of a *vs.* $[HA]/[A^-]$. Values of k_H and k_{OH} are determined in a similar manner from plots of the intercepts, b, as a function of the hydrogen and hydroxyl ion concentrations, respectively. The intrinsic rate constant, k_0, is given by the intercept of either of the latter two plots.

The variation of the observed rate constant as a function of the analytical concentration of acetic acid is shown in Figure 4. Analysis of these data according to the procedure outlined above indicates that the ring-opening reaction is general base catalyzed. The values of the several catalytic constants are summarized

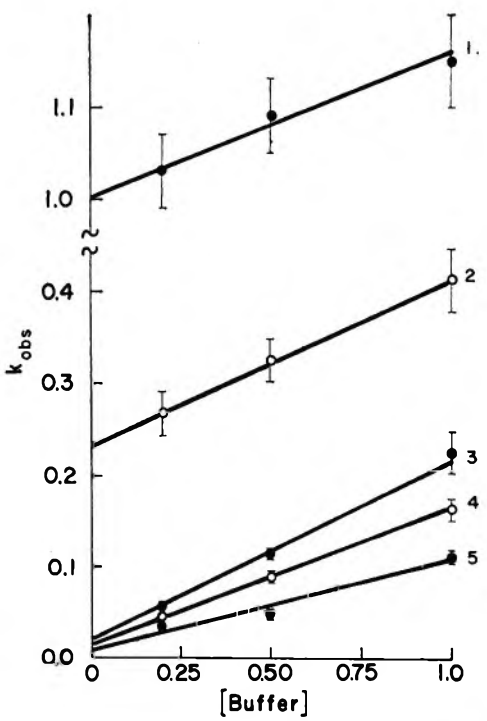


Figure 5.—Dependence of the rate constant for the ring opening of 8a-hydroxy-2,2,5,7,8-pentamethyl-6-chromanone on the analytical concentration of the buffer and pH: (1) pH 2.60, 10% chloroacetate; (2) pH 3.40, 50% chloroacetate; (3) pH 3.99, 80% chlororacetate; (4) pH 4.20, 90% chloroacetate; and (5) pH 4.57, 20% acetate.

in Table I. Although no evidence could be found in this limited pH range (5.20–6.70) to indicate general acid catalysis, its presence would probably not be

TABLE I

CATALYTIC CONSTANTS FOR THE RING OPENING OF 8a-HYDROXY-2,2,5,7,8-PENTAMETHYL-6-CHROMANONE AT 23.0°

Species	k
Intrinsic	4×10^{-3} sec^{-1}
H^+	4×10^{2} M^{-1} sec^{-1}
OH^-	1×10^{7} M^{-1} sec^{-1}
CH_3COO^-	1.6×10^{-1} M^{-1} sec^{-1}

observed if k_{HOAc} were less than 4×10^{2} M^{-1} sec^{-1}.[10] Similarly, no evidence was found to suggest a concerted reaction involving both acetic acid and its conjugate base (acetate ion) in the rate-determining step.

An enhancement in the rate of the reaction with an increase in the buffer concentration was also seen at lower pH (Figure 5). While this result is consistent with catalysis by components of the buffer systems, the addition of an inert salt also causes an increase in the rate constant in this pH range. The data of Table II not only indicate the magnitude of this salt effect, but also indicate a differential salt effect (compare, for example, expt 4 and 5). The occurrence of a marked dependence of the rate constant on the concentration of

(10) This limit is variable, however, and dependent upon the precision of the electrochemical measurements, the concentrations of the several buffer components, and effect of inert salt. The necessity of maintaining an appreciable buffer capacity (protons are involved in both electrochemical redox processes as well as in the addition of water to the carbonium ion, IIb) with respect to the substrate concentration fixes the lower limit for the study of ionic strength effects. Since inert salts undergo varying amounts of ion pairing at these relatively large concentrations, differential salt effects will appear, affecting catalysis in those reactions which are sensitive to changes in ionic strength.

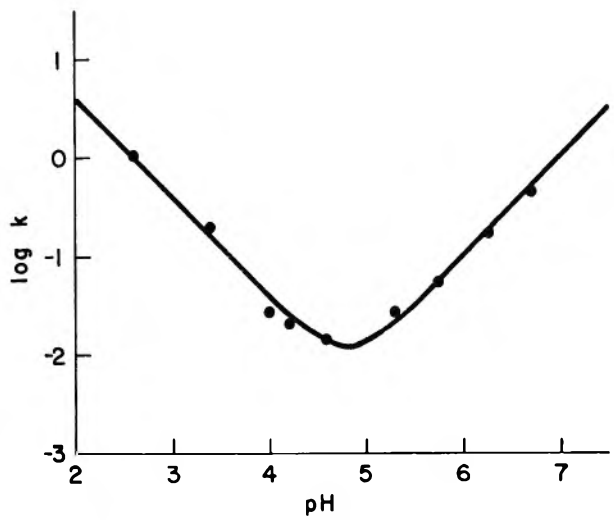


Figure 6.—Plot of log k *vs.* pH for the ring opening of 8a-hydroxy-2,2,5,7,8-pentamethyl-6-chromanone at zero ionic strength and zero buffer concentration. The line is calculated from the data in Table I.

TABLE II

DEPENDENCE OF THE RATE CONSTANT FOR THE RING OPENING OF 8A-HYDROXY-2,2,5,7,8-PENTAMETHYL-6-CHROMANONE ON BUFFER AND INERT SALT CONCENTRATIONS AT 23.0°

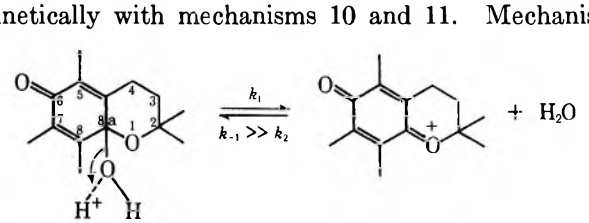
Expt	pH	[HA], M[a]	[A$^-$], M	[NaClO$_4$], M	[NaNO$_3$], M	k_{obsd}, sec^{-1}
1	4.20	0.02	0.18			0.047 ± 0.002
2	4.20	0.05	0.45			0.089 ± 0.005
3	4.20	0.10	0.90			0.162 ± 0.012
4	4.20	0.02	0.18		0.80	0.108 ± 0.007
5	4.20	0.02	0.18	0.80		0.130 ± 0.008
6	4.20	0.05	0.45	0.50		0.166 ± 0.006
7	2.60	0.18	0.02			0.90 ± 0.11
8	2.60	0.18	0.02	1.00		1.12 ± 0.16
9	5.20	0.10	0.10			0.055 ± 0.004
10	5.20	0.10	0.10	0.90		0.051 ± 0.003
11	5.80	0.10	0.10			0.150 ± 0.018
12	5.80	0.10	0.10	0.90		0.248 ± 0.031

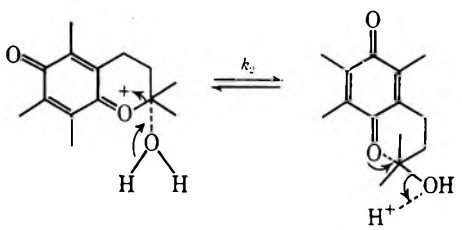
[a] pH 4.20 and 2.60, chloroacetic acid; pH 5.20, acetic acid; pH 5.80, pyridinium perchlorate.

inert salt in slightly more acidic media suggests a change in the mechanism of the rate-determining step. Indeed, there is, as indicated by Figure 6, a minimum in the rate of the reaction near pH 4.8 followed by an increase in the rate with an increase in the hydrogen ion concentration. The slope of the linear plot of log k_{obsd} *vs.* pH is −1 in this region (at zero buffer concentration and zero ionic strength), indicating that the reaction is also specific acid catalyzed. Because of the differential salt effect noted here, it is not possible to determine a rate constant for chloroacetic acid catalysis. For a similar reason, the determination of the effectiveness of chloroacetate ion as a general base is also precluded.

Discussion

The specific acid catalyzed reaction is consistent kinetically with mechanisms 10 and 11. Mechanism

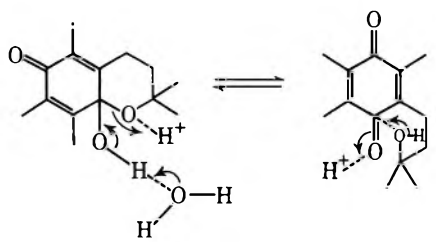




(10)

10, which is probably important in the acid-catalyzed hydrolysis of acetals and ketals,[11,12] can be ruled out on the basis of ^{18}O studies. The chemical oxidation of 2-methoxyphenol[13] and α-tocopherol[14] in the presence of $H_2{}^{18}O$ results in the incorporation of ^{18}O into the quinone nucleus. Since no ^{18}O is incorporated into the hydroxy group of the side chain, the oxidation of Ia and IVa in acidic solution cannot involve dehydration of the 8a-hydroxy-6-chromanone (II) and the subsequent attack of water on the carbon in the 2 position.

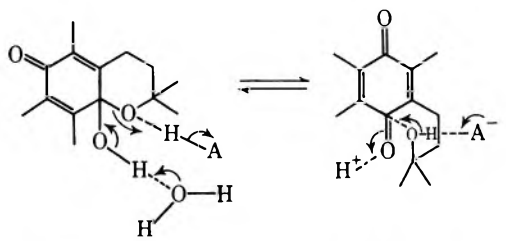
According to mechanism 11, the oxygen in the 1 position is protonated to form the corresponding



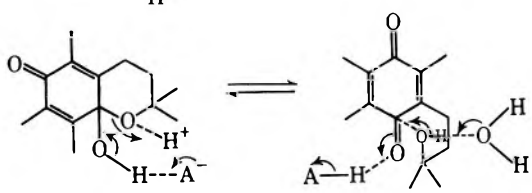
(11)

oxonium salt. Removal of the proton from the hydroxy group in the 8a position by the solvent results in the quinone IVb with the ^{18}O derived from the solvent incorporated into the quinone nucleus. Since this mechanism is consistent with the observed kinetics and correctly determines the disposition of the oxygen atom derived from the solvent, it is suggested as the major reaction pathway in solutions of strong acids.

Kinetically, mechanisms 12 and 13 involve catalysis by general acids. Although measurements of the values for the catalytic constants of chloroacetic and



(12)



(13)

acetic acids were precluded by the differential salt effect, there is, nevertheless, considerable evidence for catalysis by general acids. First, when the data of Table II are used to estimate rate constants in the presence of larger amounts of acetic acid (pH 4.57), the calculated rate constants are considerably smaller than the observed rate constants. A catalytic constant for acetic acid which varies from 0.04 to 0.08 M^{-1} sec^{-1} as the analytical concentration of the buffer increases from 0.2 to 1.0 M is required to account for the differences between the calculated and experimental rates. Precedent for catalysis by carboxylic acids is found in the mutarotation of glucose (a ring opening of hemiacetal).[15-17] Although the rate of the ring-opening reaction of IIIb is *ca.* an order of magnitude greater than the mutarotation of glucose, the ratios of k_{OAc^-}/k_{HOAc} are similar in both reactions. Important also from the work of Brønsted and Guggenheim[15] is the result that both chloroacetic acid and chloroacetate anion were only *ca.* one-fifth as effective catalysts on an equimolar basis as acetate anion. In view of the magnitude of the differential salt effect,[18] the presence of general acid catalysis could easily be missed under some of our reaction conditions.

Second, and more compelling, a significant salt effect is anticipated if the ring-opening reaction is general acid catalyzed. In mechanism 12, positive and negative species (the hydronium ion and the anion of the carboxylic acid) are formed from uncharged reactants. According to the theory of Bateman, Church, Hughes, Ingold, and Taher,[19] the effect of salt on the highly polarized transition state complex, and hence on the rate constant k, is given by eq 14. In this equation, μ

$$\log k/k_0 = (9.12 \times 10^{15})\sigma\mu/D^2T^2 \qquad (14)$$

is the ionic strength, D is the dielectric constant, and $\sigma = Z^2d$, which is a measure of the distance of the charge separation in the transition state complex. Although the latter quantity is unknown, a plausible value of $\sigma = 2 \times 10^{-8}$ cm leads to the prediction that a fourfold increase in the rate constant should result from a tenfold increase in the ionic strength. The results reported in Table II (compare expt 1, 4, and 5) are in qualitative agreement with this prediction at pH 4.20. At either lower or higher pH (expt 7–10) the effect of added inert salt is insignificant. This result is anticipated with decreasing pH as the reaction becomes predominately specific acid catalyzed. As seen in eq 11, the pathway involves protonation of the oxygen in the 1 position and loss of a proton from the hydroxy group in the 8a position. Since no additional charged species is either created or destroyed, a neglible salt effect should be observed.[19] For an analogous reason (*vide infra*), the effect of salt also diminishes when the reaction proceeds *via* a base-catalyzed pathway at higher pH.

According to mechanism 13, protonation of the oxygen in the 1 position and the removal of a proton from the hydroxy group in the 8a position by the negatively charged base will behave kinetically as general acid catalysis. Although this mechanism has been

(11) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill Book Co., New York, N. Y., 1968, p 306.

(12) W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 92 (1964).

(13) E. Adler, I. Falkehag, and B. Smith, *Acta Chem. Scand.*, **16**, 529 (1962).

(14) H. Mayer, W. Vetter, J. Metzger, R. Rüegg, and O. Isler, *Helv. Chim. Acta*, **50**, 1168 (1967); P. Schudel, H. Mayer, J. Metzger, R. Rüegg, and O. Isler, *ibid.*, **46**, 333 (1963).

(15) J. N. Brønsted and E. A. Guggenheim, *J. Amer. Chem. Soc.*, **49**, 2554 (1927).

(16) C. G. Swain and J. F. Brown, Jr., *ibid.*, **74**, 2534, 2538 (1952).

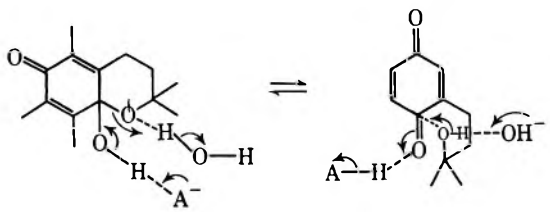
(17) C. G. Swain, A. J. Di Milo, and J. P. Cordner, *ibid.*, **80**, 5983 (1958).

(18) For other reports of differential salt effects, see, for example, E. F. J. Duynstee, E. Grunwald, and M. L. Kaplan, *ibid.*, **82**, 5654 (1960); J. F. Bunnett and N. S. Nudelman, *J. Org. Chem.*, **34**, 2038 (1969).

(19) L. C. Bateman, M. G. Church, E. D. Hughes, C. K. Ingold, and N. A. Taher, *J. Chem. Soc.*, 979 (1940).

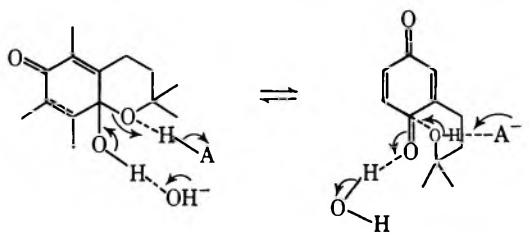
suggested to be important in the acid-catalyzed hydrolysis of a formamidium compound,[20] reaction by this pathway would lead to the prediction that the rate of the ring-opening reaction would decrease significantly with an increase in inert salt concentration.[19] Since this prediction is contradictory to the experimental results, this mechanism cannot be important here.

Little or no effect of salt is predicted and observed (Table II, expt 9 and 10) for the reaction catalyzed by monobasic anions. According to mechanism 15, a



(15)

proton is removed from the hydroxy group by the negatively charged general base, A^-, while a molecule of water functions as the acid. In mechanism 16, a



(16)

proton is transferred from the general acid to the oxygen in the 1 position, while a proton is removed from the hydroxy group in the 8a position by hydroxide ion. This reaction, which proceeds by specific base and general acid catalysis mechanistically, will behave kinetically as catalyzed by general base.

A distinction between the two pathways on the basis of salt effects should be feasible if the general base were unchanged. A change from a negatively to a neutrally charged base leads to the predictions that with an increase in the inert salt concentration the rate constant should increase if the reaction proceeds by mechanism 15 and decrease if the reaction proceeds by mechanism 16. As seen by the results of expt 11 and 12 (Table II), addition of inert salt (sodium perchlorate) to a pyridinium perchlorate–pyridine buffer system results in a marked increase in the experimental rate constant. We conclude from this result that general base catalysis for pyridine proceeds *via* mechanism 15 and suggest that catalysis by carboxylic anions occurs by this reaction pathway also.

It is of final interest to compare the stability of IIIb to that of IIIa.[21] The latter intermediate was reported to exhibit a bell-shaped pH–rate profile with maximum stability at pH 5.5. While maximum stability for IIIb is also noted in this study near this pH, the rate law for the decomposition of IIIb is first order in both hydrogen and hydroxide ions. The apparent difference in the two rate laws probably arises from the different methods used for the preparation of the two intermediates (IIIa,b). In the work of Dürckheimer and Cohen,[21] IIIa was prepared by the chemical oxidation of Ia using N-bromosuccimide as the oxidant. A change in the rate-determining step from the decomposition of IIIa to the oxidation of Ia would satisfactorily account for the observed differences in the rate law.

Registry No.—Ib, 950-99-2; IIIb, 24165-02-4.

Acknowledgment.—These studies were supported by the U. S. Public Health Service Research Grant No. 1 RO1 AM 13258-01.

(20) D. R. Robinson and W. P. Jencks, *J. Amer. Chem. Soc.*, **89**, 7088 (1967). For a complete discussion of carbonyl addition reactions, see ref 11, pp 63–128.

(21) W. Dürckheimer and L. A. Cohen, *ibid.*, **86**, 4388 (1964).

Axially Dissymmetric Molecules. Characterization of the Four 1-Carbethoxy-4-methylspiropentanes

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In order to map the energy surface of various reactions of substituted spiropentanes, the four diastereomers of 1-carbethoxy-4-methylspiropentane were synthesized by methylene addition to *syn*- and *anti*-1-carbethoxy-2-ethylidenecyclopropane. The relative stereochemical configurations of the spiropentane esters were determined by their conversion into the dimethylspiropentanes which were, in turn, synthesized from the spiropentane-1,4-dimethanols, whose configurations were determined by ir hydrogen bonding and nmr studies.

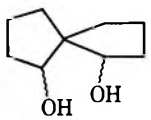
Axially dissymmetric molecules such as allenes and spirans are of historical interest because their synthesis and optical resolution provide experimental confirmation of the predicted geometry of bonds emanating from carbon centers.[1] Spirans with substituents or heteroatoms in each ring having nonsuperimposable mirror images have, in addition, the possibility of existing as diastereomers depending on the nature and point of attachment of the substituents. A few examples of this situation have been reported;[1] however, to our knowledge, the only cases where all possible diastereomers of a disubstituted spiran were separated and characterized are due to Cram[2] and to Applequist[3]

(1) For reviews, see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 12.

(2) E. Hardegger, E. Maeder, M. Semarne, and D. J. Cram, *J. Amer. Chem. Soc.*, **81**, 2729 (1959).

(3) D. E. Applequist and E. G. Alley, *J. Org. Chem.*, **33**, 2741 (1968).

who identified all three diastereomers of spiro[4.4]-nonane-1,6-diol (**1**) and of 1,4-dichlorospiropentane (**2**), respectively.[4] These molecules each have two

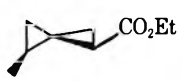


1

2

dissymmetric centers as well as an axis of dissymmetry; thus, four diastereomeric *dl* pairs of each are possible. Examination of the molecules reveals, however, that one of the *dl* pairs is equivalent to another in each case by virtue of the equivalent substitution in the two rings.

We wish to report the preparation, characterization, and spectroscopic properties of all four diastereomers of 1-carbethoxy-4-methylspiropentane, **3**–**6**, not simply to provide more examples of axially dissymmetric molecules but because it has proven possible to utilize these materials in providing a partial geographic survey of the energy surface associated with the thermal isomerization of isopropenylspiropentane.[5] Furthermore, these materials are well suited as stereochemically labeled materials for investigation of the possible multiple cyclopropylcarbinyl-type rearrangements of the spiropentylcarbinyl charged and uncharged species.



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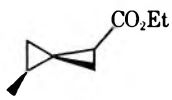

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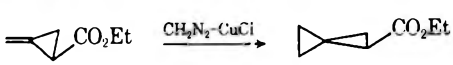
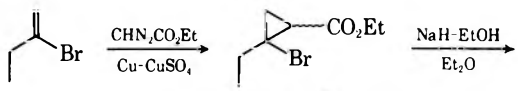
Results

Synthesis of the Four 1-Carbethoxy-4-methylspiropentanes.—Synthetic entry into the substituted spiropentane system is best accomplished by carbene addition to allenes or to methylenecyclopropanes. For instance, carbethoxyspiropentane (**7**) was prepared by treating 1-carbethoxy-2-methylenecyclopropane with the Simmons–Smith reagent.[6] Since relatively large quantities of materials were desired, the Gaspar–Roth cyclopropanation procedure[7] involving cuprous chloride catalyzed addition of methylene from diazomethane was attempted and found to be superior to the previously reported synthesis of **7**.

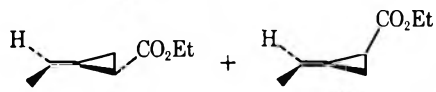


7

The syntheses of **3**, **4**, **5**, and **6** followed that for production of **7**.[6] Thus, the *cis*- and *trans*-2-bromo-2-ethyl-1-carbethoxycyclopropanes (**8** and **9**) were prepared by copper-catalyzed addition of ethyl diazoacetate to 2-bromo-1-butene and were subjected to sodium ethoxide in diethyl ether according to the procedure reported by Ullman to give a mixture of *syn*- and *anti*-1-carbethoxy-2-ethylidenecyclopropane (**10** and **11**), respectively. This mixture (1:4 ratio of two compounds by capillary vpc) was separated by preparative vpc. However, assignment of stereochemistry was not attempted at this point because of the near-identical spectroscopic properties of **10** and **11**.



8 and **9**



10 : **11**

1 : 4

Each ethylidene derivative was cyclopropanated using the Gaspar–Roth procedure which is known to preserve the stereochemistry about the double bond attacked (ref 7 and references contained therein). In these cases, two isomers were expected from each ethylidene derivative because there are two possible orientations for methylene addition, *syn* or *anti*, to the carbethoxy group. Indeed, two and only two 1-carbethoxy-4-methylspiropentanes were produced from reaction with one of the ethylidene substrates, and two different 1-carbethoxy-4-methylspiropentanes were formed using the other ethylidene material. These conclusions derive from the analysis and spectroscopic properties of vpc purified materials. At this point, it was still not possible to assign the stereochemistry of the precursors, **10** or **11**, or of the product spiropentanes, **3**, **4**, **5**, and **6**. Yet already relationships between the diastereomers were established since two of the four possible compounds were produced in a known stereospecific synthesis from one precursor while the other two possible isomers were derived from the other precursor.

Relative Configurations of the Four 1-Carbethoxy-4-methylspiropentanes.—Examination of Figure 1 reveals that stereospecific addition of methylene to (*R*),-1(*R*)-*syn*-1-carbethoxy-2-ethylidenecyclopropane (**10**) should give (*R*),1(*R*),4(*S*)- and (*S*),1(*R*),4(*R*)-1-carbethoxy-4-methylspiropentane (**3** and **4**), respectively, while (*R*),1(*S*)-*anti*-1-carbethoxy-2-ethylidenecyclopropane, (**11**) should give (*S*),1(*S*),4(*S*)- and (*R*),1(*S*),4(*R*)-1-carbethoxy-4-methylspiropentane (**5** and **6**), respectively. Throughout, however, racemic starting materials were utilized, and the two sets of *dl* pairs derived from racemic **10** are merely epimeric at C-1. Similarly, the two *dl* pairs derived from racemic **11** are epimeric at C-1. To distinguish between these isomers, it was convenient to utilize a system of trivial stereochemical designations. The terms *proximal*, *medial*, and *distal* refer to the relative distances (on a line) between the substituents in the four compounds. The two *medial* compounds can further be distinguished by the terms *syn* and *anti* which refer to the relative positions of substituents using as the plane of reference the plane of the ring bearing the higher priority sub-

(4) Mention should be made of the elegant work of G. E. McCasland and S. Proskow [*J. Amer. Chem. Soc.*, **76**, 4688 (1955)], who prepared the four diastereomers of 3,4,3′,4′-tetramethylspiro[1,1′]bipyrrolidinium *p*-toluenesulfonate and verified that one of the *trans,trans* compounds which had neither a plane nor a center of symmetry was optically inactive by virtue of a fourfold alternating axis of symmetry.

(5) J. J. Gajewski, *ibid.*, **92**, 3688 (1970).

(6) E. F. Ullman and W. J. Fanshawe, *ibid.*, **83**, 2379 (1961).

(7) W. von E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963).

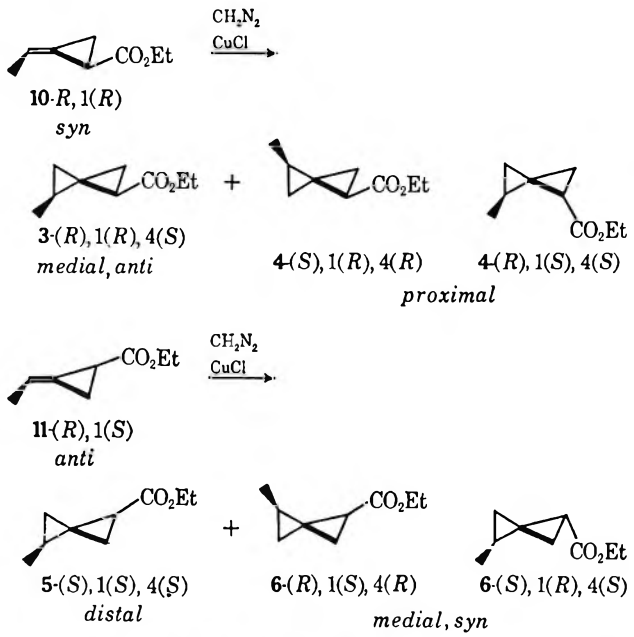
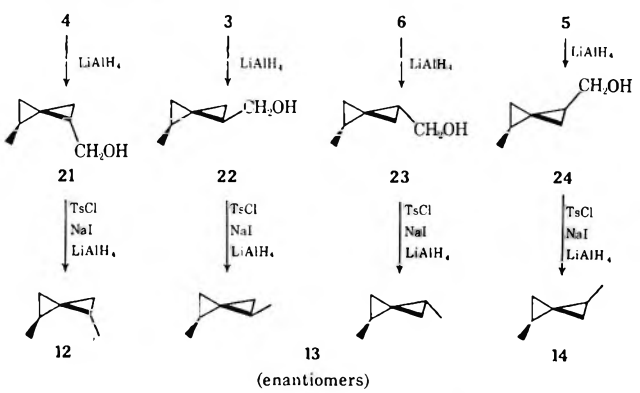


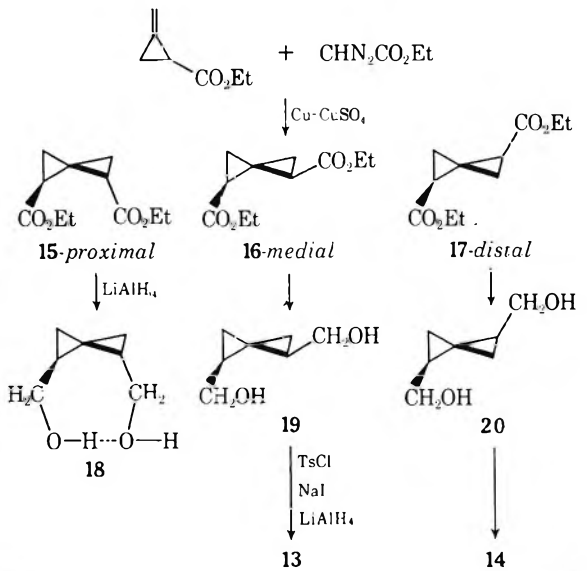
Figure 1.—Cuprous chloride catalyzed addition of diazomethane *syn*- and *anti*-1-carbethoxy-2-ethylidenecyclopropane (**10** and **11**).

stituent. Thus, **3** is *medial,anti;* **4** is *proximal;* **5** is *distal;* and **6** is *medial,syn.*

A reduction of the stereochemical problem was possible by virtue of the fact that the two different *medial*-1-carbethoxy-4-methylspiropentanes could be made to be identical if the substituents of the two isomers could be made equivalent. Thus, the four carbethoxy derivatives were converted by a reduction, tosylation, iodide displacement, hydride displacement sequence to the 1,4-dimethylspiropentane isomers. As expected, one ester from each of the pairs of spiropentane esters from the ethylidene compounds gave a common hydrocarbon, namely, *medial*-1,4-dimethylspiropentane (**13**), so it was clear that **3** and **6** were *medial* derivatives, but complete assignment of stereochemistry was not yet possible. However, merely determining which hydrocarbon was *proximal*, **12**, or, alternatively, which was *distal*, would serve to establish the configurations of **3**, **4**, **5**, and **6** as well as their precursors, **10** and **11**. This was accomplished by direct synthesis of *distal*-1,4-dimethylspiropentane (**14**), from precursors whose stereochemistry was assigned by chemical and spectroscopic studies.



Syntheses and Relative Configurations of the Symmetrically 1,4-Disubstituted Spiropentanes.—Copper-catalyzed addition of ethyl diazoacetate to 1-carbethoxy-2-methylenecyclopropane gave a mixture of three isomeric 1,4-dicarbethoxyspiropentanes, **15**, **16**, and **17**, in the ratio 1:4:2, respectively, which were separated by preparative vpc. The major product was easily identified as the *medial* compound because its pmr spectrum indicated the presence of two different ethoxy groups and two different sets of ABX ring proton resonances. The *medial* compound, **16**, has no symmetry elements, while the *proximal* and *distal* materials each have a C_2 axis passing through the central carbon. Thus, a single ethoxy group and an ABX ring proton resonance pattern were expected and found for the other two isomers. The *proximal* and *distal* isomers were further distinguished by reduction to the dimethanols, **18** and **20**, the latter of which (*distal*) showed no evidence for intramolecular hydrogen bonding in the ir in carbon disulfide solvent, while the former (*proximal*) had a sharp, third absorption at 3480 cm^{-1} (see Table I). *medial*-Dimethanol (**10**) showed no evidence of intramolecular hydrogen bonding. The *distal*-1,4-spiropentanedimethanol was then converted by the tosylation, iodide displacement, hydride displacement route to the same 1,4-dimethylspiropentane derived from **5**. Finally, the *medial*-1,4-spiropentanedimethanol (**19**) was converted to the same 1,4-dimethylspiropentane derived from both **3** and **6**.



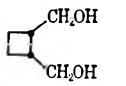
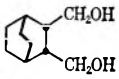
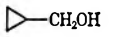
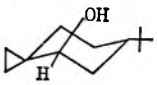
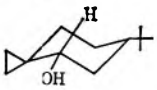
Thus, the relative configurations of the following compounds were assigned: all three 1,4-dicarbethoxyspiropentanes, all three 1,4-spiropentanedimethanols, all three 1,4-dimethylspiropentanes, all four 4-methyl-1-carbethoxyspiropentanes, and, therefore, the two 1-carbethoxy-2-ethylidenecyclopropanes.

Discussion

Assignment of Configuration. Hydrogen-Bonding Studies.—The stereochemical assignment of all the compounds described results ultimately on the distinction between the diols **18**, **19**, and **20**. Since **19** was clearly the *medial* diol on the basis of its nmr spectrum, the problem was reduced to characterization of **18** and **20** by infrared hydrogen bonding studies using the carbon disulfide solvent.[8] The data of Table

(8) For an extensive study of intramolecular OH–O bonding, see L. P. Kuhn, P. von R. Schleyer, W. F. Battinger, Jr., and L. Eberson, *J. Amer. Chem. Soc.*, **86**, 650 (1964).

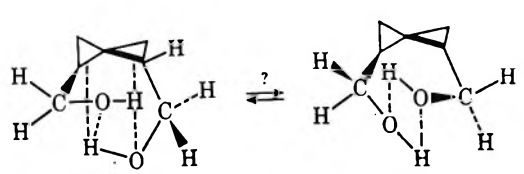
TABLE I
IR O–H STRETCHING ABSORPTIONS OF 18, 19, 20, AND COMPARISON COMPOUNDS

		ν, cm⁻¹
	18[a]	3620 (1),[b] 3480 (2)[b]
	19[a]	3640, 3610[c]
	20[a]	3640, 3610[c]
	25[d]	3634 (1.2), 3507 (1.0)
	26[a]	3623 (0.9), 3490 (1.0)
	27[e]	3633 (1.0), 3615 (1.1)
	28[e]	3621 (0.3), 3612 (1.0)
	29[e]	3636 (1.0), 3625 (0.4)

[a] Very dilute solutions in CS_2. [b] Numbers in parentheses denote relative intensities. [c] Low-intensity shoulders. [d] Dilute solutions in CCl_4 (ref 8). [e] Dilute solutions in CCl_4 (ref 9).

I are most revealing in this respect, indicating that **18** is, indeed, the *proximal* diol. Thus, the frequency shift between the free and the bonded O–H stretching absorptions of **18** is very similar to that of the dimethanols **25** and **26**. While the relative intensities of the two absorptions in **18** and the model compounds are not the same, they are of the same order of magnitude and indicate that hydrogen bonding occurs to a greater degree in **18** relative to **25** or **26**.[8] This latter observation may be consistent with other data included in Table I; *i.e.*, the position of the "free" O–H stretches in **18** is shifted about 20 cm^{-1} from that of **19** and **20**. Furthermore, both **19** and **20** have low-intensity shoulders around 3610 cm^{-1}. This is reminiscent of OH to cyclopropane interactions studied by Joris, Schleyer, and Gleiter,[9] *e.g.*, **27**, **28**, and **29** of Table I.

A reasonable explanation for these facts recalls that OH to cyclopropane bonding occurs most efficiently to the "edge" of the cyclopropane ring rather than from above the plane of the ring; *cf.* **28** and **29**. In **19** and **20** both OH groups can bond either to the cyclopropane ring bearing them or to the other ring. However, in one conformation of **18** (**18a** below) the OH groups can easily be disposed toward bonding with each other as well as to the edge of the other ring. (That **18a** and **18b** are the two conformations to consider here derives from the fact that at closest approach the O···O distance is about 0.6 Å in **18** which is much too close for efficient OH···OH hydrogen bonding.) Thus, the shift to lower frequencies of the "free" OH in **18** appears reasonable and is analogous to the shift seen for **28** relative to its model, **29**. A qualitative comparison of

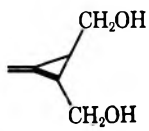


18a **18b**

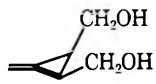
(9) L. Joris, P. von R. Schleyer, and R. Gleiter, *J. Amer. Chem. Soc.*, **90**, 327 (1968).

the solubilities of **18**, **19**, and **20** reinforces the conclusions based on the ir studies. The *proximal* diol, **18**, was much more soluble in CS_2 solvent than **19** or **20**. Thus, a saturated solution of **18** in CS_2 had a broad bonded OH absorption in the ir at 3260, while saturated CS_2 solutions of **19** or **20** showed no intermolecularly bonded OH groups.

A final interesting point along these lines is the nmr chemical shift difference between the carbinol hydrogens of **18**, 0.7 ppm in $CDCl_3$, a relatively good hydrogen bonding solvent.[10] On the other hand, the chemical shift difference in **20** is practically zero, and in **19** a narrow multiplet is observed. Whether or not this can be related to a conformational preference in **18** due to hydrogen bonding is not yet clear. Similar effects have been noted in instances where intramolecular hydrogen bonding is not possible; for instance, 3-methylenecyclopropane-*trans*-1,2-dimethanol (**30**) has a 0.7-ppm chemical shift difference between the carbinol hydrogens; the corresponding *cis* compound, **31**, has a carbinol hydrogen chemical shift difference of 0.63 ppm.[11]



30



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Experimental Section

General.—Nuclear magnetic resonance spectra were recorded on Varian A-60, HA-100, and HR-220 spectrometers. Carbon tetrachloride was used as a solvent with chloroform as an internal lock in frequency sweep mode; chemical shifts are reported as δ values in ppm relative to TMS. Infrared spectra were obtained with Perkin-Elmer Model 621, 137, and 137G spectrophotometers in the indicated solvent. Vapor phase chromatography was performed on Varian Aerograph A90P-3 and Series 1220-2 (capillary) instruments using the indicated columns. Analyses were performed by Spang Microanalytical Laboratory.

Ethyl Spiropentanecarboxylate (7).—To a 0° stirred mixture of 3.35 g (0.0266 mol) of ethyl methylenecyclopropanecarboxylate[4] and 0.3 g of cuprous chloride in 10 ml of *n*-pentane was added gaseous diazomethane generated from 15 g (0.14 mol) of N-methyl-N-nitroso urea in the manner described by Doering and Roth.[7] The reaction mixture was filtered, concentrated by removal of the solvent through a Vigreux column at atmospheric pressure, and separated by repeated 300-μl injections on a 10 ft × 3/8 in. XF1150 column operated at 135° and 200 ml/min helium flow rate. In addition to 1 g of starting ester, 2 g of ethyl spiropentanecarboxylate[6] was collected: ir of **7** (neat) 3030, 1730, and 1180 cm^{-1}; nmr (60 MHz) δ 0.88 (broad singlet, 4 H), 1.08–1.48 (multiplet, 5 H), 1.87 (doublet of doublets, J = 8.0 and 4.0 Hz, 1 H), 4.05 (quartet, J = 7.5 Hz, 2 H).

***cis*- and *trans*-1-Carbethoxy-2-bromo-2-ethylcyclopropanes (8 and 9).**—To a stirred refluxing mixture of 500 ml of 90% pure 2-bromo-1-butene (Columbia Organic), 3 g of anhydrous cupric sulfate, and 3 g of electrolytic copper dust was added 140 g (1.23 mol) of ethyl diazoacetate dropwise over a period of 12 hr. After the mixture was allowed to stir at reflux for 10 hr more, it was cooled, then filtered. Distillation of the filtrate through a large Vigreux column at atmospheric pressure gave 300 ml of starting bromo olefin. Rapid vacuum distillation of the residue gave 150 ml of light brown oil, bp 25–110° (15 Torr). Redistillation of the distillate at 11 Torr through a 15-in. spiral wire column gave 33 g of forerun; 59 g of fraction I, bp 86–90°; 5 g of fraction II, bp 90–97°; and 22 g of fraction III, bp 97.0–98.3°. Fraction I was a single isomer of 1-carbethoxy-2-bromo-2-ethylcyclopropane (**8** or **9**), from its analysis and nmr spectrum at 60 MHz: nmr δ 0.9–2.43 (multiplet, 11 H) and 4.13 (quartet, J = 7 Hz, 2 H).

(10) A. Allerhand and P. von R. Schleyer, *ibid.*, **85**, 1715 (1963).
(11) J. J. Gajewski, unpublished observations.

Anal. Calcd for $C_8H_{13}BrO_2$: C, 43.44; H, 5.98; Br, 36.16. Found: C, 43.48; H, 5.86; Br, 36.16.

Fraction III appeared to be the other isomer of 1-carbethoxy-2-bromo-2-ethylcyclopropane (**8** or **9**) contaminated with about 15% of diethyl fumarate: nmr (60 MHz) of fraction III δ 0.9–2.0 (complex multiplet, relative area 3.5), 4.14 (center of two nearly superimposed quartets, relative area 7.9), and 6.77 (singlet, relative area 1). Fraction II was a mixture of fractions I and III.

Subsequent experiments indicated that fractions I, II, and III could be dehydrobrominated to the same 1:4 mixture of the *syn*- and *anti*-2-ethylidene-1-carbethoxycyclopropanes, **10** and **11**.

syn- and *anti*-**2-Ethylene-1-carbethoxycyclopropanes (10 and 11).**—To a rapidly stirred, refluxing slurry of 17.5 g (0.738 mol) of sodium hydride and 30.0 g (0.136 mol) of **8** and/or **9** (fractions I, II, or III) in 300 ml of diethyl ether under nitrogen was added 2.0 ml of ethanol.[12] Refluxing with stirring was continued for 80 min; then the reaction mixture was allowed to cool. The sodium hydride was decomposed by careful addition of excess acetic acid; then water was added. This treatment resulted in a clear, two-layer solution. The layers were separated and the aqueous layer was extracted with ether. The combined ether layers were washed with a 10% sodium bicarbonate solution until washings were basic. After being washed with saturated brine and dried over anhydrous sodium sulfate, the ethereal solution was concentrated by removal of the solvent through a Vigreux column at atmospheric pressure giving 27 g of a brown residue which was distilled at aspirator vacuum. A total of 5.2 g of a clear distillate, bp 74–82° (25 Torr), was collected. The pot residue consisted of starting bromide and materials containing alkylethoxy groups by nmr. The distillate contained two materials in the ratio of 1:4. The mixture was separated by repeated 100-μl injections on a 20 ft × $^3/_8$ in. UCON 50HB2000 vpc column operated at 125° and 200-ml/min helium flow. The minor product which, in addition, had the shorter retention time of the two was later shown to be *syn*-2-ethylidene-1-carbethoxycyclopropane (**10**). The major product was later found to be *anti*-2-ethylidene-1-carbethoxycyclopropane (**11**).

Properties of *syn*-1-carbethoxy-2-ethylidenecyclopropane (**10**): ir (neat) 2995, 1735, 1160, 1090, 1075, 1050, 1030 (sh), 990, 945, 915, 860 (w), 825, 785 (w), and 755 (w) cm^{-1}; nmr (100 MHz) δ 1.23 (triplet, 3 H, J = 7.0 Hz), 1.37–1.73 (multiplet, 2 H), 1.73–1.87 (complex multiplet centered at δ 1.77, 3 H), 2.00–2.20 (symmetrical multiplet centered at δ 2.10, 1 H), 4.08 (quartet, J = 7.0 Hz, 2 H), and 5.55–6.0 (symmetrical multiplet centered at δ 5.78, 1 H); nmr (220 MHz) δ 1.25 (triplet, J = 7 Hz, 3 H), δ 1.54 (triplet with fine structure, J = 7 Hz, 1 H), 1.7 (multiplet, 1 H), 1.78 (doublet of quartets, J = 7 and 2 Hz, 3 H), 2.1 (multiplet, 1 H), 3.98 (quartet, J = 7 Hz, 2 H), and 5.70 (multiplet, 1 H).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.57; H, 8.54.

Properties of *anti*-1-carbethoxy-2-ethylidenecyclopropane (**11**): ir (neat) 2995, 1735, 1160, 1090, 1075, 1045, 1025, 960 (sh), 940, 855 (w), 830 (w), and 750 (w) cm^{-1}; nmr (100 MHz) δ 1.25 (triplet, J = 7.0 Hz, 3 H), 1.35–1.75 (multiplet, 2 H), 1.87 (doublet of quartets, J = 6.5 and 1.8 Hz, 3 H), 2.00–2.20 (symmetrical multiplet of 11 lines each separated by 1.8 Hz, centered at δ 2.10 1 H), 4.12 (quartet, J = 7.0 Hz, 2 H), and 5.60–6.10 (symmetrical multiplet, centered at δ 5.85, 1 H); nmr (220 MHz) δ 1.25 (triplet, J = 7 Hz 3 H), 1.47 (triplet with fine structure, J = 8 Hz, 1 H); 1.63 (multiplet, 1 H), 1.85 (doublet of quartets, J = 7.5 and 2 Hz, 3 H), 2.11 (multiplet, 1 H), 3.97 (quartet, J = 7 Hz, 2 H), and 5.75 (multiplet, 1 H).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.68; H, 8.62.

Cyclopropanation of 10. *medial,anti*- and *proximal*-1-Carbethoxy-4-methylspiropentanes (3 and 4).—gaseous diazomethane generated from 40 g (0.39 mol) of N-methyl-N-nitrosourea was bubbled into a solution of 1.87 g (0.0135 mol) of **10** in 5 ml of *n*-pentane containing 0.2 g of cuprous chloride at 0°, according to the Gaspar–Roth recipe.[7] After filtration and bulb-to-bulb distillation under vacuum, 1.45 g of colorless liquid was obtained. Vpc analysis revealed the presence of three peaks in the ratio 0.4:0.8:1 (in order of increasing retention time) with the minor component being unreacted starting material. Preparative vpc on a 20 ft × $^3/_8$ in. UCON 50HB2000 column operated at 148° and 75-ml/min helium flow gave 0.40 g of 99+% homogeneous **3**, subsequently identified as *medial,anti*-1-carbethoxy-4-methylspiropentane, and 0.56 g of 99+% homogeneous **4** which was subsequently identified as *proximal*-1-carbethoxy-4-methylspiropentane.

Properties of *medial,anti*-1-carbethoxy-4-methylspiropentane, **3**: ir (CCl_4) 3080, etc., 1730, 1450, 1360, 1340, 1255, 1170, 1135, 1125, 1090, 1065, 1040, 1005, and 925 cm^{-1}; nmr (60 MHZ) δ 0.42 (broad singlet, 1 H), 0.9–1.55 (multiplet, 10 H), 1.78 (doublet of doublets, J = 7.5 and 4 Hz, 1 H), and 4.06 quartet, J = 7.5 Hz).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.39; H, 9.27.

Properties of *proximal*-1-carbethoxy-4-methylspiropentane, **4**: ir (CCl_4) 3060, etc., 1725, 1450, 1360, 1340, 1300, 1260, 1160, 1120, 1070, 1035, 1010, 940, and 895 cm^{-1}; nmr (60 MHz) δ 0.46 (triplet, J = 4 Hz, 1 H), 0.7–1.58 (complex multiplet, 10 H), 1.82 (doublet of doublets, J = 7 and 4 Hz, 1 H), and 4.08 (quartet, J = 7 Hz, 2 H).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.81; H, 9.01.

Cyclopropanation of 11. *distal*- and *medial,syn*-1-Carbethoxy-4-methylspiropentanes (5 and 6).—As described above for production of **3** and **4**, a total of 2.38 g (0.017 mol) of **11** was treated with a total of 51 g (0.49 mol) of N-methyl-N-nitrosourea. Vpc analysis revealed the presence of three components in the ratio 4:1:2 in order of retention times on a 20 ft × $^3/_8$ in. UCON 50-HB2000 preparative vpc column with the minor (middle) component being starting material. Vpc separation under the same conditions described for **3** and **4** allowed isolation of 0.76 g of 99% pure **6** which was later identified as *medial,syn*-1-carbethoxy-4-methylspiropentane and 0.43 g of 99+% pure **5** which was subsequently identified as *distal*-1-carbethoxy-4-methylspiropentane.

Properties of *medial,syn*-1-carbethoxy-4-methylspiropentane (**6**): ir (neat) 3080, etc., 1730, 1450, 1375, 1345, 1325, 1265, 1185, 1130, 1070, 1040, 890 (broad weak), 845, and 775 cm^{-1}; nmr (60 MHz) δ 0.49 (broad singlet, 1 H), 0.8–1.50 (multiplet, 10 H), 1.85 (doublet of doublets, J = 7 and 4 Hz, 1 H), and 4.05 (quartet, J = 7.5 Hz, 2 H).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.18; H, 9.15.

Properties of *distal*-1-carbethoxy-4-methylspiropentane (**5**): ir (neat) 3075, etc., 1730, 1450, 1410, 1390, 1380, 1350, 1320, 1270, 1180, 1160, 1120, 1090, 1070, 1030, 980, 945, 925, 880, 855, and 750 cm^{-1}; nmr (60 MHz) δ 0.58 (center of multiplet, 1 H), 0.75–1.45 (multiplet, 10 H), 1.83 (doublet of doublets, J = 7 and 4 Hz, 1 H), and 4.08 (quartet, J = 7 Hz, 2 H).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.23; H, 9.12.

1,4-Dicarbethoxyspiropentanes (15, 16, and 17).—Ethyl diazoacetate (4.6 g, 0.040 mol) dissolved in 30 ml of *n*-octane was added over a period of 24 hr to a refluxing solution of 2.6 g (0.021 mol) of methylenecarbethoxycyclopropane in 10 ml of *n*-octane containing 0.03 g of copper bronze and 0.07 g of anhydrous cupric sulfate. After addition the mixture was cooled and filtered, and the solvent was removed by distillation. Vacuum distillation of the residue gave 3.62 g (87%) of material boiling at 84–88° (0.5 Torr). Vpc analysis (5 ft × $^1/_4$ in. SE-30 column) of the mixture showed three peaks in a ratio of about 1:4:2. The mixture was separated using an 18 ft × $^3/_8$ in. 25% SE-30 column at 150°.

Fraction I. *proximal*-1,4-Dicarbethoxyspiropentane (15).—About 0.1 g of the first fraction was recovered after repassing through the 18-ft SE-30 column. The material was subsequently shown to be *proximal*-1,4-dicarbethoxyspiropentane, **15**: ir ($CHCl_3$) 2984, 2935, 2909, 1725, 1378, 1349, 1323, 1274, 1165, 1121, 1098, 1071, and 1019 cm^{-1}; nmr (100 MHz) (CCl_4) δ 1.03 (triplet, J = 7 Hz) superimposed on a multiplet between 0.95 and 1.25 (total of 10 H), 1.89 (doublet of doublets, J = 7.5 and 5 Hz, 2 H), and 3.86 (quartet, J = 7 Hz, 4 H).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.26; H, 7.57.

Fraction II. *medial*-1,4-Dicarbethoxyspiropentane (16).—Approximately 1.4 g of the second fraction was obtained after repassing through the $^3/_8$-in. SE-30 column. This was *medial*-1,4-dicarbethoxyspiropentane (**16**): ir ($CHCl_3$) 2978, 2933, 2904, 1720, 1393, 1370, 1340, 1323, 1267, 1163, 1117, 1092, 1058, 1028, and 1015 (sh) cm^{-1}; nmr (100 MHz) (CCl_4) δ 1.13 (two nearly superimposed triplets, J = 7 Hz, 6 H), 1.33 (multiplet,

(12) J. A. Carbon, W. B. Martin, and L. R. Swett, *J. Amer. Chem. Soc.*, **80**, 1002 (1958).

4 H), 1.83 (multiplet, 2 H), and 3.92 (two nearly superimposed quartets, J = 7 Hz, 4 H).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.36; H, 7.58.

Fraction III. *distal*-**1,4-Dicarbethoxyspiropentane (17).**—Approximately 0.8 g of fraction III was recovered after repassing through the $^3/_8$-in. SE-30 column. This material was later shown to be distal-1,4-dicarbethoxyspiropentane, **17**: ir ($CHCl_3$) 2980, 2938, 2904, 1710, 1365, 1341, 1311, 1289, 1268 (sh), 1160, 1091, 1055 (sh), and 1021 cm^{-1}; nmr (100 MHz), (CCl_4) δ 1.14 (triplet, J = 7 Hz) superimposed on a multiplet between 1.04 and 1.29 (total of 8 H), 1.45 (triplet, J = 4.5 Hz, 2 H), 1.85 (doublet of doublets, J = 6 and 4.5 Hz, 2 H), and 3.92 (quartet, J = 7 Hz, 4 H).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.22; H, 7.56.

proximal-**1,4-Spiropentanedimethanol (18).**—To a suspension of 0.1 g (2.6 mmol) of lithium aluminum hydride in about 5 ml of dry ether was added 0.05 g (0.24 mmol) of **15**. After 1 hr of reflux, a freshly prepared, saturated solution of anhydrous sodium sulfate was added dropwise until a white precipitate was obtained. The solid was filtered from the ether solution and washed several times with tetrahydrofuran. The washings were combined with the original filtrate and the solvent was removed. After passing through a 5 ft × $^1/_4$ in. 20% SE-30 column at 130° twice, pure **18** was obtained: ir (CS_2) 3620, 3480, and 3260 (broad) cm^{-1}; ($CHCl_3$) 2950, 2915, 2870, 1430, 1360, 1310, 1210 (broad), and 1153 cm^{-1}; nmr (100 MHz) ($CDCl_3$) δ 0.72 (unsymmetrical triplet, J = 4.5 Hz, 2 H), 0.90 (doublet of doublets, J = 8 and 4 Hz, 2 H), 1.55 (symmetrical seven-line multiplet with 4-Hz separation between each line, 2 H), 3.42 doublet of doublets, J = 11 and 7.5 Hz, 2 H); 4.10 (doublet of doublets, J = 11 and 4 Hz, 2 H), and 4.50 (broad singlet, 2 H).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.40; H, 9.38.

medial-**1,4-Spiropentanedimethanol (19).**—Reduction of **16** by lithium aluminum hydride to give *medial*-1,4-spiropentanedimethanol (**19**) was accomplished in near-quantitative yield after vpc purification as described above for production of **18**: ir (CS_2) 3640 cm^{-1} (intermolecularly bonded hydroxyl absorption was not observed at the low concentration employed in this measurement, which was necessitated by the poor solubility of **19** in the solvent); ir ($CHCl_3$) 3610, 3360 (broad,) 1382, 1310, 1220 (broad), 1138, 1090, and 990 cm^{-1}; nmr (100 MHz) ($CDCl_3$) δ 0.60–1.06 (multiplet, 4 H), 1.10–1.60 (multiplet, 2 H), 2.63 (singlet, 2 H), and 3.64 (ten-line multiplet, 4 H).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.68; H, 9.40.

distal-**1,4-Spiropentanedimethanol (20).**—Reduction of **17** to *distal*-1,4-spiropentanedimethanol (**20**) was accomplished in good yield in the same manner as described above for reduction of **15** to give **18**: ir (CS_2) 3640 cm^{-1} (no other hydroxyl absorptions were observed at the low concentrations employed in this measurement owing to limited solubility of **20** in the solvent); ir ($CHCl_3$) 2948, 2910, 2868, 1430, 1358, 1310, and 1152 cm^{-1}; nmr (100 MHz) ($CDCl_3$) δ 0.62 (unsymmetrical triplet, J = 4.5 Hz, 2 H), 1.06 (doublet of doublets, J = 8.0 and 4.5 Hz, 2 H), 1.46 (doublet of quartets, J = 6.5 and 4.5 Hz, 2 H), 1.92 (singlet, 2 H), and 3.58 (doublet, J = 6.5 Hz, 4 H).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.71; H, 9.48.

distal-**1,4-Dimethylspiropentane (14).**—The diol **20** (0.37 g, 0.0029 mol) was dissolved in 0.1 ml of pyridine; the solution was cooled to 0° and added dropwise to a solution of 1.25 g (0.0066 mol) of *p*-toluenesulfonyl chloride dissolved in about 3 ml of pyridine also cooled to 0°. After stirring at 0° for 2.5 hr, the reaction mixture was taken up in ether and washed twice with 50-ml portions of ice-cold 5% hydrochloric acid, once with 50 ml of cold water, and once with saturated sodium bicarbonate solution. Drying over anhydrous magnesium sulfate and removal of the ether gave 0.91 g (71%) of a clear oil: nmr (60 MHz) ($CDCl_3$) 0.58 (triplet, J = 5 Hz, 2 H), 0.90–1.50 (multiplet, 4 H), 2.43 (singlet, 6 H), 3.95 (symmetrical five-line pattern with 6-Hz separation between lines, 4 H), 7.33 (unsymmetrical doublet, J = 8 Hz, 4 H), and 7.70 (unsymmetrical doublet, J = 8 Hz, 4 H).

This ditosylate (0.91 g, 0.021 mol) was dissolved in acetone, added to an acetone solution of 0.80 g (0.0053 mol) of sodium iodide, and refluxed for 1.5 hr. After this time the mixture was filtered, the acetone was distilled from the filtrate, and the residue was dissolved in ether. The ether solution was washed with saturated sodium sulfite and dried over anhydrous magnesium sulfate. Upon distillation of the ether at atmospheric pressure, there remained 0.65 g (89%) of a yellow oil: nmr (60 MHz) (CCl_4) δ 0.58 (triplet, 2 H), 1.13–2.13 (multiplet, 4 H), and 3.16 (doublet of doublets, 4 H).

This diiodide was added dropwise to a large excess of lithium aluminum hydride suspended in diethoxydiethylene glycol at 80° and 185 Torr. The hydrocarbon, *distal*-1,4-dimethylspiropentane (**32**), was trapped in a U tube cooled by liquid nitrogen; about 90 μl of material was obtained. The compound was purified by vpc using a 5 ft × $^1/_4$ in. 20% SE-30 column at room temperature and 25-ml/min helium flow rate (50–60 μl recovered): ir (CCl_4) 3045, 2987, 2946, 2863, etc., 1380, 1078, 1029, 999, 957, and 850 cm^{-1}; nmr (100 MHz) δ 0.22 (broad singlet with fine structure, 2 H) and 1.02 (doublet, J = 2 Hz) superimposed on a multiplet 0.74–1.12 (total of 10 H).

Anal. Calcd for C_7H_{12}: C, 87.42; H, 12.58. Found: C, 87.49; H, 12.60.

medial-**1,4-Dimethylspiropentane (13).**—*medial*-1,4-Dimethylspiropentane (**13**) was prepared from **19** in the same manner as described for production of **14** from **20**: ir (CCl_4) 3050, etc., 1378, 1305, 1089, 1045, 1030, 999, and 848 cm^{-1}; nmr (100 MHz) (CCl_4) δ 0.33 (unsymmetrical multiplet, 2 H) and 1.03 (broad doublet) superimposed on a multiplet between 0.70 and 1.14 (total of 10 H).

Anal. Calcd for C_7H_{12}: C, 87.42; H, 12.58. Found: C, 87.33; H, 12.54.

medial,syn-**4-Methyl-1-spiropentanemethanol (23).**—Reduction of **6** to *medial,syn*-4-methyl-1-spiropentane-methanol (**23**) was accomplished as described above for reduction of **17** to **20**: ir of (CCl_4) 3614, 3350 (broad), 3050, etc., 1380, and 1055 cm^{-1}; nmr (100 MHz) (CCl_4) δ 0.30 (unsymmetrical triplet, J = 3.5 Hz), 0.48 (unsymmetrical triplet, J = 4 Hz, 1 H), 1.00 (doublet, J = 2 Hz) superimposed on a multiplet from 0.70 to 1.40 (total of 7 H), 2.56 (broad singlet, 1 H), and 3.39 (doublet, J = 7 Hz, 2 H).

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.79. Found: C, 75.05; H, 10.75.

medial-**1,4-Dimethylspiropentane (13) from 23.**—The alcohol **23** was converted to *medial*-1,4-dimethylspiropentane (**13**) in the same manner as described for conversion of **20** to **14**. The spectral properties and vpc retention time on a 250-ft UCON 50-HB2000 capillary column of vpc purified hydrocarbon were identical with those of the hydrocarbon prepared from **19**.

proximal-**4-Methyl-1-spiropentanemethanol (21).**—Reduction of **4** to *proximal*-4-methyl-1-spiropentane-methanol (**21**) was accomplished as described above for reduction of **17** to **20**: ir (CCl_4) 3614, 3360 (broad), 3050, etc., 1377, and 995 cm^{-1}; nmr (100 MHz) (CCl_4) δ 0.35 (broad singlet, 1 H), 0.53 (unsymmetrical triplet, J = 4.5 Hz, 1 H), 0.82 (doublet of doublets, J = 7 and 4 Hz, 2 H), 1.08 (doublet, J = 1.5 Hz, 4 H), 1.40 (multiplet, 1 H), 2.30 (broad singlet, 1 H), 3.31 (unsymmetrical triplet with 7-Hz separation between lines, 1 H), and 3.63 (broad singlet, 1 H).

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.79. Found: C, 75.06; H, 11.04.

proximal-**1,4-Dimethylspiropentane (12).**—The alcohol **21** was converted to *proximal*-1,4-dimethylspiropentane (**12**) in the same manner as described for conversion of **20** to **14** ir of vpc-purified **12** (CCl_4) 3050, 1505, 1381, 1373, 1183, 1093, 1043, 998, and 850 cm^{-1}; nmr (100 MHz) (CCl_4) δ 0.33 (broad singlet, 2 H), 0.80 (broad singlet, 2 H), and 1.00–1.10 (doublet, J = 1 Hz, superimposed on a multiplet, total of 8 H). The capillary vpc retention time of this material was similar to but not the same as that of **13** or of **14**. Because of the limited amounts of starting material and losses on vpc purification, it was not possible to obtain an elemental analysis of this hydrocarbon.

medial,anti-**4-Methyl-1-spiropentanemethanol (22).**—Reduction of **3** to *medial,anti*-4-methyl-1-spiropentanemethanol (**22**) was accomplished as described above for reduction of **17** to **20**: ir (CCl_4) 3618, 3400 (broad), 3053, etc., 1379, and 999 cm^{-1}; nmr (100 MHz) (CCl_4) δ 0.38 (broad singlet, 1 H), 0.59 (unsymmetrical triplet, J = 3.5 Hz, 1 H), 1.01 (broad singlet) superimposed on a multiplet between 0.77 and 1.39 (total of 7 H), 1.99 (broad singlet, 1 H), and 3.47 (doublet, J = 7 Hz, 2 H).

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.79. Found: C, 74.90; H, 10.71.

medial-**1,4-Dimethylspiropentane (13) from 22.**—The alcohol **22** was converted to *medial*-1,4-dimethylspiropentane (**13**) in the

same manner as described for conversion of **20** to **14**. The spectral and vpc retention time on a 250-ft UCON 50HB2000 capillary column of vpc-purified material were identical with those of the hydrocarbon prepared from **19**.

distal-**4-Methyl-1-spiropentanemethanol** (**24**).—Reduction of **5** to *distal*-4-methyl-1-spiropentanemethanol (**24**) was accomplished as described above for reduction of **17** to **20**: ir (CCl_4) 3620, 3370 (broad), 3050, etc., 1380, and 1022 cm^{-1}; nmr (100 MHz) (CCl_4) δ 0.23 (broad singlet, 1 H), 0.44 (unsymmetrical triplet, 1 H), 1.01 (broad singlet) superimposed on a multiplet between 0.75 and 1.44 (total of 7 H), 2.53 (broad singlet, 1 H), and 3.40 (doublet, J = 7 Hz 2 H).

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.79. Found: C, 74.84; H, 10.61.

distal-**1,4-Dimethylspiropentane** (**14**) **from 24**.—The alcohol **24** was converted to *distal*-1,4-dimethylspiropentane (**14**) in the same manner as described for conversion of **20** to **14**. The spectral properties and vpc retention time on a 250-ft UCON 50-HB2000 capillary column of vpc purified hydrocarbon were identical with those of the hydrocarbon prepared from **30**.

Registry No.—**3**, 24298-73-5; **4**, 24298-74-6; **5**, 24298-75-7; **6**, 24299-28-3; **7**, 6142-68-3; **8**, 24299-29-4; **9**, 24299-30-1; **10**, 24299-31-8; **11**, 24299-32-9; **12**, 24299-33-0; **13**, *medial*, 24299-34-1; **14**, 24299-35-2; **15**, 24299-36-3; **16**, 24299-37-4; **17a**, 24375-89-1; **18**, 24299-39-6; **19**, 24299-40-9; **20**, 24343-79-1; **21**, 24299-41-0; **22**, 24299-42-1; **23**, 24343-80-4; **24**, 24299-43-2.

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The *ortho* Claisen Rearrangement. VIII. Solvent Effects[1,2]

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The rates of rearrangement of allyl *p*-tolyl ether in the gas phase and in 17 solvents of different polarities have been determined. The rates varied over a 300-fold range, indicating a considerable solvent effect. The normal rearrangement product was formed in every case. The results cannot be explained solely on the basis of the hydrogen-bonding ability of the solvent and it is necessary to invoke other solvent properties to account for the findings.

The Claisen rearrangement has often been cited as a reaction insensitive to solvent effects, in spite of the fact that early studies[3] indicated that this was probably not so. A couple of more recent investigations[1a,4] have also indicated that the reaction is influenced by the nature of the medium. A more complete evaluation of solvent effects and their origin was attempted in this investigation.

Results

The rates of rearrangement of allyl *p*-tolyl ether in the gas phase and in 17 solvents of differing polarities were determined. The specific rate constant was measured in one of three different ways, depending on the nature of the solvent. If the solvent had negligible absorption in the ultraviolet–visible range, aliquots of the reaction mixture were dissolved in aqueous or alcoholic base and the formation of product was followed through the absorption of the 2-allyl-4-methylphenoxide ion. The reaction in solvents that have significant absorption in the ultraviolet–visible region was monitored by observing the change in a band at 12.91 μ that appears in the infrared spectrum of allyl *p*-tolyl ether. In the gas phase runs, samples of the ether were sealed in evacuated tubes and thermostated for various intervals. The sample size was such that all of the reactant and/or product was in the gas phase at the reaction temperature. The extent of reaction was determined from the ultraviolet spectrum of a solution of the partially reacted sample in alcoholic sodium hydroxide solution. The absence of a wall effect in the gas phase reaction was obvious from the constancy of per cent reaction in normal tubes and in tubes packed with glass wool. The rate constants obtained by these methods are listed in Table I. These values were used to obtain rate constants at 170° by extrapolation or interpolation (Table II).

The reaction product in all of the solvents was shown to be 2-allyl-4-methylphenol by isotope dilution analysis. A solution of allyl-C^{14} *p*-tolyl ether in the solvent under study was rearranged; *n*-2-allyl-4-methylphenol was mixed in and then was converted into the 3,5-dinitrobenzoate for isolation and purification. The per cent yield of 2-allyl-4-methylphenol was calculated from the specific activity of the purified product. The yields in the various solvents are shown in Table III. The expected product, 2-allyl-4-methylphenol, was formed in greater than 80% yields in all of the solvents except 2-aminoethanol, 2-octanol, propylene carbonate, sulfolane, and *p*-chlorophenol. Because of the possibility for decomposition of the product during the long reaction period, the rearrangement in these five solvents was carried out for a shorter period. In all cases, the yields were improved indicating that the product was being destroyed by prolonged heating.

Discussion

As is evident from the data listed in Table II, the rate of the *ortho* Claisen rearrangement is significantly

(1) Previous papers in this series: (a) W. N. White, D. Gwynn, R. Schlitt, C. Girard, and W. K. Fife, *J. Amer. Chem. Soc.*, **80**, 3271 (1958); (b) W. N. White and B. E. Norcross, *ibid.*, **83**, 1968 (1961); (c) W. N. White and B. E. Norcross, *ibid.*, **83**, 3265 (1961); (d) W. N. White and W. K. Fife, *ibid.*, **83**, 3846 (1961); (e) W. N. White and C. D. Slater, *J. Org. Chem.*, **26**, 3631 (1961); (f) W. N. White and C. D. Slater, *ibid.*, **27**, 2908 (1962); (g) W. N. White and E. F. Wolfarth, *ibid.*, **26**, 3509 (1961); (h) W. N. White, C. D. Slater, and W. K. Fife, *ibid.*, **26**, 627 (1961).

(2) This investigation was supported by Grants G-7345 and GP-1970 from the National Science Foundation.

(3) J. F. Kincaid and D. S. Tarbell, *J. Amer. Chem. Soc.*, **61**, 3085 (1939), found that the rate of rearrangement of allyl *p*-tolyl ether in the absence of solvent increased about fourfold as the reaction progressed implying that the reaction occurred faster in the phenolic product than in the original ether.

(4) H. L. Goering and R. R. Jacobsen, *ibid.*, **80**, 3277 (1958).

TABLE I

REARRANGEMENT RATES OF ALLYL *p*-TOLYL ETHER IN VARIOUS SOLVENTS

Solvent	Method[a]	T,[b] °C	$10^5 k$ (sec^{-1})	Solvent	Method[a]	T,[b] °C	$10^5 k$ (sec^{-1})
Gas phase	A	185.3	0.309	1-Decanol	B	160.3	0.501 ± 0.003
		199.7	1.63			180.3	2.41 ± 0.01
		217.3	5.96			199.7	9.48 ± 0.03
		231.9	12.2				
Tetradecane	B	160.3	0.123 ± 0.002	$Et(OCH_2CH_2)_2OH$	B	160.3	0.784 ± 0.004
		180.3	0.728 ± 0.002			180.3	3.94 ± 0.05
		199.7	3.30 ± 0.02			199.7	15.7 ± 0.7
$(n\text{-}C_4H_9)_2O$	B	170.3	3.27 ± 0.2	$n\text{-}C_7H_{15}COOH$	B	170.3	24.2 ± 0.3
$n\text{-}C_{10}H_{21}NH_2$	B	160.3	0.187 ± 0.001	$HOCH_2CH_2NH_2$	B	160.3	1.22 ± 0.01
		180.3	1.05 ± 0.01			180.3	5.79 ± 0.03
		199.7	4.64 ± 0.01			199.7	24.2 ± 0.3
$(EtOCH_2CH_2)_2O$	B	170.3	5.33 ± 0.4	$HOCH_2CH_2OH$	B	155.3	2.06 ± 0.02
						170.3	6.73 ± 0.15
						185.3	20.4 ± 0.1
Propylene carbonate	B	160.3	0.392 ± 0.008	$p\text{-}MeC_6H_4OH$	C	150.3	1.90
		180.3	2.18 ± 0.06			170.3	7.31
		199.7	8.59 ± 0.14			190.3	21.6
2-Octanol	B	160.3	0.411 ± 0.003	C_6H_5OH	C	150.3	2.42
		180.3	2.18 ± 0.05			165.3	7.11
		199.7	8.15 ± 0.04			180.3	20.4
$NC(CH_2)_4CN$	B	160.3	0.436 ± 0.003	28.5% EtOH-H_2O	B	148.7	2.23 ± 0.01
		180.3	2.42 ± 0.01			159.7	5.13 ± 0.03
		199.7	10.4 ± 0.3			170.3	10.7 ± 0.3
Sulfolane[c]	B	160.3	0.459 ± 0.002	$p\text{-}ClC_6H_4OH$	C	148.2	7.47
		180.3	2.36 ± 0.02			158.8	13.2
		199.7	11.0 ± 0.1			170.3	30.3

[a] Method A—gas phase, ultraviolet spectrophotometric analysis; method B—solution, ultraviolet spectrophotometric analysis; method C—solution, infrared spectrophotometric analysis. [b] Temperature maintained to within ±0.1°. [c] Tetramethylene sulfone.

TABLE II

RATE CONSTANTS AND ACTIVATION PARAMETERS FOR REARRANGEMENT OF ALLYL *p*-TOLYL ETHER IN VARIOUS SOLVENTS

Solvent	$10^5 k$ (sec^{-1})[a]	$\Delta H^{\ddagger}$[b,g]	$\Delta S^{\ddagger}$[c,g]	Z
Gas phase	1.01	35.1	− 7.7	
Tetradecane	3.01	33.1	− 9.8	60.1
n-Butyl ether	3.27			60.1
n-Decylamine	4.52	32.4	−10.7	
Ethylcarbitol[d]	5.33			65.2
Propylene carbonate	9.42	31.0	−12.4	72.4
2-Octanol	9.65	29.3	−16.2	78.6
Adiponitrile	10.5	32.0	−10.0	70.7
Sulfolane[e]	10.7	32.0	− 9.8	76.9
1-Decanol	11.1	29.6	−15.2	78.0
Carbitol[f]	17.9	30.1	−13.1	78.1
Octanoic acid	24.2			77.6
2-Aminoethanol	27.1	30.1	−12.2	84.4
Ethylene glycol	67.3	28.9	−13.1	85.1
p-Cresol	73.1	22.9	−26.6	88.8
Phenol	103	26.3	−18.2	
28.5% ethanol-water	107	26.2	−18.5	91.9
p-Chlorophenol	303	22.9	−23.8	

[a] Rate constants at 170°. [b] In kcal/mol. [c] cal/deg mol. [d] $EtOCH_2CH_2OCH_2CH_2OEt$. [e] Tetramethylene sulfone. [f] $EtOCH_2CH_2OCH_2CH_2OH$. [g] The average error of $\Delta H^{\ddagger}$ is ±0.2 kcal/mol and that of $\Delta S^{\ddagger}$ is ±0.3 eu (calculated by the procedure of E. L. Purlee, R. W. Taft, Jr., and C. A. DeFazio, *J. Amer. Chem. Soc.*, **77**, 837 (1955)].

TABLE III

YIELDS OF 2-ALLYL-4-METHYLPHENOL FROM REARRANGEMENT OF ALLYL *p*-TOLYL ETHER IN VARIOUS SOLVENTS

Solvent	Reaction time, half-lives	% yield
Ethylene glycol	10	101
2-Aminoethanol	10	17
	2	58[b]
Carbitol[a]	10	91
1-Decanol	10	94
2-Oetanol	10	81
n-Decylamine	10	77
Adiponitrile	10	95
Propylene carbonate	10	25
	2	87[b]
Sulfolane[c]	10	55
	2	81[b]
Tetradecane	10	90
Octanoic acid	10	86
Ethylcarbitol[d]	10	92
n-Butyl ether	10	94
28.5% ethanol–water	10	93
p-Chlorophenol	10	5
	2	68[b]
Phenol	10	86
p-Cresol	10	88
Gas phase	10	96

[a] $EtOCH_2CH_2OCH_2CH_2OH$. [b] Based on an expected 75% yield. [c] Tetramethylene sulfone. [d] $EtOCH_2CH_2OCH_2CH_2OET$.

affected by the nature of the solvent. The rate was found to vary by a factor of 100 in going from the least polar to the most polar solvent studied, and a factor of 300 in going from the gas phase to the most polar solvent. It is interesting to compare these rate factors with those observed in well-established polar reactions. One of the few reactions of this type which has been carried out in both polar and nonpolar solvents is the Menschutkin reaction. The rate of formation of tetraethylammonium iodide from ethyl iodide and triethylamine at 100° is very solvent sensitive; the rate in methanol is 290 times as great as that in hexane[5]

(5) N. Menschutkin, *Z. Phys. Chem.* (Leipzig), **6**, 41 (1890).

and the difference in rates in nitrobenzene and in hexane[6] is even greater, 2800-fold. On the other hand, the solvent effects in the reaction between pyridine and methyl iodide are much smaller; the reaction is only 5.4 times faster in 56% ethanol–water than in benzene[7] and 25 times as fast in nitrobenzene as in benzene.[7]

A cursory examination of the data of Table II leaves the impression that hydrogen bonding between the solvent and substrate or acid catalysis may influence the rate of the Claisen rearrangement. Thus, the solvents in which the reaction was fastest are hydroxylic while those in which it was slowest are, in general, nonhydroxylic. Furthermore, the phenols, which are actually weak acids, were about the most accelerative (with *p*-chlorophenol, the strongest acid of the three phenols, showing this effect the most and *p*-cresol, the least acidic, showing it the least).

However, closer scrutiny of the data shows several inconsistencies in this interpretation. For one thing, the rate effects of the solvents do not fall in exactly the order expected from their room-temperature acid dissociation constants. Thus, the rate in octanoic acid was 2.8 times slower than in *p*-chlorophenol. Likewise, aqueous ethanol promoted the reaction to about the same extent as phenol. Furthermore, the reaction was as fast in some nonhydroxylic solvents as in certain hydroxylic ones (compare propylene carbonate, adiponitrile, and tetramethylene sulfone with 2-octanol and 1-decanol). Clearly, factors other than hydrogen bonding must be involved in solvent effects on the Claisen rearrangement.

This conclusion is reinforced by the existence of a good correlation ($r = 0.97$) between the $\Delta H^{\pm}$'s and $\Delta S^{\pm}$'s for the rearrangement in different solvents. Such an isokinetic correlation has been assumed to imply that there is no change in mechanism on passing from one system to another. Thus, the same mechanism must be operating in each solvent studied. This would tend to rule out the operation of any special effects (*e.g.*, hydrogen bonding, acid catalysis, etc.) that might be associated with some solvents but not with others.

One feature generally associated with hydroxylic solvents that might be the cause of their effectiveness in facilitating the Claisen rearrangement is their high polarity. Solvent polarity is a rather nebulous term depending as it does on many different solvent properties (dipole moment, polarizability, hydrogen-bonding ability, etc.). The best definitions of solvent polarity are empirical. Kosower[8] has established a measure of solvent polarity based on the charge-transfer absorption maxima of 1-ethyl-4-carbomethoxypyridinium iodide in various solvents. Absorption wave-lengths were converted to their equivalents in kilocalories/mole and designated as solvent polarity or Z factors.

The qualitative parallelism of the rates of the Claisen rearrangement in several solvents with the polarities of the solvents suggested that a correlation of the rates might be obtained by use of the empirical Z factors.[8] The following equation was obtained

$$Z = 15.93(\log k + 6) + 58.79$$

($r = 0.892$, $s = 13.93$). Three of the solvents in which rates were determined are not included in this correlation because their Z values could not be ascertained (*n*-decylamine reacted with the pyridinium iodide and phenol and *p*-chlorophenol absorbed in the charge-transfer region). It is evident that the fit is not perfect. However, it appears to be about as good as the correlations of the rates of iodide-ion exchange, of the rates of the Menschutkin reaction (pyridine and methyl iodide), and of the rates of solvolysis of *t*-butyl chloride; all cases cited and treated by Kosower[8] in support of the usefulness of Z values. Thus, there is a reasonably good correlation between the Z values and the rates of rearrangement of allyl *p*-tolyl ether in different solvents. It should be noted that, while the rates were determined at 170°, the Z values for each solvent were measured at 25°. In an attempt to measure Z as a function of temperature, it was observed that the 1-ethyl-4-carbomethoxypyridinium iodide decomposed below 70°.

Since the Z value of a solvent is a measure of the interaction between a dipolar ion pair and the solvent, the correlation between the Z values and the rates of rearrangement suggests that a dipolar or charge-separated transition state must also be formed during the Claisen rearrangement. Such an activated complex has been previously proposed.[1d,f,h]

In conclusion, the sensitivity of the rate of rearrangement of allyl *p*-tolyl ether to the nature of the reaction medium can be attributed either to the hydrogen-bonding abilities or to the polar character of the solvent.[9] Both of these interpretations leave much to be desired, but correlation in terms of solvent polarities seems to involve the fewest inconsistencies.

Experimental Section

Preparation of Allyl *p*-Tolyl Ether.—This compound, bp 90.0–90.5° at 12 mm (lit.[6] bp 97.5–98.5° at 17 mm), was prepared as previously described[1a] with one minor modification. Before final distillation, the ether was chromatographed on a 15 × 120 mm column of activity grade I alumina using Skellysolve B as eluent. The solvent was then removed and the residue distilled.

Purification of Solvents.—All of the solvents except the ethanol–water mixture were commercially available. They were purified by slow distillation through a 45-cm Vigreux column. A centercut with a boiling range of a degree of less was selected for the kinetic work.

The ethanol–water mixture was prepared by pipetting 30 ml of grain alcohol into a 100-ml volumetric flask and diluting to volume with distilled water to give a 28.5% ethanol–water mixture.

Kinetic Measurements. Method B (Nonaromatic Solvents).—The spectrophotometric procedure outlined in a previous paper[1a] was employed with those reaction solvents which had negligible light absorption in the visible and ultraviolet region.

Method A (Gas Phase).—About 15 mg of allyl *p*-tolyl ether was placed in a 25-ml Pyrex test tube and frozen. The tube was evacuated to 0.4–0.9 mm, and sealed off. At the reaction temperature, this amount of ether would be completely in the gas phase at a pressure of 95–105 mm. The tubes were immersed in in a constant-temperature bath for varying intervals and then removed and cooled. The contents of the sample tube were dissolved in a measured quantity of alcoholic sodium hydroxide solution and the absorbance of the resulting solution was determined at 278 mμ (allyl *p*-tolyl ether) and 301 mμ (2-allyl-4-methylphenoxide ion). The concentration of each of these substances was obtained by solution of a set of simultaneous equations.

(6) H. G. Grimm, H. Ruf, and H. Wolff, *Z. Phys. Chem.* (Liepzig), **B18**, 301 (1931).

(7) R. A. Fairclough and C. N. Hinshelwood, *J. Chem. Soc.*, 538 (1937); K. J. Laidler and C. N. Hinshelwood, *ibid.*, 858 (1938).

(8) E. M. Kosower, *J. Amer. Chem. Soc.*, **80**, 3253, 3261, 3267 (1958).

(9) Referee I suggests that a multiparameter equation may fit the data better than a single parameter correlation.

Method C (Aromatic Solvents).—Approximately 3-g aliquots of a 10–20% solution of allyl *p*-tolyl ether in the aromatic solvent were sealed in test tubes, and the tubes were thermostated for various periods of time. The tube was then weighed and the contents were quantitatively transferred to a volumetric flask and diluted with carbon disulfide to give a solution with an easily measurable absorbance at 12.91 μ. The empty tube was weighed and the sample size was obtained by difference. The absorbance values were normalized, using the sample weight, to eliminate variations due to sample size. The absorbance at infinite time was available from the known concentrations of the solutions and the extinction coefficients of the solvent and 2-allyl-4-methylphenol at 12.91 μ. Plots of log $(D_\infty - D_t)$ *vs.* t were excellent straight lines.

Preparation of Allyl-^{14}C *p*-Tolyl Ether.—In a small distillation flask equipped with an efficient magnetic stirrer were placed 0.605 g (0.1 mC: 10.5 mmol) of allyl-1-^{14}C alcohol and 1.40 g (24.2 mmol) of ordinary allyl alcohol (a total of 34.7 mmol of allyl alcohol). After the addition of 8.0 ml (69.0 mmol) of 48% hydrobromic acid, the mixture was warmed to 70°. Then 3.8 ml (69.0 mmol) of concentrated sulfuric acid was added over a period of 20 min, and the product was allowed to distil as it was formed. The distillate was collected in a receiver immersed in an ice bath and containing 3 g of solid potassium carbonate. There was obtained 3.15 g (75%) of allyl-^{14}C bromide.

To the flask containing the allyl-^{14}C bromide were added an additional 4 g of potassium carbonate, 5.6 g (52.0 mmol) of *p*-cresol, and 30 ml of dry acetone. The slurry was stirred and refluxed for 24 hr. After cooling, 30 ml of water was added, and the mixture was extracted twice with 60-ml portions of ether. The combined ether extracts were washed twice with 20-ml portions of 10% sodium hydroxide solution and once with 20 ml of brine and then dried over magnesium sulfate. The ether was removed and the residue was taken up in a small volume of Skellysolve B and chromatographed on a 15 × 120 mm column of Woelm activity grade I alumina, using Skellysolve B as eluent. After evaporation of the solvent, the residue was distilled, giving 3.37 g (88%) of allyl-^{14}C *p*-tolyl ether, bp 89–91° at 12 mm (lit.[1a] bp 97.5–98.5° at 17 mm), or a 66% overall yield based on allyl alcohol.

Preparation of 2-Allyl-4-methylphenyl 3,5-Dinitrobenzoate.—Using the procedure of Phillips and Kennan,[10] crude 2-allyl-4-methylphenyl 3,5-dinitrobenzoate was prepared. The air-dried solid was taken up in a small volume of 10% ether–benzene and chromatographed on a 15 × 125 mm column of activity grade I alumina, using the same solvent as eluent. After evaporation of the solvent, the residue was recrystallized three times from 1:1 benzene–Skellysolve B and three times from 1:1 chloroform–Skellysolve B. Colorless needles of 2-allyl-4-methylphenyl 3,5-dinitrobenzoate, mp 141.2–142.4°, were obtained.

Anal. Calcd for $C_{17}H_{14}N_2O_6$: C, 59.65; H, 4.12; N, 8.18. Found: C, 59.88; H, 4.12; N, 7.93.

Identification of Reaction Product and Determination of Yield.—An accurately weighed sample of 25–50 mg of allyl-^{14}C *p*-tolyl ether was dissolved in 0.5–3.2 g of solvent and sealed in a small test tube. The tube was thermostated for a period of either two or ten half-lives. The contents of the tube were then quantitatively rinsed with 30 ml of 10% sodium hydroxide solution into a flask containing a carefully weighed sample (1.2–1.8 g) of normal 2-allyl-4-methylphenol. The resulting mixture was thoroughly stirred, acidified with hydrochloric acid, and extracted with 30 ml of ether. The solution was dried over magnesium sulfate and then evaporated. The residue was taken up in 20 ml of pyridine and the 3,5-dinitrobenzoate was prepared and purified as described directly above. The melting point and mixture melting point showed the material was 2-allyl-4-methylphenyl 3,5-dinitrobenzoate.

The specific activities of the samples were obtained by converting the samples to carbon dioxide which was collected in an ionization chamber and analyzed for activity with a vibrating reed electrometer.[11]

The activity of the orginal allyl-^{14}C *p*-tolyl ether was obtained by converting it to 2-allyl-4-methylphenyl 3,5-dinitrobenzoate after dilution with the normal ether.

Registry No.—Allyl *p*-tolyl ether, 23431-48-3; 2-allyl-4-methylphenyl 3,5-dinitrobenzoate, 24454-16-8.

(10) M. Phillips and G. L. Keenan, *J. Amer. Chem. Soc.*, **53**, 1926 (1931).
(11) O. K. Neville, *ibid.*, **70**, 3501 (1958); V. F. Raaen and G. A. Ropp, *Anal. Chem.*, **25**, 174 (1953).

Kinetics of the Condensation of 2-Picoline with Aromatic Aldehydes in Acetic Anhydride[1]

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Condensation of 2-picoline with *p*-nitrobenzaldehyde to give *trans*-2-(4′-nitrostyryl)pyridine has been studied kinetically in acetic anhydride, acetic acid, or N,N-dimethylformamide as solvent. The rate in acetic anhydride is shown by the third-order equation $v = k_3$[2-picoline][*p*-nitrobenzaldehyde][acetic acid], where k_3 is 2.4×10^{-5} M^{-2} sec^{-1} at 135°. Acetic acid is formed in the reaction in acetic anhydride and acts as a catalyst. The catalytic ability of carboxylic acids increases with increasing acidity of the acid, the order being as follows: $CH_3CO_2H <$ $PhCO_2H <$ $ClCH_2CO_2H$. The intermediate alcohol, 1-(4′-nitrophenyl)-2-(α-pyridyl)ethanol (1), was obtained from the reaction in N,N-dimethylformamide or dimethyl sulfoxide in the presence of acetic acid. Dehydration of 1 occurs readily both in acetic acid and in acetic anhydride; the rate of dehydration in N,N-dimethylformamide with acetic anhydride is higher than that with acetic acid. Therefore, dehydration of 1 may proceed *via* the acetate, followed by the elimination of acetic acid. Only a little olefin and intermediate alcohol were obtained in the reaction of 2-picoline with benzaldehyde in the presence of basic catalyst such as potassium hydroxide, tributylamine, or potassium acetate by refluxing for 100 hr. The results are explicable by a mechanism involving rate-determining addition of 2-picoline to aromatic aldehyde, where acetic acid acts as an acid catalyst.

The condensation of 2- or 4-picoline with benzaldehyde to give styrylpyridine is satisfactory *via* ethyl pyridylacetate, picoline methiodide, or its N-oxide with basic catalysts,[2] but with picoline itself no basic condensation has been reported, though 2- and 4-picolines are convertible to their conjugate bases by the action of ordinary bases.[3] On the other hand, the condensation of picoline with benzaldehyde is successful

(1) Contribution No. 144.
(2) (a) D. R. Bragg and D. G. Wiberly, *J. Chem. Soc.*, 5074 (1961); (b) L. Pentimalli, *Tetrahedron*, **14**, 151 (1961); (c) H. C. Beyerman, J. Enshnistra, E. Eveleens, and A. Zweistra, *Rec. Trav. Chim. Pays-Bas*, **78**, 43 (1959); (d) K. Raniaiah and V. R. Srinivasan, *Indian J. Chem.*, **1**, 351 (1963); [*Chem. Abstr.*, **60**, 500g (1963)]; (e) A. P. Phillips, *J. Org. Chem.*, **12**, 333 (1947).
(3) (a) D. A. Brown and M. J. S. Dewar, *J. Chem. Soc.*, 2406 (1953); (b) H. C. Longuet-Higgins, *Proc. Roy. Soc., Ser., A*, **207**, 121 (1951); (c) J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin Inc., New York, N. Y., 1964, p 1003; (d) L. A. Daquette, "Principles of Modern Heterocyclic Chemistry," W. A. Benjamin Inc., New York, N. Y., 1968 pp 245, 293.

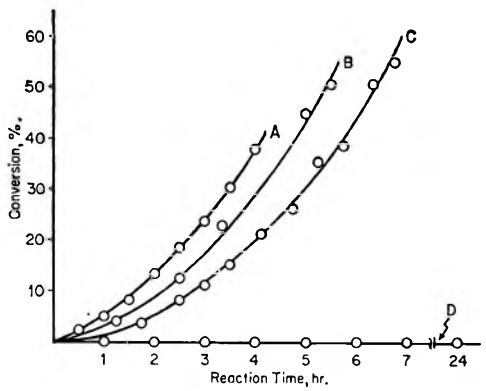


Figure 1.—Effect of acetic anhydride on the condensation of 2-picoline with *p*-nitrobenzaldehyde at 135° in xylene. Initial concentration: *p*-nitrobenzaldehyde, 0.779 *M*; 2-picoline, 2.381 *M*; acetic anhydride, (A) 4.613 *M*, (B) 2.307 *M*, (C) 0.923 *M*, (D) 0 *M*.

by using acetic anhydride as a solvent[4] or zinc chloride as a catalyst.[4a,5] Isolation of 1-phenyl-2-(α-pyridyl)-ethanol as an intermediate has been reported.[4a] The present paper is a summary of our data of kinetic studies on the condensation of 2-picoline with *p*-nitrobenzaldehyde together with the effect of acetic anhydride and carboxylic acids to enable the mechanistic speculation.

Results and Discussion

The condensation of 2-picoline with benzaldehyde gave 2-styrylpyridine by refluxing a mixture in acetic anhydride at 140°. The rate is too slow for the convenient measurement (10% in 30 hr). The rate with *p*-nitrobenzaldehyde is much faster than with benzaldehyde; this acceleration with an electron-withdrawing substituent in benzaldehyde, which has been observed also by Shaw[4a] and Williams,[4b] agrees with a positive Hammett constant ($\rho = +1.2$) for the zinc chloride catalyzed condensation in dimethyl sulfoxide.[6] The product was identified by melting point and uv and ir spectra as *trans*-2-(4′-nitrostyryl)pyridine. No appreciable amount of *p*-nitrobenzaldiacetate could be isolated, but the diacetate was formed on the addition of sulfuric acid, as will be stated later. In the absence of acetic anhydride or acetic acid the condensation failed. 2-(4′-Nitrostyryl)pyridine in a methanolic solution (10^{-5} *M*) showed rapid *trans–cis* photoisomerization (λ_{max} 338 mμ → 323 mμ for 6 hr), which was avoided by interception of a diluted sample solution from light until the uv measurement (see Experimental Section).

Rate Law.—The reaction in acetic anhydride shows a S-shaped conversion curve, suggesting an autocatalysis. An apparent induction period is 1–2 hr as shown in Figure 1. In xylene as a solvent, the rate increased with an increasing amount of added acetic anhydride without disappearance of the apparent induction period. On addition of acetic acid the rate of reaction in acetic anhydride increased with increasing initial concentration of acetic acid and the apparent induction period is shortened. As a limiting case, the reaction in neat acetic acid solvent showed no induction. The reaction follows third-order kinetics, where k_3 is 2.4 × 10^{-5} M^{-2} sec^{-1} at 135°. Here, *a*, *b*, and *c* are initial

$$dx/dt = k_3 (a - x)(b - x)(c + 2x) \quad (1)$$

concentrations of *p*-nitrobenzaldehyde, 2-picoline, and acetic acid, respectively, and *x* is the concentration of formed 2-(4′-nitrostyryl)pyridine at time *t*. The kinetic data are shown in Table I.

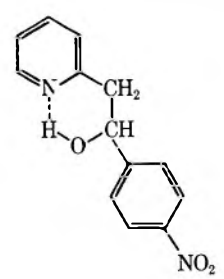
TABLE I

THIRD-ORDER RATE CONSTANT, k_3, FOR THE REACTION OF 2-PICOLINE WITH *p*-NITROBENZALDEHYDE IN ACETIC ANHYDRIDE AT 135°

Initial concentration, *M*			Rate constant, M^{-2} sec^{-1},
p-Nitrobenzaldehyde	2-Picoline	Acetic acid	$10^5 k_3$
0.779	2.381	0	2.4
0.779	2.381	0.515	2.8
0.779	2.381	0.773	2.5
0.779	2.381	1.030	2.4
0.779	2.381	1.803	1.9
1.177	1.177	0.585	2.3
		Average	2.4

The results indicate a catalysis by acetic acid. Even without addition of acetic acid, the reaction is started by a trace of acetic acid which is contained in the original system. The reaction in acetic anhydride should produce 2 molar equiv of acetic acid, and so the rate tends to increase gradually as the reaction proceeds. An alternative possibility that styrylpyridine should promote the reaction as a basic catalyst is excluded, because the basicity of styrylpyridine is lower than that of 2-picoline and because the kinetics is only first order in 2-picoline.

Intermediates.—The following facts present evidence that 1-(4′-nitrophenyl)-2-(α-pyridyl)ethanol (**1**) is an intermediate and that acetic acid and anhydride act as dehydrating agents. Heating a mixture of 2-picoline and *p*-nitrobenzaldehyde in N,N-dimethylformamide or dimethyl sulfoxide in the presence of acetic acid gave **1** (18%) but not 2-(4′-nitrostyryl)pyridine. Its uv spectrum shows a resemblance to that of 2-picoline. A broad OH band at 3100 cm^{-1} in its ir spectrum suggests a chelation as shown in **1**. 1-(4′-Nitrophenyl)-2-(α-pyridyl)ethanol (**1**) was converted readily to 2-(4′-nitrostyryl)pyridine (64 and 58% at 2 hr by heating at 115° in acetic acid and acetic anhydride, respectively), but neither *p*-nitrobenzaldehyde nor 2-picoline was obtained. This is evidence that **1** is an intermediate. It has been reported that **1** is a main product at 130–



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(4) (a) B. S. Shaw and E. A. Wagstaff, *J. Chem. Soc.*, 77 (1933); (b) J. L. Williams, R. E. Adel, J. M. Carlson, G. A. Reynolds, D. G. Borden, and J. A. Ford, Jr., *J. Org. Chem.*, **28**, 387 (1963); (c) W. Baker, K. M. Buggle, J. F. W. McOmie, and D. A. M. Watkins, *J. Chem. Soc.*, 3594 (1958); (d) R. Royer, *ibid.*, 1803 (1949).

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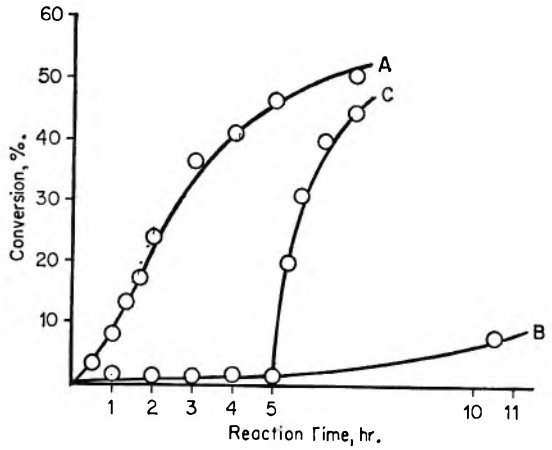


Figure 2.—Conversion curves for the reaction of 2-picoline with *p*-nitrobenzaldehyde at 135° in N,N-dimethylformamide in the presence of (A) 1.730 *M* of acetic anhydride; (B) 1.030 *M* of acetic acid; (C) 1.030 *M* of acetic acid at first and on further addition of 1.730 *M* of acetic anhydride after 5 hr. Initial concentration: *p*-nitrobenzaldehyde, 0.779 *M*; 2-picoline, 2.381 *M*.

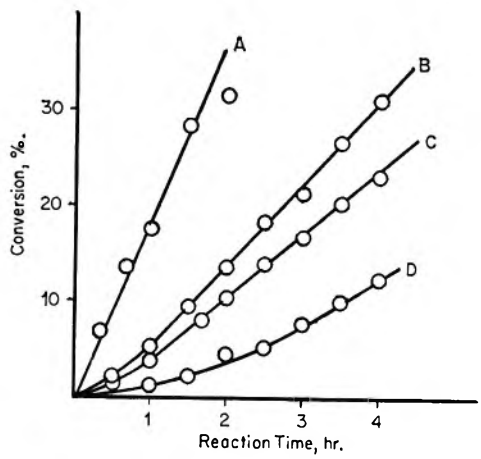


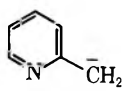
Figure 3.—Effect of carboxylic acids on the conversion of 2-picoline to 2-styrylpyridine in acetic anhydride at 135°. Initial concentration: carboxylic acid, 0.585 *M*; *p*-nitrobenzaldehyde, 1.177 *M*; 2-picoline, 1.177 *M*, (A) $ClCH_2CO_2H$, (B) $PhCO_2H$, (C) CH_3CO_2H, (D) no carboxylic acid.

150° in the presence of water and that **1** is converted in part to 2-picoline and aromatic aldehyde by heating in the presence of water at 140–200°. Therefore, the formation of **1** is reversible.[4b] The rate of dehydration of the intermediate alcohol (**1**) is much faster than that of decomposition at least in acetic anhydride or acetic acid. The conversion curves for the formation of 2-(4′-nitrostyryl)pyridine in N,N-dimethylformamide are shown in Figure 2. Although the formation of 2-(4′-nitrostyryl)pyridine proceeds smoothly in the presence of excess acetic anhydride (curve A in Figure 2), the reaction is very slow in the presence of acetic acid (curve B in Figure 2). On addition of acetic anhydride to the latter system, represented by curve B after 5 hr, 2-(4′-nitrostyryl)pyridine is formed rapidly (curve C in Figure 2) to the corresponding conversion in the former system (A). The higher rate in C than that in A suggests accumulation of a considerable amount of the intermediate alcohol **1** in B in agreement with the isolation of **1** from system B. As **1** is formed either in the presence of acetic acid or acetic anhydride, the rate of formation of 2-(4′-nitrostyryl)pyridine is controlled by the dehydration (or elimination) step of **1** at least in N,N-dimethylformamide in the absence of acetic anhydride. The superior ability of acetic anhydride to that of acetic acid suggests that the formation of 2-(4′-nitrostyryl)pyridine from **1** proceeds not by a simple dehydration but *via* acetate, followed by elimination of acetic acid.

Acid Catalysis.—Acetic acid and some other carboxylic acids show catalysis in acetic anhydride (Figure 3). The order of catalytic power is in the order of acidity, *i.e.*, $ClCH_2CO_2H > PhCO_2H > CH_3CO_2H$.

However, the reaction stopped at *ca.* 40% conversion on addition of hydrochloric acid instead of carboxylic acid; little olefin, together with a large amount of *p*-nitrobenzaldiacetate, was obtained with sulfuric acid. *p*-Nitrobenzaldiacetate was obtained in a 66% yield with hydrochloric acid in a reaction system without 2-picoline. Accordingly, for the reaction with mineral acids in acetic anhydride, the suppression of the olefin formation is due to a side reaction, *i.e.*, the rapid formation of unreactive *p*-nitrobenzaldiacetate.

A weak base catalysis was observed, since the yield of a mixture of olefin and intermediate alcohol was only below 10% with potassium hydroxide (3.5%), tributylamine (9.6%), or potassium acetate (1%) for the attempted condensation of 2-picoline with benzaldehyde by refluxing for 100 hr. These observations suggest that the conjugate base of 2-picoline, **2**, is not important as a reactive species for the condensation in acetic anhydride.



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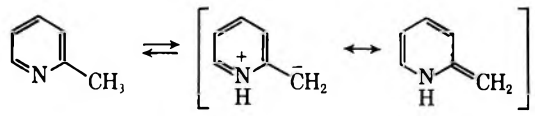
The Mechanism.—The observed facts are summarized as follows. (i) The condensation in acetic anhydride was overall third order; *i.e.*, $v = k$[2-picoline][*p*-nitrobenzaldehyde][acetic acid]. (ii) Only a little base catalysis was observed. (iii) The condensation proceeds *via* 1-(4′-nitrophenyl)-2-(α-pyridyl)ethanol (**1**) (or its acetate). (iv) The elimination of intermediate **1** to 2-(4′-nitrostyryl)pyridine was faster with acetic anhydride than with acetic acid. These facts



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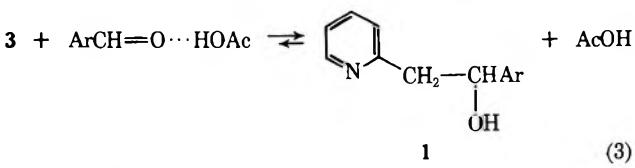

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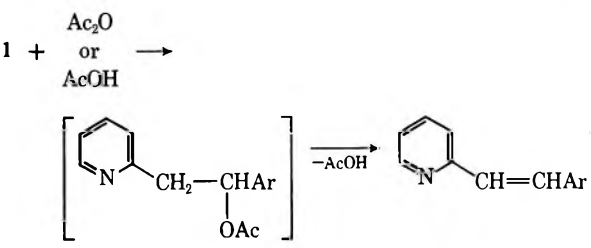
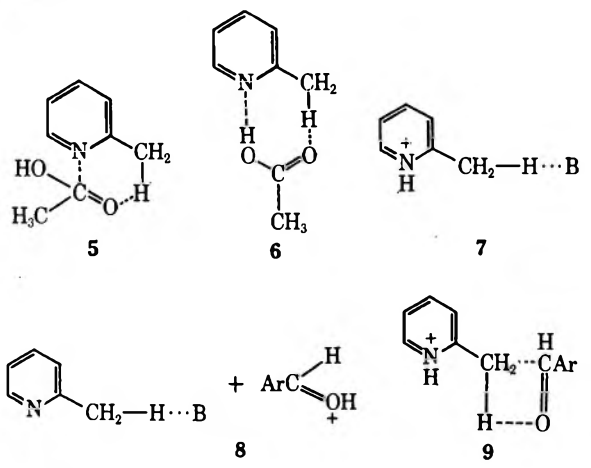


(4)

and the observation described below suggest the preceeding mechanism as the most probable one.

The rate-determining step is the formation of intermediate alcohol **1** (addition step), since the dehydration of **1** was rapid in acetic anhydride and the rate showed first-order dependence on acetic acid but not on acetic anhydride, whereas acetic anhydride in N,N-dimethylformamide was more efficient than acetic acid as a dehydrating agent. The fact that *p*-nitrobenzaldehyde reacts much faster than unsubstituted benzaldehyde supports the rate-determining attack of **3** on benzaldehyde. For the specific acid-catalyzed condensation of substituted benzaldehydes with acetophenone a small negative ρ value of -0.25 has been reported,[7] while for the general acid catalyzed condensation of substituted acetophenones with semicarbazide a positive ρ value of $+0.91$ has been reported.[8] Hence, the present mechanism involving association between benzaldehyde and the general acid catalyst prior to the rate-determining step is acceptable. The acceleration by electron-withdrawing substituents in benzaldehyde has been reported for the zinc chloride catalyzed condensation of substituted benzaldehydes with 2-picoline in dimethyl sulfoxide ($\rho = 1.2$)[6] and for the condensation in acetic anhydride.[4,5a] Conversely, the elimination of 1-phenylethyl chloride ($\rho^+ = -1.36$)[9] and acetate ($\rho^+ = -0.64$)[10] and 1-aryl-2-phenylethanol ($\rho^+ = -3.9$)[11] is retarded by an electron-withdrawing substituent.

An alternative possibility of the intermediacy of **5**, **6**, **7**, **8**, or **9** might be implied in view of the rate equation, but they are less plausible because of the following reasons. (i) The observed kinetics is not first order in acetic anhydride (excluding **5**). (ii) 4-Picoline, which cannot have such a cyclic mechanism, reacts more rapidly than 2-picoline (excluding **5** and **6**). (iii) The condensation of 4-picoline was also promoted by acetic acid (excluding **5** and **6**). (iv) No general base catalyzed addition of the saturated C—H bond to the C=O group for aldol-type reactions has been reported (excluding **7** and **8**). (v) No four-centered mechanism with saturated C—H bond has been reported (excluding **9**).

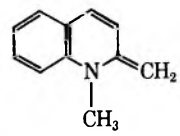


5 **6** **7**

8 **9**

B = base

In view of the observed acid catalysis and weakness of base catalysis, the participation of the conjugate base of 2-picoline (**2**) is less plausible; the methyl group of 2-picoline is not so acidic as to transfer its proton to an ordinary base. The probable reactive species may be **3**. An intermediate similar to **3** has been reported in base-catalyzed condensation of picoline methiodide and picoline N-oxide and in the hydrogen–deuterium exchange at methyl group of quinaldine with deuterated alcohols.[12] Moreover, it has been reported that 1-methyl-2-methylene-1,2-dihydroquinoline (**10**) is isolated.[13]



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Intermediate alcohols are obtained even in the absence of acid catalyst in water for the condensation of benzaldehydes with 2-picoline,[4a] while intermediate alcohols (adducts) were obtained without an acid catalyst in a reaction with neat quinaldine, where an uncatalyzed reaction has been observed by kinetic study in acetic anhydride.[14] These facts support the participation of **3** as a reactive species.

Since eq 2 does not require the acetic acid catalysis, the first-order dependence of the rate on acetic acid suggests that acetic acid acts as shown in **4**. The catalysis is more effective with stronger carboxylic acids, *i.e.*, $ClCH_2CO_2H > PhCO_2H > CH_3CO_2H$.

The formation of intermediate **1** is reversible, because **1** is known to produce the parent aldehyde and 2-picoline by heating at 200°.[4a] Dehydration of **1** proceeds probably *via* its acetate, since (i) acetic anhydride was more effective than acetic acid in N,N-dimethylformamide (in Figure 2), and (ii) an acyloxy group is a better leaving group than a hydroxy group.[15a] 2-Styrylquinoline is also known to be formed through the acetate intermediate.[16]

Xanthates (the Chugaev reaction) and carboxylate esters are known to undergo *cis* elimination,[15b] and this may be applied to this case. Consideration of the steric course of the elimination implies that the predominant product would be *trans* olefin in view of the steric requirement for the transition state and this is the case.

Experimental Section

Materials.—Benzaldehyde and 2-picoline were purified by distillation under nitrogen atmosphere; boiling points were 87.0° (41.5 mm) and 49.8° (40.3 mm), respectively. *p*-Nitrobenzaldehyde was prepared from *p*-nitrotoluene,[17] mp 105–106° (lit.[17] 106°). Ordinary purification was applied to acetic acid, bp 108°, and acetic anhydride, bp 140°.

Products. 2-Styrylpyridine.—A mixture of 2-picoline (0.33 mol), benzaldehyde (0.33 mol), and acetic anhydride (190 ml)

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(14) Unpublished data.

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(16) A. F. Walton, R. S. Tipson, and L. H. Cretcher, *J. Amer. Chem. Soc.*, **67**, 1501 (1945).

(17) S. U. Liebeman and R. Cormor, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 441.

was refluxed at 140° for 30 hr. The mixture was steam distilled and the distillate was made alkaline by aqueous NaOH to give precipitate of 2-styrylpyridine, which was recrystallized from aqueous ethanol: 10 g (18.1%), mp 90.0–90.5° (lit.[4a] 90.0–91.0°).

2-(4′-Nitrostyryl)pyridine.—A mixture of *p*-nitrobenzaldehyde (0.033 mol), 2-picoline (0.051 mol), and acetic anhydride (0.053 mol) was refluxed for 10 hr and further heated without the reflux condenser for 30 min to remove any acetic acid, which was produced, 2-picoline, and acetic anhydride. The filtered product was washed with water and recrystallized from aqueous ethanol, yielding yellow crystals (81.5%): mp 134–135° (lit. 126°,[18] 136°,[4a] 142°[19]); ir (KBr disk) 960 ~ 970 cm^{-1} (characteristic to *trans* –CH=CH– group); uv λ_{max} (MeOH) 338 mμ (log ε 4.50), λ_{max} (protonated by 1 or 2 drops of concentrated HCl in a methanolic solution) 340 mμ (log ε 4.50) [lit.[4b] 355 mμ (log ε 4.48) in MeOH].

Effect of Light on *trans–cis* Isomerization of *trans*-2-(4′-Nitrostyryl)pyridine.—It is known that irradiation causes the *trans–cis* isomerization[20] of 2-styrylpyridine derivatives under nitrogen atmosphere, and also dimerization[20,21] and cyclization[22] *via* the *trans–cis* isomerization in the presence of oxygen. We also observed that 2-(4′-nitrostyryl)pyridine suffered *trans–cis* photoisomerization in methanol or dioxane (10^{-5} *M*) by standing in the diffused light in a room. The change in its uv spectra is listed in Table II. Irrespective of the presence or absence of oxygen the photoisomerization which disturbs the precise rate measurement was avoided by the interception of light with aluminum foil.

TABLE II
EFFECT OF DIFFUSED LIGHT IN A ROOM ON *cis–trans* ISOMERIZATION OF 2-(4′-NITROSTYRYL)PYRIDINE

Solvent	At the moment of dilution, λ_{max} (log ε)	Interception from light (after 6 hr), λ_{max} (log ε)	Standing in diffused light (after 6 hr), λ_{max} (log ε)
Methanol	338 (4.52)	338 (4.54)	323 (4.20)
Dioxane	345 (4.41)	344 (4.43)	330 (4.07)

Rate Measurement.—The rate of reaction was measured by following the extinction at 338 mμ (log ε 4.50) of *trans*-2-(4′-nitrostyryl)pyridine. The reaction was carried out in a 100-ml two-necked flask furnished with a Dimroth condenser, at 135°. Aliquots were taken out at appropriate intervals of time, diluted with methanol, and kept standing in a test tube covered with aluminum foil in the dark; extinctions at 338 mμ were determined. The third-order rate constant, k_3, in eq 1 was calculated by the following equation, $k_3 = 2.303A/(2a + c)(2b + c)(a - b)$, if $a \neq b$, where A is the slope in a plot of $[(2b + c) \log (a - x) + (a + c) \log (b - x) + 2(a - b) \log (c + 2x)]$ *vs.* time, or $k_3 = B/(2a + c)_2$, if $a = b$, where B is a slope in a plot of $[-2 \ln (a - x) + (2a + c)/(a - x) + 2x \ln (b + 2x)]$ *vs.* time. a, b, c, and x are defined in eq 1. The third-order plot showed a good linearity except at an early stage of the reaction at low concentration of acetic acid (c ~0).

Intermediate Criterion. 1-(4′-Nitrophenyl)-2-(α-pyridyl)ethanol (1).—A mixture of *p*-nitrobenzaldehyde (1 g), 2-picoline (2 ml), acetic acid (0.5 ml), and N,N-dimethylformamide or dimethyl sulfoxide (5 ml) was heated at 135° for 4–5 hr. The reaction mixture was poured into water, made alkaline by aqueous NaOH, and precipitated. The precipitate was dissolved in benzene, treated with saturated $NaHSO_3$ to remove aldehyde, and dried (Na_2SO_4), and the solvent was evaporated. The residue was recrystallized from aqueous methanol, giving yellow crystals (18%), mp 154–160°. The uv spectrum showed a strong resemblance to that of 2-picoline; ir spectrum (KBr) 3140 (OH···N chelation as shown in 1), 2920, 2850, 1465 (CH_2), 1094 cm^{-1} (α-phenyl OH).

Dehydration of 1-(4′-Nitrophenyl)-2-(α-pyridyl)ethanol (1) in Acetic Acid or in Acetic Anhydride.—1 (10 mg) in acetic acid (1 ml) or acetic anhydride (1 ml) was heated at 115° for 2 hr. The reaction mixture was made alkaline with aqueous NaOH, the products being filtered and dried (Na_2SO_4). The yield was 64% (in acetic acid) and 58% (in acetic anhydride): mp 133–133.5°; uv λ_{max} (MeOH) 338 mμ; ir (KBr disk) 960–970 cm^{-1} (*trans* –CH=CH–). The product was *trans*-2-(4′-nitrostyryl)pyridine alone.

Attempted Condensation of 2-Picoline with Benzaldehyde by a Basic Catalyst.—A mixture of 2-picoline (0.1 mol), benzaldehyde (0.1 mol), and tri-*n*-butylamine (0.01 mol) was refluxed for 100 hr. The mixture, after being treated with water, was extracted with benzene. The benzene solution was treated with aqueous HCl and the aqueous layer was neutralized with K_2CO_3 to give precipitate of a mixture of 2-styrylpyridine and 1-phenyl-2-(α-pyridyl)ethanol, 1.7 g (9.2%).

Registry No.—2-Picoline, 109-06-8; acetic anhydride, 108-24-7; *p*-nitrobenzyldehyde, 555-16-8; **1**, 20151-01-3; *trans*-2-(4′-nitrostyryl)pyridine, 24470-06-2.

(18) K. Feist, *Ber.*, **34**, 465 (1901).
(19) L. Horwitz, *J. Org. Chem.*, **21**, 1039 (1956).
(20) J. L. R. Williams, S. K. Webster, and J. A. Van Allen, *ibid.*, **26**, 4893 (1961).
(21) J. L. R. Willams, *ibid.*, **25**, 1839 (1960).
(22) C. E. Loader and J. T. Timmons, *J. Chem. Soc., C*, 1078 (1966).

Acid-Catalyzed Decarboxylation of Glycidic Acids. "Abnormal" Products

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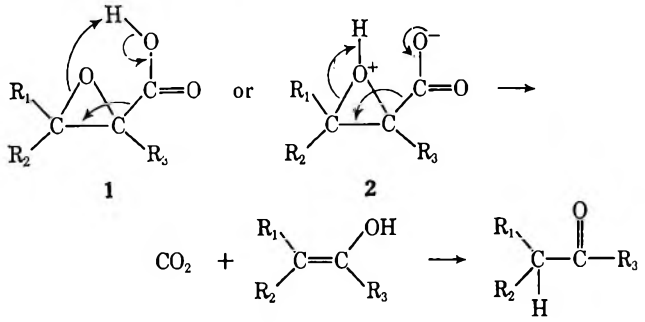
The acid-catalyzed decarboxylation of α-phenylglycidic acids yields carbonyl compounds in which the carbonyl is at the original β carbon of the starting material, and the accepted concerted mechanism for the decarboxylation of glycidic acids must therefore be revised. Consideration of the energy of the two carbonium ions formed by isomerization of the oxirane-protonated species explains the "normal" as well as the "abnormal" behavior of the glycidic acids. The energy of a benzylic carbonium ion adjacent to a carboxyl group is lower than that of a primary or secondary β-alkyl carbonium ion, but is comparable with that of a tertiary β-alkyl carbonium ion since 9 yielded the "normal" as well as the "abnormal" product (11). This latter conversion represents the first example of group migration in the decarboxylation of glycidic acids.

A classical preparative method for aldehydes and ketones utilizes sodium glycidates prepared by Darzens synthesis,[2] followed by Claisen saponification. Decarboxylation and epoxide ring opening take place after acid treatment, usually in the presence of heat. The method has been particularly reliable since no group migration has ever been detected,[3] and the carbonyl in the final product has always been found at the carbon atom bearing the carboxyl in the starting material. The accepted mechanism for the reaction[4,5] involves a *concerted* process in which decarboxylation and epoxide ring opening occur simultaneously, yielding an enol which finally ketonizes. The reacting species

(1) To whom inquiries should be directed.
(2) M. S. Newman and B. J. Magerlein, *Org. React.*, **5**, 413 (1951).
(3) H. H. Morris and M. L. Lusth, *J. Amer. Chem. Soc.*, **76**, 1237 (1954).
(4) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 242.
(5) R. C. Fuson, "Chemistry of the Carbonyl Group," S. Patai, Ed., Interscience Publishers, Inc., 1966, New York, N. Y., p 211.

is often pictured as a glycidic acid (1) which decarboxylates in a cyclic process, although such a species cannot be distinguished kinetically from the oxirane-protonated sodium glycidate 2.[6]

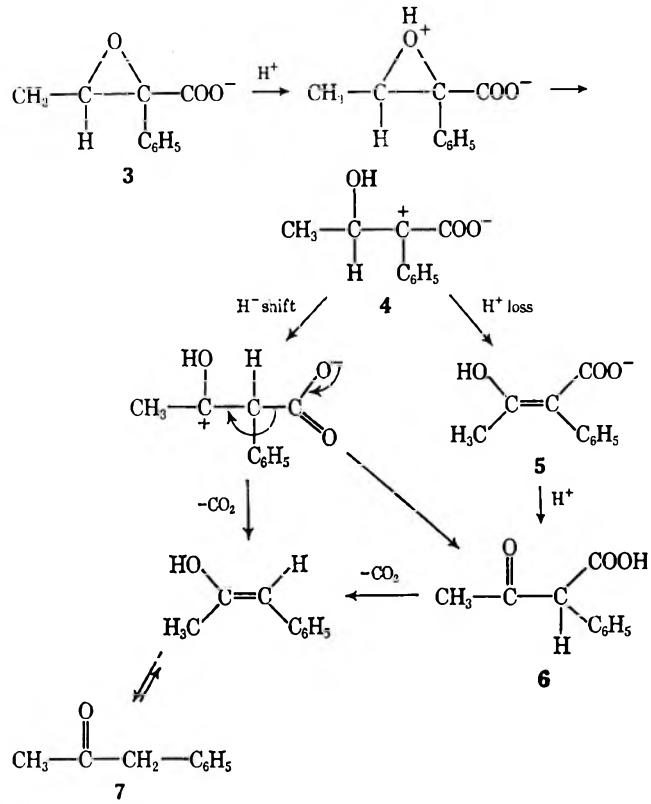


Perhaps the only report in the literature which conflicts with the above mechanism is that of the *thermal* decomposition of dihydro-α-picrotoxininic acid.[7] Since there is no assurance that the same mechanism prevails for the decarboxylation under acid-catalyzed and thermal conditions, we will limit the present discussion to the acid-catalyzed decarboxylation reactions of glycidic acids.

Electrostatic repulsion of like charges usually prohibits the formation of a carbonium ion adjacent to a carbonyl group,[8] but the energy barrier is significantly lowered when the carbonium ion is stabilized by resonance, and we have recently reported[9] our observations concerning the acid-catalyzed isomerization of α-phenylglycidic esters which yield β-keto esters instead of the usual α-keto esters.[10a] We have extended our study to the corresponding glycidic acids, and we now wish to report the first examples of "abnormal" decarboxylation of glycidic acids in aqueous solution. These were found in the sodium α-phenylglycidate series, which is not accessible through the Darzens synthesis.[10b]

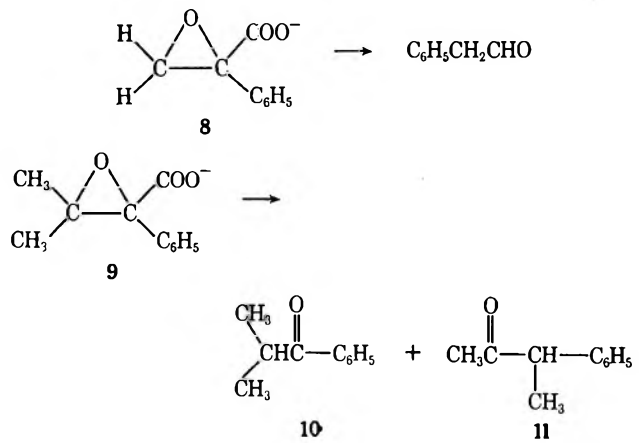
Acid-Catalyzed Decomposition of α-Phenylglycidic Acids.—In a typical experiment, sodium α-phenyl-β-methylglycidate (3) was obtained from ethyl α-phenylcrotonate by epoxidation followed by saponification. The nmr spectrum indicated that there was obtained only one crystalline isomer, of undetermined stereochemistry. It was acidified and refluxed in water for 2 hr, and the nmr and gc-mass spectral analyses of a carbon tetrachloride extract revealed that phenylacetone 7 was the sole neutral reaction product.

We explain this result in terms of the decomposition of the protonated glycidic acid (or its salt) to the resonance-stabilized benzylic ion 4. This protonation is probably taking place intermolecularly at low pH, but an intramolecular process cannot be completely ruled out at this time. Conversion of 4 to the β-keto acid 6, which yields 7 by decarboxylation, or to the enolic form of 7 could occur either through a hydride shift giving the oxygen-protonated form of 6 or through a proton loss yielding the enol 5. We proved this latter mechanism to be correct by carrying out the decomposition in deuterium oxide. If a hydride shift had occurred,



the product 7 should have one hydrogen and one deuterium at the methylene position, in the absence of further exchange *via* acid-catalyzed enolization. If the enol 5 is the intermediate, two deuterium atoms must be present at the methylene position in the product 7. The reaction was carried out to low conversion (10 min reflux), and we observed that 7 contained two deuterium atoms at the methylene position, whereas it still contained 0.45 and 0.75 hydrogen in control experiments with 6 and 7, respectively.

The "abnormal" reaction was also observed in the acid treatment of the congeners of 5 having either no substituent (8) or two alkyl substituents (9) at the β position.

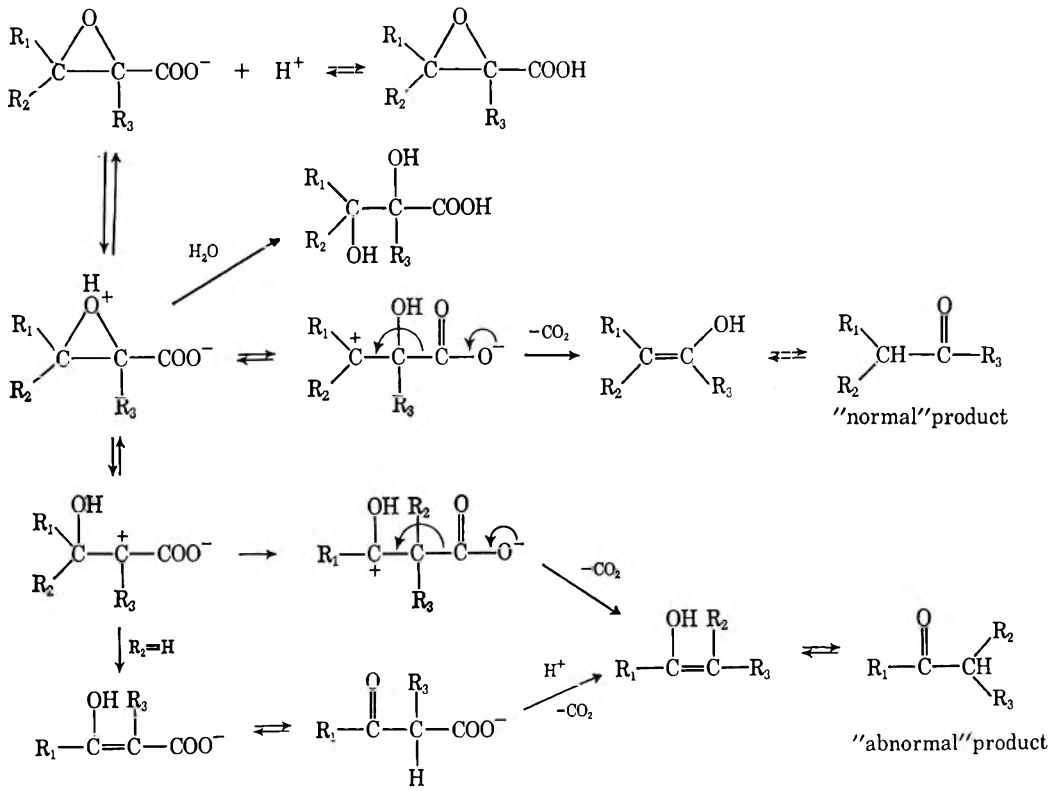


In the case of 8 the alternative to the benzylic carbonium ion intermediate is a very unfavorable primary carbonium ion and, predictably, phenylacetaldehyde was the only neutral decarboxylation product. The decarboxylation of 9, however, yielded two neutral products, 10 and 11, in the ratio 4:1, and the conversion of 9 to 11 represents the first example of group migration in the decarboxylation of glycidic acids. Our

(6) V. J. Shiner, Jr., and B. Martin, *J. Amer. Chem. Soc.*, **84**, 4824 (1962).
(7) H. Conroy, *ibid.*, **79**, 1726 (1957).
(8) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1948, p 199.
(9) S. P. Singh and J. Kagan, *J. Amer. Chem. Soc.*, **91**, 6198 (1969).
(10) (a) H. O. House, J. W. Blaker, and D. A. Madden, *ibid.*, **80**, 6386 (1958), and references cited therein; (b) H. H. Morris, R. H. Young, Jr., C. Hess, and T. Sottery, *ibid.*, **79**, 411 (1957).

SCHEME I

ACID-CATALYZED DECARBOXYLATION OF GLYCIDIC ACIDS

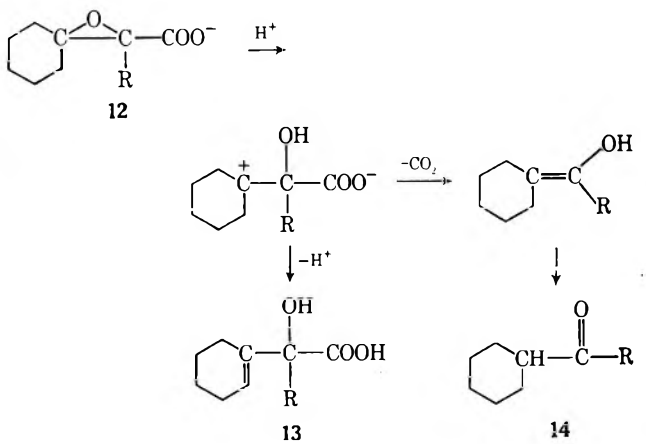


findings also indicate that a tertiary benzylic carbonium ion destabilized by an adjacent carboxyl group is favored over a primary or a secondary aliphatic β-carbonium ion, and that its stability is comparable to that of a tertiary aliphatic β-carbonium ion. These results are in complete agreement with those described by House and his collaborators in the epoxy ketone series.[11]

Mechanism of Decarboxylation of Glycidic Acids.—The results which we have described argue in favor of a carbonium ion intermediate formed by isomerization of the initially oxirane-protonated glycidic acid or of its salt. Furthermore, we believe that the simple consideration of carbonium ion stability satisfactorily explains these three aspects of the behavior of glycidic acids in acidic solution.

(1) Aromatic glycidic acids decarboxylate more easily than aliphatic ones. Although no comparative rate study has been described, the published data[12] as well as our own experience indicate little difficulty in decarboxylating aromatic glycidic acids. In contrast, the decarboxylation of the aliphatic acids has often been reported to be quite difficult and has required the elaboration of alternate procedures, such as the preliminary conversion into the chlorohydrin[13,14] or the pyrolysis of the isolated acid,[15] its sodium salt,[13] or its *t*-butyl ester.[16] In order to illustrate the point, we have compared the extent of decarboxylation of β-methyl- and β-phenylglycidic acids under identical conditions and found that none had taken place in the former when *ca.* 35% of the latter had already decarboxylated.

(2) Among aliphatic acids, the least substituted ones decarboxylate the most reluctantly. For instance, glycidic acid itself does not decarboxylate at all.[17] In the most substituted ones, furthermore, the carbonium ion species need not become neutralized *via* decarboxylation, but, instead, proton loss may occur. Thus, Johnson, *et al.*,[14] observed that **12** (R = H or CH_3) yielded mainly the unsaturated hydroxy acid **13** in addition to some normal product (**14**).



(3) In cases where decarboxylation does not take place readily (which we explain by the high energy of

(11) H. O. House, D. J. Reif, and R. L. Wasson, *J. Amer. Chem. Soc.*, **79**, 2490 (1957); H. O. House and D. J. Reif, *ibid.*, **79**, 6491 (1957); and previous papers in this series.

(12) C. F. H. Allen and J. van Allan, "in Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p 733.

(13) W. A. Yarnall and E. S. Wallis, *J. Org. Chem.*, **4**, 270 (1939).

(14) W. S. Johnson, J. C. Belew, L. J. Chinn, and R. H. Hunt, *J. Amer. Chem. Soc.*, **75**, 4995 (1953).

(15) H. H. Morris and R. H. Young, Jr., *ibid.*, **77**, 6678 (1955), and references cited therein.

(16) E. P. Blanchard, Jr., and G. Büchi, *ibid.*, **85**, 955 (1963).

(17) P. Melikoff, *Chem. Ber.*, **13**, 271 (1880).

the required carbonium ions), the competing attack of the protonated epoxy acid form by nucleophiles, typically water or the anion from the mineral acid, predominates. Glycidic acid, for example, is easily hydrated to glyceric acid[17] or converted to chlorolactic acid in presence of HCl.[18] Application of this criterion to the decarboxylation of phenylglycidic acids supports the concept that a benzylic carbonium ion in the α-phenyl series has a higher energy than in the β-phenyl series. In the former, decarboxylation accounted for only *ca.* 10%, while glyceric acids, stable in the experimental conditions, were the major products of the reaction; in the latter, no appreciable formation of glyceric acid took place under the same conditions.

In their careful kinetic study[6] of the decarboxylation of β-phenyl-β-methylglycidic acid in the pH range of 4–5.5, Shiner and Martin concluded that the reaction involved a simple decomposition of a free epoxy acid (in a cyclic fashion as proposed by Arnold[19]) or an acid-catalyzed decomposition of the anion of the acid. They also stated that the difference between the two mechanisms was probably more semantic than real. We believe, however, that the processes are energetically different since inspection of the models indicates that an appreciable strain is required in the intramolecular protonation reaction. Although a more complete discussion will have to await additional kinetic data, especially for the formation of the "abnormal" products, our product analysis illustrates the fact that the decarboxylation mechanism formulated by either Arnold or Shiner and Martin *does not* have a general applicability.

Using Shiner and Martin's findings[6] that only one proton was required in the pH range which they investigated, a general mechanism accounting for both the "normal" and "abnormal" decarboxylation products is outlined in Scheme I. The actual course followed by a given glycidic acid will depend primarily on the energy relationship between the protonated epoxide and the isomeric carbonium ions.[20] Secondary factors, however, such as the energy of the enol intermediate, are undoubtedly significant in determining the extent of the reaction.

A detailed probe of the reaction mechanism is in progress and will be described later.

Experimental Section

The nmr spectra were recorded on Varian A-60A or T-60 spectrometers and are expressed on the δ scale in parts per million downfield from an internal TMS standard. The mass spectra were obtained at 70 and 12 eV on a Perkin-Elmer 270 gas chromatograph–mass spectrometer, using a column of 20% SE-30 on Chromosorb. The melting points were determined in a Thomas–Hoover capillary apparatus. Comparisons of retention times with standards were also performed with SE-52 and DEGS columns in a F & M 402 gas chromatograph. The starting materials were prepared according to the literature showed satisfactory nmr spectra. The epoxidation reactions were carried out with a slight excess of 85% *m*-chloroperoxybenzoic acid in $CHCl_3$ at reflux for 15–20 hr. The solution was cooled, extracted with 5% aqueous bicarbonate, dried, and concentrated. The residue was purified by silica gel column chromatography. Saponification of the ethyl glycidates was performed according to Claisen[22] with 1 equiv of sodium ethoxide and of water. After standing overnight, the solid was filtered, washed thoroughly with ether, and dried. No attempt was made to maximize the yield of decarboxylation products. Identical products were obtained using either hydrochloric or sulfuric acids.

Sodium α-Phenylglycidate (8).—The ethyl ester was prepared from ethyl atropate[23] in 90% yield: nmr (CCl_4) phenyl at 7.20 (5 H, br), epoxide protons at 3.22 and 2.70 (each a d, J = 7 Hz), 4.15 (q, 2 H) and 1.20 (tr, 3 H). Saponification of 1.92 g of ester yielded 1.7 g of **8**: nmr (DMSO-d_6) 7.25 (5 H, br), 3.18 and 2.75 (each a d, J = 6 Hz). Recrystallization from ethanol gave needles which sintered at 260° but did not melt up to 300°. *Anal.* Calcd for $C_9H_7O_3Na$: C, 58.06; H, 3.76. Found: C, 58.06; H, 3.95.

Sodium α-Phenyl-β-methylglycidate (3).—The ethyl ester was prepared as a mixture of isomers from ethyl α-phenylcrotonate[24] (itself a mixture of isomers) in 78% yield: nmr (CCl_4) phenyl at 7.25 (br, 5 H), epoxide proton at 3.5 and 3.0 (each a q, total of 1 H, J = 6 Hz), OCH_2– at 4.20 (m, 2 H), and methyls at 1.25 (m, 6 H). Saponification of 4.12 g of ester yielded 1.8 g of a single crystalline isomer of **3**: nmr (D_2O) 7.30 (br, 5 H), 3.40 (q, J = 6 Hz, 1 H) and 0.94 (d, 3 H, J = 6 Hz). Recrystallization from ethanol gave needles, mp 292–293° dec. *Anal.* Calcd for $C_{10}H_9O_3Na$: C, 60.00; H, 4.50. Found: C, 60.01; H, 4.35.

Sodium α-Phenyl-β,β-dimethylglycidate (9).—Ethyl dimethylatropate[25] was epoxidized in 77% yield: nmr (CCl_4) 7.20 (br, 5 H), 4.2 (q, 2 H) and 1.22 (tr, 3 H), 1.4 and 1.0 (each a s, 3 H). Saponification of 2.2 g of ester yielded 1.2 g of **9**: nmr (D_2O) 7.40 (br, 5 H), 1.48 (s, 3 H) and 1.10 (s, 3 H). Recrystallization from ethanol gave crystals, mp >300° dec. *Anal.* Calcd for $C_{11}H_{11}O_3Na$: C, 61.68; H, 5.14. Found: C, 61.83; H, 4.83.

Decarboxylation of Sodium α-Phenylglycidate.—A solution of 0.5 g of **8** in 10 ml of water was acidified to congo red with 0.2 ml of concentrated H_2SO_4, refluxed for 10 min, cooled, and extracted with 20 ml of CCl_4. The organic layer was dried over $MgSO_4$ and was concentrated to yield 30 mg (9%) of phenylacetaldehyde: nmr (CCl_4) 7.20 (s, 5 H), 9.60 (tr, J = 2.5 Hz, 1 H), 3.60 (d, 2 H, J = 2.5 Hz); gc-mass spectrum identical with an authentic sample (major peaks at m/e 120, 92, and 91). The aqueous layer was further extracted thoroughly with ether, which was dried and concentrated to yield 350 mg (72%) of α-phenylglyceric acid, mp 147–148° (lit.[26] mp 149°). The ethyl ester was prepared by ethanol–H_2SO_4 treatment of the previous sample: nmr (DMSO-d_6) phenyl at 7.30 (br, 5 H), α-OH at 5.60 (s, 1 H), β-OH at 4.92 (d of d, 1 H), β protons at 4.10 and 3.55 (each a d of d, 1 H, with J_{gem} = 11 and J_{vic} = 5 Hz), ester at 4.20 (q, 2 H) and 1.15 (tr, 3 H). Upon addition of D_2O, the signals at 5.60 and 4.92 disappeared, and those at 4.10 and 3.55 became doublets, J = 11 Hz.

Decarboxylation of Sodium α-Phenyl-β-methylglycidate.—A solution of 250 mg of **3** in 10 ml of water was acidified with HCl (congo red), refluxed for 2 hr, cooled, and extracted with CCl_4. The extract was concentrated to yield 25 mg (15%) of phenylacetone: nmr (CCl_4) 7.20 (s, 5 H), 3.52 (s, 2 H), and 2.00 (s, 3 H); gc-mass spectrum identical with an authentic sample (major peaks at m/e 134, 91, and 43). Extraction of the aqueous layer with ether, which was dried and concentrated, yielded 125 mg (51%) of oily α-phenyl-β-methylglyceric acid which was esterified with diazomethane. The nmr (DMSO-d_6) of the methyl ester showed signals at 7.40 (br, 5 H), 5.60 (s, 1 H), *ca.* 4.35 (complex, 2 H), 3.60 (s, 3 H), and 1.10 (d, J = 6 Hz, 3 H). The signal at 5.60 disappeared and a quartet at 4.30 (J = 6 Hz, 1 H) became clear upon addition of D_2O. Overnight oxidation at room temperature of 200 mg of ester with 460 mg of potassium periodate in 25 ml of 1 *N* H_2SO_4 yielded methyl benzoylformate which was extracted with ether and had a gc-mass spectrum identical with an authentic sample (main peaks at m/e 164, 133, 105, 77).

(18) P. Melikoff, *Chem. Ber.*, **13**, 956 (1880).

(19) R. T. Arnold, Abstracts, 10th National American Chemical Society Organic Symposium, Boston, Mass., 1947.

(20) As this manuscript was first ready to be submitted for publication, there appeared a study of the acid-catalyzed decarboxylation-dehydration of a β-hydroxy acid pointing to the intermediacy of a dipolar species.[21] By analogy, the authors suggested a β-carbonium ion intermediate in the "normal" decarboxylation reaction of glycidic acids.

(21) D. S. Noyce and E. C. McGoran, *J. Org. Chem.*, **34**, 2558 (1969).

(22) L. Claisen, *Chem. Ber.*, **38**, 693 (1905).

(23) G. R. Ames and W. Davey, *J. Chem. Soc.*, 1794 (1958).

(24) M. A. Phillips, *ibid.*, 220 (1942).

(25) J. Farakas and J. K. Novak, *Collect. Czech. Chem. Commun.*, **25**, 1815 (1960).

(26) W. C. Craig and H. R. Henze, *J. Org. Chem.*, **10**, 16 (1945).

Decarboxylation of 3 in D_2O.—A solution of 200 mg of **3** in 10 ml of D_2O was acidified with 1 ml of 1 *N* HCl in D_2O, refluxed for 10 min, cooled, and extracted with 10 ml of CCl_4. The organic layer was dried and concentrated, and the phenylacetone showed only two nmr signals (CCl_4) at 7.20 and 2.00 in the ratio of 5:1.5. The above experiment was repeated, keeping all the conditions as above, but replacing **3** by 30 mg of phenylacetone which dissolved completely. The nmr of the recovered product showed signals at 7.20, 3.52, and 2.00 in the ratio 5:0.75:2.5. When the experiment was repeated using 500 mg of sodium α-phenylacetoacetate instead of **3**, the spectrum of the phenylacetone had signals at 7.20, 3.52, and 2.00 in the ratio 5:0.45:0.90.

Decarboxylation of Sodium α-Phenyl-β,β-dimethylglycidate.—A solution of 0.5 g of **9** in 15 ml of water was acidified with 0.2 ml of concentrated H_2SO_4, refluxed for 10 min, cooled, and extracted with 25 ml of CCl_4. The extract was dried and concentrated, yielding 75 mg (21%) of residue which was identified by nmr and by gc-mass spectroscopy as a mixture of four parts isobutyrophenone (major peaks at *m/e* 148, 105, and 77) and one part 3-phenyl-2-butanone (major peaks at *m/e* 148, 105, 79, 77, and 43). Further ether extraction of the aqueous phase and work-up yielded 225 mg (46%) of α-phenyl-β,β-dimethylglyceric acid which was treated with diazomethane. The methyl ester had nmr (DMSO-d_6) at 7.40 (br, 5 H), 5.60 (s, 1 H), 4.42 (s, 1 H), 3.70 (s, 3 H), 1.18 (s, 3 H), and 1.10 (s, 3 H). The signals at 5.60 and 4.42 disappeared in presence of D_2O. Periodate oxidation yielded methyl benzoylformate which had gc-mass spectrum identical with an authentic sample.

Comparative Decarboxylation of β-Phenyl- and β-Methylglycidic Acids.—A solution of 35 mg of sodium β-methylglycidate in 10 ml of water was acidified with 3 ml of 0.1 *N* H_2SO_4. Titration with phenolphthalein as indicator either immediately or after 10-min reflux required 3.0 ml of 0.1 *N* NaOH. In a parallel experiment, a solution of 53 mg of sodium β-phenylglycidate in 10 ml of water consumed 2.01 ml of 0.1 *N* NaOH after a 10-min reflux with 3 ml of 0.1 *N* H_2SO_4.

Registry No.—**3**, 24568-16-9; **8**, 24568-17-0; **9**, 24568-18-1.

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Oxidation of Amine Salts in Dimethyl Sulfoxide[1,2]

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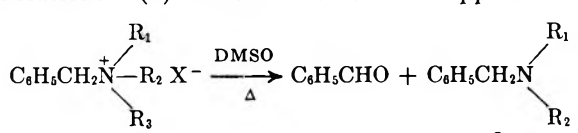
Benzylic amine salts of the type C_6H_5CHRX, when heated in DMSO at 160–180° for 20 hr, undergo oxidation to carbonyl compounds and in some instances elimination to olefins. When R = H and X = $NH_2 \cdot HCl$, $NHCH_3 \cdot HCl$, $N(CH_3)_2 \cdot HCl$, or $N^+(CH_3)_3I^-$, benzaldehyde was formed in varying amounts. With R = CH_2CH_3 and X = $NH_2 \cdot HCl$ the reaction gave isopropenyl phenyl ketone and α-hydroxymethylpropiophenone, while R = CH_2CH_3 and X = $N(CH_3)_2 \cdot HCl$ gave similar oxidation products along with 1-phenylpropene. When R = $CH(CH_3)_2$ and X = $NH_2 \cdot HCl$, the major product was isobutyrophenone, while R = $CH_2C_6H_5$ and X = $NH_2 \cdot HCl$ gave α-hydroxymethyldesoxybenzoin and 2,3,5,6-tetraphenylpyridine and R = $CH_2C_6H_5$ and X = $N(CH_3)_2 \cdot HCl$ produced only *trans*-stilbene. The oxidation reactions which formed carbonyl compounds are explained by an ionic pathway similar to the mechanism for the Pfitzner–Moffatt DMSO oxidation of alcohols. A suggestion was made that olefinic products arose *via* an E1 process. When alkyl groups are on the benzylic carbon, the initial ketone oxidation product undergoes further reaction with formaldehyde (from the acid or thermal decomposition of DMSO) and ammonium chloride. Reactions of the ketone, paraformaldehyde, and ammonium chloride in DMSO under the above experimental conditions gave products similar to the amine salt–DMSO reaction.

During the past 12 years numerous applications of the use of dimethyl sulfoxide (DMSO) as an oxidant have appeared in the literature.[4,5] An alternative nonoxidative reaction with these substrates and DMSO proceeds with elimination and the formation of olefinic products.[4,6] We now wish to report results from the reactions of amine salts in DMSO which occur by oxidation and/or elimination processes.

When benzylamine hydrochloride (0.1 mol), or its various N-methylated derivatives (0.1 mol), was heated in DMSO (0.7 mol) at 165–185° for 20 hr, benzaldehyde was formed in 25–60% yield in addition to a mixture of N-methylated benzylamines. Formation of the latter products may arise from an Eschweiler–Clark reaction since DMSO is known to decompose to produce formaldehyde. A study of this oxidation reaction with various conditions and additives led to the following conclusions. (1) The ammonium ion appears necessary for reaction, and the small amount of oxidation observed with the free base may be attributed to formation of some acid on prolonged heating of DMSO. (2) DMSO is the oxidant. (3) In contrast to the oxidation of benzyl alcohols in DMSO, the benzylamine salt oxidation does not appear to involve a radical process.



1 2

1	Benzaldehyde, %	2, %	2
$R_1 = R_2 = R_3 = H$	60	24	$R_1 = H$; $R_2 = CH_3$
		5	$R_1 = R_2 = CH_3$
$R_1 = R_2 = H$; $R_3 = CH_3$	53	14	$R_1 = H$; $R_2 = CH_3$
		18	$R_1 = R_2 = CH_3$
$R_1 = H$; $R_2 = R_3 = CH_3$	27	51	$R_1 = R_2 = CH_3$
$R_1 = R_2 = R_3 = CH_3$	62		

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(2) Presented in part at the Central Regional Meeting of the American Chemical Society, Akron, Ohio, April 1968.

(3) Abstracted from part of the Ph.D. dissertation of R. H. O., submitted in June 1968.

(4) W. W. Epstein and F. W. Sweat, *Chem. Rev.*, **67**, 247 (1967).

(5) J. R. Parikh and W. von E. Doering, *J. Amer. Chem. Soc.*, **89**, 5505 (1967).

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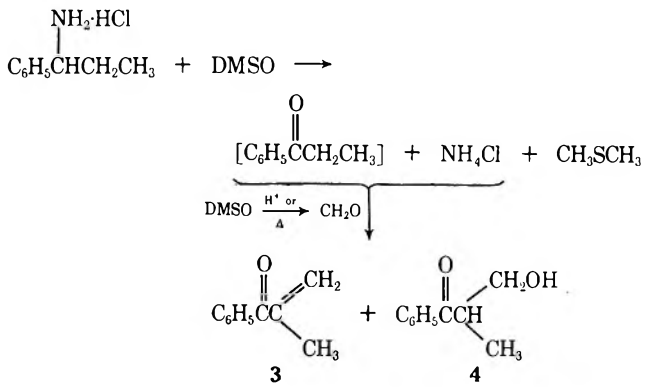
The reaction of benzylic amine hydrochloride salts of the type $C_6H_5CHRNH_2 \cdot HCl$ and $C_6H_5CHRN(CH_3)_2 \cdot HCl$, where R = CH_2CH_3, $CH(CH_3)_2$, and $CH_2C_6H_5$, with DMSO provided only oxidative products from primary amine salts while tertiary amine salts showed a decrease in yield of oxidative products and the appearance of olefinic products. In the experiment with N,N-dimethyl-1,2-diphenylethylamine hydrochloride only elimination to *trans*-stilbene (39%) was observed. A basic fraction was also isolated from these reactions and contained a mixture of N-methylated amines.

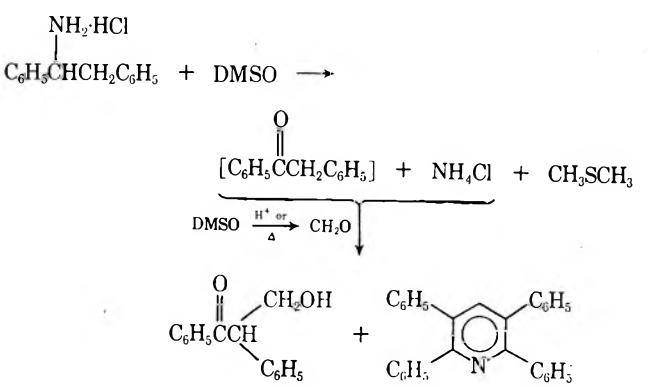
The primary oxidation product, propiophenone, from the reaction of 1-phenyl-1-propylamine hydrochloride and DMSO underwent subsequent condensation with formaldehyde (from decomposition of DMSO)[7,8] to produce isopropenyl phenyl ketone (**3**) (18%) and α-hydroxymethylpropiophenone (**4**) (13%). A minor product in this reaction was isobutyrophenone (1%) whose origin remains obscure. When a mixture of propiophenone, ammonium chloride, paraformaldehyde,



3 4

and DMSO was exposed to reaction conditions, the expected condensation products **3** and **4** were isolated in 12% and 39% yield, respectively.

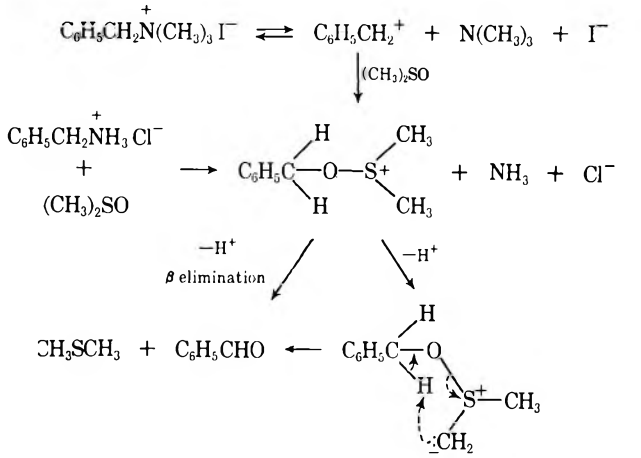
The reaction of 1-phenyl-2-methyl-1-propylamine hydrochloride and DMSO provided mainly isobutyrophenone (56%) with only a small conversion to the condensation product of α-hydroxymethylisobutyrophenone (6%); however, 1,2-diphenylethylamine hydrochloride gave only condensation products in the form of α-hydroxymethyldesoxybenzoin (**5**) (31%) and 2,3,5,6-tetraphenylpyridine (**6**) (5%). The latter compound may be rationalized by a Hantzsch-type pyridine synthesis with deoxybenzoin (primary oxidation product), ammonia (from ammonium chloride), and formaldehyde. When these reactants were subjected to experimental conditions in DMSO, the yields of **5** and **6** were 50 and 11%, respectively.



5 6

Previous mechanistic studies by Torssell[9,10] have shown that oxidation of benzylic halides and sulfonates proceeds by an SN2 pathway to give a dimethylalkoxysulfonium ion which decomposes to produce the carbonyl compound and dimethyl sulfide. In view of Torssell's work and the above conclusions the mechanism of Chart I is offered to rationalize the benzylamine salt oxidations. The declining yield of oxidation products in the series of primary, secondary, tertiary amine

CHART I



salts could be rationalized by the steric influence of increased substitution on an SN2 process, while the dramatic increase in oxidation yield with the quaternary ammonium iodide suggests a mechanistic change such as ionization *via* an SN1 process. An observation in support with the latter carbonium ion explanation was the formation of 2-naphthyl benzyl ether (30%) when benzyltrimethylammonium iodide was heated in dimethylformamide and 2-naphthol.

A similar mechanistic pathway can account for the primary oxidation product in the reaction with α-alkyl-substituted benzylamine salts. In addition the decreased yield of oxidation products and the appearance of olefinic products when one compares the reaction of primary amine hydrochlorides with the corresponding tertiary amine hydrochlorides supports the above proposed steric influence on the oxidative reaction and suggests contributions from an E1 (SN1) mechanistic process for the tertiary amine salts. When the corresponding quaternary ammonium iodides were exposed to reaction conditions in DMSO, olefinic products predominated and in most cases were the only products.[11] If both ketonic and olefinic products were formed through a single pathway (either SN2 or SN1), one would expect to find both elimination and oxidation products in all examples.

The only successful examples of amine salts reported above for oxidation and/or elimination are benzylic amines or α-substituted benzylic amines. One exception to this generalization was the failure of either 1-phenylethylamine hydrochloride or 1-phenylethyldimethylamine hydrochloride and DMSO to lead to iden-

(7) V. J. Traynelis and W. L. Hergenrother, *J. Org. Chem.*, **29**, 221 (1964).
(8) H. R. Nace and J. J. Monagle, *ibid.*, **24**, 1792 (1959).
(9) K. Torssell, *Tetrahedron Lett.*, 4445 (1965).
(10) K. Torssell, *Acta Chem. Scand.*, **21**, 1 (1967).
(11) V. J. Traynelis and R. H. Ode, unpublished results.

TABLE I
STARTING AMINE HYDROCHLORIDES

Amine	% yield	Amine hydrochlorid emp, °C Obsd	Lit.	% C Obsd	% C Calcd	% H Obsd	% H Calcd
Benzylamine	[a]	263–265	260[b]				
N-Methylbenzylamine	[a]	178–179	173–174[c]				
N,N-Dimethylbenzylamine	[a]	177–178		62.79	62.97	8.37	8.22
1-Phenethylamine	[d]	160–162	158[e]				
1-Phenyl-1-propylamine	70	195–197	189.5[f]				
N,N-Dimethyl-1-phenyl-1-propylamine	73	167–169		66.38	66.15	8.88	9.08
1-Phenyl-2-methyl-1-propylamine	98	285–286	275[g]				
N,N-Dimethyl-1-phenyl-2-methyl-1-propylamine	66	207–208		67.43	67.43	9.44	9.43
1,2-Diphenylethylamine	[d]	262–264	254–256[h]				
N,N-Dimethyl-1,2-diphenylethylamine	98	215–216	210[i]				
N,N-Dimethyldodecylamine	[d]	200–202		67.52	67.30	13.09	12.91
2-Aminooctane	[d]	89–91	91–92[j]				
2-Dimethylaminooctane	85	134–135	144–146[k]				

[a] A sample was provided by Miles Laboratories, Inc., for which the authors express their appreciation. [b] A. Martell and R. M. Herbst, *J. Org. Chem.*, 6, 885 (1941). [c] H. Bohme, A. Dick, and G. Driesen, *Chem. Ber.*, 94, 1882 (1961). [d] Commercially available. [e] A. N. Kost, A. P. Terent'ev, and G. A. Shvekhgeimer, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 150 (1951); *Chem. Abstr.*, 45, 1019e (1951). [f] W. H. Hartung and J. C. Munch, *J. Amer. Chem. Soc.*, 53, 1878 (1931). [g] M. Konowalow, *Chem. Ber.*, 28, 1859 (1895). [h] P. Pratesi, A. LaManna, and L. Fontanella, *Farmaco, Ed. Sci.*, 10, 673 (1955); *Chem. Abstr.*, 50, 10057b (1956). [i] T. Morikawa, *Yakugaku Zasshi*, 80, 475 (1960); *Chem. Abstr.*, 54, 19588g (1960). [j] F. G. Mann and J. W. G. Porter, *J. Chem. Soc.*, 459 (1944). [k] F. G. Mann and J. Reid, *J. Chem Soc.*, 3385 (1950).

tifiable products. Acetophenone, ammonium chloride, and DMSO react to give tar-like products, thus precluding the isolation of any reaction products from the above amine salts and DMSO. Three amine salts which failed to undergo reaction were 2-octylamine hydrochloride, N,N-dimethyldodecylamine hydrochloride, and 1-octyltrimethylammonium iodide; thus applications of aliphatic amine salts in which the amino function is attached to a primary or secondary carbon are excluded.

Experimental Section[12]

Preparation of Starting Amines and Amine Hydrochlorides.—1-Phenyl-1-propylamine and 1-phenyl-2-methyl-1-propylamine were prepared by the Leuckart reaction,[13] while N,N-dimethyl-1-phenyl-2-methyl-1-propylamine, N,N-dimethyl-1,2-diphenylethylamine, and 2-dimethylaminooctane were obtained by the Eschweiler–Clarke procedure[13] (see Table I).

The amine hydrochlorides were precipitated from an ether solution by addition of ethereal hydrogen chloride or by neutralization of the amine with hydrochloric acid and removal of water *in vacuo*. The crude hydrochloride salts were purified by crystallization from ethanol–ethyl acetate mixtures (see Table I).

Oxidation of Amine Salts in DMSO. General Procedure.—A solution of amine hydrochloride (0.1 mol) and dimethyl sulfoxide[14] (0.7 mol) was heated at 165–185° for 20 hr in an atmosphere of either air or nitrogen. The reaction mixture was cooled, acidified with 10% hydrochloric acid (100 ml), and extracted with ether (neutral fraction). The acidified reaction mixture was treated with 40% NaOH (50 ml) and extracted with ether (basic fraction).

Each of the ether extracts (neutral fraction, basic fraction), treated separately, was washed with water and dried, and the solvent was removed. Analysis of the residue from each fraction and separation into its components were achieved by vpc or column chromatography. The details are listed in Tables II and III.

Benzyl 2-Naphthyl Ether.—A solution of benzyltrimethylammonium iodide (13.9 g, 0.05 mol), 2-naphthol (7.9 g, 0.055 mol), and dimethylformamide (100 ml) was refluxed for 20 hr. The reaction mixture was cooled, diluted with 5% aqueous HCl, and extracted with ether. The ether extract was washed with base and water and dried, and after the solvent was removed gave 3.5 g (30%) of benzyl 2-naphthyl ether, mp 97–99° (lit.[15] mp 99–100°). The nmr spectrum was consistent for this structure.

Reaction of Propiophenone, Ammonium Chloride, and Paraformaldehyde in Dimethyl Sulfoxide.—Propiophenone (13.4 g, 0.10 mol), paraformaldehyde (3.0 g, 0.10 mol), ammonium chloride (5.4 g, 0.10 mol), and dimethyl sulfoxide (54.6 g, 0.70 mol) were heated at 180–185° for 20 hr and the reaction was worked up by the above procedure. The neutral fraction was chromatographed on alumina and gave 1.7 g (12%) of isopropenyl phenyl ketone, 0.2 g (1%) of isobutyrophenone, 0.7 g (5%) of propiophenone, and 6.5 g (39%) of α-hydroxymethylpropiophenone.

Isopropenyl phenyl ketone had an ir spectrum identical with that of an authentic sample, nmr ($CDCl_3$) τ 2.50 (m, C_6H_5), 4.20 and 4.40 (q, 2, $=CH_2$), 7.98 (d, 3, $-CH_3$), and gave the 1,3-diphenylpyrazoline derivative, mp 117–119° (lit.[16] mp 119–121°).

Isobutyrophenone was characterized as the 2,4-dinitrophenylhydrazone, mp 158–161° (lit.[17] mp 161–162°), and a mixture melting point with an authentic sample was not depressed. α-Hydroxymethylpropiophenone had an ir spectrum identical with that of an authentic sample.

α-Hydroxymethylpropiophenone.—A mixture of propiophenone (20.0 g, 0.15 mol), aqueous formaldehyde (37%, 3.7 g, 0.12 mol), and 30 ml of 5% NaOH was stirred at room temperature for 13 hr and treated with 10% hydrochloric acid (10 ml). The acidified reaction mixture was extracted with ether, the extract dried, and the solvent removed. Distillation of the residue gave 6.7 g (49% corrected for recovered propiophenone) of α-

(12) Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Infrared spectra were recorded on a Perkin-Elmer infrared or Beckman IR-8 spectrophotometer, while ultraviolet spectra were determined on a Bausch and Lomb Spectronic 505 ultraviolet–visible spectrophotometer. Mr. Robert Smith recorded the nmr spectra using a Varian Model HA-60 high-resolution spectrometer employing tetramethylsilane as an internal standard. Gas–liquid partition chromatography was performed on a Perkin-Elmer Model 154 vapor fractometer and the relative areas were determined utilizing the peak height times half-width method.

(13) M. L. Moore, *Org. React.*, 5, 301 (1949).

(14) We wish to thank Crown Zellerbach Corp. for a generous supply of DMSO. Purification of DMSO, bp 189°, was achieved as described previously; see ref 6.

(15) H. Baw, *J. Indian Chem. Soc.*, 3, 103 (1926).

(16) J. H. Burckhalter and R. C. Fuson, *J. Amer. Chem. Soc.*, 70, 4186 (1948).

(17) H. M. Kissman and J. Williams, *ibid.*, 72, 5323 (1950).

TABLE II

OXIDATION OF BENZYLAMINE SALTS IN DIMETHYL SULFOXIDE[a]

$C_6H_5CH_2X$ X	Reaction temp, °C	% yield[b] of C_6H_5CHO[c]	Recovered amines[d] Amine	% yield	Amine	% yield
(1) $NH_2 \cdot HCl$	167–172	60	$C_6H_5CH_2NHCH_3$	24	$C_6H_5CH_2N(CH_3)_2$	5
(2) $NHCH_3 \cdot HCl$	163–167	53	$C_6H_5CH_2NHCH_3$	14	$C_6H_5CH_2N(CH_3)_2$	18
(3) $N(CH_3)_2 \cdot HCl$	165–170	27			$C_6H_5CH_2N(CH_3)_2$	51
(4) $\overset{+}{N}(CH_3)_3I^-$	175–180	62				
(5) NH_2	165–170	15	$C_6H_5CH_2NH_2$	61	$C_6H_5CH_2NHCH_3$	7
(6) $NH_2 \cdot HCl$[e]	160–164	14	$C_6H_5CH_2NH_2$	47		
(7) $NH_2 \cdot HCl$[f]	160–164		$C_6H_5CH_2NH_2$	28		
(8) $NH_2 \cdot HCl$[g]	170–175	60	$C_6H_5CH_2NHCH_3$	11	$C_6H_5CH_2N(CH_3)_2$	14
(9) $NH_2 \cdot HCl$[h]	165–170	44	$C_6H_5CH_2NHCH_3$	13	$C_6H_5CH_2N(CH_3)_2$	11
(10) $NH_2 \cdot HCl$[i]	160–165	55	$C_6H_5CH_2NHCH_3$	11	$C_6H_5CH_2N(CH_3)_2$	20
(11) $NH_2 \cdot HCl$[j]	170–175	5	$C_6H_5CH_2NHCH_3$	10	$C_6H_5CH_2N(CH_3)_2$	12

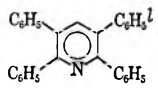
[a] The reactions involved a 1:7 amine salt:DMSO ratio and ranged in quantity from 0.01 to 0.10 mol of amine salt. Reaction time was 20 hr. [b] Determined by vpc using a 10-ft column of 10% Carbowax 20M on Chromosorb G at 150° with a helium flow rate of 54 cc/min. Dimethyl disulfide was also observed in varying amounts and identified as described earlier (see ref 7). [c] Benzaldehyde was identified by comparison of retention time and its ir spectrum with those of an authentic sample; also by preparation of the 2,4-dinitrophenylhydrazone, mp 237–238° (lit. mp 237°; "Tables for Identification of Organic Compounds," C. D. Hodgman, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1960, p 71). [d] Yields were determined by using a 10-ft column of 25% Carbowax 20M and 2.5% NaOH on Chromosorb P at 175° with a helium flow rate of 54 cc/min. The amines were identified by comparison of retention times and peak enhancement with those of authentic samples. [e] The reaction mixture contained 0.10 mol of amine salt, 0.10 mol of DMSO, and 100 ml of diglyme. [f] The reaction mixture contained 0.10 mol of amine salt in 100 ml of diglyme. [g] Air was bubbled through the reaction mixture. [h] Reaction was performed in a nitrogen atmosphere. [i] Reaction was performed in a nitrogen atmosphere and with *m*-dinitrobenzene (0.025 mol) added. [j] *t*-Butyl peroxide (0.0040 mol total) was added in two 0.0020-mol portions 10 hr apart.

TABLE III

OXIDATION OF AMINE SALTS IN DIMETHYL SULFOXIDE[a]

Amine·HCl (Registry no.)	Temp, °C	Neutral fraction[b] % yield	Neutral fraction[b] Products	Basic fraction[c] % yield	Basic fraction[c] Products
$C_6H_5CHCH_2CH_3$ (NH_2) (24301-86-8)[d]	170–175	18	$C_6H_5C(=O)C(=CH_2)CH_3$[e]	25	$C_6H_5CHCH_2CH_3$ (NH_2)[h]
		1	$C_6H_5C(=O)CH(CH_3)_2$[f]	36	$C_6H_5CHCH_2CH_3$ ($NHCH_3$)
		13	$C_6H_5C(=O)CH(CH_3)CH_2OH$[g]		
$C_6H_5CHCH_2CH_3$ ($N(CH_3)_2$) (24301-87-9)	172–175	7	$C_6H_5CH=CHCH_3$[i]	67	$C_6H_5CHCH_2CH_3$ ($N(CH_3)_2$)
		4	$C_6H_5C(=O)CH(CH_3)CH_2OH$[g]		
$C_6H_5CHCH(CH_3)_2$ (NH_2) (24290-47-9)	180–190	56	$C_6H_5C(=O)CH(CH_3)_2$[f]	3	$C_6H_5CHCH(CH_3)_2$ (NH_2)[k]
		6	$C_6H_5CC(OCH_2OH)(CH_3)_2$[j]	25	$C_6H_5CHCH(CH_3)_2$ ($NHCH_3$)
				5	$C_6H_5CHCH(CH_3)_2$ ($N(CH_3)_2$)
$C_6H_5CHCH(CH_3)_2$ ($N(CH_3)_2$) (24301-88-0)	180–190	5	$C_6H_5CH=C(CH_3)_2$[i]	59	$C_6H_5CHCH(CH_3)_2$ ($N(CH_3)_2$)
		27	$C_6H_5C(=O)CH(CH_3)_2$		
		1	$C_6H_5C(=O)C(CH_2OH)(CH_3)_2$[j]		

TABLE III (*Continued*)

Amine·HCl (Registry no.)	Temp., °C	Neutral fraction[b] % yield	Neutral fraction[b] Products	Basic fraction[c] % yield	Basic fraction[c] Products
$C_6H_5CH(NH_2)CH_2C_6H_5$ (24301-89-1)	165–170	5		8	$C_6H_5CH(NH_2)CH_2C_6H_5$[n]
		31	$C_6H_5C(=O)CH(CH_2OH)C_6H_5$[i]	35	$C_6H_5CH(NHCH_3)CH_2C_6H_5$
			Trace unidentified[m]	5	$C_6H_5CH[N(CH_3)_2]CH_2C_6H_5$
$C_6H_5CH[N(CH_3)_2]CH_2C_6H_5$[o] (24301-90-4)	170–175	39	*trans*-$C_6H_5CH{=}CHC_6H_5$[p]	42	$C_6H_5CH[N(CH_3)_2]CH_2C_6H_5$
$C_6H_5CH(NH_2)CH_3$ (20938-48-1)	173–177			53	$C_6H_5CH(NH_2)CH_3$[q]
				33	$C_6H_5CH(NHCH_3)CH_3$
				2	$C_6H_5CH[N(CH_3)_2]CH_3$
$C_6H_5CH[N(CH_3)_2]CH_3$[r] (24301-92-6)	175–185			53	$C_6H_5CH[N(CH_3)_2]CH_3$
$CH_3(CH_2)_9N(CH_3)_2$ (10237-16-8)	180–185			57	$CH_3(CH_2)_9N(CH_3)_2$
$CH_3(CH_2)_5CH(NH_2)CH_3$[s] (24301-94-8)	170–172			49	$CH_3(CH_2)_5CH(NH_2)CH_3$[t]
				28	$CH_3(CH_2)_5CH(NHCH_3)CH_3$
				1	$CH_3(CH_2)_5CH[N(CH_3)_2]CH_3$

[a] The reaction involved a 1:7 amine salt:DMSO ratio and ranged in quantity from 0.01 to 0.15 mol of amine salt. Reaction time was 20 hr. Registry no. for amine·HCl are given in parentheses. [b] Reported yields were of isolated products which were separated by column chromatography on alumina. [c] When mixtures of amines were obtained, the yields were determined by vpc. The identification of the primary and tertiary amines was by comparison of retention time and peak enhancement with those of authentic material. The secondary amines were suggested on the basis of vpc retention times. When the tertiary amine was the only product, this was identified by comparison of its ir spectrum with that of an authentic sample. In addition the N,N-dimethyl-1-phenyl-1-propylamine picrate, mp 167–169° (lit. mp 166.5–167.5°; H. M. Taylor and C. R. Hauser, *J. Amer. Chem. Soc.*, **82**, 1965 (1960)), was prepared. [d] *m*-Dinitrobenzene (0.062 mol) was added. [e] Identified by preparation of 1,3-diphenylpyrazoline, mp 117–119°; ir and nmr spectra, see experiment Reaction of Propiophenone, Ammonium Chloride and Paraformaldehyde in DMSO. [f] Identified by 2,4-dinitrophenylhydrazone, mp 158–161°, and comparison of ir spectrum with that of an authentic sample; see experiment cited in footnote *e*. [g] Identified by compairson of ir spectrum with that of an authentic sample. [h] For vpc separation the column and conditions used were the same as described in Table II, footnote *d*. [i] Identified by comparison of the ir and nmr spectra with those of an authentic sample. [j] This structure is suggested by comparison of the ir spectrum with that from α-hydroxymethylpropiophenone. [k] Vpc analysis was accomplished using the column described in Table II, footnote *d*, at a temperature of 200° and a helium flow rate of 60 cc/min. [l] Identified by comparison to authentic sample; see Experimental Section, Reaction of Deoxybenzoin, Ammonium Chloride, and Paraformaldehyde in Dimethyl Sulfoxide. [m] The crude solid had a mp 115–120°. [n] Vpc analysis was performed with a 3-ft column of 15% Carbowax 20-M on Chromosorb W at a temperature of 225° and a helium flow rate of 67 cc/min. [o] Reaction time was 60 hr. [p] *trans*-Stilbene was identified by mp 122–124° (lit. mp 124–125°; R. L Shriner and A. Berger, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 786) and by comparison of its ir spectrum with that of an authentic sample. [q] Vpc analysis used the column and helium flow rate described in Table II, footnote *d*, at a temperature of 190°. [r] Reaction time was 72 hr. [s] Reaction time was 71 hr. [t] Vpc analysis employed the column described in Table II, footnote *d*, at a temperature of 125° and a helium flow rate of 40 cc/min.

hydroxymethylpropiophenone, bp 130–132° (2.5 mm) (lit.[18] bp 158–162° (17 mm)); nmr (neat) τ 2.3 (m, 5, C_6H_5), 5.27 (s, 1, OH), 6.2 (m, 3 >CH–CH_2–), 8.88 (d, 3, CH_3).

A 2,4-dinitrophenylhydrazone derivative was prepared in the usual manner and recrystallization from ethanol–ethyl acetate gave an analytical sample, mp 151–153°.

(18) J. Colonge and G. Weinstein, *Bull Soc. Chim. Fr.*, 463 (1952).

Anal. Calcd for $C_{16}H_{16}N_4O_5$: C, 55.81; H, 4.68. Found: C, 55.66; H, 4.59.

Reaction of Deoxybenzoin, Ammonium Chloride, and Paraformaldehyde in Dimethyl Sulfoxide.—A solution of deoxybenzoin (3.92 g, 0.020 mol), paraformaldehyde (0.60 g, 0.020 mol), and ammonium chloride (1.06 g, 0.020 mol) in dimethyl sulfoxide (22.0 g, 0.28 mol) was heated at 176–180° for 20 hr. The reaction mixture was processed as described in Oxidation of

Amine Salts using $CHCl_3$ as extracting solvent. After removal of the $CHCl_3$, the residue was chromatographed on Fischer alumina and gave 0.83 g (11%) of 2,3,5,6-tetraphenylpyridine and 2.24 g (50%) of α-hydroxymethyldeoxybenzoin.

2,3,5,6-Tetraphenylpyridine was recrystallized from dioxane–water and had mp 241–242° (lit.[19] mp 232–233°); nmr ($CDCl_3$) τ 2.75 (m); uv ($CHCl_3$) λ_{max} 248 mμ (ε 29,600), 303 (16,400).

Anal. Calcd for $C_{29}H_{21}N$: C, 90.82; H, 5.52; N, 3.65. Found: C, 90.54; H, 5.82; N, 3.55.

α-Hydroxymethyldeoxybenzoin gave an ir spectrum (neat) consistent with the assigned structure: 3430 cm^{-1} (bonded OH), 1670 (C=O), 1050 (COH).

Attempted Reaction of Acetophenone and Ammonium Chloride in Dimethyl Sulfoxide.—A solution of acetophenone (0.10 mol) and ammonium chloride (0.10 mol) in dimethyl sulfoxide (0.70 mol) was heated at 170–178° for 23 hr. Aliquots were removed periodically, processed as above, and analyzed by tlc observing the disappearance of acetophenone. After 23 hr, when all the acetophenone was gone, the reaction mixture was processed as above and gave a dark resinous residue.

(19) H. Carpenter, *Justigs Liebigs Ann. Chem.*, **302**, 234 (1898).

Registry No.—$C_6H_5CH_2NH_2$, 100-46-9; $C_6H_5CH_2NH_2 \cdot HCl$, 3287-99-8; $C_6H_5CH_2NHCH_3 \cdot HCl$, 13426-94-3; $C_6H_5CH_2N(CH_3)_2 \cdot HCl$, 1875-92-9; $C_6H_5CH_2N^+(CH_3)_3I^-$, 4525-46-6; α-hydroxymethylpropiophenone, 16735-22-1; α-hydroxymethylpropiophenone 2,4-dinitrophenylhydrazone, 24301-96-0; 2,3,5,6-tetraphenylpyridine, 24301-97-1.

Ring–Chain Tautomerism of Derivatives of 1-(α-Aminobenzyl)-2-naphthol with Aromatic Aldehydes[1]

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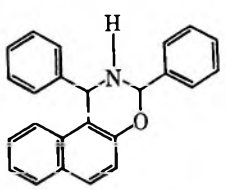
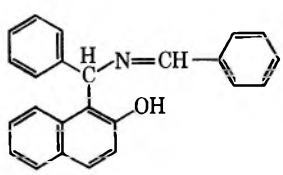
The ir spectra of the condensation products of 1-(α-aminobenzyl)-2-naphthol with benzaldehyde and substituted benzaldehydes indicate that in the crystalline state they have the 2,3-dihydro-1H-naphth[1,2-*e*][1,3]-oxazine structure. The nmr spectra show that in chloroform-*d* they equilibrate to a mixture of the *cis*- and *trans*-naphthoxazine (ring) and the corresponding Schiff base (chain) tautomers. The ring/chain ratio depends on the substituent in the benzaldehyde moiety. The greater the electron-withdrawing power of the substituent, the larger is the ring/chain ratio. In trifluoroacetic acid there is an equilibrium between *cis*- and *trans*-2,3-dihydro-1H-naphth[1,2-*e*][1,3]oxazonium and the corresponding immonium ions. Electron-withdrawing substituents in the benzaldehyde moiety increase the proportion of the naphthoxazonium ions.

Betti[2] reported the condensation of 2-naphthol, benzaldehyde, and ammonia in a ratio of 1:2:1. The crystalline product was first assigned the 1,3-diphenyl-2,3-dihydro-1H-naphth[1,2-*e*][1,3]oxazine structure (1).[3] Later, on the basis of its reaction in benzene with ethereal ferric chloride, which results in an intense reddish-violet color,[2a] the isomeric Schiff base structure, N-benzylidine-1-(α-aminobenzyl)-2-naphthol (2), was



1



2

proposed.[4] Hydrolysis of the condensation product in hydrochloric acid gives 1-(α-aminobenzyl)-2-naphthol hydrochloride which can be converted to the free base.[2b,3] The latter condenses readily with aliphatic and aromatic aldehydes, including benzaldehyde, and with aliphatic ketones.[4b] It was concluded that aliphatic aldehydes give 3-alkyl-1-phenyl-2,3-dihydro-1H-naphth[1,2-*e*][1,3]oxazines whereas aromatic aldehydes and aliphatic ketones give the Schiff bases.[4b]

In subsequent work, 1-(α-aminobenzyl)-2-naphthol was resolved,[5] and the dextrorotatory isomer was condensed with benzaldehyde and with various substituted benzaldehydes.[6] These condensation products are of substantial interest in that they show unusual differences in their rotatory powers. In benzene, they range from $[M]_D$ −990.7° for the *o*-nitrobenzaldehyde derivative to $[M]_D$ +2676.0° for the *p*-dimethylaminobenzaldehyde derivative.[7] In addition, the rotatory powers of the condensation products in benzene vary in a regular way and are correlated with the strength (pK_a) of the substituted benzoic acid corresponding to the aldehyde condensed with dextrorotatory 1-(α-aminobenzyl)-2-naphthol.[7] Inferences were drawn concerning the influence of the various substituents on the rotatory powers of these substances, all assumed to have the Schiff base structure.[7,8] More recently, the circular dichroism curves of a number of these condensation products were measured in ethyl alcohol.[9] It was assumed that the Schiff base chromophore would be dominant for all of these condensation products in ethyl alcohol.

It has been found, however, that the condensation product of 2-naphthol, benzaldehyde, and ammonia when treated in ethyl ether with nitrous acid gives a compound with the N-nitroso-1,3-diphenyl-2,3-dihydro-1H-naphth[1,2-*e*][1,3]oxazine structure.[10] On this

(1) Taken from the M.S. Thesis of N. E. C., Vanderbilt University, 1969.

(2) (a) M. Betti, *Gazz. Chim. Ital.*, **30** (II), 310 (1900); *J. Chem. Soc.*, **80** (I), 81 (1901); (b) "Organic Syntheses," Coll. Vol. I, 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1947, p 381.

(3) M. Betti, *Gazz. Chim. Ital.*, **31** (I), 377 (1901); *J. Chem. Soc.*, **80** (I), 611 (1901).

(4) (a) M. Betti, *Gazz. Chim. Ital.*, **33** (I), 17 (1903); *J. Chem. Soc.*, **84** (I), 510 (1903); (b) M. Betti and V. Foa, *Gazz. Chim. Ital.*, **33** (I), 27 (1903); *J. Chem. Soc.*, **84** (I), 511 (1903).

(5) M. Betti, *Gazz. Chim. Ital.*, **36** (II), 392 (1906).

(6) (a) M. Betti, *ibid.*, **37** (I), 62 (1907); (b) *ibid.*, **37** (II), 5 (1907); (c) M. Betti and G. C. Conestabile, *ibid.*, **46** (I), 200 (1916).

(7) M. Betti, *Trans. Faraday Soc.*, **26**, 337 (1930).

(8) T. M. Lowry, "Optical Rotatory Power," Dover Publications, Inc., New York, N. Y., 1964, p 326.

(9) A. Bertoluzza and A. Marinangeli, *Ann. Chim.* (Rome), **59**, 295 (1969).

(10) N. Ahmed, M. G. Hemphill, and F. E. Ray, *J. Amer. Chem. Soc.*, **56**, 2403 (1934).

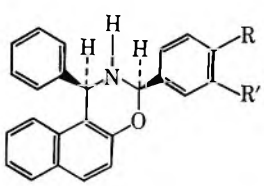
basis, the original condensation product was assigned structure **1**.

Recent quantitative studies of the ring–chain tautomerism of derivatives of *o*-hydroxybenzylamine with aldehydes and ketones[11] suggest that the reactivity of the condensation products of 1-(α-aminobenzyl)-2-naphthol with benzaldehyde and substituted benzaldehydes as well as the unusual differences in the rotatory powers of the optically active derivatives are the result of an equilibrium in solution between tautomers with the naphthoxazine (ring) (**1**) and the corresponding Schiff base (chain) (**2**) structures. The nature of the substituent on the aldehyde moiety would determine the amount of each tautomer present, electron-withdrawing substituents increasing the proportion of ring tautomer.

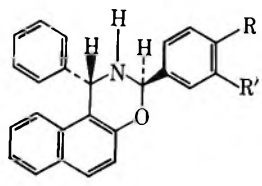
We have now prepared a number of condensation products of racemic 1-(α-aminobenzyl)-2-naphthol with benzaldehyde and substituted benzaldehydes (**3–9**) and have examined them spectroscopically in the solid state and as solutions in chloroform and in trifluoroacetic acid (TFA).

Results and Discussion

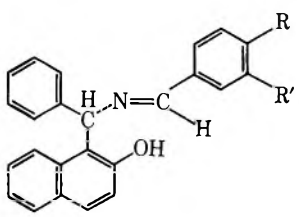
Solid State.—In the solid state, all of these condensation products have the naphthoxazine structure (**A** or **B**). The crystalline substances melt over a range of no more than 1° and do not show ir absorption (KBr disk) for the azomethine moiety. Among the absorption bands are two sharp bands at 1600–1610 and 1620–1630 cm^{-1}, except for **9** which has broad absorption from 1570 to 1630 cm^{-1}. In chloroform, an additional sharp absorption band at 1650–1660 cm^{-1} appears in the spectra of **5–8** while the bands at 1600–1610 and 1620–1630 cm^{-1} remain unchanged. This new band is assigned to the azomethine moiety of the Schiff base (chain) tautomer (**C**) in equilibrium with *cis*- and *trans*-naphthoxazine (ring) tautomers (**A** and **B**). A band at 1650–1660 cm^{-1} is not shown by **3** in chloroform since the concentration of the Schiff base tautomer is very small (see below). Both **4** and **9** are too insoluble in chloroform for the band to be observed.



A
D, protonated on N



B
E, protonated on N



C
F, protonated on N (*trans*)

3, R = NO_2; R′ = H
4, R = Cl; R′ = Cl
5, R = Br; R′ = H
6, R = Cl; R′ = H
7, R = H; R′ = H
8, R = $CH(CH_3)_2$; R′ = H
9, R = $N(CH_3)_2$; R′ = H

(11) A. F. McDonagh and H. E. Smith, *J. Org. Chem.*, **33**, 1 (1968).

Although there is no direct evidence for the configuration of the naphthoxazines in the solid state, they all probably have and are assigned the *cis* configuration (**A**).

Chloroform-*d* Solutions.—The nmr spectra (Table I) of the condensation products **3–9** in chloroform-*d* show the presence of the *cis*-naphthoxazine tautomer (**A**). In addition, in the spectra of **3** and **6–8**, evidence is found for the *trans*-naphthoxazine tautomer (**B**); in those of **6–9**, evidence is found for the Schiff base tautomer (**C**).

In each spectrum there is a singlet or a pair of singlets of equal intensity at 5.5–6.6 ppm assigned to the C-1 and C-3 protons of the *cis*-naphthoxazine tautomer (**A**).[12] For **3** and **6–8**, which have an appreciable solubility in chloroform-*d*, there is also a broad singlet or a pair of singlets of equal intensity at 5.7–5.9 ppm. These signals are less intense and at a slightly lower field than those assigned to the C-1 and C-3 protons of **A** and are assigned to the C-1 and C-3 protons of the *trans*-naphthoxazine tautomer (**B**). The respective assignments of the C-1 and C-3 proton signals to **A** and to **B** are made on the basis that the naphthoxazine tautomer with the *cis* configuration, for which both phenyl groups have a preferred pseudoequatorial conformation, is the more stable. Integration of the respective signals gives the *cis*/*trans* ratio as about 5 or 6 (Table I). In the spectra of **3**, **6**, and **7**, the amino proton signal is a broad hump centered at 2.3–2.6 ppm.

In the spectra of **6–9** in chloroform-*d* there are also two additional signals at 6.4–6.8 and 8.4–8.5 ppm. In each spectrum, these signals have equal integrated intensities and are assigned respectively to the methylidyne and the azomethine proton of the Schiff base tautomer (**C**). This tautomer presumably exists as a single stereoisomer[13] with the *trans* configuration.[14] In none of the spectra was the hydroxyl proton signal observed, and integration of the spectra indicates that it is obscured among the aromatic protons from 6.8 to 8.3 ppm. In the spectrum of **3**, the Schiff base tautomer was not detected and it is estimated that its concentration is less than 10% of that of **3A**. The Schiff base tautomer was also not detected in the nmr spectra of **4** and **5** for two reasons. First, the solubility of each in chloroform-*d* is less than that of **3** and **6–8** but about the same as **9**. Second, the amount of Schiff base tautomer, in comparison to the naphthoxazine tautomers, is less than that for **6–9**.

As shown in Table I, integration of those spectra in which both the naphthoxazine (ring) and Schiff base (chain) tautomers were detected gives the ratio of the former (*cis* and *trans* together) to the latter. Two factors limit the precision of these measuremens. First, the condensation products generally have a low solubility in chloroform-*d*, and in a variety of other solvents. Second, the relative number of nonaromatic protons is small. Nevertheless the data, of only qualitative significance, given in Table I clearly show that the greater the electron-withdrawing power of the

(12) For **9A**, the C-1 and C-3 proton signals are at an unusually low field. Also, since the ring/chain ratio is about 1, there is an ambiguity concerning the assignment of the respective signals to **9A** and to the methylidyne proton of **9C**.

(13) D. Y. Curtin, E. J. Grubbs, and C. G. McCarty, *J. Amer. Chem. Soc.*, **88**, 2775 (1966).

(14) G. Wettermark, *Ark. Kemi*, **27**, 159 (1967).

TABLE I

NMR DATA AND RING–CHAIN TAUTOMER RATIOS IN CHLOROFORM-*d* FOR DERIVATIVES OF 1-(α-AMINOBENZYL)-2-NAPHTHOL WITH AROMATIC ALDEHYDES

	Nmr[a]							
	Naphthoxazines (ring)			Schiff base (chain)				
	C-1 and C-3 protons[b]							
Condensation product	*cis*	*trans*	NH	CH—N	N=CH	Ratios *cis/trans*	Ratios Ring/chain	Concn, g/ml, $CDCl_3$
	Chemical shifts assigned, ppm downfield from TMS = 0							
3	5.53, 5.64	5.83	2.58	...[c]	...[c]	6		0.12
4	5.63	...[c]	...[c]	...[c]	...[c]			~0.06
5	5.62	...[c]	...[c]	...[c]	...[c]			~0.06
6	5.60	5.75	2.31	6.40	8.53	5	4	0.12
7	5.57, 5.65	5.77, 5.90	2.52	6.40	8.53	5	3	0.11
8[d]	5.56, 5.65	5.75, 5.90	...[c]	6.37	8.50	5	1	0.26
9[e]	6.35,[f] 6.60[f]	...[c]	...[c]	6.75[f]	8.45		1	~0.06

[a] Singlets measured at 60 MHz and *ca.* 35°. [b] No differentiation between these protons is made or implied. [c] Not detected. [d] For $CH(CH_3)_2$, 1.22 ppm (doublet, J = 6.5 Hz); 2.90 ppm (multiplet, J = 6.5 Hz). [e] For $N(CH_3)_2$, 3.02 ppm (singlet). [f] There is some ambiguity concerning these assignments. See footnote 12.

substituent in the phenyl ring of the aldehyde moiety, the larger is the ring/chain ratio. For a given aldehyde moiety, the percentage of ring tautomer is greater for the 1-(α-aminobenzyl)-2-naphthol derivative than for the derivative of *o*-hydroxybenzylamine.[11] This difference may be related in part to the slightly greater acidity of a 2-naphthol as compared with a phenol.[15]

Trifluoroacetic Acid Solutions.—All of the condensation products **3**–**9** have an appreciable solubility in TFA. Except for that of **8**, the nmr spectra of these solutions (Table II) show evidence for the *cis*-naphthoxazonium ion (**D**). This ion shows two singlets at 5.7–6.7 ppm of equal intensity which are assigned to the C-1 and C-3 protons. The spectra of **3**, **4**, and **9** shown an additional broad singlet at slightly lower field and of reduced intensity. This is assigned to the respective *trans*-naphthoxazonium ions (**E**). The *cis*/*trans* ratio appears to be about the same for the condensation products in TFA as in chloroform-*d*. This additional signal was not detected in the spectra of **5**–**7**, and it may be obscured by other signals. In the spectrum of **8** no signal for a naphthoxazonium ion was detected. It is estimated that the concentration of the *cis*-naphthoxazonium ion **8D** is less than 10% of that of the immonium ion **8F**.

TABLE II

NMR DATA AND RING–CHAIN TAUTOMER RATIOS IN TRIFLUOROACETIC ACID FOR DERIVATIVES OF 1-(α-AMINOBENZYL)-2-NAPHTHOL WITH AROMATIC ALDEHYDES

	Nmr[a]				
	Naphthoxazonium ions (ring) C-1 and C-3 protons[b]		Immonium ion (chain)		
Condensation product	*cis*	*trans*	N=CH	Ring/chain ratio	Concn, g/ml, TFA
	Chemical shifts assigned, ppm downfield from TMS = 0				
3	6.50, 6.73	6.90	...[c]		0.25
4	6.25, 6.65	6.80	9.05	2	0.26
5	6.23, 6.65	...[c]	9.08	1	0.21
6	6.23, 6.65	...[c]	9.05	0.5	0.26
7	5.70, 6.15	...[c]	8.59[d]	0.3	0.21
8[e]	...[c]	...[c]	8.57[d]		0.25
9[f]	5.95, 6.25	6.40	...[c]		0.24

[a] Singlets, except where noted otherwise, measured at 60 MHz and *ca.* 35°. [b] No differentiation between these protons is made or implied. [c] Not detected. [d] Doublet, J = 17 Hz. [e] For $CH(CH_3)_2$, 1.37 ppm (doublet, J = 6.5 Hz); 3.12 ppm (multiplet, J = 6.5 Hz). [f] For $N^+(CH_3)_2$, 3.53 ppm (singlet).

Also seen in the spectra of **4**–**8** in TFA is a broad singlet or a doublet at 8.6–9.1 ppm. This is assigned to the azomethine proton of the immonium ion (**F**). In none of the spectra was the hydroxyl or NH^+ proton signal or the methylidyne proton signal detected. The latter is obscured by the aromatic proton signals. When an extremely strong electron-withdrawing group is present on the aldehyde moiety, as in **3** and **9** in TFA, the immonium ion was not detected and its concentration in TFA is less than 10% of that of the naphthoxazonium ions. For **4F**–**6F**, with strong electron-withdrawing groups, the basicity of the azomethine nitrogen is decreased such that coupling of the azomethine proton with the rapidly exchanging immonium proton is not observed. Without a substituent (**7F**) or with an electron-injecting group (**8F**) the azomethine proton signal appears as a doublet. The coupling constant is 17 Hz and is good evidence that the configuration of the nitrogen to carbon double bond in **4F**–**8F** is *trans*, as expected.[16]

Table II shows the ring/chain ratio in those solutions in which both naphthoxazonium (ring) and immonium (chain) ions were detected. Again these data are of only qualitative significance. They clearly show, however, that the greater the electron-withdrawing ability of the substituent on the aldehyde moiety, the greater is this ratio. In contrast to the condensation products of *o*-hydroxybenzylamine with benzaldehyde and substituted benzaldehydes in TFA, for which no benzoxazonium ion was detected,[16] the 1-(α-aminobenzyl)-2-naphthol derivatives, except for **8**, have substantial concentrations of the naphthoxazonium ions present in TFA. This difference may also be related to the slightly greater acidity of a 2-naphthol as compared with a phenol.[15]

Experimental Section

Melting points were taken in open capillary tubes and are corrected. Elemental analyses were done by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared absorption spectra were obtained with a Beckman Model IR-10 spectrophotometer. Ir spectra of solids were obtained in potassium bromide disks and of chloroform solutions using matched 0.1-mm sodium chloride cells. Nmr spectra were determined at *ca.* 35° with a Varian A-60 spectrometer operating at 60 MHz. In all spectra, tetramethylsilane (TMS) was used as an internal standard, and chemical shifts are reported in parts per million downfield from the standard. Solutions in TFA were prepared by adding the acid (Baker Analyzed Reagent) to a known weight of sample in an

(15) A. Bryson and R. W. Matthews, *Aust. J. Chem.*, **16**, 401 (1963).

(16) A. F. McDonagh and H. E. Smith, *J. Org. Chem.*, **33**, 8 (1968).

nmr tube. The spectra were then run immediately. Tautomer ratios were estimated by integration of the respective spectra.

cis-**1,3-Diphenyl-2,3-dihydro-1H-naphth[1,2-*e*][1,3]oxazine (7A).**—As described previously,[2b] 2-naphthol was condensed with ammonia and benzaldehyde in 95% ethanol. After recrystallization from 95% ethanol, **7A** (71%) had mp 144–145°, ir $\nu_{max}^{CHCl_3}$ 1650 cm^{-1} (lit.[2b] mp 148–150°).

1-(α-Aminobenzyl)-2-naphthol.—Using the reported procedure,[2b] **7** was hydrolyzed with 20% hydrochloric acid. After recrystallization from ether–methanol 1-(α-aminobenzyl)-2-naphthol hydrochloride (85%) had mp 196–198° dec (lit.[2b] mp 190–220° dec).

The hydrochloride was decomposed in the usual way.[2b] The free base (98%) had mp 120–122°; nmr 5.68 (broad hump, 2 H, NH_2), 5.87 ppm (singlet, 1 H, methylidyne proton) (lit.[2b] mp 124–125°).

Condensation of 1-(α-Aminobenzyl)-2-naphthol with Aldehydes.—To *ca.* 0.03 mol of the free base in 75 ml of warm 95% ethanol was added a 10% molar excess of the aldehyde in 50 ml of warm 95% ethanol. The mixture was allowed to stand at room temperature overnight. The crystals which separated were collected by filtration and recrystallized to a constant melting point from an appropriate solvent. The reported yield was calculated on the basis of the weight of material with the constant melting point. A sample for elemental analysis was dried overnight at 56° (0.02 mm).

cis-**3-(*p*-Nitrophenyl)-1-phenyl-2,3-dihydro-1H-naphth[1,2-*e*][1,3]oxazine (3A)** resulted: light yellow needles (88%) from 95% ethanol, mp 174–175° (lit.[6b] mp 196° for an optically active isomer).

Anal. Calcd for $C_{24}H_{18}N_2O_3$: C, 75.38; H, 4.74. Found: C, 75.24; H, 5.10.

cis-**3-(3,4-Dichlorophenyl)-1-phenyl-2,3-dihydro-1H-naphth[1,2-*e*][1,3]oxazine (4A)** resulted: microscopic, white needles (48%) from benzene, mp 193°.

Anal. Calcd for $C_{24}H_{17}Cl_2NO$: C, 70.94; H, 4.22. Found: C, 71.34; H, 4.20.

cis-**3-(*p*-Bromophenyl)-1-phenyl-2,3-dihydro-1H-naphth[1,2-*e*][1,3]oxazine (5A)** resulted: microscopic, white needles (68%) from benzene, mp 181–182°, ir $\nu_{max}^{CHCl_3}$ 1650 cm^{-1}.

Anal. Calcd for $C_{24}H_{18}BrNO$; C, 69.24; H, 4.36. Found: C, 69.47; H, 4.50.

cis-**3-(*p*-Chlorophenyl)-1-phenyl-2,3-dihydro-1H-naphth[1,2-*e*][1,3]oxazine (6A)** resulted: microscopic, white needles (64%) from benzene, mp 173°, ir $\nu_{max}^{CHCl_3}$ 1660 cm^{-1} (lit.[6c] mp 158° for an optically active isomer).

Anal. Calcd for $C_{24}H_{18}ClNO$: C, 77.52; H, 4.88. Found: C, 77.49; H, 4.56.

cis-**3-(*p*-Isopropylphenyl)-1-phenyl-2,3-dihydro-1H-naphth[1,2-*e*][1,3]oxazine (8A)** resulted: white needles (57%) from 95% ethanol, mp 134–135°, ir $\nu_{max}^{CHCl_3}$ 1650 cm^{-1} (lit.[6a] mp 155–156° for an optically active isomer).

Anal. Calcd for $C_{27}H_{25}NO$: C, 85.45; H, 6.64. Found: C, 84.96; H, 6.69.

cis-**3-(*p*-Dimethylaminophenyl)-1-phenyl-2,3-dihydro-1H-naphth[1,2-*e*][1,3]oxazine (9A)** resulted: yellow needles (58%) from ethylene chloride, mp 192–193° (lit.[6c] mp 219–220° for an optically active isomer).

Anal. Calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36. Found: C, 81.57; H, 6.06.

Registry No.—**3A**, 24609-72-1; **3B**, 24609-73-2; **4A**, 24609-74-3; **5A**, 24609-75-4; **6A**, 24609-76-5; **6B**, 24609-77-6; **6C**, 24605-71-8; **7A**, 24609-78-7; **7B**, 24609-79-8; **7C**, 24609-80-1; **8A**, 24609-81-2; **8B**, 24609-82-3; **8C**, 24609-84-5; **9A**, 24609-85-6; **9C**, 24609-86-7.

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Isolation of Primary Decomposition Products of Azides. II. Azidopyrazoles[1]

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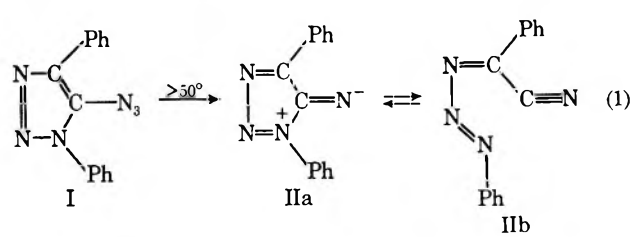
Variously substituted 5-aminopyrazoles have been converted into the azides, which lose nitrogen above room temperature to form red, monomeric products analogous to those from 5-azidotriazoles. The same or isomeric substances are formed by oxidations of 5-aminopyrazoles, along with variable quantities of 5,5′-azopyrazoles. Both are converted back into 5-aminopyrazoles by reducing agents, in some instances through an isolable open-chain β-hydrazono nitrile. The overall behavior of the fragmentation products of 5-azidopyrazoles indicates a β-azoacrylonitrile structure, which may equilibrate with a kinetically significant concentration of a cyclic form. Whereas some of them are identical with the β-azoacrylonitriles obtained by oxidizing the hydrazones of β-ketopropionitriles, many are geometrical isomers, such as the product from 1-phenyl-3-methyl-5-azidopyrazole, which is distinct from the known β-phenylazocrotononitrile, into which it can be converted by acid, and from the "azipyrazole" of Michaelis and Schäfer. The fragmentation product of 1,4-diphenyl-5-azidotriazole can be reduced to 1-phenyl-3-(α-cyanobenzyl)triazene, which then isomerizes to the 5-aminotriazole.

We recently reported[2] the fragmentation of 5-azido-1,4-diphenyltriazole, which loses 1 mol of nitrogen at temperatures above about 50° to form a deep red, monomeric compound (II), whose chemical and physical characteristics suggested a mobile equilibrium in solution between an open-chain and a cyclic structure (eq 1). Most of the reactions of this substance involved further loss of nitrogen, which added complications to the investigation although at the same time giving



(1)

interesting information. In order to reduce such complications and to gain further information about fragmentation products of heterocyclic azides, we have now investigated the analogous pyrazole systems.

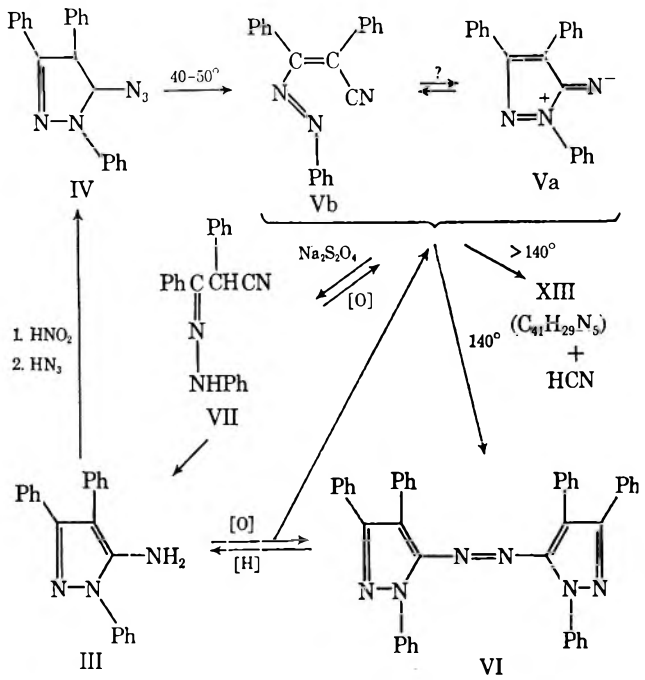
(1) Presented in part at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., March 1967. Address correspondence to P. A. S. S.

(2) P. A. S. Smith, L. O. Krbechek, and W. Resemann, *J. Amer. Chem. Soc.*, **86**, 2025 (1964).

Results

The analogous azidopyrazole (IV) was prepared from the known[3] 5-amino-1,3,4-triphenylpyrazole (III). It decomposed in solution slightly above room temperature, losing 1 mol of nitrogen, and forming a deep red product (V) nearly quantitatively (Scheme I). The

SCHEME I



infrared spectrum of V in concentrated solution showed only a very weak nitrile band at 2150 cm^{-1}.

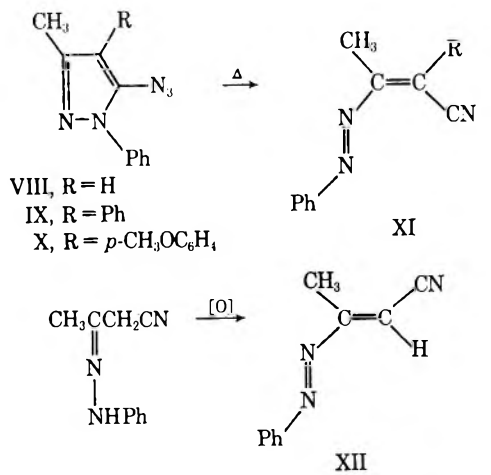
The same substance, V, was obtained by treating the amine (III) with oxidizing agents, such as dilute aqueous permanganate; the equivalent of two hydrogen atoms was consumed. The formation of V by permanganate oxidation was always accompanied by a yellow substance (VI) having the same analysis; under certain conditions, notably in solutions of low acidity, VI was overwhelmingly the major product. Molecular weight determinations were only approximate, owing to the low solubility of VI, but indicated a dimer of V. Both V and VI could be reduced to the original amine in high yield, but V was not converted to VI under the conditions of the oxidation experiments. The infrared spectrum of VI was similar to those of III and IV and was compatible with an azopyrazole structure.

Although reduction of V ordinarily gave back the aminopyrazole III, with sodium dithionite an intermediate stage could be isolated. When the reactants were mixed in aqueous alcoholic solution at room temperature, the red color of V disappeared at once. If the solution was drowned in water promptly, a colorless solid was precipitated whose melting behavior indicated a mixture, and whose infrared spectrum was consistent with an open-chain β-hydrazono nitrile structure, VII, contaminated with III. On standing, this product was converted completely to III.

The crude β-hydrazono nitrile VII was oxidized back to V (free of VI) very rapidly by treatment with N-bromosuccinimide. The cyclic isomer, III, was oxidized relatively slowly under the same conditions and gave rise to both V and VI. The chemistry of the fragmentation products of the 1-*p*-tolyl and 4-*p*-chlorophenyl analogs of IV was completely parallel to that of the triphenyl system. The permanganate oxidation of the 1-*p*-tolyl analog of III, however, gave only the azoxypyrazole rather than the azopyrazole, whereas phenyliodoso acetate gave, very slowly, the analog of V.

Three 5-azidopyrazoles bearing a methyl group in the 3 position [1-phenyl-3-methyl- (VIII), 1,4-diphenyl-3-methyl- (IX), and 1-phenyl-3-methyl-4-*p*-anisyl-5-azidopyrazole (X)] each gave rise to red substances analogous to V in high yields at mild temperatures. However, oxidation of the corresponding β-hydrazono nitriles gave substances isomeric with, but functionally similar to, the fragmentation products of the azides, and only in one case, the phenylhydrazone of α-anisylacetoacetonitrile, was any of the fragmentation isomer formed as well.

Azide VIII lost nitrogen to form a red substance, mp 61°, whose nmr and ultraviolet spectra were distinct from, although similar to, those of the oxidation product, mp 81°, of the phenylhydrazone of acetoacetonitrile. These isomers could not be interconverted by heating in various solvents, but brief exposure of the 61° compound to hydrochloric acid converted it to the 81° compound. The small differences in their spectra are consistent with their formulation as geometrical isomers (XI and XII). Permanganate oxidation of 5-amino-1-phenyl-3-methylpyrazole gave the azo dimer accompanied by products of more deep-seated changes, which were not further investigated. Oxidation with hydrogen peroxide in acetic acid gave only the oxygenated dimer reported by Searles and Hine.[4] In hydrochloric acid, oxidation by peroxide gave instead 4,4-dichloro-3-methyl-1-phenylpyrazol-5-one, and oxidation



with N-bromosuccinimide in the presence of pyridine gave 2-bromo-3-phenylazocrotononitrile. The cleanest oxidation was with phenyliodoso acetate, which gave XI in high yield. In no case were we able to detect formation of the phenylazocrotononitrile of mp 109° reported by Searles and Hine[4] and Michaelis and Schäfer.[5] The thermolysis product of IX and the oxidation product of the phenylhydrazone of α-phenylacetoacetonitrile showed similar differences.

(3) R. Walter and P. G. Schickler, *J. Prakt. Chem.*, [II] **55**, 305 (1897).

(4) S. Searles, Jr., and W. R. Hine, Jr., *J. Amer. Chem. Soc.*, **79**, 3175 (1957).

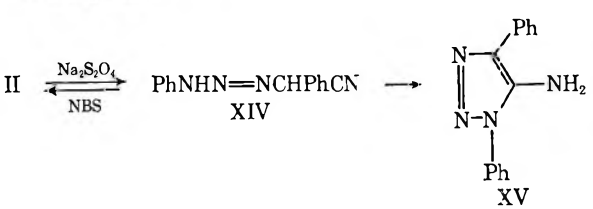
(5) A. Michaelis and A. Schäfer, *Ann.*, **397**, 119 (1913); **407**, 234 (1915).

The *p*-methoxy analog of IX, 1-phenyl-3-methyl-4-*p*-anisyl-5-azidopyrazole (X), gave a single product upon thermolysis, which could be reduced to the phenylhydrazone of α-anisylacetoacetonitrile. Oxidation of the phenylhydrazone gave a mixture of two isomers, the nmr spectrum of which corresponded to that of the product from thermolysis of the azide plus an isomer in smaller amount with methyl resonances slightly shifted from those of the other in the ratio 3:1.

In none of the foregoing three systems could interconversion of the isomeric products be observed under the conditions of the thermolyses or oxidations. The β-hydrazono nitriles, however, readily cyclized to the aminopyrazoles. No conditions could be found that would accomplish partial reduction to the intermediate hydrazopyrazole stage.

Although the fragmentation product V did not show detectable conversion to the azo dimer VI under the experimental conditions used to produce V and/or VI, other ways to bring about such a conversion were found. Heating at temperatures below 100° left V unchanged, and heating at 170° formed XIII, $C_{41}H_{29}N_5$ (dimerization with loss of hydrogen cyanide, a study that will be reported separately), but heating under vacuum at intermediate temperatures, such that sublimation took place, converted V slowly and incompletely to its azo dimer (with concurrent formation of some XIII). The fragmentation products of the other triaryl-5-azidopyrazoles also dimerized under these conditions. In another investigation, dealing with the reaction of Grignard reagents with V and analogs, dimerization was also encountered quite unexpectedly. Treatment of V with phenylmagnesium bromide (among others) resulted in rapid reaction (change of color, qualitative disappearance of Grignard reagent); work-up produced the azo dimer VI in high yields. The function of the Grignard reagent in this conversion has not been fully elucidated, but it is not reduction followed by oxidation by air. Treatment with strong sodium hydroxide solution also caused dimerization.

The isolation of β-hydrazono nitrile intermediates in the reduction of V and its analogs was found to be paralleled by the reduction of the fragmentation product (II) of the azidotriazole I which we had earlier observed[2] to result in formation of the aminotriazole (XV). Treatment of II with sodium dithionite under the same mild conditions as used with V formed a highly labile, colorless, crystalline substance isomeric with the aminotriazole XV, to which it could be isomerized. This substance was easily oxidized back to II and must possess the triazene structure XIV or a tautomer thereof.



5-Amino-1,4-diphenyltriazole (XV) was also found to undergo oxidation in a manner analogous to the aminopyrazoles. The azo dimer predominated in oxidation by permanganate, the amount depending on the acidity of the medium.

Discussion

The foregoing results show that decomposition of 5-azidopyrazoles and 5-azidotriazoles results in fragmentation with ring opening to form nitriles such as Vb, IIb, and XI. The observations that the first stage in reduction has an open-chain structure, which is more easily reoxidized than is the cyclic tautomer (*e.g.*, III), neutralize the earlier argument that exceptionally easy reduction to cyclic products implied the electronically stabilized, cyclic, singlet nitrene structure (Va, etc.).

On the other hand, dimerization of the fragmentation products upon heating is not so simply reconciled with an open-chain structure and is best explained by equilibration with a significant (although perhaps quite small) concentration of the cyclic, nitrenoid form such as Va. The structure of the dimers as symmetrical azo compounds is well supported by spectrographic similarity between them and compounds of known pyrazole (or triazole) structure, by the fact that, when aliphatic protons are present, a symmetrical dimer is indicated by the nmr spectrum and by the observation that the chemistry of the dimers parallels that of aromatic azo compounds.

The observations on oxidation of the amines (*e.g.*, III) and hydrazono nitriles (*e.g.*, VII) raise two important questions: why were the monomeric products in some cases isomeric with those from fragmentation of the corresponding azides, and how did the dimeric products arise under conditions where the monomers were stable? Three explanations of the first question suggest themselves. One possible answer, that the conditions of the oxidation experiments were sufficient to catalyze conversion to a more stable geometrical isomer, is not tenable. The oxidations were for the most part carried out in neutral or mildly basic media in which the isomers, such as X and XI, were observed to be quite stable to interconversion.

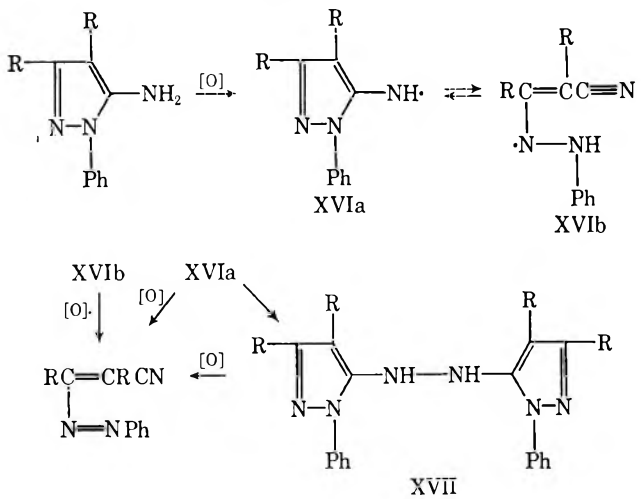
A more likely explanation is a consequence of the fact that the geometry about the α,β carbon–carbon bond in β-hydrazono nitriles is not fixed as it is in the cyclic tautomers. The geometry of the oxidation product, whether kinetically or thermodynamically determined, need not then be the same as that from the azide. Ring–chain tautomerism in certain amino azoles is well established,[6] and it is reasonable to assume that it can occur with the amino pyrazoles. The fact that oxidation of the open-chain forms is demonstrably much faster than oxidation of the cyclic tautomers is consistent with the hypothesis that ring opening to the β-hydrazono nitrile structure may precede the oxidation step for amino azoles.

Lastly, oxidation may proceed in two stages through an amino radical (XVI) which may also undergo ring–chain tautomerization before further oxidation to the isolated product. This possibility provides an explanation for the second question. Dimerization of amino radicals to form hydrazopyrazoles (XVII) (or hydrazotriazoles) provides a reasonable route to the observed azo dimers.[7] Further oxidation of the amino radicals would, of course, be competitive with dimerization and would be influenced by conversion to their

(6) For example, see F. R. Benson, "Heterocyclic Compounds," Vol. 8, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1967, p 63.

(7) L. Horner and J. Dehnert, *Ber.*, **96**, 786 (1963).

conjugate acids with the result that the proportion of monomer to dimer in the products would vary with the oxidation conditions, as observed. An alternative explanation is that the azo compounds may arise by reaction of a nitroso compound with unchanged amine



XVIa XVIb XVII

(Mills reaction) as demonstrated by Konaka, Koruma, and Terabe for basic oxidation of primary arylamines.[8] This path would not, of course, be available in thermolysis of azides. Although the fact that no nitroso compounds or derived oxygenated functional groups could be detected with most of the amines does not encourage the view that nitroso compounds are involved in our oxidations (which were mostly carried out in neutral to acidic medium); the fact that one example (1-*p*-tolyl-3,4-diphenyl-5-aminopyrazole) did give an azoxy compound demands that involvement of a nitroso intermediate be taken seriously. Unfortunately, the nitrosopyrazoles could not be prepared for investigation, but in other situations it has been shown[8] that azoxy compounds may arise from N-hydroxyhydrazine intermediates in the Mills reaction.

The two isomeric, orange-red β-phenylazocrotononitriles that we have obtained, mp 61 and 81°, do not correspond with the one obtained by Searles and Hine,[4] mp 109°, "ivory" in color from the peroxide oxidation of 1-phenyl-3-methyl-5-aminopyrazole followed by sublimation and from oxidation of acetoacetonitrile phenylhydrazone, and which they felt to be the same as "azipyrazole" obtained by Michaelis and Schäfer.[5] Since we were not able to obtain this substance by any procedure, we have not been able to compare it with our substances. The isomer of mp 81° is presumably the same one reported by Quilico and coworkers[9] and also obtained by Searles and Hine. It sublimed unchanged without detectable conversion to the substance of mp 109°. There are, of course, four possible geometrically isomeric β-phenylazocrotononitriles, whose electronic spectra would vary with the effectiveness of conjugation.

The isomer obtained from the azide must have a *trans*-azo configuration with the methyl group *trans* to the cyano group (XI) as fixed by the ring structure from which it is derived. Since the isomer of mp 81° is thermodynamically more stable, it, too, must have the *trans*-azo configuration and consequently must have the methyl group *cis* to the cyano group (XII). Isomerization of XI to XII would reduce interference and lower energy only when R = H; it is thus understandable that only in this instance was isomerization observed. The "azipyrazole" of Michaelis, which Searles and Hine[4] have convincingly deduced to be a β-phenylazocrotononitrile, would then have to have a *cis*-azo configuration.

There is no compelling reason not to accept a concerted fragmentation process for thermolysis of the foregoing 5-azido azoles to unsaturated nitriles, but it should be noted that the bicyclic azirine structure assigned to "azipyrazole" by Michaelis and Schäfer[5] is analogous to the cyclohexadienoazirine that has been proposed as an intermediate in certain reactions of arylnitrenes,[10] perhaps in equilibrium with the singlet nitrene.

A number of examples of the analogous opening of pyrazole, indolizine, and pyrrolopyrimidine rings by an alternative nitrene-forming reaction, deoxygenation of nitro and nitroso azoles, have recently been reported.[11]

Experimental Section[12]

α-*p*-Chlorophenylbenzoylacetonitrile was prepared by adding 8 g of potassium *t*-butoxide to 10 g of ethyl benzoate and 10 g of *p*-chlorophenylacetonitrile in 50 ml of dimethylformamide. After the initial exothermic reaction, the mixture was stirred for 2 hr and then poured into ice water with stirring. After extraction of insoluble material with ether, the aqueous solution was acidified, precipitating 7.0 g (30%) of a cream-colored solid, mp 100°. Recrystallization from aqueous ethanol gave an analytical sample, mp 102–104°.

Anal. Calcd for $C_{15}H_{10}ClNO$: C, 70.49; H, 3.94; N, 5.45. Found: C, 70.63; H, 4.04; N, 5.39.

α-*p*-Anisylacetoacetonitrile.—This substance was prepared in 60% yield from *p*-anisylacetonitrile and ethyl acetate in dimethylformamide solution in the presence of 1 equiv of potassium *t*-butoxide, as described for the foregoing compound. It formed cream-colored needles, mp 83–85°.

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.99; H, 5.78; N, 7.35.

Aminopyrazoles. 5-Amino-3,4-diphenyl-1-*p*-tolylpyrazole.—An aqueous solution of 5.0 g of *p*-tolylhydrazine hydrochloride was added to a warm solution of 7.5 g of α-benzoylphenylacetonitrile in 100 ml of glacial acetic acid, and the mixture was heated on a steam bath for 25 hr. Drowning the mixture in 300 ml of ice-cold water precipitated 7.0 g (65%) of the pyrazole. Recrystallization from chloroform–ethanol mixture gave an analytical sample, pale yellow needles, mp 183–185°.

Anal. Calcd for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N, 12.91. Found: C, 80.96; H, 6.11; N, 12.76.

5-Amino-4-*p*-anisyl-3-methyl-1-phenylpyrazole was prepared in a similar manner, colorless needles, mp 137–139°.

Anal. Calcd for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.13; N, 15.04. Found: C, 72.85; H, 6.03; N, 15.02.

5-Amino-4-*p*-chlorophenyl-1,3-diphenylpyrazole, mp 149–150°, was also prepared in this way.

Anal. Calcd for $C_{21}H_{16}N_3Cl$: C, 72.93; H, 4.66; N, 12.15; Cl, 10.26. Found: C, 73.05; H, 4.64; N, 12.10; Cl, 10.26.

5-Azido-1,3,4-triphenylpyrazole.—Benzoylphenylacetonitrile was treated with phenylhydrazine to obtain 5-amino-1,3,4-triphenylpyrazole, mp 168–169°, originally reported[3] as the phenylhydrazone of the keto nitrile, mp 169°. Diazotization of

(8) R. Konaka, K. Koruma, and S. Terabe, *J. Amer. Chem. Soc.*, **90**, 1801 (1968).

(9) A. Quilico and R. Justoni, *Rend. Ist. Lomb. Sci. Lett.*, **69**, 587 (1963); A. Quilico, R. Fusco, and V. Rosanti, *Gazz. Chim. Ital.*, **76**, 30 (1946).

(10) R. A. Abramovitch and B. A. Davis, *Chem. Rev.*, **64**, 149 (1964).

(11) (a) J. B. Wright, *J. Org. Chem.*, **34**, 2474 (1969); (b) W. J. Irwin and D. G. Wibberley, *Chem. Commun.*, 878 (1968); (c) H. Dounchis, doctoral dissertation, University of Michigan, 1968.

(12) Melting points are corrected. Infrared spectra were taken on a Perkin-Elmer Model 237B instrument. Nmr spectra were determined with a Varian Model A60 instrument. Ultraviolet spectra were measured with a Cary Model 11 spectrophotometer. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich., and Micro-Tech Laboratories, Skokie, Ill.

TABLE I

5-AZIDOPYRAZOLES AND THEIR THERMOLYSIS PRODUCTS

5-Azidopyrazole	Mp, °C	Thermolysis product		
		Yield, %	Mp, °C	Color
1-Phenyl-3-methyl[a] (a)	Oil	50[b]	59.5–61	Deep red
1-*p*-Tolyl-3,4-diphenyl[c] (b)	110 dec	87[d]	135–137	Red
1,4-Diphenyl-3-methyl[e] (c)	73–74 dec	60[f]	102–104	Deep red
1-Phenyl-3-methyl-4-*p*-nitrophenyl[g] (d)	108 dec	88[h]	167–169	Bronze-red
1,3-Diphenyl-4-*p*-chlorophenyl[g] (e)		*i*	157–158	Red
1-Phenyl-3-methyl-4-*p*-anisyl[g] (f)		80[j]	126–127	Red
1,4-Diphenyl[g] (g)	68–69 dec	90[k]	100	Garnet

[a] Accompanied by 10–15% of 1-phenyl-3-methyl-4-nitroso-5-aminopyrazole, mp 202° (lit. 200°), and not obtained pure. [b] Nmr ($CDCl_3$) δ 2.13 ppm (C–CH_3); uv max (ethanol) 323 (ϵ 38,900), 238 (3000) and 232 mμ (3000); ir (Nujol) 2220, 1820 (w), 1620, 1595, 1585, 1485 cm^{-1}. *Anal.* Calcd for $C_{10}H_9N_3$: C, 70.15; H, 5.30; N, 24.55. Found: C, 70.40; H, 5.40; N, 24.60. [c] *Anal.* Calcd for $C_{22}H_{17}N_5$: C, 75.19; H, 4.88; N, 19.93. Found: C, 75.25; H, 5.06; N, 19.79. Yield, 80%. [d] Nmr ($CDCl_3$) δ 2.40 (s, 3), 7.0–7.6 (m, 12), 7.77 (s, 1), and 7.92 ppm (s, 1); ir (Nujol) 2230 (w) 1610, 1595 (w), 1575 (w) cm^{-1}. *Anal.* Calcd for $C_{22}H_{17}N_3$: C, 81.71; H, 5.30; N, 13.00. Found: C, 81.63; H, 5.37; N, 13.06. [e] Attempts at recrystallization resulted in decomposition; estimated yield 60%. [f] Based on amine. Nmr (CCl_4) δ 2.33 (s, 3), 7.3–7.7 (m, 8), and 7.9–8.2 ppm (m, 2); ir (Nujol) 2210, 1575–1600, 1445, and 1430 cm^{-1}. *Anal.* Calcd for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.62; H, 5.44; N, 16.91. [g] Not purified or analyzed. [h] Based on amine. Nmr ($CDCl_3$) δ 2.20 (s, 3), 7.4–8.4 (m, 7), 8.25 (s, 1), and 8.4 ppm (s, 1); ir (Nujol) 2220 (w), 1610, 1600, 1520–1530, 1410 cm^{-1}. *Anal.* Calcd for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.82; H, 4.21; N, 19.10. [i] Ir (Nujol) 2220 (w), 1595, 1490, 1445, 1435 cm^{-1}. *Anal.* Calcd for $C_{21}H_{14}N_3Cl$: C, 73.35; H, 4.11; N, 12.22. Found: C, 73.34; H, 4.13; N, 12.16. [j] Based on amine. Nmr ($CDCl_3$) δ 2.25 (s, 3, C–CH_3), 3.81 (s, 3, O–CH_3), 6.87 (s, 1), 7.03 (s, 1), 7.3–7.7 (m, 5), and 7.05–8.05 ppm (m, 2); ir (Nujol) 2220, 1610, 1590, 1515, 1420 cm^{-1}. *Anal.* Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.59; H, 5.47; N, 15.17. [k] Based on amine. *Anal.* Calcd for $C_{15}H_{11}N_3$: C, 77.24; H, 4.76; N, 18.02. Found: C, 77.36; H, 4.82; N, 18.00.

1.56 g (0.01 mol) of amine dissolved in 100 ml of concentrated hydrochloric acid with the help of *ca.* 25 ml of glacial acetic acid was accomplished by adding a concentrated solution of 0.38 g of sodium nitrite all at once to the chilled solution, which became red. After 15 min, a little urea was added, followed by 0.4 g of sodium azide dissolved in a little water; some gas was evolved slowly. Addition of water in portions (total *ca.* 50 ml) precipitated a cream-colored, crystalline substance. The mixture was filtered after 3 hr and the solid was washed with water; wt 1.55 g (89%), mp 90° with gas evolution and formation of a red melt. Recrystallization from cold acetone by addition of water gave an analytical sample: mp 93–96° dec; ir (Nujol) 2128, 2080 (w) cm^{-1} (–N_3).

Anal. Calcd for $C_{21}H_{15}N_5$: C, 74.76; H, 4.48; N, 20.76. Found: C, 74.80; H, 4.20; N, 20.70.

The other 5-azidopyrazoles were prepared similarly; they are listed in Table I.

Thermolysis of 5-Azido-1,3,4-triphenylpyrazole.—A solution of 1.19 g of the azide in 30 ml of ligroin was heated near the boiling point for 30 min. The blood-red solution deposited clusters of deep red needles of V on cooling; they were collected by filtration and washed with light petroleum ether: wt 1.00 g (96%); mp 140–141° after partial liquefaction and resolidification over the range 125–135°; uv max (hexane) 359 mμ (ϵ 2.13 × 10^4); ir (Nujol) 2220 (w), 1610 (w), 1595 (w), 1570 (w), and 1305 cm^{-1}; nmr ($CDCl_3$) δ 8.7 (m, 13) and 9.45 ppm (m, 2). An analytical sample recrystallized from isopropyl alcohol had mp 141–142° (softened 125–130°).

Anal. Calcd for $C_{21}H_{15}N_3$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.78; H, 4.95; N, 13.50.

The thermolysis products of the other 5-azidopyrazoles are listed in Table I.

Reduction of V. A. With Mercaptoacetic Acid.—A suspension of 0.35 g of V in 6 ml of isopropyl alcohol was mixed with 0.3 ml of 80% aqueous mercaptoacetic acid. The red color disappeared in a few moments after slight warming was applied without apparent gas evolution. Filtration of the cooled mixture left pale, cream-colored crystals of amine III which were washed with methanol, wt 0.19 g (55%), mp 168° (undepressed by an authentic sample). From the filtrates, a further 0.11 g was obtained (total yield 85%).

B. With Sodium Dithionite.—When samples of V were shaken in ethereal solution with aqueous sodium dithionite, the red color took nearly 30 min to disappear, and the product obtained was amine III. When 0.3 g of V was dissolved in 50 ml of ethanol and added all at once to 50 ml of a concentrated aqueous solution of sodium dithionite, the color disappeared at once. The resulting mixture was immediately poured into 250 ml of cold water (total elapsed time ~30 sec), and the off-white precipitate was filtered off and washed with water: mp 60–80°, with resolidification at *ca.* 100° and remelting at 168–169° (mp of amine III); ir (Nujol) 3300 (s) (NH) and 2200 (s) (–C≡N) cm^{-1}. All attempts at purification by recrystallization or sublimation gave only amine III, and the spectrum of freshly prepared solutions corresponded to a mixture containing 50% or more of amine III. Thin layer chromatography showed two components, one of which was amine III and the other a more mobile substance. Treatment of the crude reduction product with 1.3 mol equiv of N-bromosuccinimide and twice its weight of pyridine in methylene chloride resulted in immediate formation of a deep red color. Evaporation of the solvent, extraction of the residue with ether, washing of the ether with dilute hydrochloric acid and with water, drying, evaporating, and crystallizing from ethanol gave pure V, mp 150°; no dimer (VI) could be detected.

Thermolysis of V.—A flask containing 100 mg of V was repeatedly evacuated and flushed with nitrogen, after which the pressure was reduced to 20 mm and the vessel was heated at 140° for 18 hr. When the cooled residue was stirred with acetone and then filtered, 15 mg (15%) of VI, mp 269°, was obtained. Addition of water to the filtrate precipitated a red substance (XIII), the major product, in varying but substantial yields. Recrystallization from aqueous acetone gave an analytical sample as bright red plates: mp 149–151°; uv max (ethanol) 262 mμ (ϵ 17,000), 387 (7000), 430 (shoulder, 5000).

Anal. Calcd for $C_{41}H_{29}N_5$: C, 83.22; H, 4.94; N, 11.84; mol wt, 591.68. Found: C, 83.07; H, 4.79; N, 12.11; mol wt (mass spectroscopy), 591.

Similar results were obtained from experiments in which the residual atmosphere was oxygen instead of nitrogen. At higher temperatures (*e.g.*, 145°), no VI was produced, and the only product was XIII in yields up to 80%; at lower temperatures, little or no reaction occurred in a reasonable time.

Similar results were obtained with the 1-*p*-tolyl analog of V (the thermolysis product of 1-*p*-tolyl-3,4-diphenyl-5-azidopyrazole) which at 115° gave rise in 20% yield to the azopyrazole dimer. At temperatures of 130° and above, this substance was not detected; instead, a red compound was formed, analogous to that from the triphenyl derivative: mp 170–172°; uv max (ethanol) 251 mμ (ϵ 15,000), 356 (6000), 380 (shoulder, 3500).

Anal. Calcd for $C_{43}H_{33}N_5$: C, 83.33; H, 5.37; N, 11.30. Found: C, 83.32; H, 5.31; N, 11.41.

Reaction of V with Sodium Hydroxide.—A suspension of 500 mg of V in 25% sodium hydroxide solution was overlaid with tetrahydrofuran and allowed to stand for 20 hr. The residual solid was collected and extracted with warm ethanol which left 50 mg (10%) of the dimer VI, mp 270°. The filtrate deposited crystals of 5-amino-1,3,4-triphenylpyrazole on cooling, wt 200 mg (40%), mp 170°.

Oxidation of Aminopyrazoles.—The various aminopyrazoles were oxidized in a manner similar to the experiments described here for the representative example, 5-amino-1,3,4-triphenylpyrazole (III). A solution of 0.50 g (1.6 mmol) of III in 10 ml of benzene was stirred briefly with a solution of 0.20 g (1.25 mmol) of potassium permanganate in 10 ml of water; no visible reaction took place until *ca.* 1 ml of glacial acetic acid was added, whereupon the benzene layer gradually became vermilion, and a sludge of manganese dioxide formed. After 18 hr, the mixture was filtered, and the filter cake was washed well with hot benzene. The combined benzene solutions were washed with water, filtered through cotton, and evaporated, leaving a vermilion powder, wt 0.41 g (82%), mp 214–218°. Washing with boiling isopropyl alcohol removed the red color and left a bright yellow powder, mp 269–270°. Recrystallization from benzene or glacial acetic acid gave an analytical sample of VI: mp 271–272°; nmr (CF_3COOH) δ 8.3–9.3 ppm (m); ir (Nujol) 1650, 1600, and 1500 cm^{-1}.

Anal. Calcd for $C_{42}H_{30}N_6$: C, 81.53; H, 4.89; N, 13.59. Found: C, 81.13; H, 4.84; N, 13.85.

A similar experiment in which the reaction medium was 30 ml of 5% of sulfuric acid and 10 ml of acetone produced VI in 30% yield and V in 10% yield (separated by extracting the latter with chloroform or benzene and recrystallizing from 2-propanol). The actual yield of V was presumably somewhat higher for there were evident losses in separation. Experiments carried out in glacial acetic acid gave VI in approximately 80% yields accompanied by ~5% of V. The addition of about 2 ml of 2% sulfuric acid per gram of amine accelerated the disappearance of the permanganate color and caused small increases in the yield of V at the expense of VI.

Oxidation of 5-amino-4-*p*-chlorophenyl-1,3-diphenylpyrazole in a similar manner gave orange-yellow **4,4′-bis-*p*-chlorophenyl-1,1′,3,3′-tetraphenyl-5,5′-azopyrazole** in 70% yield: mp 282°; ir (Nujol) 1600, 1545, 1500, 1420 cm^{-1}.

Anal. Calcd for $C_{42}H_{28}Cl_2N_6$: C, 71.72; H, 4.10; N, 12.25. Found: C, 72.02; H, 3.95; N, 12.01.

Similarly, oxidation of 5-amino-1,4-diphenylpyrazole in glacial acetic acid gave **1,1′,4,4′-tetraphenyl-5,5′-azopyrazole**, orange needles, in 60% yield: mp 209–211°; nmr ($CDCl_3$) δ 7.25 (s, 10) and 7.72 ppm (s, 1).

Anal. Calcd for $C_{30}H_{22}N_6$: C, 77.23; H, 4.75; N, 18.02. Found: C, 77.01; H, 4.94; N, 18.06.

5-Amino-3-methyl-4-*p*-nitrophenyl-1-phenylpyrazole in glacial acetic acid when treated with aqueous potassium permanganate at ambient temperature gave **4,4′-bis-*p*-nitrophenyl-3,3′-dimethyl-1,1′-diphenyl-5,5′-azopyrazole**, orange needles, in 40% yield: mp 278–280°; ir (Nujol) 1605, 1525, 1505, 1355 cm^{-1}.

Anal. Calcd for $C_{32}H_{24}N_8O_4$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.57; H, 4.11; N, 19.20.

Oxidation of 5-Amino-3-methyl-1-phenylpyrazole. A. With Permanganate.—A solution of 0.50 g of the amine in 40 ml of glacial acetic acid and 20 ml of chloroform was titrated with aqueous potassium permangante and was then diluted with water and extracted with chloroform. The extracts were concentrated to a yellow-brown oil after washing successively with solutions of sodium bicarbonate, sodium bisulfite, and sodium chloride. Trituration with methanol gave 100 mg (21%) of **3,3′-dimethyl-1,1′-diphenyl-5,5′-azopyrazole**, yellow needles: mp 205–206° after recrystallization from ethanol; nmr ($CDCl_3$) δ 2.37 (s, 3) and 6.32 ppm (s, 1).

Anal. Calcd for $C_{20}H_{18}N_6$: C, 70.15; H, 5.30; N, 24.55. Found: C, 70.14; H, 5.24; N, 24.58.

When the oxidation was attempted in a mixture of glacial acetic acid and acetone, or in 5% aqueous sulfuric acid, only reddish oils and gums were obtained, sometimes accompanied by up to 5% of the substance $C_{20}H_{19}N_5O_2$, mp 228–229°, obtained by Searles and Hine[4] from oxidation with hydrogen peroxide. The infrared spectra of the oils and gums were consistent with mixtures of this substance and the foregoing azopyrazole.

B. With Hydrogen Peroxide.—Treatment of 2.00 g of the aminopyrazole in 15 ml of 50% acetic acid with 3 ml of 30% hydrogen peroxide and with warming for 5 hr caused precipitation of 1.14 g (60%) of a cream-colored solid: mp 228–229° dec, red melt (lit.[7] mp 229–230°); nmr (CF_3COOH) δ 2.21 (s, 1.3), 2.31 (s, 2.5), and 7.2–7.9 ppm (m, 5); ir (Nujol) 3425, 3330, 1715, 1620, 1600 cm^{-1}.

Anal. Calcd for $C_{20}H_{19}N_5O_2$: C, 66.48; H, 5.26; N, 19.39. Found: C, 66.50; H, 5.44; N, 19.49. No other product could be isolated.

C. With Hydrogen Peroxide and Hydrochloric Acid.—To a solution of 2.00 g of 5-amino-3-methyl-1-phenylpyrazole in 15 ml of concentrated hydrochloric acid was added 3 ml of 30% hydrogen peroxide. Heat was evolved and a yellow oil separated. After 2 hr of heating on a steam bath, the mixture was diluted with water and extracted with ether. Concentration of the extracts left an oil which crystallized on standing. Two recrystallizations from aqueous ethanol gave 0.35 g (12%) of yellow prisms of 4,4-dichloro-3-methyl-1-phenylpyrazol-5-one: mp 61.5–63° (lit.[13] mp 65°); nmr ($CDCl_3$) δ 2.30 (s, 3) and 7.1–8.0 ppm (m, 5).

Anal. Calcd for $C_{10}H_8N_2Cl_2O$: C, 49.42; H, 3.29; N, 11.53. Found: C, 49.12; H, 3.25; N, 11.44.

D. With NBS.—A mixture of 3.0 g of N-bromosuccinimide and 1.0 g of 5-amino-3-methyl-1-phenylpyrazole dissolved in 80 ml of methylene chloride and 2 ml of pyridine was stirred for 2 hr, during which time it became red. Water was added, and the heavy layer was washed with water, dried, and evaporated. Crystallization of the red residue from aqueous ethanol gave 0.40 g (28%) of red plates of **2-bromo-3-phenylazocrotononitrile**: mp 73–76°; nmr ($CDCl_3$) δ 2.25 (s, 3) and 7.2–7.9 ppm (m, 5).

Anal. Calcd for $C_{10}H_8N_3Br$: C, 48.01; H, 3.22; Br, 31.96. Found: C, 47.97; H, 3.32; Br, 31.89.

E. With Phenyliodoso Acetate.[14]—A solution of 0.40 g of phenyliodoso acetate in 15 ml of methylene chloride was added dropwise to a solution of 0.22 g of the aminopyrazole in 15 ml of methylene chloride with ice-cooling, and the resulting orange mixture was stirred overnight. The solution was washed with sodium bicarbonate solution and water, and concentrated at the aspirator. The residual red oil crystallized over 2 days to give massive red prisms of phenylazocrotonitrile: mp 61–62° undepressed with the thermolysis product of 5-azido-3-methyl-1-phenylpyrazole; ir spectra superimposable; wt 0.16 g (70%).

Oxidation of 5-Amino-3,4-diphenyl-1-*p*-tolylpyrazole. A. With Permanganate.—A solution of 1.0 g of the aminopyrazole in 50 ml of glacial acetic acid was titrated with 4% aqueous potassium permanganate until the purple color persisted, whereupon the mixture was diluted with 200 ml of water and treated with enough 2% aqueous sodium bisulfite to destroy the precipitate manganese dioxide. The residual yellow solid (0.78 g, 75%) was recrystallized from chloroform–ethanol mixture to give an analytical sample of **1,1′-bis-*p*-tolyl-3,3′,4,4′-tetraphenyl-5,5′-azoxypyrazole**: mp 293–295°; ir (Nujol) 1605 (w), 1540 (w), 1520 (azoxy N=N?) cm^{-1}.

Anal. Calcd for $C_{44}H_{34}N_6O$: C, 79.73; H, 5.17; N, 12.68. Found: C, 79.45, 79.83; H, 5.07, 5.00; N, 12.46, 12.65.

B. With Phenyliodoso Acetate.—A solution of 52 mg of the aminopyrazole and 52 mg of phenyliodoso acetate in 20 ml of methylene chloride was stirred for 19 hr at ambient temperature; it became orange. Concentration on a steam bath left a vermilion oil containing a few crystals; trituration with light petroleum ether left 35 mg of crude starting material, mp 173–181°. Concentration and refrigeration of the filtrate yielded red crystals: wt, 4 mg (12%); mp 138–140°; ir identical with that of the thermolysis product of the azide.

Under the same conditions, 5-amino-1,3,4-triphenylpyrazole (III) gave the corresponding product (V) in 95% yield in only 1.5 hr, and 5-amino-4-*p*-chlorophenyl-1,3-diphenylpyrazole gave the corresponding α-*p*-chlorophenyl-β-phenylazocinnamonitrile in 90% yield after 18 hr.

Oxidation of 5-Amino-1,4-diphenyltriazole.—A 4% aqueous solution of potassium permanganate was added to a solution of 1.0 g of 5-amino-1,4-diphenyltriazole in 30 ml of glacial acetic acid until the permanganate color persisted. Sodium bisulfite was added to dissolve the manganese dioxide, and the mixture was then diluted with much water, precipitating a brown material. The precipitate was collected and washed and taken up in chloroform, from which red needles of **1,1′,4,4′-tetraphenyl-5,5′-azotriazole**, mp 226–228°, slowly formed after addition of ethanol, wt 0.30 g (30%). The mother liquors yielded only brown gum on evaporation.

Anal. Calcd for $C_{28}H_{20}N_8$: C, 71.78; H, 4.30; N, 23.92. Found: C, 71.64; H, 4.30; N, 23.92.

Reduction of 1,1′,4,4′-Tetraphenyl-5,5′-azotriazole.—A solution of 300 mg of the azotriazole in 30 ml of chloroform was stirred with 3 ml of 98% hydrazine hydrate while 300 mg of 5%

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palladium on charcoal was added. After 1 hr, the mixture was filtered, and the filtrate was washed with water and brine, and was dried over magnesium sulfate. Evaporation left 270 mg (91%) of 5-amino-1,4-diphenyltriazole, mp 168° alone and when mixed with an authentic sample.

Reduction of II.—Saturated aqueous sodium dithionite was added to a solution of 2.0 g of II in 100 ml of 95% ethanol until the red color was discharged, and the resulting mixture was poured at once into a large volume of ice water. The resulting nearly colorless solid **1(3)-phenyl-3(1)-α-cyanobenzyltriazene** (XIV) was collected, washed with water, and dried: wt 1.8 g (91%); mp 138° with violet decomposition. An analytical sample was prepared by extraction with hot alcohol and recrystallization from aqueous tetrahydrofuran: mp 155° dec alone and 145–146° dec when mixed with 5-amino-1,4-diphenyltriazole (mp 178–180°); ir (Nujol) 3240, 2260 (w), 1610, 1535, 1495 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.16; H, 5.12; N, 23.72. Found: C, 71.27; H, 5.08; N, 23.73.

Oxidation of Acetoacetonitrile Phenylhydrazone.—This substance was dissolved in methanol or ethanol and refluxed for 2 hr with mercuric oxide from various commercial batches. The cooled mixtures were filtered with the aid of Celite and the components were separated by column chromatography on alumina or by thin layer chromatography. In the several experiments without added base, only two significant substances were found: unreacted phenylhydrazone, and a red substance, mp 80–81°, apparently identical (ir and nmr) with the phenylazocrotononitrile (XII) reported by Quilico and coworkers,[9] and by Searles and Hine.[4] Yields varied from low to moderate. In other experiments sodium hydroxide, potassium hydroxide, triethylamine, or pyridine were added to the reaction mixtures. The only products in significant quantities were 1-phenyl-3-methyl-5-aminopyrazole (50 to 80% of the mixture) and the phenylazocrotononitrile (XII) of mp 80–81°: ir (Nujol) 2210, 1615 (w), 1505 (w), 1585 (w), cm^{-1}; nmr (CCl_4) δ 2.28 (d, 3, J = 0.8 Hz) (q, 1, J = 0.8 Hz) and 7.3–8.0 ppm (m, 5). In no case could any substance of mp 109° (isomeric phenylazocrotononitrile) be obtained. Sublimation of the material of mp 80–81° alone or when mixed with the aminopyrazole produced only unchanged substrate.

Isomerization of Phenylazocrotononitrile XI.—A dilute ethereal solution of 150 mg of XI was refluxed with 5 drops of 10 N HCl for 5 hr. Concentration and cooling caused crystallization of the isomer XII essentially quantitatively: mp 80° undepressed by admixture with XII obtained by oxidation of acetoacetonitrile phenylhydrazone; ir spectrum identical with that of XII. No isomerization was observed without the addition of acid or when ammonium hydroxide was used.

Oxidation of α-Acetylphenylacetonitrile Phenylhydrazone.—A solution of 0.8 g of the phenylhydrazone[15] in 30 ml of ethanol was refluxed for 5 hr with 1.5 g of yellow mercuric oxide. Thin layer chromatography showed the resulting mixture to contain 5-amino-1,4-diphenyl-3-methylpyrazole and another red substance. The filtered and concentrated mixture was digested with light petroleum ether, which left the aminopyrazole behind. The chilled and filtered extracts left a red oil on evaporation; crystallization from aqueous ethanol gave brilliant red plates of an **α-phenyl-β-phenylazocrotononitrile**: mp 110–111° (mp 80–84° when mixed with the thermolysis product of 5-azido-1,4-diphenyl-3-methylpyrazole); nmr ($CDCl_3$) δ 2.47 (s, 3) and 7.3–7.9 ppm (m, 10).

Anal. Calcd for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.55; H, 5.28; N, 17.00.

Oxidation of α-Acetyl-p-methoxyphenylacetonitrile Phenylhydrazone.—A suspension of 2.5 g of yellow mercuric oxide in ethanol was heated to boiling and 1.0 g of the phenylhydrazone was added in portions over 5 min after which refluxing was continued for 2 hr. Filtration and concentration gave a red gum which was taken up in benzene and filtered through a short column of silica gel; 380 mg (40%) of red needles, mp 100–110°, separated from the filtrate on standing. Recrystallization from aqueous ethanol did not change the mp which was not depressed by admixture with the thermolysis product of 5-azido-1-phenyl-4-p-methoxyphenyl-3-methylpyrazole (mp 126–127°), and the infrared spectra of the two substances were essentially the same: nmr ($CDCl_3$) δ 2.77 (s, 2.25, C–CH_3), 2.48 (s, 0.75, C–CH_3), 3.87 (s, 3, O–CH_3), and 6.85–8.1 ppm (m, 9) (C–CH_3 intensities correspond to a 3:1 mixture).

Registry No.—Table I—a, 24515-19-3; a (cyclic product),[16] 24514-90-7; a (noncyclic product), 24515-82-0; b, 24514-91-8; b (cyclic product), 24515-20-6; b (noncyclic product), 24515-83-1; c, 24514-92-9; c (cyclic product), 24515-21-7; c (noncyclic product), 24515-84-2; d, 24514-93-0; d (cyclic product), 24515-22-8; d (noncyclic product), 24515-85-3; e (cyclic product), 24514-94-1; e (noncyclic product), 24515-86-4; f (cyclic product), 24515-23-9; f (noncyclic product), 24515-87-5; g, 24514-95-2; g (cyclic product), 24515-24-0; g (noncyclic product), 24515-88-6; Va, 24514-96-3; Vb, 24514-99-6; VI, 24514-97-4; XII, 24514-98-5; XIV, 24515-14-8; α-p-chlorophenylbenzoylacetonitrile, 5415-05-4; α-p-anisylacetoacetonitrile, 5219-00-1; 5-amino-3,4-diphenyl-1-p-tolylpyrazole, 24515-02-4; 5-amino-4-p-anisyl-3-methyl-1-phenylpyrazole, 24515-03-5; 5-amino-4-p-chlorophenyl-1,3-diphenylpyrazole, 24515-04-6; 5-azido-1,3,4-triphenylpyrazole, 24515-05-7; 4,4′-bis-p-chlorophenyl-1,1′,3,3′-tetraphenyl-5,5′-azopyrazole, 24515-06-8; 1,1′,4,4′-tetraphenyl-5,5′-azopyrazole, 24515-07-9; 4,4′-bis-p-nitrophenyl-3,3′-dimethyl-1,1′-diphenyl-5,5′-azopyrazole, 24515-08-0; 3,3′-dimethyl-1,1′-diphenyl-5,5′-azopyrazole, 24515-09-1; 4,4-dichloro-3-methyl-1-phenylpyrazol-5-one, 24515-10-4; 2-bromo-3-phenylazocrotonitrile, 24515-11-5; 1,1′-bis-p-tolyl-3,3′,4,4′-tetraphenyl-5,5′-azoxypyrazole, 24523-23-7; 1,1′,4,4′-tetraphenyl-5,5′-azotriazole, 24515-12-6; α-phenyl-β-phenylazocrotononitrile, 24515-13-7.

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(16) Cyclic product refers to structure type Va and noncyclic product refers to structure type Vb (Scheme I).

Studies on Indoles, Carbazoles, and Related Compounds. I. Carbazole Leuco Derivatives Related to 4,4′-Diaminodiphenylmethanes. Bis(3-carbazolyl)methanes and Bis(9-carbazolyl)methanes

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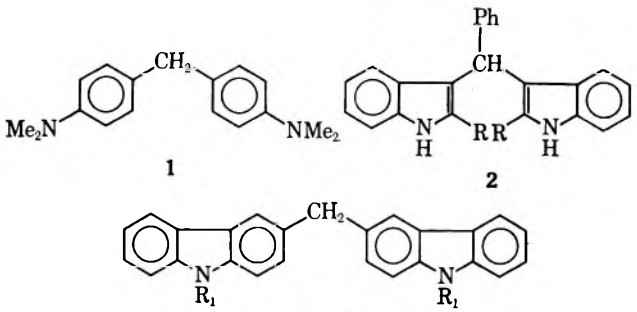
Bis(3-carbazolyl)methane and some bis(9-alkyl-3-carbazolyl)methanes have been synthesized, the former *via* the Borsche synthesis from 4,4′-dihydrazinodiphenylmethane and the latter by condensation of 6-blocked 9-alkylcarbazoles with formaldehyde, followed by removal of the blocking 6 substituent. These compounds are compared and contrasted with the products obtained from the acetic acid catalyzed condensation of carbazole, or of unblocked 9-alkylcarbazoles, with formaldehyde. Infrared and proton magnetic resonance studies establish that the carbazole–formaldehyde condensation product is bis(9-carbazolyl)methane, in contrast to some literature reports.

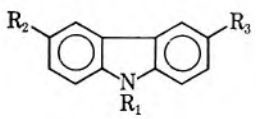
In a comparative study of leuco compounds related to 4,4′-diaminodiphenylmethane derivatives, *e.g.*, tetramethyl base **1**, and to phenylbis(3-indolyl)methanes (leuco rosindoles) **2**, we recently required bis(3-carbazolyl)methane (**3a**) and some bis(9-alkyl-3-carbazolyl)methanes, *e.g.*, **3b** and **3c**. According to three standard reference works,[1-3] these latter compounds



1 **2**

3a, $R_1 = H$
b, $R_1 = Me$
c, $R_1 = Et$

are accessible *via* the direct acid-catalyzed condensation of carbazole, or 9-alkylcarbazoles, respectively, with formaldehyde (or formaldehyde progenitors), analogous to, for example, the well-known preparation of tetramethyl base **1** from formaldehyde and N,N-dimethylaniline in acid solution. On consulting the original literature, however, it became apparent that some confusion and conflicting conclusions exist as to the final products obtained from carbazole, or 9-alkylcarbazoles, and formaldehyde in various acidic media.[4-20] The products obtained from such reactions vary with the reaction conditions. Thus, the reaction product from carbazole and formaldehyde in concentrated sulfuric acid forms a blue solution or precipitates as a blue dye,[5,7,8,11,15,16] while under less stringent conditions, *e.g.*, carbazole and formaldehyde (or formaldehyde progenitors) in acetic acid, the major product is a biscarbazolylmethane, mp "above 280°,"[4,6] 287°,[10] 301–303°.[13] This compound is also obtained by warming 9-hydroxymethylcarbazole (**4a**) in acetic acid.[9] Where-



4a, $R_1 = CH_2OH$; $R_2 = R_3 = H$
b, $R_1 = CH_2OCOCH_3$; $R_2 = R_3 = H$
c, $R_1 = H$; $R_2 = R_3 = Cl$
d, $R_1 = H$; $R_2 = R_3 = Br$
e, $R_1 = H$; $R_2 = R_3 = I$
f, $R_1 = Et$; $R_2 = H$; $R_3 = CHO$
g, $R_1 = Et$; $R_2 = Br$; $R_3 = CHO$

as the structure of the blue dye still remains obscure, the biscarbazolylmethane has been reported by some workers[4,13,19] as bis(9-carbazolyl)methane (**5a**) but by others[6,10,14a] has bis(3-carbazolyl)methane (**3a**). The latter assignment has been generally accepted previously,[1-3] mainly owing to (i) a suggestion[10] that a free 3 position is necessary before condensation can occur and (ii) the preparation of authentic bis(9-carbazolyl)methane, mp 314–315°, from 9-acetoxymethylcarbazole (**4b**) and carbazolylmagnesium iodide.[14a] However,

(1) "Beilstein's Handbuch der Organischen Chemie," 4th ed, Springer-Verlag, Berlin: (a) Vol. 20, Hauptwerk, p 436; (b) Vol. 23, Hauptwerk, p 239; 1st Suppl., p 96.

(2) W. C. Sumpter and F. M. Miller, "The Chemistry of Heterocyclic Compounds," Vol. 8, A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1954, pp 107–108.

(3) E. H. Rodd, "Chemistry of Carbon Compounds," Vol. 4, Elsevier Publishing Co., Amsterdam, 1957, p 124.

(4) G. Pulvermacher and W. Loeb, *Chem. Ber.*, **25**, 2766 (1892).

(5) E. Votocek, *Rozpravy Cesk. Akad.*, **22**, 5 (1896); *Chem. Zentralbl.*, **67** (II), 490 (1896).

(6) E. Votocek and V. Vesely, *Chem. Ber.*, **40**, 414 (1907).

(7) H. Ditz, *Chem.-Ztg.*, **31**, 486 (1907); *Chem. Zentralbl.*, **78** (II), 33 (1907).

(8) E. Gabutti, *Boll. Chim. Farm.*, **46**, 349 (1907); *Chem. Zentralbl.*, **78** (II), 98 (1907).

(9) M. Lange, German Patent 256,757 (1913).

(10) S. Dutt, *J. Chem. Soc.*, **125**, 802 (1924).

(11) Z. Dische, *Biochem. Z.*, **189**, 77 (1927); *Chem. Abstr.*, **22**, 559 (1928).

(12) G. Kranzlein and R. Dereser, German Patent 699,774 (1940).

(13) J. R. Feldman and E. C. Wagner, *J. Org. Chem.*, **7**, 31 (1942). These workers referred to the carbazole–formaldehyde condensation product simply as "methylenebiscarbazole," with no opinion expressed in their text as to the point of formaldehyde condensation on the carbazole molecule. A condensed structural formula (p 37 of their paper) indicates, however, that these workers also preferred the 9,9′-condensed structure **5a**.

(14) (a) K. Mizuch, *Zh. Obshch. Khim.*, **16**, 1471 (1946); (b) K. Mizuch and Ts. M. Gel'fer, *J. Appl. Chem. USSR*, **19**, 939 (1946); (c) *Dokl. Akad. Nauk SSSR*, **79**, 807 (1951); (d) K. G. Mizuch, N. M. Kasatkin, and Ts. M. Gel'fer, *Zh. Obshch. Khim.*, **27**, 189 (1957).

(15) K. Fürst, *Mikrochem. Ver. Mikrochim. Acta*, **33**, 348 (1948).

(16) M. Cermak, *Chem. Listy*, **45**, 35 (1951).

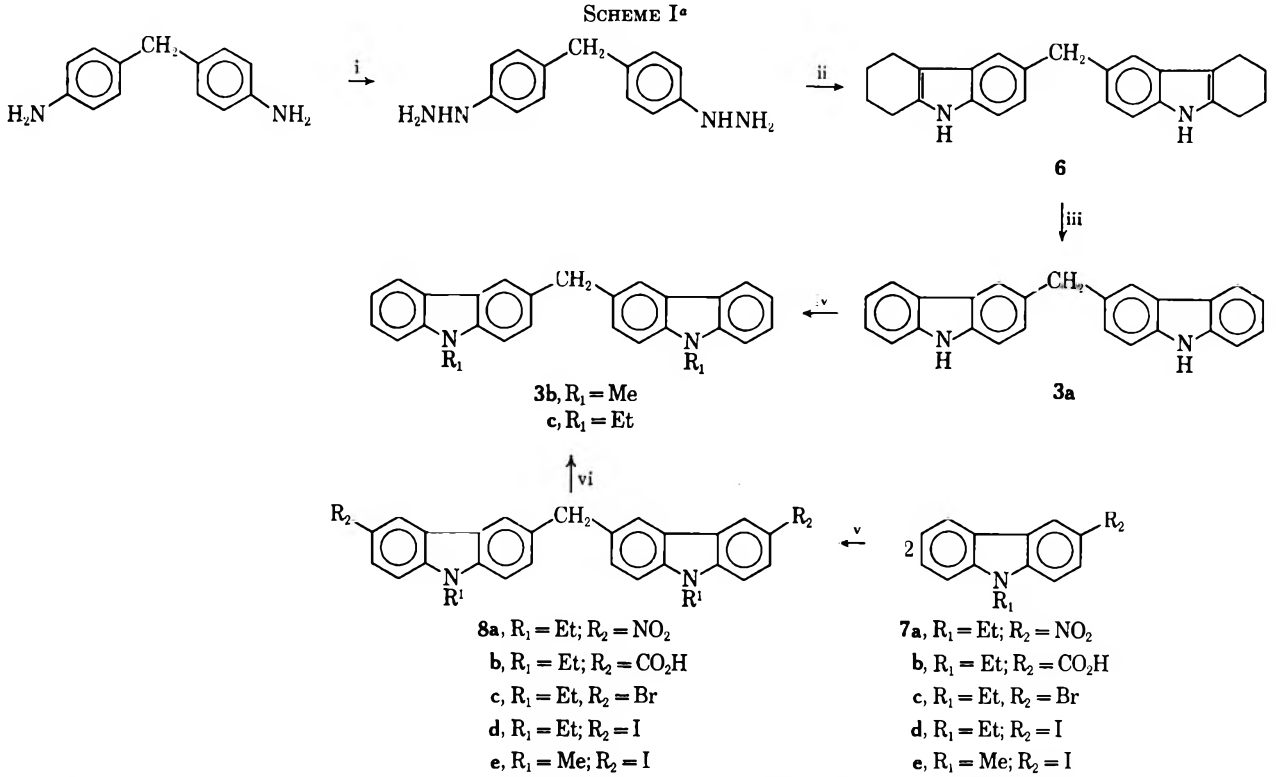
(17) F. Muzik and Z. J. Allan, *Collect. Czech. Chem. Commun.*, **22**, 641 (1957).

(18) (a) V. F. Traven and B. I. Stepanov, *Tr. Mosk. Khim. Tekhnol. Inst.*, **48**, 118 (1965); *Chem. Abstr.*, **65**, 12159 (1966); (b) V. F. Traven, V. A. Smrchek, and B. I. Stepanov, *Khim. Geterotsikl. Soedin.*, 568 (1967); *Chem. Abstr.*, **68**, 39407 (1968); (c) V. F. Traven, V. A. Plakhov, and B. I. Stepanov *Khim. Geterotsikl. Soedin*, 756 (1967); *Chem. Abstr.*, **68**, 104884 (1968).

(19) S. Nakade and M. Imoto, *Kogyo Kagaku Zasshi*, **69**, 100 (1966); *Chem. Abstr.*, **65**, 3822 (1966).

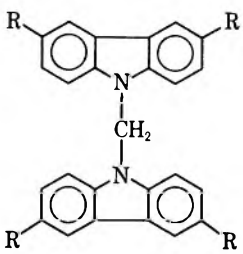
(20) S. Nakade, U. Funayama, and A. Gomi, *Kogyo Kagaku Zasshi*, **69**, 2214 (1966); *Chem. Abstr.*, **66**, 116188 (1967).

SCHEME I[a]



[a] Reagents: i, HNO_2, $SnCl_4$–HCl; ii, cyclohexanone, AcOH; iii, Pd–C; iv, dialkyl sulfate; v, CH_2O, H^+; vi, Li-*t*-BuOH–THF (on **8c**) or $LiAlH_4$ (on **8d**, **8e**).

it has been shown more recently[17] that 3,6-dichlorocarbazole (**4c**) and 3,6-dibromocarbazole (**4d**) readily condense with formaldehyde, yielding **5b** and **5c**, respectively. Finally, another report[21] describes the isolation of a product alleged to be bis(3-carbazolyl)methane (**3a**), mp 234°.



5a, R = H
b, R = Cl
c, R = Br
d, R = I

We have accordingly reexamined the products obtained from (a) carbazole and formaldehyde in acetic acid,[4,13] (b) carbazole and methylal in acetic acid,[6] (c) 9-hydroxymethylcarbazole in acetic acid,[9] and (d) 9-carbazolylmagnesium iodide and 9-acetoxymethylcarbazole in ether.[14a] After purification by crystallization from N,N-dimethylformamide or from benzene, the products from all routes were identical with respect to melting point (314–317°), infrared spectra, and nmr spectra. A typical infrared spectrum of the product showed the complete absence of a –NH group and the typical benzene substitution patterns at 700–770 and 1700–1950 cm^{-1}, characteristic of 1,2-substituted benzene rings only (equivalent to no nuclear substituents in the carbazole ring system); these findings are in excellent agreement with structure **5a** and preclude the product being the 3,3 isomer **3a**. The nmr spectrum exhibits signals for 16 aromatic protons and two methylene protons and is thus also in accord with structure **5a**; absorptions occur at δ 6.9 (doublet of doublets, 4 H, 4 and 5 nuclear carbazole protons), 5.9–6.5 (multiplet, 12 H, remaining carbazole nuclear protons), and 5.7 (singlet, 2 H, methylene protons). The major product from each of the mild acid-catalyzed reactions, therefore, is bis(9-carbazolyl)methane (**5a**), as originally postulated by Pulvermacher and Loeb.[4]

The 9,9′-condensed structure of the carbazole–formaldehyde product was confirmed by unambiguous synthesis. Acid-catalyzed condensation of 3,6-diiodocarbazole (**4e**) with formaldehyde affords bis(3,6-diiodo-9-carbazolyl)methane (**5d**), analogous to the similar condensation products **5b** and **5c** obtained by Muzik and Allan[17] from 3,6-dichlorocarbazole and 3,6-dibromocarbazole; in these compounds, no possibility exists for 3,3 condensation. Reductive deiodination of **5d** by means of lithium aluminum hydride in tetrahydrofuran affords bis(9-carbazolyl)methane **5a**, identical in all respects with the product obtained from the direct carbazole–formaldehyde condensations.

We synthesized the required bis(3-carbazolyl)methane (**3a**) apparently for the first time, *via* the more extended Borsche tetrahydrocarbazole synthesis,[22,23] Scheme I. The preparation of the intermediate bis(5,6,7,8-tetrahydro-3-carbazolyl)methane (**6**) has been described.[23] Dehydrogenation of this material with palladium on charcoal[24] gave **3a**, mp 350–352°. The

(21) D. Jerchel and H. Fischer, *Chem. Ber.*, **88**, 1595 (1955).

(22) W. Borsche, A. Witte, and W. Bothe, *Justus Liebigs Ann. Chem.*, **359**, 49 (1908).

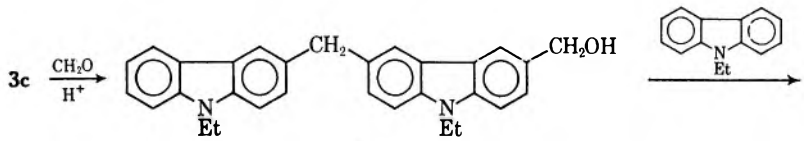
(23) (a) W. Borsche and G. A. Kienitz, *Chem. Ber.*, **43**, 2335 (1910); (b) W. Borsche and R. Manteuffel, *ibid.*, **67B**, 144 (1934).

(24) (a) E. C. Horning, M. G. Horning, and G. N. Walker, *J. Amer. Chem. Soc.*, **70**, 3935 (1948); (b) P. H. Carter, S. G. P. Plant, and M. Tomlinson, *J. Chem. Soc.*, 2210 (1957).

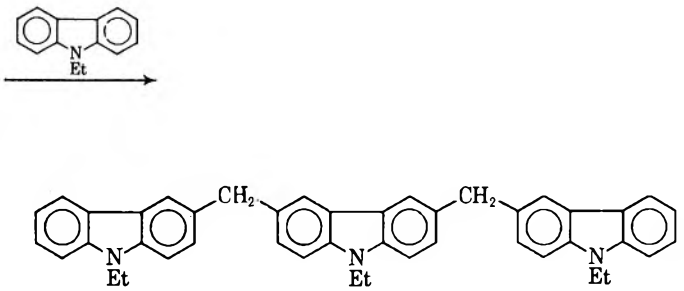
infrared spectrum of the product was in excellent agreement with the required structure, showing absorption peaks at 725 and 750 cm^{-1} (1,2-disubstituted benzene ring), 800 (1,2,4-trisubstituted benzene ring), and 3300 (NH). The nuclear magnetic resonance spectrum (in DMSO) exhibits absorptions at δ 7.7 (doublet, 4 H, 4 and 5 nuclear protons), 6.5–7.3 (multiplet, 10 H, remaining aromatic protons), and 3.9 (singlet, 2 H, 3,3-methylene protons), all relative to DMSO at 2.25. At the concentration employed, the NH protons appeared at δ 9.7 (very broad peak).

This material is clearly distinct from the above bis(9-carbazolyl)methane, mp 314–317°, and it appears to be also distinct from another compound, mp 234°, reported by Jerchel and Fischer[21] as bis(3-carbazolyl)methane.

We then turned our attention to synthesizing the alkylated leuco derivatives, the bis(9-alkyl-3-carbazolyl)methanes, *e.g.*, **3b** and **3c**. Although, as shown above, the preferred site of reaction in N-unsubstituted carbazoles with formaldehyde (or protonated formaldehyde intermediates) is the N position, it appeared that, if this position were occupied, *viz.* by an alkyl group, then substitution would be directed to the *para* nuclear position, *i.e.*, the 3 position. We were thus initially hopeful that condensation of 9-methylcarbazole and 9-ethylcarbazole with formaldehyde would lead to the required **3b** and **3c**, respectively. The only literature reports on this reaction prior to the commencement of our study appear to be a passing mention by Votocek and Vesely,[6] with no experimental details, and a note in an early German patent[25] which describes the preparation of "di-9-ethylcarbazylmethane" by condensation of 9-ethylcarbazole with formaldehyde in acetic acid in the presence of a trace of mineral acid. Kränzlein and Dereser[12] have commented, however, that such condensation products are nonhomogeneous resinous materials and recent patent claims[26] have also commented on the polymeric nature of these products. We also found this to be the case. The material obtained from the direct condensation of 9-ethylcarbazole with formaldehyde was an amorphous solid (mol wt 1600) which melted over a wide range. The formation of polymeric resins has also been observed in the analogous diphenylamine–formaldehyde condensation reaction.[27] The polymerization reaction may proceed *via* the unoccupied 6,6′ nuclear positions of the initially formed bis(9-alkyl)-3-carbazolyl)methane, these positions being readily accessible for further attack and subsequent chain growth, *via* intermediates such as **9**, leading to **10**. The process may then be repeated on **10**, leading to higher oligomers.

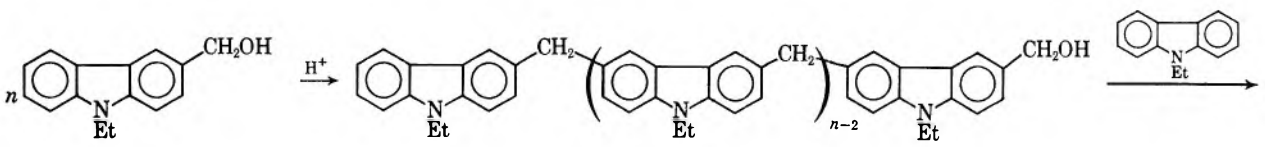


9

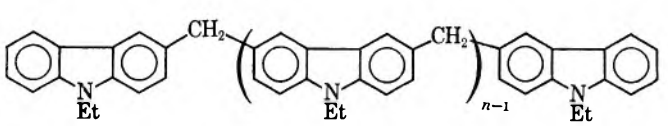


10

Alternatively, the process may partly involve self-condensation of the corresponding 3-hydroxymethyl-9-alkylcarbazole **11**, formed initially *in situ* from 9-ethylcarbazole and formaldehyde, the chain growth being finally terminated by reaction of the resultant long-chain methylol compound **12** with 9-ethylcarbazole. The facile self-condensation of **11** was readily demonstrated by treatment of this material, prepared separately from 9-ethylcarbazole-3-carboxaldehyde, with warm acetic acid. The resultant product, which softened at 157° and finally melted at 163–164°, had an average molecular weight of 1600–1800, *i.e.*, n = 8 or 9 in **12**.



11 **12**



13

These conjectures are supported by the observation of Kränzlein and Dereser[12] that 9-alkylcarbazoles containing one occupied *para* position, *viz.* 3-nitro-9-ethylcarbazole (**7a**) (Scheme I) or 9-ethylcarbazole-3-carboxylic acid (**7b**) condense smoothly with formaldehyde in acetic acid solution to give the corresponding bis(6-nitro-9-ethyl-3-carbazolyl)methane (**8a**) and bis(6-carboxy-9-ethyl-3-carbazolyl)methane (**8b**), respectively, as crystalline materials in good yields; in these cases the linear chain growth cannot occur.

The authentic bis(9-alkyl-3-carbazolyl)methanes **3b** and **3c** were obtained by blocking the carbazole 6 posi-

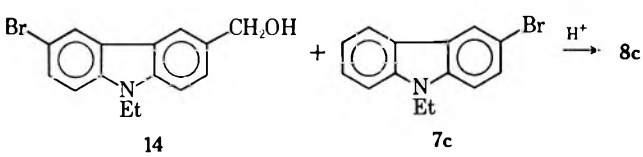
(25) German Patent 293,578 (1913).

(26) (a) French Patent 1,399,095 (1965); (b) U. S. Patent 3,240,597 (1966).

(27) D. Craig, *J. Amer. Chem. Soc.*, **55**, 3723 (1933).

tion, utilizing halogen substituents as blocking groups. Condensation of 3-bromo-9-ethylcarbazole (**7c**) (Scheme I) or 3-iodo-9-ethylcarbazole (**7d**) with formaldehyde in acetic acid yielded bis(6-bromo-9-ethyl-3-carbazolyl)methane (**8c**) or bis(6-iodo-9-ethyl-3-carbazolyl)-methane (**8d**), respectively, as homogeneous crystalline materials. Reductive dehalogenation of either the bisbromo compound by means of the lithium–*t*-butyl alcohol–tetrahydrofuran procedure[28] or of the bisiodo compound by reduction with lithium aluminum hydride in ether afforded bis(9-ethyl-3-carbazolyl)methane (**3c**), mp 143°. A similar reaction sequence starting with 3-iodo-9-methylcarbazole (**7e**) yielded bis(6-iodo-9-methyl-3-carbazolyl)methane (**8e**) and thence, by $LiAlH_4$–ether reduction, bis(9-methyl-3-carbazolyl)-methane (**3b**), mp 191°. The infrared and nmr spectra of these products and of the intermediate compounds were in perfect agreement with the required structures. After our study was completed Traven, Plakhov, and Stepanov[18c] isolated a product, mp 223°, from the direct 9-methylcarbazole–formaldehyde condensation reaction, which they designated as bis(9-methyl-3-carbazolyl)methane, and Nakade, Funayama, and Gomi[20] obtained a material from the corresponding 9-ethylcarbazole–formaldehyde reaction which they claimed to be bis(9-ethyl-3-carbazolyl)methane, mp 183–186°. In the light of the foregoing discussion and previous literature[12,26] commenting on the nonhomogeneous, resinous nature of the products from such reactions, and in view of the melting point discrepancies, when compared with our materials, we conjecture that these products are, in fact, higher oligomeric species, *e.g.*, **10**, **13**, etc.

As stated above, the condensation reaction may be visualized as proceeding *via* the initial formation of a 3-hydroxymethylcarbazole intermediate, *e.g.*, **11**, formed *in situ*. In the case of the carbazoles containing nuclear blocking substituents, it was felt that the intermediate bis(6-halogeno-9-alkyl-3-carbazolyl)methanes **8** would also be accessible by direct condensation of the appropriate 6-halogeno-3-hydroxymethylcarbazole **14** with the corresponding 3-halogeno-9-alkylcarbazole, *e.g.*

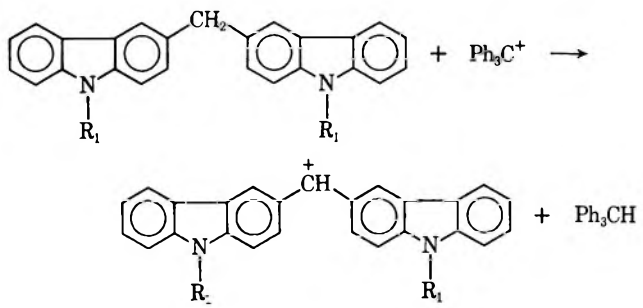


14 7c

Mild acid treatment of an equimolar mixture of 3-hydroxymethyl-6-bromo-9-ethylcarbazole (**14**) and 3-bromo-9-ethylcarbazole (**7c**) afforded bis(6-bromo-9-ethyl-3-carbazolyl)methane (**8c**), identical in all respects with the material obtained from the direct 3-bromo-9-ethylcarbazole–formaldehyde condensation. The intermediate 3-hydroxymethyl-6-bromo-9-ethylcarbazole (**14**) was easily accessible from the sodium borohydride reduction of 6-bromo-9-ethylcarbazole-3-carboxaldehyde (**4g**).

Finally the alkylated biscarbazolylmethanes **3b** and **3c** may also be obtained (Scheme I) by N-alkylation of the parent bis(3-carbazolyl)methane **3a** the synthesis of which is reported above. Ethylation of this material with diethyl sulfate in acetone[29] afforded bis-(9-ethyl-3-carbazolyl)methane (**3c**) in moderate yield, the product being identical in all respects with the material obtained from the dehalogenations of bis(6-bromo-9-ethyl-3-carbazolyl)methane (**8c**) and bis(6-iodo-9-ethyl-3-carbazolyl)methane (**8d**). Similarly, methylation of bis(3-carbazolyl)methane with dimethyl sulfate afforded bis(9-methyl-3-carbazolyl)methane (**3b**), identical with the product from $LiAlH_4$–ether reduction of bis(6-iodo-9-methyl-3-carbazolyl)methane (**8e**).

As leuco derivatives analogous to 4,4′-diaminodiphenylmethane derivatives **1**, the bis(3-carbazolyl)-methanes were good color formers (yielding blue dyes) with hydride abstractors such as tropylium fluoroborate or trityl hexachloroantimonate.[30] The kinetics of



such color-forming reactions will be described in a second forthcoming paper.[31]

Experimental Section

Melting points were taken on a Fisher-Johns melting point apparatus in most cases; compounds which melted above 280° or which sublimed at atmospheric pressure were examined in sealed capillaries in an electrothermal melting point apparatus, the cavity temperature of which was monitored with a chromel–alumel thermocouple. Infrared spectra were run in potassium bromides pellets on a Perkin-Elmer Model 21 double beam spectrophotometer. ^1H nmr spectra were obtained on a Varian Associates A60-A spectrometer utilizing various solvents. Chemical shifts are in δ values downfield from the standard tetramethylsilane (δ 0) position. Microanalyses were performed by Elek Microanalytical Laboratories, Torrance, Calif.

Materials.—Carbazole was J. T. Baker practical grade, recrystallized from 2-propanol; 9-ethylcarbazole was obtained from the Aldrich Chemical Co. and was recrystallized from methanol. Pyridine was dried over potassium hydroxide pellets, decanted, and redistilled from fresh pellets. Tetrahydrofuran and diethyl ether were dried by distillation from lithium aluminum hydride. The following compounds were prepared according to the cited literature references: 9-hydroxymethylcarbazole[9] (**4a**), mp 128–129° (lit.[9] 127–128°); 9-acetoxymethylcarbazole[14b] (**4b**), mp 80–82° (lit.[14b] 81–82°); 3-iodocarbazole,[32] mp 194–196° (lit.[32] 192–194°); 3-iodo-9-methylcarbazole[29] (**7e**), mp 78–79° (lit.[29] 77–79°); 3-iodo-9-ethylcarbazole[32] (**7d**), mp 82–83° (lit.[32] 83–84°); 3,6-diiodocarbazole[32] (**4e**), mp 206–207° (lit.[32] 202–204°); 3-bromo-9-ethylcarbazole[33] (**7c**), mp 81–82° (lit.[33] 81–82°); 4,4′-dihydrazinodiphenylmethane,[33,34] mp 139–141° (lit.[33b] 141–143°) (previous workers[33,34] prepared this hydrazine by reduction of the intermediate diphenylmethane-4,4′-tetrazonium dichloride with sodium sulfite, but we found the general method

(28) P. Bruck, D. Thompson, and S. Winstein, *Chem. Ind.* (London), 405 (1960).

(29) T. S. Stevens and S. H. Tucker, *J. Chem. Soc.*, **123**, 2140 (1923).

(30) A. Ledwith, A. M. North, and K. E. Whitelock, *Eur. Polym. J.*, **4**, 133 (1967).

(31) P. Bruck, A. Ledwith, and A. C. White, *J. Chem. Soc. B*, in press.

(32) S. H. Tucker, *J. Chem. Soc.*, 547 (1926).

(33) R. H. Meen and H. Gilman, *J. Org. Chem.*, **20**, 73 (1955).

(34) (a) H. Finger, *J. Prakt. Chem.*, **74**, 155 (1906); (b) G. D. Parkes and R. H. H. Morley, *J. Chem. Soc.*, 315 (1936).

of Hunsberger, *et al.*,[35] utilizing stannous chloride, to be more convenient); 9-ethylcarbazole-3-carboxaldehyde[36,37] (4f), mp 89–91° (lit.[36] 94°).

Bis(3,6-diiodo-9-carbazolyl)methane (5d).—Methylal (0.7 g) and **4e** (6.2 g) were dissolved in acetic acid (110 ml). At 65–70°, 1 ml of a 4% solution (v/v) of sulfuric acid in acetic acid was added. An immediate white precipitate formed. The collected product, which was almost insoluble in most of the conventional organic solvents, recrystallized from a large volume of boiling anisole as felted needles: mp 314–316° dec, ir (KBr) 805 cm^{-1} (1,2,4-trisubstituted benzene ring).

Anal. Calcd for $C_{25}H_{14}N_2I_4$: C, 35.32; H, 1.66; N, 3.30. Found: C, 35.18; H, 1.72; N, 3.56.

Bis (9-carbazolyl)methane (5a). (A) From Lithium Aluminum Hydride Reductive Deiodination of 5d.—The difficultly soluble **5d** (3.4 g) was extracted for 4 days in a Soxhlet apparatus with tetrahydrofuran (150 ml) containing lithium aluminum hydride (3 g). During this time, 1 g of **5d** dissolved. The solution was treated with saturated ammonium chloride solution and then with 2 *N* HCl (200 ml) to dissolve inorganic salts. After further dilution with H_2O, the resultant precipitate was dissolved in hot benzene (200 ml), filtered, and concentrated to 50 ml. Fine white crystalline needles of **5a** (0.271 g), mp 314–315° (lit.[14a] 313–314°), were obtained.

(B). From the Reaction of 9-Carbazolylmagnesium Iodide with 9-Acetoxymethylcarbazole (4b).—This experiment followed the procedure given by Mizuch.[14a] The resultant product was recrystallized from N,N-dimethylformamide and afforded **5a**, mp 314–316° (lit.[14a] 313–314°).

Anal. Calcd for $C_{25}H_{18}N_2$: C, 86.67; H, 5.24; N, 8.09. Found: C, 86.70; H, 5.20; N, 7.97.

(C). From Condensation of Carbazole and Formaldehyde.—The procedure of Feldman and Wagner[13] was followed. The crude reaction product was recrystallized from N,N-dimethylformamide and then sublimed at 280° (0.15 mm), yielding **5a**, mp 315–317° (lit. "above 280",[4,6] 287,[10] 301–303,[13] 313–314°[14a]).

(D). From Condensation of Carbazole and Methylal.— The preparation of the biscarbazolylmethane *via* this route was mentioned by Votocek and Vesely,[6] but with no experimental details. A solution of carbazole (17.7 g) in acetic acid (350 ml) was refluxed while a solution of methylal (3.8 g) in acetic acid (20 ml) was added. The resultant crystalline product was recrystallized from N,N-dimethylformamide and afforded **5a**, mp 316–317°.

Anal. Calcd for $C_{25}H_{18}N_2$: C, 86.67; H, 5.24; N, 8.09. Found: C, 86.99; H, 5.37; N, 8.21.

(E) From 9-Hydroxymethylcarbazole.—The preparation of a biscarbazolylmethane from **4a** in acid medium was described by Lange,[9] but with no experimental details. A solution of **4a** (2.5 g) in acetic acid (25 ml) was warmed to 90° and held at this temperature for 30 min. The resultant crystalline precipitate of **5a** was collected, washed with acetone, and dried *in vacuo*, mp 315–317°.

The products from steps A–E were taken in various combinations for mixture melting point determinations. Node pressions were observed. The infrared spectra were superimposable and were noteworthy for the complete absence of the NH absorption in the 3300–3500-cm^{-1} range; ir (KBr) 3030 (aromatic CH), 1460 (CH_2), 1120, 745, and 720 cm^{-1} (1,2-substituted benzene ring). The integrated ^1H nmr spectrum (CH_3CONMe_2 at 120°) showed absorptions corresponding to 16 aromatic protons and 2 methylene protons (for details, see text).

Bis(5,6,7,8-tetrahydro-3-carbazolyl)methane(6).—This compound was prepared from cyclohexanone and 4,4′-dihydrazinodiphenylmethane by the method of Borsche and Kienitz.[23a] The crude tetrahydrocarbazole was recrystallized from acetone, mp 281–283° (lit. 265,[23a] 281–283°[23b]); ir (KBr) 3400 (NH), 2940 (CH_2), 880, and 795 cm^{-1} (1,2,4-trisubstituted benzene ring; nmr (DMSO-d_6) δ 6.7–7.2 (m, 6 H, aromatic protons), 4.0 (s, 2 H, methylene group), 2.6 (m, 4 H, alicyclic protons), and 1.8 (m, 4 H, alicyclic protons).

Bis(3-carbazolyl)methane (3a).—An intimate mixture of palladium on charcoal (1.2 g) and **6** (3.6 g) was heated in a stream of nitrogen (Woods metal bath). A vigorous evolution of gaseous products occured at approximately 250°. The reaction mixture was cooled and extracted twice with hot xylene; the combined xylene extracts were filtered. The product (1.3 g) crystallized as large off-white nacreous plates, mp 350–352°; ir (KBr) 3300 (NH), 800 (1,2,4-trisubstituted benzene ring), 750, and 725 cm^{-1} (1,2-disubstituted benzene ring); nmr (DMSO) δ 9.7 (2 H, NH), 7.7 (d, 4 H, 4 and 5 aromatic protons), 6.5–7.3 (m, 10 H, aromatic protons), and 3.9 (s, 2 H, CH_2).

Anal. Calcd for $C_{25}H_{18}N_2$: C, 86.67; H, 5.24; N, 8.09. Found: C, 86.72; H, 5.19; N, 8.10.

6-Bromo-9-ethylcarbazole-3-carboxaldehyde (4g).—This material had previously been obtained[36] by bromination of **4f**. We found dimethylformamide–phosphorous oxychloride formylation of **7c** to be equally convenient.

Dimethylformamide (2.5 g) and **7c** (8.2 g) were dissolved in *o*-dichlorobenzene (20 ml) and $POCl_3$ (4.6 g) was added. The red-brown mixture, after being heated for 4 hr at 90–100°, was cooled, poured into H_2O, and extracted with ether. The ethereal extract was washed with H_2O, dried (K_2CO_3), filtered, and evaporated. The oily residue crystallized from ethanol at 0° as fine pale yellow needles, mp 133–134° (lit.[36] 136°).

3-Hydroxymethyl-9-ethylcarbazole (11).—A solution of **4f** (5.5 g) in methanol–2% sodium hydroxide was treated with sodium borohydride (0.5 g). After being allowed to stand overnight at room temperature, the solution was diluted with H_2O and extracted with benzene. The benzene extract was dried, filtered, and evaporated. The residue crystallized from ethanol at −10° as felted needles, mp 75–76° (3.8 g); nmr ($CDCl_3$) δ 7.8 (m, 2 H, 4 and 5 carbazole protons), 6.9–7.3 (m, 5 H, remaining aromatic protons), 4.6 (s, 2 H, CH_2OH), 4.1 (q, 2H, N-CH_2CH_3, J = 7 cps), 2.5 (s, 1 H, OH), and 1.2 (t, 3 H, N-CH_2CH_3).

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71. Found: C, 80.02; H, 6.70.

3-Hydroxymethyl-6-bromo-9-ethylcarbazole (14).—In a similar reduction to the above, **4g** (1.7 g) was refluxed for 6 hr with $NaBH_4$ (3 g) in methanol (50 ml) containing KOH (1 g). After cooling, unchanged aldehyde was removed by filtration and the filtrate was diluted with H_2O. The collected product was crystallized from carbon tetrachloride and then from benzene as transparent spars, mp 143–144° (0.63 g); nmr ($CDCl_3$) δ 8.1 (d, 1 H, 5 proton), 7.9 (s, 1 H, 4 proton), 4.7 (s, 2 H, CH_2OH), 4.2 (q, 2 H, N-CH_2CH_3), 2.0 (s, 1 H, OH), and 1.3 (t, 3 H, N-CH_2CH_3).

Anal. Calcd for $C_{15}H_{14}BrNO$: C, 59.22; H, 4.64; N, 4.60. Found: C, 59.17; H, 4.59; N, 4.68.

Bis(6-bromo-9-ethyl-3-carbazolyl)methane (8c). (A) From 3-Bromo-9-ethylcarbazole and Formaldehyde.—A solution of **7c** (27.4 g) in a mixture of glacial acetic acid (100 ml) and sulfuric acid (2 ml) was warmed to 85° with stirring. At this temperature 37% formalin solution (4.1 ml) in acetic acid (10 ml) was added at once. A greenish blue precipitate formed. The collected material was taken in hot benzene and acetone was added dropwise until solution was completed; the solution was then treated twice with charcoal. The resultant wine red filtrate deposited crystalline needles, mp 185–188° (13 g, 45%). Two recrystallizations of this material from benzene afforded **8c**, mp 193–194°; nmr ($CDCl_3$) δ 8.1 (d, 2 H, 5 protons), 7.8 (s, 2 H, 4 protons), 7.0–7.5 (m, 8 H, remaining aromatic protons), 4.3 (s, 2 H, Ar-CH_2-Ar), 4.2 (q, 4 H, N-CH_2CH_3), and 1.3 (t, 6 H, N-CH_2CH_3).

Anal. Calcd for $C_{29}H_{24}Br_2N_2$: C, 62.16; H, 4.32; N, 5.00. Found: C, 62.72; H, 4.61; N, 5.01.

(B) From 3-Hydroxymethyl-6-bromo-9-ethylcarbazole and 3-Bromo-9-ethylcarbazole.—A solution of **7c** (100 mg) and **14** (100 mg) in acetic acid (3 ml) was treated with one drop of a solution made by adding sulfuric acid (2 drops) to acetic acid (10 ml). The solution was boiled for 3 min, cooled, diluted with H_2O dropwise until turbid, and then allowed to stand. The resultant product was crystallized from benzene (2 ml) and yielded 40 mg, mp 193–194°, undepressed in melting point upon admixture with the product obtained from route A above.

Bis(6-iodo-9-ethyl-3-carbazolyl)methane (8d).—A suspension of **7d** (16.0 g) in a solution of 50% aqueous sulfuric acid (2 ml) in acetic acid (75 ml) was treated with a solution of methylal (1.9 g) in acetic acid (10 ml). The mixture was stirred and heated under reflux; the iodocarbazole passed into solution and subsequently a blue precipitate appeared. The product was filtered, taken in benzene (500 ml), and treated twice with charcoal. The pale green filtrate was treated with piperidine (2 drops) and the resultant yellow solution was concentrated to 75 ml and allowed to stand at room temperature. The resultant pinkish needles

(35) I. M. Hunsberger, E. R. Shaw, J. Fugger, R. Ketcham, and D. Lednicer, *J. Org. Chem.*, **21**, 394 (1956).

(36) Ng. P. Buu-Hoi and Ng. Hoan, *ibid.*, **16**, 1327 (1951).

(37) L. Burgardt, E. Reckziegel, and O. Wahl, German Patent 950,617 (1956).

were recrystallized from benzene and afforded **8d**, mp 204–205° (6.4 g).

Anal. Calcd for $C_{29}H_{24}I_2N_2$: C, 53.23; H, 3.70; N, 4.16. Found: C, 53.22; H, 3.91; N, 4.28.

Bis(6-iodo-9-methyl-3-carbazolyl)methane (8e).—In a similar experiment to the one above, **7e** (9.2 g) was treated with methylal (1.3 g) in refluxing acetic acid. The mixture was worked up as above and the reaction product was recrystallized from benzene, yielding **8e**, mp 249–252° (5.7 g).

Anal. Calcd for $C_{27}H_{20}I_2N_2$: C, 51.77; H, 3.22; N, 4.47. Found: C, 51.54; H, 3.18; N, 4.40.

Bis(9-ethyl-3-carbazolyl)methane (3c). (A) From Lithium–*t*-Butyl Alcohol–Tetrahydrofuran Dehalogenation of 8c.—A solution of **8c** (5.6 g) in a mixture of dry tetrahydrofuran (50 ml) and *t*-butyl alcohol (3 g) was stirred under a nitrogen atmosphere while lithium shot (0.7 g) was added, followed by methyl iodide (5 drops). The mixture was refluxed for 2 hr and was then poured onto crushed ice. After the excess lithium had decomposed, the mixture was acidified with 2 *N* HCl and extracted with ether (two 100-ml portions). The ether extract was washed with H_2O, dried (K_2CO_3), filtered, and evaporated. The yellow oily residue was chromatographed on alumina (Woehlm, basic, activity grade 1), utilizing petroleum ether (bp 30–40°) as initial eluent. This solvent removed an oily product (0.4 g), which was not investigated. The major product was subsequently eluted with petroleum ether–5% ether. Crystallization of this material from ether afforded **3c**, mp 143–144°, as shimmering flakes; ir (KBr) 2940 (CH_3), 800 (1,2,4-trisubstituted benzene ring), and 750 and 725 cm^{-1} (1,2-disubstituted benzene ring); nmr ($CDCl_3$) δ 8.0 (d, 4 H, 4 and 5 protons), 6.8–7.4 (m, 10 H, aromatic protons), 4.3 (q, 4 H, N–CH_2CH_3), 4.3 (s, 2 H, Ar–CH_2–Ar), and 1.4 (t, 6 H, N–CH_2CH_3).

Anal. Calcd for $C_{29}H_{26}N_2$: C, 86.53; H, 6.51; N, 6.96. Found: C, 86.37; H, 6.47; N, 7.25.

If crystallization of the product was attempted from benzene–ether mixtures, a form apparently containing benzene of crystallization, mp 109–110°, was obtained. The solvent of crystallization could be driven off by holding the liquid melt at 120–125°; the residue then solidified and finally melted at 142–143°.

(B) From Lithium Aluminum Hydride Reduction of 8d.—A solution of **8d** (1.07 g) in tetrahydrofuran (50 ml) containing $LiAlH_4$ (1 g) was refluxed overnight. After destruction of excess hydride with ethyl acetate, benzene (100 ml) was added and the mixture was treated with 2 *N* HCl (100 ml). The organic layer was separated, washed with H_2O (three 50-ml portions), dried (Na_2SO_4), filtered, and evaporated to dryness. The residue (406 mg) was crystallized twice from ether and afforded **3c**, mp 142–143° (undepressed upon admixture with the material obtained from route A above).

(C) From Ethylation of 3a.—A suspension of **3a** (420 mg) in acetone (75 ml) was treated with a solution of sodium hydroxide (2.5 g) in water (3 ml), followed by diethyl sulfate (6 ml). The mixture was stirred and refluxed for 4 hr and filtered (much unchanged bis(3-carbazolyl)methane was recovered), and the filtrate was diluted with H_2O. The product was extracted into ether and the ether extract was washed with water, dried (K_2CO_3), filtered and concentrated to approximately 2 ml volume. Crystalline plates of **3c** (73 mg) were obtained, mp 139–140°, mixture melting point with material prepared by debromination of bis(6-bromo-9-ethyl-3-carbazolyl)methane, 140–142°.

Bis(9-methyl-3-carbazolyl)methane (3b). (A) From Lithium Aluminum Hydride Reduction of 9e.—Bis(6-iodo-9-methyl-3-carbazolyl)methane (2.9 g) was reduced with lithium aluminum hydride (1.4 g) in tetrahydrofuran (100 ml) in a similar manner to the treatment of the 9-ethyl compound above. The resultant product was recrystallized from ether and afforded **3b**, mp 190–191° (0.95 g); nmr ($CDCl_3$) δ 8.0 (d, 4 H, 4 and 5 protons), 6.8–7.5 (m, 10 H, remaining aromatic protons), 4.3 (s, 2 H, Ar–CH_2–Ar), and 3.7 (s, 6 H, N–CH_3).

Anal. Calcd for $C_{27}H_{22}N_2$: C, 86.59; H, 5.92; N, 7.48. Found: C, 86.42; H, 6.03; N, 7.42%.

(B) From Methylation of 3a.—A suspension of **3a** (720 mg) in acetone (100 ml) containing potassium hydroxide (3 g) and water (4 ml) was treated, at the reflux point, with dimethyl sulfate (10 ml). The mixture was stirred and refluxed for 4 hr and was then worked up in the manner of the corresponding ethylation reaction above. The yield of bis(9-methyl-3-carbazolyl)methane, mp 191–192°, was 183 mg (25%).

Condensation of 9-Ethylcarbazole with Formaldehyde.—A solution of ethylcarbazole (4.9 g; 0.025 mol) in acetic acid (100 ml) containing sulfuric acid (0.2 g) was heated to 85° and a solution of formaldehyde (0.013 mol) in acetic acid (11 ml) was added dropwise at this temperature. After addition was complete, the mixture was refluxed for 5 min, then poured into xylene (650 ml), and the acetic acid removed by distillation. The resultant blue xylene solution was evaporated to small bulk and treated with piperidine (2 drops); the resultant pale yellow solution was filtered. The product was obtained at 0° as pale buff microcrystalline prisms, which partly melted in the range 190–200°, but did not melt further up to 270°; mol wt 1649, 1784; ir (KBr) 804 (1,2,4-trisubstituted benzene rings) and 735 and 750 cm^{-1} (weak only, 1,2-disubstituted benzene ring, carbazole end group).

Self-Condensation of 11.—A cold solution of **11** (8 g) in acetic acid (25 ml) was added to a second portion of acetic acid (75 ml) held at 90–95°; a bluish white precipitate appeared. The collected product was dissolved in tetrahydrofuran and poured into an excess of sodium bicarbonate solution. The resultant white product (4.7 g) had mp 163–164°, with prior softening at 157°; mol wt 1699, 1775, 1756; ir (KBr) 3400 (OH), 800 (1,2,4-trisubstituted benzene ring), and 735 and 750 cm^{-1} (weak only, 1,2-disubstituted benzene ring, carbazole end group).

Registry No.—**3a**, 24290-44-6; **3b**, 18152-70-0; **3c**, 16391-67-6; **4g**, 24301-72-2; **5a**, 6510-63-0; **5d**, 24301-74-4; **6**, 24301-75-5; **8c**, 24301-76-6; **8d**, 24301-77-7; **8e**, 24301-78-8; **11**, 24301-79-9; **14**, 24301-80-2.

Synthesis of 1,2,3,4-Tetrahydro-2,3-disubstituted 10-Hydroxy-1,4-dioxopyrazino[1,2-*a*]indoles

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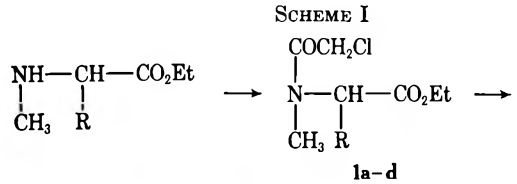
1,2,3,4-Tetrahydro-2,3-disubstituted 10-hydroxy-1,4-dioxopyrazino[1,2-*a*]indoles have been prepared by two methods: cyclization of the corresponding *dl-o*-carbomethoxyphenylglycyl-N-methylamino acid esters in the presence of sodium methoxide, and from 3-methoxyindole-2-carboxylic acid by acylation of N-methylamino acid esters followed by spontaneous base-catalyzed cyclization and demethylation in the last stage.

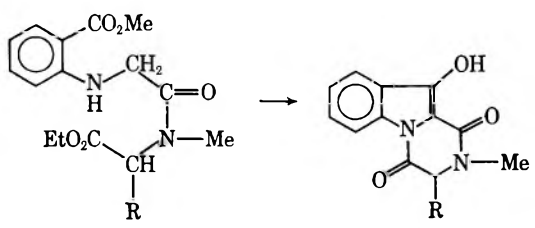
Synthesis of 1,2,3,4-tetrahydro-2,3-dimethyl-10-hydroxy-1,4-dioxopyrazino[1,2-*a*]indole (**3a**) was carried out in connection with studies on the structure of anhydrodethiogliotoxin,[1] one of the degradation products of the mold antibiotic gliotoxin. The above 10-hydroxypyrazinoindole was selectively reduced with sodium amalgam to the 10:11-dihydro derivative, which was eventually shown by spectral analysis and other evidence to be different from anhydrodethiogliotoxin.[2,3]

However, the 10-hydroxy-1,4-dioxopyrazinoindole ring system with its closed peptide structure is interesting enough in itself to stimulate a rational synthesis. Two independent syntheses of 1,2,3,4-tetrahydro-2,3-disubstituted 10-hydroxy-1,4-dioxopyrazino[1,2-*a*]indoles have been worked out in Schemes I and II.

SCHEME I



1a–d

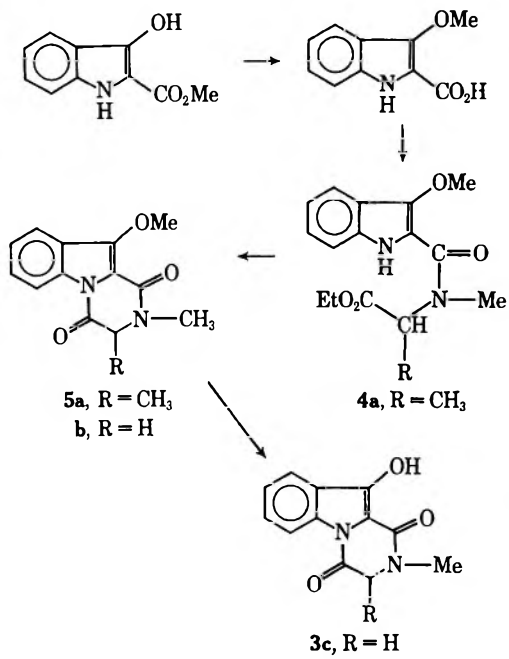


2a–d **3a–d**

a, R = CH_3
b, R = CH_2CH_3
c, R = H
d, R = $CH_2C_6H_5$

In Scheme I, *dl*-N-methyl-α-amino acid esters were chloroacetylated, and the chloroacetyl derivatives (**1**) were condensed with methyl anthranilate by heating them either in alcoholic solution[4] or neat to give *dl-o*-carbomethoxyphenylglycyl-N-methylamino acid esters (**2**). In both cases, the condensation proceeded without formation of amides, polymerization, or intramolecular cyclization to form the pyrazine ring. *dl-o*-Carbomethoxyphenylglycyl-N-methylamino acid esters (**2**) were cyclized in the presence of sodium methoxide to give 10-hydroxypyrazinoindoles (**3**). Our findings regarding this base-catalyzed cyclization are in agreement with earlier reports[5,6] that this cyclization takes place only if there is no active hydrogen on the amide nitrogen.

SCHEME II



5a, R = CH_3
b, R = H

4a, R = CH_3

3c, R = H

In Scheme II, N-methylamino acid esters were condensed with preformed indoxylic acid. Fusion of methyl 3-hydroxyindole-2-carboxylate with sodium hydroxide at 300°[7] resulted in extensive decarboxylation and subsequent oxidation to indigo. The ester was hydrolyzed smoothly in 30% sodium hydroxide at 60°.

Since direct condensation of indoxylic acid with N-methylamino acid esters in the presence of N,N′-dicyclohexylcarbodiimide (DCCI) was not possible because of the strongly phenolic nature of the 3-hydroxy group, the latter had to be suitably protected. Acylation of indoxylic acid leads preferably to N-acyl derivatives.[4] Choice of benzyl group was not very fortunate. Alkaline hydrolysis of methyl 3-benzyloxyindole-2-carboxylate invariably led to decarboxylation. The ester was eventually hydrolyzed in

(1) J. R. Johnson and A. R. Kidwai, unpublished observations; doctoral thesis, Cornell University, 1950.
(2) J. R. Johnson and L. R. Harper, unpublished observations; doctoral thesis, Cornell University, 1954.
(3) M. R. Bell, J. R. Johnson, B. S. Wildt, and R. B. Woodward, *J. Amer. Chem. Soc.*, **80**, 1001 (1958).
(4) J. R. Johnson and J. H. Andreen, *ibid.*, **72**, 2862 (1950).
(5) J. R. Johnson, J. H. Andreen, and A. D. Holley, *ibid.*, **69**, 2370 (1947).
(6) J. D. Dutcher, J. R. Johnson, and W. F. Bruce, *ibid.*, **66**, 617 (1944).
(7) A. Baeyer, *Ber.*, **14**, 1741 (1881).

the presence of concentrated sulfuric acid,[8] but the carboxyl group in 3-benzyloxyindole-2-carboxylic acid was too hindered sterically to condense effectively with amino acid esters in the presence of DCCI. On treatment with thionyl chloride, the acid was recovered unchanged at low temperatures and was decarboxylated under more stringent conditions. Consequently, methyl 3-hydroxyindole-2-carboxylate was methylated, the product was hydrolyzed, and 3-methoxyindole-2-carboxylic acid was condensed with N-methylamino acid esters either in the presence of DCCI or after conversion to the acid chloride. In the presence of a slight excess of amino acid esters, the 3-methoxyindole-2-carboxylamino acid esters formed first cyclized spontaneously to the corresponding pyrazinoindoles in high yields. Other basic catalysts like triethylamine and pyridine gave lower yields. Demethylation of 10-methoxypyrazinoindoles was affected with hydriodic acid and red phosphorus.[6]

Experimental Section

Melting points were taken in capillary tubes on Gallenkamp melting point apparatus. All melting and boiling points are uncorrected. Ir spectra were taken on Perkin-Elmer Infracord and uv spectra on a Perkin-Elmer 220.

1,2,3,4-Tetrahydro-2,3-dimethyl-1,4-dioxo-10-hydroxypyrazino[1,2-*a*]indole (3a). (a) ***dl*-Chloroacetyl-N-methylalanine Ethyl Ester (1a).**—An ethereal solution of *dl*-N-methylalanine ethyl ester prepared from 10 g (0.097 mol) of *dl*-N-methylalanine was treated with freshly distilled chloroacetyl chloride, (5.4 g, 0.048 mol) in 30 ml of dry ether under anhydrous conditions. The reaction mixture was allowed to stand in an ice bath for 2 hr. Half of the ester was converted into its hydrochloride which separated as a liquid. The *dl*-N-chloroacetyl-N-methylalanine ethyl ester remaining in the ether solution was washed free of unreacted ester and chloroacetyl chloride. It distilled at 119–125° (2 mm under N_2), $n^{20}D$ 1.47, yield 7.5 g (75% on the basis of chloroacetyl chloride used).

Anal. Calcd for $C_8H_{14}ClNO_3$: C, 46.3; H, 6.7; N, 6.7. Found: C, 46.2; H, 6.7; N, 6.5.

(b) ***dl*-*o*-Carbomethoxyphenylglycyl-N-methylalanine Ethyl Ester (2a).**—Methyl anthranilate (40.7 g, 0.27 mol) and **1a** (14 g, 0.0675 mol) were heated on a steam bath for 8 hr when a large quantity of methyl anthranilate hydrochloride separated. Dry benzene (150 ml) was added and the hydrochloride was filtered off. After removing benzene under reduced pressure, the reaction mixture was heated for another 8 hr and the hydrochloride was separated as before. Further heating resulted in separation of only a negligible quantity of the ester hydrochloride. In all 11.6 g of methyl anthranilate hydrochloride was collected (theoretical 12.6 g). Unreacted methyl anthranilate was distilled off from the residual mass at 110–111° (2–3 mm under N_2) keeping the bath temperature at 165°. The residue (25.5 g) was crystallized from benzene and recrystallized from absolute alcohol, mp 89–90°, yield 15 g (69%). Another crystallization from 1-butanol raised the melting point to 89.5–90°; ir (KBr) 3375 (NH), 1750, 1700, 1675 (amide, ester and NH), 1262, 1225 cm^{-1} (C–O–C); uv max (EtOH) 345, 253, 225 mμ.

Anal. Calcd for $C_{16}H_{22}N_2O_5$: C, 59.6; H, 6.9; N, 8.7. Found: C, 59.8; H, 6.85; N, 8.7.

(c) **1,2,3,4-Tetrahydro-2,3-dimethyl-1,4-dioxo-10-hydroxypyrazino[1,2-*a*]indole (3a).**—A solution of 10 g of **2a** in 50 ml of dry benzene was added to a suspension of sodium methoxide (prepared from 0.7 g of sodium) in dry benzene, and the mixture was heated slowly on a steam bath under anhydrous conditions. First a turbidity appeared and within 10 min a yellow gelatinous precipitate of the sodium salt started separating. The reaction mixture was heated for 1 hr and cooled, 100 ml of dry ether was added, and the sodium salt was filtered, washed with ether, and dissolved in ice-cold water. The aqueous solution was filtered and the 10-hydroxypyrazinoindole was quickly precipitated by adding solid carbon dioxide. After washing with dilute acetic acid and water, the crude, dry product weighed 4 g. Carbon dioxide saturated filtrate on saturation with sodium chloride gave an additional 500 mg. The crude product was crystallized from methanol (leaving 200 mg of an insoluble residue which darkens at 255° and decomposes at 265°), yield 3.25 g (42%), mp 137–139°. For further purification the product was dissolved in cold 1% sodium hydroxide, reprecipitated with solid carbon dioxide, and washed as before. After one crystallization from ethanol and another from 1-butanol, the pure product weighed 2.2 g, mp 138–139°. It gives a dark green color with alcoholic ferric chloride: ir (KBr) 3250 (broad, chelated OH), 1700 (indole NC=O), 1625 cm^{-1} (amide C=O); uv max (EtOH) 302 mμ.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.9; H, 4.95; N, 11.45. Found: C, 64.0; H, 4.9; N, 11.3.

The carbon dioxide saturated mother liquor left after removal of the 10-hydroxypyrazinoindole gave a precipitate on acidifying with HCl, which was crystallized from ethanol. It weighed 1.55 g, melted to a red liquid at 195–200°, and gave a red color with alcoholic ferric chloride. This is probably the acid formed by hydrolysis of the pyrazine ring.

1,2,3,4-Tetrahydro-2-methyl-3-ethyl-1,4-dioxo-10-hydroxypyrazino[1,2-*a*]indole (3b). (a) ***dl*-Chloroacetyl-N-methyl-α-aminobutanoic Acid Ethyl Ester (1b).**—Chloroacetylation of *dl*-N-methylaminobutanoic acid ethyl ester gave **1b** in 53.6% yield, bp 140° (4 mm under N_2), $n^{30}D$ 1.40.

Anal. Calcd for $C_9H_{16}ClNO_3$: C, 48.7; H, 7.2; N, 6.3. Found: C, 49.1; H, 7.4; N, 6.1.

(b) ***dl*-*o*-Carbomethoxyphenylglycyl-N-methyl-α-aminobutanoic Acid Ethyl Ester (2b).**—This was prepared by condensation of **1b** with methyl anthranilate in 68% yield. It crystallized from absolute alcohol, mp 83°.

Anal. Calcd for $C_{17}H_{24}N_2O_5$: C, 60.7; H, 7.1; N, 8.3. Found: C, 60.6; H, 7.1; N, 8.3.

(c) **1,2,3,4-Tetrahydro-2-methyl-3-ethyl-1,4-dioxo-10-hydroxypyrazino[1,2-*a*]indole (3b).**—**2b** cyclized to **3b** in 40% yield in the presence of sodium methoxide. **3b** was crystallized from absolute alcohol in white prisms: mp 146°; ir (KBr) 3250 (broad), 1700, 1625 cm^{-1}; uv max (EtOH) 302 mμ.

Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.1; H, 5.6; N, 10.8. Found: C, 65.2; H, 5.6; N, 10.6.

1,2,3,4-Tetrahydro-2-methyl-1,4-dioxo-10-hydroxypyrazino-[1,2-*a*]indole (3c). (a) **Chloroacetyl-N-methylglycine Ethyl Ester (1c).**—Chloroacetylation of N-methylglycine ethyl ester gave **1c** in 46% yield, bp 145° (2 mm under N_2), $n^{30}D$ 1.472.

Anal. Calcd for $C_7H_{12}ClNO_3$: C, 43.4; H, 6.2; N, 7.2. Found: C, 43.2; H, 6.3; N, 7.3.

(b) **1,2,3,4-Tetrahydro-2-methyl-1,4-dioxo-10-hydroxypyrazino-[1,2-*a*]indole (3c).**—The above chloroacetyl derivative (**1c**) was condensed with methyl anthranilate to give **2c**. The latter failed to crystallize, and therefore it was dried (P_2O_5) and cyclized as such with sodium methoxide to give **3c** in 33% yield. **3c** crystallized from absolute ethanol: mp 215° dec; ir (KBr) 3250 (broad), 1700, 1620 cm^{-1}; uv max (EtOH) 300 mμ.

Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.6; H, 4.4; N, 12.2. Found: C, 62.3; H, 4.3; N, 11.9.

1,2,3,4-Tetrahydro-2-methyl-3-benzyl-1,4-dioxo-10-hydroxypyrazino[1,2-*a*]indole (3d).—*dl*-Chloroacetyl-N-methylphenylalanine ethyl ester (**1d**) obtained by chloroacetylation of *dl*-N-methylphenylalanine ethyl ester did not distil even at 200° (2 mm). Above this temperature it started decomposing; therefore, it was condensed as such with methyl anthranilate to give **2d**, which was cyclized in the presence of sodium methoxide to give **3d** in 23% yield. **3d** crystallized from alcohol: mp 148°; ir (KBr) 3100 (broad), 1670, 1620 cm^{-1}; uv max (EtOH) 304 mμ.

Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.2; H, 5.0; N, 8.7. Found: C, 71.0; H, 5.0; N, 8.2.

Indoxylic Acid.—A solution of 5 g of methyl 3-hydroxyindole-2-carboxylate[4,5] in 25 ml of 30% sodium hydroxide solution was warmed on a water bath at 60° for 1 hr. The cold reaction mixture was acidified with hydrochloric acid to give 4 g (87%) of indoxylic acid, which was dried (P_2O_5), mp 123°.

Methyl 3-Benzyloxyindole-2-carboxylate.—Methyl 3-hydroxyindole-2-carboxylate (19.1 g, 0.1 mol) was benzylated with freshly distilled benzyl chloride (12.65 g, 0.1 mol) over anhydrous potassium carbonate (10 g) in dry acetone using potassium iodide as a catalyst. It crystallized from ethyl acetate–petroleum ether (bp 40–60°): mp 95–96°; yield 19.7 g (70%).

(8) H. P. Treffers and L. P. Hammett, *J. Amer. Chem. Soc.*, **59**, 1708 (1937).

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.6; H, 5.3; N, 5.0. Found: C, 72.2; H, 5.3; N, 4.85.

3-Benzyloxyindole-2-carboxylic Acid.—Methyl 3-benzyloxyindole-2-carboxylate (8.43 g, 0.03 mol) was finely powdered and dissolved completely in 30 ml of concentrated sulfuric acid; the solution was poured into a large amount of crushed ice with vigorous stirring. The precipitated acid was extracted with ether, the ethereal layer was washed, the ether was evaporated off under reduced pressure at room temperature, and the residue crystallized from ethanol, mp 120°, yield 7 g (87%).

Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.9; H, 4.9; N, 5.2. Found: C, 72.3; H, 5.0; N, 4.9.

Methyl 3-Methoxyindole-2-carboxylate.—Methyl 3-hydroxyindole-2-carboxylate (16 g, 0.083 mol) was methylated with dimethyl sulfate (10.5 g) over anhydrous potassium carbonate in 200 ml of dry acetone. It crystallized from ethyl acetate, mp 106°, yield 13.7 g (80%).

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.4; H, 5.4; N, 6.8. Found: C, 64.0; H, 5.3; N, 7.1.

3-Methoxyindole-2-carboxylic Acid.—A solution of methyl 3-methoxyindole-2-carboxylate (20 g, 0.096 mol) in 200 ml of 1 *N* methanolic potassium hydroxide was refluxed for 3 hr in a water bath. Methanol was distilled off and the acid precipitated from cold aqueous solution of the sodium salt with hydrochloric acid. It crystallized from dry benzene, mp 135° dec, yield 16 g (86%).

Anal. Calcd for $C_{10}H_9NO_3$: C, 62.8; H, 4.7; N, 7.3. Found: C, 62.9; H, 4.9; N, 6.9.

1,2,3,4-Tetrahydro-2-methyl-1,4-dioxo-10-methoxypyrazino-[1,2-*a*]indole (5b).—An ethereal solution of 3-methoxyindole-2-carboxylic acid (5.7 g, 0.03 mol) was treated with thionyl chloride (7.1 g, 0.06 mol). After it was maintained for 1 hr at room temperature, ether and thionyl chloride were removed *in vacuo* without external heating. The residual acid chloride was flushed with fresh lots of dry ether to remove traces of thionyl chloride. The slightly pigmented semicrystalline residue was dissolved in dry ether and treated with an ethereal solution of N-methylglycine ethyl ester (prepared from 8 g, 0.09 mol, of N-methylglycine). The reaction mixture warmed up slightly and was left at room temperature overnight. The ester hydrochloride was filtered off. The ethereal filtrate was washed well with distilled water, the ether was evaporated, and the solid residue was crystallized from aqueous methanol: mp 155°; yield 5.2 g (72%); ir (KBr) 1700, 1640, 1250, 1089 cm^{-1} (=COMe); uv max (EtOH) 296 mμ.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.9; H, 4.9; N, 11.6. Found: C, 64.2; H, 5.2; N, 11.2.

1,2,3,4-Tetrahydro-2-methyl-1,4-dioxo-10-hydroxypyrazino-[1,2-*a*]indole (3c).—**5b** (732 mg, 0.003 mol) was demethylated by boiling gently for 3 hr with red phosphorus (1.4 g) and a mixture of acetic anhydride (5 ml) and hydriodic acid (4 ml, sp gr 1.7). The demethylated product was worked up in the usual way. It crystallized from ethanol, mp 215° dec, yield 600 mg (87%), mmp with **3c** 215° dec: uv and ir spectra were also identical with **3c**.

3-Methoxyindole-2-carboxyl-*dl*-N-methylalanine Ethyl Ester (4).—An ethereal solution of 3-methoxyindole-2-carbonyl chloride prepared from 3.6 g (0.019 mol) of 3-methoxyindole-2-carboxylic acid was treated with an ethereal solution of *dl*-N-methylalanine ethyl ester prepared from 4 g (0.038 mol) of *dl*-N-methylalanine. The reaction mixture was left at room temperature for 2 hr; the ethereal layer was decanted from the precipitated ester hydrochloride and washed with 1 *N* HCl, 1 *N* $KHCO_3$, and water. After evaporating ether, the residue was crystallized twice from ethanol: mp 113°; yield 4 g (70%); ir (KBr) 3250 (indole NH), 1740 (ester C=O), 1600 (amide C=O), 1250, 1089 cm^{-1} (=COMe); uv max (EtOH) 295 mμ.

Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 63.1; H, 6.6; N, 9.2. Found: C, 62.7; H, 6.6; N, 9.3.

1,2,3,4-Tetrahydro-2,3-dimethyl-1,4-dioxo-10-methoxypyrazino[1,2-*a*]indole (5a).—A methanolic solution of **4** (0.5 g, 0.0016 mol) was treated with 5 ml of an ethereal solution of *dl*-N-methylalanine ethyl ester containing approximately 0.002 mol of the ester. The mixture was left at room temperature overnight. When concentrated and cooled, 10-methoxypyrazinoindole crystallized out in colorless crystals, mp 116°, yield 0.3 g (75%).

Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.1; H, 5.4; N, 10.8. Found: C, 64.8; H, 5.4; N, 10.5.

Direct Condensation of 3-Methoxyindole-2-carboxylic Acid with N-Methylglycine Ethyl Ester.—3-Methoxyindole-2-carboxylic acid (1 g, 0.005 mol) in dry ether was added to a dry ethereal solution of N-methylglycine ethyl ester (prepared from 0.89 g, 0.01 mol, of N-methylglycine) containing DCCI (1 g, 0.005 mol). The reaction mixture was left at room temperature for 24 hr. Dicyclohexylurea was filtered, yield 1 g (theoretical 1.08 g). 1,2,3,4-Tetrahydro-2-methyl-1,4-dioxo-10-methoxypyrazino[1,2-*a*]indole was crystallized from aqueous methanol, mp 155°, mmp with **5b** 155°; uv ir spectra were also identical with **5b**.

Registry No.—**1a,** 24463-58-9; **1b,** 24515-52-4; **1c,** 24515-53-5; **2a,** 24463-59-0; **2b,** 24463-60-3; **3a,** 24463-61-4; **3b,** 24463-62-5; **3c,** 24463-63-6; **3d,** 24463-64-7; **4,** 24463-65-8; **5a,** 24463-66-9; **5b,** 24463-67-0; methyl 3-benzyloxyindole-2-carboxylate, 24463-68-1; 3-benzyloxyindole-2-carboxylic acid, 24463-69-2; methyl 3-methoxyindole-2-carboxylate, 21716-59-6; 3-methoxyindole-2-carboxylic acid, 21598-04-9.

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Hydrogen Bonding and Isomerism in Arylazo Oximes

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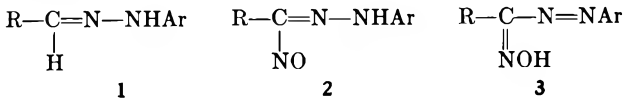
Several new arylazo oximes are reported. Infrared, electronic, and pmr spectra of arylazo oximes and deuterated arylazo oximes were examined. No evidence for the tautomeric nitrosohydrazone form could be obtained. Arylazo oximes show n → π^* and $\pi \rightarrow \pi^*$ transitions characteristic of azo compounds. In the solid state they exist in hydrogen-bonded form(s) only. However, in the solution phase, equilibria between monomeric and associated species are clearly observable. Pmr spectra of some arylazo oximes show the existence of two distinct species in solution. It is concluded that the results are best explained in terms of *cis–trans* isomerism around C=N.

An important class of reactions of arylhydrazones (**1**) is their electrophilic substitution.[1] One such reaction, *viz.*, that of aldehyde arylhydrazones with *n*-amyl nitrite, was discovered by Bamberger and Pemsel many years ago.[2] The initial product of the reaction is



probably the C-nitroso compound **2** which readily isomerizes to the arylazo oxime **3**.

Arylazo oximes form stable chelates with various metal ions. During our investigations of these chelates[3-5] it was found that the ligands themselves have not been subjected to any detailed structural investigations. Several questions are relevant in this context. Is the tautomeric nitrosohydrazone structure **2** completely excluded? What is the geometric structure, *e.g.*, with respect to N=N or C=N of the ligand system? To what extent does inter- and/or intramolecular hydrogen bonding complicate the behavior of the arylazo oximes? The present investigation was undertaken in order to answer these questions at least qualitatively.

The arylazo oximes are stable both in the solid state and in solution. Physical evidence, presented below, show that the C-nitroso structure **2** makes no contribution to the composition of any of these phases.

Physical Data

Electronic Spectra.—The characteristic red color of simple azo compounds generally arises from an n–π^* transition located primarily on the azo group.[6-8] This transition normally centers around 440 mμ. In the specific case of azobenzene[8] (chloroform solution), the n–π^* transition is at 438 mμ (ϵ 1150) for the *cis* isomer and at 445 mμ (ϵ 300) for the *trans* isomer. In the electronic spectra of arylazo oximes, the n–π^* azo band is clearly seen in the region 400–440 mμ. Some typical results are shown in Table I. The band at ~300 mμ is also characteristic of azo compounds. For azobenzene it is at 324 mμ (ϵ 15,000) for the *cis* isomer and at 319 mμ (ϵ 19,500) for the *trans* isomer. The transition is undoubtedly of the π–π^* type.

TABLE I

ABSORPTION MAXIMA (λ_{max}) AND EXTINCTION COEFFICIENTS OF ELECTRONIC BANDS FOR SOME ARYLAZO OXIMES TAKEN IN BENZENE

Compound		
R	Ar	λ_{max}, mμ (ϵ, l. mol^{-1} cm^{-1})
H (a)	C_6H_5	435 (330), 310 (21,400)
CH_3 (b)	C_6H_5	440 (260), 305 (20,700)
$C_6H_4CH_3$-*p* (c)	C_6H_5	420 sh[a] (660), 300 (15,300)
C_6H_5 (d)	$C_6H_4CH_3$-*p*	400 sh (1760), 315 (15,400)

[a] sh is shoulder.

C-Nitroso groups[9] may be expected to show a weak (ϵ ~ 20) band around 700 mμ due to a σ–π^* transition.[10] No such absorption could be located in concentrated solutions for the compounds studied by us. Thus electronic spectral data exclude the nitrosohydrazone structure. Our spectral data are in accord with an earlier report.[11]

Molecular Weight Data.—The observed molecular weight of an arylazo oxime in solution is generally higher than that calculated for the monomeric structure. Further, the molecular weight increases with increasing solute concentration. Some representative data for chloroform solutions of two arylazo oximes are shown in Table II. Clearly, associated species are present in solution.

TABLE II

CONCENTRATION DEPENDENCE OF MOLECULAR WEIGHTS OF TWO ARYLAZO OXIMES IN CHLOROFORM

Compound	Concn, *M*	Molecular weight Calcd (monomer)	Found
Phenylazoacetaldoxime	0.006	163	200
	0.015		237
	0.031		294
	0.046		320
Phenylazo-*p*-tolualdoxime	0.004	239	261
	0.012		301
	0.028		343

Infrared Spectra.—Vibration spectra of arylazo oximes in the solid state and in solution show an intense and somewhat broad band (width at half-height, ~50 cm^{-1}) in the region 1000–1050 cm^{-1}. Deuteration of the oxime group has very slight effect on this frequency. We assign this band to ν_{N-O} of the azo oxime structure. The similarity of the shape and

(1) J. Buckingham, *Quart. Rev.* (London), **23**, 37 (1969).
(2) E. Bamberger and W. Pemsel, *Ber.*, **35**, 85 (1903).
(3) A. Chakravorty and K. C. Kalia, *Inorg. Nucl. Chem. Lett.*, **3**, 319 (1967).
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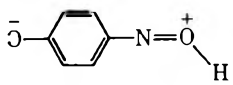
(6) A. Burawoy, A. G. Salem, and A. R. Thompson, *J. Chem. Soc.*, 4793 (1952).
(7) A. Burawoy, *ibid.*, 1865 (1937).
(8) A. E. Gillams and E. S. Stern, "Electronic Absorption Spectroscopy," Edward Arnold, London, 1960, p 271.
(9) Reference 8, p 34.
(10) L. E. Orgel, *J. Chem. Soc.*, 1276 (1953).
(11) P. Grammaticakis, *C. R. Acad. Sci., Paris*, **235**, 684 (1947).

intensity of this band with those of the ν_{N-O} of simple oximes[12] is very striking indeed.

In hydroxylamine[13] ν_{N-O} is at 912 cm^{-1}. In N-methyl- and N,N-dimethylhydroxylamine[14] the frequency shifts to ~950 cm^{-1}, whereas in the O-methyl derivatives the frequency is at 858 cm^{-1}. Palm and Werbin[12] investigated the infrared spectra of several aromatic oximes in both α and β forms. ν_{N-O} was observed as a medium to strong band in the frequency range 930–960 cm^{-1}. On the other hand, in quinone monoximes,[15] ν_{N-O} shifts to 975–1075 cm^{-1}. This is attributed to resonance contribution from a structure of type **4**. The high value of ν_{N-O} of arylazo oximes can similarly be due to the contribution from structure **5**.



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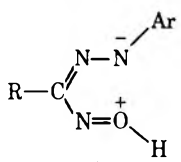

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The N=N stretch[16] is expected at ~1400 cm^{-1}. However, arylazo oximes show a complex spectrum in this region, and we did not attempt to identify the $\nu_{N=N}$ frequency.

Infrared data throw considerable light on the question of hydrogen bonding in arylazo oximes. Two typical cases, phenylazoacetaldoxime and phenylazo-*p*-tolualdoxime, were examined in detail (Table III). In the solid state and in solution, they show a number of broad and overlapping bands in the 2800–3200-cm^{-1} region. Similar bands are seen in the solution phase as well. Most probably they arise from overlapping O–H (associated) and C–H stretches. The solution phase shows an additional sharp feature at ~3580 cm^{-1} which is completely absent in the spectra of solids. This can be assigned to ν_{O-H} of the monomeric non-hydrogen-bonded species. In order to put this assignment scheme on a more sound basis the deuterated ligands were examined (Table III).

TABLE III

FREQUENCIES (cm^{-1}) OF INFRARED BANDS[a] OF TWO ARYLAZO OXIMES AND THEIR DEUTERATED DERIVATIVES

Phenylazoacetaldoxime[b,c]		Phenylazo-*p*-tolualdoxime[b]		
KBr disk	CCl_4 soln	KBr disk	CCl_4 soln	Assignment
1050	1025	1043	1020	ν_{N-O} (in NOH)
1052	1030	1045	1020	ν_{N-O} (in NOD)
1130	1115	...[d]	...[d]	δ_{O-D}[e]
...[f]	3160	...[g]	3160	ν_{O-H} (associated)
Absent	3578	Absent	3585	ν_{O-H} (monomer)
2155[h]	2380[h]	2260[h]	2360[h]	ν_{O-D} (associated)
Absent	2645	Absent	2640	ν_{O-D} (monomer)

[a] Among the frequencies that could be assigned with reasonable certainty, only those that are significant for structure elucidation are tabulated. They are all medium to strong in intensity. [b] There are at least two ν_{C-H} bands in the 2800–3050-cm^{-1} region. They do not disappear on deuteration or complex formation. [c] A weak band at 1635 cm^{-1} (KBr disk and CCl_4 solution) shifts to 1605 cm^{-1} (where it overlaps with the nearby aromatic frequency) on deuteration. A probable assignment is $\nu_{C=N}$ (ref 20). The shift on deuteration may be indicative of interaction (ref 6) with δ_{O-H} at ~1400 cm^{-1}. [d] Could not be definitely located. [e] δ_{O-H} is probably at ~1400 cm^{-1}. There are several overlapping bands of different origin in the region 1400–1500 cm^{-1}. Deuteration reduces the intensity in this region considerably and δ_{O-D} appears at 1120 cm^{-1}. [f] Overlap with ν_{C-H} precludes proper identification; using ν_{O-D} (associated) = 2155 cm^{-1} and ν_{O-H}/ν_{O-D} = 1.35, the frequency is calculated as 2910 cm^{-1}. [g] Calculated value is 3050 cm^{-1}. [h] Center of a broad band showing some structure.

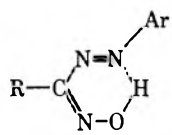
In phenylazoacetaldoxime-*d*, the relatively broad feature at 2155 cm^{-1} (solid) or 2380 cm^{-1} (solution) is unambiguously assignable to ν_{O-D} of associated species. The band is quite intense and this is indicative of intermolecular rather than intramolecular hydrogen bonding.[15] The sharp feature at 2645 cm^{-1} (solution only) is assigned to ν_{O-D} of monomers existing in equilibrium. Note that ν_{O-H}/ν_{O-D} = 1.35. Other arylazo oximes behave similarly. We therefore propose the following general solution equilibrium, where LH is an arylazo oxime. The molecular weight data of

$$n\mathrm{LH} \rightleftharpoons (\mathrm{LH})_n \qquad (1)$$

Table II is in full accord with this. The present data do not give any specific information about the value of n nor do they imply that only a single associated species is existent.

The infrared spectra of several aldoximes and ketoximes were studied by Palm and Werbin.[17] In crystalline α and β oximes, the O–H stretches were found to be at ~3250 and ~3120 cm^{-1}, respectively. The bands are broad and are of medium intensity. In the solution (chloroform or benzene) phase, however, both α and β isomers show a broad ν_{O-H} at ~3250 cm^{-1}. Some oximes show an additional sharp band at ~3500 cm^{-1}. Clearly the pattern is parallel to that shown by arylazo oximes. A similar equilibrium pattern is also shown by some quinone monooximes.[15]

Proton Magnetic Resonance Spectra.—Hunter and Roberts[18] assumed that arylazo oximes have an internally hydrogen-bonded structure **6**. As already



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pointed out, our infrared and molecular weight data suggest the presence of extensive intermolecular hydrogen bonding although the existence of some intramolecular association cannot be excluded. Concentration dependence of the pmr chemical shift of the oxime proton of arylazo oximes further substantiates the presence of intermolecular association. Even though the solution phase contains monomeric and associated species in equilibrium, only a single averaged NOH pmr signal is observed. In phenylazoacetaldoxime, the chemical shift of this signal drops from 11.19 to 10.36 ppm as the concentration is lowered from 1.5 to 0.6 *M* (in chloroform-*d* solution). The pmr signal of hydrogen-bonded protons appear at relatively low fields.[19] The disruption of the hydrogen-bonding

(12) A. Palm and H. Werbin, *Can. J. Chem.*, **32**, 858 (1954).
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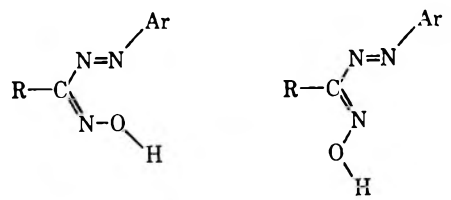
(15) D. Hadži, *ibid.*, 2725 (1956).
(16) K. Ueno, *J. Amer. Chem. Soc.*, **79**, 3066 (1957).
(17) A. Palm and H. Werbin, *Can. J. Chem.*, **31**, 1004 (1953).
(18) L. Hunter and C. B. Roberts, *J. Chem. Soc.*, 823 (1941).
(19) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 400.

interaction generally shifts the resonance to higher fields. If **6** is the sole structure of the associated species, dilution should produce little or no change in the pmr frequency. However, if process 1 is involved, dilution will shift the equilibrium toward the monomeric species, resulting in a shift of the frequency to higher fields as is actually observed.

Infrared and pmr evidences taken collectively with molecular weight data leave little doubt that equilibrium 1 correctly represents the behavior of arylazo oximes in solution. The internally hydrogen-bonded structure **6**, if present, is not a major contributor to solution composition.

Assuming that the stereochemistry around the azo group is *trans*, intermolecular hydrogen bonding will be compatible with a structure such as **7** in which the rotameric configuration around the N–O bond is such as to put the proton away from the azo group. In this structure the R and O–H groups are *trans* with respect to C=N. However, structure **8**, in which R and OH groups are *cis*, can also explain the observed pattern of



7 **8**

hydrogen bonding. It is quite possible that both **7** and **8** will contribute in practice. This brings us to the question of isomerism of arylazo oximes.

All arylazo oximes show pmr signals for aromatic protons in the region 7–8 ppm. The NOH signal appears in the range 9–12 ppm (Table IV). The pmr spectrum of phenylazoacetaldoxime in chloroform-*d* or benzene shows a single peak for the methyl protons. The protons of the R group of all other arylazo oximes with R = H or alkyl behave in a similar fashion (Table IV). If these arylazo oximes exist in isomeric forms in solution, the isomers either have insignificant chemical shift difference or they interconvert too fast by nmr criterion.

More interesting is the behavior of arylazo oximes with R = aryl. Several individual cases will be described separately.

Phenylazo-*p*-tolualdoxime (**9**) shows two distinct but overlapping methyl signals (Table IV). The relative areas under the signals are found to be dependent on the nature of the solvent. In a given solvent the relative areas also depend on the solute concentration. Addition of a small amount of sodium methoxide (*i.e.*, to generate a small concentration of the anion of the oxime) to the methanolic solution of the oxime leads to a single though broad methyl signal. The sodium salt of the oxime also gives rise to a single methyl signal in D_2O solution. These results are summarized in Table V.

TABLE IV

PROTON RESONANCE FREQUENCIES[a] OF A FEW ARYLAZO OXIMES

Compound R	Compound Ar	Group	Chemical shift,[b] δ (ppm)
H	C_6H_5	=NOH	9.85[c]
		H	8.68
CH_3	C_6H_5	=NOH	10.36[c]
		CH_3	2.37
n-C_3H_7 (c)	C_6H_5	=NOH	11.19[c]
		$CH_3CH_2CH_2$	1.15[d]
		$CH_3CH_2CH_2$	1.82[e]
		$CH_3CH_2CH_2$	3.09[d]
C_6H_5 (d)	C_6H_5	=NOH	10.98[c]
C_6H_5	$C_6H_4CH_3$-*p*	=NOH	11.75[c]
		$C_6H_4CH_3$-*p*	2.37, 2.42
$C_6H_4CH_3$-*p*	C_6H_5	=NOH	10.61[c]
		$C_6H_4CH_3$-*p*	2.33, 2.39
$C_6H_4CH_3$-*p* (g)	$C_6H_4CH_3$-*p*	=NOH	11.14[c]
		$C_6H_4CH_3$-*p*	2.39[f]
$C_{10}H_7$ (h)	$C_6H_4CH_3$-*p*	=NOH	10.50[c]
		$C_6H_4CH_3$-*p*	2.28
$C_{14}H_9$ (i)	$C_6H_4CH_3$-*p*	=NOH	[g]
		$C_6H_4CH_3$-*p*	2.35

[a] Aromatic protons give signals in the region 6.80–8.80 ppm. [b] From tetramethylsilane at 100 MHz in $CDCl_3$; solute concentration lies in the range 0.3–0.6 *M*. [c] Center of a broad signal. [d] Center of a triplet ($J \backsim 7.5$ Hz). [e] Center of a sextet ($J \backsim 7.5$ Hz). [f] Center of a complex pattern showing at least three lines of unequal intensity. [g] Not located.

TABLE V

CONCENTRATION AND SOLVENT DEPENDENCE OF THE INTENSITY OF THE METHYL SIGNALS OF PHENYLAZO-*p*-TOLUALDOXIME[a,b]

Solvent	Concn, *M*	Ratio of intensity[c]
Chloroform-*d*	0.6	1:1.8
	0.3	1:1.4
	0.2	1:0.9
Benzene	0.3	1:1.8
Pyridine	0.3	1:2.3
Methanol	0.3	1:2.2

[a] Sodium salt in D_2O gives a single methyl signal at 283 Hz (upfield) from HDO. [b] Addition of small amount of sodium methoxide to the methanolic solution of the ligand leads to single, relatively broad methyl signal. [c] Higher field signal: lower field signal; measured planimetrically.

***p*-Tolylazobenzaldoxime** (**10**) also shows two separate methyl signals in chloroform-*d* (Table IV) and in pyridine. As with the previous compound, the relative areas under the signals are solvent and concentration dependent. In benzene, however, a single methyl signal is observed. On addition of successive amounts of benzene to the chloroform-*d* solution, the relative separation between the two methyl peaks decreases and finally (benzene $\geq 50\%$) a single signal is all that is observed.

***p*-Tolyazo-*p*-tolualdoxime** (**11**) was investigated only in chloroform-*d*. The methyl region consists of at least three signals of unequal intensity. The presence of at least two distinct species is clearly indicated.

***p*-Tolylazo-α-naphthaldoxime** (**12**) **and *p*-Tolylazo-9-anthraldoxime** (**13**).—In chloroform-*d* each of these systems shows a single sharp methyl signal (Table IV).

We shall not aim at any detailed interpretation of all the results described above. However, it is clear that in the case of compounds **9**, **10**, and **11** there are at least two distinct species existing in equilibrium. Several alternatives to explain the observation of single and double nmr signals in the various cases were considered. All facts taken collectively support the contention that isomerism around the C=N group of **3** is involved.

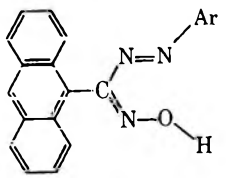
TABLE VI

CHARACTERIZATION OF ARYLAZO OXIMES

Compound R	Compound Ar	Formula	Mp, °C[a]	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
H (a)	$C_6H_4CH_3$-*o*	$C_8H_9N_3O$	97	58.88	58.82	5.56	5.50	25.74	25.52
H (b)	$C_6H_4CH_3$-*p*	$C_8H_9N_3O$	133	58.88	59.43	5.56	5.58	25.74	25.90
n-C_3H_7	C_6H_5	$C_{10}H_{13}N_3O$	80	62.81	62.39	6.85	6.90	21.96	21.88
C_6H CH_2 (d)	C_6H_5	$C_{14}H_{13}N_3O$	78	70.30	70.51	5.40	5.94	17.56	17.47
C_6H_4-*p*-CH_3	$C_6H_4CH_3$-*p*	$C_{15}H_{15}N_3O$	136	71.14	70.80	5.97	5.66	16.60	16.52
$C_{10}H_7$	$C_6H_4CH_3$-*p*	$C_{18}H_{15}N_3O$	175	74.72	74.37	5.23	5.85	14.55	14.37
$C_{14}H_9$	$C_6H_4CH_3$-*p*	$C_{22}H_{17}N_3O$	200	77.84	77.90	5.04	4.80	12.40	12.02

[a] All melting points reported in this table are uncorrected.

The observation of single resonance lines for the compounds **12** and **13** can be rationalized on the basis of steric interaction of the rotating naphthyl or anthryl group with the O–H group. This group, therefore, prefers to stay exclusively in the *trans* (*e.g.*, **14**) position



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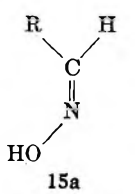
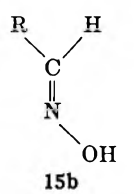
with respect to the bulky aryl group. When R = phenyl or *p*-tolyl, the hindrance will be much less and the pmr observation of two isomers can be understood. The single resonances observed for the R = alkyl cases remain to be explained. Steric factors are certainly unimportant here. We strongly suspect that these systems also exist as isomeric mixtures, but the rate of interconversion is very fast. A temperature-dependent pmr study will be extremely useful for proving this point. Such studies are planned to be undertaken.

The solvent and concentration dependence of the relative amounts of two pmr-observable species of **9** and **10** is not surprising in view of the complexity of the solutions. Such solutions probably contain monomeric and several polymeric species in isomeric forms. We propose that all species with the *cis* configuration are pmr averaged. The same separately happens for all *trans* species.

In conclusion, we shall summarize some of the earlier pmr studies. In the solution phase aliphatic aldoximes exist in two isomeric forms **15** which give rise to characteristic C–H signals.[20] As the bulk of the R group



15a



15b

increases, the population of the isomer **15a** decreases. The arylazo oximes (compare **9** with **12**) show a parallel behavior. The isomeric stability of aromatic aldoximes is much better than that of aliphatic aldoximes.[21–23] Similarly the rate of *cis–trans* interconversion appears to be faster in arylazo oximes having R = H or alkyl than in those having R = phenyl or *p*-tolyl. Unsymmetrical ketoximes also exhibit solution equilibria of isomers which can be identified by their pmr spectra.[24] Here again, steric factors can heavily tilt the equilibrium toward one of the isomers. Isomeric equilibria of aliphatic ketoximes are known to be more facile than those of their aromatic counterparts.[21]

Experimental Section

The arylazo oximes were prepared by following the procedure of Bamberger,[2] with slight modifications. We found *n*-butyl nitrite to be as effective as *n*-amyl nitrite (which was used in the original procedure of Bamberger). Of the arylazo oximes studied by us, benzeneazobenzaldoxime and benzeneazoacetaldoxime were already reported by Bamberger and Pemsel,[2] benzeneazo-*p*-tolualdoxime and *p*-tolueneazobenzaldoxime by Hunter and Roberts,[18] and benzeneazoformaldoxime by Grammaticakis.[11] The characterization data of compounds not reported in literature before are shown in Table VI. The compounds usually form yellow to orange crystalline solids which readily dissolve in a variety of organic solvents. They also dissolve in aqueous alkali giving dark reddish brown solutions.

Deuteration of arylazo oximes was carried out by precipitating their solutions in dry dioxane with deuterium oxide.

Proton resonance measurements were done on a Varian HR-100 spectrometer. Tetramethylsilane was used as the internal standard and frequencies were measured by the side-band technique. Areas were measured planimeterically. **Visible and ultraviolet spectra** were measured on a Cary-14 recording spectrophotometer. **Infrared spectra** were taken on a Perkin-Elmer 521 recording spectrophotometer.

Molecular weights were determined on a Mechrolab vapor pressure osmometer, Model 301A, in chloroform at 37°.

Registry No.—Table I—a, 4471-49-2; b, 4413-26-7; c, 24621-45-2; d, 24621-46-3; Table IV—c, 24621-47-4; d, 4430-12-0; g, 24621-49-6; h, 24621-50-9; i, 24621-51-0; Table VI—a, 24605-72-9; b, 24621-52-1; d, 24621-53-2.

(20) W. D. Phillips, *Ann. N. Y. Acad. Sci.*, **70**, 817 (1958).

(21) I. T. Millar and H. D. Springall, "Sidgwick's Organic Chemistry of Nitrogen," Clarendon Press, Oxford, 1966, p 310.

(22) I. Pejković-Tadić, M. Hranisavljevic, S. Nesic, C. Pascual, and W. Simon, *Helv. Chim Acta*, **48**, 1157 (1965).

(23) W. Buehler, *J. Org. Chem.*, **32**, 261 (1967).

(24) E. Lustig, *J. Phys. Chem.*, **65**, 491 (1961).

Reactions of Norbornyl-Type Ketones with Diazomethane[1]

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Ethereal diazomethane containing 10% methanol reacts stereoselectively with norbornen-7-one to produce a mixture of spiro[norborn-2-en-*anti*-7,2′-oxacyclopropane] (34%) and bicyclo[2.2.2]oct-5-en-2-one (44%). Under similar conditions norbornan-7-one is four times less reactive and yields spiro[norbornan-7,2′-oxacyclopropane] (<2%) and bicyclo[2.2.2]octan-2-one (>73%). Dehydronorcamphor is much less reactive and produces a mixture of the ketopyrazolines *exo*-3,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-3-en-8-one (~30%) and *exo*-3,4-diazatricyclo-[5.2.1.$0^{2,6}$]dec-3-en-9-one (~60%). The probable mechanism of each of these reactions is discussed and explanations are offered for the differing reactivity of these norbornyl-type ketones with diazomethane.

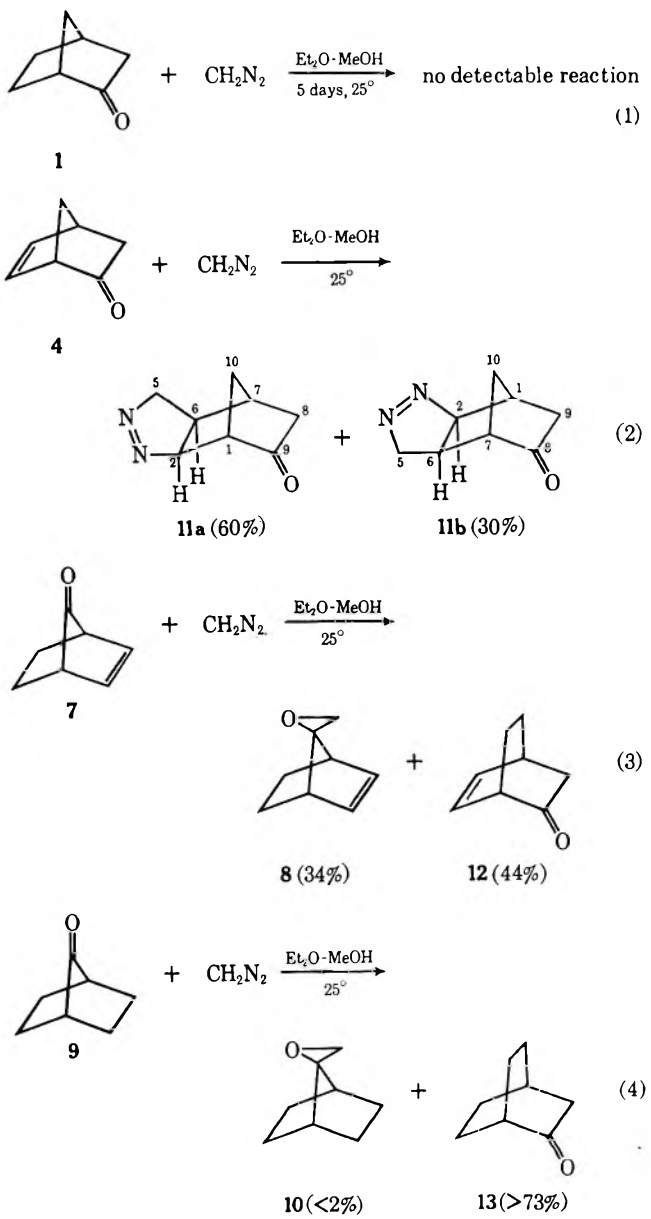
Norbornyl-type ketones show a surprising diversity in their reactivity toward the neutral nucleophile dimethyloxosulfonium methylide. Norcamphor (**1**) reacts predominantly from the *exo* side to yield a 90:10 mixture of saturated oxides: spiro[norbornan-*endo*- and *exo*-2,2′-oxacyclopropane], **2** and **3**, respectively.[2] Dehydronorcamphor (**4**) reacts about twice as rapidly but is attacked preferentially from its more hindered *endo* side to produce a 29:71 mixture of unsaturated oxides: spiro[norbornen-*endo*- and *exo*-5,2′-oxacyclopropane], **5** and **6**, respectively.[2] Bicyclo[2.2.1]-hept-2-en-7-one (**7**) reacts very rapidly from the side of the double bond to give the unsaturated spirooxide **8** as the sole product.[3] Bicyclo[2.2.1]heptan-7-one (**9**) also reacts rapidly to yield some of the expected spirooxide **10**, but, in addition, produces large amounts of sulfoxides: methyl 7-(7-hydroxynorbornyl)carbinyl sulfoxide and bis[7-(7-hydroxynorbornyl)carbinyl sulfoxide.[4]

These reactivity differences toward dimethyloxosulfonium methylide have been attributed to an electronic effect of the double bond in **4** and **7** which stabilizes the transition state for *syn* attack and fixes the resulting zwitterion in the proper conformation for oxide formation[2,3] to a steric effect of the *endo*-5,6-hydrogens in **1** which hinders *endo* attack,[2] and to the cumulative steric effect of the *exo*-hydrogens in **9** which makes it difficult for the intermediate to attain the preferred *trans*-coplanar conformation for the displacement of dimethyl sulfoxide.[4] In order to test these conclusions and to determine whether these norbornyl-type ketones exhibit a similar pattern of behavior with other neutral nucleophiles, we have examined their reactivity toward diazomethane.

Results

Each of the ketones was dissolved in ether containing 10% methanol, combined with an excess of ethereal diazomethane, and allowed to stand in the dark at room temperature for 1–5 days. The reaction mixtures were analyzed by gas–liquid partition chromatography (glpc) on a Quadrol–SAIB column.[2] The results are summarized in eq 1–4.

The structures of the volatile products **8**, **10**, **12**, and **13** were established by spectral comparison of collected samples with the authentic compounds.[3–5]



The structures of the two ketopyrazolines, **11a** and **11b**, obtained as a mixture from the reaction of diazomethane and dehydronorcamphor (**4**), were inferred as follows. Both the elemental analysis, $C_8H_{10}ON_2$, and the mass spectrum, $[M]\cdot^+ = 150$, indicate that **11** corresponds to the addition of one molecule of diazomethane to each molecule of the ketone. The presence of strong C=O stretches (1757 and 1722 cm^{-1}) in the

(1) Portions of this work were presented at the 14th Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., Nov 1962; *cf.*, "The Branched Chain," Vol. XVIII, No. 3, 1962, p 71.

(2) R. S. Bly, C. M. DuBose, Jr., and G. B. Konizer, *J. Org. Chem.*, **33**, 2188 (1968).

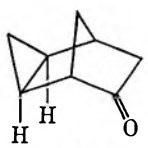
(3) R. K. Bly and R. S. Bly, *ibid.*, **28**, 3165 (1963).

(4) R. K. Bly and R. S. Bly, *ibid.*, **34**, 304 (1969).

(5) (a) W. C. Wildman, and R. R. Saunders, *ibid.*, **19**, 381 (1954); (b) H. M. Walborsky and D. F. Loncrini, *J. Amer. Chem. Soc.*, **76**, 5396 (1954).

infrared spectrum of the product mixture and the fact that a *p*-nitrophenylhydrazone can be prepared indicate that the keto group remains intact in the product(s). The Δ^1-type pyrazoline ring is suggested by the absence of C=C, C=N, and N—H stretches in the infrared and Raman spectra and by the presence of a strong N=N stretch at 1553 cm^{-1} in the infrared[6] and 1549 cm^{-1} in the Raman.[7] That the pyrazoline ring is fused *exo* to the norbornane skeleton is indicated by the large difference in the chemical shifts of the methano hydrogens at C-10, δ 1.53 and 0.83 ppm, respectively, in the nmr spectrum of this material.[8] Finally, it is clear from the two perturbed singlets at δ 3.18 (W_H = 7.5 Hz) and 3.03 (W_H = 4 Hz) which together integrate for one hydrogen and correspond to norbornane-type bridgehead protons on the side nearest the azo group,[9-11] that this material is a mixture of the two ketopyrazolines **11a** and **11b**. Since the broader of these two resonances, *i.e.*, at δ 3.18, corresponds to a bridgehead proton flanked by carbonyl-adjacent methylene hydrogens, *i.e.*, to the C-1–H of **11b**,[12] it is apparent from integrations of these two bridgehead-hydrogen resonances that the ketopyrazoline mixture **11** consists of about one-third **11b** and two-thirds **11a**.

In spite of the fact that the mass spectrum of the ketopyrazoline mixture **11** exhibits a fragment of low intensity corresponding to the loss of nitrogen from the molecular ion, *e.g.*, $[M]\cdot^+ - 28 = 122$, all attempts to isolate a cyclopropanonorbornanone, **14**, from its pyrolysis were unsuccessful. A similar failure has been reported in the case of the pyrazoline **15** formed from the addition of diazomethane to norbornene.[6]



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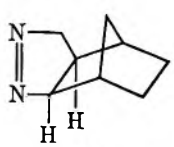

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In order to estimate the relative reactivity of ketones **7** and **9**, an equimolar mixture of the two was allowed to react with a less-than-stoichiometric amount of diazomethane. After the yellow color of the unreacted diazomethane had disappeared, the composition of the reaction mixture was determined by glpc analysis on a Quadrol–SAIB column. From these data it was calculated[13] that the unsaturated ketone **7** is about four times *more* reactive than the saturated ketone **9**.

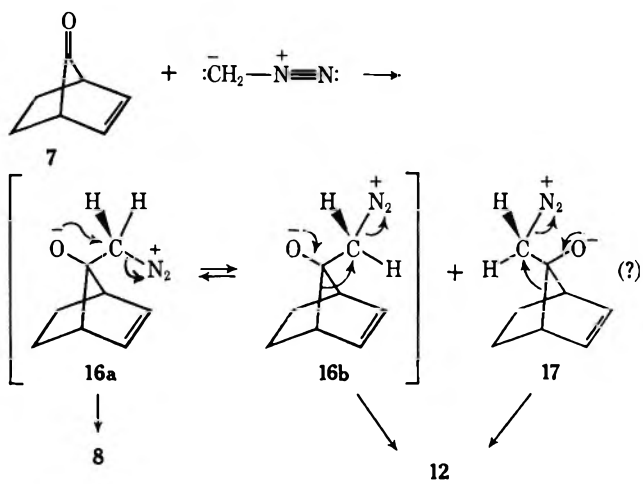
From the relative rates of reaction of norbornene and dehydronorcamphor (**4**) with alcoholic, ethereal diazomethane,[6,14] it is estimated that the former is about three times *less* reactive than the latter under similar conditions.

Although the data of Sauers and Tucker[15] indicate that norcamphor (**1**) reacts slowly with diazomethane to produce a complex mixture containing the 2- and 3-ketobicyclo[3.2.1]octanes in the ratio of 1.0:1.6, it is clear from our data that **1** is the least reactive of the ketones examined here toward this neutral nucleophile.

Discussion

The reaction of 7-ketonorbornene (**7**) with diazomethane is notable in three respects: it is more facile than that of the saturated analog 7-ketonorbornane (**9**), it produces a much higher proportion of epoxide than does that of **9**, and it yields the *anti*-oxide **8**, stereoselectively. The reaction may be formulated as shown in Scheme I.

SCHEME I



Although **17** is a possible intermediate on the route to the unsaturated ketone **12**, it appears that little if any of the ring-enlarged ketone is formed from this zwitterion. Assuming that the rate of conversion of **9** to **18** (Scheme II) is at least twice as great as the rate of *anti* attack on **7** to form **18**,[2] it may be estimated that no more than (0.98 × 0.5)/(0.56 × 4) or about one-fifth of the total ketone, **12**, is produced from the "*anti*" zwitterion **17**.

The tendency of **7** to react with diazomethane from the side of the double bond may simply reflect the fact that this path is less hindered. Certainly **7** reacts with other nucleophiles predominantly or exclusively from the *syn* direction[2] and, in the case of the 7-carbometh-

(6) N. S. Zefirov, P. Kadziauskas, and Yu. K. Yuriev, *J. Gen. Chem. USSR*, **36**, 23 (1966); *Zh. Obshch. Khim.*, **36**, 23 (1966).

(7) (a) *Cf.* L. J. Bellamy "The Infra-red Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 272, and references cited therein. (b) We thank Dr. James R. Durig and Mr. John Casper for this determination.

(8) The effect of the azo group on chemical shifts of the C-10 hydrogens of **11** is similar to, though of smaller magnitude than, the effect of the etheno bridge on the positions of the C-9 hydrogen resonances in 1,4,4a,5,6,7,8,8a-octahydro-1,4-*exo*,*endo*-5,8-dimethanonaphthalene; *cf.* A. P. Marchand and J. R. Rose, *J. Amer. Chem. Soc.*, **90**, 3724 (1968), compound VI. Similar shifts are apparent in the *exo* adducts of phenylazide and norbornadiene,[9a] and diazomethane and norbornene.[6,9b]

(9) (a) S. McLean and D. M. Findlay, *Tetrahedron Lett.*, 2219 (1969); (b) R. K. B., unpublished work.

(10) The effect of the azo group on the chemical shift of the norbornane bridgehead hydrogens in **11** is much greater than that of the carbonyl. In norcamphor the C-1 hydrogen appears at δ 2.48, the C-4 hydrogen at δ 2.62.[11]

(11) (a) R. R. Sauers and P. E. Sonnet, *Chem. Ind.* (London), 786 (1963); (b) E. J. Corey, L. Casanova, Jr., P. A. Vatakencherry, and R. Winter, *J. Amer. Chem. Soc.*, **85**, 169 (1963); (c) see also, K. D. Berlin and R. Ranganathan, *Tetrahedron*, **25**, 793 (1969).

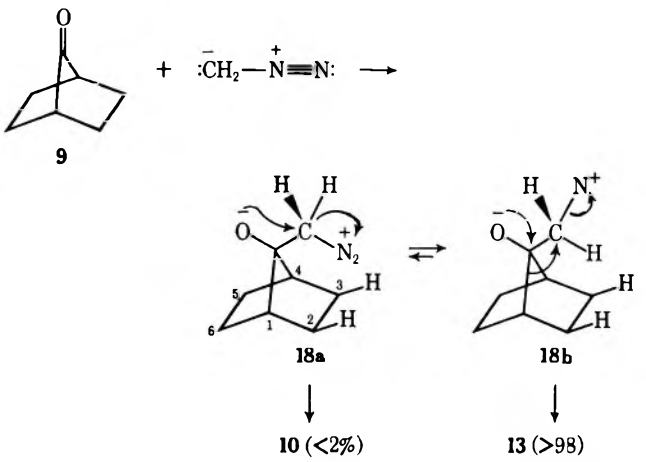
(12) We base this conclusion upon the fact that in the nmr spectrum of the keto–pyrazoline mixture which results from the reaction of diazomethane with dehydronorcamphor containing 1.6 equiv of deuterium at the C-3 position, the W_H of the higher field resonance, *i.e.*, δ 3.03, remains unchanged at ~4 Hz while that of the lower field resonance at δ 3.18 is decreased from 7.5 to ~5 Hz; *cf.* Experimental Section.

(13) T. S. Lee in "Technique in Organic Chemistry," Vol. VIII, S. L. Friess and A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1953, p 100 ff.

(14) C. H. Norton, Ph.D. Dissertation, Harvard University, 1955, pp 151–152.

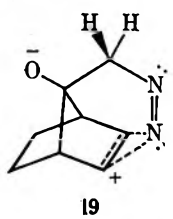
(15) R. R. Sauers and R. J. Tucker, *J. Org. Chem.*, **28**, 876 (1963).

SCHEME II



oxynorbornenes, at least, the *syn* isomer is the more stable.[16]

Whether the increased reactivity of 7-ketonorbornene (**7**) with respect to 7-ketonorbornane (**9**) can also be attributed to a decrease in steric hindrance is less certain. Brown and Muzzio[17] have shown that **7** is less reactive than **9** toward reduction with sodium borohydride and have attributed the decreased rate to the inductive effect of the double bond. Our previous studies of the reaction of **7** with sulfur ylides indicate that the double bond may decrease the rate of *anti* attack and increase the rate of *syn* attack.[2] We have ascribed the latter effect to charge delocalization. Similar delocalization may also act to enhance the reactivity of **7** toward diazomethane by stabilizing any positive charge which develops on the terminal nitrogen in the transition state, *i.e.*



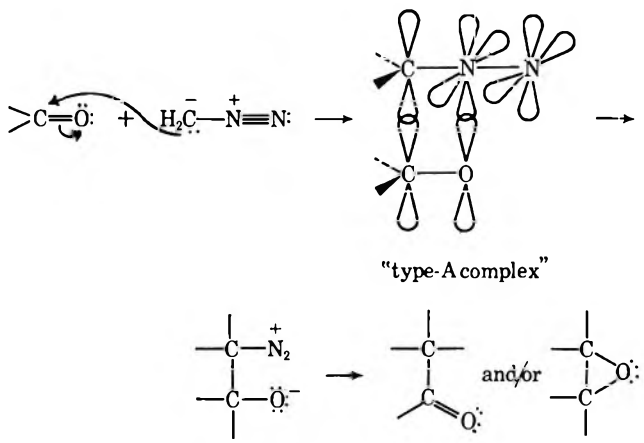
The relatively greater tendency of 7-ketonorbornene to produce epoxide rather than ring-enlarged ketone (*cf.* eq 3 and 4) can probably be attributed to the absence of *exo* hydrogens at C-2 and C-3. Thus the intermediate "*syn*" zwitterion is able to adopt a conformation, **16a**, which is favorable for the intramolecular displacement of nitrogen by the nucleophilic oxide (Scheme I). In the corresponding zwitterion **18** (Scheme II), formed in the reaction of 7-ketonorbornane (**9**) and diazomethane, the *exo* hydrogens at C-2 and C-3 destabilize **18a** with respect to **18b** and ring enlargement is the preponderant reaction. A related effect on the extent of hydrogen migration *vs.* ring enlargement has been observed in the acetolyses of *syn*- and *anti*-7-brosyloxymethylnorbornenes and to a lesser extent in the acetolysis of 7-brosyloxymethylnorbornane.[18]

(16) R. R. Sauers and R. M. Hawthorne, Jr., *J. Org. Chem.*, **29**, 1685 (1964).
(17) H. C. Brown and J. Muzzio, *J. Amer. Chem. Soc.*, **88**, 2811 (1966).
(18) (a) J. A. Berson and J. J. Gajewski, *ibid.*, **86**, 5020 (1964); (b) R. K. Bly and R. S. Bly, *J. Org. Chem.*, **31**, 1577 (1966); (c) J. A. Berson and M. J. Poonian, *J. Amer. Chem. Soc.*, **88**, 170 (1966); (d) J. A. Berson, J. J. Gajewski, and D. S. Donald, *ibid.*, **91**, 5550 (1969); (e) J. A. Berson, M. S. Poonian, and W. J. Libbey, *ibid.*, **91**, 5567 (1969); (f) J. A. Berson, D. S. Donald, and W. J. Libbey, *ibid.*, **91**, 5580 (1969).

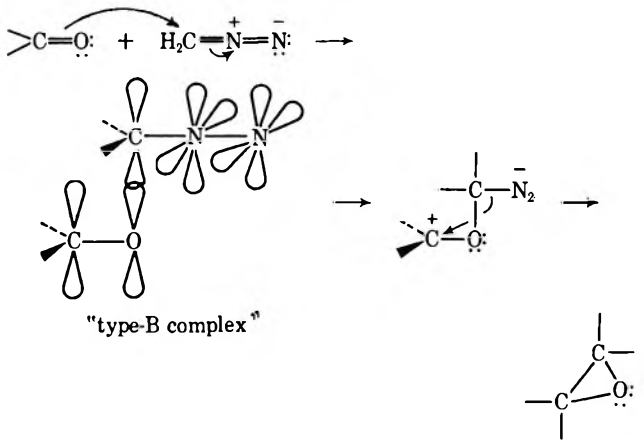
Charge delocalization as depicted in **19** could also act to increase the epoxide-to-ketone ratio in the unsaturated case, **7**, by further stabilizing **16a** with respect to **16b**.

Gutsche, *et al.*,[19] following an earlier suggestion of Bradley, Cowell, and Ledwith,[20] postulate that some cyclic ketones may react with a diazoalkane by either or both of two paths: nucleophilic attack of the diazoalkane at the carbonyl carbon of the ketone to produce a "type-A complex" which is converted *via* the usual zwitterion to a mixture of epoxide and ketone (Scheme III), or by electrophilic attack of diazomethane on the carbonyl oxygen of the ketone to produce a "type-B complex" (Scheme IV) which yields only epoxide.

SCHEME III



SCHEME IV



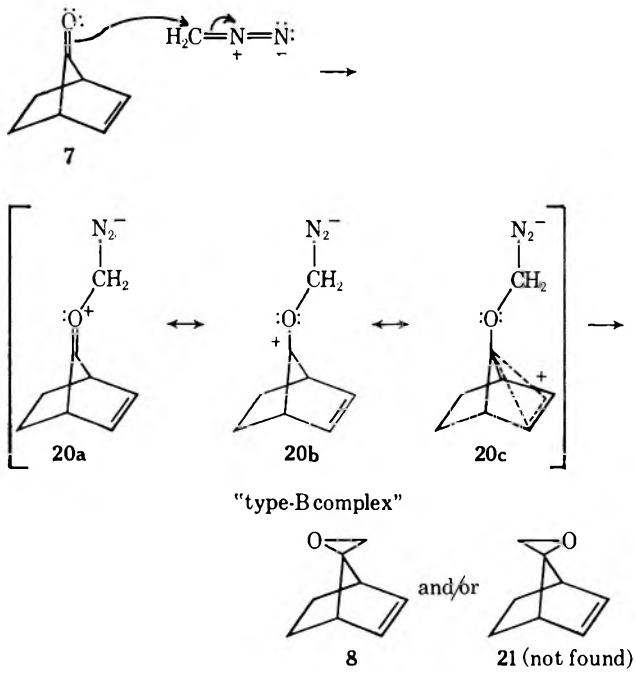
They argue that the well-known tendency of a hindered ketone to produce a high proportion of epoxide-to-ketone[21] reflects its greater propensity to react *via* the less hindered type-B complex.

We doubt that the increased tendency of 7-ketonorbornene (**7**) relative to 7-ketonorbornane (**9**) to produce epoxide when treated with diazomethane can be due to type-B complex formation, since such a complex, **20**, even though it might involve relatively little π-electron delocalization[22] (*e.g.*, **20c**) would not be expected

(19) (a) C. D. Gutsche and J. E. Bowers, *J. Org. Chem.*, **32**, 1203 (1967); (b) C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968, p 81 ff.
(20) J. N. Bradley, G. W. Cowell, and A. Ledwith, *J. Chem. Soc.*, 4334 (1964).
(21) C. D. Gutsche, *Org. React.*, **8**, 364 (1954), and references cited therein.
(22) Because most of the stabilization is expected to be achieved by delocalization of the positive charge to oxygen, *e.g.*, **20a**.

to decompose *exclusively* to the *anti* oxide, **8** (Scheme V).[23]

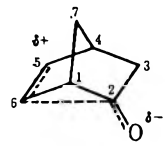
SCHEME V



The exclusive double bond attack that is observed when diazomethane reacts with dehydronorcamphor (**4**) is reminiscent of the unique formation of pyrazoline which is typically observed in the non-Lewis acid-catalyzed reactions of this "1,3-dipole"[24] with α,β-unsaturated aldehydes and ketones.[21] Attempts to induce carbonyl attack on **5** by the addition of boron trifluoride etherate or aluminum trichloride[25] were unsuccessful.[26]

The reaction of diazomethane with a double bond to produce a Δ^1-pyrazoline can probably be formulated as a [2 + 3] cycloaddition.[27] Even though such reactions are thought to occur in a concerted manner by way of an "isopolar" transition state,[28] the formation of the two new σ bonds need not be completely synchronous, and such additions usually respond to electronic effects in a predictable manner.[24,27] In particular, the substitution of electron-withdrawing groups such as cyano, carbalkoxy, carbonyl, or carboxyl on the double bond of the 1,3-dipolarophile enhances the rate of addition and causes diazoalkanes to produce predominately 3- rather than 4-substituted Δ^1-pyrazolines.[24]

Though such effects are predictably smaller in a β,γ-unsaturated ketone such as dehydronorcamphor (**4**), they are still apparent nevertheless. Not only does the nucleophilic carbon of diazomethane react twice as rapidly at the δ position (C-5) as it does at the γ (C-6), but the reaction is also enhanced by the electron-withdrawing effect of the carbonyl,[29] *viz.*



This result implies that in [2 + 3] cycloaddition reactions of diazoalkanes with double bonds, C–C bond formation is more important in the transition state than is N–C bonding.[24,27] The enhanced double bond reactivity of dehydronorcamphor (**4**) coupled with the decreased electrophilicity of its carbonyl (compared with that of **7**)[2,3,17] is apparently sufficient to render pyrazoline formation the exclusive reaction in this case.[30]

Experimental Section[31]

Reaction Products of Bicyclic Ketones with Diazomethane. A. 7-Ketonorbornene (7).—To a solution of 1.0 g (0.093 mol) of 7-ketonorbornene (**7**) in 10 ml of ether containing 10% methanol was added 30 ml of 0.45 *M* ethereal diazomethane. The mixture was allowed to stand in the dark at room temperature overnight. At this time the solution was still a pale straw color. The reaction mixture was analyzed by glpc at 110° on a Quadrol–SAIB column.[2] Two components with relative retention times and (abundance) of 1 (42%) and 5.3 (58%) were found to be present. A small sample of each of the products was collected from the Quadrol column. The ir and nmr spectra of the first component were found to be identical with those of authentic spiro[bicyclo[2.2.1]hept-2-en-*anti*-7,2′-oxacyclopropane] (**8**).[3] The second component was identical in all respects with authentic bicyclo[2.2.2]oct-5-en-2-one (**12**).[5a] The ethereal solution was concentrated under atmospheric pressure, and the residue was distilled in a short-path still at 100–110° (20 mm) to give a total of 0.873 g (78%) of product. An nmr analysis of the distillate showed the presence of epoxide **8** (44%) and ketone **12** (56%).

B. 7-Ketonorbornane (**9**) (1.0 g, 0.092 mol) was treated with ethereal diazomethane exactly as described for **7** (part A). After 24 hr, glpc analysis of the reaction mixture showed two components with relative retention times and (abundance) of 1 (<2%) and 5.0 (>98%). The major component was collected from the Quadrol column and was found to be identical with authentic bicyclo[2.2.2]octanone (**13**).[5b] The minor component was not isolated in pure form, but we believe it to be spiro[bicyclo[2.2.1]heptan-7,2′-oxacyclopropane] (**10**), since the glpc retention time of this component was identical with that of authentic **10**[4] on Quadrol–SAIB, Carbowax 20M, and Ucon (nonpolar) columns.[31] The remaining solution was concentrated at atmospheric pressure and the residue sublimed at 100° (15 mm) to give 0.845 g (75%) of product.

C. Dehydronorcamphor (**4**) (2.2 g, 0.020 mol) was allowed to react with the ethereal diazomethane solution (see part A) for ~3 days. The solvent was removed under reduced pressure and the residue distilled in a short-path still at 110° (0.08 mm). Redistillation of the reddish oil at 100° (0.08 mm) gave 2.6 g (93%)

(23) Actually, to the extent that **20c** contributes to its stability, **20** would be expected to yield **21** predominantly or exclusively; *cf.* (a) S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Amer. Chem. Soc.*, **77**, 4143 (1955); (b) S. Winstein and M. Shatavsky, *ibid.*, **78**, 592 (1956); (c) A. Diaz, M. Brookhart, and S. Winstein, *ibid.*, **88**, 3133 (1966); (d) M. Brookhart, A. Diaz, and S. Winstein, *ibid.*, **88**, 3135 (1966).

(24) R. Huisgen, *Angew. Chem. Int. Ed. Engl.*, **2**, 565, 633 (1963), and references cited therein.

(25) (a) H. O. House, E. J. Grubbs, and W. F. Gannon, *J. Amer. Chem. Soc.*, **82**, 4099 (1960); (b) E. Müller, M. Bauer, and W. Rundel, *Z. Naturforsch, B*, **15**, 268 (1960); *Tetrahedron Lett.*, No. 13, 30 (1960); No. 4, 136 (1961); (c) W. S. Johnson, M. Nieman, S. P. Birkeland, and N. A. Fedorak, *J. Amer. Chem. Soc.*, **84**, 989 (1962). (d) For a comprehensive review see E. Müller, H. Kessler, and B. Zeek, *Fortschr. Chem. Forsch.*, **7**, 128 (1966).

(26) The only product that could be isolated under these conditions was polymethylene, R. K. B., unpublished.

(27) E. M. Kosower, "An Introduction to Physical Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1968, p 209 ff.

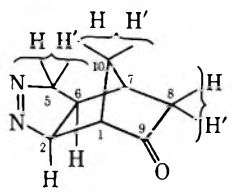
(28) Reference 27, p 195.

(29) Attack by the nucleophilic carbon of diazomethane occurs twice as rapidly at C-6 in **4** as it does at either end of the double bond in norbornene.

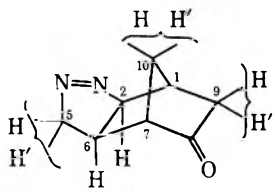
(30) A referee has suggested that the greater tendency of these bicyclic ketones to yield epoxides with ylides may reflect the displacement-promoting properties of the solvent DMSO. This may be a valid point for we have yet to investigate this aspect of the problem.

(31) Microanalyses were performed by Bernhardt Mikroanalitisches Laboratorium 5251 Elbach über Engelskirchen, Germany. Spectra were determined on a Perkin-Elmer grating spectrophotometer, Model 337, a Varian A-60A nmr spectrometer, and a Hitachi Model RMU-6E mass spectrometer. Gas chromatographic analyses were carried out in an F & M Model 500 chromatograph using 8 ft × 0.25 in. coiled copper columns packed with 20% Quadrol–SAIB[2] on 60–80 mesh Gas-chrom CL and 20% Carbowax 20M or Ucon oil (non polar) on Gas-chrom A.

of a viscous liquid (11): ir (neat) 2970, 2930 (sh), 2900 (sh) (CH); 1757, 1722 (C=O); 1553 cm^{-1} (N=N); Raman (neat) 1549 cm^{-1} (N=N)[7a]; mass spectrum $[M]\cdot^{+}$ = 150. The nmr (CCl_4) spectrum of the product mixture 11 exhibits a complex three-



11a



11b

hydrogen multiplet between δ 5.0 and 3.83 which we attribute to the hydrogens that flank the azo group.[9,10,32] The C-2 and the C-5 hydrogens apparently have similar chemical shifts in each isomer. One of the methylene hydrogens at C-5 is split by the other nonequivalent C-5 hydrogen,[33a] and by those at C-2 and C-6 into an eight-line multiplet centered at δ 4.63 that is superimposed on a second complex multiplet centered at $\sim\delta$ 4.7 which is due to the single hydrogen at C-2. The other C-5 hydrogen (H′) is also coupled to the three hydrogens at C-2, C-5 (H), and C-6, and appears as a pair of asymmetric quartets centered at $\sim\delta$ 4.18. The principal coupling is apparently between the nonequivalent C-5 hydrogens H and H′; $J = -18$ Hz.[33] The bridgehead hydrogens at C-1 in **11b** and **11a** respectively give rise to broad singlets at δ 3.18 (W_H = 7.5 Hz) and 3.03 (W_H = 4 Hz) corresponding to $^1/_3$ and $^2/_3$ of a hydrogen each.[10] The bridgehead hydrogen at C-7 in **11b** appears as a broad (W_H = 7.5 Hz) singlet at δ 2.44,[12] while the C-7 hydrogen of **11a** constitutes a portion of a complex $3^1/_3$ proton multiplet extending from δ 2.33 to 1.87 which includes the C-8 hydrogens of **11a**, the C-9 hydrogens of **11b**, and the C-6 hydrogen of each isomer. The C-10 hydrogens of both **11a** and **11b** have similar chemical shifts and appear as a 2 proton, AB quartet,[33b,34] $J_{H,H'} = -12$ Hz, centered at δ 1.18. This quartet collapses into two broad singlets when irradiated at δ 1.53 + 44 Hz or at δ 0.83 − 44 Hz.

Anal. Calcd for $C_8H_{10}ON_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.70; H, 6.74; N, 18.01.

A *p*-nitrophenylhydrazone was prepared in the usual manner, mp 221–223° dec.

Anal. Calcd for $C_{14}H_{15}N_5O_2$: C, 58.93; H, 5.30; N, 24.55. Found: C, 58.87; H, 5.40; N, 24.44.

D. Norcamphor (1) (1.0 g, 0.091 mol) was mixed with an ethereal solution of diazomethane as described in part A and allowed to stand at room temperature for 5 days. A glpc analysis of the still yellow solution revealed only the unreacted starting ketone 1. Removal of the solvent followed by sublimation of the residue at 100° (20 mm) led to the recovery of 0.865 g (87%) of unreacted norcamphor.

Preparation of 3,3-Dideuteriodehydronorcamphor.[35]—Dehydronorcamphor[2] (0.50 g, 4.6 mmol) was dissolved in 20 ml of a 1:2 D_2O–dioxane mixture containing 0.03 *N* sodium deuterioxide. The solution was heated at 85° for 4 days, cooled, and poured into a separatory funnel containing 20 ml of pentane and 10 ml of 0.4 *N* aqueous nitric acid. The aqueous solution was extracted with three additional portions of pentane. The pentane extract was dried (Na_2SO_4) and the solvent was removed at atmospheric pressure. Distillation of the residue in a short-path still at ~100° (30–40 mm) gave 280 mg (55%) of partially deuterated product: ir (CCl_4) 2235, 2175, 2125 cm^{-1} (C–D); mass spectrum $[M]\cdot^{+}$ = 109 (37%) and $[M]\cdot^{+}$ = 110 (63%). The nmr spectrum (CCl_4) showed a broad singlet at δ 1.85–1.65 (–COCHD–) with an area corresponding to ~0.4 hydrogen (compared to 2.0 hydrogens in dehydronorcamphor) but was otherwise identical with that of nondeuterated **4**.

Reaction of Mono- and Dideuterated Dehydronorcamphor with Diazomethane.—A mixture of 3-deuterio- and 3,3-dideuteriodehydronorcamphor (*vide supra*) was treated with ethereal diazomethane in the manner described for the nondeuterated ketone **4** to yield a mixture of the deuterated ketopyrazolines 8-deuterio- and 8,8-dideuterio-*exo*-3,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-3-en-9-one and 9-deuterio- and 9,9-dideuterio-*exo*-3,4-diazatricyclo-[5.2.1.$0^{2,6}$]dec-3-en-8-one: ir(CCl_4) 2800, 2735, 2680, and 2630 cm^{-1} (C–D); mass spectrum $[M]\cdot^{+}$ = 151 (38%) and $]M]\cdot^{+}$ = 152 (62%). The nmr spectrum (CCl_4) of this mixture showed a complex multiplet at δ 2.2–1.8 corresponding to 2.4 hydrogens and a singlet at δ 3.17 (W_H = 5 Hz). In other respects the spectrum did not differ significantly from that of the nondeuterated ketopyrazoline mixture 11.

Competitive Reaction of 7-Ketonorbornene (7) and 7-Ketonorbornane (9) with Diazomethane.—To a solution containing 42 mg (0.39 mmol) of **7** and 40 mg (0.36 mmol) of **9** in 2 ml of ether was added 2 drops of methanol and 1 ml of 0.4 *M* ethereal diazomethane. The solution was allowed to stand at room temperature for 2 hr and then analyzed on the Quadrol–SAIB column at 110°. The mixture was found to contain 16% **7**, 41% **9**, 14% epoxide **8**, 21% ketone **12**, and 8% ketone **13**; *i.e.*, the relative reactivity of ketones **7** and **9** is approximately 1:4.[13]

Relative Reactivity of Norbornene and Dehydronorcamphor (4) with Diazomethane.—Solutions containing (a) 75 mg (0.80 mmol) of norbornene and 0.03 ml of ethanol, and (b) 86 mg (0.80 mmol) of dehydronorcamphor (**4**), 0.03 ml of ethanol and 0.05 ml of anisole, in 4 ml of 0.25 *M* ethereal diazomethane were allowed to stand in the dark at room temperature. Samples were withdrawn at various times and analyzed on the Quadrol–SAIB column. The extent of each reaction was estimated by comparison of the peak area of the unreacted starting material with that of an unreactive component: ethanol in solution a, anisole in solution b. The time required to consume 75% of the starting material was 25 hr for norbornene and 7.5 hr for dehydronorcamphor.

Registry No.—Diazomethane, 334-88-3; **1**, 497-38-1; **4**, 694-98-4; **7**, 694-71-3; **9**, 10218-02-7; **11a**, 24627-23-4; **11b**, 24627-24-5.

Acknowledgment.—It is a pleasure to thank the Petroleum Research Fund of the American Chemical Society, Grant No. 911-A4, for their generous support of the major portion of this work.

(32) We designate two magnetically nonequivalent hydrogens of a methylene group as H and H′ but make no attempt to attribute uniquely an observed chemical shift to either one of the two individual hydrogens.

(33) The geminal coupling constant of nonequivalent hydrogens on a methylene group adjacent to an azo linkage is reported to range from −16.8 to −19.6 Hz; *cf.* (a) R. Cahill, R. C. Cookson, and T. A. Crabb, *Tetrahedron*, **25**, 4681 (1969), and references cited therein; (b) *ibid.*, **25**, 4711 (1969).

(34) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, pp 89–90.

(35) We thank Dr. Thomas T. Tidwell for helpful advice on the preparation of this material.

Quinoxaline Studies. XVI.[1a] Unequivocal Synthesis of (S)-2-Methyl-1,2,3,4-tetrahydroquinoxaline

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Received November 24, 1969

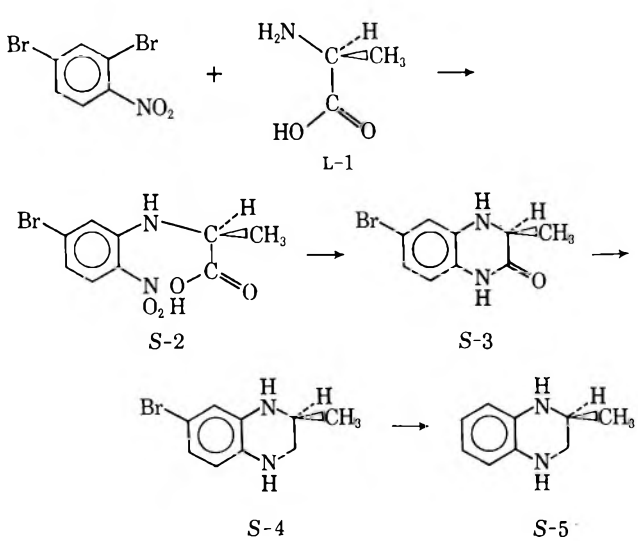
The unequivocal synthesis of (*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline *via* the sequence L-α-alanine (L-**1**), (*S*)-N-(2-nitro-5-bromophenyl)-α-alanine (*S*-**2**), (*S*)-3-methyl-6-bromo-3,4-dihydro-2(1H)-quinoxalinone (*S*-**3**), (*S*)-2-methyl-7-bromo-1,2,3,4-tetrahydroquinoxaline (*S*-**4**), and (*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline (*S*-**5**) is described, as well as the resolution of *RS*-**5** into *R*-**5**. Physical properties and derivatives are reported for the above compounds.

The 2-quinoxaloyl unit present in triostin and quinomycin antibiotics[2] has not as yet had its biological source elucidated. The authors conjecture that the 2-quinoxalinecarbonyl unit may form *in vivo* initially in the reduced state *via* condensation of 2,3-diaminopropanoic acid with catechol to give 1,2,3,4-tetrahydro-2-quinoxalinecarboxylic acid, or with 5-dehydroshikimic acid to give 2-decahydroquinoxalinecarboxylic acid. Tetrahydroquinoxalines are also of interest as models for tetrahydrofolic acid.[3]

The purpose of this paper is to report the unequivocal synthesis of (*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline (*S*-**5**) as a potential configurational standard for all future work dealing with 2-substituted reduced quinoxalines. Because of ready availability, L-α-alanine was utilized to provide the asymmetric center of **5**.

The synthesis of **5** was executed *via* the sequence L-α-alanine (L-**1**), (*S*)-N-(2-nitro-5-bromophenyl)-α-alanine (*S*-**2**), (*S*)-3-methyl-6-bromo-3,4-dihydro-2(1H)-quinoxalinone (*S*-**3**), (*S*)-2-methyl-7-bromo-1,2,3,4-tetrahydroquinoxaline (*S*-**4**), and finally (*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline (*S*-**5**) (Scheme I).

SCHEME I



Initial work commenced with DL-α-alanine, and after chemical problems related to the preparation of the above series had been solved, the work was repeated using optically active α-alanine. No marked differences between the racemic and the optically active compounds were observed. As expected, *RS*-**2**, *RS*-**3**, and *RS*-**5** were lower melting than *S*-**2**, *S*-**3**, and *S*-**5**; however, *RS*-**4** was higher melting than *S*-**4**.

The Br atom of *o*-bromonitrobenzene was not displaced by the nucleophilic amine nitrogen attack of α-alanine. Hence, increased activity of the Br was sought by having a second negative group appropriately disposed on the benzene ring. Although the carboxyl,[4,5] the carbomethoxy,[6] and the nitro[7,8] groups have been utilized for just such activation roles, the replacement of these groups with H requires too lengthy a synthetic sequence. Therefore, 2,4-dibromonitrobenzene was chosen as the portal compound for the above series, because the *p*-Br was expected, by a one-step hydrogenolysis reaction, to subsequently yield its place (in **4**) to H.

N-(2-Nitro-5-bromophenyl)-α-alanine (**2**) was prepared by condensing α-alanine (**1**) with 2,4-dibromonitrobenzene by a modification of the method of Van Dusen and Schultz.[9] Inverse addition of the reagents (aqueous $KHCO_3$–alanine to alcoholic 2,4-dibromonitrobenzene) was found effective in preserving homogeneity of the reaction solution and affording good yields of **2**.

Stannous chloride reduction of **2** to **3** gave consistently good yields. However, catalytic reduction displayed the following surprising results. Raney nickel catalyst reduction of the K salt of **2** in H_2O afforded moderate yields of **3**. Palladium–charcoal catalyst gave infuriatingly nonreproducible results: generally (but not always) in aprotic THF good yields of **3** were obtained, whereas in protic EtOH tars and/or hydrogenolysis of Br were observed, yielding 3-methyl-2(1H)-quinoxalinone (*via* 3-methyl-3,4-dihydro-2(1H)-quinoxalinone, which spontaneously dehydrogenated during isolation).

The Br of **3** played the fortuitous role of stabilizing **3**; however, **3** dehydrogenated to 3-methyl-6-bromo-2(1H)-quinoxalinone[9] with heating, prolonged standing in organic solvents, or passage through an alumina

(1) (a) Part XV: H. R. Moreno and H. P. Schultz, *J. Med. Chem.*, **13**, 119 (1970); (b) NSF Trainee, 1969–present; (c) NSF Trainee, 1966–1967; abstracted in part from the M. S. thesis of P. J. W.

(2) H. Otsuka and J. Shoji, *Tetrahedron*, **23**, 1535 (1967), and references therein.

(3) S. J. Benkovic, P. A. Benkovic, and D. R. Comfort, *J. Amer. Chem. Soc.*, **91**, 5270 (1969).

(4) F. Micheel, K. Weichbrodt, and J. Plenikowski, *Justus Liebigs Ann. Chem.*, **581**, 242 (1953).

(5) W. Blackburn, M. Danzig, H. Hubinger, D. Soisson, and H. P. Schultz, *J. Org. Chem.*, **26**, 2805 (1961).

(6) R. W. Holley and A. D. Holley, *J. Amer. Chem. Soc.*, **74**, 1110, 5445 (1952).

(7) L. Horner, U. Schwenk, and E. Junghanns, *Justus Liebigs Ann. Chem.*, **579**, 220 (1953).

(8) K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, **34**, 395 (1969), and many references in all above.

(9) R. Van Dusen and H. P. Schultz, *ibid.*, **21**, 1326 (1956).

column. Curiously, **3** was stable in boiling water, but not in boiling organic solvents!

Reduction of **3** to **4** was effected with $LiAlH_4$ in dioxane. Aliquot portions of the reaction solution, monitored for disappearance of the carbonyl peak in the ir spectrum, indicated 12 hr as the optimum reduction time. Similar reduction executed in THF required longer reaction times (24–48 hr) and resulted in considerable racemization of the active isomer. Reduction did not occur in diethyl ether, contrary to what was expected in light of the findings of Smith, Rebel, and Beach.[10]

Compound **4** was smoothly hydrogenolyzed to **5** by Pd–C catalyst in $KHCO_3$–EtOH solution.

Several experiments shortened the work required for the transformation of **2** into **5** without isolation of the intermediate compounds by executing chemical and catalytic reductions one after the other in the appropriate solvent. Although analytically pure *R*-**5** and *S*-**5** were thus obtained, optical activities indicated that extensive racemization of the compounds had occurred.

The optical antipode (*R*-**5**) of *S*-**5** was prepared by resolution of *RS*-**5**[11] (obtained by catalytic reduction of 2-methylquinoxaline[12]) with dibenzoyl-*d*-tartaric acid.[13] *R*-**5** possessed optical activity virtually identical with (but of opposite sign) the unequivocally prepared *S*-**5**, indicating that racemization of *S*-**5** did not occur to a significant extent during its synthesis. This resolution, the consequence of the fortuitous circumstance that the dibenzoyl derivative of readily available *d*-tartaric acid effected isolation of *R*-**5** from *RS*-**5**, provided a source of *R*-**5** which avoided its lengthy unequivocal synthesis with the attendant demand for costly D-α-alanine as starting material.

Experimental Section[14]

N-(2-Nitro-5-bromophenyl)-α-alanine (**2**).—A warm (60°) solution of 36 g (0.4 mol) of α-alanine, 40 g (0.4 mol) of $KHCO_3$, and 125 ml of H_2O was added dropwise in 0.5 hr to a refluxing solution of 113 g (0.4 mol) of 2,4-dibromonitrobenzene[9] in 500 ml of 95% EtOH; the homogeneous solution was refluxed for 48 hr. Filtration, concentration to 250 ml, addition of 300 ml of H_2O, and again filtration afforded 68 g (60.2%) of recovered 2,4-dibromonitrobenzene. After clarification with decolorizing carbon, the filtrate was brought to pH 1 with HCl to give 50.4 g (42.2%) of crude **2**, mp 161–166°. The solid was dissolved in 300 ml of 1 *N* NH_4OH, clarified, reprecipitated with HCl, and then recrystallized from C_6H_6 (40 ml/g) to give 42.3 g (35.5%) of yellow plates.

S-**2**: 35%; mp 188–189°; uv max 205 mμ (ε 12,000), 241 (19,300), 289 (7300), 412 (6500); ir (KBr) 3340 (NH), 1720 (C=O), 480 cm^{-1} (CBr); $[\alpha]^{24}D$ +8.91° (*c* 1.0, THF), +47.0° (*c* 1.5, 95% EtOH), +60.0° (*c* 1.2, HOAc).

Anal. Calcd for $C_9H_9BrN_2O_4$: C, 37.39; H, 3.14; Br, 27.64; N, 9.69. Found: C, 37.60; H, 3.00; Br, 27.70; N, 9.70.

RS-**2**: 38.5%; mp 174–175° (lit.[9] 175–177°); uv and ir same as *S*-**2**.

R-**2**: 33.5%; mp 186.5–187.5°; mmp (*R*-**2** and *S*-**2**) 174–176°; $[\alpha]^{27}D$ −8.00° (*c* 2.5, THF), −59.0° (*c* 1.5, HOAc); uv and ir same as *S*-**2**. *Anal.* Found: C, 37.60; H, 3.38; Br, 27.95; N, 9.81.

3-Methyl-6-bromo-3,4-dihydro-2(1H)-quinoxalinone (**3**). **Method A (SnCl₂ Reduction)**.—A solution of 11.5 g (0.04 mol) of **2** in 250 ml of 95% EtOH was mixed with a solution of 45.2 g (0.2 mol) of $SnCl_2 \cdot 2H_2O$ in 400 ml of EtOH–12 *N* HCl (1:1) and stirred until colorless (40 hr) in a sealed desiccator initially evacuated to 10 mm. After concentration *in vacuo* to 100 ml, 200 ml of H_2O was added and the mixture was cooled at 0° and filtered. The moist product was thoroughly washed with water (otherwise the material obtained is a $SnCl_x$ complex of the quinoxalinone) and dried to give 7.24 g (75%) of white needles. Recrystallization from hot water (55 ml/g) with filtration through glass wool gave 6.35 g (66%) of solid; again recrystallization by dissolving in cold (24°) $CHCl_3$ (10 ml/g) and, after treatment with decolorizing carbon and Filter Aid, addition of ligroin (bp 66–75°, 10 ml/g) and cooling at 0° gave 5.32 g (55%) of white fibrous needles.

S-**3**: 42%; mp 132.5–133.5°; uv max 229 mμ (ε 39,400), 274 (4000), 315 (6300); ir (KBr) 3375, 3400 (NH), 1676 (C=O), 490 cm^{-1} (CBr); pmr ($CDCl_3$) δ 1.38 (d, *J* = 7 Hz, 3 H, CH_3), 3.98 (m, 2 H, CH and NH), 6.74 (m, 3 H, aromatic), 9.63 (broad s, 1 H, CONH), multiplet at 3.98 became a quartet (*J* = 7 Hz) upon exchange with D_2O; $[\alpha]^{24}D$ +59.8° (*c* 1.0, THF), +63.7° (*c* 0.9, HOAc), +71.3° (*c* 1.0, 95% EtOH).

Anal. Calcd for $C_9H_9BrN_2O$: C, 44.84; H, 3.76; N, 11.62. Found: C, 45.07; H, 3.68; N, 11.77.

RS-**3**: 55%; mp 128–130°; uv, ir, and pmr same as *S*-**3**. *Anal.* Found: C, 44.60; H, 3.84; N, 11.60.

Method B (Raney Nickel Reduction).—A mixture of 0.43 g (1.5 mmol) of **2**, 0.7 g (7 mmol) of $KHCO_3$, and 3 g of W-2 Raney nickel catalyst[15] in 20 ml of water was reduced at 47 psi for 3 hr at 24° until the orange color disappeared. The mixture was filtered into an equivalent amount of 1 *N* HCl, cooled, and filtered to give 0.18 g (50%) of tan solid, mp 123–126°. Recrystallization of the crude material as above gave 0.12 g (33%) of white crystals of constant melting point.

S-**3**: 33%; mp 130–132°; the mixture melting point with sample prepared by $SnCl_2$ reduction gave no depression; $[\alpha]^{24}D$ +57.3° (*c* 1.0, THF).

RS-**3**: 31.5%; mp 128–130°; mixture melting point with sample prepared by $SnCl_2$ reduction gave no depression.

Method C (Palladium Reduction).—A solution of 2.89 g (0.01 mol) of **2** in 25 ml of THF was reduced over 1 g of 10% Pd–C catalyst[16] at 40 psi and 30° for 12 hr until colorless. Filtration and removal of the solvent under vacuum, 40°, gave an oily residue which was dissolved in 10 ml of hot Me_2CO, treated with decolorizing carbon and Filter Aid, filtered, and diluted with 40 ml of ligroin (bp 60–90°). After cooling at 0°, 1.4 g (58%) of white crystals were obtained, mp 126–128°. Two recrystallizations from Me_2CO–ligroin (1:5, 40 ml/g) gave 1.2 g (50%) of white platelets of constant melting point.

S-**3**: 50%; mp 131–132.5°; uv and ir, as above; $[\alpha]^{27}D$ +52.0° (*c* 2.0, THF), +61.8° (*c* 2.5, HOAc). *Anal.* Found: C, 44.85; H, 4.05; N, 11.63.

R-**3**: 50%; mp 131–132.5°; uv and ir, as above; $[\alpha]^{27}D$ −52.9° (*c* 2.0, THF), −61.1° (*c* 2.5, HOAc); mmp (*S*-**3** and *R*-**3**) 126–127°. *Anal.* Found: C, 45.08; H, 3.47; N, 11.70.

2-Methyl-7-bromo-1,2,3,4-tetrahydroquinoxaline (**4**).—A mixture of 1.19 g (4.9 mmol) of **3** and 0.76 g (20 mmol) of $LiAlH_4$ in 30 ml of dry dioxane was refluxed 12 hr with stirring under N_2. After the solution was cooled in an ice bath, excess $LiAlH_4$ was destroyed by successive dropwise addition of 0.75 ml of H_2O, 0.55 ml of 20% NaOH, and 2.6 ml of H_2O. After 1–2 hr of stirring, the solid was filtered and the filtrate was evaporated to dryness. The residue from evaporation was dissolved in 40 ml of $CHCl_3$, treated with decolorizing carbon and Filter Aid, and then extracted three times with 20-ml portions of 1 *N* HCl and once with 5 ml of 6 *N* HCl. The acid extracts were clarified, basified with 6 *N* NaOH, cooled, and filtered to give 0.67 g (60%) of tan solid. Three recrystallizations from hot ligroin (bp 66–75°) (50 ml/g) gave shiny white plates of constant melting point.

S-**4**: 33%; mp 131–132° dec; uv max 225 mμ (ε 27,000),

(10) R. F. Smith, W. J. Rebel, and T. N. Beach, *J. Org. Chem.*, **24**, 205 (1959).

(11) M. Munk and H. P. Schultz, *J. Amer. Chem. Soc.*, **74**, 3433 (1952).

(12) K. Bottcher, *Ber.*, **46**, 3085 (1913).

(13) C. L. Butler and L. H. Cretcher, *J. Amer. Chem. Soc.*, **55**, 2605 (1933). M. Semonsky, A. Cerny, and V. Zikan, *Chem. Listy*, **50**, 116 (1956); *Collect. Czech. Chem. Commun.*, **21**, 382 (1956); *Chem. Abstr.*, **50**, 13059*a* (1956).

(14) Uv absorption spectra were obtained from samples at concentrations of 5 mg/l. of 95% EtOH with a Bausch and Lomb Spectronic 505 spectrophotometer using 1-cm silica cells. H nmr spectra, all referred to internal TMS, were determined on a Hitachi Perkin-Elmer R-20 spectrometer at 60 MHz, 34°; the δ values for multiplets were taken at the center of gravity. All optical activities were observed on a Rudolph Model 63 polarimeter. Melting points, determined on a Thomas–Hoover apparatus, were uncorrected. Elemental analyses were performed by Peninsular ChemResearch, Gainesville, Fla.

(15) R. Mozingo, *Org. Syn.*, **21**, 15 (1941).

(16) Aceto Chemical Co., Inc., Flushing, N. Y.

268 (4500), 324 (4500); ir (KBr) 3320 (NH), 455 cm^{-1} (CBr); pmr ($CDCl_3$) δ 1.18 (d, J = 6.5 Hz, 3 H, CH_3), 2.8–3.8 (m, 5 H, CH, CH_2, NH), 6.5 (m, 3 H, aromatic); $[\alpha]^{24}D$ +13.0° (*c* 1.0, THF).

Anal. Calcd for $C_9H_{11}BrN_2$: C, 47.60; H, 4.88; N, 12.33. Found: C, 47.74; H, 4.99; N, 12.41.

RS-**4**: 25.5%; mp 156.5–158°; uv and ir same as *S*-**4**; pmr (acetone-d_6) δ 1.12 (d, J = 6.5 Hz, 3 H, CH_3), 2.87 (s, 1 H, NH), 2.9–3.4 (m, 3 H, CH_2, CH), 4.81 (broad s, 1 H, NH), 6.52 (m, 3 H, aromatic), the broad singlets at 2.87 and 4.81 disappear upon exchange with D_2O. *Anal.* Found: C, 47.90; H, 5.07; N, 12.41.

N,N′-Diacetyl-2-methyl-7-bromo-1,2,3,4-tetrahydroquinoxaline.—In 1 ml (10 mmol) of Ac_2O was dissolved 0.24 g (1 mmol) of compound **4**. After 24 hr at 24°, 1 ml of H_2O was added to the reaction solution which was clarified, filtered, and evaporated to dryness to give 0.27 g (87%) of yellow crystals. Three recrystallizations from ligroin (bp 66–75°, 40 ml/g) gave 0.23 g (74%) of white crystals of constant melting point.

S derivative: 74%; mp 131–132.5°; uv max 234 mμ (ϵ 39,000), 258 (15,000); ir (KBr) 1656 (C=O), 496 cm^{-1} (CBr); pmr ($CDCl_3$) δ 1.14 (d, J = 6.5 Hz, 3 H, CH_3), 2.19 (s, 6 H, $COCH_3$), 2.7–3.3 (m, 1 H, CH), 4.5–5.3 (m, 2 H, CH_2), 7.48 (m, 3 H, aromatic); $[\alpha]^{24}D$ +29.9° (*c* 1.1, THF).

Anal. Calcd for $C_{13}H_{15}BrN_2O_2$: C, 50.18; H, 4.86; N, 9.00. Found: C, 50.07; H, 4.83; N, 9.04.

RS derivative: 75%; mp 129–130°; uv, ir, and pmr same as *S* derivative. *Anal.* Found: C, 50.19; H, 4.85; N, 8.96.

2-Methyl-1,2,3,4-tetrahydroquinoxaline (**5**).—A mixture of 0.12 g (0.53 mmol) of **4**, 0.1 g (1 mmol) of $KHCO_3$, and 0.1 g 10% Pd–C catalyst in 20 ml of 95% EtOH was hydrogenated for 20 hr at 46 psi and 24°. After removal of the catalyst, the filtrate was evaporated to dryness, and the solid residue extracted two times with 10-ml portions of hot ligroin (bp 66–75°). The hot extracts were clarified, cooled, and filtered to give 0.05 g (64%) of yellow solid. Two recrystallizations from hot ligroin (bp 66–75°, 20 ml/g) gave white plates of constant melting point.

S-**5**: 40%; mp 90–90.5°; uv max (95% EtOH) 220 mμ (ϵ 25,700), 258 (2960), 311 (2960); uv max (0.1 *N* HCl) 210 (6600), 243 (5160), 294 (1300); ir (KBr) 3310, 3355 cm^{-1} (NH); pmr ($CDCl_3$) δ 1.10 (d, J = 6 Hz, 3 H, CH_3), 2.7–3.5 (m, 3 H, CH_2, CH), 3.51 (s, 2 H, NH), 6.54 (m, 4 H, aromatic), singlet at 3.51 disappears upon exchange with D_2O; $[\alpha]^{24}D$ +60.2° (*c* 1.0, THF), −6.1° (*c* 1.0, $CHCl_3$), −35.8° (*c* 1.0, 95% EtOH).

Anal. Calcd for $C_9H_{12}N_2$: C, 72.94; H, 8.16; N, 18.90. Found: C, 72.78; H, 8.08; N, 18.78.

RS-**5**: 34%; mp 70–71° (lit.[11,17] mp 70–71°; lit.[18] 71°); uv, ir, and pmr same as *S*-**5**.

(17) C. Ris, *Ber.*, **21**, 383 (1888).

(18) S. Maffei and S. Pietra, *Gazz. Chim. Ital.*, **88**, 562 (1958).

R-**5**: prepared by a continuous sequence of reactions involving *R*-**2**, *R*-**3**, and *R*-**4** including THF–$LiAlH_4$ reduction to *R*-**4**, without any isolation or purification steps; 20%; mp 73–74°; uv and ir same as *S*-**5**; $[\alpha]^{27}D$ −3.8° (*c* 2.0, THF). *Anal.* Found: C, 72.80; H, 7.93; N, 19.02.

R-**5**: prepared by resolution of *RS*-**5**. To a solution of 7.52 g (20 mmol) of dibenzoyl-*d*-tartaric acid[13] in 35 ml of C_6H_6–95% EtOH (4:1) was added a solution of 2.96 g (20 mmol) of *RS*-**5**[11] in 20 ml of C_6H_6. After 12 hr at 24°, 5.16 g (44.1%) of white solid, mp 149–153°, $[\alpha]^{24}D$ −63.2° (*c* 1.0, 95% EtOH), was obtained. Three recrystallizations from hot Me_2CO (4 ml/g) solution poured into hot C_6H_6 (5 ml/g) gave 2.75 g (23.5%) of material of constant melting point and $[\alpha]$ that analyzed for the monobenzene solvated 1:1 salt, mp 150–151°, $[\alpha]^{24}D$ −60.0° (*c* 1.0, 95% EtOH).

Anal. Calcd for $C_9H_{12}N_2 \cdot C_{18}H_{14}O_8 \cdot C_6H_6$: C, 67.80; H, 5.52; N, 4.79. Found: C, 67.56; H, 5.65; N, 4.89.

Addition of 10 ml of 1 *N* NaOH to the salt, followed by filtration, gave 0.55 g (37.2% yield of total *R*-**5** isomer initially present), mp 90–91°, $[\alpha]^{24}D$ +31.7° (*c* 1.0, 95% EtOH). Two recrystallizations from ligroin (20 ml/g) gave 0.32 g (21.6%) of material of constant melting point and $[\alpha]$: mp 90.5–91°; $[\alpha]^{24}D$ −60.3° (*c* 1.0, THF), +6.07° (*c* 1.0, $CHCl_3$), +35.1° (*c* 1.0, 95% EtOH); uv, ir, and pmr, same as *S*-**5**. *Anal.* Found: C, 72.75; H, 8.33; N, 18.92.

N,N′-Diacetyl-2-methyl-1,2,3,4-tetrahydroquinoxaline.—This was prepared and purified as was the related bromo compound above.

S derivative: 82.5%; mp 143–144°; uv max 226 mμ (ϵ 23,200), 251 (12,300); ir (KBr) 1645 cm^{-1} (C=O); pmr ($CDCl_3$) δ 1.15 (d, J = 6 Hz, 3 H, CH_3), 2.18 and 2.21 (2 s, 6 H, $COCH_3$), 2.4–3.2 (m, 1 H, CH), 4.5–5.3 (m, 2 H, CH_2), 7.34 (m, 4 H, aromatic); $[\alpha]^{24}D$ +133.2° (*c* 1.0, THF).

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.23; H, 6.90; N, 12.13.

RS derivative: 76.5%; mp 141–143° (lit.[18] mp 138–139°); uv, ir and pmr same as *S* derivative.

Registry No.—*R*-**2**, 24463-23-8; *S*-**2**, 24463-22-7; *R*-**3**, 24463-24-9; *RS*-**3**, 24463-25-0; *S*-**3**, 24463-26-1; *RS*-**4**, 24463-27-2; *S*-**4**, 24515-51-3; *R*-**5**, 24463-30-7; *S*-**5**, 24463-31-8; N,N′-diacetyl-2-methyl-7-bromo-1,2,3,4-tetrahydroquinoxaline, *S* derivative, 24463-28-3; N,N′-diacetyl-2-methyl-7-bromo-1,2,3,4-tetrahydroquinoxaline, *RS* derivative, 24463-29-4; N,N′-diacetyl-2-methyl-1,2,3,4-tetrahydroquinoxaline, *S* derivative, 24463-32-9.

Quinazolines and 1,4-Benzodiazepines. XLVII.[1,2] A Novel Alcoholytic Ring Contraction of an Oxazirinobenzodiazepine

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7-Chloro-4,5-epoxy-5-phenyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (1) undergoes a facile alcoholytic ring contraction to give 3-alkoxymethyl-6-chloro-3,4-dihydro-4-hydroxy-4-phenylquinazolin-2(1H)-ones (2a,b) in good yields. The structures of 2a and 2b were established by chemical correlations as well as by direct synthesis. A mechanism for this conversion is discussed.

The study of the chemistry of oxazirinobenzodiazepines of type 1[1] led to the finding that solutions of 1 in lower primary and secondary alcohols are unstable even at room temperature. The oxaziridine undergoes an unusual transformation which results in the addition of one molecule of the respective alcohol with concomitant ring contraction to 3-alkoxymethyl-3,4-dihydro-4-hydroxyquinazolin-2(1H)-ones of type 2. In this paper, we wish to report the ethanolysis and the methanolysis of 1 which occur with 60–70% yield.

The physical and chemical properties indicated structures 2a and 2b for these alcoholysis products. The ir spectra showed the presence of NH and OH groups and amide carbonyls (1670 cm^{-1}). The nmr spectrum also showed the OH and NH protons; in addition the methylene groups attached to the 3-N appeared as AB quartets centering at about 4.7 ppm. The uv spectra were typical for systems of this type.[3]

On treatment with alcohols, the quaternary hydroxyl groups could be readily replaced by alkoxyl groups as shown by the conversion of 2a to 7. Hydrogenolysis of 2a over a platinum catalyst yielded 8. Both 2a and 2b were readily hydrolyzed by aqueous acids to the 6-chloro-4-phenyl-2(1H)-quinazolinone (5) which was identical with the quinazolinone prepared by the fusion of 2-amino-5-chlorobenzophenone (9) with urea.[4] Both 2a and 5 gave the 2-*p*-toluenesulfonyloxyquinazoline 6 when treated with *p*-toluenesulfonyl chloride in pyridine. Reduction of 2a with lithium aluminum hydride gave the tetrahydroquinazoline derivative 3 which was also obtained by reduction of 4.[3] Finally we identified 2b by an unequivocal synthesis from the aminochlorobenzophenone 9. Reaction of 9 with methoxymethyl isocyanate[5] gave the expected[3] compound 2b, which was found to be identical (mixture melting point and ir) with the methanolysis product of 1 (see Scheme I). The formation of compounds 2 from the oxaziridine 1 may be explained by a mechanism such as that shown in Scheme II. Thus, the oxazirinobenzodiazepine opens to form an imino isocyanate I which recyclizes readily by intramolecular attack of the basic imino nitrogen on the isocyanate function to give an intermediate II, which in turn is converted into 2 by the addition of alcohols. Formation of 2 from II is probably rapid since acylated imines are known[6–10] to add alcohols readily. This mechanism is supported by the observation that the 1-methyl analog of 1 (10) is stable in alcoholic solutions. It also suggests the possibility of base catalysis in these reactions. Indeed, catalytic amounts of hydroxide ions or even triethylamine reduce the reaction time from days to minutes. The presence of acid stops the reaction.

This mechanism also accommodates the observation that compound 1 is converted to 5 in aqueous tetrahydrofuran. Here, the formation of 3-hydroxymethylquinazoline is postulated as an intermediate which loses formaldehyde and water to yield 5. Compound 5 appeared as a bluish fluorescent spot on silica gel chromatograms when viewed under uv light. The presence of 5 was detected in all chromatograms of crude product mixtures resulting from the alcoholyses of 1, since the alcohols used were not rigidly dried.

Experimental Section[11]

7-Chloro-4,5-epoxy-5-phenyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (1).—This oxaziridine, mp 136° dec, was obtained by photoisomerization of 7-chloro-1,3 dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide[12] as reported elsewhere.[1] Proof of structure along with some physical and chemical properties will appear elsewhere.[1]

6-Chloro-3,4-dihydro-3-ethoxymethyl-4-hydroxy-4-phenyl-2-(1H)-quinazolinone (2a).—A suspension of 25.0 g (87 mmol) of 1 in 4 l. of ethanol was stirred at room temperature for 8 days. In this period a clear solution formed and no starting material was detectable by tlc or starch–iodide test. The solvent was evaporated; recrystallization of the residual solid from acetonitrile gave 20.0 g (69%) of 2a as colorless needles: mp 168.5–169.5°; ir (KBr) 3325, 3225, and 1670 cm^{-1}; uv max (*i*-PrOH) 251 mμ (ε 16,400), 295 (1850), and 304 (1600); molecular ion (low resolution) *m/e* 332 (calcd 332); δ (DMSO-d_6) 0.85 (3, t, CH_3), 3.23 (2, q, CH_2), 4.65 (2, ABq, NCH_2); 6.7–7.6 (8, m, aromatic), 7.20 (1, s, D_2O exchangeable, OH), and 10.00 ppm (1, s, D_2O exchangeable, NH).

Anal. Calcd for $C_{17}H_{17}ClN_2O_3$: C, 61.36; H, 5.15; N, 8.42; Cl, 10.65. Found: C, 61.34; H, 5.20; N, 8.22; Cl, 10.87.

(1) Part XLVI: R. Y. Ning, G. F. Field, and L. H. Sternbach, *J. Heterocycl. Chem.*, in press.

(2) Presented in part at the 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970.

(3) W. Metlesics, G. Silverman, V. Toome, and L. H. Sternbach, *J. Org. Chem.*, **31**, 1007 (1966).

(4) T. S. Sulkowski and S. J. Childress, *ibid.*, **27**, 4424 (1962).

(5) This isocyanate was prepared by a modification of the procedure described by L. W. Jones and D. H. Powers [*J. Amer. Chem. Soc.*, **46**, 2518 (1924)].

(6) J. E. Banfield, G. M. Brown, F. H. Davey, W. Davies, and T. H. Ramsay, *Aust. J. Sci. Res., Ser. A*, 330 (1948).

(7) W. Davies, T. H. Ramsay, and E. R. Stove, *J. Chem. Soc.*, 2633 (1949).

(8) Y. H. Suen, A. Horeau, and H. B. Kagan, *Bull. Soc. Chim. Fr.*, **5**, 1454, 1457 (1965).

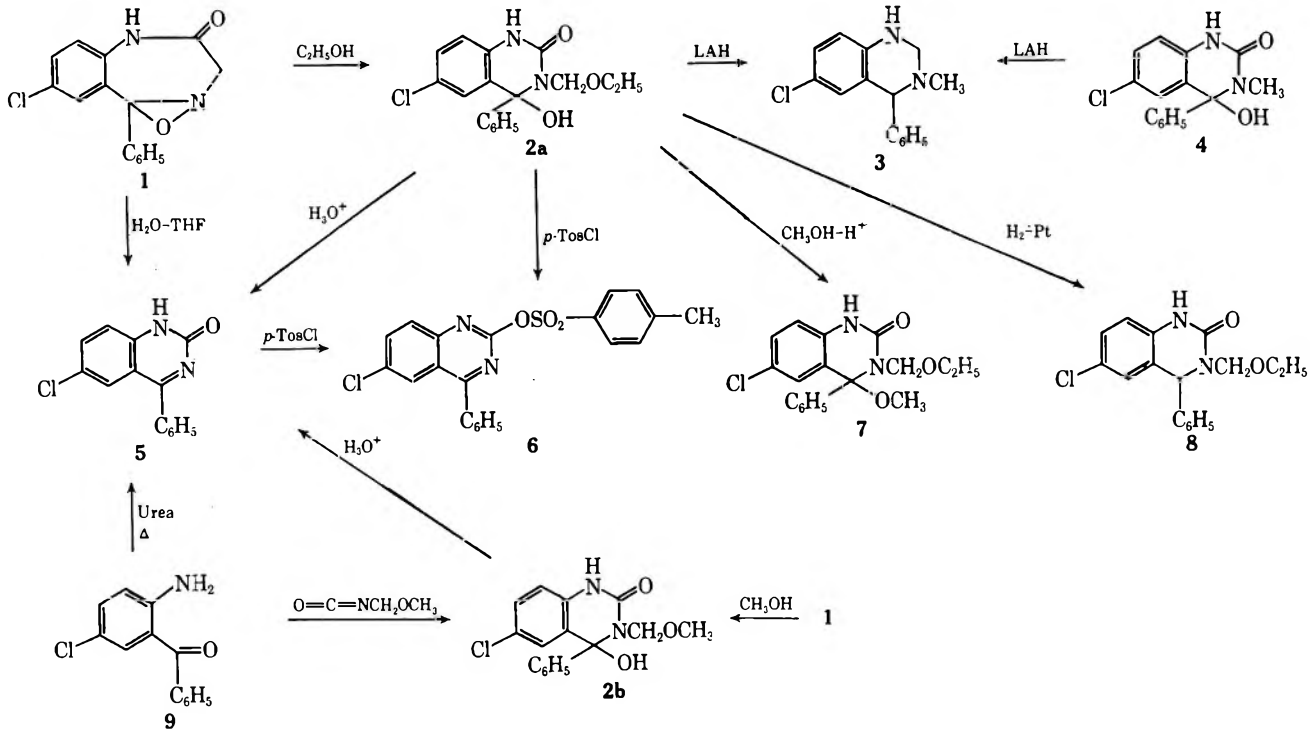
(9) S. W. Breuer, T. Bernath, and D. Ben-Ishai, *Tetrahedron*, **23**, 2869 (1967).

(10) S. C. Bell, R. J. McCaully, and S. J. Childress, *J. Org. Chem.*, **33**, 216 (1968).

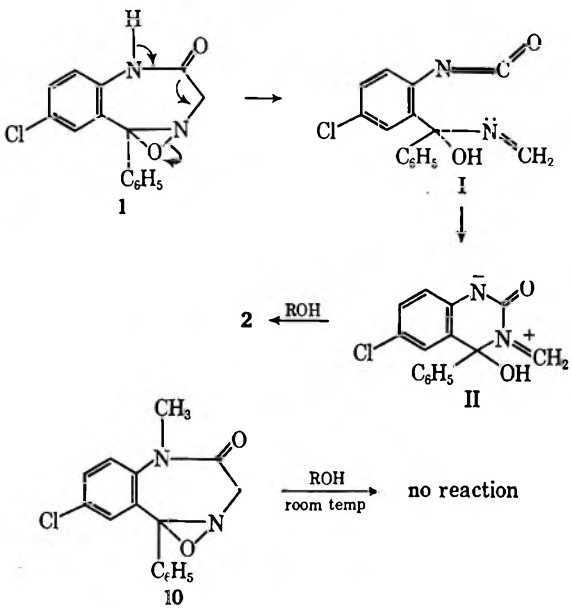
(11) All melting points were taken in a Thomas–Hoover melting point apparatus and are corrected. Infrared spectra were determined using a Beckman IR-9 or a Perkin-Elmer 621 grating spectrophotometer, mass spectra with a CEC-21-110 spectrometer, nmr spectra with a Varian A-60 spectrometer using tetramethylsilane as internal standard, and uv spectra with a Cary 14M or 15 recording spectrophotometer. All solvents used were of reagent grade purity. Ether refers to anhydrous diethyl ether. Unless otherwise specified, all solvents were evaporated with a Büchi Rotavapor evaporator, under water-aspirator pressure using a water bath set at 35–40°.

(12) L. H. Sternbach and E. Reeder, *ibid.*, **26**, 4936 (1961).

SCHEME I



SCHEME II



Methoxymethyl Isocyanate.[5]—To a stirred suspension of 200 g (1.30 mol) of silver cyanate in 1 l. of anhydrous xylene was added, at room temperature, 81.0 g (1.00 mol) of freshly prepared and redistilled chloromethyl methyl ether.[13] The temperature rose from 23 to 49°. The reaction mixture was cooled to room temperature and stirred in an aluminum foil covered flask for 24 hr. The solids were removed by filtration and washed with xylene. The combined filtrate and washings were distilled and redistilled at atmospheric pressure through a Vigreux column. The fraction boiling between 89 and 94° (lit.[5] 89–90°) was collected: yield 53.5 g (61%); ir (film) 2280 cm^{-1}; δ (DMSO-d_6) 3.38 (CH_3), and 4.86 ppm (CH_2).

6-Chloro-3,4-dihydro-4-hydroxy-3-methoxymethyl-4-phenyl-2(1H)-quinazolinone (2b). A. From Oxaziridine 1.—A suspension of 17.5 g (61 mmol) of 1 in 2.6 l. of methanol was stirred at room temperature for 8 days. A clear solution was formed which did not contain any starting material 1. The methanol was evaporated and the residual solid recrystallized from acetonitrile to give 12.1 g (62%) of **2b**: colorless plates; mp 179.5–182.5°; ir (KBr) 3240 and 1670 cm^{-1}; uv max (*i*-PrOH) 251 mμ (ε 16,050), 295 (1900), and 304 (1600); molecular ion (low resolution) *m/e* 318 (calcd 318); δ (DMF-d_7) 3.10 (3, s, CH_3), 4.75 (2, AB q, CH_2), 6.8–7.6 (8, m, aromatic), 7.14 (1, s, D_2O exchangeable, OH), and 9.92 ppm (1, broad s, D_2O exchangeable, NH).

Anal. Calcd for $C_{16}H_{15}ClN_2O_3$: C, 60.29; H, 4.74; N, 8.79; Cl, 11.12. Found: C, 60.47; H, 4.76; N, 8.49; Cl, 11.26.

Catalytic Effects of Acid and Bases on the Methanolysis of Oxaziridine (1). i. Control without Catalyst.—A suspension of 1.75 g (6.1 mmol) of oxaziridine 1 in 750 ml of methanol was stirred at room temperature. A clear solution formed overnight. The course of the reaction was monitored by tlc analyses (silica gel, ether) at intervals. After 38 hr, a small amount of 1 remained (tlc and starch–iodide test). Conversion to **2b** was complete in 2 days.

ii. With *p*-Toluenesulfonic Acid.—A suspension of 1.75 g (6.1 mmol) of 1 in 750 ml of methanol containing 10 mg of *p*-toluenesulfonic acid monohydrate was stirred at room temperature. A clear solution formed overnight. Tlc analysis of the solution at intervals showed that after 3 days no **2b** was detectable, and the bulk of 1 remained unchanged.

iii. With Benzyltrimethylammonium Hydroxide.—A suspension of 1.75 g (6.1 mmol) of 1 in 750 ml of methanol containing 1.0 ml of a 35% methanolic solution of benzyltrimethylammonium hydroxide was stirred at room temperature. A clear solution formed in 10 min. Tlc analysis showed that conversion to **2b** was complete within 15 min. After 1 hr, the methanolic solution was concentrated. Crystalline **2b** which precipitated was collected and washed thoroughly with methanol, yield 754 mg. A second crop of **2b** was obtained by concentration of the methanolic mother liquor and washings followed by dilution with water, yield 809 mg. The two crops were combined and recrystallized from acetonitrile to yield 1.40 g (72%) of **2b** as colorless platelets, mp 180–182°. A mixture melting point with authentic **2b** was undepressed.

iv. With Triethylamine.—A suspension of 1.75 g (6.1 mmol) of 1 in 500 ml of methanol containing 1.0 ml of triethylamine was stirred at room temperature for 20 min. The resulting clear solution was evaporated to dryness. The residual solid was recrystallized from acetonitrile to give 1.60 g (82%) of **2b** as colorless platelets, mp 183–184°. A mixture melting point with an authentic sample was undepressed.

B. Direct Synthesis.—A solution of 178 mg (0.77 mmol) of 2-amino-5-chlorobenzophenone and 65 mg (0.70 mmol) of methoxylmethyl isocyanate[5] in 5 ml of pyridine was allowed to stand at room temperature for 24 hr. The reaction mixture was

(13) A. H. Blatt, Ed. "Organic Syntheses," Coll. Vol. I, 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1941, p 377.

heated for 30 min on the steam bath and then poured onto ice. A yellow, partially solidified oil containing predominantly unreacted starting material which separated on standing was removed. The clear aqueous layer was diluted with more water until cloudy, then seeded with **2b**. On standing at 0°, **2b** crystallized. The yield, after washing with ether, was 53 mg (24%), mp 181–183°. A mixture melting point with **2b** obtained from methanolysis of **1** was undepressed; ir spectra and tlc in several solvent systems were identical.

6-Chloro-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinazoline (3). **A. From 2a.**—A solution of 1.0 g (3.0 mmol) of **2a** in 20 ml of dry tetrahydrofuran was added dropwise with stirring at room temperature over 30 min to a suspension of 1.14 g (30 mmol) of lithium aluminum hydride in 10 ml of tetrahydrofuran. The mixture was stirred at room temperature for 30 min, then heated to a gentle reflux for 2 hr. Excess hydride was decomposed with 2.4 ml of water and the solids were removed by filtration through a pad of Celite. Evaporation of the solvents gave 770 mg of an oil which partially crystallized on standing. This oily solid was triturated with hexane, chilled, and filtered to give 220.5 mg of crude **3**, mp 90–94°. The hexane filtrate was evaporated to dryness, and the oily residue, dissolved in benzene, was chromatographed on a short column of silica gel. After washing with 25% ether in benzene to remove fast moving impurities, 300 mg of relatively pure **3** was obtained by elution with ether. Combined crops of **3** after recrystallizations from hexane weighed 384 mg (50%): mp 95–96°; ir (KBr) 3200 cm^{-1}; δ (DMSO-d_6) 2.24 (3, s, CH_3), 3.46–3.88 (2, m, CH_2), and 4.49 ppm (1, s, CH).

Anal. Calcd for $C_{16}H_{15}ClN_2$: C, 69.63; H, 5.84; N, 10.83; Cl, 13.70. Found: C, 69.52; H, 6.06; N, 10.76; Cl, 13.21.

B. From 6-Chloro-3,4-dihydro-4-hydroxy-3-methyl-4-phenyl-2(1H)-quinazolinone (4).—To a suspension of 2.70 g (70 mmol) of lithium aluminum hydride in 80 ml of dry tetrahydrofuran was added batchwise with stirring at room temperature, 2.00 g (70 mmol) of **4**.[3] A mildly exothermic reaction occurred. Stirring at room temperature was continued for 30 min. After refluxing for 2 hr, the reaction mixture was decomposed with 5.4 ml of water, stirred vigorously for 10 min, and then filtered through a pad of Celite. The filtrate was evaporated to dryness and the residue was crystallized from hexane to give 1.25 g of **3**, mp 90–93°. After recrystallization from hexane, the yield was 1.04 g (57%), mp 92–95°. This material was identical with **3** obtained from **2a** by tlc and ir spectrum.

6-Chloro-4-phenyl-2(1H)-quinazolinone (5).[4] **A. From 1.**—A solution of 1.00 g (3.5 mmol) of **1** in a mixture of 25 ml of tetrahydrofuran and 12 ml of water was allowed to stand at room temperature. After 7 days, the solid that precipitated weighed 964 mg, mp 309–312°, and was found by tlc to be predominantly **5**. After recrystallizations from large volumes of acetonitrile, there was obtained 387 mg (43%) of pure **5**, mp 311–313°, identical with the authentic sample[4] by mixture melting point, ir, and tlc.

B. From 2b.—To a mixture of 25 ml of water and 35 ml of 6 *N* hydrochloric acid was added 1.00 g (3.0 mmol) of **2b**. The suspension was kept in a sealed flask inside an oven at 85–95° for 1 day. Water was evaporated. The residual solid was stirred with aqueous sodium bicarbonate, filtered, and washed with water. The dried solid was pure **5** by tlc: mp 311–314°; yield 777 mg (100%). A mixture melting point with an authentic sample was undepressed.

C. From 2a.—A solution of 1.0 g (3.0 mmol) of **2a** and 570 mg of *p*-toluenesulfomic acid monohydrate in 750 ml of methylene chloride was allowed to stand for 20 hr. The mixture was evaporated to dryness. The residual solid was washed with aqueous sodium bicarbonate then with water. The crude **5** obtained was recrystallized from acetonitrile: yield 692 mg (90%), mp 311–313.5°. A mixture melting point with an authentic sample was undepressed.

6-Chloro-4-phenyl-2-*p*-toluenesulfonyloxyquinazoline (6). A. From 2a.—A solution of 250 mg (0.75 mmol) of **2a** and 429 mg (2.25 mmol) of *p*-toluenesulfonyl chloride in 2 ml of pyridine was allowed to stand overnight at room temperature. The reaction mixture was poured into water. The oil that separated crystallized on standing, weight 211 mg. The solid was dissolved in methylene chloride and on standing, 9.6 mg of 6-chloro-4-phenyl-2(1H)-quinazolinone (**5**) crystallized, mp 303–310°. After recrystallization from acetonitrile, the yield was 4.0 mg (2.1%), mp 309–311°, mixture melting point with **5** undepressed.

The methylene chloride mother liquor was passed through a bed of silica gel. Elution with ether gave 194 mg of an oil which crystallized on standing. Recrystallizations from benzene–hexane mixtures gave 114 mg (37%) of **6**; mp 122–123.5°; ir (KBr) no NH band, 1600–1700 cm^{-1} clear; uv max (*i*-PrOH) 233 mμ (ε 53,500), 269 (10,000), and 336 (6700).

Anal. Calcd for $C_{21}H_{15}ClN_2O_3S$: C, 61.39; H, 3.67; N, 6.81; Cl, 8.62; S, 7.80. Found: C, 61.38; H, 3.74; N, 6.91; Cl, 8.84; S, 7.86.

B. From 5.—A solution of 192.5 mg (0.75 mmol) of **5** and 858 mg (4.50 mmol) of *p*-toluenesulfonyl chloride in 33 ml of dry pyridine was allowed to stand at room temperature for 4 days. The reaction mixture was poured onto ice. The tosylate **6** crystallized as flakes, yield 73.7 mg, mp 118–121°. After recrystallizations from benzene–hexane mixtures, the yield was 44 mg (14%), mp 122–124°; a mixture melting point with the tosylate obtained from **2a** above was undepressed.

6-Chloro-3,4-dihydro-3-ethoxymethyl-4-methoxy-4-phenyl-2-(1H)-quinazolinone (7).—A solution of 7.0 g (20 mmol) of **2a** and 58 mg of *p*-toluenesulfonic acid monohydrate in 350 ml of methanol was stirred at room temperature for 2 hr. The reaction mixture was passed through a bed of Florisil which was then washed with some methanol. The filtrate was evaporated to dryness. The residue was dissolved in methylene chloride and filtered through a fresh bed of Florisil, which was then eluted with ether. The combined effluent was evaporated to dryness. The residual oil, crystallized from ether and hexane and then recrystallized from acetonitrile, gave 5.55 g (76%) of **7** as prisms: mp 172–173°; ir (KBr) 3200 and 1680 cm^{-1}.

Anal. Calcd for $C_{18}H_{19}ClN_2O_3$: C, 62.33; H, 5.52; N, 8.08; Cl, 10.22. Found: C, 62.42; H, 5.55; N, 8.09; Cl, 10.13.

6-Chloro-3,4-dihydro-3-ethoxymethyl-4-phenyl-2(1H)-quinazolinone (8).—A solution of 10.0 g (30 mmol) of **2a** in 250 ml of tetrahydrofuran was hydrogenated (1 atm) in the presence of 2.50 g of platinum oxide until the rate of hydrogen uptake became very slow. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residual gum crystallized from ethanol to give 3.30 g (35%) of **8** as plates: mp 172–174°; ir (KBr) 3200 and 1680 cm^{-1}.

Anal. Calcd for $C_{17}H_{17}ClN_2O_2$: C, 64.46; H, 5.41; N, 8.84; Cl, 11.19. Found: C, 64.28; H, 5.44; N, 8.64; Cl, 10.79.

7-Chloro-4,5-epoxy-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (10).—A solution of 30 g (0.10 mol) of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide[12] in 1.4 l. of tetrahydrofuran was irradiated with a Hanovia 250 W medium-pressure mercury lamp (No. 654 A) through a Pyrex filter under nitrogen at 20° for 22 hr. The solution was evaporated to dryness and the residual gum was crystallized from ethanol. One recrystallization from ethanol gave 22.1 g (74%) of **10** as colorless prisms: mp 99–100°; ir (KBr) 1690 cm^{-1}; uv max (*i*-PrOH) 252 mμ (ε 11,300).[14]

Anal. Calcd for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.31; Cl, 11.78. Found: C, 63.71; H, 4.42; N, 9.36; Cl, 11.92.

Compound **10** also gave the positive starch–iodide test typical of oxaziridines.[15]

Attempted Alcoholyses of Oxaziridine 10.—A solution of 1.13 g (4.0 mmol) of **10** in 100 ml of methanol was allowed to stand for 2 weeks at room temperature. The reaction mixture gave a strongly positive starch–iodide test and tlc indicated negligible reaction. Repetition of the experiment using ethanol gave the same results.

Registry No.—**2a**, 24605-69-4; **2b**, 24621-38-3; **3**, 24621-39-4; **6**, 24621-40-7; **7**, 24621-41-8; **8**, 24621-42-9; **10**, 24605-70-7.

Acknowledgment.—Valuable discussions with Professor G. Büchi and Dr. G. Field are gratefully acknowledged. We thank Dr. P. Bommer and his staff in our physical chemistry department: in particular, Dr. W. Benz for mass spectra, Dr. F. Scheidl for elemental analyses, Dr. V. Toome for uv spectra, Mr. S. Traiman and Dr. H. Wyss for ir spectra, and Dr. T. Williams for nmr spectra.

(14) The absence of a nitrone chromophore is evident from comparison with the uv spectrum of the starting material: uv max (*i*-PrOH) 239 mμ (ε 31,000), 266 (inflection, 15,000), and 310 (11,500).

(15) For a recent review, see J. F. Dupin, *Bull. Soc. Chim. Fr.*, 3085 (1967).

Protection by Acylation in the Selective Alkylation of Heterocycles

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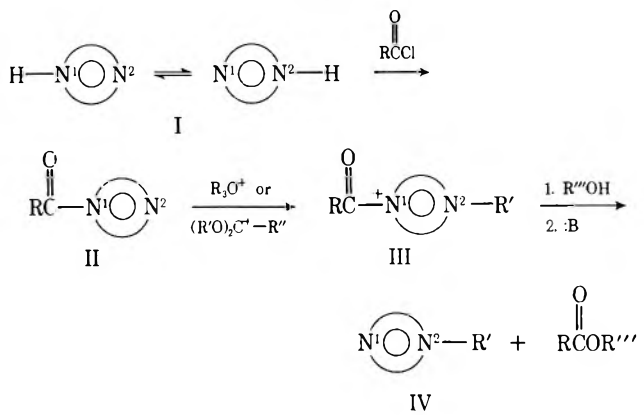
The use of different acyl (acetyl, benzoyl, carbethoxy) protecting groups as aids in accomplishing exclusive alkylation at normally unfavored positions in polynitrogen heterocycles is described. Examples of the new synthetic scheme include the isomer-free preparation of 1-ethyl-5-phenylimidazole from 4-phenylimidazole in 86% overall yield (best literature yield for 1-methyl compound is 7% plus isomer), 4-methyl-1,2,4-triazole from 1,2,4-triazole in 77% yield (other methods: 10 and 31% plus isomer and other alkylation products), 4-isopropyl-1,2,4-triazole from 1,2,4-triazole in 52% yield, and 1-ethylbenzotriazole from benzotriazole in 89% yield (best literature yield: 37% plus 36% 2 isomer).

The difficulties involved in alkylating a specific ring nitrogen atom in a polynitrogen heteroaromatic compound in which alkylation at another nitrogen is preferred still constitute a major problem in heterocyclic chemistry. Sometimes the trouble may be circumvented by preparing the required substance by a method in which the N-alkyl group is incorporated into the system prior to closure of the ring, but often such syntheses are unavailable. If the experimenter is lucky he may then, in specific cases, accomplish the desired alkylation, at least in small yield, by changing the alkylating agent (*i.e.*, from methyl sulfate to diazomethane), by first converting the substrate into its deprotonated metal salt, or by varying solvent and temperature, but as yet this problem has found no general solution. Even if the experimenter does obtain some of the required product, he must then devise procedures for separating it from its isomers, the dialkylated cation by-products, and any remaining starting material.

Historically, problems of this general type have been overcome by the selective blocking of the offending reaction site. Such has not been the case in this area primarily because it has been believed (a) that the introduction of the protecting group would be subject to the same selectivity difficulties, and (b) that most easily removable blocking groups would strongly deactivate the compound and thus inhibit the next step in which an N-alkyl cation would be formed. The recent development of the powerful oxonium[1] and carboxonium[2] ion alkylating agents has substantially mitigated the final objection, and we suggest that these alkylation methods in combination with simple acylation as the method of protection will lead to the essential elimination of the difficulties above.

In detail, we propose a three-step process (Scheme I) in which the heterocycle is first acylated by classical procedures (I → II), then alkylated with an oxonium or carboxonium ion reagent (II → III), and finally deacylated by treatment with an alcohol or water (III → IV). The conversion of an N–H to an N-acyl group in heteroaromatic rings is known to be a high yield reaction[3] though the product is usually sensitive to hydrolysis. Of special value is the ordinarily greater selectivity in isomer preference in acylation *vs.* alkylation.[3] This is probably a consequence of the fact that, unlike alkylations, acylations are reversible; any of the

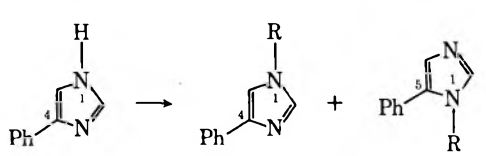
SCHEME I



thermodynamically less stable isomers formed in the kinetically determined product mixture usually rearrange spontaneously and rapidly to the thermodynamically stable isomer and one thus gets maximum use of the energy difference in isomer stability. Of further significance is the near impossibility of diacylation of the ring, a major problem in some ring alkylation processes (acylation also eliminates this side reaction in the alkylation step II → III).

We have found that N-acyl heterocycles (including acetyl, benzoyl, and carbethoxy derivatives) can be cleanly alkylated with oxonium or carbonium salts, the products while unstable can be characterized in solution, and the acyl moiety is quickly and quantitatively removed on addition of alcohol or water to the reaction mixture. The three very different reactions described in the following paragraphs are attempts to demonstrate the applicability of Scheme I in systems in which the position preference in alkylation (1) is a result of steric hindrance, (2) has a basis in relative electron-pair nucleophilicity and availability, and (3) is of more complex origin.

Extensive studies on the methylation of 4-phenylimidazole (V) have shown that the isomer VI (R = Me) is the primary product[4-6] (Table I). Only small amounts of the sterically hindered isomer VII (R =



(1) H. Meerwein, *Org. Syn.*, **46**, 113 120 (1966), and earlier references therein; see also R. B. Silverman and R. A. Olofson, *Chem. Commun.*, 1313 (1968), footnote.

(2) S. Kabuss, *Angew. Chem. Int. Ed. Engl.*, **5**, 675 (1966); K. Dimroth and P. Heinrich, *ibid.*, **5**, 676 (1966); R. F. Borch, *J. Org. Chem.*, **34**, 627 (1969).

(3) For review see H. A. Staab, *Angew. Chem. Int. Ed. Engl.*, **1**, 351 (1962).

(4) C. E. Hazeldine, F. L. Pyman, and J. Winchester, *J. Chem. Soc.*, 1431 (1924); J. H. Ridd and B. V. Smith, *ibid.*, 1363 (1960).

(5) A. Pinner, *Chem. Ber.*, **35**, 4131 (1902).

(6) W. G. Forsyth and F. L. Pyman, *J. Chem. Soc.*, 573 (1925).

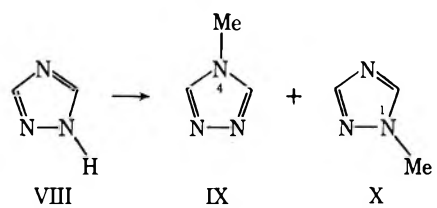
TABLE I

Alkylating agent	Yield, % VI	Yield, % VII	Recovered V, %	Ref
Me_2SO_4	29.8	6.2	27.3	4
Me_2SO_4 or MeI + NaOH	(poor solubility and product decomposition)			4,5
CH_2N_2	15	7	66	6
EtI + NaOMe	44	6.9	41	This work[a]

[a] See Experimental Section.

Me) are found, and it would be expected that the unknown and even more hindered 1-ethyl-5-phenylimidazole (VII R = Et) would prove to be an even more elusive synthetic target. We have, however, been able to obtain VII[7] (R = Et) in 86% overall yield uncontaminated by its isomer VI (R = Et) using the new procedure postulated in Scheme I. 1-Benzoyl-4-phenylimidazole can be isolated in 95% yield as the exclusive product from V and benzoyl chloride in base.[8] On alkylation with triethyloxonium fluoroborate[1,9] followed by treatment with methanol, this acylimidazole is converted in 91% yield to 1-ethyl-5-phenylimidazole (VII, R = Et). No trace of the isomer VI (R = Et) was detected.

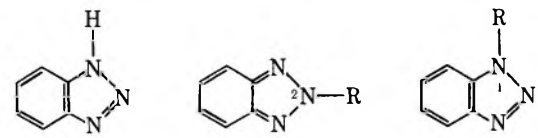
It might be anticipated that commercially available 1,2,4-triazole VIII would be a useful precursor to 4-methyl-1,2,4-triazole (IX). Alkylation methods in



VIII IX X

this system, however, are either poor and indiscriminate or else yield the 1 isomer X as the major product; for example, methyl iodide and sodium methoxide in methanol gives X (65%) and IX (10%)[10] while $Me_3O^+BF_4^-$ in nitromethane gives X (16%), IX (31%), residual VIII (27%), and 1,4-dimethyl-1,2,4-triazolium cation (25%, see Experimental Section). However, when 1,2,4-triazole is acetylated, the 1 isomer is the exclusive product (87%)[11] and reaction of this with trimethyloxonium fluoroborate[1] followed by methanolysis of the unstable 1-acetyl-4-methyl-1,2,4-triazolium fluoroborate affords 4-methyl-1,2,4-triazole in 88% yield (77% overall from VIII). Similarly, 4-isopropyl-1,2,-4-triazole is formed in 60% yield by treatment of the same 1-acetyl-1,2,4-triazole with diisopropoxycarbonium fluoroborate[2] followed by decomposition of the intermediate salt with methanol. The only other detectable product is protonated 1,2,4-triazole indicating that some of the acyltriazole reacts with the incipient isopropyl carbonium ion at hydrogen to eliminate propylene. This well-known and important side reaction in all isopropylation procedures is only a minor annoyance, since the unsubstituted heterocycle can be separated from the N-alkyl derivative and recycled through the synthetic Scheme I when economically advantageous.

Benzotriazole (XI) yields primarily the 2-methyl derivative XII on treatment with diazomethane[12] and only a slight preponderance of the 1-alkyl isomer XIII when allowed to react with an alkyl halide and base (Et, 37% XIII, 36% XII; *n*-Pr, 41% XIII, 33% XII; *n*-Bu, 37% XIII, 32% XII).[13,14]



XI XII XIII

When ethylation is accomplished with triethyloxonium fluoroborate[1] on 1-carbethoxybenzotriazole[14] (from XI and ethyl chloroformate cleanly in base, 95%) followed by methanolysis, 1-ethylbenzotriazole (XIII, R = Et) is the only product in 94% yield (overall yield from XI, 89%); no isomer XII (R = Et) was detected.

We suggest that the above examples demonstrate that protection by acylation can be a valuable tool in the selective alkylation of heterocyclic compounds. Acyl heterocycles, even those derived from very weak bases,[15] can be alkylated with the powerful oxonium and carboxonium alkylating agents, and the product cations are stable enough to await a specific clean hydrolytic decomposition.

Experimental Section[16]

1-Benzoyl-4-phenylimidazole.—Benzoyl chloride (2.4 g, 0.017 mol) was slowly added to a stirred cooled solution of 4-phenylimidazole (2.0 g, 0.014 mol) and sodium hydroxide (1.2 g, 0.028 mol) in 10 ml of acetone and 40 ml of water. During the addition the product precipitated and after 30 min 50 ml of cold water was added to ensure complete precipitation. The solid was filtered, washed with water, and dried: yield, 3.3 g (95%); mp 124–125°; white platelets after recrystallization from chloroform–ether; mp 124–124.5° (lit.[8] mp 132°); nmr ($CDCl_3$) δ 8.10 (d, J = 1.5 cps), 7.2–8.0 (m, 11).

Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.12; H, 4.79; N, 11.15.

1-Ethyl-5-phenylimidazole (VII, R = Et).—1-Benzoyl-4-phenylimidazole (4.00 g, 0.016 mol) and triethyloxonium fluoroborate[1] (3.06 g, 0.016 mol) were dissolved in 20 ml of methylene chloride, and the reaction mixture was stirred for 48 hr at room temperature. After the solvent was removed at reduced pressure, an nmr spectrum was taken of the residue and

(7) It is very easy to distinguish compounds of structure VII from their isomers VI by comparing their nmr spectra. The phenyl resonance in VII shows up as a sharp spike, because coplanarity of the two aromatic rings and the resulting resonance interaction is inhibited by the *o*-alkyl substituents; in VI the optimum dihedral angle between the two rings is smaller and the expected broad multiplet for a conjugated phenyl is found.

(8) R. L. Grant and F. L. Pyman, *J. Chem. Soc.*, 1893 (1921).

(9) Examination of the alkylation mixture by nmr indicated essentially complete formation of 1-N-benzoyl-3-methyl-4-phenylimidazolium fluoroborate: δ 9.28 (d) imidazole C_2 H, 7.77–8.20 (m) benzoyl and imidazole C_5 H, 7.60 (s?) phenyl, 4.43 (q), and 1.46 (t) ethyl. The substance was too sensitive to easily isolate and purify. For comparison, see the hydrolytic rate study of 1-acetyl-3-methylimidazolium chloride by R. Wolfenden and W. P. Jencks, *J. Amer. Chem. Soc.*, **83**, 4390 (1961).

(10) M. R. Atkinson and J. B. Polya, *J. Chem. Soc.*, 141 (1954); G. Pellizzari and A. Soldi, *Gazz. Chim. Ital.*, **35***I*, 373 (1905); see also Experimental Section, present paper.

(11) H. A. Staab, *Chem. Ber.*, **89**, 1927 (1956).

(12) N. O. Cappel and W. C. Fernelius, *J. Org. Chem.*, **5**, 40 (1940).

(13) F. Krollpfeiffer, A. Rosenberg, and C. Mühlhausen, *Justus Liebigs Ann. Chem.*, **515**, 113 (1934).

(14) F. Krollpfeiffer, H. Pötz, and A. Rosenberg, *Chem. Ber.*, **71**, 596 (1938).

(15) We have also methylated the very weakly basic N-acetyltetrazole in another connection: R. A. Olofson and D. M. Zimmerman, unpublished results. A different hydrolysis mechanism is observed in this system.

(16) Melting points were determined in Kimax, soft-glass capillary tubes using a Thomas–Hoover melting point apparatus with a calibrated thermometer. Nmr spectra were run on a Varian A-60 spectrometer using an internal tetramethylsilane standard. The solvents and reactants were of the best commercial grade available and were used without further purification.

this showed that the reaction had given the expected 1-benzoyl-3-ethyl-4-phenylimidazolium fluoroborate: nmr (CD_3NO_2) δ 9.28 (d, J = 1.5 cps, 1), 7.77–8.20 (m, 6), 7.65 (s, 5), 4.43 (q, J = 7.5 cps, 2), 1.46 (t, J = 7.5 cps, 3). The salt was then dissolved in 25 ml of water and the acidic solution was made slightly basic with sodium carbonate. The product was extracted with chloroform (four 50-ml portions), the extracts were dried (K_2CO_3), and, after removal of the solvent, 2.50 g (91%) of VII was isolated by distillation: bp 109–110° (0.4 mm); nmr ($CDCl_3$) δ 7.53 (d, J = 1.5 cps, 1), 7.40 (sharp s, 5), 7.03 (d, J = 1.5 cps, 1), 3.96 (q, J = 7.5 cps, 2), 1.28 (t, J = 7.5 cps, 3).

Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.94; H, 6.77; N, 16.00.

VII was also converted to the crystalline 1,3-diethyl-4-phenylimidazolium fluoroborate on treatment with additional triethyloxonium fluoroborate and recrystallization from methylene chloride–ether: mp 103°; nmr ($CDCl_3$) δ 8.90 (d, J = 1.5 cps, 1), 7.44 (s, 5), 7.38 (d, J = 1.5 cps, 1), 4.23 (m, 4), 1.57 (t, J = 7.5 cps, 3), 1.38 (t, J = 7.5 cps, 3).

Anal. Calcd for $C_{13}H_{17}N_2BF_4$: C, 54.20; H, 5.95; N, 9.72. Found: C, 54.44; H, 6.13; N, 9.53.

1-Ethyl-4-phenylimidazole (VI, R = Et).—4-Phenylimidazole (5.5 g, 0.038 mol) and ethyl iodide (6.3 g, 0.040 mol) were refluxed for 48 hr in 30 ml of methanolic sodium methoxide (from 0.90 g, 0.039 mol of sodium). After evaporation of the solvent, the residual oil was extracted with chloroform. The extract was distilled *in vacuo* and the fraction of bp 105–155° (0.4 mm) was collected: yield, 5.6 g. This was shown by nmr to be composed of VI (R = Et, 44% yield), VII (R = Et, 6.9%), and recovered 4-phenylimidazole (41%). VI (R = Et) was isolated pure by fractional distillation followed by several recrystallizations from chloroform–ether: mp 54–55°; nmr ($CDCl_3$) δ 7.05–7.90 (m, 7), 3,80 (q, J = 7.5 cps, 2), 1.23 (t, J = 7.5 cps, 3).

Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.37; H, 6.91; N, 16.47.

VI was also converted to 1,3-diethyl-4-phenylimidazolium fluoroborate by treatment with additional triethyloxonium fluoroborate (identical with sample above).

1-Acetyl-1,2,4-triazole.—This was prepared in 87% yield from 1,2,4-triazole and acetyl chloride: mp 40–41° (lit.[11] mp 41–42°); nmr ($CDCl_3$) δ 8.98 (s, 1), 8.07 (s, 1), 2.75 (s, 3).

4-Methyl-1,2,4-triazole (IX).—Trimethyloxonium fluoroborate[1] (4.0 g, 0.027 mol) in 20 ml of nitromethane was added quickly from a dropping funnel to a cooled nitromethane (5 ml) solution of 1-acetyl-1,2,4-triazole (3.0 g, 0.027 mol) in a system isolated from atmospheric moisture. An nmr spectrum of the reaction mixture showed only the desired 1-acetyl-4-methyl-1,2,4-triazolium fluoroborate [nmr (CH_3NO_2) δ 10.03 (s, 1), 8.80 (s, 1), 4.15 (s, 3), 2.85 (s, 3)] was present. Methanol was added to hydrolyze the acyl cation to the protonated salt which was obtained as a white solid after removal of the solvent. The salt was taken up in water (15 ml), and the acidic solution was neutralized with sodium carbonate and then taken to dryness *in vacuo*. 4-Methyl-1,2,4-triazole was extracted from the solid residue with chloroform (five 50-ml portions), isolated by evaporation of the solvent, and recrystallized from chloroform–ether: 2.0 g (88%); mp 88–89° (lit.[17] mp 90°); nmr ($CDCl_3$) δ 8.24 (s, 2), 3.83 (s, 3).

1-Methyl-1,2,4-triazole (X, Control).—This synthesis is a modification of the procedure of Atkinson and Polya.[10] Methyl iodide (20.6 g, 0.145 mol) was slowly added to 70 ml of a cooled methanolic solution of sodium methoxide (from 3.35 g, 0.145 mol of sodium) containing 1,2,4-triazole (10.0 g, 0.145 mol). The stoppered reaction vessel was warmed at 38° for 18 hr. The methanol was removed yielding an oil which analyzed (nmr in D_2O) as a 6.5:1 mixture of X:IX (plus a trace of VIII). The product was extracted from the oil with hot benzene (50 ml) and then hot chloroform (three 50-ml portions) and isolated by distillation: bp 175–176° (lit.[10] bp 177°); 7.8 g of (65%) X; nmr ($CDCl_3$) δ 8.10 (s, 1), 7.83 (s, 1), 3.87 (s, 3).

Reaction of Trimethyloxonium Fluoroborate with 1,2,4-Triazole (Control).—Trimethyloxonium fluoroborate[1] (4.54 g, 0.031 mol) in nitromethane (20 ml) was slowly added to a cooled solution of 1,2,4-triazole (2.1 g, 0.031 mol) in nitromethane. After 30 min the nitromethane was removed and the residual oil was analyzed by nmr: VIII (27%); IX (31%), X (16%), 1,4-dimethyl 1,2,4-triazolium cation (25%) (the nmr sample was prepared by dissolving a small amount of oil in D_2O and neutralizing to pH 9 with sodium carbonate; peak assignments were made by direct comparison with the authentic sample spectra).

4-Isopropyl-1,2,4-triazole.—1-Acetyl-1,2,4-triazole (4.0 g, 0.036 mol) in 10 ml of methylene chloride was added to a 25% excess of crude diisopropoxycarbonium fluoroborate (see Borch, ref 2) in an equal amount of the same solvent. The reaction mixture was stirred and kept cool in an ice bath. After 10 min a white solid began to precipitate from the solution and after an additional 20 min the solvent was removed *in vacuo* yielding a white solid which in turn was dissolved in 30 ml of methanol to cleave the acetyl group. The methanol was removed on a rotary evaporator, the residual oil (a mixture of HBF_4 salts of 1,2,4-triazole and 4-isopropyl-1,2,4-triazole) was dissolved in 20 ml of H_2O, and the acidic solution was made slightly alkaline by addition of sodium carbonate. The product was extracted with chloroform (four 80-ml portions), the combined extracts were dried (K_2CO_3), and the solvent was removed under vacuum. The oil (2.90 g) was analyzed by nmr as a mixture containing only 1,2,4-triazole (yield, 21%) and 4-isopropyl-1,2,4-triazole (yield, 60%), and was then distilled under reduced pressure affording pure 4-isopropyl-1,2,4-triazole: bp 119–120° (0.5 mm); nmr ($CDCl_3$) δ 8.30 (s, 2), 4.58 (h, J = 7 cps, 1), 1.72 (d, J = 7 cps, 6).[18]

Anal. Calcd for $C_5H_9N_3$: C, 54.04; H, 8.16; N, 37.81. Found: C, 53.89; H, 8.14; N, 37.78.

1-Carbethoxybenzotriazole.—Ethyl chloroformate (6.0 g, 0.056 mol) was slowly added to a stirred and cooled aqueous solution of benzotriazole (6.0 g, 0.05 mol) and sodium hydroxide (2.0 g, 0.05 mol). After completion of the addition, the reaction mixture was stirred for an additional 15 min, and the precipitated white solid was then filtered, washed with water, dried, and recrystallized from ethyl ether: 9.1 g (95%); mp 70–71° (lit.[14] mp 71–72°); nmr ($CDCl_3$) δ 7.92–8.20 (m, 2), 7.30–7.80 (m, 2), 4.71 (q, J = 7.3 cps, 2), 1.58 (t, J = 7.3 cps, 3).

1-Ethylbenzotriazole (XIII, R = Et).—Triethyloxonium fluoroborate[1] (3.03 g, 0.016 mol) in 5 ml of methylene chloride was added to a cooled solution of 1-carbethoxybenzotriazole (3.05 g, 0.016 mol) in 5 ml of methylene chloride. After 20 min the solvent was removed *in vacuo* yielding a white solid which from its nmr was the desired 1-carbethoxy-3-ethylbenzotriazolium fluoroborate: nmr (CH_2Cl_2) δ 7.90–8.05 (m, 4), 4.7–5.2 (m, 4), 1.80 (t, J = 7.3 cps, 3), 1.60 (t, J = 7.3 cps, 3). This was dissolved in 30 ml of methanol, the methanol evaporated, the residual oil dissolved in 15 ml of water, and the acidic solution neutralized with sodium carbonate. The product was extracted into ethyl ether (three 50-ml portions), dried (K_2CO_3), and isolated by distillation: bp 150–151° (13 mm) [lit.[13] bp 149.5° (12 mm)]; nmr ($CDCl_3$) δ 7.90–8.17 (m, 1), 7.13–7.63 (m, 3), 4.63 (q, J = 7 cps, 2), 1.56 (t, J = 7 cps, 3). The product was spectroscopically identical with an authentic sample.[13]

Registry No.—VI, R = Et, 24463-49-8; VII, R = Et, 24463-50-1; IX, 10570-40-8; X, 6086-21-1; XIII, R = Et, 16584-05-7; 1-benzoyl-4-phenylimidazole, 24463-54-5; 1-benzoyl-3-ethyl-4-phenylimidazolium fluoroborate, 24464-49-1; 1,3-diethyl-4-phenylimidazolium fluoroborate, 24464-50-4; 1-acetyl-1,2,4-triazole, 15625-88-4; 1-acetyl-4-methyl-1,2,4-triazolium fluoroborate, 24464-51-5; 4-isopropyl-1,2,4-triazole, 24463-56-7; 1-carbethoxybenzotriazole, 830-67-1; 1-carbethoxy-3-ethylbenzotriazolium fluoroborate, 24464-52-6.

Acknowledgment.—We are very grateful to the U. S. Public Health Service for a grant (GM-13980) to support this research.

(17) M. Freund, *Chem. Ber.*, **29**, 2483 (1896).

(18) The nmr equivalence of the two triazole C–H's eliminates the alternative 1-isopropyl structure.

Mechanism of Thietane Formation from the Reaction of 1,3-Dioxan-2-ones with Thiocyanate Ion. A Stereochemical Investigation

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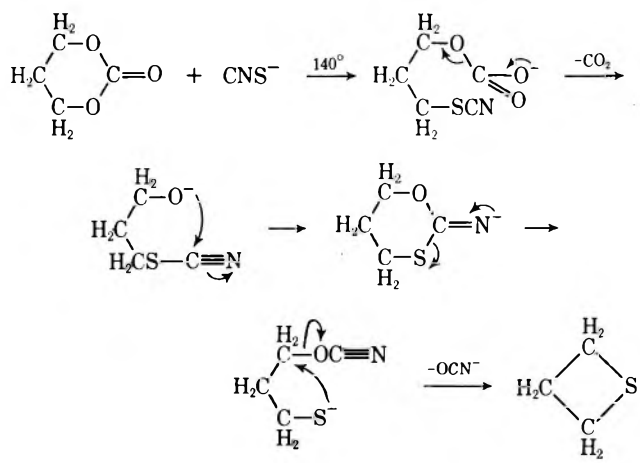
The stereochemical fate of C-4 in a 1,3-dioxan-2-one in its decomposition to a 2-substituted thietane has been examined. Lithium aluminum hydride reduction of (*R*)-(−)-3-acetoxybutyric acid, obtained from quinine resolution of β-hydroxybutyric acid, afforded (*R*)-(−)-1,3-butanediol. This diol was then converted to (*R*)-(−)-4-methyl-1,3-dioxan-2-one, which was in turn heated with potassium thiocyanate at 170–180°. The resulting thietane was oxidized to give (*S*)-(−)-2-methylthietane 1,1-dioxide with a high degree of stereospecificity. The absolute configuration of this sulfone was established in the following manner. (*R*)-(−)-1,3-Dibromobutane was prepared by hydride reduction of (*S*)-(+)-3-acetoxybutyric acid, dimesylation of the resulting (*S*)-(+)-1,3-butanediol, and treatment of the dimesylate with lithium bromide in hot dioxane. Cyclization of the dibromide with thiourea and base, followed by oxidation of the cyclic sulfide, gave (*S*)-(−)-2-methylthietane 1,1-dioxide. The *S* absolute configuration is demanded by the double displacement incurred in passing from the dimesylate to the cyclic sulfone. Assessment of the magnitude of the stereoselectivity was gained by resolving (with *d*-camphor-10-sulfonic acid) *trans*-2-methyl-3-piperidinothietane 1,1-dioxide followed by carefully controlled Hofmann degradation of its methiodide. Hydrogenation of the (*R*)-(−)-4-methylthiete 1,1-dioxide so produced gave (*R*)-(+)-2-methylthietane 1,1-dioxide of maximum rotation. From these data, the stereospecificity realized in the 1,3-dioxan-2-one to thietane conversion was very high. The overall stereochemical course provides compelling support for the mechanism advanced earlier. The stereochemical interconversions have also demonstrated that both possible antipodes of a 2-substituted thietane can be cleanly prepared from a single enantiomer of a disymmetric 1,3-diol.

In 1958, Searles and Lutz discovered that fusion of equimolar quantities of potassium thiocyanate and the cyclic carbonate ester of a 1,3-diol (a 1,3-dioxan-2-one) resulted in formation of carbon dioxide and the related thietane.[2a] Subsequently, this same group established that the scope of this thietane synthesis is rather wide;[2b] in actuality, the simplicity of the method and ready availability of the starting materials has given this reaction considerable importance as a practical synthesis of this four-membered heterocyclic system.[3] The mechanism which has been advanced in explanation of this transformation is illustrated for the simplest case in Scheme I. The intervention of hydroxy thiocyanates

SCHEME I



(as the alkoxide ions) was thought to take place by analogy to the mechanism by which 1,3-dioxol-2-ones[4] and epoxides[5] are converted to episulfides with thiocyanate ion. Some measure of further support for the scheme was derived from the observation that higher temperatures (~200°) are required for the reaction as the level of steric hindrance at the α-carbon atoms of the 1,3-dioxan-2-one is increased. A direct relationship between the degree of steric hindrance at the α positions and the per cent of oxetane by-product produced was also noted. However, all of the evidence to date has been inferential.

The purpose of this study was twofold: (a) to obtain evidence relating to the mechanism of the title reaction by examining the stereochemical course of the process, and (b) to determine if the synthesis of optically active thietanes could be achieved by this method.

The first consideration was the preparation of an optically active 1,3-dioxan-2-one of known absolute configuration. To this end, commercially available *dl*-β-hydroxybutyric acid was acetylated and partially resolved with quinine. Lithium aluminum hydride reduction of the liberated (*R*)-(−)-3-acetoxybutyric acid (**1**)[6] afforded (*R*)-(−)-1, 3-butanediol (**2**), $[\alpha]^{22}D$ −8.2 ± 0.8° (*c* 5.385, C_2H_5OH).[7] This series of transformations (Scheme II) was completed by conversion of **2** to (*R*)-(−)-4-methyl-1,3-dioxan-2-one (**3**), $[\alpha]^{22}D$ −9.4 ± 0.5° (*c* 10.310, C_2H_5OH). Fusion of **3** with an equimolar quantity of potassium thiocyanate at 170–180° afforded 2-methylthietane (**4**) which was directly oxidized with *m*-chloroperbenzoic acid for the purpose of characterization. The pure 2-methylthietane 1,1-dioxide (**5**) so obtained exhibited $[\alpha]^{21}D$ −5.8 ± 1.7° (*c* 2.410, C_2H_5OH) and gave infrared and nmr spectra which were superimposable upon those of an optically inactive sample (see Experimental Section).

(1) American Chemical Society Petroleum Research Fund Graduate Fellow, 1968–1969; National Science Foundation Graduate Fellow, 1966–1968.

(2) (a) S. Searles, Jr., and E. F. Lutz, *J. Amer. Chem. Soc.*, **80**, 3168 (1958); (b) S. Searles, Jr., H. R. Hays, and E. F. Lutz, *J. Org. Chem.*, **27**, 2828 (1962).

(3) Y. Etienne, R. Soulas, and H. Lumbroso in "The Chemistry of Heterocyclic Compounds," Vol. 19, Part II, A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1964, pp 686, 687.

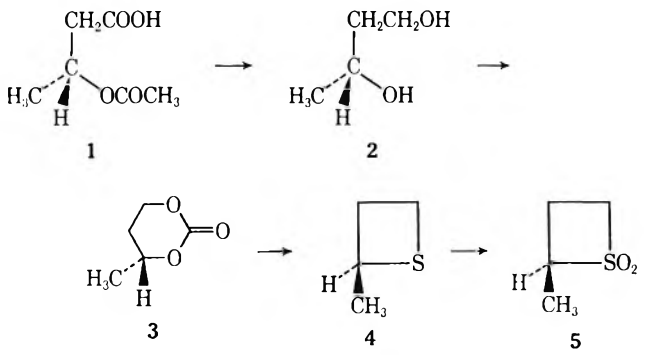
(4) S. Searles, Jr., H. R. Haynes, and E. F. Lutz, *J. Org. Chem.*, **27**, 2832 (1962).

(5) E. E. van Tamelen, *J. Amer. Chem. Soc.*, **73**, 3444 (1951); C. C. Price and P. F. Kirk, *ibid.*, **75**, 2396 (1953).

(6) For the absolute configurational assignment, see (a) K. Serck-Hanssen, *Ark. Kemi*, **8**, 401 (1955); (b) K. Serck-Hanssen, S. Stallberg-Stenhagen, and E. Stenhagen, *ibid.*, **5**, 203 (1953).

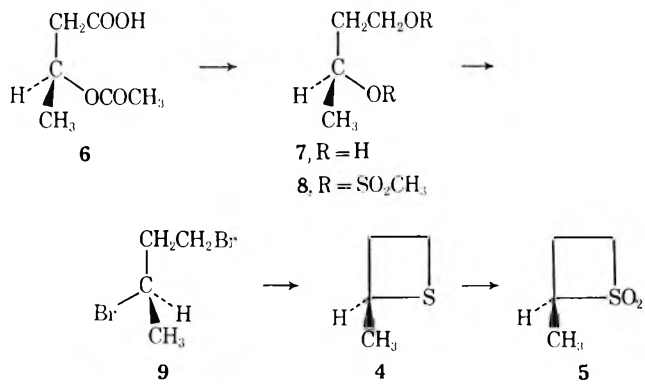
(7) 1,3-Butanediol possessing a maximum rotation of $[\alpha]^{23}D$ +27.3 ± 0.5° (*c* 5, C_2H_5OH) has been shown to be of the (*S*)-(+) configuration.[6a]

SCHEME II



The optical activity of **5** clearly signaled that total racemization was not occurring in the passage from **3** to **4**. To reveal whether net retention or inversion had taken place at C-4 in **3**, determination of the absolute configurations of (+)- and (−)-2-methylthietane 1,1-dioxides was made. For this purpose, partially resolved (*S*)- (+)-3-acetoxybutyric acid (**6**) was reduced by means of lithium aluminum hydride to (*S*)-(+)-1,3-butanediol (**7**), $[\alpha]^{24}D$ +10.1 ± 0.5° (*c* 10.17, $CHCl_3$).[6a,8] Treatment of **7** with methanesulfonyl chloride in pyridine gave dimesylate **8** which was directly exposed to the action of lithium bromide in refluxing dioxane (Scheme III). Cyclization of **9** with thiourea in

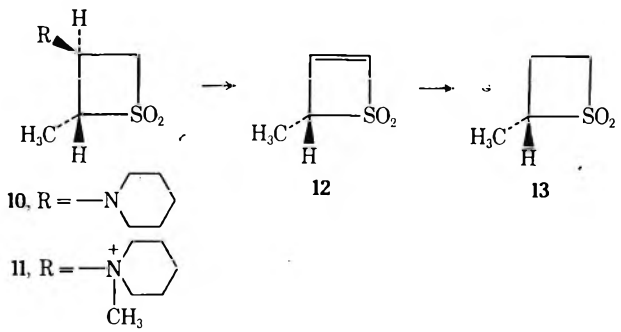
SCHEME III



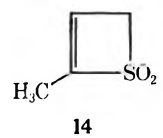
aqueous sodium hydroxide and oxidation of the resulting sulfide afforded 2-methylthietane 1,1-dioxide possessing $[\alpha]^{24}D$ −8.4 ± 0.7° (*c* 5.620, C_2H_5OH).[9] In view of the double SN2 displacement which intervenes in the passage from **8** to the thietane, the asymmetric carbon in the derived sulfone must be of the *S* configuration. Because **5** is likewise levorotatory, it now follows that the chemical change at C-4 in **3** occurs with inversion of configuration.

In the final attack on this mechanistic question, assessment of the magnitude of the stereospecificity realized in the production of **4** from **3** was highly desirable. The synthesis of 2-methylthietane 1,1-dioxide of maximum rotation began with the preparation of *trans*-2-methyl-3-piperidinothietane 1,1-dioxide *d*-camphor-10-sulfonate. Four successive recrystallizations of this salt from absolute ethanol gave a solid of mp 244.5–246° dec, from which pure **10**, $[\alpha]^{22}D$ + 70.0 ± 0.3° (*c* 3.100, C_2H_5OH), was obtained. Additional recrystallizations of the diastereomeric salt from ethanol and acetonitrile failed to increase further its melting point or the optical rotation of free amine **10**. Quaternization of this material gave in essentially quantitative yield the methiodide **11**, $[\alpha]^{21}D$ +21.6 ± 0.2° (*c* 4.829, H_2O) (Scheme IV). Hofman elimination of **11** was achieved

SCHEME IV



readily by means of dry silver oxide in anhydrous tetrahydrofuran to which had been added some calcium sulfate. This modification of the standard Hofmann procedure was devised in order to maximize the yield of 4-methylthiete 1,1-dioxide (**12**). Under the stated conditions, **12** containing no more than 7 ± 1% (nmr analysis) of the more stable but optically inactive 2-methylthiete 1,1-dioxide (**14**), could be routinely prepared.



In contrast, **14** is readily available as the major product from the silver oxide induced Hofmann elimination of *dl*-**11** in water solution. Submission of pure **12**, $[\alpha]^{21.5}D$ −21.2 ± 0.4° (*c* 5.995, $CHCl_3$), to catalytic hydrogenation afforded optically pure **13**, $[\alpha]^{21.5}D$ +21.0 ± 0.2° (*c* 9.740, C_2H_5OH).

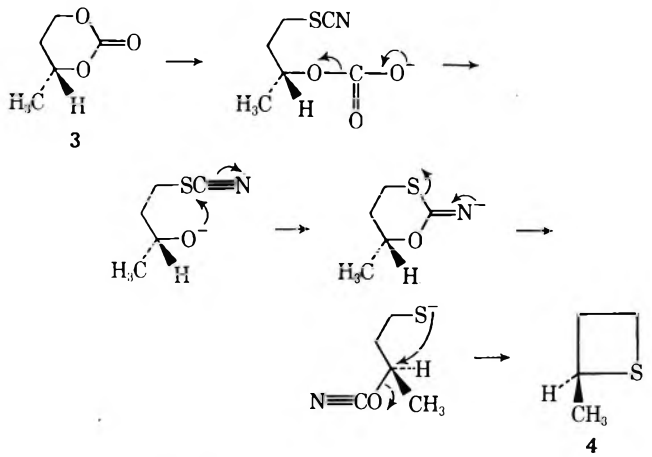
On this basis, the 2-methylthietane 1,1-dioxide obtained from chiral 1,3-dioxan-2-one **3** was approximately 28% optically pure. Since the (*R*)-(−)-1,3-butanediol employed in Scheme II was of 30% optical purity, the stereospecificity realized in this experiment is clearly very high.

The overall stereochemical course of the 1,3-dioxan-2-one to thietane conversion substantiates the previously proposed mechanism (Scheme I) and parallels that found in the analogous reaction of thiocyanate ion with 1,3-dioxol-2-ones to give episulfides.[3b] Thus, the requirement that a Walden inversion at C-4 in **3** necessarily accompany the substitution of oxygen by sulfur can be attributed to the operation of an SN2 process at this site. Because of the unsymmetrical nature of **3**, this inversion of configuration could occur in either step 1 or 5 (Scheme I). It would seem most reasonable from steric considerations that attack by thiocyanate ion at the lesser substituted α carbon, *i.e.*, C-6, would be kinetically preferred. This would imply that the intramolecular displacement of cyanate ion by mercaptide is the principal stereochemical step in the present instance (Scheme V).

(8) R. Lukes, J. Jary, and J. Nemec, *Collect. Czech. Chem. Commun.*, **27**, 735 (1962).

(9) For a preliminary account of this synthesis in a different context, see L. A. Paquette and J. P. Freeman, *J. Amer. Chem. Soc.*, **91**, 7548 (1969).

SCHEME V



Of added significance, the stereochemical interrelationships uncovered in the present study have also demonstrated that a single enantiomer of a dissymmetric 1,3-diol can be cleanly converted into the *R* or *S* antipode of a 2-substituted thietane either by decomposition of the 1,3-dioxan-2-one derivative (single inversion, Scheme II) or cyclization of the derived 1,3-dibromide with thiourea (double inversion, Scheme III). However, for ease in the resolution method and for the yields obtained, the sulfene route (Scheme IV) is superior for synthetic access to chiral thietane derivatives which are needed in further stereochemical studies currently in progress.

Experimental Section

All melting points were determined with a Thomas–Hoover melting point apparatus and are corrected. Nuclear magnetic resonance spectra were taken with Varian Associates A-60 and A-60A spectrometers.

(±)-**3-Acetoxybutyric Acid**.[6b]—(±)-3-Hydroxybutyric acid (50.0 g, 0.485 mol) was stirred into an ice-cooled solution of 68 ml (0.709 mol) of acetic anhydride in 97 ml of pyridine. Stirring was continued until the ice melted and at room temperature for an additional 6 hr. The reaction mixture was stored at 0° for 8 hr and then concentrated by removal of 127 ml of liquid (mostly pyridine) at 35–49° and 15 mm. The residue was cooled, 50 ml of 6 *N* hydrochloric acid was added, and the mixture was extracted four times with ether. Concentration of the combined dried ether extracts and distillation of the residue afforded 36.9 g (52%) of (±)-3-acetoxybutyric acid, bp 102–105° (0.03 mm), n^{28}D 1.4283 [lit.[6b] bp 80–85° (0.25 mm), n^{25}D 1.4270]. The lower boiling fractions contained considerable amounts of crotonic acid. The infrared spectrum of the product exhibited strong infrared absorption at 1730 and 1242 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.28 (sextet, J = 6.4 Hz, H-3), 2.63 (d of d, J = 6.4 Hz, H-2), 2.04 (s, CH_3CO–), and 1.32 (d, J = 6.4 Hz, CH_3–).

(*R*)-(−)- and (*S*)-(+)-**3-Acetoxybutyric Acid** (**1** and **6**).—(±)-3-Acetoxybutyric acid (31.89 g, 0.218 mol) was mixed in ethyl acetate (*ca.* 100 ml) with 70.8 g (0.218 mol) of anhydrous quinine, and the mixture was heated until most of the quinine had dissolved. The quinine residue was removed by filtration through a glass wool plug. The filtrate was reheated to near the boiling point and petroleum ether (bp 60–110°) was added until cloudiness persisted. The solution was again rewarmed to produce homogeneity, seeded, and cooled to room temperature and then to 0°. After 3 days at 0°, the white crystalline salt was filtered and washed twice with ethyl acetate–petroleum ether (1:1). Fractional crystallization of this solid from ethyl acetate–petroleum ether gave 20 g of quinine salt, mp 101.5–104°.

(*S*)-(+)-3-Acetoxybutyric acid (**6**) was recovered quantitatively by treatment of this quinine salt with 5% hydrochloric acid, saturation of the solution with sodium chloride, extraction with ether, and concentration of the combined organic extracts. Molecular distillation at 70° (0.01 mm) gave a colorless oil, $[\alpha]^{24}$D +3.6 ± 0.3° (*c* 10.175, C_2H_5OH) [lit.[6b] $[\alpha]^{23}$D +2.78° (homogeneous, *l* 1)].

(*R*)-(−)-3-Acetoxybutyric acid (**1**) was obtained similarly from the mother liquor residues from several resolutions by treatment with 5% hydrochloric acid and extraction in the above manner. The concentrated oil was distilled at 95–99° (0.05 mm) and there was obtained 25.4 g of **1**. This acid was reduced directly to **2** for measurement of optical rotation.

(*R*)-(−)-**1,3-Butanediol** (**2**).—To a stirred slurry of 19.8 g (0.522 mol) of lithium aluminum hydride in 150 ml of anhydrous tetrahydrofuran was added dropwise a solution of 25.4 g (0.174 mol) of **1** in 75 ml of the same solvent at such a rate that gentle reflux was maintained. The reaction mixture was stirred at reflux for 9 hr and cooled, and the hydride was decomposed by cautiously adding 19.8 ml of water, 19.8 ml of 12% sodium hydroxide solution, and 60 ml of water. The solid aluminates were removed by filtration, the filter pad was carefully washed with tetrahydrofuran, and the combined filtrates were dried and evaporated. Distillation of the residue gave 14.13 g (90%) of **2**, bp 64.5–74° (0.03 mm), $[\alpha]^{22}$D −8.2 ± 0.8° (*c* 5.385, C_2H_5OH),[7] with a satisfactory infrared spectrum.

(*S*)-(+)-**1,3-Butanediol** (**7**) was prepared as above from 4.01 g (0.0274 mol) of **6** and 3.12 g (0.082 mol) of hydride. Work-up and distillation led to the isolation of 1.38 g (56%) of **7**, bp 52–56° (0.01 mm), $[\alpha]^{24}$D + 13.0 ± 0.6° (*c* 10.01, $CHCl_3$),[6a,7] with an infrared spectrum identical with that of racemic diol. An additional 1.09 g of diol was obtained from the pot residue by molecular distillation. The total yield was quantitative.

(*R*)-(−)-**4-Methyl-1,3-dioxan-2-one** (**3**).—Into a three-necked flask equipped with a mechanical stirrer, addition funnel, and Claisen head was added 14.13 g (0.157 mol) of **2** and a catalytic amount of sodium ethoxide. When the external oil-bath temperature reached 90°, 20.40 g (0.173 mol) of diethyl carbonate was added dropwise. Heating was continued along with the carbonate addition and continued until the theoretical amount of ethanol had been distilled. Ether (50 ml) was added to the cooled residue and this solution was extracted twice with water. The aqueous extracts were saturated with sodium chloride and reextracted with ether. The combined organic layers were dried, concentrated, and distilled to give 2.14 g of **3**, bp 62–79° (0.04 mm) [lit.[10] bp 100–110° (0.8 mm)], $[\alpha]^{22}$D −9.4 ± 0.5° (*c* 10.310, C_2H_5OH). Vpc analysis indicated this sample to be of *ca.* 85% purity.

(*S*)-(−)-**2-Methylthietane 1,1-Dioxide** (**5**) **from 3**.—Using the procedure of Searles, Hays, and Lutz,[3] 2.68 g (0.0276 mol) of potassium thiocyanate and 2.14 g of **3** (85% purity) were allowed to react at 170–180°. The total yield of thietane–oxetane mixture was 0.83 g. This material was oxidized directly with 1.82 g of *m*-chloroperbenzoic acid in 17 ml of methylene chloride for 20 min at −10° and for 10 hr at room temperature. Purification of the mixture by molecular distillation at 55–60° (0.03 mm) gave 70 mg (4%) of **5** as a colorless liquid, $[\alpha]^{21}$D −5.8 ± 1.7° (*c* 2.410, C_2H_5OH). The infrared and nmr spectrum of this material were superimposable on those of an analytical sample of (±)-2-methylthietane 1,1-dioxide (see below).

(±)-**1,3-Butanediol Dimethanesulfonate**.—Neat methanesulfonyl chloride (4.65 g, 0.0406 mol) was added dropwise to a stirred solution of 1.83 g (0.0203 mol) of (±)-1,3-butanediol in 9 ml of pyridine at −10 to −5°. The reaction mixture was stored at 0° for 20 hr, poured onto twice its volume of crushed ice, and extracted with methylene chloride. To this organic solution was added ice-cold 5% hydrochloric acid solution with shaking until the aqueous layer remained acidic. The organic layer was separated, dried, and evaporated to give 4.49 g of a yellow oil. Absolute ethanol (*ca.* 2.5 ml) was added followed by the dropwise addition of chloroform until the mixture became homogeneous. After a few minutes, crystallization began. The flask was cooled in ice and the solid was filtered. After rinsing the solid with cold absolute ethanol and drying, there was obtained 3.60 g (72%) of white crystalline dimesylate: mp 41.5–43° (lit.[11] mp 40–41°); $\nu_{max}^{CHCl_3}$ 1360 and 1175 cm^{-1} (–SO_2–); $\delta_{TMS}^{CHCl_3}$ 4.87 (sextet, J = 6.2 Hz, H-3), 4.28 (t, J = 6.0 Hz, H-1), 3.05 (s, 6, CH_3SO_2–), 2.07 (q, J = ~6.1 Hz, H-2), and 1.47 (d, J = 6.2 Hz, CH_3–).

(10) S. Searles, Jr., D. G. Hummel, S. Nukina, and P. E. Throckmorton, *J. Amer. Chem. Soc.*, **82**, 2928 (1960).

(11) A. G. Kostsova and L. B. Leout'eva, *J. Gen. Chem. USSR*, **30**, 3508 (1960).

(*S*)-**1,3-Butanediol dimethanesulfonate** (**8**) was prepared in analogous fashion from a 3.03-g (0.0336 mol) sample of **7**, $[\alpha]^{22}D$ +10.1 ± 95° (*c* 10.170, $CHCl_3$), and 7.70 g (0.0672 mol) of methanesulfonyl chloride in 27 ml of pyridine. There was obtained 7.14 g (86%) of **8** with spectral characteristics identical with those of the racemic material.

(*R*)-(−)-**1,3-Dibromobutane** (**9**).—To a slurry of 12.6 g (0.145 mol) of lithium bromide (dried 2 days *in vacuo* at 80° over phosphorus pentoxide) in 50 ml of dry dioxane was added the 7.14 g (0.0289 mol) of **8** prepared above, and the heterogeneous mixture was allowed to stir at reflux for 5 hr. After cooling and standing at room temperature overnight, the mixture was poured into 150 ml of water and extracted with five portions of pentane. The combined pentane layers were washed four times with water and the combined aqueous layers reextracted once with pentane. The combined pentane extracts were shaken with brine, dried, and evaporated to give 5.25 g of **9** of *ca.* 92% purity by vpc analysis (77%), $[\alpha]^{25}D$ −29.9 ± 0.5° (*c* 17.780, $CHCl_3$). The spectral properties of **9** were identical with those of the *dl* mixture.

(*S*)-(−)-**2-Methylthietane 1,1-Dioxide** (**5**) **from 9.**—The 5.02-g sample of **9** (92% purity, 0.0214 mol), prepared above, was added to a prewarmed (60°) solution of 1.95 g (0.0257 mol) of thiourea and 3.09 g (0.0771 mol) of sodium hydroxide in 25 ml of water. The mixture was heated at reflux for 1.2 hr, 10 ml more water was added, and the volatile organic components were steam distilled. The steam distillate was extracted with four small portions of methylene chloride and the combined extracts were dried; the thietane was oxidized directly as above with 8.44 g of 87.5% *m*-chloroperbenzoic acid (0.0428 mol) in 55 ml of methylene chloride at −10°. Upon molecular distillation of the residual crude product at 55–63° (0.03 mm), there was obtained 0.54 g (21%) of **5**, $[\alpha]^{24}D$ −8.3 ± 0.4° (*c* 10.615, C_2H_5OH), whose spectra perfectly matched those of analytically pure (±)-2-methylthietane 1,1-dioxide (see below).

(±)-*trans*-**2-Methyl-3-piperidinothietane 1,1-Dioxide** [(±)-**10**].—N-Propenylpiperidine[12] (7.40 g, 0.059 mol) and 5.97 g (0.059 mol) of triethylamine were dissolved in 250 ml of ether and the solution was cooled to −5° with stirring under nitrogen. Methanesulfonyl chloride (6.75 g, 0.059 mol) in 50 ml of ether was added at such a rate that the temperature remained below −5°. Stirring was continued at room temperature for 7 hr, the triethylammonium hydrochloride was filtered off through Celite, and the filtrate was evaporated; 11.57 g of orange oil remained.

This crude amine was redissolved in ether and precipitated as the hydrochloride salt by the addition of ethereal hydrogen chloride: yield, 12.06 g (85%). Recrystallization from ethanol and acetonitrile gave colorless crystals, mp 215–216° dec (lit.[13] mp 210–211°). Liberation of the free base with aqueous potassium carbonate gave the sulfone as a white crystalline solid: mp 41–43° (lit.[13] mp 17–23°); $\nu_{max}^{CCl_4}$ 2950, 1440, 1320, 1198, and 1135 cm^{-1}; $\delta_{TMS}^{CCl_4}$ 4.22 (q, *J* = 7.0 Hz, H-2), 3.98 (d, *J* = 3 Hz, one H-4), 3.83 (d, *J* = 1.5 Hz, other H-4), 2.1–2.8 (m, 5, H-3 and α-piperidino), 1.4–1.7 (m, 6, other methylenes), and 1.45 (d, *J* = 7.0 Hz, $-CH_3$).

Resolution of *trans*-**2-Methyl-3-piperidinothietane 1,1-Dioxide.**—A 15.00-g (73.8 mmol) sample of amino sulfone (±)-**10** was dissolved in 150 ml of acetone and mixed with a solution of 17.15 g (73.8 mmol) of *d*-camphor-10-sulfonic acid in 130 ml of the same solvent. After 5 hr the precipitated solid was filtered and dried, 27.72 g (86%), mp 231.5–233° dec. Four successive recrystallizations of this salt from absolute ethanol produced crystals of mp 244.5–246° dec. Liberation of the free base with aqueous potassium carbonate solution afforded pure **10**, mp 54.5–56.0°, $[\alpha]^{22}D$ +70.0 ± 0.3° (*c* 3.100, C_2H_5OH). The melting point of the salt and the optical rotation of the base failed to increase after further recrystallizations of the former substance from both ethanol and acetonitrile.

Methiodide of (±)-*trans*-**2-Methyl-3-piperidinothietane 1,1-Dioxide** [(±)-**11**].—To 3.00 g (14.8 mmol) of amino sulfone (±)-**10** dissolved in 15 ml of reagent grade acetone was added 4.20 g (29.6 mmol) of methyl iodide, and the solution was heated (55°) for 6 hr with stirring. An additional 4.20 g of methyl iodide was then added and heating was continued for an additional 12 hr. Cooling of the mixture to 0° and filtration gave 5.00 g (98%) of white, powdery solid, mp 163–169° dec. Recrystallization of this material from absolute ethanol gave pure methiodide, mp 169–175° dec.

Anal. Calcd for $C_{10}H_{20}INO_2S$: C, 34.79; H, 5.84; S, 9.29. Found: C, 34.90; H, 5.88; S, 9.32.

The (+)-methiodide **11** was prepared analogously from 3.10 g (15.25 mmol) of **10** to give 5.17 g (98%) of flat, white needles, mp 196–197.5° dec, $[\alpha]^{21}D$ +21.6 ± 0.2° (c 4.829, H_2O).

(±)-**4-Methylthietane 1,1-Dioxide** [(±)-**12**].—A 2% excess (8.87 mmol) of silver oxide was prepared by treating 3.02 g (17.75 mmol) of silver nitrate with 0.71 g (17.75 mmol) of sodium hydroxide in water solution. The resulting solid was repeatedly washed with water until the washings were neutral. The silver oxide was then washed with absolute ethanol, acetone, and ether; the last traces of solvent were removed *in vacuo*.

The powdery solid was shaken in anhydrous diethyl ether (25 ml) for 15 min with 3.00 g (8.70 mmol) of 2-methyl-3-piperidinothietane 1,1-dioxide methiodide. The initially heterogeneous black and white mixture of solids was soon replaced by a grayish, flocculent precipitate. The ether was evaporated and the residue was heated in a rotary evaporator at 80° to decompose the quaternary hydroxide and to remove methylpiperidine byproduct. The residue was extracted with ether, dried, and evaporated. The yellowish oil so obtained exhibited an nmr spectrum which denoted a product mixture of 94 ± 1% of 4-methylthietane 1,1-dioxide and 6 ± 1% of the 2-methyl isomer **14**: yield 0.55 g (53%); $n^{24.5}D$ 1.4813; bp 67–72° (0.05 mm); $\nu_{max}^{CCl_4}$ 1320, 1300, 1188, and 1145 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 7.10 (dd, $J_{2,3}$ = 4.0 Hz, $J_{3,4}$ = 1.5 Hz, H-3), 6.71 (d, *J* = 4.0 Hz, H-2), 4.85 (qd, *J* = 1.5 and 6.9 Hz, H-4), and 1.51 (d, *J* = 6.9 Hz, $-CH_3$).

Anal. Calcd for $C_4H_6O_2S$: C, 40.66; H, 5.12; S, 27.14. Found: C, 40.72; H, 5.23; S, 26.75.

(*R*)-(−)-**4-Methylthietane 1,1-Dioxide** (**12**).—Silver oxide (50 mmol) was prepared as above from 4.00 g of sodium hydroxide and 17.00 g of silver nitrate. A slurry of the silver oxide, 13.3 g of fine mesh anhydrous calcium sulfate, 16.88 g of **11**, and 50 ml of dry tetrahydrofuran was heated at reflux for 2 hr. After cooling, the solvent was removed on a rotary evaporator and the solids were heated on a steam bath *in vacuo* for 1 hr. The resulting mass was extracted three times with ether, and the combined organic layers were filtered and evaporated to give 4.23 g of crude product. Sublimation of this material at 55° and 0.05 mm gave 3.91 g (68%) of **12** as a white solid, mp 59–61°, $[\alpha]^{25}D$ −20.4 ± 0.2° (*c* 4.802, $CHCl_3$). Recrystallization from petroleum ether–chloroform afforded thick cubic crystals, mp 59.5–16.5°, $[\alpha]^{21.5}D$ −21.2 ± 0.4° (*c* 5.995, $CHCl_3$). Infrared and nmr analyses revealed no trace of the 2-methyl isomer **14**.

2-Methylthietane 1,1-Dioxide (**14**).[14]—To a slurry of 300 g (1.43 mol) of silver oxide in 200 ml of water was added a solution of 264.8 g (0.72 mol) of (±)-*trans*-2-methyl-3-piperidinothietane 1,1-dioxide methiodide in 700 ml of water. The mixture was stirred for 15 min and filtered. The filtrate was heated on a steam bath for 30 min and then evaporated to three-fourths its original volume *in vacuo*. After cooling, the remaining solution was extracted continuously with ether overnight. The ether solution was dried and evaporated to give 51.4 g (64%) of an oil which by nmr analysis was found to be a mixture of **14** (67%) and 4-methylthietane 1,1-dioxide (33%). After standing at −16° for 2 days, this material partially solidified. The solid was separated by filtration, washed with cold ether, and recrystallized from ether to afford 20.7 g (25.8%) of **14**: mp 51.5–52.5°; $\nu_{max}^{CHCl_3}$ 1310 and 1135 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 6.77 (q, 1, *J* = 1.8 Hz, H-2), 4.38 (m, 2, H-4), and 2.03 (m, 3, $-CH_3$).

Anal. Calcd for $C_4H_6O_2S$: C, 40.67; H, 5.08; S, 27.15. Found: C, 40.74; H, 5.12; S, 26.76.

(±)-**2-Methylthietane 1,1-Dioxide.**—A 68:32 mixture of 4-methyl- and 2-methylthietane 1,1-dioxides (1.7 g) dissolved in 50 ml of absolute methanol was shaken on a Parr apparatus for 5.5 hr under 50 psig of hydrogen in the presence of 0.2 g of 10% palladium on carbon. After filtration, the solvent was evaporated and the residue was molecularly distilled at 39° and 0.05 mm to give 1.03 g (61%) of mobile, water-white liquid, $n^{24.5}D$ 1.4680, which was homogeneous on vpc analysis and thin layer chromatography: $\nu_{max}^{CCl_4}$ 1332, 1217, 1163, and 1135 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 3.6–4.8 (m, 3, α-sulfonyl), 1.6–2.8 (m, 2, H-3), and 1.45 (d, *J* = 7.2 Hz, $-CH_3$).

Anal. Calcd for $C_4H_8O_2S$: C, 39.98; H, 6.71; S, 26.68. Found: C, 39.96; H, 6.70; S, 26.48.

(12) C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1936); G. Opitz, H. Hellman, and H. W. Schubert, *Justus Liebigs Ann. Chem.*, **623**, 112 (1959).

(13) G. Opitz, H. Schempp, and H. Adolph, *ibid.*, **684**, 92 (1965).

(14) The authors thank Mr. R. W. Houser for this preparation.

(*R*)-(+)-2-Methylthietane 1,1-dioxide (13) was prepared similarly from 12, 85% yield, $n^{26.5}D$ 1.4689; $[\alpha]^{25}D$ +21.0 ± 0.2° (*c* 9.740, C_2H_5OH).

Registry No.—(±)-3-Acetoxybutyric acid, 24621-58-7; (±)-1,3-butanediol dimethanesulfonate, 24605-74-1; (±)-2-methylthietane 1,1-dioxide, 24609-83-4; **2**, 6290-03-5; **5**, 24621-60-1; **7**, 24621-61-2; **9**, 24621-62-3; (+)-**10**, 24621-63-4; (±)-**10**, 24621-64-5; (+)-**11**, 24621-65-6; (±)-**11**, 24621-66-7; (−)-**12**, 24621-67-8; (±)-**12**, 24605-75-2; **13**, 24605-76-3; **14**, 24621-57-6;

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Chemistry of Isocyanurates. I. Synthesis of Disubstituted Isocyanuric Acids from the Reaction of Alkali Metal Cyanates with Organic Isocyanates[1]

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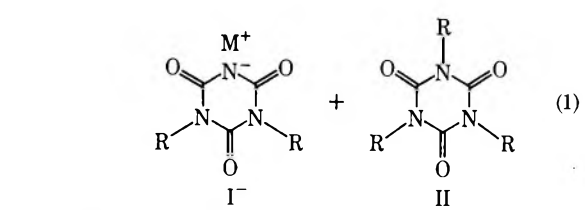
Cyanate ion, unlike other anions, reacts with organic isocyanates to give salts of disubstituted isocyanurates (I^-) which are readily converted to the corresponding acid (I). Trimerization of the isocyanate to the trisubstituted isocyanurate (II) is a competing reaction which can seriously detract from the yield of I. The selectivity to I^- was found to be sensitive to the concentration of cyanate ion, temperature, solvent type, isocyanate structure, concentration of isocyanate, and ionic strength of medium. The mechanistic implication of these parameters on selectivity is discussed.

In the course of a recent investigation into the mechanism by which cyanate ion (NCO^-) reacts with organic halides, a new and convenient synthesis of disubstituted isocyanuric acids (I) evolved.[3] Thus, it was shown that alkali metal cyanates (MOCN) in dipolar aprotic media react with organic isocyanates (RNCO) to give the salt (I^-) of the corresponding disubstituted isocyanuric acid (eq 1). The singular



(1)

by-product is the trisubstituted isocyanurate (II), a product anticipated in view of the ease with which isocyanates undergo base-catalyzed trimerization.[4,5]

Salt I^- is readily separated from trimer II by extracting the solvent-free reaction mixture with water (II is insoluble); subsequent acidification of the aqueous salt solution with hydrochloric acid precipitates the acid I. The present paper deals with the scope of the reaction of eq 1 in terms of the parameters governing the selectivity to I^-.

Results

Although the preparation of disubstituted isocyanurates from RNCO and MOCN is quite general, the selectivity to I^- is dependent on a number of reaction variables. The following parameters were shown to have a marked influence on the competition between trimerization and salt formation.

Isocyanate Structure.—As shown in Table I, a large number of structurally divergent isocyanates are applicable in this synthesis. It is clear that the nature of R has a profound influence on selectivity. The order in decreasing selectivity is aryl > benzyl, allyl ≫ alkyl. This is the same order of reactivity reported for the reaction of RNCO with amines to form ureas;[6] the most electrophilic isocyanate gives the highest selectivity.

Concentration of RNCO.—Selectivity varies inversely with the initial concentration of RNCO. As shown in Table II, a tenfold increase in the initial isocyanate concentration reduced the selectivity by nearly 50%.

Solvent.—A modest study was undertaken to determine the effect of solvent on selectivity. As shown in Table III, the dipolar solvents, such as dimethylformamide (DMF), afford the highest selectivities in addition to rate acceleration. These findings probably reflect changes in KNCO solubility (*vide infra*) rather than changes in dielectric constant or solvent polarity. DMF was employed throughout this study because of its availability and ease of purification.

Temperature.—At moderate temperatures, the selectivity gradually increases with temperature reaching a plateau at 75°. Unfortunately, the temperature effect is complicated by the fact that increasing the reaction temperature also increases the solubility of the metal cyanate (see Table IV).

Concentration of NCO^-.—Owing to the limited solubilities of NaOCN and KOCN (the only readily available alkali metal cyanates), the NCO^- concentra-

(1) Presented in part at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., March 1968.

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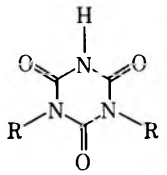
TABLE I

DISUBSTITUTED ISOCYANURIC ACIDS (I) FROM THE REACTION OF NCOR WITH KOCN IN DMF (1 HR AT 75°)[a]



I

R	Registry no.	Selectivity, %[b]	Crude yield, %[c]	Mp, °C (solvent[d])
C_6H_5	20931-62-8	93	91	265-266[e] (E-W)
o-$CH_3C_6H_4$	24807-22-5	86	76	241-242 (E)
m-$CH_3C_6H_4$	24807-23-6	84	76	200-202 (B-H)
p-$CH_3C_6H_4$	24807-24-7	93	84	255-256 (E)
m-ClC_6H_4	24807-25-8	95	92	198-200 (E-B)
p-ClC_6H_4	24807-26-9	82	76	259-260 (T)
p-$CH_3OC_6H_4$[f]	24807-27-0	58	48	220-223 (E)
o-$NO_2C_6H_4$	24807-28-1	89	75	300-301 (E-W)
$C_2H_5OCOCH_2$	24807-29-2	59	56	149-151 (D-W)
CH_2=$CHCH_2$	6294-79-7	64	49	147-148[g] (B)
$C_6H_5CH_2$	21742-97-2	59	50	179-180 (E)
CH_3[h]	6726-48-3	42	26	222-223[i] (W)
n-C_4H_9[h]	24807-33-8	33	20	89-90[j] (H)

[a] Satisfactory analytical values (±0.30%) for C, H, and N were reported for all compounds. [b] Per cent of reacted RNCO converted to I. [c] Mole per cent RNCO converted to I. [d] Recrystallization solvent: B = benzene, D = dioxane, E = ethanol, H = hexane, T = toluene, W = water. [e] A. Hofmann, *Ber.*, **18**, 3217 (1885). [f] Difficult to remove water from crude product. [g] H. Priebe, B. Falk, and K. Deutsch, *Plaste Kaut.*, **13** (4), 223 (1966). [h] Carried out for 24 hr at 100°. [i] A. Hofmann, *Ber.*, **14**, 2728 (1881). [j] British Patent 928,637 (1963) to Olin Mathieson Chemical Corp.

TABLE II

EFFECT OF ISOCYANATE CONCENTRATION ON SELECTIVITY FOR THE REACTION OF PHENYL ISOCYANATE WITH KOCN[a]

[PhNCO]$_0$, mol/l.	Selectivity to diphenyl isocyanurate, %	Conversion of PhNCO, %[b]
2.00	56	96
1.00	72	85
0.20	98	64

[a] Carried out in DMF at 75° for 1 hr. [b] Per cent of PhNCO reacted.

TABLE III

EFFECT OF SOLVENT ON SELECTIVITY FOR THE REACTION OF PHENYL ISOCYANATE WITH KOCN[a]

Solvent	Selectivity to diphenyl isocyanurate, %	Conversion of PhNCO, %
Dimethylformamide	82	95
Dimethyl sulfoxide	84	89
Acetonitrile	19	82
Acetone	0	20

[a] Carried out at 35° for 1 hr.

tion is essentially constant throughout the reaction. From a practical point, the low solubilities of NaOCN and KOCN in dipolar aprotic solvents necessitate an indirect method be used to vary the concentration of NCO^- to determine its effect on selectivity. In view of the solubility differences of the alkali metal cyanates, NaOCN, KOCN, and LiOCN, it appeared that a means was available for varying NCO^- concentration. As shown in Table V, an increase in NCO^-

TABLE IV

EFFECT OF TEMPERATURE ON SELECTIVITY FOR THE REACTION OF PHENYL ISOCYANATE WITH NaOCN[a]

Temp, °C	Selectivity to diphenyl isocyanurate, %	Conversion of PhNCO, %	[NaOCN] × 10^3, mol/l.
6	52	85	
35	61	91	5.51
75	83	92	
100	81	89	7.26

[a] Carried out in DMF for 1 hr.

TABLE V

EFFECT OF CYANATE ION CONCENTRATION ON SELECTIVITY FOR THE REACTION OF PHENYL ISOCYANATE WITH MOCN[a]

M	MOCN × 10^3, mol/l.[b]	Selectivity to diphenyl isocyanurate, %	Conversion of PhNCO, %
Na	5.51	61	91
K	21.2	82	95
Li	800	79	91

[a] Carried out in DMF at 35° for 1 hr. [b] Determined by the method of F. C. Trusell, P. A. Argabright, and W. F. McKenzie, *Anal. Chem.*, **39**, 1025 (1967).

TABLE VI

EFFECT OF ADDED ELECTROLYTES ON SELECTIVITY FOR THE REACTION OF PHENYL ISOCYANATE WITH NaOCN[a]

Electrolyte	Concn, mol/l.	Selectivity to diphenyl isocyanurate, %	Conversion of PhNCO, %
None		61	91
$LiClO_4$	0.25	41	82
KI	0.25	39	89
$LiClO_4$	0.50	8	70

[a] Carried out in DMF at 35° for 1 hr.

by a factor of 4 leads to a 33% increase in selectivity. Surprisingly enough, when the concentration was increased by an additional factor of 40, the selectivity failed to increase. One other change was made in the system when the NCO^- concentration was dramatically increased in going from KOCN to LiOCN: the ionic strength of the medium was also raised.

Ionic Strength.—The possibility that an adverse ionic strength effect was responsible for the absence of a selectivity increase in passing from KOCN to the very soluble LiOCN was tested. Thus, phenyl isocyanate was allowed to react with NaOCN in the presence of $LiClO_4$ (an inert electrolyte) at different concentrations, and selectivities were compared with those in the absence of added electrolyte. As summarized in Table VI, the ionic strength of the medium has a marked effect on selectivity. For example, when the ionic strength of the medium is adjusted with $LiClO_4$ to coincide with that when LiOCN is employed, the selectivity drops from 61 to 8%. The fact that KI had essentially the same effect as $LiClO_4$ on selectivity discounts the possibility of a specific cation (Li^+) effect.

In the absence of an adverse ionic strength effect, the LiOCN experiment of Table V would have resulted in a selectivity near 100%.

A general reaction of organic isocyanates is their base-catalyzed trimerization to 1,3,5-trisubstituted isocyanurates, II.[5] Basic salts (*e.g.*, sodium acetate) and tertiary amines are particularly effective catalysts.

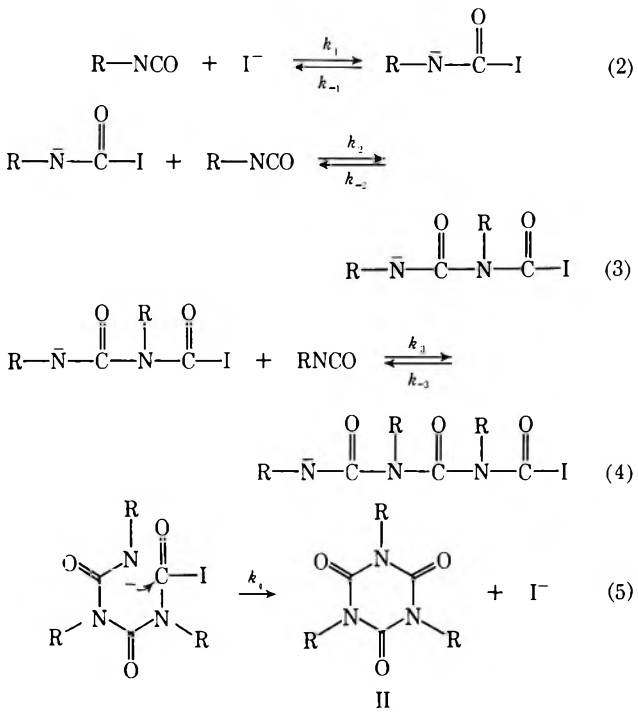
In the reaction of RNCO with MOCN, then, there

are several candidates for the active catalyst for the concomitant trimerization of RNCO to II. However, the most probable catalysts, from the standpoint of concentration, are NCO^- and the product, I^-. Of the two, the latter appears to be the more likely catalyst for the following reasons: (1) I^-, for example potassium diphenyl isocyanurate, is an effective trimerization catalyst at temperatures as low as 25°, and (2) the concentration of I^-, as derived from NaOCN or KOCN, exceeds by nearly an order of magnitude the concentration of NCO^- (after 1–4% reaction). Again, the low concentration of NCO^- is a consequence of the limited solubility of NaOCN (5×10^{-3} *M*) and KOCN (2.2×10^{-2} *M*) in DMF; on the other hand, the salts of disubstituted isocyanuric acids are extremely soluble in DMF.

From the immediate foregoing, it becomes apparent that the reaction of RNCO with NCO^- is quite unique in that the desired product, I^- induces the undesired trimerization of RNCO, thereby detracting from the selectivity to the product, I^-.

Discussion

Selectivity.—In accordance with the mechanism proposed by Shashoua *et al.*,[7] the I^- catalyzed trimerization of RNCO may be considered a series of isoenergetic addition reactions (eq 2–4) terminated by displacement of catalyst (eq 5).

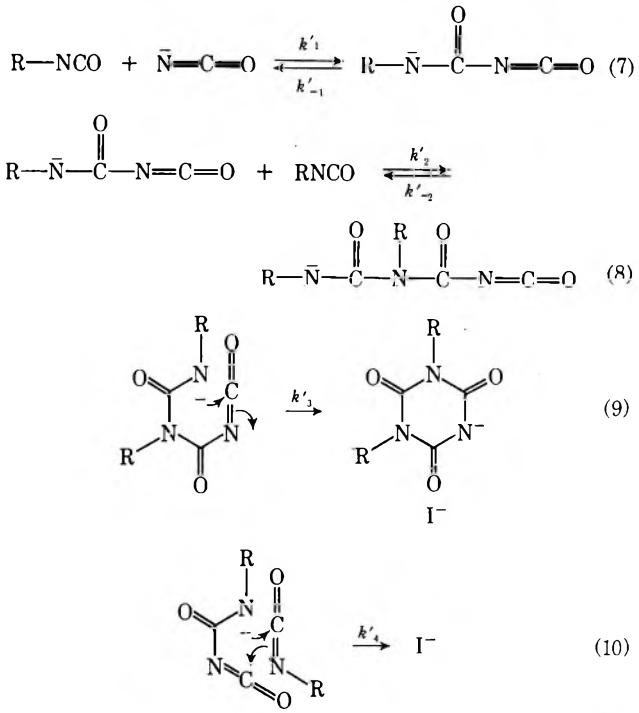


If step 4 or 5 is rate controlling, the rate expression for the formation of II is

$$\frac{d[II]}{dt} = k_T[I^-][RNCO]^3 \qquad (6)$$

if $k_{-1} \gg k_2$, $k_{-2} \gg k_3$, and $k_{-3} \gg k_4$, where k_T is the overall rate constant for trimerization.

When I^- is replaced by NCO^-, other paths are made available for one or more of the reaction intermediates. As illustrated in the following reaction sequence (eq 7–10), either intramolecular ring closure (eq 9) or a quasi Diels–Alder reaction (eq 10) can



account for the formation of I^-. At present, a choice cannot be made between the two steps.

If step 9 or 10 is rate controlling, the overall rate expression for the formation of I^- is

$$\frac{d[I^-]}{dt} = k_S[NCO^-][RNCO]^2 \qquad (11)$$

if $k'_{-1} \gg k'_2$, and $k'_{-2} \gg k'_3$, or $k'_{-1} \gg k'_4$ where k_S is the overall rate constant for salt formation.

It follows from eq 6 and 11 that the fraction of RNCO converted to I^- (*i.e.*, the selectivity to I^-) may be defined by the general expression given in eq 13.

$$\frac{\frac{d[I^-]}{dt}}{\frac{d[I^-]}{dt} + \frac{d[II]}{dt}} = \frac{k_S[NCO^-][RNCO]^2}{k_S[NCO^-][RNCO]^2 + k_T[I^-][RNCO]^3} \qquad (12)$$

or

$$\text{selectivity} = \frac{k_S[NCO^-]}{k_S[NCO^-] + k_T[I^-][RNCO]} \qquad (13)$$

The kinetic expression (eq 13) for selectivity is consistent with the observation that the selectivity is an inverse function of the initial RNCO concentration (Table II). For synthetic purposes, the technique used to obtain maximum selectivities is dropwise addition of the RNCO to the MOCN–DMF slurry.

The observation that the selectivity increases with increasing NCO^- concentration (in spite of an adverse ionic strength effect) further supports eq 13.

The relative influence of ionic strength on the rates of formation of I^- and II (as reflected by the selectivity) can be rationalized in terms of the relative changes in charge dispersal between reactants and transition state for the primary steps (eq 2 and 7) for both processes. It has been demonstrated by Ingold and coworkers[8] that increasing the ionic strength of the

(7) V. Shashoua, W. Sweeny, and R. Tietz, *J. Amer. Chem. Soc.*, **82**, 867 (1960).

(8) For a good review of the subject, see C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 361.

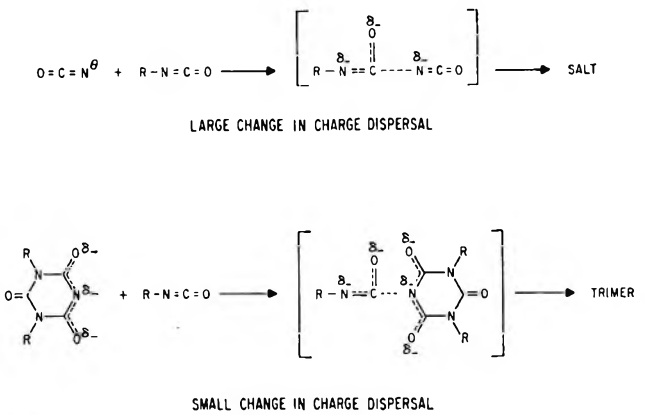


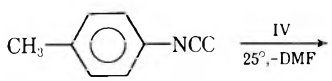
Figure 1.—Comparison of reactant with transition state for salt formation and trimerization.

medium for a reaction in which the charge is more diffuse in the transition state than in the reactants will result in rate retardation.

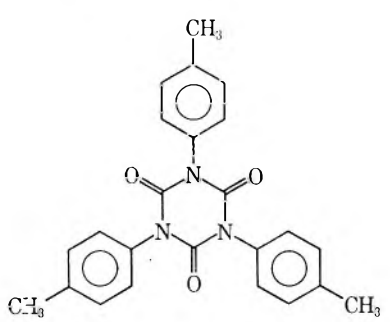
As shown in Figure 1, the initial steps for both the formation of I^- and II involve an increase in charge dispersal on passing from reactants to transition state. However, the increase in charge dispersal for I^- formation is greater than that for the formation of II owing to the greater charge delocalization in ground state I^- than NCO^-. Thus, increasing the ionic strength of the medium suppresses the overall rate of I^- formation more than the formation of II resulting in a decrease in the selectivity to I^-.

This concept is consistent with the effect of isocyanate structure on selectivity (Table I). That is, electron-withdrawing groups are associated with high selectivities. Referring again to the transition states in Figure 1, it is apparent that negative charge is more localized on the nitrogen in the transition state to I^- than in the case of II. Therefore, electron-withdrawing groups (*e.g.*, aryl and, to a lesser extent, benzyl and allyl) should play a bigger role in charge delocalization in the transition state to product, I^-, than in the transition state leading to trimer, II.

Trimerization.—The I^- induced trimerization of RNCO is a straightforward process, not involving ring opening of I^-. This was demonstrated by the following experiment. When 2 equiv of *p*-tolyl isocyanate (III) and 1 equiv of potassium diphenyl isocyanurate (IV) were contacted for 18 hr at 25° in DMF, the only product isolated was tri-*p*-tolyl isocyanurate (V), as shown in eq 14.



III



V

(14)

At least 90% of the starting salt, IV, was recovered.

If the catalyst, IV, underwent ring opening and retrogression, the reaction product would consist of a mixture of cotrimers and disubstituted isocyanurate salts in addition to IV and V.

Experimental Section

Materials.—DMF was purified by drying over CaH_2 followed by distillation at reduced pressure through a packed column. A center cut was used for all experiments. Reagent grade isocyanates were used as received from the manufacturer; technical grade isocyanates were purified by distillation. Benzyl isocyanate was prepared by reacting benzylamine hydrochloride with phosgene in refluxing xylene. After removal of the solvent, the product, bp 110–111° at 40 mm (lit.[9] bp 104–110° at 31–36 mm), was collected. Potassium cyanate (Matheson Coleman and Bell) and sodium cyanate (Fairmount Chemical Co.) were vacuum dried at 60° and stored in desiccators. Lithium cyanate was prepared according to the method of ter Horst.[10] Reagent grade lithium perchlorate (G. Frederick Smith Chemical Co.) and potassium iodide (Mallinckrodt) were used as received.

Infrared spectra were recorded on a Perkin-Elmer Model 521 spectrophotometer using KBr disks. Nuclear magnetic resonance spectra were run on a Varian A-60 spectrometer in hexadeuteriodimethyl sulfoxide solution using TMS as an internal standard. The ir and nmr spectra of the compounds in Table I were consistent with the assigned structures. The melting points reported are uncorrected. Elemental analyses were performed by Huffman Laboratories, Inc., Wheatridge, Colo.

Diphenyl Isocyanurate.—The procedure for preparing diphenyl isocyanurate is typical of that used for treating the aromatic isocyanates, benzyl isocyanate, and allyl isocyanate with metal cyanates.

A slurry of 13.0 g (0.16 mol) of KOCN and 200 ml of DMF was heated to 75° in a nitrogen atmosphere. A solution of 35.7 g (0.30 mol) of phenyl isocyanate in 100 ml of DMF was added dropwise over 1 hr. After stirring at 75° for an additional 30 min, the reaction mixture was allowed to cool, then transferred to a flash evaporator where the DMF was removed *in vacuo*. The residue obtained was stirred with 300 ml of distilled water and the insoluble material was collected by filtration and dried giving 3.70 g. The nmr spectrum of this fraction indicated its composition was 67% triphenyl isocyanurate, 27% 1,3-diphenylurea, and 6% DMF. The aqueous filtrate was acidified with concentrated HCl to precipitate 38.50 g of a white solid. This material was recrystallized from ethanol–water giving pure diphenyl isocyanurate, mp 265–266°.

It should be noted that in some instances the crude product precipitated on acidification was an infusible complex (nmr and infrared) of the desired acid and the potassium salt. The salt component could be removed by stirring the infusible solid with distilled water at room temperature for 24–72 hr. After filtration and drying, the product melted completely and was then purified by recrystallization.

Di-*n*-butyl Isocyanurate.—The preparation of di-*n*-butyl isocyanurate is typical of the reaction of aliphatic isocyanates with metal cyanates.

A mixture of 10.5 g (0.16 mol) of sodium cyanate, 29.7 g (0.30 mol) of butyl isocyanate, and 300 ml of DMF was stirred at 100° for 24 hr. The cooled reaction mixture was filtered, and the DMF was distilled at reduced pressure from the filtrate. The residue was stirred with distilled water causing an oil to separate. The oil was removed, dissolved in $CHCl_3$, and dried over $MgSO_4$. Removal of the solvent left 14.6 g of an oil which consisted of (nmr) 84% tri-*n*-butyl isocyanurate and 16% di-*n*-butylurea. The aqueous phase was acidified with concentrated HCl giving a precipitate of 7.1 g. This product was recrystallized from hexane to give di-*n*-butyl isocyanurate, mp 89–90°.

Effect of Isocyanate Concentration (Table II).—The KOCN (0.53 mol/mol of phenyl isocyanate) and DMF were equilibrated at 75° and the phenyl isocyanate added rapidly to the slurry. The initial exotherm was moderated as required with an

(9) J. N. Tilley and A. A. R. Sayigh, *J. Org. Chem.* **28**, 2076 (1963).

(10) W. P. ter Horst (to Mathieson Chemical Corp.), U. S. Patent 2,690,957 (1954).

ice bath to maintain 75°; later heating was commenced as necessary. The reaction was allowed to proceed for 1 hr and was then worked up as described above.

Effect of Solvent (Table III).—A solution of 0.30 mol of phenyl isocyanate in 100 ml of the appropriate solvent was added dropwise over 1 hr to a slurry of 0.16 mol of KOCN in 200 ml of solvent. The temperature (initially ambient) rose to 35–40° during the addition. The reaction was stirred for 0.5 hr after completing the addition and then worked up in the usual manner. In the reactions using acetone and acetonitrile, part of the reaction product precipitated from solution and was therefore isolated in admixture with KOCN. The organic materials were separated by stirring the mixture with DMF, filtering, and distilling off the DMF.

Effect of Temperature (Table IV).—A solution of 0.30 mol of phenyl isocyanate in 100 ml of DMF was added over 1 hr to a stirred slurry of 0.16 mol of sodium cyanate in 200 ml of DMF at the appropriate reaction temperature. After stirring at temperature for 1 hr additional, the reaction was worked up in the usual manner.

Effect of Cyanate Ion Concentration (Table V).—Phenyl isocyanate (0.3 mol) in 100 ml of DMF was added over 1 hr to a mixture of 0.16 mol of the appropriate metal cyanate and 200 ml of DMF. The temperature rose from ambient to 35–40° during the addition, and the reaction was stirred 1 hr thereafter. The products were isolated as usual.

Effect of Added Electrolytes (Table VI).—The $LiClO_4$ or KI (to give the indicated concentration in the total amount of DMF used) was dissolved in 200 ml of DMF and cooled to ambient. A charge of 0.16 mol of NaOCN was added to the solution, and 0.30 mol of phenyl isocyanate in 100 ml of DMF was added over 1 hr. The reaction was stirred at ambient for 1 hr afterward, and the products were then isolated as previously described.

Registry No.—Phenyl isocyanate, 103-71-9; NaOCN, 917-61-3; KOCN, 590-28-3; LiOCN, 2363-79-3.

Acknowledgment.—The authors wish to express their gratitude to Dr. F. C. Trusell and Mr. D. D. Conway for their analytical assistance and to Mr. J. T. Kelly and Dr. L. C. Gibbons for their encouragement and guidance.

Studies on Reactions of Isoprenoids. IX.[1] The Ritter Reaction of 5,5-Dimethyl-1-vinylbicyclo[2.1.1]hexane

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Treatment of the olefin (**1**) in the title with benzonitrile in H_2SO_4 afforded 2,3,3-trimethyl-1-benzamidobicyclo[2.2.1]heptane (**2**), 2-phenyl-4,4-dimethyl-8-ethyl-3-azabicyclo[3.3.0]octa-2,7-diene (**3**), and 2-phenyl-4,4-dimethyl-8-ethyl-8-benzamido-3-azabicyclo[3.3.0]oct-2-ene (**4**), indicating that this Ritter reaction involved the competing reactions between the cyclobutane ring expansion (C-5 migration) to give a 2,3,3-trimethylbicyclo[2.2.1]heptyl-1 cation and the cyclobutane ring opening at the C-1–C-5 linkage. In the reactions of **1** with a large excess of acetonitrile in H_2SO_4 and with a small excess of acetonitrile in $AcOH–H_2SO_4$, 2,3,3-trimethyl-1-hydroxybicyclo[2.2.1]heptane (**7**), 2,3,3-trimethyl-1-acetamidobicyclo[2.2.1]heptane (**9**), and, furthermore, 2,3,3-trimethyl-1-acetoxybicyclo[2.2.1]heptane (**8**) only in the latter reaction, together with a small amount of 8-(2,3,3-trimethylbicyclo[2.2.1]heptyl)-γ-sultone (**6**), were obtained, while treatment of **1** in $AcOH–H_2SO_4$ afforded **7** and **8**. These results suggest that only the cyclobutane ring expansion of **1** occurred in diluted sulfuric acid. The C-2 stereochemistry of **2**, **7**, **8**, and **9** disclosed that the cyclobutane ring enlargement is nonstereospecific. A plausible mechanism for the formation of **2**–**9** was proposed.

Heterocyclic syntheses with nitriles under the Ritter reaction conditions have attracted much attention from the preparative point of view.[2] Most of the examples, however, are limited to intramolecular cyclizations of appropriate 1,*n*-bifunctional systems *via* intermediate nitrilium cations.[3] In a previous paper,[4] we reported the ring-enlargement reaction of 5,5-dimethylbicyclo[2.1.1]hexane-1-epoxyethane to a bicyclo[2.2.1]heptane ring system by acidic hydrolysis, where no cyclobutane ring-fission products were isolated. This paper deals with the results of the Ritter reaction of 5,5-dimethyl-1-vinylbicyclo[2.1.1]hexane (**1**) with benzonitrile and acetonitrile under several reaction conditions.

We expected that the cyclobutane ring fission of **1** might be caused by initial protonation of the vinyl group in such strongly acidic media as H_2SO_4, and subsequent reactions of the resulting carbonium ions with nitriles might afford azabicyclic compounds after rearrangement and cyclization.

Results and Discussion

Structural Elucidation of Products.—Products **2**–**9** were isolated in the Ritter reaction of **1** with benzonitrile and acetonitrile under several conditions as summarized in Table I. Their melting points and analyses are summarized in Table II. Products **2**–**5** were produced only in the presence of benzonitrile, and **9** was formed in the presence of acetonitrile, indicating that these might be derived from **1** and nitriles, but **6**–**8** were produced also in absence of nitriles, indicating that these were derived only from **1** and solvents.

The structural elucidation of **2**–**9** was carried out as follows. Product **2** ($C_{17}H_{23}NO$) contained a benzamido group (ir); the nmr spectrum had a doublet at τ 9.20 assignable to $CHCH_3$ as well as two singlets (τ 8.96 and 9.08) assignable to a *gem*-dimethyl protons, suggesting that **2** is not a normal Ritter reaction product of **1** involving the same ring system, but a cyclobutane ring-expansion product, 2,3,3-trimethyl-1-benzamidobicyclo[2.2.1]heptane or 2,7,7-trimethyl-1-benzamido-

(1) Part VIII: T. Sasaki, S. Eguchi, and T. Ishii, *Bull. Chem. Soc. Jap.*, **43**, 543 (1970).

(2) (a) F. Johnson and R. Madronero, *Advan. Heterocycl. Chem.*, **6**, 95 (1966); (b) L. I. Krimen and D. J. Cota, *Org. React.*, **17**, 213 (1969); (c) A. Hassner, R. A. Arnold, R. Geult, and A. Terada, *Tetrahedron Lett.*, 1241 (1968).

(3) Recently an example of the double intermolecular Ritter reactions of 4-methyl-3-pentenenitrile has been reported: J. W. Ducker and M. J. Gunter, *Aust. J. Chem.*, **21**, 2809 (1968).

(4) Part VII of this series: T. Sasaki, S. Eguchi, and T. Ishii, *J. Org. Chem.*, **35**, 219 (1970).

TABLE I

SUMMARY OF THE PRODUCTS ISOLATED IN THE RITTER REACTION OF 1

Expt no.[a]	Nitrile[b]	Solvent system	Products,[c] (yield, %)[d]			
i	C_6H_5CN	H_2SO_4	**2** (10.5)	**3** (11.5)	**4** (5)	**5** (trace)
ii	C_6H_5CN	H_2SO_4	**6** (5)			
iii	CH_3CN	H_2SO_4	**7** (12)	**9** (trace)		
iv	CH_3CN	$AcOH-H_2SO_4$	**6** (2.7)	**7** (20.5)	**8** (21.0)	**9** (0.1)
v	CH_3CN	H_2SO_4	**6** (3)	**7** (4)	**9** (18)	
vi	None	$AcOH-H_2SO_4$	**6** (trace)	**7** (13)	**8** (34)	

[a] Generally a mixture of 1 and nitrile was added to the solvent system, except ii where 1 was added to a mixture of benzonitrile and H_2SO_4. For the detailed procedure, see Experimental Section. [b] In v, a large excess amount of acetonitrile was used compared with small excess amounts of nitrile in i–iv. [c] Products only from nitriles such as benzamide are not included. [d] Yields are based on 1.

TABLE II

ANALYSES AND MELTING POINTS OF THE RITTER REACTION PRODUCTS OF 1

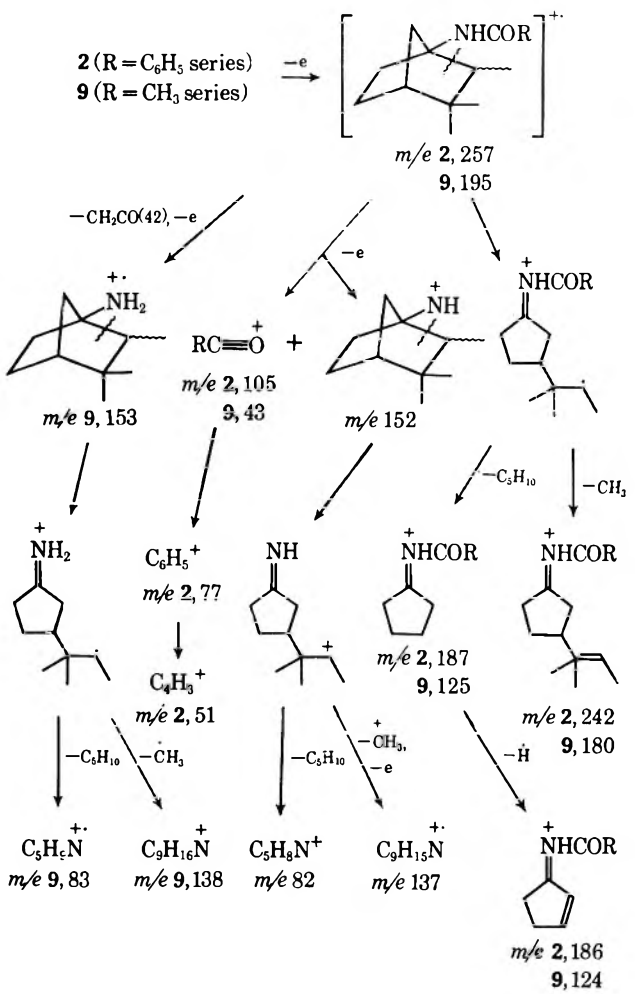
Products	Mp, °C	Formula	Calcd, %			Found, %		
			C	H	N	C	H	N
2	219–221	$C_{17}H_{23}NO$	79.33	9.01	5.44	79.38	8.99	5.42
3	102–103	$C_{17}H_{21}N$	85.30	8.84	5.85	85.33	9.13	6.12
4	177–178	$C_{24}H_{28}N_2O$	79.96	7.83	7.77	79.94	8.04	7.79
5	247–247.5	$C_{24}H_{30}N_2O_2$	76.15	7.99	7.40	76.24	7.87	7.29
6	101–103	$C_{10}H_{16}O_3S$	55.52	7.46		55.65	7.34	
7	98–100	$C_{10}H_{18}O$	77.86	11.76		77.43	12.05	
9	159–163	$C_{12}H_{21}NO$	73.79	10.84	7.17	73.81	11.11	7.40

bicyclo[2.2.1]heptane. The former structure for **2** was established by the fact that treatment of 2-*exo*-methyl-3,3-dimethyl-1-hydroxybicyclo[2.2.1]heptane (**7**) with benzonitrile under similar conditions afforded **2**, which was identified by vpc retention time. Vpc analysis revealed also that **2** was a mixture of 2-*exo*-methyl and 2-*endo*-methyl isomers in approximately 4.5:1 ratio. The mass spectral main fragmentations are explained in Chart I, in which some common fragmentations to the corresponding acetamide derivative **9** due to a 1-acylamido-2,3,3-trimethylbicyclo[2.2.1]-heptane skeleton were observed in addition to those (*m/e* 105 → 77 → 51) due to a benzamido moiety.[5]

Product **3** ($C_{17}H_{21}N$) had no amide absorptions but an absorption at 1635 cm^{-1} (C=C, C=N) in the ir spectrum; the uv spectrum had λ_{max}^{EtOH} 236 nm (ϵ 12,300) which shifted to 265 nm (ϵ 16,700) in a 1% HCl–EtOH solution. This uv spectral behavior is similar to that reported for 2-phenyl-3,3-diphenyl-Δ^1-pyrroline,[6] suggesting the presence of a 2-phenyl-Δ^1-pyrroline moiety in **3**. The nmr spectrum (Figure 1) contained a multiplet at τ 4.68 (1 H) which changed to a partly overlapped double triplet (d, J = 2.1 Hz, and t, J = *ca.* 1.8 Hz) when H_d and H_e were irradiated and to a doublet (J = 2.1 Hz) when H_d, H_e, and $-CH_2CH_3$ were irradiated. This fact suggested the presence of a vinyl proton H_a in a partial structure $-CH_2CH{=}C(Et)CH-$. A triplet at τ 9.08 and an asymmetrical broad multiplet at τ 8.05–8.48 were assignable to an ethyl group. A broad doublet (J = *ca.* 8.5 Hz) at τ 5.58 was assignable to an allylic methine proton (H_b) which coupled with H_c (J = 8.5 Hz), H_a (J = *ca.* 2.1 Hz), H_d, H_{5e}, and $-CH_2CH_3$ from the spin–spin decoupling experiment (Figure 1). A double triplet at τ 7.16 (J = 8.5 and *ca.* 5.0 Hz) was assignable to a methine proton (H_c) which coupled with *vic*-methylene protons (H_d and H_e) with J = *ca.* 5.2.[7] A complex multiplet at τ 7.40–7.75 (2 H) was assigned to H_d and H_e. Two sharp

CHART I

MASS SPECTRAL FRAGMENTATION OF 2 AND 9



(5) J. L. Cotter, *J. Chem. Soc.*, 5477 (1964); 5742 (1965).

(6) (a) $\lambda_{max}^{i\text{-PrOH}}$ 249 nm (ϵ 12,000) and $\lambda_{max}^{0.01\ N\ HCl\text{-}90\%\ i\text{-PrOH}}$ 271.4 nm (ϵ 10,500): P. J. A. Demoen and P. A. J. Janssen, *J. Amer. Chem. Soc.*, **81**, 6281 (1959). (b) 2-Phenyl-Δ^1-pyrroline, λ_{max}^{MeOH} 244 nm (log ϵ 4.33): F. Korte and H.-J. Steinen, *Chem. Ber.*, **95**, 2444 (1962).

(7) The same magnitude of the coupling constants between the *cis*- and *trans*-*vic* protons in five-membered-ring systems has been often observed; for example, see E. D. Becker and M. Beroza, *Tetrahedron Lett.*, 157 (1962).

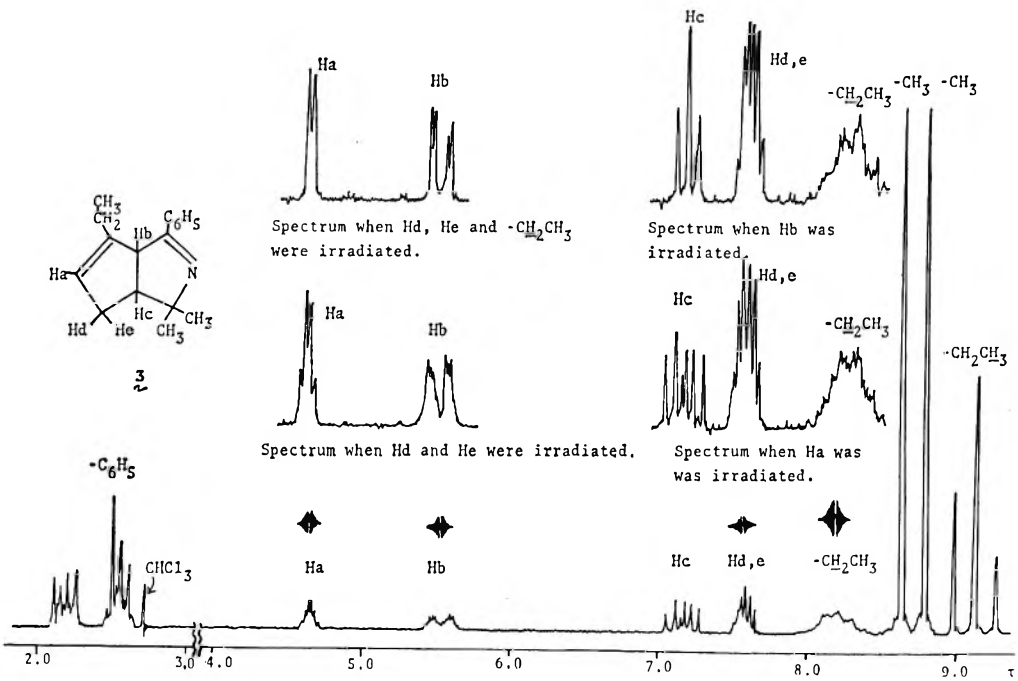


Figure 1.—Nmr spectrum of **3** in $CDCl_3$ at 100 MHz.

singlets at τ 8.62 and 8.79 were assigned to *gem*-dimethyl protons. All these data led us to formulate the structure as 2-phenyl-4,4-dimethyl-8-ethyl-3-azabicyclo[3.3.0]octa-2,7-diene. In the mass spectrum, ion peaks due to loss of CH_3, C_6H_5, and C_6H_5CN[8] from M^+ (*m/e* 239, 67.5) were observed at *m/e* 224 (5.5), 162 (12.5), and 136 (94.1), respectively. The base ion peak appeared at *m/e* 121 (100) which can be derived from the *m/e* 136 ion on loss of CH_3. The skeletal fragmentation between C–1∼C–2 and C–4∼C–5 was observed in ion peaks at *m/e* 145 (52.9) and 94 (28.2) which might be ascribable to 3,3-dimethyl-2-phenylazirine ($C_{10}H_{11}N$) and ethylcyclopentadiene (C_7H_{10}), respectively. These mass spectral data were consistent with the assigned structure.

Product **4** ($C_{24}H_{28}N_2O$, M^+ *m/e* 360) was assigned as 2-phenyl-4,4-dimethyl-8-ethyl-8-benzamido-3-azabicyclo[3.3.0]oct-2-ene, a secondary Ritter reaction product of **3**: the presence of a benzamido group was supported by ir spectrum; the uv spectral behavior (λ_{max}^{EtOH} 232 nm and $\lambda_{max}^{1\%\ HCl\text{-}EtOH}$ 270 nm) was very similar to that of **3**, indicating the presence of the same chromophore as **3**. From the fact that **3** was isolated together with **4** and from the reaction mechanism (Chart IV), we assigned the above structure to **4**, but further study shall be necessary for the definite determination.

The structure of **5** might be a dibenzamide derivative such as 1-benzamido-1-ethyl-3-(2-benzamido-2-propyl)-cyclopentane from the analytical (Table II) and ir data; this product seems plausible as one of the possible products from the cyclobutane ring fission (Chart IV) but the isolated amounts were too small to be further investigated.

The structure of sultone **6** was shown by ir (SO_2, 1342, 1173; no OH, C=O, or C=C) and nmr (Figure 2). The typical ABC pattern (τ 6.57, H_b; 6.96, H_a; 7.64, H_c)

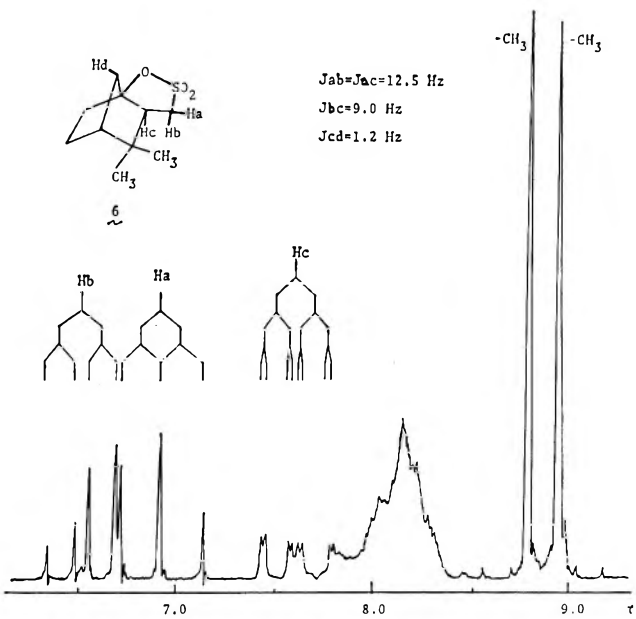


Figure 2.—Nmr spectrum of **6** in $CDCl_3$ at 60 MHz.

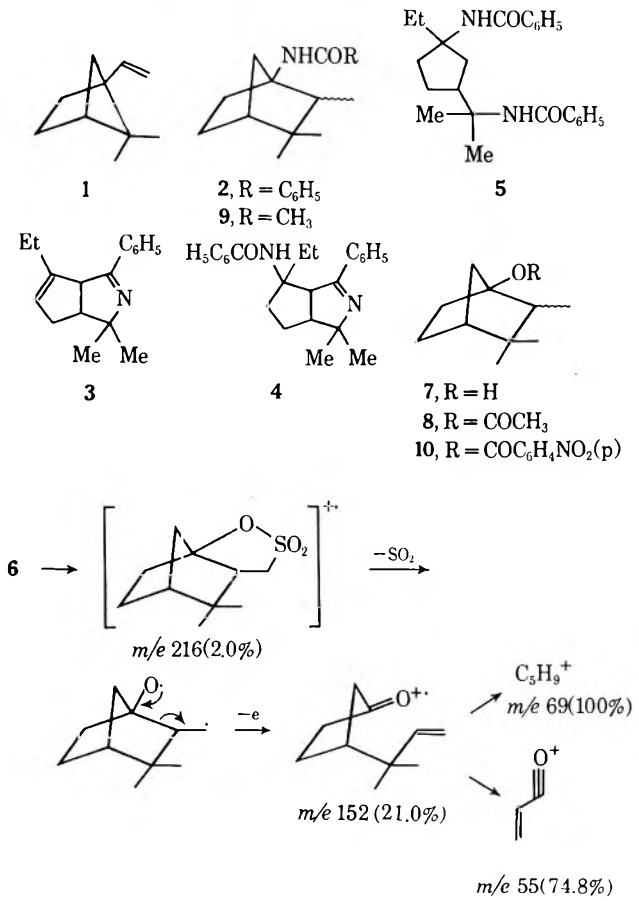
suggested the $-CHCH_2SO_2O-$ group. The chemical shift of H_b and H_a were very similar to those reported for $-CH_2SO_2O-$ protons of camphene sultone (τ 6.95) and 10-isobornyl sultone (τ 6.75).[9] The lack of any lower field signal corresponding to the $-CHOSO_2-$ proton which appeared at τ 5.60 in 10-isobornyl sultone[9] led us to formulate such a cyclic sultone between the C–1 and C–8 positions in a 2,3,3-trimethylbicyclo[2.2.1]heptane ring. The presence of a long-range coupling between H_c and H_d (Figure 2) supported the above formulation. In the mass spectrum, the loss of SO_2 from the parent ion (*m/e* 216) was observed by appearance of the ion at *m/e* 152 (Chart II), which can be further cleaved to ions at *m/e* 137, 123, 96, 82, 69,

(8) This fragment appeared at *m/e* 104 (38.4) after hydrogen abstraction (ion–molecule reaction) as often observed in the mass spectra of nitriles: F. W. McLafferty, *Anal. Chem.*, **34**, 26 (1962).

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

CHART II

MASS SPECTRAL FRAGMENTATION OF 6

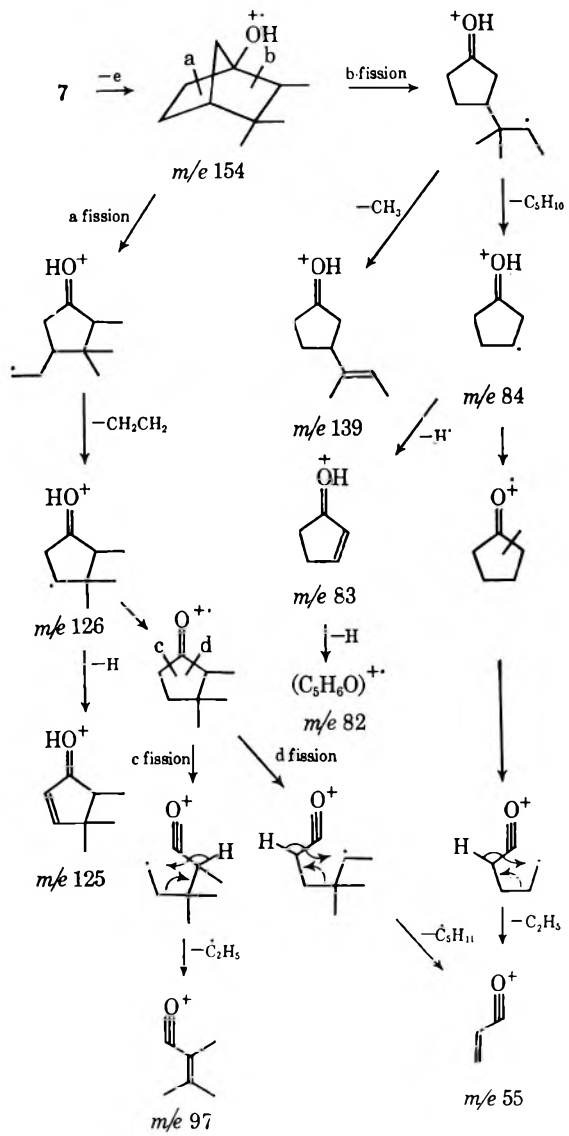


and 55, etc, similar to those observed in the known spectrum of 3-(1,1-dimethyl-2-propenyl)cyclopentanone.[4] An ion peak at *m/e* 41 (62.0) appeared in a higher abundance supporting the structure, since this ion is known to be common for all norbornane derivatives, and, furthermore, its relative abundance is known to be enhanced by the presence of a *gem*-dimethyl group.[10]

Product **7** ($C_{10}H_{18}O$) was a saturated alcohol from ir (3300 and 1106 cm^{-1}); the nmr had signals at τ 7.60 (1 H, s, OH), 7.80–8.90 (7 H, m, methylene, and methine protons), 9.01 (*ca.* 4.5 H, s, methyl protons overlapped with a half of a doublet due to $-CHCH_3$), 9.08 (3 H, s, methyl protons), 9.17 (*ca.* 1.5 H, a half of a doublet due to $CHCH_3$), and 9.50 (1 H, m, C-2 *endo* proton),[11] suggesting that **7** is 2-*exo*-methyl-3,3-dimethyl-1-hydroxybicyclo[2.2.1]heptane, a cyclobutane ring-expansion product.[12] The structure and stereochemistry of **7** were justified by the chemical conversion to *exo*-isocamphane (2,2-dimethyl-3-*exo*-methylnorbornane).[13] **7** gave the corresponding acetate and *p*-nitrobenzoate **10**. The main mass spectral fragmentations can be explained by two ring cleavages (a and b fission

CHART III

MASS SPECTRAL FRAGMENTATION OF 7



in Chart III), which are quite different from those of 2-norbornanols.[10] The most interesting feature is the appearance of an ion at *m/e* 83 as the base peak and the relatively lower abundances of the ions at *m/e* 43 and 41. The b fission can yield ions at *m/e* 84, 83, and 82 as well as those at *m/e* 69 ($C_5H_9^+$) and 55, etc. The a fission can afford ions at *m/e* 126, 125, 97, and 55, etc.[14]

An oily product **8** showed the ir spectrum quite similar to that of an acetate derived from **7**, suggesting the **8** might be **7**-acetate. Vpc, however, revealed that **8** is a mixture of *ca.* 1:1 *endo* and *exo* isomers. Hydrolysis of **8** afforded a crystalline product which had a superimposable ir spectrum on that of **7**, and a satisfactory analysis for $C_{10}H_{18}O$. Its nmr spectrum was also similar to that of **7**. The hydrolyzed product was treated with *p*-toluenesulfonyl chloride, followed by lithium aluminum hydride reduction to afford a mixture of *exo*- and *endo*-isocamphane in *ca.* 1:1 ratio (vpc),

(10) D. R. Dimmel and J. Wolinsky, *J. Org. Chem.*, **32**, 2735 (1967).

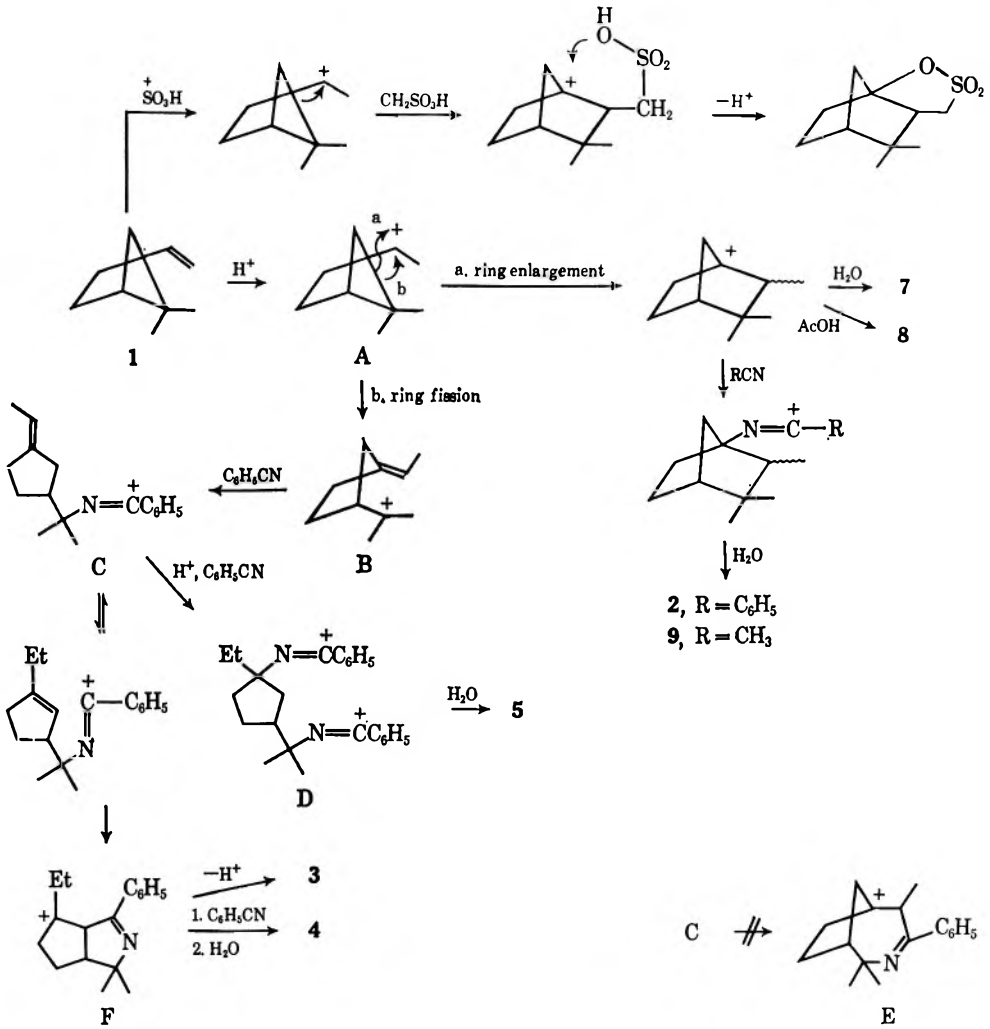
(11) E. Pretsch, H. Immer, C. Pascual, and W. Simon, *Helv. Chim. Acta*, **50**, 105 (1967); R. G. Foster and M. C. McIvon, *Chem. Commun.*, 280 (1967); J. A. Claisse and D. I. Davies, *J. Chem. Soc., B*, 679 (1962).

(12) Vpc analysis of **7** purified by sublimation showed a single peak, though that of crude **7** obtained by chromatography had two peaks in *ca.* 3:1 ratio, indicating that both C-2 *exo* and C-2 *endo* isomers were produced but in favor of the C-2 *exo*-methyl isomer.

(13) (a) S. Beckmann and B. Geiger, *Chem. Ber.*, **94**, 1910 (1961); (b) J. A. Berson, C. J. Olsen, and J. S. Walia *J. Amer. Chem. Soc.* **84**, 3337 (1962).

(14) For mass spectra of alcohols see (a) J. H. Beynon R. A. Saunders, and A. E. Williams, "The Mass Spectra of Organic Molecules," Elsevier Publishing Co., New York, N. Y., 1968, pp 132–153, 190–210; (b) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, pp 94–128.

CHART IV



indicating **8** to be a 1:1 mixture of **7** acetate and its 2-*endo*-methyl isomer.

Product **9** was characterized as 2,3,3-trimethyl-1-acetamidobicyclo[2.2.1]heptane from the analytical (Table II) and spectral data. Vpc revealed a very unsymmetrical peak, suggesting that **9** might be a mixture of C-2 stereoisomers. The ratio was estimated as roughly 2:1. The major peak had the same retention time with a product obtained by treatment of **7** with acetonitrile in H_2SO_4, supporting the above structural assignment. In the mass spectrum, a characteristic fragmentation due to loss of the ketene molecule[15] was observed by an ion at *m/e* 153 which can afford ions at *m/e* 138 and 83, etc., in addition to the common fragmentation patterns to **2** by ions at *m/e* 180, 152, 137, 125, 124, and 82, etc., as depicted in Chart I.

Mechanistic Consideration.—A plausible mechanism for the formation of **2**–**9** is summarized in Chart IV. A cyclobutane ring expansion of **1** to a cyclopentane (path a) *via* a secondary cation (A) affords a 2,3,3-trimethylbicyclo[2.2.1]heptyl-1 cation which can give the corresponding Ritter reaction products **2** and **9** by addition to benzonitrile and acetonitrile, followed by hydrolysis. Before additions to nitrile, the addition to acetic acid can afford **8** and the hydrolysis can give **7**. In the above ring expansion, the selective rearrangement of C-5 can be rationalized by the larger migration aptitude of a tertiary carbon (C-5) than that of a primary carbon (C-6).[16a] The observed stereoselectivity in favor to the C-2 *exo*-methyl isomer suggests the presence of a conformational effect.[16] A cyclobutane ring cleavage (path b) *via* A affords an olefinic tertiary cation B, which could be the precursor of **3**, **4**, and **5** as illustrated in Chart IV. The preferred fission of the C-1–C-5 bond to C-1–C-6 can be explained by the more stable nature of the tertiary cation B than that of the primary cation from C-1–C-6 fission. The practical isolation of **3** and **4** indicates that a path to F from C is preferable to a direct cyclization of C to E. The formation of **5** in a very small amount could be understood by the unstable dication structure of an intermediate D.[17]

The formation of sultone **6** can be explained similarly to that of camphene sultone.[9] A cyclobutane ring expansion will be caused by the attack of $^+SO_3H$ at the vinyl group to afford a bridgehead cation, followed by cyclization.

Treatment of benzonitrile with sulfuric acid is known to afford benzamide, dibenzamide, and 2,4,6-triphenyl-

(15) Reference 14b, pp 336–366.

(16) (a) C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968, pp 3–60. (b) Further studies are necessary for exploring the stereoselectivity in such conformationally mobile systems; *cf.* C. J. Cheer and C. R. Johnson, *J. Amer. Chem. Soc.*, **90**, 178 (1968), and ref 4.

(17) In order to demonstrate the above possibility, synthesis and the Ritter reaction of 1-vinyl-3-isopropenylcyclopentane are to be studied.

1,3,5-triazine,[18] all of which were also isolated as by-products in i and ii (Table I).

As a conclusion, an expected azabicyclic compound like **3** was obtained when **1** and benzonitrile were added to sulfuric acid but not when **1** and acetonitrile were treated similarly where a heterogeneous reaction afforded mostly intractable by-products; even in the homogeneous reaction of **1** with a large excess acetonitrile, the products were seemingly all derived from a bicyclo[2.2.1]heptyl cation, suggesting the difficulty of A → B conversion in such media as sulfuric acid diluted with acetonitrile, and/or acetic acid. However, the mechanistic consideration suggested a possibility that such azabicyclic compounds like **3** can be produced by the Ritter reaction of appropriately substituted 1,3-bifunctional cyclopentane derivatives.[17]

Experimental Section[19a]

5,5-Dimethyl-1-vinylbicyclo[2.1.1]hexane (1) with Benzonitrile. i.[19b]—A mixture of 3.0 g (0.022 mol) of **1**[20] and 3.4 g (0.033 mol) of benzonitrile was slowly added to 8.0 g of ice-cooled sulfuric acid (sp gr 1.84) with stirring during 15 min, and the stirring was continued for 7 hr at room temperature. The mixture was poured onto ice–water (200 ml) and extracted with chloroform (200 + 100 + 100 ml). The combined chloroform extracts were washed with aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride successively, and dried (Na_2SO_4). Removal of the solvent under reduced pressure left a brownish oil (5.02 g) which was purified by chromatography on a silica gel column (Mallinckrodt, 100 mesh) eluting with dichloromethane and then with dichloromethane–methanol solvent system. The first fraction gave a paraffin-like oil (0.5 g) which was not identified. The second fraction gave recovered benzonitrile (0.5 g). The third fraction afforded **2** (0.6 g) as colorless needles: mp 219–221° (*n*-hexane–CH_2Cl_2); ir (KBr) 3450, 1647, 1550, 1315 (NHCO), 1610, 1585, 1503, and 639 (phenyl) cm^{-1}; nmr ($CDCl_3$) τ 2.10–2.75 (5, m, C_6H_5), 3.80 (1, broad s, NH), 7.60–8.80 (8, m, methylene and methine), 8.96 and 9.08 (6, s, $C(CH_3)_2$), and 9.20 (3, d, J = 7.0 Hz, $CHCH_3$); mass spectrum *m/e* 257 (35.7), 242 (15.0), 187 (15.0), 186 (76.4), 168 (10.4), 152 (8.0), 149 (15.7), 137 (8.0), 136 (12.1), 124 (22.5), 121 (11.5), 105 (100), 83 (12.0), 82 (16.5), 81 (8.5), 77 (35.0), 71 (7.0), 70 (8.0), 69 (11.0), 57 (11.5), 55 (9.5), 51 (10.0), 43 (10.0), and 41 (14.0).

The fourth fraction gave **5** as colorless crystals (0.007 g): mp 247–247.5° (EtOH); ir (KBr), 3340, 3086, 2930, 1648, 1605, 1580, 1546, 1315, and 700 cm^{-1}.

The fifth fraction gave **3** (0.6 g): mp 102–103° (*n*-hexane); ir (KBr) 1635, 1608, 782, and 639 cm^{-1}; mass spectrum *m/e* 239 (67.5), 224 (5.5), 162 (12.5), 145 (52.9), 136 (94.1), 121 (100), 107 (54.9), 104 (38.4), 94 (28.2), and 77 (13.7).

The sixth fraction gave benzamide (1.0 g) and the seventh, a brownish oil (1.0 g) which was further purified on alumina (neutral, Merck, activity grade I) column eluting with benzene to give **4** (0.3 g): mp 177–178° (*n*-hexane–CH_2Cl_2); ir (KBr) 3375, 1635, 1580, 1524, 1303, 767, 713, and 690 cm^{-1}; mass spectrum *m/e* 360 (34.2), 345 (3.1), 239 (18.2), 198 (14.4), 186 (19.9), 185 (100), 184 (32.4), 170 (41.8), 149 (15.9), 105 (67.1), 104 (22.0), 77 (36.7), 71 (14.2), 69 (14.3), 57 (29.4), 56 (16.8), 55 (16.5), 44 (29.8), 43 (31.2), and 41 (29.0).

The residual portion eluted with methanol gave 0.6 g of noncrystalline mass which was not further identified.

The water layer after extraction with chloroform was neutralized with 10% aqueous potassium hydroxide and extracted with chloroform to give benzamide (0.26 g).

ii.—**1** (5 g, 0.037 mol) was stirred to an ice-cooled mixture of benzonitrile (5 g, 0.048 mol) and sulfuric acid (10 g). After 5 hr of stirring at room temperature, the mixture was treated as above, and the chloroform extracts (4.5 g) were purified on a silica gel column to give 0.8 g of recovered **1** and 0.6 g of 2,4,6-triphenyl-1,3,5-triazine, mp 239–240° (lit.[21] mp 239°), from the first fraction eluted with dichloromethane. The second fraction gave the sultone **6** (0.4 g) as colorless crystals which showed a positive sulfur test:[22] mp 118–119° (*n*-hexane); ir (KBr) 2964, 1342, 1173, 1059, 838, and 807 cm^{-1}; mass spectrum *m/e* 216 (2.0), 201 (7.3), 187 (5.0), 152 (21.0), 137 (12.0), 123 (10.5), 109 (18.5), 96 (42.5), 83 (69.0), 82 (36.5), 69 (100), 55 (75.0), and 41 (62.0).

From the third and fourth fractions eluted with methanol–dichloromethane, 0.4 g of dibenzamide, mp 148–149° (lit.[23] mp 148°), and 2.0 g of benzamide were obtained.

1 with Acetonitrile. iv.—A mixture of **1** (3 g, 0.022 mol) and acetonitrile (1.5 g, 0.036 mol) in acetic acid (6 ml) was stirred into an ice-cooled mixture of acetic acid (4 ml) and sulfuric acid (7 ml) during 0.5 hr. After 3 hr of stirring at room temperature, the chloroform extracts (3.5 g) were purified on a silica gel column eluting with chloroform. The first fraction gave 0.66 g of a paraffin-like oil which had no C=O bands in the ir and was discarded. The second fraction gave 0.90 g of the acetate **8** as an oil: ir (neat) 2965, 1735, 1373, 1250, and 1090 cm^{-1}; vpc (silicone SE-30 at 140°) showed two peaks with area ratio of *ca.* 1:1, one of which had the same retention time as the **7** acetate.

The third fraction afforded 0.13 g of **6**. The fourth fraction gave 0.71 g of the alcohol **7** as needles after several sublimations at 40–45° (20 mm):[12] mp 98–100° (sealed tube); ir (KBr) 3300, 2955, 1308, and 1106 cm^{-1}; mass spectrum *m/e* 154 (2.7), 139 (50.2), 125 (11.4), 111 (8.1), 97 (8.4), 84 (23.3), 83 (100), 82 (17.5), 71 (8.9), 69 (12.0), 67 (8.8), 55 (33.2), 53 (9.5), 43 (27.3), 41 (23.9), and 39 (12.3).

The fifth fraction gave 0.005 g of the acetamide **9**: mp 159–163° (*n*-hexane); ir (KBr), 3350, 2950, 1646, 1550, 1370, and 1312 cm^{-1}; nmr ($CDCl_3$) τ 4.10 (1, broad, s, NH), 8.09 (3, s, $COCH_3$), 7.00–8.80 (8, m, methylene and methine protons), 9.02, 9.16, and 9.15 [9, s, s, and d, J = 7.8 Hz, $C(CH_3)_2$ and $CHCH_3$]; mass spectrum *m/e* 195 (36.8), 180 (68.6), 168 (13.5), 166 (14.0), 153 (9.0), 152 (14.4), 149 (11.0), 139 (13.5), 138 (65.3), 137 (7.0), 136 (17.5), 125 (40.8), 124 (100), 121 (28.0), 93 (23.1), 83 (53.4), 82 (94.2), 81 (17.5), 71 (19.0), 70 (20.5), 69 (26.5), 67 (25.0), 55 (65.7), 44 (20.0), 43 (95.3), 42 (45.0), and 41 (97.8).

The last fraction eluted with methanol afforded 0.4 g of brownish oil which might be amide derivatives (ir 1653 and 1550 cm^{-1}), but further identification was unsuccessful.

iii.[19b]—A mixture of **1** (3 g, 0.022 mol) and acetonitrile (1.35 g, 0.022 mol) was stirred into ice-cooled sulfuric acid (7 g). The resulting heterogeneous mixture underwent an exothermic reaction and afforded after chromatography 0.4 g of **7**, trace amount of **9**, and 0.2 g of paraffinlike oil.

v.[19b]—A mixture of **1** (1.19 g, 0.0087 mol) and acetonitrile (4.03 g, 0.098 mol) was added during 40 min into ice-cooled sulfuric acid, and the mixture was stirred for 18 hr at room temperature. Work-up as above afforded **6** (0.05 g), **7** (0.05 g), and **9** (0.31 g).

Hydrolysis of 8.—A mixture of 0.6 g of **8** and 10 ml of 5% aqueous potassium hydroxide in 25 ml of methanol was stirred for 1 week at room temperature. Extraction with chloroform after dilution with water (*ca.* 300 ml) and work-up gave 0.4 g of crystalline solids which were sublimed at 40–45° (20 mm) to give 0.35 g of needles: mp 65–69° (sealed tube); ir (KBr) 3335, 2944, 1310, and 1110 cm^{-1}; nmr ($CDCl_3$) 7.69 (1, s, OH), 7.80–9.80 (*ca.* 7, m, methylene and methine protons), 8.90–9.30 (9, m, $C(CH_3)_2$ and $CHCH_3$), and 9.40–9.80 (*ca.* 0.5, broad m, C-2 *endo* proton); vpc (Silicone SE-30, at 100°) had two peaks in *ca.* 1:1 ratio, one of which had the same retention time as **7**.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.43; H, 12.19.

Acetylation of 7.—Treatment of **7** (0.055 g) with acetic anhydride (2.5 ml) and *p*-toluenesulfonic acid (0.07 g) at room temperature for 24 hr gave 0.06 g (87%) of **7** acetate as an oil: ir (neat) 2960, 1736, 1480, 1327, 1253, and 1087 cm^{-1}; nmr

(18) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. 1, W. A. Benjamin, Inc., New York, N. Y., 1965, pp 209–231.

(19) (a) Uv spectra were determined with a JASCO Model ORD/UV-5 spectrometer and mass spectra with a JEOL Model JMS-01SG mass spectrometer at 70 eV. Vpc analyses were performed on a Hitachi K-23 gas chromatograph or a Yanagimoto gas chromatograph, Model GCG-220, using a 2-m column packed with silicone SE-30, DOP, or Apiezon L; see also ref 4, footnote 9. (b) Corresponds to experiment number in Table I.

(20) R. H. Liu and G. S. Hammond, *J. Amer. Chem. Soc.*, **89**, 4936 (1967).

(21) B. W. Frizmmon, C. Hewlett, and R. A. Shaw, *J. Chem. Soc.*, 4779 (1965).

(22) R. I. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1956, pp 57–62.

(23) E. Fischer and H. Troschke, *Ber.*, **13**, 708 (1880).

($CDCl_3$) τ 7.95 (3, s, $COCH_3$), 7.40–8.70 (*ca.* 8, m, methylene and methine protons), 8.97, 9.08, and 9.16 [9, s, $C(CH_3)_2$ and $CHCH_3$]; mass spectral mol wt 196.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.28; H, 10.42.

p-Nitrobenzoylation of 7.—Treatment of **7** (0.15 g) with *p*-nitrobenzoyl chloride (0.25 g) in dry pyridine (2 ml) at room temperature for 40 hr and work-up gave 0.2 g (68%) of the *p*-nitrobenzoate of **7** (**10**): mp 125° (EtOH); ir (KBr) 3120, 2964, 1720, 1605, 1526, 1350, 1295, 1122, 1110, and 715 cm^{-1}; nmr ($CDCl_3$) τ 1.79 (4, s, phenyl protons), 7.50–8.80 (8, methylene and methine protons), 8.91 and 9.02 [6, s, $C(CH_3)_2$], and 9.17 (3, d, J = 8.0 Hz, $CHCH_3$).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.29; H, 7.01; N, 4.63.

Formation of 2 from 7.—A mixture of **7** (0.15 g) and benzonitrile (0.20 g) was treated with sulfuric acid (2.0 g) for 1 day at room temperature. Work-up gave 0.14 g of crude product which exhibited a peak having the same retention time (7.5 min) with that of the main peak of **2** (the minor peak, 6.5 min) on vpc (silicone SE-30, at 250°).

Formation of 9 from 7.—A mixture of **7** (0.19 g) and acetonitrile (1.0 g) was treated with sulfuric acid (1.5 g) similarly. Vpc analysis (200°) of the products showed a peak having the same retention time with **9** (4.7 min).

Conversion of 7 to *exo*-Isocamphane.—Treatment of **7** (0.15 g) with *p*-toluenesulfonyl chloride (0.20 g) in pyridine (2 ml) gave **7**-tosylate (0.15 g) as an oil: ir (neat) 2960, 1603, 1365, 1195, 1180, 1043, 1030, 880, and 675 cm^{-1}. The tosylate was reduced with lithium aluminum hydride (0.5 g) in tetrahydrofuran (5 ml) under refluxing for 1 week. The product was taken in ether and was analyzed on vpc to reveal two main peaks. The major peak was recovered tosylate and the minor (*ca.* 5% peak area of the main peak) had the same retention time (6 min) with that of *exo*-isocamphane, which was prepared as a mixture of *exo* (85%) and *endo* (15%) isomers by catalytic reduction of camphene with Pd–C (10%) in ethanol,[13b] and had bp 160–165° and mp 54–60°.[24] Similar treatment of the alcohol from **8** revealed also isocamphane peaks in a low yield (*ca.* 3%).

Reaction of 1 with a Mixture of Sulfuric Acid and Acetic Acid. vi.—**1** (1.0 g, 0.008 mol) was stirred into an ice-cooled mixture of sulfuric acid (2.5 g) and acetic acid (4 ml), and the mixture was stirred for 20 hr at room temperature. Work-up as above afforded 0.45 g of paraffin-like oil, 0.16 g (13%) of the acetate **8**, and 0.38 g (34%) of the alcohol **7** in addition to a trace amount of **6**.

Registry No.—**1**, 16626-39-4; **2** (*exo*), 24454-04-4; **3**, 24454-00-0; **4**, 24454-01-1; **5**, 24454-02-2; **6**, 24454-03-3; **7**, 24454-05-5; **7** acetate, 24454-07-7; **9**, 24454-08-8; **10**, 24454-06-6; **8** (*endo*), 24454-35-1; **2** (*endo*), 24454-36-2.

(24) The isomer ratio was estimated from the relative peak area on vpc and nmr signal at τ 9.51; *cf.* ref 11.

Steroid Rearrangements. Reactions of a 16,17α-Epoxypregnan-20-one with Hydrogen Fluoride and Thermal Dehydrofluorinations

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Treatment of 16,17α-epoxypregnan-3α-ol-11,20-dione acetate (**1**) with anhydrous hydrogen fluoride afforded a mixture from which three fluorine-containing steroids and three rearranged olefins were separated and their structures established. Two of the products were the unrearranged 16β-fluoro- and 17α-fluoropregnanes **11** and **12**, respectively. The remaining four products had formed as a result of migration of the 18-methyl to C-17, and were identified as the three isomeric C-ring olefins **2**, **3**, and **6**, and the 14-fluoro steroid **8**. Stereospecific thermal elimination of hydrogen fluoride from the tertiary fluoro steroids was employed to interrelate certain of the reaction products and as an aid to elucidation of their stereochemistry.

The reaction of steroid epoxides with hydrogen fluoride is a frequently used method for introduction of fluorine into various selected ring positions. Utility of this reaction for synthesis of 16-fluoro steroids, however, has been hampered by the well-documented[1,2] tendency for 16,17α-epoxy-20-keto steroids to undergo Wagner–Meerwein rearrangements involving shift of the angular methyl group from C-13 to C-17. Shapiro and coworkers,[3] for example, found that 16,17α-epoxyprogesterone was transformed into a rearranged Δ^{13} steroid upon treatment with hydrogen fluoride in chloroform containing ethanol.

Beyler and Hoffman[4] reported lack of success in preparing 16-fluoropregnanes by the action of hydrogen fluoride on the epoxy steroid **1** under a variety of conditions. An early patent report[5] claims synthesis of a 9,16-difluoro steroid by means of simultaneous opening of both oxirane rings in a 9,11β:16,17α-bisepoxy steroid with HF, but the properties of the 16-fluoro steroid were not described.

The original objective of this investigation, *i.e.*, synthesis of 16-fluorinated cortical steroids,[6] was broadened as the complexity of the HF-catalyzed reactions of **1** became apparent. Structures of the several reaction products were determined in order to provide a more detailed understanding of the multiple transformations involved.

Results

When **1** was allowed to react in a 1:1 HF–THF mixture for 5 hr at room temperature, about 70% of the epoxide was consumed, giving rise to a complex mixture of products. Examination of the mixture using tlc revealed six well-defined spots, and combinations of

(1) N. L. Wendler in "Molecular Rearrangements," Vol. II, P. DeMayo, Ed., Interscience Publishers, New York, N. Y., 1964, Chapter 16.

(2) W. F. Johns, *J. Org. Chem.*, **26**, 4583 (1961), and references cited therein.

(3) E. L. Shapiro, M. Steinberg, D. Gould, M. J. Gentles, H. L. Herzog, M. Gilmore, W. Charney, E. B. Hershberg, and L. Mandel, *J. Amer. Chem. Soc.*, **81**, 6483 (1959).

(4) R. E. Beyler and F. Hoffman, *J. Org. Chem.*, **21**, 572 (1956).

(5) C. G. Bergstrom, U. S. Patent 2,703,799 (March 8, 1955); *Chem. Abstr.*, **50**, 1935 (1956).

(6) Fluorohydrin E (**11**) served as an intermediate for synthesis of 16β-fluoroprednisone, mp 243–246°, $[\alpha]^{25}D$ +108° ($CHCl_3$), using standard procedures (D. R. Hoff, J. K. Bennett, and G. E. Arth, unpublished). Entirely different syntheses of the closely related 16β-fluorohydrocortisone acetate and 16β-fluoroprednisolone acetate were subsequently disclosed by other workers.[7]

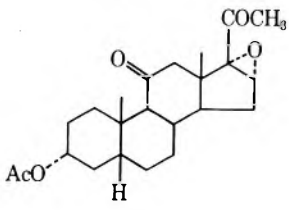
(7) (a) D. E. Ayer and M. P. Schneider, *J. Amer. Chem. Soc.*, **82**, 1249 (1960); (b) Fred Kagan, B. J. Magerlein, and R. D. Birkenmeyer, *J. Org. Chem.*, **28**, 3477 (1963).

preparative chromatography and fractional crystallization allowed resolution of the mixture into six components plus unchanged starting material.

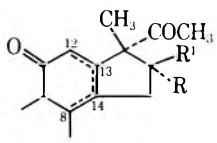
Each of three of the reaction products was the result of isomerization of the starting epoxy ketone, a process which generated an acetylatable hydroxy group and a double bond. In addition to the olefins, three fluorine-containing products, representing addition of hydrogen fluoride to the oxirane with or without subsequent rearrangements, were obtained.

For convenience in discussion, the reaction products will be designated olefins A, B, C and fluorohydrins D, E, and F, respectively. The assigned structures for these substances are shown in Chart I. Selected nmr data are presented in Table I.

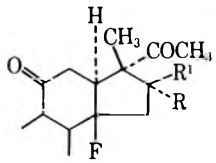
CHART I



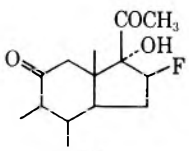
1



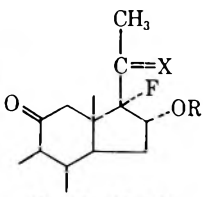
2, Δ^{12}; R = OAc; R¹ = H (olefin A)
3, Δ^{13}; R = OH; R¹ = H (olefin B)
4, Δ^{13}; R = OAc; R¹ = H
5, Δ^{13}; R = H; R¹ = OAc
6, $\Delta^{8(14)}$; R = OAc; R¹ = H (olefin C)
7, $\Delta^{8(14)}$; R = H; R¹ = OAc



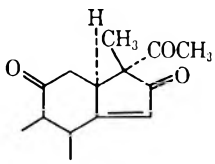
8, R = OH; R¹ = H (fluorohydrin D)
9, R = OAc; R¹ = H
10, R = H; R¹ = OAc



11 (fluorohydrin E)



12, R = H; X = O (fluorohydrin F)
13, R = Ac; X = O
14, R = H; X = NOCH₃



15

CrO_3
C_5H_5N

8

The structural assignments for the olefinic products rest on their elemental composition and spectral properties. Migration of the angular methyl group from C-13 to C-17 was assumed by analogy with the earlier reports,[1,2] and this assumption was supported in all three cases by shifts of the pertinent methyl signal downfield in the nmr spectrum. Finally, satisfactory assignment of the double bond positions required a methyl migration, since the signal due to the C-16 proton was observed in the 16-acetate of each compound, and vinyl protons were present only in olefin A, in which the double bond is conjugated with the 11-carbonyl group.

Placement of the double bond in olefin A (**2**) at the 12 position was dictated by the ultraviolet ($\lambda_{max}^{CH_3OH}$ 239, mμ, ε 11,000) and infrared spectra and by the C-12 vinyl proton resonance at τ 4.21 appearing as a doublet (allylic coupling with the C-14 proton, J = 2.4 Hz) in the nmr spectrum. The downfield position of the 10-methyl resonance (τ 8.63) and the intermediate position of the 17-methyl signal (τ 8.97) relative to that of olefins B and C (Table I) are consistent with the effects to be expected from polarization of the 11-keto-Δ^{12} system.

Olefins B (**3**) and C (**6**) are tetrasubstituted, as deduced from lack of vinyl proton resonances in the nmr spectra and from strong end absorption in the ultraviolet. Differentiation between the alternative Δ^{13} and $\Delta^{8(14)}$ bond position follows from the position of the nmr signal due to the shifted 17-methyl group. The 17-methyl in olefin B is strongly deshielded (τ 8.77), requiring placement of the double bond at the 12 position. That olefin C has the $\Delta^{8(14)}$ structure is supported by the higher position of its 17-methyl resonance at τ 9.10.

Olefin B 16-acetate (**4**), exhibits a strong positive Cotton effect in the ORD (a = +187) which is a composite of the strong dispersion curve expected from the 20-carbonyl and the weaker curve attributed to the 11-carbonyl. The ORD curve shown by olefin C 16-acetate is, on the other hand, characterized by a strong negative Cotton effect (a = −167). Although distinction between the $\Delta^{3(14)}$ and Δ^{13} olefins rests on the chemical shift of the rearranged 17-methyl protons, these ORD curves provided useful supportive information for correlating structures with unsaturation in these positions. In each of the four isomers **3** through **7**, those with the double bond at 13 exhibited the characteristic strong positive curve, whereas the $\Delta^{8(14)}$ olefins were characterized by similar strong negative curves. Furthermore, the shape and magnitude of the curves were substantially identical whether the acetoxy group at C-16 was α or β. These observations can be satisfyingly rationalized by inspections of models. In contrast to 17β-acetyl steroids, in which the dispersion curves are influenced by orientation of substituents at C-16, the ORD curves and hence the 17α-acetyl side-chain disposition in the rearranged steroids depend on the geometry of the C–D ring junction but not at all on the nature of substitution at C-16.

Fluorohydrin E was readily recognized as the normally expected 16β-fluoro-17α-ol (**11**) by its easy reconversion to the starting epoxide **1** by means of mild alkaline treatment. Protons at C-21 are coupled with the fluorine (J = 4 cps), but the C-18 hydrogens appear as a singlet in the 60-MHz spectrum.

Location of the fluorine in fluorohydrin F (**12**) at the 17 position was established by these observations. The C-21 protons are split into a doublet (J = 6 cps). Acetylation gave the 3,16-diacetate (**13**) in which the C-16 hydrogen was revealed as a pair of triplets centered at τ 4.59. The vicinal H–F coupling constant was 16.2 Hz. The angular methyl resonances in **12** appeared at the expected positions (τ 8.86 and 9.33, respectively) for an unrearranged steroid, and the C-18 protons were not coupled to the fluorine. Thus the gross structure was revealed as a 16-hydroxy-17-fluoro steroid. The ORD curve of fluorohydrin F

TABLE I
NMR ASSIGNMENTS[a]

Compound	Methyl resonances[b] C-21	C-19	C-18	17-CH_3	16-H	Other
2	7.82	8.63		8.97	4.81	C-12 proton: τ 4.21; J = 2.4 Hz
3	7.77	8.77		8.77		
4	7.82	8.77		8.75	4.78	
5	7.77	8.88		8.78	4.49	
6	7.88	8.88		9.10	4.73	
7	7.93	8.83		9.00	4.33	
8	7.76	8.92		9.03		
9	7.86	8.82		9.03	4.78	C-13 proton: τ 6.86[c]
10	7.80	8.89		9.03	4.45	
11	7.63[d]	8.83	9.00		5.00[e]	17α-OH doublet: τ 5.72; J = 1.8 Hz
12	7.77[f]	8.86	9.33			
13	7.83[f]	8.84	9.32		4.59[g]	
14	8.19	8.86	9.38			
15	7.68	8.87		8.69		C-15 proton: τ 4.06[h]
16	8.16	8.82	9.22			
17	8.16	8.82	9.03		4.03[i]	
18	8.22	8.82	8.72		4.76[j]	
20	8.22	8.88		8.88	4.65	
21	8.22	8.87		8.87		
22	8.16	8.88	9.15		6.18	
23	8.00	8.88	9.21		6.20	
24	8.17	8.89		8.78	4.63	
26	7.76	8.85	8.90		4.23	

[a] Determined in $CDCl_3$, using TMS as the internal standard, with Varian Associates A-60D spectrometer. The observations in footnotes *c*, *i*, and *j* were taken from spectra obtained with the Varian HA-100 instrument. [b] Singlets, except where noted. [c] Octet, J_{FH} = 35 Hz; J_{HH} = 14, 6 Hz. [d] Doublet, J = 4 Hz. [e] Pair of multiplets, J_{FH} = 48 Hz. [f] Doublet, J = 6 Hz. [g] Pair of triplets, J_{FH} = 16.2 Hz. [h] Quartet, J = 2.1, 0.9 Hz. [i] Octet, J_{FH} = 22 Hz. [j] Octet, J_{FH} = 24 Hz.

reveals a strong positive Cotton effect (a = +154), suggesting a 17α-fluoro-17β-acetyl configuration. Furthermore, the ORD curve measured in methanol was identical with that in dioxane. Danielewicz and Klyne[8] showed, in related models, that 16β substitution diminishes the amplitude of the positive Cotton effect arising from the 20-carbonyl in 17β-acetyl steroids, whereas 16α substitution has little effect. More significantly, 16β-hydroxy-5α-pregnan-20-one showed a positive Cotton effect in hexane, but a plain curve in methanol. This finding was explained as owing to hydrogen bonding with the solvent, resulting in loss of the preferred conformation which gives rise to the anomalous dispersion curve in the aprotic solvent. Applying this analogy to fluorohydrin F requires placement of the 16-hydroxy group in the α position. Thus the complete structure of fluorohydrin F is established as 17α-fluoropregnane-3α-16α-diol-11,20-dione 3-acetate (**12**). Assignment of the *cis*-fluorohydrin structure is supported by the high stability of this substance to prolonged treatment with alkali. It was unaffected (except for ester hydrolysis) by 18 hr of standing in a solution of 40% potassium hydroxide in 1:1 aqueous methanol.

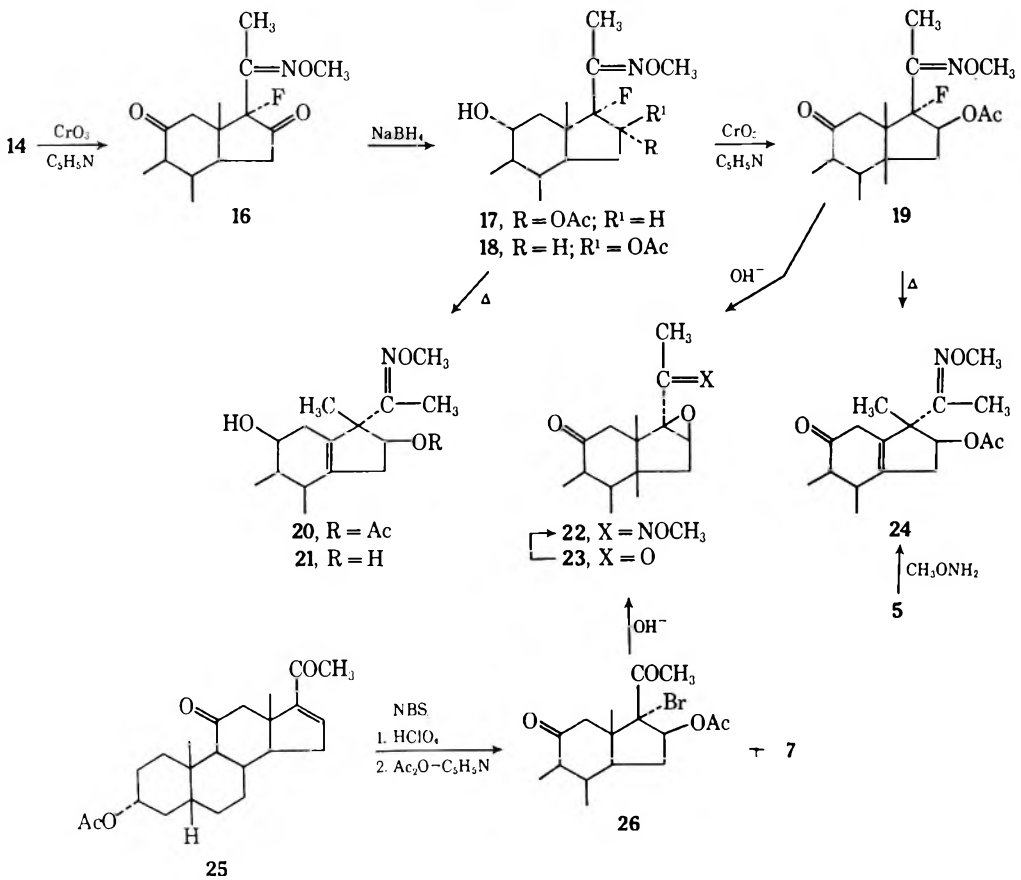
The assigned structure for fluorohydrin F was confirmed unambiguously by means of the transformations outlined in Chart II. Its 20-methoxime **14** was prepared and oxidized to the 16 ketone **16**. Sodium borohydride reduction followed by acetylation then afforded the pair of isomeric 16 acetoxy steroids **17** and **18**. Independent preparation of the 16α-acetoxy isomer **17** by sodium borohydride reduction of **14** allowed differentiation of the two isomers. The 16β-acetoxy isomer **18** was characterized by a low-field position of the C-18 methyl protons at τ 8.72. The 16,17 F–H coupling constants for **17** and **18** were 22 and 24 Hz, respectively. Determination of the nmr spectrum of **18** at 100 MHz allowed resolution of the C-18 methyl proton signal into a doublet (J = 1.3 Hz). Reoxidation of the 11-hydroxy in **18** gave the 11 ketone **19**, which readily afforded the 16,17β-oxide **22** upon alkaline treatment followed by reacetylation. When the *cis*-fluorohydrin acetate **17** was subjected to identical conditions, unchanged starting material was recovered in good yield after reacetylation. The 16,17β-epoxy steroid **22** was independently prepared from the bromohydrin acetate **26**, using similar ring-closure conditions, subsequent acetylation, and 20-methoxime formation.

The presence of the fluorine atom in fluorohydrin D had no obvious effect on the features of the 60-MHz pmr spectrum; *i.e.*, neither the angular methyl hydrogens nor the protons at C-16 and C-21 were coupled to the fluorine. The ^{19}F mr spectrum (94.1 MHz) was symmetrical and centered at −20.26 ppm relative to internal C_6F_6.[9] The 16-line pattern (five lines superimposed) yielded to a first-order analysis, fitting apparent F–H coupling constants of 35, 29, 29, and 23 Hz. One proton, located vicinal to the fluorine, moreover, was visible in the 100-MHz pmr spectrum of the 16-acetate **9**. It appeared as eight lines centered at τ 6.86, with coupling constants of 35, 14, and 6 Hz. These observations are interpreted as requiring the presence of the $(-CH)_2CFCH_2-$ grouping, since the observed F–H splittings are in the normal range for vicinal F–H coupling constants. This requirement excludes C-13 but ideally fits C-14 for the location at the fluorine atom. The eight-line methine signal at τ 6.86 is then assigned to the C-13 proton which is coupled to the 14-fluorine (35 Hz) and to the two C-12 protons (14 and 6 Hz). The alternative C-15 location for this proton is excluded

(8) J. C. Danielewicz and W. Klyne, *J. Chem. Soc.*, 1306 (1965).

(9) The author is indebted to Dr. W. L. Budde, Midwestern Research Institute, Kansas City, Mo., for measurement of this spectrum.

CHART II



since the observed splittings did not coincide with the known H-15,H-16 coupling constants.

The provisional formulation of fluorohydrin D as a 14-fluoro-17-methyl-18-nor-17-isopregnane-3,16-diol-11,20-dione (**8**) is further supported by the position (τ 9.03) of the 17-methyl resonance and the appearance of the ORD curve of its 16-acetate, which exhibits a strong negative Cotton effect ($a = -166$). These two features are comparable to the corresponding observations with olefin C, in which the corresponding C-methyl peak appears at τ 9.10, and the ORD has the same sign and amplitude (−169) of the Cotton effect.

Confirmation of the proposed fluorohydrin D formulation was obtained in the following ways.

(1) Oxidation with chromic anhydride in pyridine[10] resulted in spontaneous loss of hydrogen fluoride, yielding the Δ^{14}-16-one **15**: λ_{max}^{Nujol} 1695, 1613 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 237 mμ (ϵ 13,000). The C-15 proton resonance in **15** appeared as a quartet (τ 4.06) with splittings of 2.1 and 0.9 Hz, respectively, due to allylic coupling with the protons at C-8 and C-13. By way of contrast, fluorohydrin D itself experienced no loss of fluorine even under conditions of drastic alkaline treatment.

(2) Fluorohydrin D is unstable at its melting point, spontaneously eliminating hydrogen fluoride. When a sample of its 16-acetate (**9**) was subjected to a temperature of 211° for 2 min *in vacuo*, an elimination of hydrogen fluoride was complete, and an excellent yield (81%) of olefin B 16-acetate (**4**), was obtained.

(3) Solvolysis of fluorohydrin D 16-acetate (**9**), in the presence of aqueous sodium bicarbonate gave rise to a 60:40 mixture of two substances, separable by chromatography after reacetylation. The lesser component was identified as recovered starting material. The other was a product isomeric with **9**. The new isomer was identified as the 16β-acetoxy epimer **10** from these data: In the nmr spectra of **9** and **10**, only the resonances of the protons at C-16 differ appreciably between the two isomers. This signal shifted downfield from τ 4.78 in **9** to τ 4.45 in **10**. The ORD curves of **9** and **10** show Cotton effects with essentially the same sign, shape, and amplitude (−166 and −174, respectively), and, in fact, the two curves are distinguishable only in that **10** is shifted to more positive rotations at all wavelengths. The same product mixture was obtained by solvolysis of **10** demonstrating establishment of an equilibrium between **9** and **10**. This observation is of consequence for fixing the stereochemical assignments at C-13 and C-14 in fluorohydrin D, a subject which is conveniently deferred to the discussion section.

Although a complete quantitative separation of the products obtained by the actions of HF on **1** was not attempted, the major products were clearly the unconjugated olefins **3** and **6** and the fluorinated steroids **8** and **12**, each obtained in at least 5–10% yield. The best yield of the normally expected product **11** was 1.8%. The conjugated olefin **2** was formed in negligible (*ca.* 0.1%) quantity, and its presence could not be detected even by measurement of the ultraviolet absorption spectrum of the crude reaction mixture.

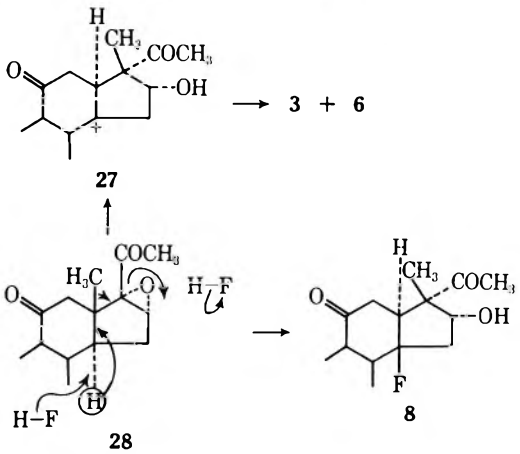
Synthesis of the bromohydrin acetate **26** by addition of HOBr to **25** followed by acetylation was complicated by formation of a bromine-free by-product. The

(10) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

elemental analysis, a negative Cotton effect in the ORD ($a = -153$), and the appearance in the nmr spectrum of a C-methyl resonance at τ 9.00 and a proton signal at τ 4.33 (16 H) allow assignment of the $\Delta^{8(14)}$ structure **7** to this product.

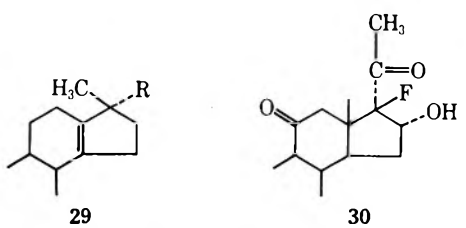
Discussion

Rearrangements Induced by Hydrogen Fluoride.—Prominence of the nonconjugated olefins **3** and **6** and of the 14-fluoro steroid **8** in the reaction mixture, coupled with the very minor amount of conjugated olefin **2** observed, elevates the significance of the center at C-14 in the rearrangement under discussion. The apparent stereochemical homogeneity in the series of observed products favors a fully concerted mechanism involving migration of the 14α hydrogen to C-13.



Alternative multistep processes entailing, for example, double-bond migration from Δ^{13} to $\Delta^{8(14)}$ or intermediate formation of a transient C-13 cation, must be considered, though the further possibility of HF addition to a tetrasubstituted olefin is not likely. Evidence, to be developed later, for the 14β orientation of the entering fluorine atom provides support for the proposed mechanism.

Numerous examples of steroid rearrangements with C-13 → C-17 methyl migration have been reported,[1,10] and the olefinic products were usually assumed to have the unsaturation at Δ^{13} position. Survey of the recent examples for which nmr data are supplied showed 13 different products assigned the C/D part structure



R = H, CH_3, or $CH(CH_3)OCOCH_3$

29. Two of these,[11] both having R = CH_3, had 17-methyl signals at τ 8.48 and 8.52 ($CDCl_3$, 60 MHz). The remaining 11 examples had 17-methyl resonances in the range of τ 9.00–9.04.[12–16] In keeping with the findings of the present study, the rearrangement products with the higher field position of the 17-methyl might reasonably be reformulated as $\Delta^{8(14)}$ olefins.

It is clear from a review of these many rearrangements that the final location of the unsaturation is determined by the reaction conditions. When the rearrangement was brought about by prolonged acid treatment, particularly in protic solvents, the $\Delta^{8(14)}$ product was formed. In the few cases where the Δ^{13} product could be isolated, the reaction conditions are found to have been much milder and briefer.

The *cis*-fluorohydrin **12** may be rationalized as a secondary product arising from a reverse epoxide cleavage, affording the 17β-fluoro steroid **30** followed by inversion of the configuration at C-17 *via* a retro-aldol–realdolization sequence. An immediate precedent for this possibility is provided by the cleavage of 16,-17β-epoxy-17-iso-5-pregnen-3β-ol-20-one acetate with hydrazoic acid, affording a mixture of *cis* and *trans* azidohydrins.[17] Direct *cis*-epoxide opening in rigid rings has been observed,[18] but the explanation invoked in that instance is not directly applicable here, since alternatives to fluorine attack at C-17 clearly exist.

The extraordinarily facile interconversion of the epimers **9** and **10** must likewise be attributed to D-ring opening and reclosure.

Thermal Dehydrofluorination Reactions.—The smooth thermal elimination of hydrogen fluoride from fluorohydrin D 16-acetate (**9**), affording **4**, was paralleled by an equally facile conversion of the 16 epimer **10** to a new tetrasubstituted olefin. The position of the 17-methyl proton resonance at τ 8.78 and the negative Cotton effect in the ORD ($a = -182$) readily established the identity of the new product as the 16β-epimer (**5**) of olefin B 16-acetate.

Although alkyl fluorides, particularly tertiary fluorides, are known to be thermally unstable, the mechanism and stereochemical significance of the thermal HF elimination appears to have been little investigated.

Decomposition of the 14-fluoro steroids **9** and **10** was virtually instantaneous at around 205°. At lower temperatures the dehydrofluorination was equally fast, but an induction period of up to several minutes was required. Plots of induction time *vs.* temperature of a variety of tertiary fluorides are smooth curves characteristic of the particular compound and provide estimates of the relative ease with which any given fluoride can undergo this elimination. As an example, 9α-fluorohydrocortisone acetate requires a temperature of 282° to promote HF elimination within 30 sec. Preparative thermal dehydrohalogenations with this steroid were unpromising owing to the higher temperatures required. Presence of impurities often hastens onset of the reaction.

Rather unexpectedly, the 17α-fluoropregnane **18** also eliminated hydrogen fluoride with ease at moderate

(11) A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, D. K. Phillips, G. O. Potts, A. Arnold, A. L. Beyler, and R. O. Clinton, *J. Med. Chem.*, **6**, 1 (1963).

(12) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *J. Org. Chem.*, **29**, 2187 (1964).

(13) A. D. Cross, H. Carpio, and H. J. Ringold, *J. Med. Chem.*, **6**, 198 (1963).

(14) E. Caspi and D. M. Piatak, *Can. J. Chem.*, **41**, 2294 (1963).

(15) R. Kirdani, R. I. Dorfman, and W. R. Nes, *Steroids*, **1**, 219 (1963).

(16) V. Tortorella and A. Romeo, *Gazz. Chim. Ital.*, **92**, 1118 (1962).

(17) K. Ponsold, B. Schönecker, and I. Pfaff, *Chem. Ber.*, **100**, 2957 (1967).

(18) N. G. Bisset, *Tetrahedron Lett.*, **27**, 3107 (1968).

temperatures. In a preparative run, a 60% yield of a single fluorine-free product **20** was obtained. Noncrystalline **20** was characterized by means of its mass spectrum (parent peak at *m/e* 462) and nmr spectrum [τ 4.65, (16 H), 8.88, (angular methyls)] which allowed its formulation as a rearranged Δ^{13} steroid. Mild hydrolysis of **20** afforded the crystalline triol **21** which was fully characterized by its mass and nmr spectra and its elemental composition.

The corresponding 11 ketone **19** similarly evolved hydrogen fluoride, yielding **24** in 90% yield. The mass and nmr spectra were again in full accord with the structure shown. The rearranged product **24** was identical with the 20-methoxime of the independently obtained Δ^{13} steroid **5**, as shown by comparison of the ir, nmr, and high resolution mass spectra of the two samples. This comparison confirmed structures previously assigned to **10** and **5**.

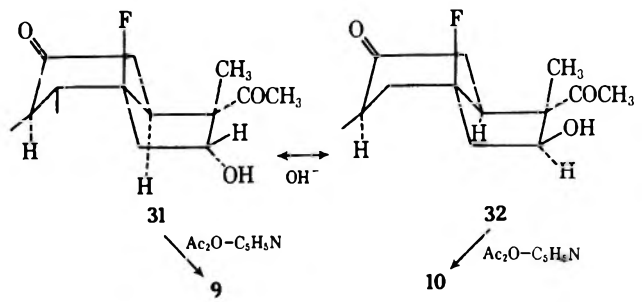
The thermal dehydrofluorination reaction is most likely an acid-catalyzed (by HF) *trans* elimination. Observation of an induction period is suggestive, and the reaction is enormously faster than uncatalyzed gas-phase eliminations of other hydrohalides. Vapor-phase elimination of HCl, HBr, or HI is presently considered to be a two-step process initiated by heterolysis of the C–X bond,[19] rather than the concerted *cis* elimination which had previously been postulated.[20] In the case of HF eliminations, two separate mechanisms are probably operating. The initial uncatalyzed elimination would be too slow to observe directly, but a buildup of product HF could promote the fast acid-catalyzed reaction.

The postulate of a *trans* elimination accounting for at least the majority of the product is buttressed by observation of eliminations with methyl migration in **18** and **19**. The migrating methyl is *trans* to the departing fluoride and the *cis*-16 proton is undisturbed.

Stereochemistry.—Use of the thermal dehydrofluorination reaction served to interrelate the olefin B and fluorohydrin D series, and the fluorohydrins D and F series were independently converted to the common product **24**. As a result of these manipulations, configurations at C-16 and C-17 were defined for all three series. Any prior uncertainty on this point arises from the demonstrated opportunity for 16-hydroxy-20-ketopregnanes to undergo ring-opening reactions which may lead to inversion at C-16 or C-17. Since no such inversion was encountered under the conditions of the HF reactions, it seems safe to assume the regular C-16 and C-17 assignments made for the olefins A and C series.

Configuration at the C–D ring junction in **8**, **9**, and **10** was initially assigned as shown (13α-H,14β-F) from consideration of the probable mechanism by which these compounds might have been formed. Several independent lines of evidence converge in support of the proposed formulation.

If the thermal HF elimination (**9** → **4** and **10** → **5**) is indeed *trans*, and if the hydrogen at C-13 arrives initially *via* a stereospecific C-14 → C-13 migration, the postulated 13α-H,14β-F configuration must be correct. The observed equilibrium between **9** and **10** in the presence of mild aqueous base is fully in accord with this conclusion. Inspection of Dreiding models of all four possible configurations about the 13–14 bond reveals that only in the 13α-H,14β-F arrangement (**29** and **30**) are the 16α and 16β substituents projected in conformations of approximately equal energy. The C-ring is in the boat form with the 9α and 13α hydrogens in the flagpole positions. Furthermore, the 17α bond has a pronounced pseudoequatorial character, an observation consonant with the finding that the more bulky acetyl group remains at the preferred 17α position in both components, **31** and **32**, of the equilibrium mixture.



The major alternative formulation to be considered, with 14α-F and 13α-H is clearly ruled out. Whether the C ring assumes a boat (or worse) chair conformation, the 16β position is overwhelmingly less favorable for substitution. Similar analysis of the remaining 13β-H, 14β-F, and 14α-F possibilities rule them out as serious competitors, with the slight reservation that the flexibility allowed the D ring in some isomers leaves a residue of uncertainty as to the actual conformation of the D ring.

Consideration of the apparent vicinal F–H coupling constants in **9** provides further corroboration for the assumed stereochemistry. The intuitive supposition that the dihedral angle dependence for F–H vicinal couplings should be qualitatively similar to the parallel H–H coupling (Karplus) relationship was supported to a degree by data collected by Williamson, Hsu, Hall, Swager, and Coulter.[21] These workers estimated maximum F–H coupling constants of 31 $COS^2\phi$ for angles (ϕ) between 0 and 90° and 44 $COS^2\phi$ for angles between 90 and 180°.

These estimated values fit the observed coupling constants in **9** quite well. The required assumption of a boat configuration for the C ring in the 13α-H,14β-F structure confers a degree of rigidity which may allow a fairly accurate estimate of the associated dihedral angles from the Dreiding model. The measured angles, along with the calculated and observed coupling constants for this structure are listed in Table II.

TABLE II

Dihedral angle		F–H, Hz	
Between 14β-F and	Degree	Calcd	Obsd[a]
13α-H	165	42	35
8β-H	150	33	29
15α-H	155	32	29
15β-H	25	26	23

[a] Individual assignments are of course arbitrary except for that of the 13α-H–14β-F coupling constant which was observed in the proton spectrum.

(19) A. Maccoll, *Advan. Phys. Org. Chem.*, 91 (1965).
(20) D. H. R. Barton, *J. Chem. Soc.*, 2174 (1949).
(21) K. L. Williamson, Y-F. L. Hsu, F. H. Hall, S. Swager, and M. S. Coulter, *J. Amer. Chem. Soc.*, **90**, 6717 (1968).

Although analogous analyses are possible for the remaining isomeric possibilities, conclusions are necessarily hazardous because of the greater flexibility in these models and related uncertainty surrounding the actual D-ring conformation. Nonetheless, the 13α-H,-14α-F possibility again seems clearly ruled out. Regardless of the conformation (C-ring boat or chair, or twist form), models show that one of the protons at C-15 must assume a dihedral angle with the C–F bond close to 90°, thus observation of at least one smaller coupling constant would be expected in this isomer.

Long-Range F–H Coupling.—Having in hand three new classes of D-ring fluorinated steroids, discussion of geometrical effects on long-range F–H coupling is appropriate.

Since F–H coupling constants may be quite large, long-range splitting is frequently visible in fluorinated hydrocarbons, and much discussion in the literature surrounds the questions of the mechanism and the spatial requirements for such long-range coupling. Cross and Landis[22-25] surveyed a group of fluoro steroids and formulated the "converging vector rule" defining geometric conditions which must be met if coupling between the fluorine and one of the angular methyl groups is to occur through five or more intervening σ bonds. The rule states that vectors drawn away from the carbon along the C–F bond, and the C–H bond must be capable of intersecting. The rule but states the minimum requirement for long-range coupling. Other factors may certainly prevent coupling even when the rule is satisfied. Excessive length of the σ chain[24] and internuclear distance[25] are two such factors.

Data from the present study suggest that when the angular methyl group and the fluorine are both situated on the five-membered D ring, caution is required in the application of the converging vector rule to assignment of structures.

Fluorohydrin E (**11**), with firmly established stereochemistry, provides an anchor point for the discussion. The converging vector rule predicts that long-range coupling between the 16β-fluorine and the angular methyl (C-18) protons, and the 21-methyl protons may occur. These hydrogens and the fluorine are separated by five σ bonds. In fact, the 21-methyl hydrogens were coupled to the fluorine (J = 4 Hz), but no splitting or even line broadening of the 18-methyl signal was observed. Cross and Landis[23,24] presented examples of 16β-fluoro steroids in which 16-F–18-H coupling (0.5–1.5 Hz) was seen. These examples were 17 ketones, suggesting the possibility that transmission of spin information through a sp^2-hybridized carbon atom may be more efficient than through a fully saturated σ skeleton. This possibility is enhanced by the observation of substantial (4 Hz) coupling of fluorine with the 21-methyl protons in fluorohydrin E. More likely, ring deformations in certain fused five-membered rings may interfere with effective coupling. Bonds to substituents on a cyclopentane ring, moreover, lack the parallel relationship of those to *trans* diaxial substituents on a cyclohexane ring. In the former case, the combination of greater internuclear distances and intervening bond angle distortions may suffice to prevent coupling.

Turning now to the fluorohydrin D series (**8** through **10**), it will be noted that acceptance of a β orientation for fluorine at C-14 requires consideration of the converging vector rule in this instance as well. The observation was made that the C-17 angular methyl group must possess a pseudoaxial configuration. The rule predicts the possibility that the angular methyl protons may couple with the fluorine, whereas no coupling was observed. Except for the reservations brought forth in the foregoing discussions, lack of coupling here might be taken as evidence *against* the 14β-F orientation. Because of the lack of 18-H–16β-F coupling in fluorohydrin E, however, the force of this contrary evidence is great diminished.

Finally, attention is called to the 17α-fluoropregnanes **12** to **14** and **16** to **19**. The converging vector rule does not apply (18-methyl and 21-methyl hydrogens separated from the fluorine by 4 σ bonds). A small 18-H–17α-F coupling was observed in one case (**18**, J_{FH} = 1.3 Hz). More interestingly, 21-H–F coupling to the extent of 6 Hz was seen in the ketones **12** and **13** but not with the methoxime derivatives **14** and **16** to **19**. Either the methoximino grouping does not alow transmission of spin information, or derivatization changes the side-chain orientation in a way that is unfavorable to spin coupling.

Experimental Section[26]

Reaction of 16,17α-Epoxypregnan-3α-ol-11,20-dione Acetate[27] (1) with Hydrogen Fluoride.—Anhydrous hydrogen fluoride (113.7 g, 5.68 mol) was condensed in a dry polyethylene bottle surrounded by a Dry Ice–acetone bath. Tetrahydrofuran (57.4 g, 7.96 mol) was cooled in a Dry Ice bath and added to the HF in 1 portion. To this reagent mixture was added a solution of 1 (44.6 g, 0.114 mol) in 600 ml of chloroform and 112.5 ml of tetrahydrofuran. The solution was cooled to about −30° before adding it to the HF reagent. The reaction mixture was then allowed to stand exposed to room temperature for 5 hr, after which time it was poured over a slurry of ice and water containing about 500 g of sodium bicarbonate. The steroid mixture was extracted with 3 l. of chloroform which, after washing with water and drying (Na_2SO_4), was concentrated *in vacuo* to a red oil. The oily product was dissolved twice in ether and evaporated to remove traces of chloroform, and then was dissolved in about 200 ml of ether, and the resulting solution was filtered and allowed to stand. The crystalline product, fluorohydrin F (**12**), amounted to 1.3 g, mp 239–253°. An additional 0.5 g was obtained by repeating the crystallization in ether from the total reaction product. The combined fluorohydrin F fraction was purified by recrystallization from acetone: first crop 1.30 g, mp 257–261°; second crop, 0.21 g, mp 251–259°. The analytical sample was obtained from acetone: mp 258–260°; $[\alpha]^{23}D$ +86° (c 1.11, $CHCl_3$).

Anal. Calcd for $C_{23}H_{33}FO_5$: C, 67.62; H, 8.14; F, 4.65. Found: C, 67.83; H, 8.24; F, 4.41.

Acetylation afforded the diacetate **13**: mp 179–181° (acetone–ether); $[\alpha]^{23}D$ +142° (c 1.015, $CHCl_3$).

Anal. Calcd for $C_{25}H_{35}O_6F$: C, 66.64; H, 7.83; F, 4.22. Found: C, 66.57; H, 7.65; F, 4.46.

Hydrolysis of fluorohydrin F in refluxing aqueous methanol containing sodium bicarbonate gave the diol: mp 215–216°; $[\alpha]^{23}D$ +68° (c 0.84, $CHCl_3$).

(22) A. D. Cross and P. W. Landis, *J. Amer. Chem. Soc.*, **84**, 1736 (1962).
(23) A. D. Cross and P. W. Landis, *ibid.*, **84**, 3784 (1962).
(24) A. D. Cross and P. W. Landis, *ibid.*, **86**, 4005 (1964).
(25) A. D. Cross, *ibid.*, **86**, 4011 (1964).

(26) Melting points are uncorrected. Ultraviolet spectra were determined with the Cary Model 11 recording spectrophotometer, and the ir spectra were measured with the Perkin-Elmer Model 137 infracord. ORD dispersion curves were obtained with a Cary 60 spectropolarimeter, and mass spectra were obtained with CEC 21-110 high-resolution spectrometer.
(27) P. L. Julian, W. Cole, E. W. Meyer, and B. M. Regan, *J. Amer. Chem. Soc.*, **77**, 4601 (1955).

Anal. Calcd for $C_{21}H_{31}O_4F$: C, 68.82; H, 8.53; F, 5.18. Found: C, 68.52; H, 8.57; F, 4.84.

All filtrates after isolation of fluorohydrin F were recombined. One-tenth of this material, amounting to 4.54 g, was chromatographed over a column of silica gel (1 lb). Initial elution with 20% ether–petroleum ether afforded, after a small amount of oily impurity, 1.31 g of unchanged **1**, amounting to 29%.

Continued elution with 50% ether–petroleum ether gave a mixture containing chiefly olefin B (**3**) contaminated with some fluorohydrin F. Later fractions were nearly pure olefin B. Recrystallization several times from ethyl acetate yielded a sample melting at 189–192°.

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.97; H, 8.04.

Contaminants in the olefin B fractions were more readily removed after acetylation to give the 3,16-diacetates. Thus, 605 mg of acetylated material was chromatographed over 60 g of silica gel. Elution with 33% ether–petroleum ether removed fluorohydrin F diacetate, and pure olefin B diacetate was obtained by elution with 50% ether–petroleum ether. Crystallization from 2-propanol afforded a solvate, mp 46–49°, containing 2 mol of 2-propanol.

Anal. Calcd for $C_{25}H_{34}O_6 \cdot 2C_3H_8O$: C, 67.60; H, 9.15. Found: C, 67.69; H, 8.86.

Composition of the solvate was confirmed by the nmr spectrum. Unsolvated noncrystalline olefin C diacetate, homogeneous by nmr, was employed for the rotation measurements, $[\alpha]^{25}D$ −4.0° (*c* 0.512, $CHCl_3$).

Continued elution after removal of olefin B diacetate yielded about 75 mg of crystalline olefin A (**2**): mp 188–189° (ethyl acetate–hexane); $[\alpha]^{25}D$ −98.2 (*c* 0.7965, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 11,000).

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.37; H, 8.06.

After removal of the olefin B and olefin A fractions, the original column was stripped with ether, yielding a complex mixture whose major components were fluorohydrins D (**8**) and E (**11**), and additional olefin B. This fraction, amounting to 1.35 g, was rechromatographed over 135 g of silica gel. Elution with 70% ether–petroleum ether gave first the olefin B fraction, then intractable mixtures, then pure fluorohydrin D: mp 205–206° dec; $[\alpha]^{25}D$ −156.3° (*c* 1.005, $CHCl_3$). The analytical sample was obtained from ethyl acetate, mp 206° dec.

Anal. Calcd for $C_{23}H_{33}FO_5$: C, 67.62; H, 8.14; F, 4.65. Found: C, 67.65; H, 8.19; F, 4.58.

Acetylation afforded the diacetate **9**, mp 201–203° dec. Recrystallization from acetone–ether afforded the analytical sample: mp 201–202.5° dec; $[\alpha]^{23}D$ −159° (*c* 1.145, $CHCl_3$).

Anal. Calcd for $C_{25}H_{35}FO_6$: C, 66.64; H, 7.83; F, 4.22. Found: C, 66.75; H, 8.10; F, 4.0.

After removal of as much olefin B and fluorohydrin D as possible from the fraction under investigation (obtained by eluting the original column with ether), all filtrates were recombined and acetylated. This procedure allowed isolation of fluorohydrin E (**11**) in pure form. A total of 507 mg of acetylated materials was chromatographed over 50 g of silica gel. Flurohydrin E was obtained by elution with 50% ether–petroleum ether, mp 224–230°. After three recrystallizations from ethyl acetate, material melting at 238–242° was obtained: $[\alpha]^{24}D$ +54° (*c* 0.94, $CHCl_3$).

Anal. Calcd for $C_{23}H_{33}O_5F$: C, 67.62; H, 8.14; F, 4.65. Found: C, 67.52; H, 8.37; F, 4.54.

Continued elution with ether afforded the diacetate **9** of fluorohydrin D.

The procedures outlined above served for isolation of fluorohydrins D, E, and F and olefins A and B. Separations were not always quantitative, and no effort was made to maximize the yield of any individual fraction. Olefin C was not found in the silica gel fractions, but was readily separated from the original reaction mixture after acetylation by means of chromatography over acid-washed alumina. Fluorohydrin E and the diacetate of fluorohydrin D were also obtained from the mixture of acetates by alumina chromatography. The order of elution was (1) olefin C, 20% chloroform–ether, after extensive washing of the column with 80% ether–petroleum ether; (2) fluorohydrin D diacetate, 50% chloroform–ether, early fractions; and (3) fluorohydrin E, 50% chloroform–ether, later fractions.

Olefin C was purified by repeated recrystallization from ether: mp 167–168°; $[\alpha]^{23}D$ −146° (*c* 0.92, $CHCl_3$).

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.90; H, 7.84.

Hydrolysis of olefin C (a diacetate) in aqueous methanol containing potassium carbonate (18 hr, room temperature) afforded the diol, mp 198–201°. After three recrystallizations from acetone–ether, the material melted at 202.5–204.5°, $[\alpha]^{24}D$ −158° (*c* 0.835, $CHCl_3$).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.72; H, 8.60.

Formation of 16,17α-Epoxypregnan-3α-ol-11,20-dione from Fluorohydrin E.—Fluorohydrin E (95 mg) was treated with 211 mg of anhydrous potassium carbonate in 70 ml of methanol and 10 ml of water at room temperature for 24 hr. Most of the methanol was removed by evaporation *in vacuo* at 45°, and the precipitated residue was extracted into chloroform. After washing with water and drying ($MgSO_4$), the solvent was removed *in vacuo*, and the product (65 mg, 80%) was recrystallized from ether, mp 222–225°. It was identified as 16,17α-epoxypregnan-3α-ol-11,20-dione by comparison of the infrared spectra and by a mixture melting point.

Base-Catalyzed Isomerization of Fluorohydrin D.—Fluorohydrin D diacetate (**9**) (206.6 mg) and sodium bicarbonate (256.5 mg) were dissolved in 3.5 ml of methanol and 3.5 ml of water, respectively, and then combined and heated under reflux for 15 hr. The mixture was cooled and distributed between ethyl acetate and water. The ethyl acetate layer was separated and concentrated to yield 194.3 mg of oily product which was acetylated in the usual way. The mixture of acetates was resolved by chromatography over 20 g of silica gel. The isomeric fluorohydrin **10** was eluted first with 20% ether–petroleum ether. The crude weight was 127 mg. After recrystallization from ether, 73.1 mg of material, mp 163–167°, was obtained. Recrystallization from ether twice for analysis raised the melting point to 166–169°, $[\alpha]^{25}D$ −71.7° (*c* 1.185, $CHCl_3$).

Anal. Calcd for $C_{25}H_{35}FO_6$: C, 66.64; H, 7.83; F, 4.22. Found: C, 66.90; H, 7.65; F, 4.10.

Continued elution of the column with 33% ether–petroleum ether gave 74.8 mg of recovered **9**, diminishing to 48 mg, mp 199–201° dec, after recrystallization from methanol.

Thermal Dehydrofluorination of 9.—A sample of 39.2 mg of **9** was placed in a 5-cc round-bottom flask which was evacuated (oil pump) and then immersed in an oil bath at 211° for 2 min. The rapid evolution of hydrogen fluoride commenced after melting of the sample and subsided within 90 sec. After the flask had cooled, the contents (39.3 mg) were applied to a column of 4 g of silica gel. A small amount of impurities was removed by washing the column with 20% ether–petroleum ether. Elution with 15-cc fractions of 33% ether–petroleum afforded the major reaction product followed by a mixture of three minor components (total 5.4 mg) which were not identified. The major product, identified by ir and nmr spectra as olefin B 16-acetate (**4**), was noncrystalline and amounted to 30.3 mg (81%). Crystallization from 2-propanol afforded material, mp 44–47°, identical by nmr and ir with the material prepared by acetylation of **3**.

Thermal Dehydrofluorination of 10.—A sample (90.3 mg) of **10** was placed in an evacuated flask which was immersed for 90 sec in an oil bath which has been heated to 236°. After cooling, the product (**5**) was recrystallized from ether: 81.1 mg (94%), mp 120–124°. Recrystallization from ether twice afforded a sample melting at 121–124°, $[\alpha]^{25}D$ +74.5° (*c* 0.435, $CHCl_3$).

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.45; H, 8.17.

Chromic Anhydride Oxidation of Fluorohydrin D (8).—A solution of **8** (75.9 mg) in 0.5 ml of pyridine was added to a suspension of CrO_3 (161.6 mg) in 0.5 ml of pyridine. After standing for 18 hr at room temperature, the reaction mixture was distributed between ethyl acetate and water. The organic layer was washed with 0.1 *N* HCl and, after removal of solids by filtration, was washed successively with water, 5% sodium bicarbonate solution, and water. Removal of the solvent afforded 68.1 mg of a complex mixture which was chromatographed over 8.5 g of silica gel. The column was developed by eluting first with 20% ether–petroleum ether and then with 33% ether–petroleum ether. The latter eluent removed 27.9 mg of **15** which was recrystallized from ether: 18 mg; mp 154–156°; $\lambda_{max}^{CH_3OH}$ 237 mμ (ε 13,000).

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.62; H, 7.78.

Conversion of Fluorohydrin F (12) to the 16,17β-Oxide 22.—Fluorohydrin F (512.1 mg, 1.254 mmol) and methoxyamine hydrochloride (131.8 mg, 1.578 mmol) were combined in solution

in 4 ml of pyridine and let stand for 19.5 hr at room temperature. The mixture was distributed between ethyl acetate and water; the organic layer was washed successively with 0.1 *N* HCl, water, 5% $NaHCO_3$ solution, and water and then evaporated to dryness. The residue was crystallized from ethyl acetate–hexane to afford 499.7 mg (91%) in two crops, mp 196–198 and 194–196°, respectively, and was recrystallized from ether for analysis: mp 197–198°; $[\alpha]^{25}D$ +46.1° (*c* 1.000, $CHCl_3$).

Anal. Calcd for $C_{24}H_{36}FNO_5$: C, 65.88; H, 8.29; N, 3.20; F, 4.34. Found: C, 66.18; H, 8.36; N, 3.17; F, 4.49.

Methoxime **14** (942.9 mg, 2.16 mmol) was dissolved in 5 cc of pyridine and added to a suspension of CrO_3 (1.4946 g) in 10 cc of pyridine. After 17 hr of stirring at room temperature, the mixture was distributed between ethyl acetate and water. The ethyl acetate layer was washed with 0.1 *N* HCl and then after removal of precipitated solids by filtration, was washed with water, followed by 5% $NaHCO_3$ solution, and finally water. Removal of the solvent *in vacuo* followed by recrystallization of the residue from methanol afforded 792.0 mg (84%) of **16**, mp 170–172°. After two recrystallizations from ether–hexane for analysis, the melting point was 172–173°, $[\alpha]^{25}D$ −111.5° (*c* 0.9154, $CHCl_3$).

Anal. Calcd for $C_{24}H_{34}FO_5N$: C, 66.18; H, 7.87; N, 3.22; F, 4.36. Found: C, 65.90; H, 8.12; N, 3.26; F, 4.6.

The 16 ketone **16** (754.8 mg, 1.73 mmol) was dissolved in 60 ml of methanol, and the solution was cooled to 2° in an ice bath. A cold solution of sodium borohydride (2.3 g) in 30 ml of 0.1 *N* boric acid was added. After 1 hr of standing at room temperature, the reaction mixture was treated with a few drops of acetic acid (no evolution of hydrogen) and then acidified to pH 3.4 with 2 *N* sulfuric acid. The acid treatment was required to decompose a borate ester or complex which was otherwise obtained from the reaction. After 2 min, the acidic solution was neutralized with 5% sodium bicarbonate and then extracted with ethyl acetate. After removal of the solvent, the residual extract (785.6 mg) was acetylated as usual (786.6 mg of crude product); the mixture of acetates was resolved by chromatography over 76 g of silica gel. The column was developed by washing with petroleum ether, eluting with 20% ether–petroleum ether, and taking 100-cc fractions. The two components of the mixture overlapped, but the earliest and latest fractions afforded the pure products. Rechromatography of the intermediate mixed fractions allowed fairly efficient separation of the mixture. The faster moving component was **18**: mp 132–134° from hexane, $[\alpha]^{25}D$ +78.6° (*c* 1.005, $CHCl_3$).

Anal. Calcd for $C_{26}H_{40}FNO_6$: C, 64.85; H, 8.37; N, 2.91; F, 3.95. Found: C, 65.06; H, 8.16; N, 2.83; F, 3.8.

The slower moving component **17** was recrystallized from methanol: mp 202–204°; $[\alpha]^{25}D$ +23.7° (*c* 1.001, $CHCl_3$).

Anal. Calcd for $C_{26}H_{40}FNO_6$: C, 64.85; H, 8.37; N, 2.91; F, 3.95. Found: C, 65.00; H, 8.10; N, 2.94; F, 3.6.

The two components were present in approximately equal amounts. The best isolated yields were 34% **17** and 29% **18**.

The 16α-acetoxy isomer **17** was also obtained by sodium borohydride reduction of **14**, using the same conditions described above and allowing independent assignment of isomer identification. The products were compared by means of the infrared spectra and mixed melting point.

The 16β-acetoxy isomer **18** (51.4 mg) was converted to the 11 ketone **19** by oxidation with chromic anhydride in pyridine using the procedures described for preparation of **16** above. The product **19** was obtained in 82% yield: mp 150–154°; mp 154–156° after recrystallization twice from hexane; $[\alpha]^{25}D$ +88.7° (*c* 1.0221, $CHCl_3$).

Anal. Calcd for $C_{26}H_{39}FNO_6$: C, 65.11; H, 7.99; N, 2.92; F, 3.96. Found: C, 65.37; H, 7.77; N, 2.79; F, 3.72.

Closure of the fluorohydrin acetate **19** to the epoxide **22** was accomplished by treating 27.0 mg of the former in a refluxing solution of 136 mg of potassium hydroxide in 1 ml of 1:4 water–methanol for 1 hr. The crude oxide was acetylated in the usual way, and the acetate was purified by passage over a column of 2 g of silica gel, removing the product by elution with 20% ether petroleum ether. The crude crystalline product amounted to 18.8 mg, mp 124–126°. After recrystallization from hexane, 12 mg (mp 128–131°), was obtained identical to an authentic sample prepared from **23** and methoxyamine. Comparison was made by means of the infrared spectra and a mixture melting point.

16,17β-Oxido-17-isopregnan-3α-ol-11,20-dione Acetate (23) and Its 20-Methoxime 22.—16-Pregnen-3α-ol-11,20-dione acetate[28] (**25**) (4.6886 g, 12.59 mmol) was dissolved in a mixture of 220 ml of acetone and 22 ml of water and was cooled in an ice bath. N-Bromosuccinimide (22.5 g) was added in 1 portion; then, with stirring aud continued cooling, a solution of perchloric acid (12 cc of 70% perchloric acid diluted to 120 cc with water) was added dropwise over the space of 1 hr. The mixture was allowed to stand at room temperature for 12 hr and then was poured over a slurry of ice, water, and an excess of sodium sulfite. Enough solid sodium sulfite was added until the mixture was free from oxidizing products (starch-iodide test paper) and alkaline; then the resulting mixture was extracted with ethyl acetate. After washing with water and removing of solvent, the residual product was dissolved in ether and allowed to stand. A bromine-free by-product, 1.8126 g, mp 176–179°, separated and was collected by filtration. The filtrate was concentrated to dryness and acetylated as usual, and the impure bromohydrin acetate fraction was applied to a column of 300 g of silica gel. The product, 17α-bromopregnan-3α,16β-diol-11,20-dione 3,6-diacetate (**26**), amounting to 1.573 g, mp 173–176° (ether–hexane), was eluted with 20% ether–petroleum ether. Recrystallization from hexane raised the melting point to 181–183°, $[\alpha]^{25}D$ +124.0° (*c* 0.5025, $CHCl_3$).

Anal. Calcd for $C_{25}H_{35}BrO_6$: C, 58.70; H, 6.90; Br, 15.63. Found: C, 58.61; H, 6.84; Br, 15.51.

The nonbrominated by-product, assigned structure **7**, recrystallized from ethyl acetate–hexane for analysis: mp 200.5–202°; $[\alpha]^{25}D$ +72.0° (*c* 1.0257, $CHCl_3$).

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.95. Found: C, 69.45; H, 8.27.

Formation of the epoxide **23** from the bromohydrin acetate **26** was accomplished as follows; **26** (117.7 mg) was treated with potassium carbonate (218.8 mg) in 5 cc of refluxing 4:1 methanol–water for 2 hr. The product was obtained by extraction with ethyl acetate, a water wash, and removal of the solvent under reduced pressure. The crude product was acetylated, and the acetate was purified by chromatography over 9.25 g of silica gel. After washing the column with 20% ether–petroleum ether, the product was taken off with 33% ether–petroleum ether. After crystallization from ether, 77.2 mg of material melting at 133–136° was obtained. The analytical sample, mp 138–140°, was obtained after two recrystallizations from ether–hexane.

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.36; H, 8.59.

The 20-methoxime **22** of the β-oxide was obtained by condensation of 155.3 mg of the ketone with 102.2 mg of methoxyamine hydrochloride in 2 cc of pyridine, using the procedure and work-up described above. The crude crystalline product (from hexane) melted at 121–127° and was judged an approximately equal mixture of *syn* and *anti* isomers from the appearance of double peaks for the OMe, 18-methyl, and 21-methyl signals in the nmr separated by 1–2 Hz. Repeated crystallization from hexane gave an inefficient separation of the isomers, allowing isolation of a single isomer, mp 125–129°, showing single methyl peaks. Seeding the *syn–anti* mixture with a crystal of **22** made by ring closure allowed rapid isolation of a pure sample (35.4 mg) of the desired isomer, mp 124–127°. Further recrystallization from hexane afforded material melting at 129–131°, $[\alpha]^{25}D$ +23.8° (*c* 0.960, $CHCl_3$).

Anal. Calcd for $C_{24}H_{35}NO_5$: C, 69.03; H, 8.45; N, 3.36. Found: C, 68.80; H, 8.46; N, 3.36.

Thermal Rearrangement of the 17α-Fluorides 18 and 19 with Loss of Hydrogen Fluoride.—The 11β-ol **18** (161.7 mg) was placed in an evacuated flask which was immersed for 80 sec in an oil bath which had been heated to 240°. A small amount of crystalline sublimate was recovered and identified as unchanged **18**. The remaining product, a light yellow oil, was chromatographed over 16 g of silica gel. Some impurities were removed by washing the column with 20% ether–petroleum ether, and the product was removed by elution with 33% ether–petroleum ether. A total of 91.5 mg (59%) of **20**, noncrystalline but homogeneous by nmr, was obtained: $[\alpha]^{25}D$ +69.7° (*c* 1.013, methanol). A 20 mg sample of the purified **20** was hydrolyzed at room temperature by the action of potassium carbonate (62 mg) in 8 ml of methanol and 2 cc of water (21 hr). The crystalline triol **21**, mp 138–140° (ether), was thus obtained: $[\alpha]^{25}D$ +48.9° (*c* 0.500, $CHCl_3$).

(28) P. L. Julian and W. J. Karpel, U. S. Patent 2,671,794; *Chem. Abstr.*, **49**, 4034 (1955).

Anal. Calcd for $C_{22}H_{35}NO_4$: C, 69.99; H, 9.35; N, 3.71. Found: C, 70.00; H, 9.64; N, 3.89.

Similarly, the corresponding 11 ketone **19** (77.4 mg) was heated *in vacuo* for 90 sec at 250°. The product was purified by chromatography over 7.5 g of silica gel. After removal of a slight impurity with 10% ether–petroleum ether, the main product was obtained by elution with 20% ether–petroleum ether. The noncrystalline product, homogeneous by nmr, amounted to 44.1 mg (59%). It was identical with the 20-methoxime **24** of the Δ^{13} olefin **5** by the following criteria. The infrared spectra (Nujol mull of solid films) and nmr spectra were identical. The mass spectra of the two preparations showed identical fragmentation patterns and were nearly superimposable, except that the methoxime prepared from **5** showed a small impurity at *m/e* 488, attributable to formation of a small amount of the **11**, 20-bis methoxime of **5**. The high-resolution spectrum of the purified pyrolysis product exhibited a molecular ion peak at a *m/e* of 459.2647 (calcd 459.26207), and an M + 1 peak at 460.2708 (calcd 460.26543).

The reference sample of the methoxime **24** was prepared by condensation of the Δ^{13} olefin **5** with methoxyamine hydrochloride in pyridine using the method described above. The product was noncrystalline though very nearly homogenous as judged by thin layer chromatography and the nmr spectrum. A high-resolution mass spectrum showed a strong molecular ion peak at a *m/e* of 459.2645 (calcd 459.26207) and an $(M + 1)^+$ peak at 460.2704 (calcd 460.26543). A small impurity, estimated to be less than 5% by nmr, was revealed by the presence of a small peak at *m/e* 488. The impurity is assumed to be the 11,20-bis-methoxime of the olefin **5**.

Registry No.—**1**, 24298-90-6; **2**, 24298-91-7; **3**, 24298-92-8; **4**, 24298-93-9; **5**, 24343-86-0; **6**, 24298-94-0; **7**, 24298-95-1; **8**, 24298-96-2; **9**, 24428-66-8; **10**, 24381-50-8; **11**, 24298-97-3; **12**, 24381-51-9; **13**, 24298-98-4; **14**, 24298-99-5; **15**, 24343-87-1; **16**, 24299-00-1; **17**, 24299-01-2; **18**, 24299-02-3; **19**, 24299-03-4; **20**, 24381-52-0; **21**, 24299-04-5; **22**, 24299-05-6; **23**, 5067-60-7; **24**, 24299-07-8; **25**, 4970-39-2; **26**, 24343-88-2; hydrogen fluoride, 7664-39-3; triol of **21**, 24298-71-3; diol of **12**, 24298-72-4; diol of **6**, 24298-70-2.

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Solvolysis of 19-Substituted Androstane Derivatives[1,2]

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Dehydromesylation of 19-hydroxy-5α-androst-2-en-17-one mesylate (**1**) by the action of hot pyridine gives a mixture of steroidal olefinic products, the principal constituent of which is shown to be B(9a)-homo-2,5(10)-estradien-17-one (**2a**). 19-Hydroxy-5α-androstan-17-one mesylate (**7b**) behaves in an analogous fashion and gives rise to B(9a)-homo-5(10)-estren-17-one (**8a**) and B(9a)-homo-5α-estr-1(10)-en-17-one (**9**). Chemical degradation and mass spectral analysis confirmed the proposed structures.

Solvolysis of 19-substituted steroids is of interest both from a mechanistic viewpoint and as a pathway to structurally modified steroid hormones. Previous studies have indicated that the products formed upon solvolysis of 19-substituted steroids depend largely on the substituents in rings A and B. For example, homoallylic participation of a double bond has been noted with 3-oxo-19-mesyloxyandrost-4-ene and 3-ethylenedioxy- (or acetoxy-) androst-5-ene systems. In these instances, solvolysis afforded 6β,19-cyclo and 5β,19-cyclo steroids,[3,4] respectively. Moreover, the expansion of ring A to the A-homo-19-nor system was reported in the case of 3-oxo-19-tosyloxyandrostane[5] and 3-oxo-19-mesyloxyandrosta-1,4-diene systems.[6] With 2-oxo-19-mesyloxy steroids, however, no ring enlargement occurred, and the corresponding 1β,19-cyclo steroid derivative was isolated.[7] It is noteworthy that in all cases no expansion of ring B was reported.

In the course of studies on the synthesis of C-19 radio-labeled steroids, we examined the solvolysis products of 19-hydroxy-5α-androst-2-en-17-one mesylate[8] (**1**) and the corresponding dihydro derivative (**7b**). Refluxing a solution of **1** in pyridine afforded a mixture of steroidal olefins which upon thin layer chromatography on silica gel G impregnated with silver nitrate indicated the presence of two products. Chromatography of the reaction mixture on alumina (activity II) yielded a crystalline product **2a** (25%), an oily product (20%),[9] and starting material (45%).

Compound **2a** was analyzed for $C_{19}H_{26}O$. The intense end absorption in the uv spectrum indicated the presence of nonconjugated double bonds as well as the presence of a highly substituted double bond. The nmr spectrum showed one angular methyl group corresponding to the C_{18} methyl at δ 0.97. This

(1) The work conducted in these laboratories was supported by the American Cancer Society Grant PRA-18 and National Institute of Health Grant CA-08349.

(2) (a) A preliminary account of this work has appeared: F. Kohen, L. K. Lala, W. Van Bever, and R. E. Counsell, *Chem. Commun.*, 347 (1969). (b) Presented in part at the VIth IUPAC Meeting on Steroids and Natural Products, Mexico City, April 1969, Abstract 5A, p 27.

(3) J. J. Bonet, H. Wehrli, and K. Schaffner, *Helv. Chim. Acta*, **46**, 2615 (1962).

(4) O. Halpern, P. Crabbe, A. D. Cross, I. Delfin, L. Cervantes, and A. Bowers, *Steroids*, **4**, 1 (1964).

(5) W. G. Dauben and D. A. Ben-Efraim, *J. Med. Chem.*, **11**, 287 (1968).

(6) P. Wieland and G. Anner, *Helv. Chim. Acta*, **51**, 1932 (1968).

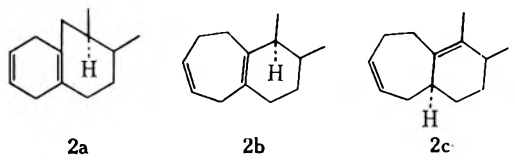
(7) M. E. Wolff and T. Morioka, *J. Org. Chem.*, **30**, 2553 (1965).

(8) R. E. Counsell, G. W. Adelstein, P. D. Klimstra, and B. Smith, *J. Med. Chem.*, **9**, 685 (1966).

(9) This product appeared homogeneous on tlc, but it showed three C-18 methyl peaks in the nmr, indicating that it was still a mixture. Because of the difficulty in purification, it was not further investigated.

indicated that the C_{19} methyl had become part of the steroid nucleus. The presence of two vinyl protons at δ 5.6 (multiplet) similar to that of starting material and the absence of cyclopropyl protons suggested that the suspected additional double bond was tetrasubstituted. This conclusion was substantiated by the formation of a monoepoxide **3**, which still showed two vinyl hydrogens at δ 5.6 and the absence of methine hydrogens attached to a carbon bearing an oxygen function. Treatment of **2a** with excess *m*-chloroperbenzoic acid, however, gave a product formulated as **4**, which can be viewed as arising from a *trans* diaxial opening in the initial diepoxide with *m*-chlorobenzoic acid. Reduction of **2a** with LiAl(*t*-OBu)$_3$H and subsequent acetylation gave a crystalline acetate **5**.

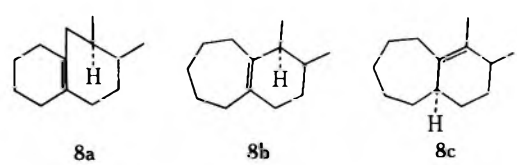
Of all the possible Wagner–Meerwein rearrangement products, only structures **2a–c** were consistent with the above data. A distinction between the A-homo structures (**2b** and **2c**) and **2a** was made by examination of the mass spectrum. The following pertinent peaks were observed: *m/e* 270 (M^+), 216 (M − 54, loss of butadiene), 106 (a C_8H_{10} fragment), 91 (loss of a methyl group from the 106 fragment to give a tropylium cation), and 65 (a cyclopentadienyl cation arising from *m/e* 91 by loss of HC≡CH). The fragments at *m/e* 106 and 91 can be easily derived from a B(9a)-homo steroid such as **2a** but not from the A-homo formulations **2b** or **2c** which would require extensive bond ruptures to form the observed fragment ions.



2a **2b** **2c**

Further proof of the correctness of **2a** was derived by chemical means. Dehydrogenation of **5** with Pd–C (5%) in diethylene glycol solution gave the aromatic derivative, **6**: *m/e* 270 (M^+); uv max (EtOH) at 278 mμ (ϵ 400), 274 (shoulder, 370), and 269 (ϵ 460). The nmr spectrum of **6** showed four aromatic hydrogens at δ 6.85 (singlet) and four benzylic hydrogens at δ 2.76.[10] (See Chart I.)

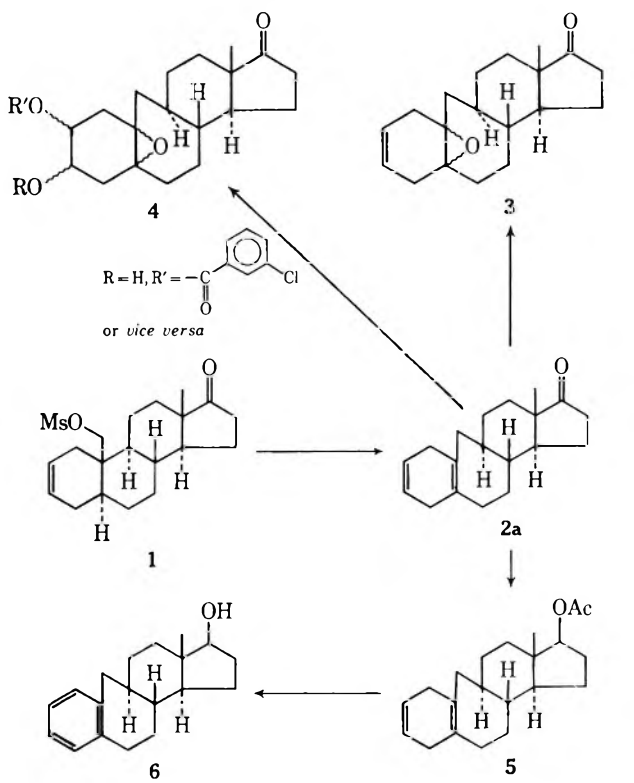
In the dihydro series we found that solvolysis of 19-hydroxy-5α-androstan-17-one mesylate (**7b**) in refluxing pyridine gave an olefinic mixture which was readily separated by chromatography into two components, **8a** and **9**. The more mobile component **8a** was analyzed for $C_{19}H_{28}O$ and displayed no vinyl or cyclopropyl protons in the nmr. Again, consideration of all the possible products that could arise from the solvolysis of **7b** revealed that only structures **8a–c** would fit the data.



8a **8b** **8c**

The correctness of the assignment of structure **8a** to the rearranged product was confirmed both by mass spectral analysis and chemical degradation. The mass spectrum of **8a** showed the following pertinent peaks: *m/e* 272 (M^+), 244 (M − 28, loss of ethylene), 108 (M − 164, a C_8H_{12} fragment), and 91 (tropylium cation). Loss of ethylene involves a retro Diels–Alder process and is typical of an olefinic linkage suitably placed in a cyclohexane ring.[11] Moreover, treatment of **8a** with *m*-chloroperbenzoic acid gave a monoepoxide **12**, identical in all respects with the product obtained by hydrogenation of **3** (Chart II).

CHART I



The more polar component **9** was isomeric with **8a**. It differed, however, in that the nmr spectrum showed the presence of one vinyl hydrogen at δ 5.40 (triplet, J = 6.5 cps) as well as the absence of a C-19 methyl group. Mass spectral analysis showed the molecular-ion peak at *m/e* 272, loss of ethylene at *m/e* 244, the C_8H_{12} fragment at *m/e* 108, and the tropylium cation at *m/e* 91. The B(9a)-homo structure **9** was thus assigned on the basis of this physical data.

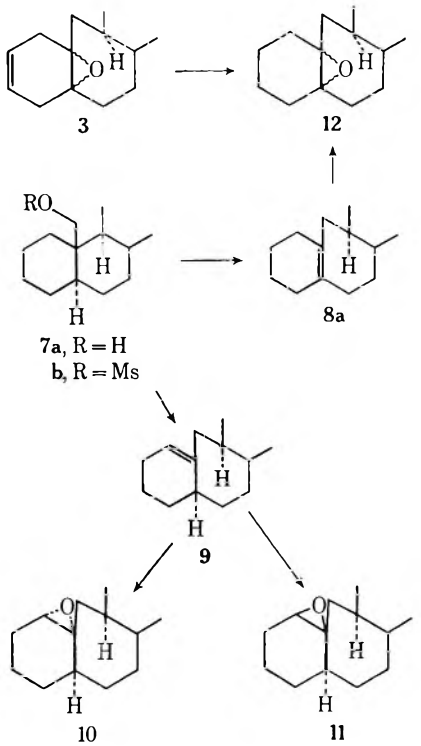
Epoxidation of **9** with *m*-chloroperbenzoic acid gave two epoxides which were separated by chromatography. Structure **10** was tentatively assigned to the more mobile α-epoxide and **11** to the more polar β-epoxide. The two epoxides exhibited different nmr spectra. In **10**, the 1β proton was less shielded and appeared at δ 3.35 (dd, J = 5 cps) in $CDCl_3$ solution and at δ 3.07 (dd, J = 5 cps) in C_6D_6 solution, whereas, in the β-epoxide, **11**, the 1α proton was more shielded and appeared at δ 3.15 (d, J = 6) in $CDCl_3$ solution and at δ 2.95 (d, J = 6 cps) in C_6D_6 solution.

Thus the solvolysis of 19-substituted steroids offers another approach to the B(9a)-homo steroid derivatives and complements the route developed by Kupchan and

(10) Compare with the nmr spectrum of tetralin, "Varian Spectra Catalog" Vol. 2, no. 577.

(11) H. Budzikiewicz, C. Djerassi, D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. II, Holden-Day Inc., San Francisco, Calif., 1964, p 98.

CHART II



coworkers which involves Wolff–Kishner reduction of 9β,19-cyclo-11-oxo steroids.[12]

Experimental Section[13]

Solvolysis of 19-Hydroxy-5α-androst-2-en-17-one Mesylate (1).—A solution of the methanesulfonate[8] (1) (1 g) in pyridine (25 ml) was heated under reflux for 1 week, then evaporated to dryness under reduced pressure. The residue was extracted with ether, and the ether extract was washed successively with water, dilute HCl, and water. The solvent was removed and the residue was examined by tlc on silica gel G impregnated with $AgNO_3$. This revealed three spots. The spot with the lowest R_f corresponded to starting material. The reaction mixture was then chromatographed.

Elution with petroleum ether–ether mixture (8:2) gave a crystalline solid (200 mg), identified as **B(9a)-homo-2,5(10)-estradien-17-one (2a)**: mp 99–100° (from CH_3OH); $[\alpha]D$ +116°; nmr ($CDCl_3$) δ 5.6 (m, 2, vinyl hydrogens at C-2 and C-3), 0.97 (s, 3, C-18 CH_3); mass spectrum (70 eV) *m/e* (relative intensity) 270 (100, M^+), 216 (32, loss of butadiene), 106 (38, C_8H_{10} fragment), 91 (46, tropylium cation), 65 (20, cyclopentadienyl cation).

Anal. Calcd for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 84.38; H, 9.61.

Further elution with the same solvent system gave an oil (150 mg) which failed to crystallize and was not examined further.[9] Further elution with petroleum ether–ether mixture (7:3) gave starting material (450 mg).

Action of *m*-Chloroperbenzoic Acid on B(9a)-Homo-2,5(10)-estradien-17-one. A.—A solution of *m*-chloroperbenzoic acid (100 mg) in chloroform (5 ml) was added to a solution of B(9a)-homoestra-2,5(10)-dien-17-one (2a) (150 mg) in the same solvent (5 ml). The mixture was allowed to stand at room temperature for 30 min and decomposed with aqueous KI solution. The organic layer was washed successively with saturated $Na_2S_2O_3$ solution, water, sodium bicarbonate solution, and water and was dried and evaporated. The oily residue was chromatographed, and elution with petroleum ether–ether (8:2) gave **5,10ξ-epoxy-B(9a)-homo-5ξ-estr-2-en-17-one (3)** (62 mg): mp 124–125° (from CH_3OH); $[\alpha]D$ +130°; nmr ($CDCl_3$) δ 5.6 (m, 2, vinyl hydrogens at C-2 and C-3), 0.97 (s, 3, C-18 CH_3).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.51; H, 9.11.

B.—Under the same experimental conditions as above excess peracid yielded after chromatography a compound tentatively identified as **5,10ξ-epoxy-2ξ,3ξ-dihydroxy-B(9a)-homo-5ξ-estra-17-one 2- or 3-*m*-chlorobenzoate (4)**: mp 228–229° (from CH_3OH); $[\alpha]D$ +210°; nmr ($CDCl_3$) δ 7.95, 7.81, 7.45, 7.35, (four aromatic protons), 5.25 (m, 1, a methine hydrogen attached to a carbon bearing a benzoate group), 4.45 (m, 1, a methine hydrogen attached to a carbon bearing a hydroxy group), 0.97 (s, 3, C-18 CH_3); mass spectrum (70 eV) *m/e* 458 (M^+).

Anal. Calcd for $C_{26}H_{31}O_5Cl$: C, 67.96; H, 6.81. Found: C, 67.61; H, 6.64.

B(9a)-Homo-2,5(10)-estradien-17β-ol Acetate (5).—A solution of **2a** (200 mg) in THF (20 ml) was reduced with $LiAl(t\text{-}OBu)_3H$ (600 mg), and the mixture was allowed to stand at room temperature for 1 hr. The excess hydride was then decomposed with dilute HCl, and the organic layer was washed with water, dried, and evaporated. The residue was then acetylated to give B(9a)-homo-2,5(10)-estradien-17β-ol acetate (5) (120 mg): mp 86–87° (from CH_3OH); $[\alpha]D$ +51°; mass spectrum (70 eV) *m/e* (relative intensity) 314 (100, M^+), 260 (8, M − butadiene), 254 (29, loss of acetic acid), 200 (59), 106 (28, a C_8H_{10} fragment), 91 (33, tropylium cation).

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.18; H, 9.52.

B(9a)-Homo-1,3,5(10)-estratrien-17β-ol (6).—A solution of B(9a)-homo-19-nor-17β-hydroxy-androsta-2,5(10)-diene acetate (5) (50 mg) in diethylene glycol (5 ml) was dehydrogenated with Pd–C (5%) (50 mg) at 180° for 7 hr. The mixture was then allowed to cool, the catalyst was filtered, diluted with water, and extracted with chloroform. The organic layer was then dried and evaporated, and the residue was chromatographed. Elution with petroleum ether–ether (1:1) gave B(9a)-homo-1,3,5(10)-estratrien-17β-ol (6) (10 mg): mp 122–124° (from hexane); $[\alpha]D$ +59°; ir (KBr) λ_{max} 2.98 μ (hydroxy); uv max (EtOH) 278 mμ (ε 400), 274 (370), and 269 (460); nmr $CDCl_3$) δ 6.85 (s, 4, aromatic protons), 2.76 (m, 4, benzylic hydrogens), 0.97 (s, 3, C-18 CH_3); mass spectrum (70 eV) *m/e* 270 (M^+).

19-Hydroxy-5α-androstan-17-one (7a).—A solution of 19-hydroxy-5α-androst-2-en-17-one[8] (1 g) in ethanol (200 ml) was hydrogenated using Pd–C (10%) as a catalyst. The residual solid, obtained after removal of solvent and catalyst was crystallized from hexane to give 19-hydroxy-5α-androstan-17-one (7a): mp 145–146°; $[\alpha]D$ +88.6°.

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.61; H, 10.41.

19-Hydroxy-5α-androstan-17-one Mesylate (7b).—A solution of 7a (1 g) in methanesulfonyl chloride (1.5 ml) and pyridine (10 ml) was allowed to stand at room temperature for 15 min. The mixture was then poured into water and the precipitate was filtered. The product was then dissolved in chloroform and the organic layer was washed with dilute HCl and water dried, and evaporated. The residue was crystallized from hexane to give **7b**: mp 155–156°; $[\alpha]D$ +51°.

Anal. Calcd for $C_{20}H_{32}O_4S$: C, 65.19; H, 8.75. Found: C, 65.23; H, 8.65.

Solvolysis of 19-Hydroxy-5α-androstan-17-one Mesylate (7b).—A solution of 7b (1 g) in pyridine (25 ml) was heated under reflux for a week. The reaction mixture was then poured into water and extracted with chloroform. The organic layer was then washed with dilute HCl and water, dried, and evaporated. Tlc analysis on silica gel G impregnated with $AgNO_3$ revealed two spots, each of equal intensity.

The reaction mixture was chromatographed on alumina (60 g), collecting 125-ml fractions. Fractions 3–6 (hexane) yielded 350 mg of 8a, **B(9a)-homo-5(10)-estren-17-one**: mp 132–134° (from CH_3OH); $[\alpha]D$ +64.5°; nmr ($CDCl_3$) δ 0.95 (s, 3, C-18 CH_3); mass spectrum (70 eV) *m/e* (relative intensity) 272 (100, M^+), 244 (22, loss of ethylene), 108 (9, a C_8H_{12} fragment), 91 (40, tropylium cation).

Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.68; H, 10.36.

Fractions 7–10 (hexane–ether 9:1) yielded 460 mg of 9, **B(9a)-homo-5α-estr-1(10)-en-17-one**: mp 88–90° (from CH_3OH); $[\alpha]D$ −17°; nmr δ 5.4 (t, 1, J = 6.5 cps), 0.87 (s, 3, C-18 CH_3); mass spectrum (70 eV) *m/e* (relative intensity) 272 (100, M^+), 244

(12) S. M. Kupchan, E. Abushanab, K. T. Shamasundra, and A. W. Bly, *J. Amer. Chem. Soc.*, **89**, 6327 (1967).

(13) The nmr spectra were obtained with a Varian A-60A spectrometer. The optical rotations were obtained in $CHCl_3$. The melting points were obtained on a Fisher-Johns apparatus and are not corrected. Woelm neutral alumina (activity II) was used for chromatography.

(43, loss of ethylene), 108 (80, a C_8H_{12} fragment), 91 (49, tropylium cation).

Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.81; H, 10.49.

5,10ξ-Epoxy-B(9a)-homo-5ξ-estran-17-one (12). A. By Epoxidation of B(9a)-Homo-5(10)-estren-17-one (8a).—*m*-Chloroperbenzoic acid (50 mg) was added to a solution of **8a** (100 mg) in chloroform (10 ml), and the mixture was allowed to stand at room temperature for 30 min. After the usual work-up, the residue was crystallized from CH_3OH to give **12**: mp 124–125°; $[\alpha]D$ +75.5°; nmr ($CDCl_3$) δ 0.97 (s, 3, C-18 CH_3).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.18; H, 9.68.

B. By Hydrogenation of 5,10ξ-Epoxy-B(9a)-homo-5ξ-estr-2-en-17-one (3).—A solution of **3** (50 mg) in EtOH (50 ml) was hydrogenated using Pd–C (5%) as a catalyst. After removal of solvent and catalyst, the residue was crystallized from CH_3OH to give **12**, mp 124–125°, identical in all respects (R_f, melting point, nmr, and ir) with the product described above.

Action of *m*-Chloroperbenzoic Acid on B(9a)-Homo-5α-estr-1(10)-en-17-one (9).—*m*-Chloroperbenzoic acid (400 mg) was added to a solution of **9** (400 mg) in chloroform (10 ml), and the mixture was allowed to stand at room temperature for 10 min. After the usual work-up the residue was chromatographed. Elution with petroleum ether–ether (9:1) (150 ml) yielded a crystalline solid (100 mg), identified as the α-epoxide **1α,10-epoxy-B(9a)-homo-5α-estran-17-one (10)**: mp 114–115° (from CH_3OH); $[\alpha]D$ +15.5°; nmr ($CDCl_3$) δ 3.30 (dd, 1, J = 4 cps, 1β proton), 0.85 (s, 3, C-18 CH_3); nmr (C_6D_6) δ 3.07 (dd, 1, J = 5 cps).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.17; H, 9.80.

Further elution with the same solvent system (600 ml) yielded a crystalline solid (200 mg) identified as the β-epoxide **1β,10-epoxy-B(9a)-homo-5α-estran-17-one (11)**: mp 140–142° (from CH_3OH); $[\alpha]D$ +32.5°; nmr ($CDCl_3$) δ 3.15 (d, 1, J = 6, 1α proton), 0.85 (s, 3, C-18 CH_3); nmr (C_6D_6) δ 2.95 (d, 1, J = 6 cps).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.15; H, 9.68.

Registry No.—**2a**, 22602-70-6; **3**, 24467-52-5; **4**, 24467-53-6; **5**, 24467-54-7; **6**, 22602-71-7; **7a**, 24467-56-9; **7b**, 24467-57-0; **8a**, 24467-58-1; **9**, 24467-59-2; **10**, 24467-60-5; **11**, 24467-61-6; **12**, 24467-62-7.

Acknowledgments.—The authors are grateful to Dr. P. Klimstra and G. D. Searle and Co. for the mass spectra.

Geminal Substitution *via* Steroidal 2- and 4-Cyano-3-ones

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The conversion of 3-cholestanone (**1**) into 2,2-dimethylcholestan-3-one (**15**) *via* 2β-cyano-2α-methylcholestan-3-one, to 2,2-dimethyl-5β-cholestan-3-one (**4**) *via* 2α-cyano-2β-methyl-5β-cholestan-3-one (**9**), and to 4,4-dimethylcholestan-3-one (**17**) *via* 4β-cyano-4α-methylcholestan-3-one (**13**) are reported as a model study of the site and stereoselectivity of alkylations. The assignments of the stereochemistry are made on the basis of nmr spectral correlations and chemical conversions. The preparation of 2,2-dimethyl-7-cholesten-3-one illustrates the conversion for an acid-sensitive compound. The syntheses of 4,4-dimethylcholestan-3β-ol-3,30-d_2 (**25**) and 4,4-dimethylcholestan-3-one-30-*d* (**26**) provide compounds for model-independent assignments of chemical shift for the axial and equatorial geminal methyls.

A key step in a number of terpene syntheses is the construction of a geminal center adjacent to the keto group on a cyclohexanone ring. A widely used method for carrying out this substitution, the carbon alkylation of enolate anions of β-keto esters, appears to give epimeric mixtures in most cases.[1,2] As part of a synthetic study designed to furnish labeled compounds for biosynthetic studies, we have carried out a model study of the site and stereoselectivity of carbon substitution in the methylation of potassium enolates of 2-cyanocholestan-3-one, 2-cyano-4-cholesten-3-one, 4-cyanocholestan-3-one, and 4-cyano-1-cholesten-3-one. Our results, which provide a route for control of the site of substitution of unsymmetrical ketones and give geminally substituted compounds which have stereochemistry not previously readily obtained, are reported herein.

2-Cyano ketones have been used occasionally in natural product synthesis.[3,4] The work of Kuehne[3,4] is especially pertinent since it suggests that alkylation of the cyanocholestanones may be stereospecific.

Results and Discussion

The synthesis of 2β-cyano-2α-methylcholestan-3-one (**4**) in 39% yield from cholestan-3-one (**1**) is outlined in Scheme I. Stereochemistry at C-2 is determined by the course of the methylation of the potassium enolate of **3**. The assignment of stereochemistry at the geminal center of **4** rests on spectral and chemical criteria (*vide infra*). The 2β-cyano-2α-methyl ketone **4** is accompanied by approximately 18% oxygen alkylated enol ether isomer. A careful search for the C-2 epimer of **4** led only to the estimate that, if present, this compound is formed in less than 5% yield. The conversion of **1** to **4** illustrates geminal substitution at the preferentially formylated α-methylene of an unsymmetrical cyclohexanone.

The effect of a Δ^4 double bond on the stereospecificity of the methylation is of interest for its potential in controlling stereoselectivity.[4] *A priori* it would be assumed that the flattening of the ring caused by the

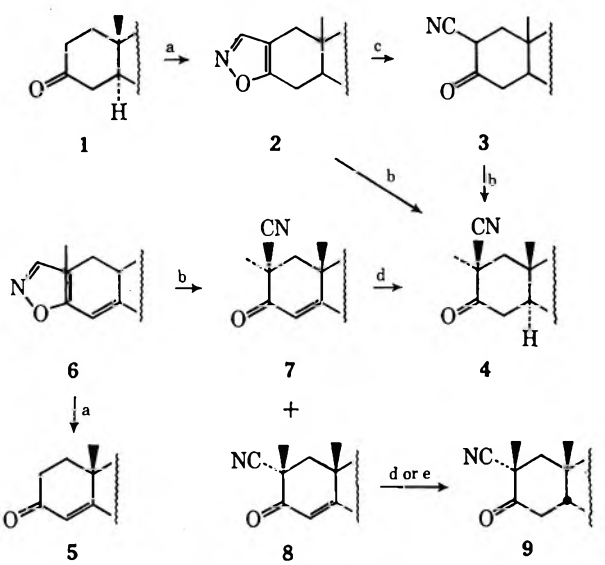
(1) (a) E. Wenkert, A. Afonso, J. Bredenberg, C. Kaneko, and A. Tahara, *J. Amer. Chem. Soc.*, **86**, 2038 (1964); (b) T. A. Spencer, T. D. Weaver, R. M. Villarica, R. F. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968); (c) R. E. Ireland and R. C. Kierstead, *ibid.*, **31**, 2543 (1966), and references cited therein.

(2) (a) L. Velluz, J. Valls, and G. Nomine, *Angew. Chem. Int. Ed. Engl.*, **4**, 181 (1965); (b) J. Mathieu and J. Valls, *Chem. Weekbl.*, **63**, 21 (1967).

(3) (a) W. S. Johnson, J. W. Peterson, and C. D. Butsche, *J. Amer. Chem. Soc.*, **69**, 2942 (1947); (b) D. K. Banerjee, S. Chatterjee, C. N. Pillai, and M. V. Bhatt, *il id.*, **78**, 3769 (1956); (c) M. Kuehne, *ibid.*, **83**, 1492 (1961).

(4) After completion of our work we learned of similar studies by M. Kuehne [*J. Org. Chem.*, **35**, 171 (1970)] and M. Kuehne and J. A. Nelson [*ibid.*, **35**, 161 (1970)] on monocyclic, bicyclic, and tricyclic systems. The stereochemical results in that work and the present report are in agreement. We are grateful to Professor Kuehne for kindly providing prepublication copies of the manuscripts.

SCHEME I[a]

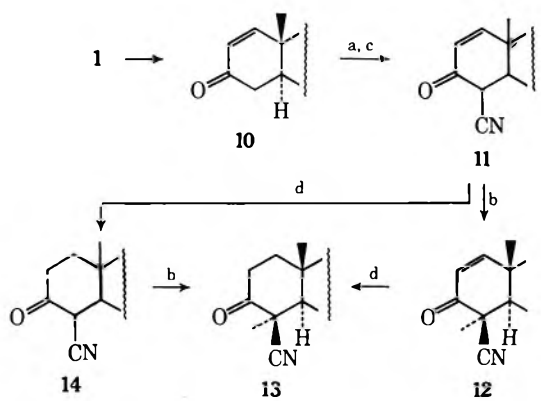


[a] a, $(C_2H_5)_2O$, CH_3ONa, $HCO_2C_2H_5$, $(CH_3)_3COH$, NH_3OHCl; b, $(CH_3)_3COH$, $(CH_3)_3COK$, CH_3I; c, CH_3OH, CH_3ONa; d, H_2, Pd-C; e, Li, NH_3, NH_4Cl.

double bond would lead to changes in 1,3-diaxial interactions between the 2 and 4 and 2 and 10 positions such that formation of both C-2 epimers might be observed. Methylation of the potassium enolate of 2-cyano-4-cholesten-3-one gives an equimolar mixture of 2β-cyano-2α-methyl-4-cholesten-3-one (**7**) and 2α-cyano-2β-methyl-4-cholesten-3-one (**8**) in 39% yield each from the enone **5** (Scheme I). The product of oxygen alkylation was not detected and it is estimated that considerably less than 10% was present. The structure of **7** is established by its catalytic reduction to **4** in 70% yield. However, **8** gives the A/B *cis* compound 2α-cyano-5β-cholestan-3-one (**9**) on catalytic reduction (68%) or on reduction with lithium in ammonia (97%).[5]

The use of a double bond as a blocking group (Scheme II) allows substitution at the C-4 position of cholestan-3-one (**1**). 1-Cholesten-3-one (**10**), prepared from **1** by

SCHEME II[a]

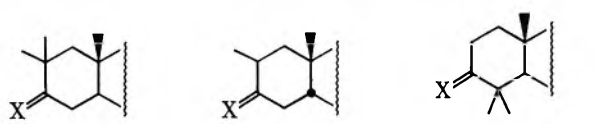


[a] See Scheme I, footnote *a* for a–d.

oxidation with 2,3-dicholoro-5,6-dicyano-1,4-benzoquinone, is readily converted (Scheme II) into 4-cyano-1-cholesten-3-one (**11**). Methylation of the potassium enolate of **11** gives 4β-cyano-4α-methyl-1-cholesten-3-one (**12**) in 68% yield from **10** and reduction of **12** produces 4β-cyano-4α-methylcholestan-3-one (**13**); **13** is also obtained if reduction to **14** precedes methylation. Attempts to find the C-4 epimer of **12** led only to the estimate that less than 5% is formed by either route. Oxygen methylation occurs to the extent of 10% in the alkylation of **11** and 27% in the alkylation of **14**. The fact that one epimer is produced in the carbon methylation of the enolate from 4-cyano-1-cholesten-3-one (**11**) while two are produced in the corresponding reaction of the enolate from 2-cyano-4-cholesten-3-one suggests that formally increasing steric hindrance to approach[7] of the alkylating agent favors the transition state which leads to the product with the nitrile in the more sterically hindered position.

The stereochemistry produced in alkylations of **12** and **14** is opposite to that observed for the major product from comparable keto esters;[1] thus, the two approaches provide reasonably efficient routes to different epimers at the 4 position. Control of the site of substitution of an unsymmetrical cyclohexanone by blocking of the favored site for formylation by a double bond introduced by dehydrogenation (*vide supra*) could prove useful for those cases in which formylation[8] and dehydrogenation[9] proceed at the same site.

The cyano group of the cyano ketones should be readily convertible to the acid, ester, aldehyde, methylenehydroxy, and methyl groups usually desired in terpenoid syntheses. By the procedures outlined in Scheme III, transformations of the cyano functions of **4**, **9**, and **13** to aldehydo and methyl groups have been achieved.[10] The geminal dimethyl ketones, 2,2-dimethylcholestan-3-one (**15**), 2,2-dimethyl-5β-cholestan-3-one (**16**), and 4,4-dimethylcholestan-3-one (**17**),



15, X = O **16**, X = O **17**, X = O
18, X = ···H, ◄OH **19**, X = ···H, ◄OH **20**, X = ···H, ◄OH

respectively, are produced in overall yields of *ca.* 30% *via* the corresponding alcohols **18**, **19**, and **20**. In addition to illustrating the conversions, this sequence provides structural confirmation by convergence with alcohols and ketones of established structure. The nonidentity of **15** and **16** supports the assignment of a *cis* A/B juncture for **9**.[11] A notable feature of this

(5) Production of a *cis* ring juncture in the lithium–ammonia reduction is in accord with the proposals of Stork and Darling,[6] provided that the relative energies of the transition states for hydrogen addition to the *cis* and *trans* conformations of the reduced anionic species from **8** are such that substituent interactions overcome the usual preference for a *trans* product. In the case of **8** the *trans* conformation of the reduced anionic intermediate has a severe 1,3-diaxial dimethyl interaction, and the *cis* conformation has a less demanding 1,3-diaxial cyano–C-9-proton interaction.

(6) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **82**, 1512 (1960).

(7) The formal difference between the two cases is an additional steric interaction involving the 6β hydrogen of the enolate of **11** and the alkylating species.

(8) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 267.

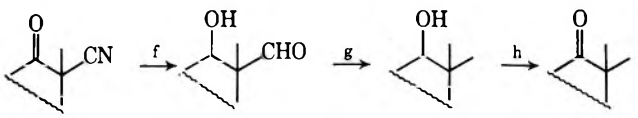
(9) L. M. Jackman, *Advan. Org. Chem.*, **2**, 329 (1960). Other methods of double-bond formation could also be used.

(10) E. Wenkert, P. Beak, R. W. J. Carney, J. W. Chamberlin, D. B. R. Johnston, C. D. Roth, and A. Tahara, *Can. J. Chem.*, **41**, 1924 (1963).

(11) The half-height widths of the C-10 methyl groups in the nmr spectra of **9** and **4** are 0.4 and 1.0 Hz, respectively, in the same order as the values reported for a series of *cis* (0.36 ± 0.07 Hz) and *trans* (0.84 ± 0.03 Hz) steroids.[12] This assignment is in agreement with the criteria for stereochemistry suggested by Williamson, Howell, and Spencer,[13] provided that the 2β-cyano function in **9** causes the same type of line broadening as does a 2β-halogen function.

(12) D. J. Cram, M. R. V. Sahyan, and R. R. Knox, *J. Amer. Chem. Soc.*, **84**, 1734 (1962); H. H. Szmant and M. N. Roman, *ibid.*, **88**, 4034 (1966).

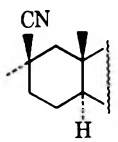
SCHEME III[a]



[a] f, $LiAlH_4$ or $LiAlH_2(OC_2H_5)_2$; H_3O^+; g, NH_2NH_2, KOH; or $HSCH_2CH_2SH$ $(C_2H_5)_2OBF_3$, RaNi; h, CrO_3–C_5H_5N or $Na_2Cr_2O_7$–H_2SO_4.

sequence is the effectiveness of the "low-temperature" Wolff–Kishner reduction[12] achieved without slow addition of the hydrazone, presumably because steric hindrance depresses the rate of competing azine formation.

Assignment of configurations of the geminal substituents of **4** and **13** is based on nmr spectroscopic and chemical correlations. The nmr chemical shifts of the C-10 methyl groups of **4** and **13** show downfield shifts of 0.25–0.36 ppm relative to cholestan-3-one (**1**) or its 2,2-dimethyl (**15**) or 4,4-dimethyl (**17**) derivatives. This deshielding is evidence for a 1,3-diaxial methyl–cyano interaction.[14,15] Reduction of the carbonyl groups of **4** and **13** of the ethane thioketal with Raney nickel produces 2β-cyano-2α-methylcholestane (**21**) and 4β-cyano-4α-methylcholestane (**22**), respectively.[17] The C-10 methyl resonances in the nmr spectra of **21** and **22** are deshielded by 0.32 and 0.34 ppm relative to cholestane. The C-10 methyl signal of **9** is within



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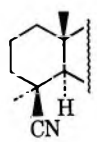

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±0.04 ppm of the C-10 methyl signals in the nmr spectra of **1**, **15**, and **17** and, as expected, is not deshielded. The deshielding effect of the cyano group in the spectra of **4**, **13**, **21**, and **22** is opposite to the shielding of the C-10 methyl observed in the spectra of analogous esters and keto esters.[1b,14a] Both effects are in agreement with expectation based on the group magnetic susceptibilities of the nitrile[14b] and ester functions,[18] provided that the latter has a conformation which places the C-10 methyl in a shielding cone of the carbonyl group. Corroboration for the axial assignment for the functionality in **4** and **13** is the characteristic long-range splitting of 2 Hz observed between the 3α proton and the aldehydo proton of the 2β- and 4β-formyl groups[14a,19] in the aldehydo alcohols obtained on reduction of the nitriles (Scheme III).

(13) K. L. Williamson, T. Howell, and T. A. Spencer, *J. Amer. Chem. Soc.*, **88**, 325 (1966).

(14) (a) E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, P. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, **30**, 713 (1965); (b) A. D. Cross and I. T. Harrison, *J. Amer. Chem. Soc.*, **85**, 3233 (1963); (c) J. Jacquesy, J. Lehn, and J. Levisalles, *Bull. Soc. Chim. Fr.*, 2444 (1961).

(15) The diamagnetic anistropy of the nitrile group also causes a large deshielding of the 4β proton in **4** (δ 2.91 ppm) and the 4α position in **9** (δ 3.37 ppm). These protons have a 1,3-diaxial location with respect to the nitrile. The assignments were confirmed by double-irradiation, "spin-tickling," and deuterium-exchange experiments. The Cotton effects of **4** and **9** confirm that ring A of these compounds has a chair conformation.[16]

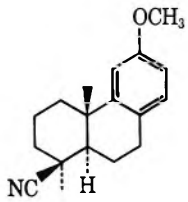
(16) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

(17) 2-Methylcholest-2-ene and 4-methylcholest-3-ene, respectively, are also produced in these reactions.

(18) H. M. McConnell, *J. Chem. Phys.*, **27**, 226 (1957).

(19) M. Fetizon, G. Moreau, and N. Moreau, *Bull. Soc. Chim. Fr.*, 3295 (1968).

Chemical evidence for the stereochemistry of the nitriles **4** and **13** is provided by a comparison of the hydrolytic characteristics of **21** and **22** with those of the models, O-methylpodocarponitrile (**23**), an axial nitrile, and dehydroabietonitrile (**24**), an equatorial nitrile.[20] Treatment of **21**, **22**, **23**, and **24** dissolved in ethylene glycol with aqueous potassium hydroxide at 150° for 24 hr gives complete hydrolysis of **24** and 85–91% recovery of unreacted **21**, **22**, and **23**. The



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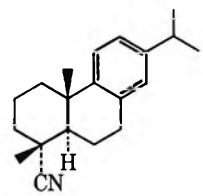
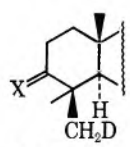


24

resistance to hydrolysis of the latter compounds is expected for these relatively hindered axial nitriles.[22,23]

Assignments of chemical shifts to the stereochemically different geminal C-4 methyl groups in the nmr spectra of 4,4-dimethyl-3-hydroxy sterols have been made on the basis of the expected similar response of the chemical shift of the 4β-methyl and C-10 methyl to 2β and 5α substituents.[24] These designations have been important in establishing that the methylation of 4-methyl-4-cholesten-3-one proceeds from the α side[25] and in determining the stereochemical course at C-4 of the enzymatic cyclization of squalene 2,3-oxide to lanosterol.[26] Nmr distinction between the 4,4-dimethyl groups has also been achieved for 3-keto-4,4-dimethyl steroids by use of model compounds and a solvent shift technique which shows that the equatorial methyl of steroidial 4,4-dimethyl-3-one shifts downfield and the axial methyl upfield when the solvent is changed from deuteriochloroform to benzene.[27] This synthetic sequence permits confirmation of the previous assignments without dependence on model compounds. The synthesis of 4,4-dimethylcholestan-3β-ol-3,30-d_2 (**25**) and 4,4-dimethylcholestan-3-one-30-*d* (**26**) was readily achieved by the previously discussed methods, with lithium aluminium deuteride being used for reduction of **13**. The nmr spectra of **25** contained a three-proton



25, X = D, OH
26, X = O

(20) The relative ease of hydrolysis of equatorial esters as contrasted with axial esters is an established method of determining stereochemistry in related systems.[1a,b,21]

(21) W. P. Campbell and D. Todd, *J. Amer. Chem. Soc.*, **64**, 928 (1942); F. E. King, D. H. Godson, and T. J. King, *J. Chem. Soc.*, 1117 (1955); J. M. Beaton and F. S. Spring, *ibid.*, 3126 (1955).

(22) E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.*, **80**, 211 (1958).

(23) M. R. Harnden, *J. Chem. Soc., C*, 960 (1969).

(24) F. Hemmert, A. Lablache-Combier, B. Lacoume, and J. Levisalles, *Bull. Soc. Chim. Fr.*, 982 (1966); F. Hemmert, B. Lacoume, J. Levisalles, and G. R. Pettit, *ibid.*, 967 (1966).

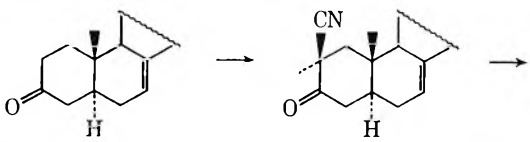
(25) D. Rosenthal, *J. Org. Chem.*, **32**, 4084 (1967).

(26) K. J. Stone, W. R. Roeske, R. B. Clayton, and E. E. van Tamelen, *Chem. Commun.*, 530 (1969).

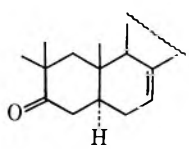
(27) N. S. Bhacca and D. H. Williams, *Tetrahedron Lett.*, 3127 (1964); N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry, Illustrations from the Steroid Field," Holden-Day, Inc., San Francisco, Calif., 1964, pp 165–170.

methyl resonance at δ 0.96 ppm (equatorial CH_3) and a *ca.* two-proton signal at 0.78 ppm (axial CH_2D), in agreement with previous work.[24] The nmr spectra of **26** show a three-proton signal which undergoes a downfield shift of 0.09 ± 0.01 ppm (equatorial CH_3) and a broadened signal which has an upfield shift of 0.14 ± 0.02 ppm (axial CH_2D) on changing the solvent from deuteriochloroform to benzene.

The synthetic sequence outlined in Schemes I–III offers a convenient route for the stereoselective introduction of geminal substituents at either methylene group of an unsymmetrical cyclohexanone. The reaction conditions are sufficiently mild that sensitive groups can be present and unaffected by the conditions for the conversions. For example, 7-cholesten-3-one (**27**), containing the sensitive Δ^7 double bond,[28] can be converted to 2β-cyano-2α-methyl-7-cholesten-3-one (**28**) and subsequently to 2,2-dimethyl-7-cholesten-3-one (**29**), if the acid hydrolysis of the imine produced on reduction of the ketonitrile is carried out at pH 3-4.



27 **28**



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Rationales for the stereochemistry of alkylation[2,4] in these and related systems should be constructed only in terms of the relative transition state energies[29] for the production of the epimeric products. Factors which should be considered in evaluation of alternative transition-state energies include electrophilicity of the alkylating agent, nucleophilicity of the enolate, steric hindrance and inductive effects of nonreacting groups in the molecule, effective sizes of the alkylating agent and groups on the enolate, the effect of the leaving group, bond distortion and torsional effects, the nature of the cation associated with the enolate, and the effect of ion aggregation. Differences in relative transition state energies of 1–2 kcal/mol could cause the differences in product ratios frequently observed in enolate alkylations; since any of the above factors could individually contribute this much difference, it may be that no broadly applicable yet unifying and rigorous analysis which has predictive value is possible.[30]

However, a useful simplifying assumption is that the same effects will be important in the different possible transition states. Kuehne and Nelson have recently analyzed the stereochemistry of methylation of enolates of 2-keto esters and 2-ketonitriles in carbocyclic six-membered rings in terms of the relative nucleophilicities of the enolates with attention given to steric hindrance, nonchair conformations, and cation chelation effects.[4] These rationales provide the best available correlation of previous results and should serve as the basis for further studies.

The stereochemistry of the alkylations of the enolates of cyanonitriles from **3**, **11**, and **14** can be rationalized in terms of twist boat productlike transition states which favor the smaller cyano group (*A* value, 0.2 kcal/mol)[31] in a sterically hindered position relative to the methyl group (*A* value, 1.7 kcal/mol),[31] with the alkylation of the enolate of 2-cyano-4-cholesten-3-one discussed in terms of reduced steric effects and flattening of ring A in the transition states for alkylation.

If different effects do have dominating significance in determining the relative energies of stereochemically different transition states for enolate alkylation, then fundamental understanding of these reactions may remain inextricable. Explanations will continue to be formulated *a posteriori*, with transition states being selected to accommodate the observed results.

In designing stereoselective alkylations of enolates at present, reliance must be placed primarily on previous experience whether stated as such or as a rationalization.

Experimental Section[32]

Materials.—Reagent grade anhydrous ether, absolute ethanol, methanol, methylene chloride, and chloroform were used without additional purification. Benzene, *t*-butyl alcohol, 1,4-dioxane, hexane, and diethylene glycol were distilled from metallic sodium. Dimethyl sulfoxide was percolated through molecular sieves and then distilled at reduced pressure. After preliminary drying over potassium carbonate, acetone was distilled from phosphorous pentoxide. Pyridine was stored over potassium hydroxide and was freshly distilled before use. The following reagents were obtained from the indicated suppliers and used without further purification: sodium methoxide and 99% hydrazine hydrate, Matheson Coleman and Bell; iodomethane, Eastman Organic Chemicals; potassium *t*-butoxide, Alfa Inorganics, Inc.; hydroxylamine hydrochloride, Mallinckrodt Chemical Works; lithium aluminum hydride and sodium borohydride, Ventron Corporation; 1,2-ethane dithiol and 2,3-dichloro-5,6-dicyano-1,5-benzoquinone (DDQ), Aldrich Chemical Co.; 10% palladium on charcoal, Engelhard Industries, Inc.; lithium aluminum deuteride, E. Merck Ag. Darmstadt (Germany); and chromium trioxide, Baker and Adamson Chemicals.

Product Isolation.—Reactions were cooled and then diluted with deionized water. The mixtures were neutralized, when necessary, and extracted at least five times with ether. The combined extracts were washed with water and saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate prior to solvent removal by evaporation at reduced pressure. Products were purified by column chromatography on Brinkmann 0.05–0.20-mm silica gel, when necessary.

(28) L. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 259.

(29) D. Y. Curtin, *Rec. Chem. Progr.*, **15**, 111 (1954).

(30) Attempts to rationalize the stereochemistry of hydride reduction of ketones and alkylations of piperidines appear to have foundered on oversimplifications. See M. Cherest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968), and D. R. Brown, R. Lygo, J. McKenna, J. M. McKenna, and B. G. Hotley, *J. Chem. Soc., B*, 1184 (1962), for relevant discussions.

(31) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1966, p 44.

(32) Melting points were determined on a Reichert block equipped with thermometers accurate to ±1°, as determined by mixture melting points for appropriate standards. Ir spectra were measured on Perkin-Elmer Model 521 and Model 137 instruments with sodium chloride cells containing 10% chloroform solutions. Uv spectra were measured with a Perkin-Elmer Model 202 spectrophotometer and 1.0-cm matched silica cells. The pmr spectra were measured with Varian Associates A-60A, A-56/60, and HA-100 spectrometers with approximately 30% solutions in chloroform-*d* unless otherwise noted. Chemical shifts are reported in δ, parts per million relative to the internal standard TMS (δ 0.0). Mr. R. L. Thrift conducted the spin-decoupling experiments with a Varian Associates HA-100 instrument. The mass spectra were determined by Mr. J. Wrona on an Atlas Model CH4 instrument equipped with a solid inlet system. Microanalyses were performed by Mr. J. Nemeth and associates. The optical rotation measurements were determined on a Zeiss 0.01° polarimeter. The optical rotatory dispersion measurements were performed by Dr. R. W. Woody on a Jasco Model ORD/UV-5 instrument. All reactions were carried out in a nitrogen atmosphere.

2β-Cyano-2α-methylcholestan-3-one (4).—2-Hydroxymethylenecholestan-3-one (5.38 g, 13 mmol), prepared from cholestan-3-one by the method of Beton, Halsall, Jones, and Phillips,[8,33,34] dissolved in 200 ml of hot *t*-butyl alcohol, was allowed to react with 1.1 g (15 mmol) of hydroxylamine hydrochloride at reflux for 1 hr. Product isolation yielded 5.2 g (12.6 mmol, 97% yield) of isoxazole as a tan solid (mp 128–132°). Recrystallization from methanol yielded 4.6 g of product (85% yield, mp 137–139°) which was free from starting material according to tlc and a ferric chloride test. The product's ir spectrum had a weak absorption at 1644 cm^{-1} and the nmr spectrum was consistent with the assigned structure.

The isoxazole, 3.9 g (9.65 mmol), was dissolved in hot methanol and 540 mg (10 mmol) of sodium methoxide was added. After 18 hr at reflux, 3.78 g (9.2 mmol, 95% yield) of light tan 2-cyanocholestan-3-one (**3**) was isolated. Recrystallization from absolute ethanol produced 3.6 g of white solid (mp 176–178°) which gave a weak ferric chloride test; ir 2200 and 1730 cm^{-1}; the nmr spectrum was consistent with the assigned structure.

Anal. Calcd for $C_{28}H_{45}NO$: C, 81.67; H, 11.04; N, 3.40. Found: C, 81.43; H, 11.09; N, 3.31.

Potassium *t*-butoxide (3 equiv, 1.5 g) was added to a solution of 1.83 g (4.46 mmol) of **3** (or the isoxazole) in *t*-butyl alcohol. A tan precipitate of the enolate formed while the solution was being heated at reflux for 10 min. Then 3 equiv of iodomethane was added and heating was continued for 45 min with repetitive additions of 1 equiv of iodomethane at 15-min intervals.

Extraction of the reaction mixture gave 1.9 g of white solid. Chromatography with 50% hexane–benzene (v/v) produced 15 mg of an unidentified oil and 1.2 g (59% yield, mp 187–190°) of 2β-cyano-2α-methylcholestan-3-one (**4**). 2-Cyano-3-methoxy-2-cholestene (505 mg, 27% yield, mp 184–187°) was then eluted. Further elution with benzene–ether gave 250 mg of an oil which appeared to be a mixture.

2β-Cyano-2α-methylcholestan-3-one (4) (905 mg, 48%, mp 194.5–196.0°) was obtained after two recrystallizations from ethanol: mass spectrum (14 eV) *m/e* 425; ir 2215 and 1720 cm^{-1}; the nmr spectrum contained 47 protons from δ 0.0–3.0 ppm with methyl singlets at δ 1.43, 1.34, and 0.68 ppm; ORD $[\alpha]^{24}D$ +104°, $[\alpha]_{316}{}^{max}$ +2616°, $[\alpha]_{270}{}^{min}$ −2642°, *A* +223° (*c* 0.422, $CHCl_3$).

Anal. Calcd for $C_{29}H_{47}NO$: C, 81.82; H, 11.13; N, 3.29. Found: C, 81.97; H, 11.20; N, 3.27.

After two recrystallizations from ethanol, 410 mg (22%, mp 190–191.5°) of 2-cyano-3-methoxy-2-cholestene was obtained: mass spectrum (14 eV) *m/e* 425; ir 2210 and 1640 cm^{-1}; the nmr spectrum was consistent with the assigned structure and was distinguished by a methyl singlet at δ 3.80 ($-OCH_3$); uv max (95% C_2H_5OH) 235 mμ (ε 1.2 × 10^4).

2α-Cyano-2β-methyl-5β-cholestan-3-one (9).—2-Hydroxymethylene-4-cholesten-3-one, 767 mg, prepared from 4-cholesten-3-one by the method of Beton, Halsall, Jones, and Phillips, was converted into the isoxazole derivative in 94% yield (724 mg, mp 105–110° after chromatography on silica gel with benzene) in the manner described above.

The isoxazole was quantitatively isomerized by basic methanol to 2-cyano-4-cholesten-3-one: mp 158–170°; ir 2230, 168, and 1610 cm^{-1}; the nmr spectrum was consistent with the assigned structure and was distinguished by a one-proton singlet at δ 5.77 ppm (C=CH). The structure of this product was confirmed by catalytic reduction with 10% palladium on charcoal in dioxane at 25° to a compound whose identity with **3** was demonstrated by melting point and mixture melting point (170–173°) and by nmr and ir spectral comparisons. In the same manner the unsaturated isoxazole was catalytically reduced to yield **2**, with identity established by mixture melting point and nmr and ir spectral criteria. These conversions establish that formylation had not proceeded at C-4 or C-6.

Alkylation with iodomethane of 2-cyano-4-cholesten-3-one, 8.35 g (or its isomeric isoxazole), by the above procedure yielded, after silical gel chromatography with 75% benzene–hexane (v/v), 3.76 g (0.89 mmol, 44%, mp 170–176°) of 2β-cyano-2α-methyl-4-cholesten-3-one (**7**) and 3.82 g (0.09 mmol, 44%, mp 111–118°) of 2α-cyano-2β-methyl-4-cholesten-3-one (**8**). These compounds were identified by ir spectra and by subsequent conversions.

2β-Cyano-2α-methyl-4-cholesten-3-one (7) (150 mg) was hydrogenated for 2 hr at room temperature and low pressure in absolute ethanol with 10% palladium on charcoal. After the catalyst had been separated by filtration, 140 mg of product was isolated (mp 180–189°). Two recrystallizations from absolute ethanol yielded 106 mg of 4 (mp 192–195°) which was identical with the previously prepared compound by nmr, ir, mass spectral, microanalytical, and mixture melting point comparisons.

Catalytic reduction of 1.12 g of **8** was achieved by the method described above. The product (1.02 g) was purified by silica gel chromatography with 50% benzene–hexane (v/v) as an elutent and recrystallization from absolute ethanol to yield 766 mg (68% yield) of 2α-cyano-2β-methyl-5β-cholestan-3-one (**9**): mp 140–141°; mass spectrum (14.5 eV) *m/e* 425; ir 2235 and 1725 cm^{-1}; the nmr spectrum was consistent with the assigned structure and contained methyl singlets at δ 1.44, 1.04, and 0.72 ppm; ORD $[\alpha]^{24}D$ −19°, $[\alpha]_{268}{}^{max}$ +2076°, $[\alpha]_{316}{}^{min}$ −1830°, *A* −165° (*c* 0.236, $CHCl_3$).

Anal. Calcd for $C_{29}H_{47}NO$: C, 81.82; H, 11.13; N, 3.29. Found: C, 81.72; H, 11.09; N, 3.33.

The reduction of **8** could be accomplished by condensation of 10 ml of ammonia into a stirred solution of 505 mg (1.2 mmol) of **8** in ether at −70° followed by the careful addition of 100 mg of lithium wire.[6] The reaction was maintained at the boiling point of ammonia for 1 hr and then the blue color was discharged by the addition of 2 g of ammonium chloride. After the ammonia had evaporated, wet ether was carefully added and extractive work-up produced a yellow oil which was chromatographed on silica gel with 50% benzene–hexane (v/v) to yield 493 mg (97% yield) of white solid identical with **9** by ir, melting point, and mixture melting point criteria.

1-Cholesten-3-one (10) was prepared[35,36] by treatment of 15.0 g (39 mmol) of **1** with 9.1 g (1.1 equiv) of DDQ at reflux in 250 ml of dioxane for 24 hr. The reaction mixture was filtered through 300 g of silica gel with methylene chloride, and evaporation of the solvent yielded 12.1 g of a mixture of cholestanone and 1-cholesten-3-one, which was purified by a modification of the procedure of Warnhoff.[37] The mixture was reduced with a large excess of sodium borohydride in methanol for 30 min at 25°. Extractive work-up yielded 12.2 g of the mixture of sterols which were oxidized[38] with 1.5 equiv of DDQ in 300 ml of *t*-butyl alcohol for 24 hr at 25°. After most of the solvent had been removed under reduced pressure and the residue had been filtered through 300 g of silica gel with methylene chloride, 7.3 g of 1-cholesten-3-one (mp 93–97°) was obtained. Two recrystallizations from absolute ethanol yielded **10**: 2.2 g; 15% yield; mp 100–101° (lit.[37] 101–102°); the nmr and ir spectra were consistent with the assigned structure.

4β-Cyano-4α-methylcholestan-3-one (13).—4-Hydroxymethylene-1-cholesten-3-one, prepared from 1.8 mmol of **10** by the method of Beton, Halsall, Jones, and Phillips,[33] was converted into the isoxazole derivative (602 mg, 81% overall yield, mp 107–112° after chromatography on silica gel with benzene) with hydroxylamine hydrochloride according to the above procedure. Recrystallization from absolute ethanol yielded an analytical sample with mp 111–114°; the nmr and ir spectra were consistent with the assigned structure.

Anal. Calcd for $C_{28}H_{43}NO$: C, 82.09; H, 10.58; N, 3.42. Found: C, 81.85; H, 10.56; N, 3.26.

This isoxazole was quantitatively isomerized to 4-cyano-1-cholesten-3-one (**11**) with sodium methoxide in methanol in the same way as previously described: mp 147–149°; ir 2250, 1680, and 1605 cm^{-1}; the nmr spectrum was consistent with the assigned structure including signals at δ 7.22 (d, 1, *J* = 10 Hz, CH=CH), 5.94 (d, 1, *J* = 10 Hz, CH=CH), 3.52 (d, 1, *J* = 13 Hz, –CHCN), 1.05 (s, 3, CH_3), and 0.70 (s, 3, CH_3). 4-Cyanocholestan-3-one (**14**) was obtained from the catalytic reduction (10% palladium on charcoal in 40 ml of dioxane at 25°) of 128 mg of **11** for 2 hr. Separation of the catalyst and removal of the solvent gave 128 mg of **14**: mp 184–186°; mass spectrum (9.5 eV) *m/e* 411, ir 2250 and 1720 cm^{-1}; the nmr spectrum was consistent with the assigned structure.

Anal. Calcd for $C_{28}H_{45}NO$: C, 81.69; H, 11.02; N, 3.40. Found: C, 81.50; H, 10.97; N, 3.22.

(33) J. Beton, T. G. Halsall, E. R. H. Jones, and P. C. Phillips, *J. Chem. Soc.*, 753 (1957).

(34) P. Morand, M. Flett, J. M. Lyall, and S. Stavric, *Steroids*, **8**, 679 (1966).

(35) A. B. Turner and H. J. Ringold, *J. Chem. Soc., C.* 1720 (1967).

(36) E. Caspi and P. J. Ramm, *Tetrahedron Lett.*, 181 (1969).

(37) E. W. Warnhoff, *J. Org. Chem.*, **27**, 4587 (1962).

(38) S. H. Burstein and H. J. Ringold, *J. Amer. Chem. Soc.*, **86**, 4952 (1964).

Alkylation with iodomethane of 128 mg of 4-cyanocholestan-3-one (14) by the method described above yielded, after chromatography on silical gel with 30% hexane-benzene (v/v), 66 mg (50% yield) of **13** and 3 mg of a mixture tentatively identified as 4-cyano-2,4-dimethylcholestan-3-one and 4β-cyano-4α-methylcholestan-3-one (**13**) on the basis of ir (2250 and 1720 cm^{-1}) and mass spectral (*m/e* 439 and 425) evidence. The analytical sample of **13** was obtained in 30% yield after recrystallization from absolute ethanol: mp 138–139°; mass spectrum (15 eV) *m/e* 425; ir 2250 and 1720 cm^{-1}; the nmr spectrum was consistent with the assigned structure and was distinguished by methyl singlets at δ 1.48, 1.36, and 0.70 ppm.

Anal. Calcd for $C_{29}H_{47}NO$: C, 81.82; H, 11.13; N, 3.29. Found: C, 81.71; H, 11.25; N, 3.23.

Elution with hexane–benzene gave 35 mg (27% yield) of 4-cyano-3-methoxy-3-cholestene: mp 174–178°; ir 2200 and 1630 cm^{-1}; the nmr spectrum was consistent with the assigned structure and was distinguished by a methyl singlet at δ 3.80 ppm.

Alkylation with iodomethane of 574 mg of 4-cyano-1-cholestene-3-one (**11**) according to the procedure described above gave, after silica gel chromatography with 50% hexane–benzene (v/v), 511 mg (86% yield) of 4β-cyano-4α-methyl-1-cholesten-3-one (**12**) which was recrystallized from absolute ethanol: mp 147–149°; 40% yield; ir 2250, 1675, and 1605 cm^{-1}; the nmr spectrum was consistent with the assigned structure, including signals at δ 7.30 (d, 1, J = 10 Hz, CH=CH), 5.98 (d, 1, J = 10 Hz, CH=CH), 1.60 (s, 3, CH_3), 1.18 (s, 3, CH_3), 0.72 ppm (s, 3, CH_3). Further elution yielded 60 mg (10% yield) of 4-cyano-3-methoxy-1,3-cholestadiene which was recrystallized from absolute ethanol: mp 165–168°; ir 2200, 1640, and 1575 cm^{-1}. 4β-Cyano-4α-methyl-1-cholesten-3-one (**12**) (350 mg) was converted into **13** (350 mg, mp 125–130°) by catalytic reduction with 10% palladium on charcoal in dioxane which after recrystallization from absolute ethanol (55% yield) was identical with the previously prepared product according to melting point, mixture melting point (138–139°) and ir and nmr spectral criteria. Catalytic reduction of 60 mg of 4-cyano-3-methoxy-1,3-cholestadiene in dioxane with 10% palladium on charcoal yielded 57 mg of 4-cyano-3-methoxy-3-cholestene, whose identity with the previously prepared product was established by melting point, mixture melting point, and ir spectral criteria.

2,2-Dimethylcholestan-3-one (15).—To an ethereal solution of 690 mg (1.62 mmol) of **4** cooled to about 5° was added a slurry of 130 mg (3.42 mmol) of lithium aluminum hydride in ether. Stirring was continued for 15 min while the mixture was allowed to warm to room temperature. The excess reducing agent was destroyed with a paste of sodium sulfate and water. Excess 10% hydrochloric acid was added and the mixture was heated at reflux on a steam bath for 2 hr. Product isolation gave a solid in 51% yield (358 mg, 0.83 mmol, mp 119–126°). Recrystallization of 60 mg from ethanol yielded 29 mg of 2β-formyl-2α-methylcholestan-3β-ol: mp 125–127°; ir 3400, 2690, and 1710 cm^{-1}; the nmr spectrum was consistent with the assigned structure and was distinguished by signals at δ 9.59 (d, 1, J = 2 Hz, CHO) and 3.4 ppm (broad, 1, CHOH).

Anal. Calcd for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found: C, 80.82; H, 11.65.

To a solution of 294 mg (0.68 mmol) of 2β-formyl-2α-methylcholestan-3β-ol in 100 ml of diethylene glycol was added 15 ml of 99% hydrazine hydrate. The reaction mixture was maintained at 115° for 5 hr and then cooled. After the addition of 16 g of potassium hydroxide the reaction was heated to 160° for 6 hr. Extractive work-up of the cooled solution produced a gelatinous white material which was chromatographed on silica gel. From the benzene elutent, 2,2-dimethylcholestan-3β-ol was isolated in 62% yield (177 mg, mp 134–138°). Recrystallization from absolute ethanol gave 2,2-dimethylcholestan-3β-ol (43%, mp 142–144°). The acetate, prepared by the method of Mazur and Sondheimer,[39] melted at 127–129° (lit. sterol mp 116–118°,[39] 118–120°,[40] acetate mp 124–126° [39,40]).[41] The alcohol and its acetate showed undepressed mixture melting points and nmr spectra identical with those of the authentic compounds.[39]

A solution of 177 mg of 2,2-dimethylcholestan-3β-ol in 25 ml of benzene was added to 10 ml of a cold chromic acid solution prepared by dissolving 13.6 g of sodium dichromate in 60 ml of water, 18 ml of sulfuric acid, and 10 ml of acetic acid.[42] After the solution had been stirred at room temperature for 24 hr, the benzene layer was separated and the aqueous phase was extracted with benzene. After the combined organic phase had been washed twice with water, once with 5% sodium hydroxide, and twice more with water and dried over magnesium sulfate, the solvent was removed at reduced pressure. A 98% yield (172 mg, mp 95–99°) of 2,2-dimethylcholestan-3-one (**15**) was obtained which was recrystallized (75% yield) from absolute ethanol: mp 97–99° (lit.[43] mp 98–100°); mass spectrum (12.5 eV) *m/e* 414; ir (CS_2) 1702 cm^{-1} (C=O); the nmr spectrum was consistent with the assigned structure.

Anal. Calcd for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 83.83; H, 11.94.

2β-Formyl-2α-methylcholestan-3β-ol (90 mg, 0.21 mmol) was dissolved in 50 ml of absolute ethanol containing 1 ml of triethylamine and 6 ml of 99% hydrazine hydrate. After the solution had been heated for 1 hr at reflux, it was poured into ether and washed with cold 10% hydrochloric acid until the amine odor was not detectable. The ethereal solution as dried over magnesium sulfate and evaporated to yield 79 mg (85% yield, mp 135–145°) of the hydrazone: ir 3400, 1640, and 1610 cm^{-1}; the nmr spectrum was consistent with the assigned structure and was distinguished by signals at δ 7.0 (s, 1, $-CH=NH_2$) and 5 ppm (broad, s, 2, NH_2). The crude hydrazone (30 mg in 0.5 ml of benzene) was added to 25 ml of dimethyl sulfoxide,[13] 200 mg of potassium *t*-butoxide, and 0.25 ml of *t*-butyl alcohol. The reaction was maintained at 70° for 30 min, after which time the product isolation produced 15 mg of oil. After silica gel chromatography with benzene, 9 mg of 2,2-dimethylcholestan-3β-ol was isolated (mp 139–142°, 32% yield, 27% yield from the aldehyde). Oxidation of this material (CrO_3) produced a ketone (mp 92–95°) which was identical with authentic 2,2-dimethylcholestan-3-one by mixture melting point and nmr and ir spectral criteria.

4,4-Dimethylcholestan-3-one (17).—4β-Cyano-4α-methylcholestan-3-one (**13**) (108 mg) was reduced with lithium aluminum hydride as described above. The isolated aldehyde (53 mg) was subjected to the Wolff–Kishner reduction and 4,4-dimethylcholestan-3β-ol (30 mg, 28% yield) was isolated after chromatography on silica gel with benzene: mp 152–155° (lit.[44] 156–157°), the ir and nmr spectra were consistent with the assigned structure. A partially reduced compound, 4β-cyano-4α-methylcholestan-3-ol, 9 mg, was recovered from the chromatography column.

4,4-Dimethylcholestan-3β-ol (30 mg) was oxidized with chromic acid as described above and 4,4-dimethylcholestan-3-one (**17**) (30 mg, mp 95–100°) was isolated after chromatography on silica gel with hexane–benzene. Recrystallization from absolute ethanol gave a 65% yield of **17**: mp 100–101° (different from 2,2-dimethylcholestan-3-one by mmp 59–76°); mass spectrum (14 eV) *m/e* 414; ir (CS_2) 1703 cm^{-1} (lit. mp[33] 100–101°; ir (CS_2)[40] 1703 cm^{-1}); the nmr spectrum was consistent with the assigned structure and showed three methyl singlets between δ 1.09 and 1.07 ppm in addition to the C-18 methyl singlet at 0.68 ppm.

Anal. Calcd for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 84.15; H, 12.04.

2,2-Dimethyl-5β-cholestan-3-one (16).—2α-Cyano-2β-methyl-5β-cholestan-3-one (**9**, 766 mg, 1.8 mmol), dissolved in ether, was treated with excess lithium diethoxyaluminohydride[45] (from 1.38 g of lithium aluminum hydride and 4.23 ml of absolute ethanol) in ether. After the mixture had been stirred at room temperature for 1 hr, the reaction was quenched. The mixture was then acidified with 10% aqueous hydrochloric acid and hydrolyzed at 60° for 12 hr. Product isolation gave 445 mg of 2α-formyl-2β-methyl-5β-cholestan-3-ol, as evidenced by ir absorptions at 3600, 2750, and 1720 cm^{-1}. The aldehyde, 90 mg, was dissolved in 0.05 ml of ethanedithiol, 0.1 ml of 98% boron trifluoride etherate was added, and the solution was allowed to stand for 30 min at room temperature. The resulting solidified mass was filtered, washed with cold methanol, and then dissolved in absolute ethanol and refluxed for 5 min with 2 cm^3

(39) Y. Mazur and F. Sondheimer, *J. Amer. Chem. Soc.*, **80**, 5220 (1958).

(40) I. Malunowicz, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **13**, 73 (1965).

(41) It has been found that at least one[40] of the previously reported 3β-sterols was impure and the corrected melting point is 143–144°: I. Malunowicz, personal communication, Feb 1968.

(42) W. F. Bruce, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley & Sons, Inc., New York, N. Y., 1943, p 139.

(43) F. Sondheimer, Y. Klibansky, Y. M. Y. Hadad, G. R. Summers, and W. Kyne, *J. Chem. Soc.*, 767 (1961).

(44) N. W. Atwater, *J. Amer. Chem. Soc.*, **82**, 2847 (1960).

(45) H. C. Brown and C. P. Garg, *ibid.*, **86**, 1085 (1964).

of W-2 Raney nickel.[46,47] After the catalyst had been separated by filtration and thoroughly washed with methylene chloride, the residue of 65 mg of material obtained by evaporation of the solvent was chromatographed on silica gel. Benzene elution gave a 2,2-dimethyl-5β-cholestan-3-ol (47 mg, mp 43–46°), which was not identical with 2,2-dimethylcholestan-3β-ol by tlc comparison. Chromic acid oxidation of 43 mg of the alcohol yielded 37 mg of 2,2-dimethyl-5β-cholestan-3-one (**16**), which was chromatographed on silica gel (31 mg isolated, 72% yield) and was not identical with 2,2-dimethylcholestan-3-one (**15**) by mixture melting point (52–79°) and tlc comparisons. 2,2-Dimethyl-5β-cholestan-3-one had mp 78–80°, mass spectrum (12.5 eV) *m/e* 414, ir 1700 cm^{-1}; the nmr spectrum was consistent with the assigned structure with methyl singlets at δ 1.24, 1.09, 1.04, and 0.72 ppm.

Anal. Calcd for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 84.12; H, 11.93.

2β-Cyano-2α-methylcholestane (**21**).—To **4** (636 mg, 1.48 mmol) dissolved in 30 ml of glacial acetic acid and 1 ml of ethanedithiol was added 10 ml of 98% boron trifluoride etherate and the mixture, which solidified within 5 min, was allowed to stand overnight. The product, obtained by evaporation of the solvent after addition of methanol, filtration, and one wash with cold methanol, was purified by dissolution in chloroform and precipitation by the addition of methanol to yield 576 mg of white thioketal: mp 189–192°; ir 2225 cm^{-1}; mass spectrum (12.5 eV) *m/e* 501; the nmr spectrum was consistent with the assigned structure and was distinguished by a four-proton multiplet at δ 3.4 ppm (-SC_2H_4S-). The thioketal was dissolved in hot acetone, 8 cm^3 of Raney nickel[48] under a small amount of ethanol was added, and the mixture was heated at reflux for 10 min. The mixture was then rapidly filtered and the catalyst was washed thoroughly with methylene chloride. Evaporation of the filtrate produced 330 mg of solid which was chromatographed on silica gel.

Elution with hexane gave an oil (79 mg, 14%) which crystallized on standing (mp 97.5–98.5°) and was identified as 2-methyl-2-cholestene (lit.[49] mp 97–97.5°): mass spectrum (13 eV) *m/e* 384; the ir and nmr spectra were consistent with the assigned structure; the nmr spectrum included a broad one-proton singlet at 5.3 ppm (C=C**H**).[50]

A 50% hexane–benzene (v/v) mixture was used to elute 248 mg (48%) of 2β-cyano-2α-methylcholestane (**21**) (mp 170–177°). Recrystallization from absolute ethanol gave 115 mg (22%) of material: mp 178.5–180°; ir 2211 cm^{-1}; mass spectrum (14.5 eV) *m/e* 411; the nmr spectrum was consistent with the assigned structure.

Anal. Calcd for $C_{29}H_{49}N$: C, 84.60; H, 12.00; N, 3.40. Found: C, 84.62; H, 11.93; N, 3.37.

4β-Cyano-4α-methylcholestane (**22**) was produced from 207 mg of 4β-cyano-4α-methylcholestan-3-one (**13**) by formation of the thioketal and reduction with Raney nickel according to the above procedure. Chromatography of the product on silica gel with hexane yielded 46 mg (23% yield) of 4-methyl-3-cholestene: mp 62–65°; mass spectrum (12.5 eV) *m/e* 384; the nmr and ir spectra were consistent with this assignment. Elution with hexane–benzene gave 52 mg (26% yield) of **22** (mp 115–130°). Two recrystallizations from absolute ethanol gave the analytical sample: mp 142–144°; 16% yield; mass spectrum (15 eV) *m/e* 411; ir 2230 cm^{-1}; the nmr spectrum was consistent with the assigned structure.

Anal. Calcd for $C_{29}H_{49}N$: C, 84.60; H, 12.00; N, 3.40. Found: C, 84.59; H, 11.77; N, 3.29.

Comparative Hydrolysis Rates.—The following compounds were sealed in 5-ml ampoules containing a basic solution prepared from 5 g of potassium hydroxide, 3 ml of water, and 25 ml of ethylene glycol: O-methylpodocarponitrile (**23**),[3c] identified by melting point and nmr, ir, and mass spectral criteria; dehydroabietonitrile (**24**),[14a] identified by melting point and nmr, ir, and mass spectra; 2β-cyano-2α-methylcholestane (**21**); and 4β-cyano-4α-methylcholestane (**22**). The ampoules were heated to 150° for 24 hr and cooled and the contents were neutralized with 10% aqueous hydrochloric acid. Product isolation resulted in a 99–100% weight balance. Ir spectra of the product mixtures showed a small amount of carbonyl absorption in every case due to amide or acid functionalites. After hydrolysis of **24** no starting material was detected by ir or tlc and a 100% weight yield of an oily acid was extracted from hexane with 10% potassium hydroxide in methanol. The dehydroabietic acid was converted to its methyl ester with diazomethane and was characterized by its nmr spectrum. Silica gel chromatography of the product mixtures gave the results summarized in Table I.

TABLE I

Compound	Weight, mg	Basic solution, ml	Isolated starting material, %
21	21	2	86
22	24	1.5	91
23	13	1	85
24	13	1	0

4,4-Dimethylcholestan-3β-ol-3,30-d_2 (**25**).—This compound was synthesized by the procedure described above for 4,4-dimethylcholestan-3β-ol by substituting lithium aluminum deuteride for lithium aluminum hydride. The deuterated product **25** was isolated in 18% yield (mp 152–154°). After recrystallization from absolute ethanol, **25** melted from 154 to 155° (10% yield) and its nmr, ir, and mass spectra (*m/e* 418 at 12.5 eV) were consistent with the assigned structure. Oxidation with chromic acid by the previously described procedure gave 4,4-dimethylcholestan-3-one-30-*d*; ir, nmr, and mass spectra were consistent with the assigned structure.

2,2-Dimethyl-7-cholesten-3-one (**27**) was prepared from 7-cholesten-3-one in 5% yield by the procedures previously described exept that hydrolysis of the imine produced by reduction of the cyano ketone with lithium aluminum hydride was achieved by making the reaction mixture slightly acidic (pH 3–4) with 10% aqueous hydrochloric acid and stirring at room temperature for 15 hr. The resultant aldehyde was reduced in dimethyl sulfoxide as described above.

2β-Cyano-2α-methyl-7-cholesten-3-one (**28**) had mp 181.5–183.0°; mass spectrum (14 eV) *m/e* 423; ir 2215 and 1720 cm^{-1}; the nmr spectrum was consistent with the assigned structure and was distinguished by signals at δ 5.2 (broad, 1, C**H**=C), 1.43 (s, 3, CH_3), 1.33 (s, 3, CH_3), and 0.57 ppm (s, 3, CH_3).

Anal. Calcd for $C_{29}H_{45}NO$: C, 82.21; H, 10.71; N, 3.31. Found: C, 81.99; H, 10.47; N, 3.13.

2,2-Dimethyl-7-cholesten-3-one (**29**) had ir 1700 and 1605 cm^{-1}; mass spectrum (15.5 eV) *m/e* 412; the nmr spectrum was consistent with the assigned structure including signals at δ 5.2 (broad, 1, C**H**=C), 1.25 (s, 3, CH_3), 1.11 (s, 3, CH_3), 1.07 (s, 3, CH_3), and 0.68 ppm (s, 3, CH_3).

Anal. Calcd for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.10; H, 11.68.

Registry No.—**3**, 24164-61-2; **4**, 24164-62-3; **7**, 24164-63-4; **9**, 24164-64-5; **11**, 24215-74-5; **12**, 24164-65-6; **13**, 24164-66-7; **14**, 24164-67-8; **15**, 2542-57-6; **16**, 24164-69-0; **17**, 2097-85-0; **21**, 24164-90-7; **22**, 24164-91-8; **25**, 24164-92-9; **28**, 24164-93-0; **29**, 24164-94-1; isoxazole derivative of 4-hydroxymethylene-1-cholesten-3-one, 24164-95-2; 4-cyano-3-methoxy-1,3-cholestadiene, 24164-96-3; 2β-formyl-2α-methylcholestan-3β-ol, 24164-97-4; 2,2-dimethylcholestan-3β-ol, 2542-65-6; 2β-formyl-2α-methylcholestan-3β-ol hydrazone, 24164-99-6; 4-methyl-3-cholestene, 6785-18-8.

(46) L. F. Fieser, C. Yuan, and T. Goto, *J. Amer. Chem. Soc.*, **82**, 1996 (1960).

(47) R. Mozingo, "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley & Sons, Inc., New York, N. Y., 1955, p 181.

(48) A. W. Burgstahler, personal communication cited in L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 729.

(49) C. Djerassi, N. Finch, R. C. Cookson, and C. W. Bird, *J. Amer. Chem. Soc.*, **82**, 5488 (1960).

(50) Elimination is known to compete with desulfurization of thioketals, particularly under the mild reaction conditions necessary for this reaction: C. Djerassi and D. H. Williams, *J. Chem. Soc.*, 4046 (1963).

Acknowledgment.—We are grateful to the Public Health Service (GM-12595) and the Alfred P. Sloan Foundation for support and to the Public Health Service for fellowship support of Tommy L. Chaffin. We wish to thank Professor Ernest Wenkert for samples of podocarpic acid and dehydroabietonitrile, Professor Robert Woody for ORD measurements, and Professor George Schroepfer for stimulating discussions.

Diborane Reductions of Oxygen Heterocycles. Synthesis of 3-Chromanols and 3-Chromanones

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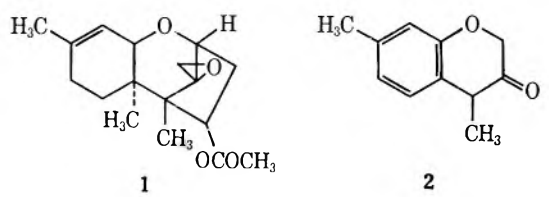
Hydroboration–oxidation of coumarin and 4,7-dimethylcoumarin affords 3-chromanol and 4,7-dimethyl-3-chromanol. Chrom-2-ene and chromone also afford 3-chromanol, and 3-methylcoumarin yields 3-methyl-4-chromanol. Oxidation of 4,7-dimethyl-3-chromanol with dicyclohexylcarbodiimide and dimethyl sulfoxide produces 4,7-dimethyl-3-chromanone, thus providing a quicker route to this type of ketone than previously reported methods. The three coumarins also yield as products of these reactions 3-(*o*-hydroxyphenyl)propane-1,2-diols. The specificity of these reactions in leading to the vicinal glycols is attributed to the effect of the phenolic oxygen. Reduction of flavone under these conditions leads to no cyclic product, but rather to a dibenzyl alcohol which results from the hydrogenolysis of a benzylic–allylic carbon–oxygen bond.

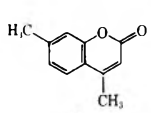
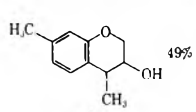
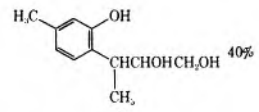
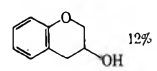
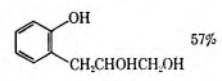
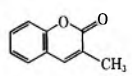
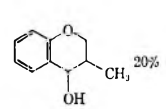
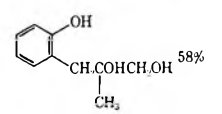
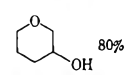
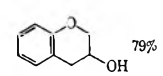
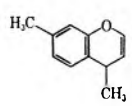
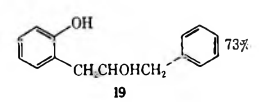
As part of a program directed toward the synthesis of trichodermin[1] (**1**) and related sesquiterpenes, we required 4,7-dimethyl-3-chromanone (**2**) as an intermediate. Previous syntheses reported for the 3-chromanone system have usually required the preparation of *o*-(carboxymethoxy)phenylacetic acids and their cyclization by either Dieckmann reaction of the corresponding diesters[2-4] or as in the original synthesis of 3-chromanone itself,[5] acetic anhydride catalyzed reaction of the diacid. In these syntheses, however, the particular 3-chromanone involved was generally the ultimate synthetic goal. Thus a lengthy route to a carboxymethylphenylacetic acid was a reasonable price to pay for obtaining the desired ketone. In our case such an expenditure of experimental effort in a multistep route to a synthetic intermediate was clearly undesirable, and we therefore sought a shorter route to **2** from readily available starting materials.



One such material is 4,7-dimethylcoumarin (**3**) (Table I), the Pechmann reaction product of *m*-cresol and acetoacetic ester. We have investigated a number of routes for the conversion of **3** to 3-oxygenated chroman systems, but one in particular, hydroboration–oxidation of **3**, has led directly to the desired structural type. Thus, continuous passage of externally generated diborane through a tetrahydrofuran solution of **3** followed by hydrogen peroxide oxidation of the intermediate alkylborane yielded 49% 4,7-dimethyl-3-chromanol (**4**). A second product, the triol **5**, obtained in 40% yield was readily separated from **4** by extraction of the reaction product mixture with aqueous base. The conversion of **4** to 4,7-dimethyl-3-chromanone (**2**) was then effected in 84% yield by Moffat oxidation[6] employing dicyclohexylcarbodiimide, dimethyl sulfoxide, and monophenyl phosphate.

TABLE I

HYDROBORATION–OXIDATION PRODUCTS OF OXYGEN HETEROCYCLES

Substrate	Cyclic product and yield	Acyclic product and yield
 **3**	 49% **4**	 40% **5**
Coumarin	 12%	 57% **14**
 **12**	 20% **13**	 58% **15**
Dihydropyran	 80%	
Chromone	 79%	
 **6**	4 88%	
Flavone		 73% **19**

The structural assignments of **4**, **5**, and **2** follow from their spectral characteristics. The nmr spectrum of **4**, for example, displays a two-proton multiplet at 3.71 ppm for the C_2-methylene group as well as a doublet for the C_4-methyl group at 1.12 ppm, and two one-proton multiplets at 2.53 and 3.43 ppm for the C_3

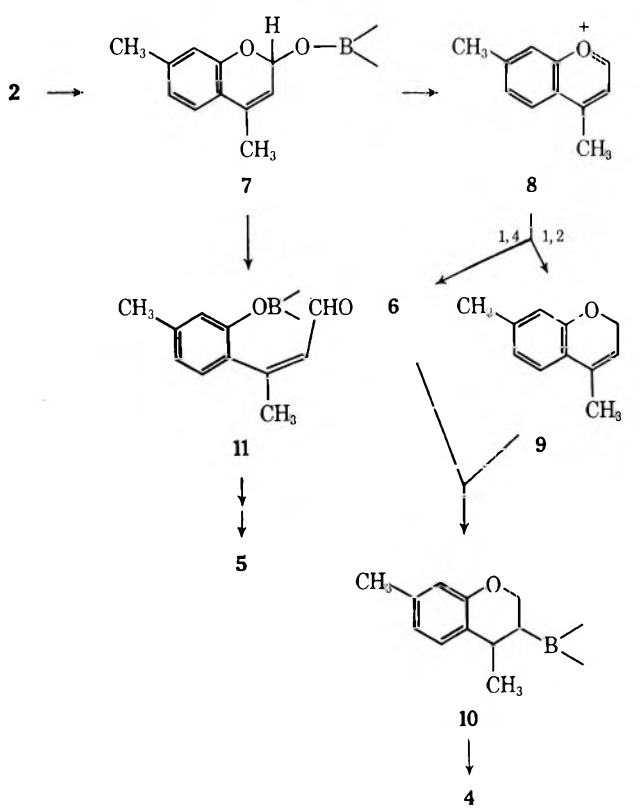
(1) S. Abrahamsson and B. Hilsson, *Proc. Chem. Soc.*, 188 (1964).
(2) A. Robertson and G. Rusby, *J. Chem. Soc.*, 212 (1936).
(3) N. S. Vul'fson, T. N. Podrezova, and L. B. Senyavina, *Zh. Obsch. Khim.*, **34**, 2676 (1964).
(4) M. Miyano and M. Matsui, *Bull. Chem. Soc. Jap.*, **31**, 267 (1958).
(5) P. Pfeiffer and E. Enders, *Chem. Ber.*, **84**, 247 (1951).
(6) K. E. Pfitzner and J. G. Moffat, *J. Amer. Chem. Soc.*, **87**, 5661 (1965).

and C_4 protons, respectively. The C_2- and C_4-proton resonances show appropriate downfield shifts from the values given above in the spectrum of the oxidation product **2**, and the signal for the C_2-methylene group occurs as an AB pattern in the latter spectrum. Chemical evidence for the structure of **4** was obtained by the demonstration that 4,7-dimethyl-2-chromene (**6**), prepared by the pyrolysis of 4,7-dimethyl chromane-2-acetate,[7] was converted to the same alcohol **4** by the action of diborane and hydrogen peroxide, and dihydropyran under the same conditions gave tetrahydropyran-3-ol.[8]

The nmr spectrum of the triol **5** shows that the two aliphatic hydroxyl groups must have a vicinal relationship since the signal for the benzylic methyl group occurs as a doublet. In addition, the mass spectrum of **5** shows prominent peaks at *m/e* 165 and 135 for loss of the fragments $\cdot CH_2OH$ and $\cdot CHOHCH_2OH$, respectively.

A likely pathway for the multistep reduction of 4,7-dimethylcoumarin can be described by the sequences shown in Scheme I. Thus, production of a 3-chromanol

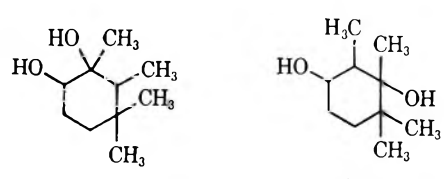
SCHEME I



from **3** would appear to require first hydride reduction to yield a hemiacetal borate **7** followed by dissociation of the latter to a pyrylium salt **8**. This species should then undergo rapid reduction by either 1,4 or 1,2 addition of hydride to yield **6** or **9**. The final reduction step, hydroboration of the double bond of either **6** or **9**, would then produce the 3-chromanylborane **10**. The second product of the overall reduction sequence, **5**, would appear to arise from the alternative pathway described in Scheme I. If **7** undergoes ring opening, the resulting aldehyde **11** would suffer further reduction to eventually yield a borane convertible to **5**.

In order to test the validity of these reaction schemes and to explore the generality of the reduction process, we undertook the investigation of the reaction of diborane with a number of oxygen heterocycles. Table I lists the compounds reduced and the products isolated in each case. In the cases of reduction of three coumarins, a 2-chromene, and dihydropyran, the chromanol type of product is clearly the result of the usual directive effects that operate in hydroboration reactions, that is, production of the least substituted alcohol from an unsymmetrically substituted olefin[9] or formation of the β-ol product from a vinyl ether system.[10] Thus, 4,7-dimethylcoumarin (**3**), 4,7-dimethyl-2-chromene (**6**), and coumarin yield 3-chromanols, and 3-methylcoumarin (**12**) affords 3-methyl-4-chromanol (**13**). The last result also indicates that reduction of the proposed pyrylium salt shown in Scheme I for the reduction of **3** occurs by a 1,2 rather than by a 1,4 process. If a 2-chromene, the product of 1,4 addition, were an intermediate in these reactions, then each of these examples should have yielded a 3-chromanol.

The second series of products shown in Table I, the ring-opened compounds **5**, **14**, and **15** all appear to arise as suggested in Scheme I by hydroboration of an intermediate *o*-hydroxycinnamyl system. In all three cases the product is a vicinal diol despite the fact that **15** must arise from carbon–boron bond formation at the *most* substituted position of a double bond. A recent study[11] of the hydroboration of cyclic conjugated enones has shown that these systems yield vicinal diols also. The authors of this work showed that the first step in these reactions was the reduction of a cyclohexenone to the corresponding allylic borate, and they ascribed their results to the directive influence of the oxygen atom of this first reduction product. None of the cases studied, however, featured alkyl substitution (as in **12**) which could be expected to counter the suggested directive effect of the borate oxygen. There are, furthermore, a number of other reports that suggest that this directive effect is less general than has been suggested.[11] For example, hydroboration of 2,3,4,4-tetramethylcyclohex-2-enone has been shown[12] to yield **16** and **17** in the ratio of approximately 2:1, and the reduction of cinnamyl alcohol with diborane has been reported[13] to lead to a mixture of 3-phenylpropane-1,2- and -1,3-diols.



16 **17**

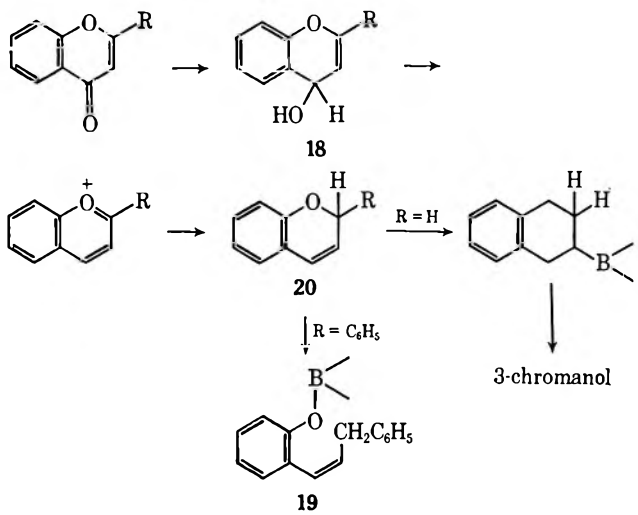
In our cases, the key to the specificity that we have found appears to be the presence of an oxygen atom conjugated with the reducible double bond. This type of effect has been shown previously to occur in the

(7) W. E. Parham and L. D. Huestis, *J. Amer. Chem. Soc.*, **84**, 813 (1962).
(8) S. A. Barker, J. S. Brimacombe, A. B. Foster, D. H. Whiffen, and G. Zweifel, *Tetrahedron*, **7**, 10 (1959).
(9) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **82**, 4708 (1960).
(10) D. J. Pasto and C. C. Cumbo, *ibid.*, **86**, 4343 (1964).
(11) J. Klein and E. Dunkleblum, *Tetrahedron*, **24**, 5701 (1968).
(12) A. Uzarewicz, I. Uzarewicz, and W. Zacharewicz, *Rocz. Chem.*, **39**, 19 (1965).
(13) K. Kratzl and P. Claus, *Monatsh. Chem.*, **94**, 1140 (1963).

hydroboration of substituted styrenes by Brown and Sharp[14] who found that styrene, *o*-methoxystyrene, and *p*-methoxystyrene afford 81, 86, and 93%, respectively, of the β-ol product. The latter two results were correlated with the electron-donating resonance effects of *o*- and *p*-methoxyl substituents. In the examples investigated in the present work this effect, now of an *o*-borate substituent, coupled with that of the aliphatic borate group,[11] is apparently sufficient to produce only the β-ol product regardless of the position of alkyl substitution on the double bond.

As noted above hydroboration–oxidation of coumarins leads to both chromanols and 3-phenylpropanediols. In contrast, the chromone system ought to yield only the cyclic product since the initial product of reduction of a chromone, **18** (Scheme II), cannot

SCHEME II



tautomerize to an open-chain isomer. This conclusion was borne out by the result of hydroboration of chromone itself which was the production of 3-chromanol in 79% yield. When the same procedure was applied to flavone, however, no cyclic alcohol product was obtained. Instead we found that the dihydroxy compound **19** was produced in 73% yield. As suggested in Scheme II the reduction sequence with chromones follows the same course as the reduction of coumarins through the step involving hydride addition to the intermediate pyrylium salt to yield a chromene **20**. At this point, however, an additional hydride transfer step appears to take place in the case of the phenylchromene that results in cleavage of the heterocycle. That this step should occur in the reduction of the flavone and not in that of chromone itself is not surprising in view of the benzylic–allylic nature of the carbon–oxygen bond which suffers hydrogenolysis in the flavone case.

Experimental Section

All melting points were determined on an Arthur A. Thomas Co. Uni-Melt capillary melting point instrument. Analyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind. Infrared spectra were taken on a Perkin-Elmer Model 257 spectrophotometer. Nmr spectra were recorded on a Varian Associates T-60 spectrometer and data are reported in parts per million from internal tetramethylsilane (TMS). All mass spectra were obtained on a Varian Associates M-66 spectrometer, and precise mass calculations were performed on a Digital, Inc., PDP-9 computer. Precise mass data are given for the molecular ion unless otherwise specified.

4,7-Dimethylcoumarin (3).—*m*-Cresol (300 g, 2.00 m) was allowed to react with acetoacetic ester (260 g, 2.78 mol) according to the method of Fries and Klostermann,[15] and the crude product was recrystallized from methanol to yield blunt needles (254 g, 73%), mp 129–130° (lit.[15] mp 132°).

4,7-Dimethyldihydrocoumarin.—4,7-Dimethylcoumarin (20 g, 0.15 mol) was dissolved in 200 ml of acetic acid containing 10% palladium on charcoal (3 g). This mixture was shaken with hydrogen at 50 psi until the theoretical amount (0.15 m) of the gas had been adsorbed (3–5 hr). The catalyst was then removed by filtration through Celite 545 and the solvent was evaporated to yield a yellow oil. This crude product was distilled *in vacuo* to give a clear oil (19.4 g, 96%): bp 122° (1.25 mm); ir (neat 1754 cm^{-1} (C=O); nmr (CCl_4) 6.95 (m, 3), 3.12 (m, 1), 2.55 (m, 2), 2.33 (s, 3), 1.27 (d, 3, J = 6 Hz).

4,7-Dimethylchroman-2-ol.—Lithium aluminum hydride (3.42 g, 0.090 mol) and 50 ml of anhydrous tetrahydrofuran were placed in a 250-ml three-neck flask fitted with an addition funnel, stirrer and reflux condenser and cooled to 0°. Anhydrous *t*-butyl alcohol (19.9 g, 0.27 mol) was added dropwise with stirring over a 1-hr period; the mixture was allowed to warm to room temperature and then stirred an additional 30 min. This hydride solution ws then diluted with an additional 100 ml of anhydrous tetrahydrofuran and transferred to an addition funnel. 4,7-Dimethyldihydrocoumarin (15.9 g, 0.090 mol) was dissolved in 100 ml of anhydrous tetrahydrofuran and cooled to −60° in a Dry Ice–acetone bath. The hydride solution was then added dropwise over a period of 2 hr and the mixture was allowed to warm to room temperature. After pouring the mixture into ice water, the precipitated salts were filtered from the solution using Celite 545, and the filtrate was extracted four times with ether. The salts were then refluxed with 200 ml of ether, the salts filtered, and all extracts combined, washed, and dried (Na_2SO_4). The solvent was removed to give a yellow oil which was distilled *in vacuo* to yield 12.9 g (82%) of a transparent oil: bp 138° (1.0 mm); ir (neat) 3420 cm^{-1} (O–H); nmr ($CDCl_3$) 6.94 (m, 3), 5.54 (t, 1, J = 4 Hz), 3.91 (s, 1, OH), 3.05 (m, 1), 2.35 (s, 3), 1.77 (m, 2), 1.28 (d, 3, J = 7 Hz).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.28; H, 8.09.

4,7-Dimethyl Chromane-2-acetate.—4,7-Dimethylchroman-2-ol (60 g, 0.337 mol) and 19 ml of pyridine were dissolved in 220 ml of acetic anhydride and stirred for 3 days at room temperature. The acetic anhydride and pyridine were then removed to yield a brown oil which upon vacuum distillation gave the colorless acetate (62 g, 84%): bp 130° (1.0 mm); ir (neat) 1749 cm^{-1} (C=O); nmr (CCl_4) 6.95 (m, 3), 6.40 (t, 1, J = 2 Hz), 2.95 (m, 1), 2.23 (s, 3), 1.94 (d, 3, J = 2 Hz), 1.89 (m, 2), 1.35 (d, 1.5, J = 7 Hz), 1.31 (d, 1.5, J = 7 Hz).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.63; H, 7.24.

4,7-Dimethyl-4H-chromene (6).—4,7-Dimethyl chromane-2-acetate (50 g, 0.227 mol) was placed in a 100-ml flask along with several boiling chips. The flask was then fitted with a 12-in. Johnson pyrolysis column[16] packed with glass helices, upon which was a 12-in. heated spiral metal fractionating column and stillhead. The lower column was heated to 450° and the upper column to 70°, and the system was evacuated (0.60–1.00 mm). The acetate was then heated to a fast reflux such that the lower boiling prouct was distilled while any unreacted starting material was returned to the flask through the side arm of the Johnson column. Crude product distilled from the column at 90° (1.00 mm) and was finally redistilled to yield a colorless oil (32 g, 79%): bp 50° (0.75 mm); ir (neat 1668 cm^{-1} (C=C); nmr (CCl_4) 6.95 (m, 3); 6.45 (d, 1, J = 6 Hz), 4.80 (d, 0.5, J = 6 Hz), 4.84 (d, 0.5, J = 6 Hz), 3.42 (m, 1), 2.23 (s, 3), 1.31 (d, 3, J = 7 Hz).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.26; H, 7.50.

Chromone.—2-Hydroxyacetophenone (28 g, 0.206 mol) was

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(16) K. L. Williamson, R. T. Keller, G. S. Fonken, J. Szmuszkovicz, and W. S. Johnson, *J. Org. Chem.*, **27**, 1612 (1962).

allowed to react with 120 ml of ethyl formate according to the procedure given by Schonberg and Sina.[17] The crude product was recrystallized from ether–hexane to yield fine needles (21.4 g, 71%), mp 58° (lit.[17] mp 59°).

4,7-Dimethylchroman-3-ol (4).—Sodium borohydride (23 g, 0.6 mol) and 100 ml of diglyme were placed in a 500-ml three-neck flask fitted with an addition funnel containing 100 g of boron trifluoride etherate, a magnetic stirrer, and two gas inlet–outlet adapters. One adapter was connected to a nitrogen tank and the other to the gas dispersion column which was filled with anhydrous tetrahydrofuran (600 ml) as were both the side bulb and chamber below the fritted disk. All joints were then secured with pressure clamps, the column was heated to approximately 50°, and **3** (60 g, 0.345 mol) was dissolved in the tetrahydrofuran. The system was then well purged with nitrogen while cooling the column to 40 ± 5° where it was maintained throughout the addition. The nitrogen was cut off and the boron trifluoride etherate added dropwise with stirring over a period of not less than 6 hr, at all times keeping the gas flow relatively slow. Occasionally, starting material crystallized in the fritted disk of the column. When this occurred, tetrahydrofuran was added from the side bulb to dissolve the obstructing material and thereby prevent pressure buildup in the generating flask. When approximately 60% of the diborane had been added, the tetrahydrofuran solution turned intensely yellow and the color persisted until shortly before the addition was completed. The solution was then transferred to a 2-l. flask and allowed to stand overnight. Aqueous sodium hydroxide (320 ml, 3 *N*) and 320 ml of 30% hydrogen peroxide were added with cooling as necessary, and the mixture was stirred for 6 hr at room temperature. The mixture as then acidified with dilute hydrochloric acid and extracted three times with ether. The combined extracts were extracted with 5% aqueous sodium hydroxide an additional three times and the aqueous was layer set aside. The ethereal layer was washed with saturated sodium chloride solution and water and dried (Na_2SO_4), and the solvent was removed to give a thick yellow oil which, upon vacuum distillation, yielded a thick colorless oil which solidified upon standing. This was recrystallized from hexane to give fine needles (29 g, 47%): bp 128–132° (0.5 mm); mp 60°; ir ($CHCl_3$) 3380 cm^{-1} (O–H); nmr (CCl_4) 6.62 (m, 3), 3.71 (m, 2), 3.43 (q, 1, J = 4 Hz), 3.07 (s, 1, OH), 2.53 (m, 1), 2.16 (s, 3), 1.12 (d, 3, J = 7 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 178 (10), 152 (1), 150 (1), 135 (7), 134 (10), 133 (5), 105 (3), 91 (5), 77 (1).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.25; H, 7.81: precise mass, 178.09930. Found: C, 74.30; H, 8.09; precise mass, 178.09804.

Treatment of **6** (5.0 g, 0.037 mol) with diborane by the procedure described above yielded 5.0 g (88%) of **4**.

4,7-Dimethylchroman-3-one (2).—4,7-Dimethylchroman-3-ol (1.78 g, 0.01 mol) was dissolved in a mixture of 15 ml of anhydrous DMSO and 15 ml of anhydrous benzene containing 6.20 g (0.03 m) of dicyclohexylcarbodiimide. A 2-ml portion of a 2.5 *M* solution of anhydrous monophenyl phosphate in DMSO was then added dropwise. After 4 min a white precipitate formed. The mixture was stirred for 2.5 hr following which 25 ml of ethyl acetate and 2.7 g of oxalic acid in 25 ml of methanol were added; stirring was continued for an additional 30 min. The mixture was then filtered, and the filtrate was washed with water, refiltered, and finally washed with aqueous sodium bicarbonate and dried over sodium sulfate. Removal of the solvent left 2.65 g of a crude oil.

The oil was chromatographed on 20 g of silica gel (100–200 mesh) with elution by a 1:4 ether–hexane mixture. The resulting material was distilled to yield 1.5 g (84%) of ketone: bp 106° (0.5 mm); ir (neat liquid) 1730 cm^{-1} (C=O); nmr (CCl_4) 6.80 (m, 4), 4.20 (AB q, 2, J = 9 Hz), 3.35 (q, 1, J = 7 Hz), 2.26 (s, 3), 1.34 (d, 3, J = 7 Hz); mass spectrum (70 eV), *m/e* (rel intensity) 176 (9), 161 (2), 133 (10), 105 (7).

For analytical purposes the ketone **2** was converted to its semicarbazone derivative, mp 216° dec.

Anal. Calcd for $C_{12}H_{15}O_2N_3$: C, 61.80; H, 6.44. Found: C, 62.02; H, 6.38.

5-Methyl-2-(1′-methyl-2′,3′-dihydroxypropyl)phenol (5).—The sodium hydroxide layer from the preparation of **4** above was acidified with dilute hydrochloric acid and extracted three times with ether. The combined extracts were then washed with water, dried (Na_2SO_4), and evaporated to give a thick green oil. This was chromatographed on 500 g of Silicar CC-7, eluting with 40:60 ether–hexane to yield a colorless translucent oil (23.6 g, 35%): ir (neat) 3330 cm^{-1} (O–H); nmr ($CDCl_3$) 6.79 (m, 3), 4.44 (s, 1, OH), 4.27 (s, 1, OH), 2.70–3.78 (m, 4), 2.25 (s, 3), 1.23 (d, 3, J = 7 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 196 (10), 165 (3), 136 (7), 135 (10), 121 (5), 117 (1), 115 (1), 100 (5), 91 (1).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.35; H, 8.16; precise mass, 196.10985. Found: C, 67.18; H, 8.07; precise mass, 196.10757.

3-Methylchroman-4-ol (13).—3-Methylcoumarin (5 g, 0.031 mol) was allowed to react according to the method described for **3**. Removal of solvent from the ethereal layer yielded a clear oil which rapidly crystallized on standing. This was recrystallized from hexane to yield large blunt needles (1.3 g, 20%): mp 96°, ir ($CHCl_3$) 3580 and 3430 cm^{-1} (O–H); nmr ($CDCl_3$) 7.05 (m, 4), 4.00 (m, 3), 2.27 (s, 1, OH), 1.94 (m, 1), 0.96 (d, 3, J = 7 Hz); mass spectrum (70 eV), *m/e* (rel intensity) 164 (10), 122 (10), 121 (9), 100 (2).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.17; H, 7.32; precise mass, 164.08366. Found: C, 73.35; H, 7.45; precise mass, 164.08213.

2-(2′-Methyl-2′,3′-dihydroxypropyl)phenol (15).—The sodium hydroxide layer from above was worked up according to the method described for **5**. The crude product was chromatographed on 30 g of Silicar CC-7 eluting with 50:50 ether–hexane to yield a transparent oil which crystallized on standing. This was recrystallized from ether–hexane to give fine white needles (3.26 g, 58%): mp 93°; ir (KBr) 3410 and 3240 cm^{-1}; nmr (DMSO-d_6) 6.90 (m, 4), 4.99 (s, 1, OH), 4.72 (t, 1, J = 5 Hz, OH), 3.20 (d, 2, J = 5 Hz), 2.70 (s, 2), 1.00 (s, 3); mass spectra (70 eV), *m/e* (rel intensity) 182 (3), 151 (5), 133 (3), 131 (2), 109 (2), 108 (10), 107 (7), 105 (2), 100 (5).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.93; H, 7.70; precise mass, 182.09421. Found: C, 65.89; H, 7.92; precise mass, 182.09407.

Chroman-3-ol.—Coumarin (10 g, 0.0685 mol) was allowed to react with diborane using the same method as in preparation of **4**. Removal of the solvent from the ethereal layer gave a clear oil which on crystallization from hexane gave fine needles (1.23 g, 12%): mp 79°; ir ($CHCl_3$) 3565 and 3420 cm^{-1} (O–H); nmr ($CDCl_3$) 6.95 (m, 4), 4.16 (s, 1, OH), 4.03 (d, 2, J = 2 Hz), 2.71 (m, 3); mass spectrum (70 eV) *m/e* (rel intensity) 150 (10), 131 (2), 121 (1), 119 (1), 107 (9), 106 (2), 91 (2), 78 (3).

Anal. Calcd for $C_9H_{10}O_2$: C, 72.00; H, 6.67; precise mass, 150.06802. Found: C, 72.19; H, 6.77; precise mass, 150.06685.

Chromone (5.0 g, 0.034 m) under the same conditions yielded 4.08 g (79%) of chroman-3-ol.

2-(2′,3′-Dihydroxypropyl)phenol (14).—The basic layer from above on acidification and extraction with ether gave a thick yellow oil. This was chromatographed on 60 g of Silicar CC-7 eluting with 50:50 ether–hexane to yield a clear thick oil (6.45 g, 57%): ir (neat) 3350 cm^{-1} (O–H); nmr (DMSO-d_6) 6.95 (m, 4), 4.50 (s, 2, OH), 3.70 (m, 1), 3.41 (d, 2, J = 2 Hz), 2.70 (d, 2, J = 5 Hz); mass spectrum (70 eV), *m/e* (rel intensity) 168 (5), 150 (1), 137 (4), 132 (2), 119 (3), 108 (10), 107 (10), 100 (2), 91 (5).

Anal. Calcd for $C_9H_{12}O_3$: C, 63.79; H, 7.14; precise mass, 168.07857. Found: C, 63.73; H, 7.12; precise mass, 168.07905.

Tetrahydropyran-3-ol.—3,4-Dihydropyran (30 g, 0.35 mol) was allowed to react with diborane using a method analogous to that of **3**. Evaporation of the ethereal layer gave a clear yellow oil which was vacuum distilled to yield a colorless oil (27.3 g, 80%): bp 83° (10 mm) [lit.[7] bp 70–72 (0.1 mm)]; ir (neat) 3320 cm^{-1} (O–H); nmr (CCl_4) 5.80 (s, 1, OH), 3.08–3.79 (m, 5), 1.25–1.87 (m, 4).

Anal. Calcd for $C_5H_{10}O_2$: C, 58.82; H, 9.81. Found: C, 58.60; H, 9.93.

2-(3′-Phenyl-2′-hydroxypropyl)phenol (19).—Flavone (5 g, 0.025 mol) was allowed to react with diborane by a procedure analogous to that of **3**. Acidification and extration with ether of the sodium hydroxide layer gave a thick yellow oil. This was vacuum distilled to yield a clear oil which was then crystallized from carbon tetrachloride to give fine transparent needles (4.2 g, 74%): mp 93°; bp 182° (0.17 mm); ir (KBr) 3390 and 3180 cm^{-1} (O–H); nmr (DMSO-d_6) 7.36 (s, 5), 6.87 (m, 4), 5.20 (d, 1, J = 4 Hz, OH), 3.60 (m, 1), 2.43 (d, 2, J = 6 Hz), 1.87 (d, 2, J = 7 Hz); mass spectrum (70 eV), *m/e* (rel intensity) 228 (1), 211 (6), 210 (10), 209 (8), 195 (7), 193 (6), 181 (1), 121 (1), 120 (1), 119 (7), 107 (8), 104 (8), 100 (2), 91 (7), 79 (6), 77 (8).

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.95; H, 7.02; precise mass ($M^+ - H_2O$), 210.10439. Found: C, 78.69; H, 7.22; precise mass, 210.10257.

(17) A. Schonberg and A. Sina, *J. Amer. Chem. Soc.*, **72**, 3396 (1950).

Registry No.—4,7-dimethyldihydrocoumarin, 18782-15-5; 4,7-dimethylchroman-2-ol, 24454-18-0; 4,7-dimethyl chroman-2-acetate, 24454-19-1; **2** semicarbazone, 24454-20-4; **4**, 24454-21-5; **5**, 24454-22-6; **6**, 24454-23-7; **13**, 24454-24-8; **14**, 24454-25-9; **15**, 24454-26-0; chroman-3-ol, 21834-60-6; tetrahydropyran-3-ol, 19752-84-2; **19**, 1481-82-9; **2**, 24454-30-6.

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Configuration and Conformation of 3-Arylideneflavanones

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The stereochemistry of 3-arylideneflavanones has been established by the preparation of both *cis* (**3a–c**) and *trans* (**2a–c**) isomers. Configurations and conformations are assigned on the basis of nmr spectra. The products obtained by the acid-catalyzed condensation of flavanones and aromatic aldehydes have the *trans* configuration. Ultraviolet irradiation produces the *cis* isomers. Allylic coupling constants show that the *trans* isomers exist in the conformation with the 2-phenyl group axial. The *cis* isomers appear to exist in both conformations. In 2,2-diphenylchromanone (**4**) the steric effect of the second phenyl group causes formation of the *cis* product 2,2-diphenyl-3-benzylidenechromanone (**5**). *o*-Hydroxybenzaldehyde with flavanone does not give the benzylidene derivative but forms *o*-hydroxybenzylflavone.

Flavanones have been condensed with a number of aromatic aldehydes to form 3-arylideneflavanones (termed flavindogenides) in high yield.[1] Flavindogenides have also been isolated as coproducts during the preparation of flavanones by the acid-catalyzed condensation of aromatic aldehydes and substituted *o*-hydroxyacetophenones.[2] Interest in 6-nitro-3-benzylideneflavanones as bacteriostats led Széll and Zarandy to reinvestigate methods for their preparation.[3] Recently two natural products, eucomin and eucomol, related in structure to flavindogenides, were isolated.[4] Eucomin is the first member of the arylidenechromanone family to be found in nature.

Two geometrical isomers are possible for the product from the condensation of aromatic aldehydes and flavanones since the β-aryl groups of the flavindogenide may be either *cis* or *trans* to the carbonyl group. In the reported cases only one of the two possible geometrical isomers was obtained. The condensation of aryl aldehydes with methylene compounds normally yields unsaturated products which have the carbonyl function *trans* to the larger group at the β-carbon atom.[5,6] However, as shown below, there was some evidence to suggest that 3-(2-nitrobenzylidene)flavanone prepared in the normal way had the *cis* configuration. Cromwell and coworkers[7] prepared *trans*-2-(2-aminobenzylidene)-4,4-dimethyltetralone by the reduction of the corresponding nitro compound with iron and acetic acid. This compound was cyclized by refluxing with hydrochloric acid or on treatment with hydrogen chloride to give 5,5-dimethyl-5,6-dihydrobenz[*c*]acridine. Algar and M'Cullagh[8] were unable to isolate the corresponding amino compound by reduction of 3-(2-nitrobenzylidene)flavanone with stannous chloride in acetic acid saturated with hydrogen chloride but obtained 2,3-(2-phenylchromano-3,4)quinoline directly. This cyclized product was the only product obtained when the flavanone was treated under the conditions described by Bell and Cromwell for formation of the amino compound.[9] These results tended to indicate a *cis* configuration for the 3-arylideneflavanones.

In view of the interest shown in flavindogenides we undertook the present work in order to assign their stereochemistry. The stereochemical assignment was also necessary for our further studies on the epoxidation reactions of flavindogenides.[10] In this paper the results of our study on *cis*- and *trans*-3-arylideneflavanones are presented.[11]

The stereochemistry of the 3-arylideneflavanones has now been unambiguously determined by the synthesis of both the *trans* (**2a–c**) and *cis* (**3a–c**) compounds. Condensation of flavanones (**1a,b**) with benzaldehyde or anisaldehyde forms *trans*-flavindogenides (**2a–c**) in yields approaching 90%. In our study, as in previous reports, only one isomer was obtained. An examination of the reaction mixture using thin layer chromatography showed no trace of a second isomer. The nmr spectra of the crude reaction product also indicated only one isomer.

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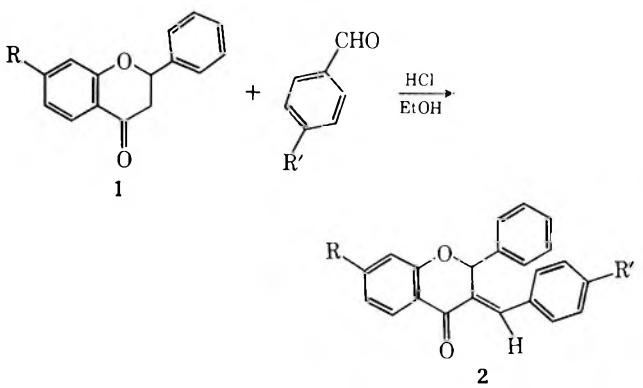
TABLE I
PHYSICAL DATA ON FLAVINDOGENIDES

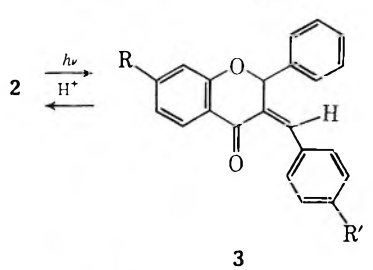
Configuration	Isomers 2a, *trans*	Isomers 3a, *cis*	Isomers 2b, *trans*	Isomers 3b, *cis*	Isomers 2c, *trans*	Isomers 3c, *cis*
Yield,[a] %	80	82	83	44	81	38
Mp, °C (lit.)	104 (104[b])	96	147.5 (149[b])	*c*	145.5	108.5
Uv, λ_{max}^{EtOH} (ϵ)	304 (16,600)[d]	307 (11,000)[d]	340 (16,900)	352 (14,500)	357 (21,800)	354 (19,400)
			242 (13,600)	250 (18,100)	239 (16,600)	239 (17,900)
Ir,[e] $\nu_{C=O}$, $\nu_{C=C}$	1670, 1610	1670, 1610	1670, 1600	1670, 1600	1675, 1610	1675, 1610
Photochemical equilibration, %	8	92	8	92	20	80
Chemical equilibration, HCl, %	100	0	100	0	100	0
Anal., %						
Calcd C, H	84.6, 5.2	84.6, 5.2		80.7, 5.3	77.42, 5.38	77.42, 5.38
Found C, H	84.6, 5.2	84.4, 5.2		80.2, 5.5	77.41, 5.47	77.42, 5.30

[a] Yields are for recrystallized products. [b] See ref 1b. [c] **3b** was not crystalline. [d] Determined in methanol. [e] Determined as 1% solution in CCl_4.



a, R = H; R′ = H
b, R = H; R′ = OCH_3
c, R = OCH_3; R′ = OCH_3

Irradiation of the *trans* compounds with ultraviolet light using a Corex or a Pyrex filter to screen out radiation below 260 mμ gave mixtures with a high percentage (80–92%) of the *cis* isomers (**3a–c**). No other products were detected. The pure *cis* isomers were isolated by either fractional crystallization or by column chromatography. The *cis* isomers are crystalline solids except for **3b** (a yellow glass) which resisted attempts at crystallization although thin layer chromatography indicated it to be pure. The structure of the *cis*-flavindogenides was inferred from elemental analyses, infrared, and electronic spectra (which were very similar to those of the *trans* compounds), nmr spectra, and the fact that they were completely and essentially quantitatively isomerized to the *trans*-flavindogenides when treated with acid. The properties of the isomeric flavindogenides are shown in Table I.



a, R = H; R′ = H
b, R = H; R′ = OCH_3
c, R = OCH_3; R′ = OCH_3

In order to assign the positions of the vinylic and the 2-proton signals in the nmr spectra of the isomeric flavindogenides, **2a–c** were prepared with deuterium in the β position by condensation of **1a** and **1b** with the respective aldehydes-1-*d*. The products have physical, electronic, and infrared spectral properties essentiolly identical with those of the nondeuterated compounds. The nmr spectra of deuterated *trans*-flavindogenides lacked the signal at τ 1.9 and allowed unequivocal assignment of this signal to the vinyl proton. The singlet in the τ 3.9 region was not so broad. Irradiation of the *trans*-flavindogenides-β-*d* and product work-up as described above yielded the *cis*-flavindogenide-β-*d*. The nmr spectra of these *cis* derivatives were essentially identical with those of the nondeuterated isomers except for the absence of a signal of τ 3.3 and a sharpening of the singlet in the region of τ 3.9. Significant nmr data for the *cis*- and *trans*-flavindogenides are listed in Table II.

TABLE II
NMR DATA OF FLAVINDOGENIDES[a,b]

Compound	Configuration	Chemical shifts, τ: Vinyl H	2 H	5 H	OCH_3
2a	*trans*	1.92	3.37	2.14	
3a	*cis*	3.30	3.89	2.08	
2b	*trans*	1.98	3.34	2.14	6.30
3b	*cis*	3.32	3.89	2.10	6.28
2c	*trans*	1.95	3.33	2.12	6.28, 6.25
3c	*cis*	3.37	3.92	2.10	6.22

[a] Determined as 10% solutions in $CDCl_3$. [b] Correct integrated area was obtained for the multiplets of the aromatic protons not listed.

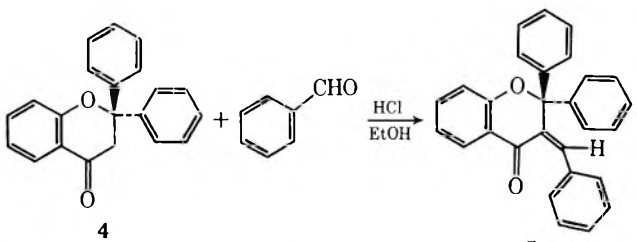
Configuration.—Nuclear magnetic resonance spectroscopy has been most definitive in allowing the stereochemical assignment of *cis* and *trans* exocyclic α,β-unsaturated ketones. The deshielding effect resulting from the diamagnetic anisotropy of the carbonyl group causes the vinyl proton in the *trans* isomer (with the proton *cis* to the carbonyl group) to display a signal at a lower field than does that of the *cis* isomer.[12] This property has been used by Cromwell, *et al.*,[6] in assignment of *cis* and *trans* configurations to benzylidenindanones and benzylidenetetralones and by Hassner and Mead[13] in assignment of the geometrical isomers of benzylidenecyclohexanones. In each instance the vinylic proton in the *trans* isomer gives a signal at a

(12) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, 1959, p 124.
(13) A. Hassner and T. C. Mead, *Tetrahedron*, **20**, 2201 (1964).

lower field (by *ca.* 1 ppm) than the *cis* isomer. With both the *cis*- and *trans*-3-arylideneflavanones available, the configuration of each pair could be established by determining the field position of the vinyl protons.

The nmr spectra of the *trans*-flavindogenides **2a–c** obtained in the acid-catalyzed condensation showed two broadened singlets (each corresponded to a single proton) at τ 1.9 and 3.3. The two singlets are due to the proton at C_2 and the vinylic proton. The observed broadening of the signal is attributed to a small long-range allylic coupling[14] between the two protons. An absorption at τ 1.9 is much lower than expected for either 2 H or an ordinary vinyl proton and indicates the *trans* configuration for the flavindogenides **2a–c** in which the vinylic proton lies well in the deshielding zone of the carbonyl group. In support of this conclusion, the *cis*-flavindogenides **3a–c** obtained by ultraviolet irradiation do not display a signal at this low-field position. The 5-H protons of **3a–c** absorb at a lower field (τ 2.08–2.10) than the other aromatic protons. The 5-H protons of **2a–c** absorb at a similar field position (τ 2.12–2.14). The shift of the aromatic 5-H proton downfield arises from the deshielding effect of the carbonyl group and is characteristic of flavanone and flavone systems.

Compared with the preparation of flavindogenides, the condensation of benzaldehyde with 2,2-diphenyl-4-chromanone (**4**) requires a lengthy reaction period. When an ethanolic solution of the chromanone and benzaldehyde was saturated with hydrogen chloride and worked up after 12 or 24 hr, only starting materials were isolated. After a reaction period of 4 days a condensation product was obtained in 39% yield. Spectral data and elemental analysis are consistent with 2,2-diphenyl-3-benzylidenechromanone (**5**). In contrast to the flavindogenides obtained in the condensation reactions, **5** has a *cis* configuration as shown by an nmr signal at τ 3.70 for the β hydrogen.



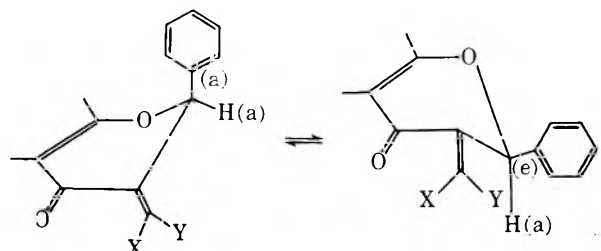
4 5

In view of the results obtained upon reduction of 3-(2-nitrobenzylidene)flavanone, it seemed of interest to prepare this compound and examine its nmr spectrum. The spectrum of this compound was consistent with a *trans* configuration since it showed a signal at τ 1.70 (assigned to the vinyl hydrogen) and a signal at τ 3.70 (assigned to the 2 hydrogen). Apparently the amino compound isomerizes under the mildly acid reduction conditions which then allow cyclization to occur.

Prior to the synthesis of the *cis*-flavindogenides an attempt was made to prepare 3-(2-hydroxybenzylidene)flavanone. It was anticipated that the presence or absence of hydrogen bonding between the hydroyl group and the carbonyl group would allow assignment of *cis* or *trans* configuration, respectively. The product of the condensation of 2-hydroxybenzaldehyde with flavanone did show hydrogen bonding as indicated by its infrared and nmr spectra. However an inspection of the spectral data showed that the endocyclic product, 3-(2-hydroxybenzyl)flavone had been obtained and not the expected flavindogenide.

Conformation.—The "sofa" conformation has been proposed by Philbin and Wheeler[15] for flavanone-type molecules. This conformation allows a strainless chromanone molecule to have all the atoms, apart from C_2, coplanar. The infrared frequencies of a series of flavanones indicate that the carbonyl group and the fused benzene ring are conjugated in each case.[16] Hence they are probably coplanar. This coplanarity is also indicated by the observation of Clark–Lewis, *et al.*,[17] that the 2,3-coupling constants in flavanones are unaltered by the presence of a 5-hydroxyl group. An hydroxyl substituent in this position forms a strong intramolecular hydrogen bond with the carbonyl group and forces the coplanarity of this group with the aromatic A ring.

Inspection of models indicates that the flavindogenides may adopt the strainless "sofa" conformation in which all the atoms of the heterocyclic ring except C_2 are coplanar. As in the flavanones two conformers are possible in which the axial and equatorial bonds at C_2 are interchanged.



6 7

a = *cis*; X = Ar; Y = H
b = *trans*; X = H; Y = Ar

An examination of the model of *trans*-flavindogenides shows that in conformation **7b** there is severe nonbonded interaction between an equatorial 2-phenyl and the β-phenyl group. Such an interaction is not present in conformation **6b** which has the 2-phenyl group in the axial position. Whereas in cyclohexane and related structures a large group normally adopts the equatorial conformation to avoid 1,3 diaxial interaction, in the flavindogenides there are no axial groups to interact with an axial 2-phenyl.

Supporting evidence for an axial 2-phenyl group is provided from an examination of the long range allylic coupling between the 2-H and β proton. Sternhell, *et al.*,[18] found that the magnitude of allylic coupling depends on the dihedral angle (ϕ) that the C–H bond of the allylic proton at position 2 makes with the plane of the double bond. The values[19] are, for ϕ = 0–65° and for ϕ = 110–180°, $J_{allylic}$ = 0–1.3 cps; for ϕ = 65–110°, $J_{allylic}$ = 1.3–3.1 cps.

(14) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).

(15) E. M. Philbin and T. S. Wheeler, *Proc. Chem. Soc. London*, 167 (1958).
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(17) J. W. Clark-Lewis, L. M. Jackman, and T. M. Spotswood, *Aust. J. Chem.*, **17**, 632 (1964).
(18) D. J. Collins, J. J. Hobbs, and S. Sternhell, *ibid.*, **16**, 1030 (1963).
(19) G. R. Newseroff and S. Sternhell, University of Sidney, personal communication.

The nmr spectra of *cis*- and *trans*-benzylidenechromanones[20] show a doublet for the protons at C_2 (*cis*, $J_{allylic}$ = 1.27 cps; *trans*, $J_{allylic}$ = 2.06 cps) indicating that these protons become equivalent by rapid inversion of the two conformers. For the *cis*- and *trans*-benzylidenechromanones the observed splitting is the average value of the allylic coupling of the vinyl proton with an axial proton at C_2 and with an equatorial proton at C_2.

The low value of the allylic coupling constant for the *trans*-flavindogenide ($J_{allylic}$ = 0.95 ± 0.5 cps) confirms that these compounds exist in conformation **6b** in which the hydrogen at position 2 is equatorial $\phi = 2°$.

Further support of conformation **6** is provided by the fact that *cis*-2,2-diphenyl-3-benzylidenechromanone (**5**) is formed on treatment of **4** with benzaldehyde (the vinyl proton of **5** is found at τ 3.70 showing little influence of the deshielding effect of the carbonyl group and thus indicates a *cis* configuration). With two phenyl groups at C_2, the steric effect prevents the formation of a *trans* isomer.

For *cis*-flavindogenides there appears to be little steric energy difference between the conformation in which the 2-phenyl group is axial (**6a**) and that in which it is equatorial (**7a**). Models indicate that some nonbonded interaction may exist in **7a** between the β hydrogen and 2-phenyl. The epoxidation reactions of *cis*-flavindogenides also seem to indicate an axial 2-phenyl group.[10] However, the allylic coupling constant (1.23 ± 0.5 cps) of **1b** is very close to the average value (1.27 cps) observed for *cis*-3-benzylidenechromanone and suggests that the *cis*-flavindogenides exist in both conformations.

Experimental Section

Melting points were taken in open capillaries and are uncorrected. Elementary analyses were performed by Alfred Bernhardt Mikroanalitisches Laboratorium, Elbach über Engelskirchen, West Germany, Galbraith Laboratories, Inc., Knoxville, Tenn., or in the departmental microanalytical laboratory of University College, Dublin. The infrared spectra were determined with either a Perkin-Elmer Model 337 or Beckman IR-5 spectrometer. Ultraviolet spectra were determined either on a Perkin-Elmer Model 202 or Bausch and Lomb Spectronic 505 spectrometer. The nmr spectra were recorded on a Varian A-60 or 60A spectrometer using tetramethylsilane (τ 10) as an internal standard. The measurements of the allylic coupling constants of *cis*- and *trans*-3-benzylideneflavanones were determined[21] as 12% solutions in $CDCl_3$ on an HA-100 spectrometer using decoupled scans and were corrected by compensating for incomplete resolution.

The Preparation of Flavanone (1a) and 7-Methoxyflavanone (1b).—Benzaldehyde was condensed with 2′-hydroxyacetophenone (Eastman Organic Chemicals) or 2′-hydroxy-4′-methoxyacetophenone[22] in ethanol in the presence of 50% sodium hydroxide solution to form the respective chalcones as previously described.[23] The 2′-hydroxychalcone was obtained as yellow needles in 78% yield, mp 87–89° (lit.[23] mp 88–89°). The 2′-hydroxy-4′-methoxyflavanone was obtained as yellow needles in 65% yield, mp 107.5–108.5° (lit.[24] mp 105°). The chalcones in turn were converted to the flavanones by ring closure in dilute aqueous sodium hydroxide as previously described:[25] **1a**, white needles (92% yield), mp 74–76° (lit.[25] 76°); **1b**, white plates (64% yield), mp 88–89° (lit.[24] mp 91°).

The Preparation of *trans*-3-Arylideneflavanones (2a–c).—The following procedure for the preparation of *trans*-3-anisylideneflavanone (**2b**) illustrates the general procedure used.

A solution of 20 g of flavanone and 25 ml of anisaldehyde in 25 ml of ethanol was saturated with anhydrous hydrogen chloride capped, and allowed to stand for 24 hr. The mixture was then cooled in an ice bath. The solid was removed by filtration and washed with 25 ml of cold ethanol giving 27 g (91%) of product. Recrystallization from 700 ml of ethanol gave 25 g (83%) of pale yellow crystals, mp 146.5–147.5° (lit.[1b] 148–149°).

Yield, physical, and spectral data of **2a–c** are recorded in Tables I and II.

trans-Flavindogenides-β-*d* **2a–c** were prepared by the above procedure from anisaldehyde-1-*d*[26] or benzaldehyde-1-*d*.[27]

Photochemical Isomerization of *trans*-3-Arylideneflavanones (2a–c) to *cis*-3-Arylideneflavanones (3a–c).—The following is a typical example of the photochemical isomerization experiments. A solution of 5 g of *trans*-3-anisylidene-7-methoxyflavanone in 100 ml of benzene was irradiated at room temperature for 12 hr by a Hanovia 450-W mercury arc lamp contained in an immersible quartz probe. A Corex filter was utilized to screen out radiation below 260 mμ. At the end of a 12-hr irradiation period the benzene was removed and a yellow oil was left. The crude product was chromatographed over 60 g of silicic acid. The column was eluted with benzene and yielded earlier fractions of a yellow oil (3 g) and later fractions which were predominantly *trans* isomer. The yellow oil was again chromatographed over 60 g of silicic acid and eluted with 3:2 hexane–benzene. This procedure resulted in a series of fractions which were induced to crystallize. These fractions, when combined and recrystallized from hexane, gave 1.9 g (38%) of *cis*-3-anisylidene-7-methoxyflavanone. Yields and physical and spectral data of the *cis*-flavindogenides are recorded in Tables I and II.

cis-Flavindogenides-β-*d* (**3a–c**) were prepared from the deuterated *trans* isomers by the general procedure described above.

Acid-Catalyzed Isomerization of 3a–c to 2a–c.—A dilute solution of the *cis* isomer in ethanol was brought to reflux and 1 drop of concentrated hydrochloric acid was added. The solution was refluxed for 30 min. On removal of the solvent a solid was left (>90% yield) which had an nmr spectrum identical with that of the corresponding *trans* isomer. No *cis* isomer could be detected by nmr.

***trans*-3-(2-Nitrobenzylidene)flavanone.**—A solution of *o*-nitrobenzaldehyde (1.1 g), flavanone (1.1 g), and ethanol (10 ml) was saturated with anhydrous hydrogen chloride. After 48 hr the solvent was removed on a water bath at reduced pressure. The resulting oil was dissolved in 20 ml of hot ethanol and deposited a solid on cooling, 0.3 g, mp 144–156°. Recrystallization from 20 ml of ethanol gave 0.2 g of a cream colored solid: mp 156–157° (lit.[8] mp 155.5–156.5°); nmr τ 3.7 (singlet, 1 proton assigned to 2 H), 1.7 (singlet, 1 proton assigned to β H), 3.2–2.8 (complex aromatic absorption, 13 protons).

2,2-Diphenyl-4-chromanone (4).—Concentrated hydrochloric acid (37 ml) was added to a refluxing solution of 5.5 g of 2′-hydroxy-β-phenylchalcone[28] in 180 ml of glacial acetic acid. The solution was refluxed for 5 hr, cooled in an ice bath, and 300 ml of water was added. The resulting solid was removed by filtration, washed thoroughly with water, dried, and recrystallized from 270 ml of hexane. The off-white crystals weighed 4.7 g (86%), mp 137–138.5° (lit.[28] 133–134°).

***cis*-2,2-Diphenyl-3-benzylidenechromanone (5).**—A solution of 1 g of **4**, 2 ml of benzaldehyde, and 3 ml of ethanol was saturated at room temperature with anhydrous hydrogen chloride, sealed, and allowed to stand for 4 days (previous reaction periods 12 and 24 hr had resulted in recovery of only starting material). The dark-colored reaction mixture was taken up in 100 ml of ether and washed successively with water, 5% sodium carbonate solution, water, 15% sodium bisulfite solution, and water. The ether was evaporated leaving a yellow oil which was dissolved in 20 ml of refluxing ethanol. The solution furnished 0.65 g (50%) of solid, mp 173–184°, upon cooling. The solid was recrystallized from 50 ml of ethanol and gave 0.5 g (39%) of yellow crystals, mp 190–191°. The infrared spectrum (CCl_4) shows significant absorptions at 1680 (C=O) and 1605 (C=C) cm^{-1}. The nmr spectrum ($CDCl_3$) has signals at τ 2.23 (pair of doublets,

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(21) The authors are grateful to Professor S. Sternhell for determining the allylic coupling constants.

(22) R. Adams, *J. Amer. Chem. Soc.*, **41**, 247 (1919).

(23) W. Feuerstein and St. von Kostanecki, *Ber.*, **31**, 715 (1898).

(24) St. von Kostanecki and M. L. Stoppani, *ibid.*, **37**, 1180 (1904).

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(26) D. Seebach, B. W. Erickson, and G. Singh, *J. Org. Chem.*, **31**, 4303 (1966).

(27) A. Streitwieser, Jr., and J. R. Wolfe, *J. Amer. Chem. Soc.*, **79**, 903 (1957).

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1, J = 2 and 8 cps, 5 H), 2.32–3.33 (m, 18, Ar H), and 3.70 (s, 1, β H).

Anal. Calcd for $C_{28}H_{20}O_2$: C, 86.57; H, 5.19. Found: C, 86.44; H, 5.39.

3-(2-Hydroxybenzyl)flavone—A solution of 0.5 g of flavanone in 1 ml of salicylaldehyde was saturated with anhydrous hydrogen chloride, stoppered, and allowed to stand for 24 hr; 3 ml of methanol was then added. A crystalline solid separated. Recrystallization from ethanol gave 0.4 g (55%) of fine off-white crystals, mp 200–201°. The ultraviolet spectrum (EtOH) has λ_{max}^{sh} 307 mμ (ϵ 11, 600), 283 (13,800), and 241 (21,800). The infrared spectrum (CCl_4) shows significant adsorptions at 3100 (bonded OH), 1640 (C=O), 1615 (C=C), and 1230 cm^{-1} (=COC–). The nmr spectrum ($CDCl_3$, very dilute owing to insolubility) has signals at τ 0.3 (singlet, bonded OH, wt 1), 1.65 (perturbed pair of doublets, J = 8 cps, 5 H, wt 1), 2.0–3.1 (complex multiplet, Ar H, wt 12), and 6.07 (singlet, CH_2, wt 2). In deuterated dimethyl sulfoxide the signal at 0.3 is missing and is replaced by a singlet (wt 1) at τ 6.52.

Anal. Calcd for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91. Found: C, 80.29; H, 5.11.

3-(2-Acetoxybenzyl)flavone.—A solution of 0.5 g of 3-(2-hydroxybenzyl)flavone, 3 ml of acetic anhydride, and 2 drops of phosphoric acid was refluxed for 5 min and then poured into 5 ml of water. An oil separated which soon solidified. An additional 50 ml of water was added, and the solid was removed by filtration and washed thoroughly with water. The solid was recrystallized from 20 ml of ethanol and gave 0.4 g (71%) of small white crystals, mp 143–144°. The infrared spectrum (CCl_4) has characteristic absorptions at 1770 (CH_3C=O), 1650 (C=O), 1625 (C=C), and 1215, 1198 cm^{-1} (=COC– and –COC=O). The nmr spectrum ($CDCl_3$) has signals at τ 1.82 (perturbed pair of doublets, J = 7.5 cps, 5 H, wt 1), 2.42–3.16 (complex multiplet, Ar H, wt 12), 6.12 (singlet, CH_2, wt 2), and 7.87 (singlet, CH_3CO, wt 3).

Registry No.—**2a**, 24467-41-2; **2b**, 24467-42-3; **2c**, 24467-43-4; **3a**, 24467-44-5; **3b**, 24467-45-6; **3c**, 24467-46-7; **5**, 24467-47-8; *trans*-3-(2-nitrobenzylidene)flavanone, 24467-48-9; 3-(2-hydroxybenzyl)flavone, 24467-49-0; 3-(2-acetoxybenzyl)flavone, 24467-50-3.

Oxidation of β-Carotene. Site of Initial Attack

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The reaction between β-carotene and molecular oxygen in toluene at 60° was investigated. A linear relation was found between the loss in β-carotene and time. The reaction rate increased with increasing temperature. The activation energy, E_a, for the oxidation of β-carotene was found to be 10.2 kcal/mol. Though free-radical initiators caused rate enhancement, the kinetics of the reaction and the light absorption characteristics of the reaction solution were altered. This indicated a difference in the mechanism of the reaction in the presence of free-radical initiators. The rate of loss of β-carotene was increased in the presence of cupric ions and decreased in the presence of diphenylamine. The products of the reaction were β-carotene 5,6-monoepoxide and its isomer, β-carotene 5,6,5′,6′-diepoxide, and β-carotene 5,8-monoepoxide and its isomer, β-carotene 5,8,5′,8′-diepoxide. A reaction mechanism was proposed.

In view of the fact that the oxidative reactivity of the β-carotene molecule may be influenced by both an electronic factor and a stereochemical factor, as was suggested by Zechmeister, *et al.*,[2] the size and reactivity of the oxidizing agent would be expected to play a predominant role. The reaction site would not only be a function of the inherent reactivity (electron density) of the β-carotene molecule but also a function of the size and reactivity (stability) of the attacking reagent. This is shown by the results of the oxidation reactions of β-carotene in the presence of the various metal oxides (and metal oxide catalysts)[3–5] and by peroxides alone or with enzyme catalysis.[6–8] The oxygen in metal oxides or in the form of peroxy radicals is in an activated (reactive) state and thus might nullify the inherent differences in reactivities in the various parts of the β-carotene molecule. From a stereochemical consideration oxidation with metal oxides, for example OsO_4 and H_2O_2 or $KMnO_4$, involves the transitory formation of a five-membered intermediate.[9] The formation of such a space-requiring transition state would favor those sites of least steric hindrance. These might give the most stable transition state even though these sites may not be the centers of the highest electron density.

Oxidation of β-carotene with molecular oxygen has two unique characteristics. (1) Owing to the smaller size of the oxygen molecule, steric hindrance is not important. (2) Owing to the relative unreactivity of the oxygen molecule compared with peroxy radicals, the competitive reactivity between different carbon atoms could be retained.

The oxidation of β-carotene with molecular oxygen may therefore reflect the inherent reactivity of the β-carotene molecule. Also, the reaction of β-carotene with oxygen could illustrate the mechanism of the uncoupled enzymatic oxidation of β-carotene *in vivo*[10] by way of model systems.

Results and Discussion

The rate of loss of β-carotene is shown in Figure 1. A straight line passing through the origin was obtained. This indicates an overall zero-order reaction kinetics. Thus

$$\beta\text{-carotene} + O_2 \rightleftharpoons [\beta\text{-carotene}\cdot O_2]^* \xrightarrow{k_0} \text{products}$$

$$\frac{d(P)}{dt} = k_{obsd} = k_0[\beta\text{-carotene}\cdot O_2]^*$$

(1) Faculty of Agriculture, University of Khartoum, Khartoum North, Sudan.

(2) L. Zechmeister, A. L. Le Rosen, W. A. Schroeder, A. Polgar, and L. Pauling, *J. Amer. Chem. Soc.*, **65**, 1940 (1943).

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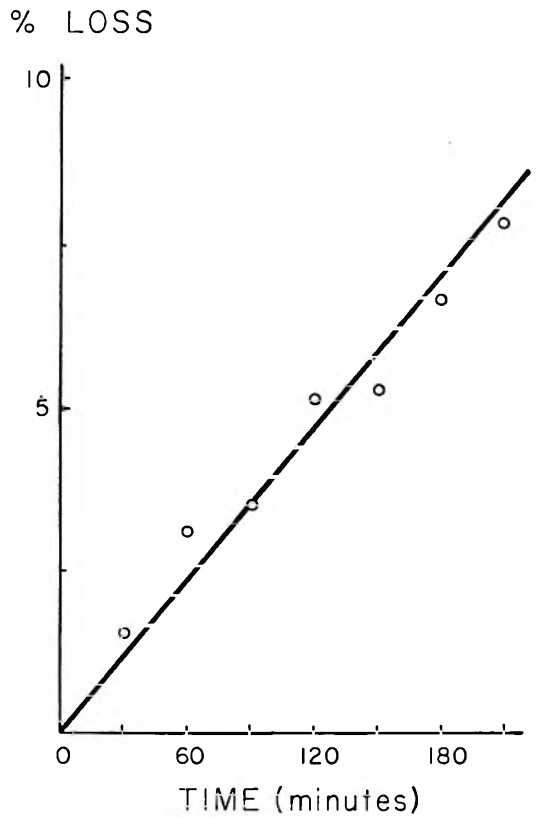


Figure 1.—Degradation of β-carotene with oxygen. Rate of loss of β-carotene.

The slope of the straight line is the observed rate constant k_{obsd}.

The overall zero-order kinetics must mean that the rate of the reaction is independent of the concentration of β-carotene in the presence of excess oxygen. The reaction between oxygen and β-carotene may go through an activated dipole association complex, formed in an equilibrium step. This activated complex may then decompose into products or go back to free oxygen and β-carotene.

It is important to notice that there is no lag phase, which is observed in the autoxidation of fats, and that the reaction is not autocatalytic; that is, there is no buildup of a reactive intermediate that decomposes into species that will further catalyze the reaction.

In order to obtain information about the energetics of the reaction between β-carotene and oxygen the effect of temperature on the reaction rate was studied. The reaction rate constants, k_{obsd}, determined at 60, 70, 80, and 90°, are, respectively, 3.93×10^{-2}, 6.12×10^{-2}, 10.54×10^{-2}, and 14.03×10^{-2}. Thus the rate of the reaction increases with increasing temperature.

When the logarithms of the rate constant are plotted against the reciprocal of the absolute temperature, a straight line relationship is obtained. From the slope of the line and using the relationship

$$\log k = -E_a/2.3RT$$

where k = the rate constant, E_a = activation energy, R = the gas constant (1.987 cal/mol), and T = the absolute temperature, the activation energy is calculated to be 10.20 kcal/mol.

The activation energy reported[11] for the autoxidation of linoleic acid is 15.2 kcal/mol and 17.2 kcal/mol for its ethyl ester. Thus the activation energy for the oxidation of β-carotene is 5.0 kcal lower than that of the free acid and 7.0 kcal lower than that of the ester. The low activation energy for the oxidation of β-carotene indicates that this reaction is more favored than the autoxidation reaction of linoleic acid. This difference in reactivity, however, can be attributed to the greater stability of an allylic (carbon 4) radical in the β-carotene molecule, which is stabilized over 11 double bonds compared with only two double bounds in the linoleic acid and ester. The possibility for the formation of an allylic radical and hence a free-radical mechanism for the destruction of β-carotene by oxygen remains open.

To further investigate the possibility of free radical participation in the oxidation of β-carotene, the reaction was run in the presence of catalytic amounts of free radical initiators. N-Bromosuccinimide (NBS) is a specific reagent for the preferential production of allylic radicals[12] *via* a free-radical chain mechanism.[13,14] Thus

$$RH \xrightarrow{NBS} R\cdot \text{ (carbon 4)} \xrightarrow{O_2} ROO\cdot \xrightarrow{RH} ROOH \longrightarrow \text{products}$$

When the data obtained in the presence of 2×10^{-4} *M* N-bromosuccinimide is plotted as per cent loss in β-carotene against time in minutes, a straight-line relationship is obtained with a positive intercept. The ratio of $k_{obsd}(NBS)/k_{obsd}(control) = 6.5$. $k_{obsd}(NBS)$ is the observed rate constant for the oxidation of β-carotene in the presence of N-bromosuccinimide and $k_{obsd}(control)$ is the observed rate constant for the oxidation of β-carotene with oxygen alone. Thus the oxidation of β-carotene in the presence of N-bromosuccinimide is 6.5 times faster than the control.

If the oxidation in the presence of N-bromosuccinimide proceeds through the formation of an allylic radical (carbon 4), then it would be expected that the relative reactivities of β-carotene and a vitamin A derivative would be similar. When the loss in vitamin A acetate brought about by oxidation in the presence of NBS is plotted against time, a curve is obtained and the slope of the tangent gives the observed rate constant. The ratio of k_{obsd}(β-carotene + NBS)/k_{obsd}(vitamin A acetate + NBS) = 1.4. Thus β-carotene is slightly more reactive than vitamin A acetate. This could be attributed to the extra six double bonds in β-carotene which will participate in the stabilization of an allylic radical.

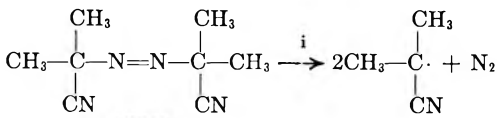
Though use of N-bromosuccinimide results in rate enhancement, the reaction is accompanied by a shift (6 mμ) of the overall absorption spectra of the β-carotene reaction mixture to longer wavelengths, loss of the fine structure, and finally the reduction to a single peak.

Though this by itself gives evidence for the incorporation of oxygen at the 4 and/or the 4′ positions as carbonyl groups and thus lengthens the conjugated chain, this behavior is not observed in the oxidation of β-carotene with oxygen alone. Further, on examination

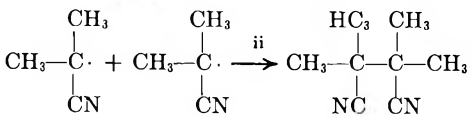
(11) J. L. Bolland and G. Gee, *Trans. Faraday Soc.*, **42**, 236 (1946).
(12) A. Wohl, *Chem. Ber.*, **52**, 51 (1919).
(13) G. Bloomfield, *J. Chem. Soc.*, 114 (1944).
(14) D. H. Heye, *Annu. Rept. Progr. Chem.*, **41**, 184 (1944).

of the reaction products in the absence of NBS, no 4-keto-β-carotene or 4,4′-diketo-β-carotene could be found. Petracek and Zechmeister[15] obtained these compounds by oxidizing β-carotene with NBS. The evidence is therefore that the reaction catalyzed by NBS is quite different from that brought about by oxygen alone and that the 4,4′ positions are probably not the sites of oxygen attack.

This is confirmed by the use of azobisisobutyronitrile (AIBN) as an initiator. Compared with NBS, AIBN is an efficient free-radical initiator and does not bring about side reactions. With catalytic amounts of AIBN, Figure 2, the initial rate of loss of β-carotene increases continuously with time, indicative of a chain process not observed in the oxidation of β-carotene with oxygen alone. Furthermore the destruction of β-carotene in the presence of AIBN is subject to catalysis by stearic acid. In the presence of (2×10^{-3} *M*) stearic acid (molar ratio of β-carotene:AIBN:stearic acid 1:1:10) the rate of loss of β-carotene increased by a factor of 2.5. The effect of stearic acid might be a dilution effect retarding the recombination between radicals to form nonradical species. Thus



AIBN



Reaction ii is subject to dilution effects.

If the oxidation of β-carotene does not occur through hydrogen abstraction at the 4,4′ positions, then the activation energy of 10.20 kcal/mol is too small and hence would exclude any such process occurring for all other hydrogens in the molecule. That is to say, the oxygen molecule does not attack a preformed free radical or assist in hydrogen abstraction to form one. The possibility, however, remains that the process might involve (a) the addition of the oxygen molecule across a double bond in a single step (this is unlikely because it will result in higher reaction order kinetics) or (b) the activation of the oxygen molecule through electron donation in a process possibly involving a dipole association product.

To obtain more information about the nature of such association between oxygen and a double bond in β-carotene the effect of free-radical inhibitors on the reaction was studied. The addition of such inhibitor, diphenylamine in excess (molar ratio of ten diphenylamine to one β-carotene), after allowing the reaction to proceed for 80 min, completely stops the loss of β-carotene. If the reaction is initiated in the presence of 2×10^{-4} *M* diphenylamine a lag phase (22 min) is introduced and the rate is reduced by 48%. This behavior in the presence of diphenylamine indicates the presence of free-radical character in the associated complex. This is further evidence against addition of oxygen across a double bond in a single step. Diphenylamine might decompose the β-carotene–oxygen associated complex.

(15) F. J. Petracek and L. Zechmeister, *J. Amer. Chem. Soc.*, **78**, 1427 (1956).

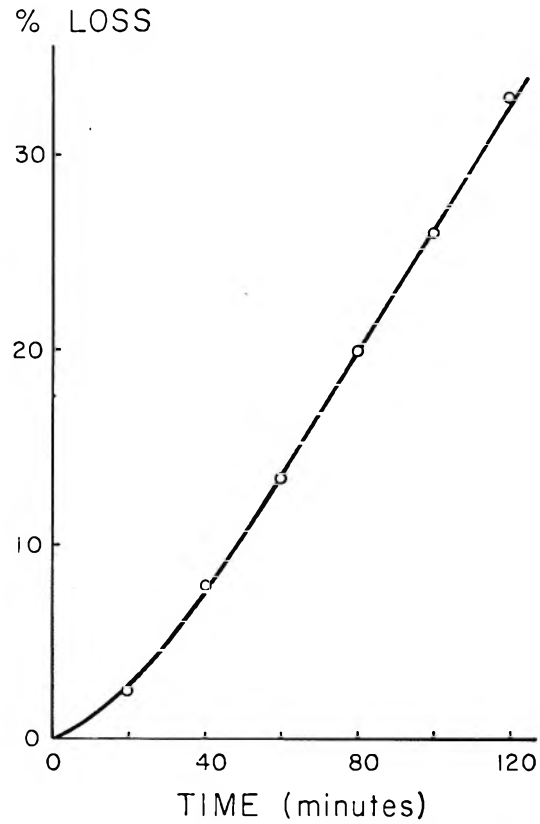


Figure 2.—Effect of azobisisobutyronitrile (2×10^{-4} *M*) on rate of loss of β-carotene.

The reaction between β-carotene and oxygen is subject to metal ion catalysis. Cupric stearate causes a rate enhancement of 4.3-fold. Cupric ions presumably stabilized the association between β-carotene and oxygen.

The products of the oxidation of β-carotene are shown in Table I. Tentative identification is given together with the evidence for the identification.

The predominant formation of epoxides is further evidence that the initial site of the oxygen attack on the β-carotene molecule occurs at the terminal double bonds. This is in agreement with the predictions of the oxidation of a conjugated system, since in a conjugated system the highest electron density is found in the terminal double bonds, with a progressive depletion of electron density as the central double bond is approached. It is therefore reasonable that reactions requiring high electron density would occur at the terminal double bonds.

Central Bond Cleavage.—As has been mentioned before, β-carotene and a number of carotenoids are converted into vitamin A in the animal body. In the mechanism of the conversion of β-carotene into vitamin A, the most obvious expectation is that *in vivo* this takes place by a hydrolytic fission of the β-carotene molecule as follows.

$$\beta\text{-carotene} + H_2O \longrightarrow 2(\text{vitamin A})$$

However, the absence of any evidence for such a hydrolytic fission and the failure of all attempts to bring about such a conversion *in vitro* makes the case

TABLE I

R_f VALUES OF BANDS SEPARATED FROM OXIDATION OF β-CAROTENE WITH OXYGEN (TIME, 60 MIN)

Compound	R_f (% acetone) 3	R_f (% acetone) 5	Color with HCl
β-Carotene	0.94	0.97	No color
β-Carotene 5,6-monoepoxide	0.88	0.93	Blue
β-Carotene 5,6-monoepoxide isomer	0.82	0.93	Blue
β-Carotene 5,6,5′,6′-diepoxide	0.77	0.90	Blue
β-Carotene 5,8-monoepoxide	0.42	0.47	No color
β-Carotene 5,8-monoepoxide isomer	0.40	0.47	No color
Polyene carbonyl	0.37	0.38	No color
β-Carotene 5,8,5′,8′-diepoxide	0.34	0.30	No color

(i) β-Carotene
- (a) Decreased R_f value
- (b) Epiphasic in phase test
- (c) Spectral properties: maxima (in hexane) at 475, 446, and 423 mμ corresponding to the recorded spectrum of Tsukida and Zechmeister:[a] 475, 446, and 423 mμ

(ii) β-Carotene 5,6-monoepoxide isomer
- (a) Decreased R_f value
- (b) Epiphasic in phase test
- (c) Spectral properties: maxima (in hexane) at 473, 444, and 423 mμ

(iii) β-Carotene 5,6,5′,6′-diepoxide
- (a) Decreased R_f values
- (b) Epiphasic in phase test
- (c) Spectral properties: maxima (in hexane) at 468, 440, and 417 mμ (Tsukida and Zechmeister:[b] 470, 440, and 417 mμ)

(iv) β-Carotene 5,8-monoepoxide
- (a) Decreased R_f value
- (b) Epiphasic in phase test
- (c) Spectral properties: maxima (in hexane) at 450, 427, and 404 mμ (Elahi:[8] 451, 426, and 440 mμ)

(v) β-Carotene 5,8-monoepoxide isomer
- (a) Decreased R_f value
- (b) Epiphasic in phase test
- (c) Spectral properties: maxima (in hexane) at 448, 427, 404, and 500 mμ. The 427mμ peak is indicative of the 5,8-epoxide

(vi) Polyene carbonyl
- (a) Decreased R_f value
- (b) Epiphasic in phase test
- (c) Spectral properties: single peak at 378 mμ (in hexane)

(vii) β-Carotene 5,8,5′,8′-diepoxide
- (a) Decreased R_f value
- (b) Mainly epiphasic in phase test
- (c) Spectral properties: maxima (in hexane) at 426, 401, and 381 mμ corresponding to the recorded spectrum (Elahi:[8] 426, 401, and 381 mμ)

[a] K. Tsukida and L. Zechmeister, *Arch. Biochem. Biophys.*, **74**, 408 (1958).

for this mechanism doubtful. Clover, *et al.*,[16] administered vitamin A aldehyde orally and parentally to vitamin A depleted rats and found that it was converted to vitamin A in the gut wall. This suggested that the transformation of β-carotene to vitamin A *in vivo* is more likely achieved by oxidation of β-carotene to vitamin A aldehyde, which is then rapidly reduced to vitamin A, rather than by hydrolytic fission. Further, this process implies that the reaction site is the central double bond, and regardless of the mechanism of the reaction the enzyme system would have to accomplish this conversion at the position of least electron density, that is, the least reactive double bond. The information obtained from the degradation of β-carotene with oxygen shows that direct cleavage of a double bond is an energetically feasible process (10–20 kcal/mol) at those sites with high electron density, namely the terminal double bonds. Therefore, it appears that the function of the enzyme system in the enzymatic oxidative cleavage of β-carotene must be to minimize or oppose the electron density depletion from the center of the molecule.

(16) J. Glover, T. W. Goodwin, and R. A. Morton, *Biochem. J.*, **43**, 109 (1948).

Experimental Section

Materials. Chemicals.—All-*trans* crystalline β-carotene was a gift from Hoffmann-La Roche. All-*trans* vitamin A acetate was a commercial material. Cupric stearate, N-bromosuccinamide, and azobisisobutyronitrile (AIBN) were commercial materials. AIBN was recrystallized from methanol, mp 105–106°. Diphenylamine was recrystallized from petroleum ether, mp 54–55°.

Solvents.—Petroleum ether refers to the fraction which distilled at 60–80°. Toluene analytical reagent, bp 110, was used. Spectroscopic grade *n*-hexane was used for spectral determinations.

Adsorbent.—Aluminium oxide thin layer chromatography plates were obtained from Brinkmann Instruments Inc., N. Y. Absorbent thickness was 250 μ. Neutral alumina supplied by Baker Chemical Co. of N. J. was used for chromatography.

Methods.—Spectra were measured using silica cells on a Cary recording spectrophotometer, Model 14.

Partition Test.—Partition tests were done by shaking a hexane solution with an equal volume of 95% methanol and determining the ratio of the concentrations in hexane by estimating (spectrophotometrically at λ_{max}) the concentration remaining in hexane.

Oxidation of β-Carotene.—β-Carotene (5 mg) was dissolved in 50 ml of toluene. The solution was incubated in a thermostat at 60° in the dark. A slow stream of oxygen was passed through the solution. Samples were withdrawn at regular time intervals and the concentration of the residual β-carotene was determined spectrophotometrically at the wavelength of maximum absorption, 464 mμ.

Identification of Major Reaction Products.—The reaction mixture was applied under a stream of nitrogen along a straight line on an alumina thin layer plate (250-mμ thickness) about 3 cm from the bottom. Drying was completed under a stream of nitrogen. The chromatogram was developed by the ascending technique empolying one of the following systems: (1) 1% acetone in petroleum ether, (2) 3% acetone in petroleum ether, and (3) 5% acetone in petroleum ether. The chromatogram was developed until the solvent front reached a distance of 15 cm from the applied mixture. Bands were removed from partially dry chromatograms, extracted with acetone, and rechromatographed for better separation. The R_f values were measured from the center of the band.

After removal from the plate, bands were again extracted with acetone and the solvent was evaporated to dryness under reduced pressure at low temperature while the products were protected from exposure to light. The absorption spectra were obtained after redissolving the products in spectroscopic hexane.

Registry No.—β-Carotene, 116-32-5.

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Extractives of *Angelica genuflexa* Nutt.

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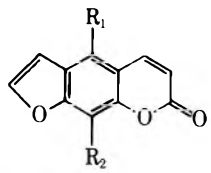
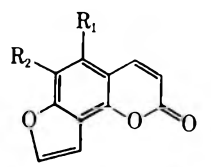
Received August 11, 1969

Imperatorin, bergapten, isobergapten, pimpinellin, and 6-isopentenyloxyisobergapten have been isolated from the extracts of *Angelica genuflexa* Nutt. (Umbelliferae). Mild acid hydrolysis of 6-isopentenyloxyisobergapten gave 6-hydroxyisobergapten, which was in turn converted by methylation into pimpinellin. 6-Hydroxyisobergapten was correlated with isopimpinellin through the quinone (**14**), hydroquinone (**15**), and 5,8-dibenzyloxypsoralen (**16**) followed by methylation and rearrangement. These correlations and spectroscopic considerations establish the structure as 6-isopentenyloxyisobergapten. Fruit of *A. genuflexa* collected the following season gave only (+)-oxypeucedanin. Oxypeucedanin (**17**) was converted into the episulfide (**20**) and trithiocarbonate (**21**). ORD and CD studies on **21** establish the absolute configuration of **17** as *R*.

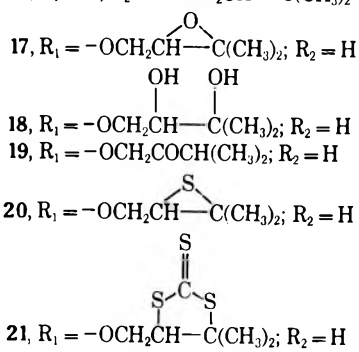
The extractives of *Angelica genuflexa* Nutt. (Umbelliferae) have been the subject of a previous study by Nikonov and coworkers.[1] They reported the isolation of imperatorin and two other new furocoumarins, genufline, $C_{16}H_{14}O_4$, mp 70–72°, and genuflinine, $C_{16}H_{16}O_6$, mp 132°. The present study has resulted in the isolation of a new angular furocoumarin, as well as imperatorin (**2**), bergapten (**1**), isobergapten (**3**), pimpinellin (**4**), and (+)-oxypeucedanin (**17**), from *A. genuflexa*.



1, $R_1 = CH_3O-$; $R_2 = H$
2, $R_1 = H$; $R_2 = -OCH_2CH{=}C(CH_3)_2$

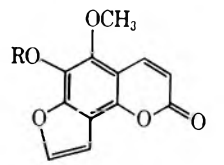


3, $R_1 = CH_3O-$; $R_2 = H$
4, $R_1 = R_2 = CH_3O-$
5, $R_1 = R_2 = H$
6, $R_1 = H$; $R_2 = CH_3O-$

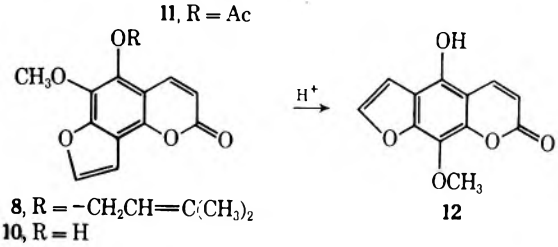


17, $R_1 = -OCH_2CH(O)C(CH_3)_2$; $R_2 = H$
18, $R_1 = -OCH_2CH(OH)C(CH_3)_2$; $R_2 = H$
19, $R_1 = -OCH_2COCH(CH_3)_2$; $R_2 = H$
20, $R_1 = -OCH_2CH(S)C(CH_3)_2$; $R_2 = H$
21, $R_1 = -OCH_2CH(SC(=S)S)C(CH_3)_2$; $R_2 = H$

The new coumarin, mp 95–96°, analyzed for $C_{17}H_{16}O_5$. Its uv spectrum was similar to that of isobergapten (**3**) and pimpinellin (**4**),[2] indicating that the compound was an isopsoralen (**5**) derivative. The nmr spectrum showed resonances for H-3 and H-4 of a coumarin lactone ring, one methoxy group, a fused furan ring, and an isopentenyl group. The chemical shift of the methylene doublet of the isopentenyl group indicated that it was attached to an ether oxygen atom rather than directly to a benzene ring.[3] The presence of an isopentenyl ether group was shown chemically by mild acid hydrolysis. A phenolic product was obtained, which corresponded to loss of the isopentenyl group. These results are consistent with two possible structures, **7** or **8**, for the natural coumarin and **9** or **10** for the dealkylated phenol respectively.



7, $R = -CH_2CH{=}C(CH_3)_2$
9, $R = H$
11, $R = Ac$



8, $R = -CH_2CH{=}C(CH_3)_2$
10, $R = H$
12

The presence of an isopsoralen system was shown chemically by methylation of the phenol to give pimpinellin (**4**). The phenol formed a monoacetate, whose uv spectrum was similar to that of isobergapten and unlike that of sphodin (**6**).[4] An acetoxy group is generally considered to cause the uv spectrum of the acetate derivative to be similar to that of the derived unsubstituted hydrocarbon.[5] This strongly supports structure **9** for the dealkylated phenol and thus **7** for the natural coumarin.

The dealkylated coumarin was recovered unchanged after treatment with base and acidification, indicating that a change from an angular furocoumarin to the linear analog, **12**, allowed by structure **10** had not taken place.[6] This provides further permissive evidence for structure **9**.

Distinction between structures **9** and **10** was finally shown chemically by correlation with isopimpinellin (**13**). Isopimpinellin (**13**) or imperatorin (**2**) was oxidized to the quinone (**14**) which was in turn reduced to the hydroquinone (**15**) by published procedures.[7] To block the free phenolic groups, the hydroquinone

(1) G. K. Nikonov, N. I. Rodian, and M. G. Pimenov, *Aptechn. Delo*, **12**, 23 (1965); *Chem. Abstr.*, **62**, 815 (1965).

(2) P. D. Desai, T. R. Govindachari, K. Nagarajan, and N. Viswanathan, *Ind. J. Chem.*, **5**, 41 (1967).

(3) Compare with nmr data on other isopentenyl substituted furocoumarin: D. L. Dreyer, *J. Org. Chem.*, **33**, 3574 (1968); *Tetrahedron*, **22**, 2923 (1966); *Phytochemistry*, **5**, 367 (1966).

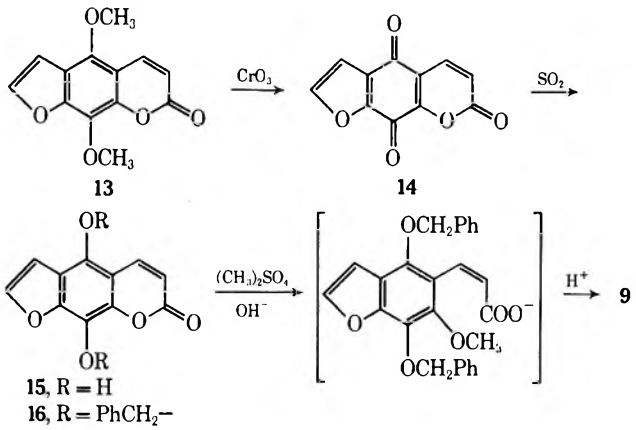
(4) T. R. Seshadri and M.S. Sood, *J. Ind. Chem. Soc.*, **39**, 539 (1962); A. Mustafa, "Furopyrans and Furopyrones," Interscience Publishers, Inc., New York, N. Y., 1967, p 24.

(5) H. Brockmann, E. H. F. Falkenhausen, R. Neeff, A. Dorlars, and G. Budde, *Chem. Ber.*, **84**, 865 (1951); H. Brockmann, *Fort. Chem. Org. Naturstuffe*, **14**, 141 (1957); A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The Macmillian Co., New York, N. Y., 1964, p 294.

(6) *Cf.* E. Spaeth and L. Socias, *Ber. Deut. Chem. Ges.*, **67**, 59 (1934).

(7) M. E. Brokke and B. E. Christensen, *J. Org. Chem.*, **24**, 523 (1959); see also E. A. Abu-Mustafa, B. A. H. El-Tawil, and M. B. E. Fayez, *Ind. J. Chem.*, **5**, 283 (1967).

(**15**) was converted into its dibenzyl ether (**16**). This allowed selective methylation of the lactone hydroxy group under basic conditions with dimethyl sulfate and aqueous base. Acid-catalyzed removal of the benzyl groups and concurrent lactonization gave the desired isobergapten derivative (**9**) in low yield, identical by spectroscopic criteria and tlc with that obtained from the natural material.



Extracts of fruit from the following season gave quite different results. The major product, mp 101–102°, $[\alpha]_D$ +11.1° was obtained in good yield. Its uv spectrum was superimposable on that of bergapten. The nmr spectrum showed a one-proton aromatic singlet as well as two sets of AB doublets assignable to H-3 and H-4, and a fused furan ring in a psoralen system. The remaining resonances were consistent with a 2′, 3′-epoxyisopentyloxy system. These data are consistent with structure **17**, (+)-oxypeucedanin, for the coumarin.[8,9]

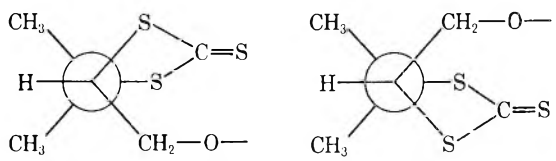
Chemical evidence for the presence of the epoxy group was obtained by acid catalyzed hydrolysis. Two products were obtained, after chromatography on alumina. One was the expected 1,2-diol (**18**), oxypeucedanin hydrate, and the other was the known 2′-oxo derivative (**19**), isooxypeucedanin.[8,9] The new coumarin found in this study differs both in analytical and physical properties from those reported for genufline and genuflinine. On the other hand, no evidence for the presence of genufline and genuflinine in *A. genuflexa* was found in this study.

Extractives with isopentenyl side chains are widely distributed in the Umbelliferae and Rutaceae. Many of these isopentenyl extractives occur epoxidized, as 1,2-diols or ring closed to isopropyldihydrobenzofurans. These extractives are, with a few exceptions, optically active. The absolute configuration of the isopentyl derivatives is known in only a few cases.[10] The stereochemical relationships between the different types of extractives in the plant are not known; *e.g.*, does oxide ring opening to the diol occur with retention or inversion of configuration in the plant? The absolute configuration of such extractives might also be of interest from a chemotaxonomic standpoint. Can the concept of absolute configuration in this class of extractives be used as a chemotaxonomic indicator?

The availability of substantial amounts of **17** from this work permitted studies to be undertaken designed to determine its absolute configuration. Trithiocarbonates are optically active chromophores which have low intensity adsorptions near 430 mμ.[11] The preparation of trithiocarbonates from epoxides with potassium methyl xanthanate proceeds through the episulfide and involves two inversions so that the stereochemistry of the trithiocarbonate product is the same as the starting epoxide.[12]

It is generally accepted that the chirality, or sense of twist, of the heterocycle ring is the major factor in determining the sign of the Cotton effect in trithiocarbonates[13,14] and the magnitude of the Cotton effect depends on the amount of twist of the ring. The position of substitutents on the ring has relatively little effect on the sign of the Cotton effect. If the chirality is positive, a positive Cotton effect would be predicted and correspondingly a negative chirality leads to a negative Cotton effect. In bicyclic systems the chirality, or sense of twist of the trithiocarbonate ring, is determined by the stereochemistry of the ring juncture and preferred conformations of the system in those cases where flexibility exists.[14]

Trithiocarbonates of open-chain systems might be expected to be nearly planar. However, twisting of the heterocycle ring would result in relief of the eclipsing interactions of the groups on the ring. Relief of these eclipsed interactions by rotation about the C–C bond will cause twisting of the trithiocarbonate ring. The sense of twist will depend on the absolute stereochemistry of the starting system. Newman projections of the two possibilities are shown in **22** and **23**. For case **22** a positive Cotton effect would be predicted and a negative Cotton effect for **23**.



After treatment of oxypeucedanin (**17**) with potassium methyl xanthanate it was possible to isolate, after chromatography, both the episulfide (**20**) and trithiocarbonate (**21**). The ORD and CD curves of the trithiocarbonate (**21**) showed the usual pattern for such compounds[11,13] with a positive Cotton effect at 443 mμ followed by a negative Cotton effect at 322 mμ. These data would indicate that (+)-oxypeucedanin has the *R* configuration. Chemical studies recently reported by Nielsen and Lemmich[15] on oxypeucedanin hydrate also lead to the *R* configuration.

(8) E. Spaeth and K. Klayer, *Ber. Deut. Chem. Ges.*, **66**, 914 (1933).

(9) A. Butenandt and A. Marten, *Ann.*, **495**, 187 (1932).

(10) B. Eichstedt, Nielsen and J. Lemmich, *Acta Chem. Scand.*, **18**, 2111 (1964); W. A. Bonner, N. I. Burk, W. E. Fleck, R. K. Hill, J. A. Joule, B. Sjoberg, and L. H. Zalkow, *Tetrahedron*, **20**, 1419 (1964); M. Nakazaki, Y. Hirose, and K. Ikematsu, *Tetrahedron Lett.*, 4735 (1966); I. Harada, Y. Hirose, and M. Nakazaki, *ibid.*, 5463 (1968).

(11) C. Djerassi, H. Wolff, D. A. Lightner, E. Bunnenberg, K. Takeda, T. Komeno, and K. Kuriyama, *Tetrahedron*, **19**, 1547 (1963).

(12) C. G. Overberger and A. Drucker, *J. Org. Chem.*, **29**, 360 (1964); see also, A. M. Creighton and L. N. Owen, *J. Chem. Soc.*, 1024 (1960); S. M. Iqbal and L. N. Owen, *ibid.*, 1030 (1960).

(13) D. A. Lightner, C. Djerassi, K. Takeda, K. Kuriyama, and T. Komeno, *Tetrahedron*, **21**, 1581 (1965); K. Kuriyama and T. Komeno, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," G. Snatzke, Ed., Heyden and Son, London, 1967, Chapter 21.

(14) A. H. Haines and C. S. P. Jenkins, *Chem. Comm.*, 350 (1969).

(15) B. E. Nielsen and J. Lemmich, *Acta Chem. Scand.*, **23**, 962 (1969).

Experimental Section[16]

Isolation.—Plant material was collected July 1967 at Neptune State Park on the Oregon Coast. Dried and ground seed heads were extracted with acetone. Solvent was removed from the extracts and the residue chromatographed on alumina. Solvent was removed from the first fractions showing fluorescence on tlc and the residue crystallized from hexane or ethyl acetate–hexane, to give the new coumarin (**7**): mp 95–96° after further crystallization from ethyl acetate–hexane; λ_{max}^{EtOH} 221 mμ (ε 27,700), 252 (26,000), 304 (12,300); nmr δ 8.09 (d, J = 10 Hz, H-4), 7.68 (d, J = 2 Hz, H-7), 7.06 (d, J = 2 Hz, H-8), 6.35 (d, J = 10 Hz, H-3), 5.60 (t, J = 7 Hz, vinyl), 4.82 (d, J = 7 Hz, α-methylene), 4.07 (s, methoxyl), 1.78, 1.72 (C-methyls) (in $CDCl_3$).

Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 68.1; H, 5,44.

The fractions following from the column eluted with benzene and chloroform gave upon work-up imperatorin (**2**), after crystallization from ethyl acetate–hexane, identical with an authentic sample.[17] The mother liquors from work-up of the imperatorin give further amounts of **7**. Large amounts of bergapten (**1**), mp 183–186° (from ethyl acetate–hexane) were recovered from the benzene eluents.

The mother liquors from these operations were combined, the solvent was removed, and the residue was heated with a trace of hydrochloric acid in acetic acid on a steam bath for 30 min. After work-up, the product was chromatographed on alumina to give isobergapten (**3**) and pimpinellin (**4**), both crystallized from ethyl acetate–hexane. The pimpinellin was identical in all respects with a sample provided by Dr. T. R. Govindachari.

Acid Hydrolysis of 6-Isopentenyloxyisobergapten (7).—A solution of the coumarin (**7**) in glacial acetic acid and a trace of hydrochloric acid was heated for 30 min on a steam bath. The solution was cooled, diluted with water, and extracted with ethyl acetate. After drying and removal of solvent, the residue was crystallized from ethyl acetate–methanol–hexane and sublimed for analysis to give **9**: mp 223–224°; λ_{max}^{EtOH} 221 mμ (ε 21,000), 254 (18,700), 308 (9,000); $\lambda_{max}^{EtOH-NaOH}$ 275, 323 mμ; nmr δ 8.14 (d, J = 10 Hz, H-4), 7.86 (d, J = 2 Hz, H-7), 7.07 (d, J = 2 Hz, H-8), 6.37 (d, J = 10 Hz, H-3), 3.97 (methoxyl) (in deuteriodimethyl sulfoxide–$CDCl_3$).

Anal. Calcd for $C_{12}H_8O_5$: C, 62.07; H, 3.47. Found: C, 62.1; H, 3.90.

Acetylation of **9** with acetic anhydride–pyridine gave the monoacetate (**11**): mp 171–173° from ethyl acetate–hexane; λ_{max}^{EtOH} 219, 249, 301 mμ; nmr δ 8.09 (d, J = 10 Hz, H-4), 7.64 (d, J = 2 Hz, H-7), 7.11 (d, J = 2 Hz, H-8), 6.40 (d, J = 10 Hz, H-3), 4.00 (methoxy), 2.47 (acetoxy) (in $CDCl_3$).

Anal. Calcd for $C_{14}H_{10}O_6$: C, 61.32; H, 3.68. Found: C, 61.6; H, 3.77.

Methylation of **9** with diazomethane gave pimpinellin (**4**), identical in all respects with an authentic sample: nmr δ 8.07 (d, J = 10 Hz, H-4), 7.67 (d, J = 2 Hz, H-7), 7.06 (d, J = 2 Hz, H-8), 6.34 (d, J = 10 Hz, H-3), 4.15, 4.06 (methoxyls) (in $CDCl_3$).

5,8-Dibenzyloxypsoralen (16).—A solution of 1.5 g of 15[7] and 2 g of benzyl chloride in dry acetone was refluxed over anhydrous potassium carbonate for 8 hr. The cooled solution was filtered and solvent was removed from the filtrates. The residue was taken up in chloroform and filtered through a short column of alumina with chloroform. Solvent was removed from the filtrates and the residue was recrystallized from methanol: mp 157.5–158°; nmr δ 8.12 (d, J = 10 Hz, H-4), 7.70 (d, J = 2 Hz, H-7), 7.47 (m, phenyl), 6.95 (d, J = 2 Hz, H-6), 6.23 (d, J = 10 Hz, H-3), 5.43, 5.33 (s, benzyl methylenes) (in $CDCl_3$); λ_{max}^{EtOH} 241, 249, 268, 312 mμ.

Anal. Calcd for $C_{25}H_{18}O_5$: C, 75.37; H, 4.55. Found: C, 75.60; H, 4.82.

6-Hydroxyisobergapten (9).—One gram of dibenzyl ether **16** was dissolved in ethanol–10% aqueous sodium hydroxide by means of heating. The solution was then diluted with more water. Dimethyl sulfate was added with stirring. Alternate additions of dimethyl sulfate and aqueous sodium hydroxide were made so that the solution was kept basic. After six times the calculated amount of dimethyl sulfate was consumed, the basic solution was warmed on a steam bath a further 20 min. The mixture was cooled and extracted with chloroform. The aqueous phase was acidified and re-extracted with chloroform. Solvent was removed from the latter chloroform extracts and the residue warmed with acetic acid–hydrochloric acid for 20 min on a steam bath. The cooled mixture was poured into water and extracted with chloroform. The chloroform extracts were dried and solvent was removed. The residue was sublimed. The sublimate was identical with natural **9** by ir, uv, and tlc criteria.

Isolation.—Fruit of *A. genuflexa* was collected at the end of Aug 1968 on the Oregon Coast along Highway 101 just south of the Drift Creek bridge, south of Lincoln City, Ore. Solvent was removed from the acetone extracts and the residue was chromatographed on alumina. Those fractions eluted with hexane which did not show fluorescence on tlc were discarded. Elution with hexane–benzene mixtures and benzene gave fractions which after work-up gave (−)-oxypeucedanin (**17**): mp 101–102° from ethyl acetate–hexane [lit.[18] mp 104° for (+) isomer]; $[\alpha]_D$ −11.1° ($CHCl_3$); nmr δ 9.23 (d, J = 10 Hz, H-4), 7.71 (d, J = 2 Hz, H-7), 7.13 (s, H-8), 7.06 (d, J = 2 Hz, H-6), 6.25 (d, J = 10 Hz), 4.50 (m, α-methylene), 3.15 (q, epoxy), 1.34, 1.39 (C-methyls) (in $CDCl_3$).

Anal. Calcd for $C_{15}H_{14}O_5$: C, 67.12; H, 4.93. Found: C, 67.3; H, 4.96.

Further work-up of the mother liquors gave mixtures of oxypeucedanin and isoimperatorin.

Acid Hydrolysis of Oxypeucedanin (17).—A solution of 1 g of crude **17** in aqueous ethanol containing 5% oxalic acid was refluxed for 1 hr. The solution was cooled and extracted with ethyl acetate. The ethyl acetate extracts were dried, the solvent was removed, and the residue was chromatographed over a short column of alumina. Isooxypeucedanin was eluted with benzene and the diol **18** was eluted with chloroform. Solvent was removed from the chloroform eluents and the residue was crystallized from benzene–acetone to give oxypeucedanin hydrate (**18**), identical in all respects with that of a sample isolated from expressed lemon oil: nmr δ 8.41 (d, J = 10 Hz, H-4), 7.79 (d, J = 2 Hz, H-7), 7.20 (s, H-8), 7.19 (d, J = 2 Hz, H-6), 6.35 (d, J = 10 Hz, H-3), 4.62 (m, α-methylene), 4.00 (q, methine), 1.40, 1.38 (C-methyls) (in $CDCl_3$).

Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.2; H, 5.22.

Workup of the benzene elutents gave isooxypeucedanin (**19**):[8,9] mp 148–149.5° from ethyl acetate–hexane; nmr δ 8.65 (d, J = 10 Hz, H-4), 7.89 (d, J = 2 Hz, H-6), 7.39 (s, H-8), 7.09 (d, J = 2 Hz, H-5), 6.50 (d, J = 10 Hz, H-3), 6.26 (s, α-methylene), 2.97 (sept, J = 7 Hz, methine), 1.30, 1.18 (C-methyls) (in $CDCl_3$).

Anal. Calcd for $C_{15}H_{14}O_5$: C, 67.12; H, 4.93. Found: C, 67.3; H, 4.96.

Reaction of Oxypeucedanin (17) with Potassium Methyl Xanthanate.—Three milliliters of CS_2 was added to a solution of 1 g of KOH in 8 ml of methanol. One gram of oxypeucedanin (**17**) was added and the mixture was warmed briefly on a steam bath to affect solution. The mixture was then allowed to stand 48 hr at room temperature. The solution was then poured into water and the aqueous mixture was extracted with ethyl acetate. Solvent was removed from the dried ethyl acetate extracts and the residue was chromatographed over a short column of alumina. Benzene eluted the episulfide (**20**), mp 125–127°, after recrystallization from ethyl acetate–hexane: nmr δ 8.16 (d, J = 10 Hz, H-4), 7.64 (d, J = 2 Hz, H-7), 7.14 (s, H-8), 6.97 (d, J = 2 Hz, H-6), 6.29 (d, J = 10 Hz, H-3), 4.58 (m, α-methylene), 3.20 (q, methine), 1.68, 1.62 (C-methyls) (in $CDCl_3$).

Anal. Calcd for $C_{16}H_{14}O_4S$: C, 63.5; H, 4.66. Found: 64.8; H, 4.76.

Further elution of the column with chloroform gave the yellow trithiocarbonate (**21**): mp 184–186° from benzene; nmr δ 8.29 (d, J = 10 Hz, H-4), 7.84 (d, J = 2 Hz, H-7), 7.34 (s, H-8), 7.02 (d, J = 2 Hz, H-6), 6.38 (d, J = 10 Hz, H-3), 4.92–4.34 (m, α-methylene and methine), 1.92, 1.78 (C-methyls) (in $CDCl_3$); ORD in dioxane (c 0.03) $[\alpha]_{473}$ +3200°, $[\alpha]_{425}$ +330°, $[\alpha]_{380}$ +2000° (last reading); CD in dioxane (c 0.0008) 500 (0), 446 (+2.5), 380 (0). A qualitative CD curve in ethanol showed

(16) Nmr spectra were taken at 60 MHz. The relative areas of the peaks were consistent with their assignments. J values are in hertz.

(17) D. L. Dreyer, *J. Org. Chem.*, **30**, 749 (1965).

(18) B. E. Nielsen and J. Lemmich, *Acta Chem. Scand.*, **18**, 1379 (1964).

positive Cotton effects at 442 and 293 mμ and a negative Cotton effect at 323 mμ.

Anal. Calcd for $C_{17}H_{14}O_4S_3$: C, 53.94; H, 3.72. Found: C, 54.0; H, 3.81.

Registry No.—**7**, 24099-29-4; **9**, 24099-3-7; **11**, 24099-31-8; **16**, 24099-32-9; **17**, 3173-02-2; **18**, 2643-85-5; **20**, 24099-34-1; **21**, 24099-35-2.

Acknowledgments.—The author is indebted to Dr. T. R. Govindachari for a comparison sample of pimpinellin, to Jim Steward for the ORD results, and to Austin Griffiths, Jr., for identification of the plant material. This work was supported, in part, by an NSF Institutional Grant to San Francisco State College.

Solvolyses of A-Norcholesteryl *p*-Toluenesulfonate Derivatives. III[1,2]

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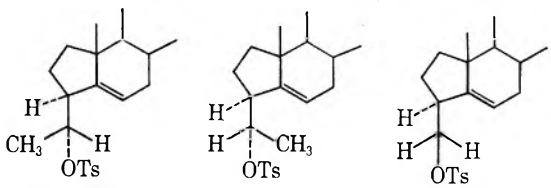
The syntheses and solvolyses of 3β-(1β-hydroxyethyl)-Δ⁵-A-norcholestenyl (**10**) and 3β-(1α-hydroxyethyl)-Δ⁶-A-norcholestenyl (**11**) *p*-toluenesulfonates are reported. The products of solvolysis in each case were similar to those formed in the solvolyses of the related ring-expanded cholesteryl derivatives, namely, 4β-methylcholesteryl (**7**) and 4α-methylcholesteryl (**4**) *p*-toluenesulfonates, respectively. The interrelationships among the various cationic intermediates in these solvolyses are discussed.

Experiments directed toward defining the structures of intermediary ions in the solvolyses of cholesteryl systems with methyl substituents in the A ring has led to a number of interesting results. The examples[4-8] shown in Scheme I summarize some of these findings.

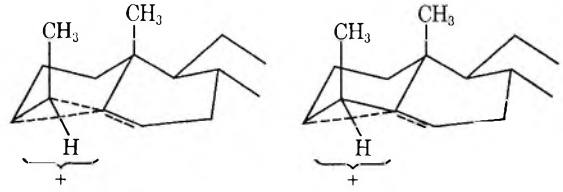
As can be seen, the configuration of the C_4 methyl group in **4** and **7** is extremely important with respect to the products of solvolysis. In the case of the 4α and equatorial orientation present in **4**, the outcome of the reaction is similar to tht observed in the unsubstituted cholesteryl system. The 4β and axial orientation of the methyl group in **7** caused the reaction to take a significantly different course, yielding the conjugated diene Δ³,⁵-4-methylcholestadiene (**8**) as the predominant product. A difference in the geometry of the A ring of **4** and **7** has been offered as an explanation for this divergent behavior.[5,6,8] Thus, the A ring of **4** is considered to exist in a chair form, while the A ring of **7**, in order to relieve the 1,3-diaxial methyl interaction, adopts either a flattened chair conformation[5,6] or a boat form.[8] These shapes should persist in the transition state. In the latter, the favorable geometry for elimination of *p*-TsOH is present, and this is obviously a very favored process. This process does not involve a homoallylic ion. The rate acceleration in solvolysis (*ca.* 200:1) for **7** compared with its saturated analog, 4β-methylcholestanyl *p*-toluenesulfonate,[6] could be due to both steric driving force and the stability of the transition state leading to the conjugated diene. On the other hand, some evidence was found to indicate that diene **8** was not a primary reaction product but rather resulted from a secondary reaction involving a highly reactive precursor.[6]

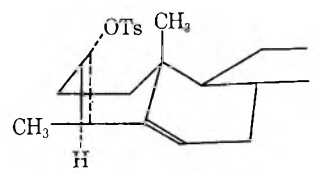
It was felt that a potential clarification of this point might be achieved from the solvolytic behavior of the A-ring-contracted compounds **10** and **11**. Whitham[9]



showed that **12** yielded the same products upon solvolysis as cholesteryl *p*-toluenesulfonate except that no hydrocarbon was formed, in contrast to the 1–2% obtained with cholesteryl toluenesulfonate. This result indicated the intermediacy of a common homoallylic ion resulting from each precursor *i.e.*, cholesteryl or A-nor-Δ⁵-cholestenyl.

The key point in the solvolyses of **10** and **11** would be whether **10** yields diene **8** upon solvolysis in amounts similar to that obtained starting from **7**. This would indicate a common intermediate. Furthermore, it is very unlikely that diene can come directly from either the symmetrical homoallylic ion **13**, or the unsym-





(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this project under Grant 1347-A4.

(2) For part II see R. M. de Sousa and R. M. Moriarty, *J. Org. Chem.*, **30**, 1509 (1965).

(3) University of Illinois, Chicago Circle Campus, Chicago, Ill.

(4) (a) R. M. Moriarty and E. S. Wallis, *J. Org. Chem.*, **24**, 1274, 1987 (1959); (b) Y. M. Y. Haddad and G. H. R. Summers, *J. Chem. Soc.*, 769 (1959); (c) G. Just, S. Winstein, R. Sneen, F. Shortland, and D. N. Gupta, unpublished results; see D. N. Gupta, G. Schilling, and G. Just, *Can. J. Chem.*, **43**, 792 (1965).

(5) R. M. Moriarty and R. M. de Sousa, *J. Org. Chem.*, **28**, 3072 (1963).

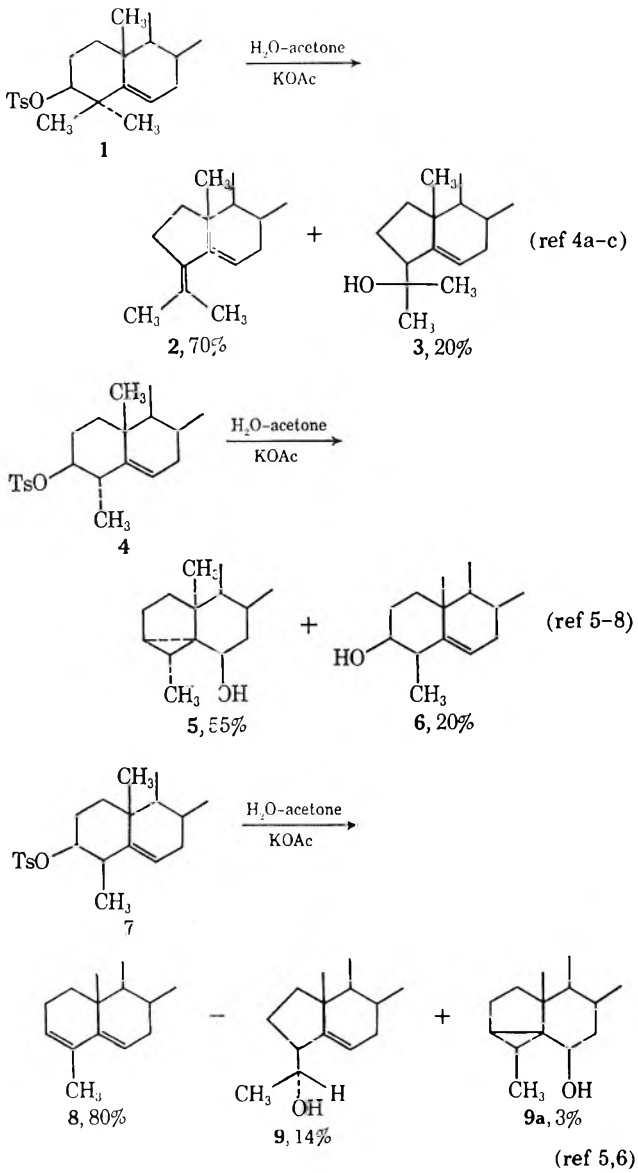
(6) R. M. de Sousa and R. M. Moriarty, *ibid.*, **30**, 1509 (1965).

(7) S. Julia, J.-P. Lavaux, S. R. Pathak, and G. H. Whitham, *C. R. Acad. Sci. Paris*, **256**, 1537 (1963).

(8) S. Julia, J.-P. Lavauax, S. R. Pathak, and G. H. Whitham, *J. Chem. Soc.*, 2633 (1964).

(9) G. H. Whitham and J. A. F. Wickramasinghe, *ibid.*, 1655 (1964)

SCHEME I



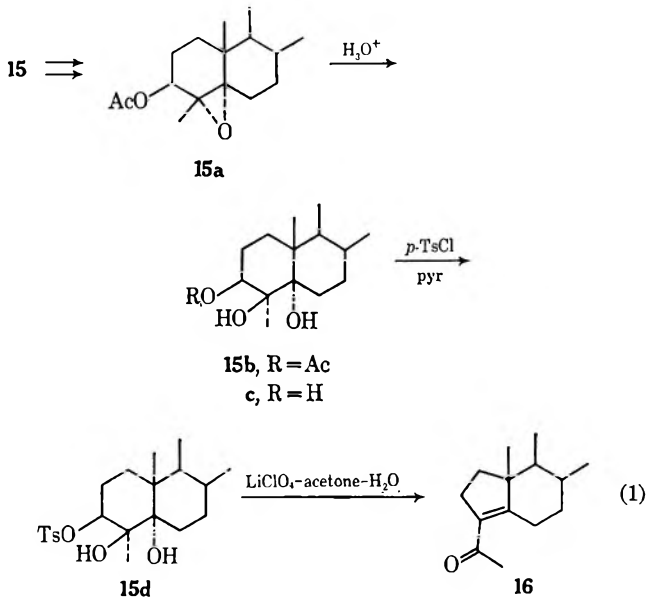
metrical ion **13a**, or that **10** would rearrange to a structure such as **14**, which has been proposed in order to explain the direct formation of diene **8** from **7**.[8] Structure **14** represents the transition state for E2 elimination of TsOH.

Solvolysis of **11** is of interest because it bears the same configurational relationship to **4** as **10** does to **7**. Comparison of the results of solvolysis of **10** and **11** offers a stringent test of the configurational integrity of intermediary ions in this series.

Results and Discussion

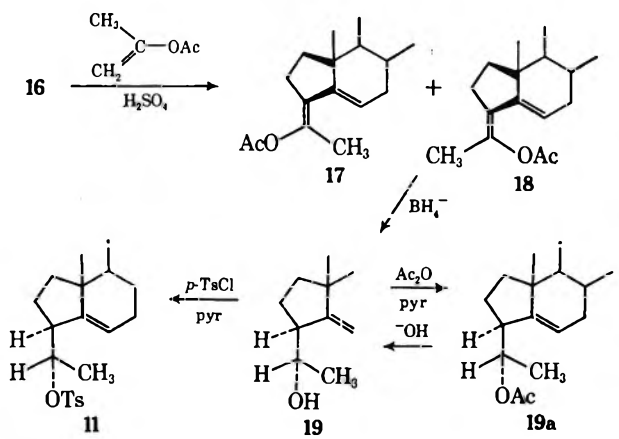
The alcohol precursor of tosylate **10**, namely ring-contracted alcohol **9**, was already available from the hydrolysis of **7**.[5,8] The synthesis of **11** proceeded from 4-methylcholestenone (**15**) using the method of Julia, Whitham, *et al.*,[8] to yield the A-ring-contracted conjugated ketone **16**. Alternatively **16** could be prepared as shown in eq 1.

Enolacetylation of **16** yielded a noncrystalline product which showed two vinyl methyl resonances possibly indicative of two stereoisomers **17** and **18** (Scheme II).



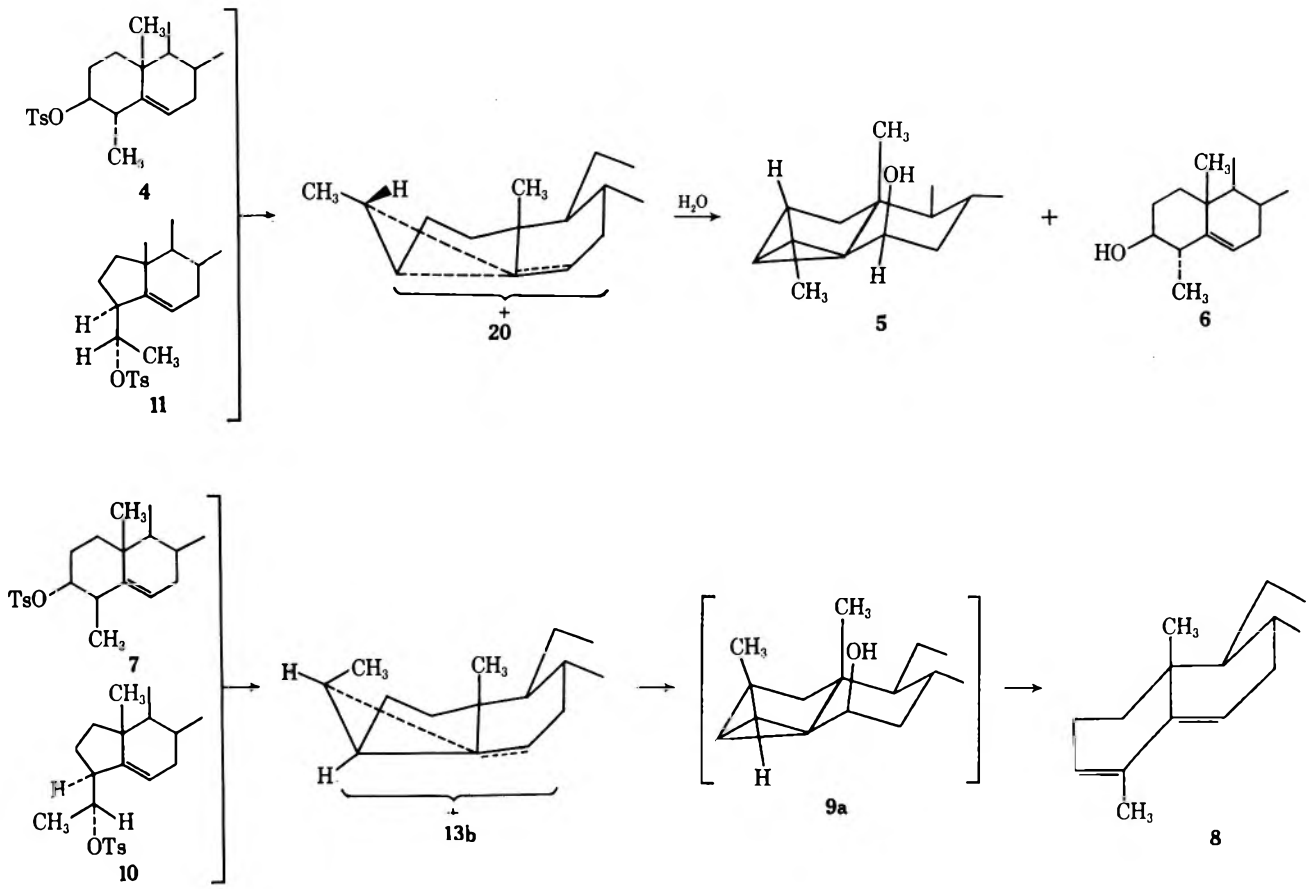
Borohydride reduction of a mixture of **17** and **18** to yield **19** requires comment since two new stereochemical centers are established, namely, at C_3 and at the carbon bearing the hydroxyl group. The initial step is probably hydrolysis of the enol acetate to yield 3-acetyl-A-nor-Δ^5-cholestene which is reduced more rapidly by borohydride than the prototropic shift to yield the conjugated ketone. The most favored mode of protonation of the enol at C_3 is from the α side.[9] Inspection of molecular models reveals that a significant steric difference exists for the carbonyl group once it is formed in the ketonization step. Thus reduction from the least hindered side, that is, away from the C_{19} angular methyl group, would lead expectedly to a predominance of 3β-(1α-hydroxyethyl)-Δ^5-A-norcholestene (**19**), and this is found to be the case. Tosylation under the usual conditions proceeds normally to yield a crystalline tosylate ester (**11**).

SCHEME II



As mentioned earlier, the epimeric ring-contracted alcohol **9** is obtained by hydrolysis of tosylate **7**. A potentially important observation was forthcoming in the attempted tosylation of **9**. Under the standard conditions, namely, *p*-toluenesulfonyl chloride in pyridine, the only product obtained was 4-methyl-$\Delta^{3,5}$-cholestadiene (**8**). In fact, attempted acetylation of **9** using acetic anhydride–pyridine at room temperature

Scheme III



also yielded 4-methyl-$\Delta^{3,5}$-cholestadiene (**8**) as the predominant product. Furthermore, acid-catalyzed treatment yielded the diene.

In another experiment **9** and 1 equiv of *p*-toluenesulfonyl chloride were allowed to stand at room temperature for 5 hr in pyridine solution. Aqueous acetone (60%) and 3 equiv of sodium acetate were added, and the reaction system was kept at reflux overnight. An 85% yield of **8** was obtained.

Solvolysis of 3β-(1α-hydroxyethyl)-Δ^5-A-norcholestenyl tosylate (**11**) under buffered conditions yielded the same products as were obtained in the solvolysis of 4α-methylcholesteryl tosylate (**4**), namely, 4α-methyl-3α,5-cyclocholestan-6β-ol (**5**) (80%) and about 4% 4α-methylcholesterol (**4a**). Scheme III summarizes the reaction pathways for **10** and **11**.

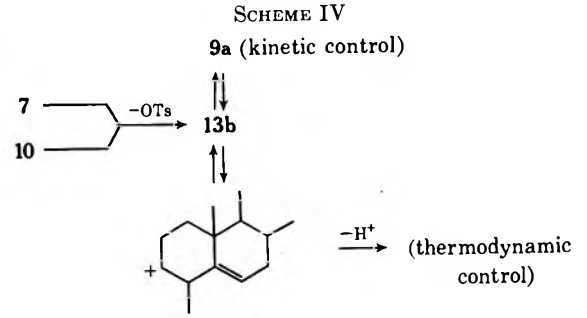
The fact that **11**, upon hydrolysis yields **5**, may be taken as indicating the incursion of the symmetrical ion **20**. Coordination with solvent occurs at C_6. This is a result completely analogous with the finding of Whitham[9] in the solvolysis of **12**.

We interpret the behavior of **10** to indicate that ion **13b** forms initially, and this ion may yield *i*-steroid **9a**, but this product is unstable. Under the reaction conditions it is converted to the product of thermodynamic control, namely **8**. The decreased stability of **13b** and the related *i*-steroid **9a** is due to the C_4–C_{10} dimethyl interaction as well as the C_6 axial hydroxyl group interaction in *i*-steroid **9a**. According to this hypothesis **9a** is the product of kinetic control.

Furthermore, it appears unlikely that diene **8** results directly from elimination of *p*-TsOH from **7** in the manner suggested by Whitham, *et al.*[9] Rather, we interpret diene **8** as coming from ion **13b** and *i*-steroid **9a**. This agrees with our earlier proposal that *i*-steroid **9a** → **8** under the buffered solvolytic conditions. The hypothesis that diene **8** derives from direct elimination of *p*-toluenesulfonic acid from the A-ring boat form **7** is rendered unlikely by the observation that only 1% diene is obtained in the solvolysis of 2,2-dimethylcholesteryl mesylate.[10] Thus if the boat form is favored in **7** owing to relief of the C_4–C_{10} dimethyl interaction, the same should apply to 2,2-dimethylcholesteryl mesylate.

The mechanism for conversion of **10** to **8** probably involves the intervention of the classical homoallylic ion. Both **7** and **10** yield the same nonclassical intermediary ion (**13b**). A small energy barrier separating the nonclassical and classical ion in this series suggests a reasonable route to diene **8** *via* deprotonation from the classical 4β-methylcholesteryl cation. Scheme IV summarizes this behavior.

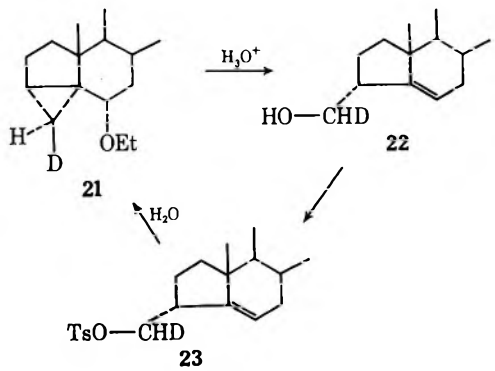
Scheme IV



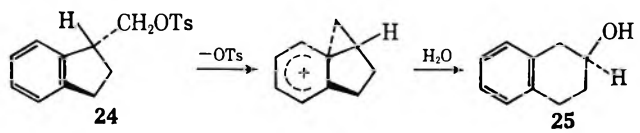
(10) S. R. Pathak and G. H. Whitham, *J. Chem. Soc.*, 193 (1968).

Finally a result found by Just, *et al.*,[11] in the 3α-A-norcholesteryl system is in complete agreement with the main ideas outlined above.

Acid-catalyzed treatment of the photolysis product **21** yields the ring-contracted alcohol **22** which upon tosylation and solvolysis regenerates **21** with retention of configuration of the deuterium.



The optical integrity of such a rearrangement has been demonstrated in the indanyl series for the conversion of (*R*)-1-indanylmethyl tosylate (**24**) to (*R*)-tetrahydro-α-naphthol (**25**) with 80% stereospecificity.[12]



Experimental Section[13]

4α-Methylcholestane-3β,4β,5α-triol 3-Acetate (15b).—To a solution of 1.65 g of **15a** in 500 ml of acetone was added a solution of 3.2 ml of 2 *N* sulfuric acid in 40 ml of water. The resulting solution was allowed to stand at room temperature for 5 days. At the end of this time the acetone was removed *in vacuo* and water was added. The reaction mixture was extracted thoroughly with ether, and the combined ether extracts were washed washed with a saturated solution of sodium bicarbonate. After drying with magnesium sulfate, the extracts were concentrated to dryness to yield a crystalline residue of 1.96 g which was recrystallized from acetone to yield 1.76 g, mp 213–216°. Recrystallization from acetone yielded 1.63 g, mp 218–220°. The analytical sample was prepared by recrystallization from acetone and had mp 218–220°.

Anal. Calcd for $C_{30}H_{52}O_4$: C, 75.60; H, 11.00. Found: C, 75.40; H, 10.91.

4α-Methylcholestane-3β,4β,5α-triol (15c).—**15b**, 1.051 g, was dissolved in 500 ml of methanol. In one portion 1.00 g of potassiumhydroxide was added and the reaction mixture was kept at reflux for 4 hr. The volume was then concentrated *in vacuo* to 50 ml and diluted with water. The solution was extracted seven times with 50-ml portions of ether. The combined extracts were washed with water and concentrated *in vacuo* to dryness. The crude product was crystallized from ether–methanol to yield 747 mg, mp 203–205° (lit.[14] 202°).

4α-Methylcholestane-3β,4β,5α-triol 3-*p*-Toluenesulfonate (15d).—The above triol (1.0 g) was dissolved in 5 ml of purified pyridine by gentle warming. The solution was cooled to 20° and 1.0 g of *p*-toluenesulfonyl chloride was added. The resulting solution solidified to a crystalline mass. After 12 hr at room temperature ice was added, and the crystalline mass was collected, washed thoroughly with water, and dried *in vacuo* to yield 1.2 g, mp 138–140°. Recrystallization from acetone yielded 900 mg of **18**, mp 141–142°. The analytical sample was prepared by recrystallization from acetone, mp 144–145°.

Anal. Calcd for $C_{25}H_{56}O_6S$: C, 71.38; H, 9.58. Found: C, 71.07; H, 9.73.

3-Acetyl-Δ³-A-norcholestene (16) by Solvolysis of 15c.—Lithium perchlorate, 1.116 g, and dry calcium carbonate, 1.25 g, in 30 ml of tetrahydrofuran were stirred at room temperature. A solution of 720 mg of **15c** in 10 ml of tetrahydrofuran was added dropwise over a period of 1 hr. The reaction mixture was stirred under nitrogen for 1 hr, then kept at reflux for 72 hr. After cooling, ether was added and the solution was filtered from the insoluble part. The ether–tetrahydrofuran solution was washed with a saturated solution of sodium bicarbonate. The ether–tetrahydrofuran solution was dried with magnesium sulfate and concentrated to dryness to yield a clear viscous gum, 610 mg, which was crystallized by trituration with cold acetone. Recrystallization from acetone yielded 430 mg of **16**: mp 97–99°, $[\alpha]_D$ +83° (*c*, 1), λ_{max}^{EtOH} 257 mμ (ε 13,000); lit.[8] mp 97–99°, λ_{max}^{EtOH} 257 mμ (ε 13,000).

Enol Acetylation of 3-Acetyl-Δ³-A-norcholestene (16).—Ketone **16**, 1.148 g, was dissolved in 80 ml of freshly distilled isopropenyl acetate, and 2 drops of concentrated sulfuric acid were added. The solution was kept at reflux for 20 hr. The isopropenyl acetate was then removed *in vacuo*. Water was added, and extraction with ether (six 30-ml portions) was carried out. The combined extracts were then washed with a saturated solution of sodium bicarbonate followed by water. The ether extracts were dried and concentrated *in vacuo* to dryness. The resulting semicrystalline mass, 1.505 g, showed in the infrared (CCl_4) 1750 (C=O) and 1675 (C=C) cm^{-1}. The nmr (TMS, CCl_4) showed CH_3CO at 2.08 and 2.17 ppm possibly corresponding to *cis* and *trans* stereoisomers of the isopropenyl part (**17** and **18**).

Sodium Borohydride Reduction of Enol Acetates 17 and 18.—The crude enol acetate, 539 mg dissolved in 20 ml of 95% ethanol, was added dropwise to a stirred solution of 1.5 g of sodium borohydride in 30 ml of 95% ethanol at 0° over a period of 2 hr. The reaction was allowed to come to room temperature and was stirred for an additional 50 hr. At the end of this time excess borohydride was decomposed by addition of glacial acetic acid. Most of the ethanol was removed *in vacuo*, and 10 ml of 6 *N* hydrochloric acid was added. After thorough extraction with ether the combined ether extracts were washed with a saturated solution of sodium bicarbonate followed by water. The extracts were dried and concentrated to dryness *in vacuo* to yield 502 mg of crystalline product. This product was acetylated in the usual way, and the crude gummy acetate was chromatographed upon 30 g of silica gel. Elution with petroleum ether gave a hydrocarbon product, 60 mg, mp 57–59°. This was shown to be homogeneous by tlc on silica gel (10% benzene–petroleum ether). Further elution with 10% benzene–petroleum ether gave 340 mg, mp 85–86°. This acetate was recrystallized from acetone to yield 290 mg of **19a**: mp 104–106°; $\lambda_{max}^{CCl_4}$ 1730 (C=O) cm^{-1}; nmr (TMS, CCl_4) 2.00 (CH_3CO) and 5.40 (C=CH) ppm; $[\alpha]_D$ −23 (*c* 1). The analytical sample was prepared by recrystallization from acetone and had mp 105–106°.

Anal. Calcd for $C_{30}H_{50}O_2$: C, 81.49; H, 11.38. Found: C, 81.49; H, 11.11.

3β-(1α-Hydroxyethyl)-Δ⁵-A-norcholestene (19).—A solution of 255 mg of acetate **19a** in 270 ml of methanol containing 10 ml of water and 2.688 g of potassium carbonate was kept at reflux for 7 hr, then left at room temperature overnight. Most of the methanol was removed *in vacuo*, and the product was crystallized out upon addition of water. It was filtered and recrystallized from acetone to yield 176 mg, mp 88–90°. Recrystallization from acetone gave a sample, mp 99–100°, $[\alpha]_D$ −38° (*c* 1.2).

Anal. Calcd for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 83.88; H, 11.81.

Chromium Trioxide–Pyridine Oxidation of 19.—The required complex was prepared by addition of 200 mg of chromium trioxide to 1.50 ml of pyridine. To this was added a solution of 50 mg of **19** in 0.50 ml of pyridine. The reaction mixture was allowed to stand at room temperature overnight. At the end of this time ice was added followed by water. Then the solution was extracted seven times with chloroform. The chloroform extracts were washed twice with water, dried, and concentrated to dryness *in vacuo*. The resulting gum was dried under high vacuum (0.001 mm) for 6 hr. Crystallization from acetone yielded 20 mg of 3β-acetyl-Δ⁵-A-norcholestene, mp 73–73° (lit.[8]

(11) G. Bauslaugh, G. Just, and E. Lee Ruff, *Can. J. Chem.*, **44**, 2837 (1966).

(12) D. Battail Robert and D. Gagnaire, *Bull. Soc. Chim. Fr.*, 208 (1966).

(13) Melting points were determined using a Kofler hot stage. Rotations were measured using chloroform solutions. Microanalyses were performed by G. I. Robertson, Florham Park, N. J. Nuclear magnetic resonance spectra were determined using a Varian A-60A.

(14) S. Julia and J-P Lavaux, *Bull. Soc. Chim. Fr.*, 1231 (1963).

73.5–75°). Warming of an ethanolic solution of 3β-acetyl-Δ⁵-A-norcholestene containing potassium hydroxide led to the development of the conjugated ketone chromophore present in 3β-acetyl-Δ⁵-A-norcholestene (16).

3β-(1α-Hydroxyethyl)-Δ⁵-A-norcholestene p-Toluenesulfonate (11).—To a solution of 600 mg of 19 in 5 ml of dry pyridine was added 600 mg of *p*-toluenesulfonyl chloride. The reaction solution was kept at room temperature for 18 hr. At the end of this time crushed ice was added, and the resulting mixture was extracted with ether. The combined ether extracts were washed in turn with a saturated solution of sodium bicarbonate, then water, and finally dilute hydrochloric acid. The dried extracts were concentrated to dryness *in vacuo* to yield 560 mg of crude tosylate. Repeated recrystallization from acetone yielded 320 mg, mp 86–89°. The infrared spectrum of this compound showed absorption characteristic of the *p*-toluenesulfonate ester at 8.43 and 8.50 μ. The nmr spectrum (TMS, CCl_4) showed an aromatic quartet at 7.23, 7.38, 7.70, and 7.85 ppm, aromatic CH_3 at 2.43 ppm, and vinyl proton at 5.30 ppm.

Anal. Calcd for $C_{35}H_{54}SO_3$: C, 75.73; H, 9.79. Found: C, 75.76; H, 9.69.

Solvolysis of 3β-(1α-Hydroxyethyl)-Δ⁵-A-norcholestenyl p-Toluenesulfonate (11).—A solution of 176 mg of 11 in 25 ml of acetone was kept at reflux for 10 hr. At the end of this period the acetone was removed *in vacuo*, and the resulting aqueous solution was extracted thoroughly with ether. The ether extracts were washed with water, dried, and concentrated to dryness *in vacuo* to yield 184 mg of an oil. The crude solvolysis product was chromatographed upon 10 g of Merck neutral alumina. Elution with pentane yielded 19.5 mg of an oil which showed four spots upon tlc. No pure compound could be isolated. Further elution with benzene yielded 59.5 mg, mp 85–91°. Recrystallization from acetone gave 46 mg, mp 95–97°, of 4α-methyl-3α,5-cyclocholestan-6β-ol (5). Repeated recrystallization from acetone raised the melting point to 102–103°. This was undepressed upon mixture melting point determination with an authentic sample[5] of melting point 101–103°. Further elution with chloroform yielded 6 mg of 4α-methylcholesterol (6), mp 164–165°. The melting point was undepressed upon admixture with an authentic sample.

Attempted Formation of 3β-(1β-Hydroxyethyl)-Δ⁵-A-norcholestenyl p-Toluenesulfonate (10).—The alcohol (100 mg, mp 114–117°) was dissolved in pyridine (1 ml), and 100 mg of *p*-toluenesulfonyl chloride was added at room temperature. After standing at room temperature for 12 hr, ice was added and the solution was extracted with ether. The ether extracts were washed with water, saturated bicarbonate solution, dilute hydrochloric acid solution, and finally with water. The dried extracts were concentrated to dryness to yield an oil which was crystallized from acetone to yield 46 mg, mp 73–74°. The properties of this material were identical with those of 4-methyl-Δ³,⁵-cholestadiene (8).

Registry No.—**11,** 24343-84-8; **15b,** 1258-92-0; **15c,** 24298-81-5; **16,** 24298-82-6; **17,** 24298-83-7; **18,** 24298-84-8; **19,** 24298-85-9; **19a,** 24298-86-0.

Syntheses of Methyl Malvalate and Methyl 5,6-Methano-5-undecenoate

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Malvalic acid, the major cyclopropene component in cottonseed oil, has been synthesized. When 1-chloro-7-hexadecyne reacts with diazoacetic ester in the presence of copper–bronze, the ester of 1-chloro-7,8-carboxymethano-7-hexadecene is formed. Treating the corresponding acid chloride with zinc chloride causes loss of carbon monoxide. Either sodium borohydride or lithium aluminum hydride reduces the resulting cyclopropenium compound to 1-chloro-7,8-methano-7-hexadecene. Replacing the chloro group with cyano yields malvalonitrile, which can be converted to methyl malvalate. An analogous sequence of steps has been applied to 1-chloro-4-decyne to produce methyl 5,6-methano-5-undecenoate. An alternate synthesis of methyl malvalate starts by using 1-chloro-7-hexadecyne as the precursor for methyl 8-heptadecynoate. This acetylenic ester is converted to 8,9-carboxymethano-8-heptadecenoic acid, the diacid chloride of which decarbonylates selectively in the presence of metallic chlorides to form the cyclopropenium acid chloride. After esterification, the resulting cyclopropenium ester is reduced with borohydride to methyl malvalate.

Malvalic acid and its homolog, sterculic acid, together with two other closely related fatty acids[1] are the only well-characterized naturally occurring cyclopropenes.[2] Methyl sterculate has been synthesized.[3,4] The present paper reports on syntheses of methyl malvalate (8)[5] as well as on the synthesis of a related cyclopropene, methyl 5,6-methano-5-undecenoate.

The malvalate synthesis starts with 1-decyne (1), which as its lithium derivative[6] couples with 1,6-dichlorohexane to form 1-chloro-7-hexadecyne (2). Dropping diazoacetic ester into a hot mixture of 1-chloro-7-hexadecyne and powdered copper–bronze produced the expected cyclopropene ester, which on saponification gave 1-chloro-7,8-(carboxymethano)-7-hexadecene (3). Our prior concern about the involvement of the carbon-to-chlorine bond was allayed when dodecyl chloride under the same conditions could be recovered largely unchanged. The acid chloride 4 from 3, when mixed with anhydrous zinc chloride, smoothly lost carbon monoxide to give cyclopropenium ion 5. Sodium borohydride in alkaline methanol or, better, lithium aluminum hydride in ether[7] reduced the cyclopropenium ion to the corresponding cyclopropene, 1-chloro-7,8-methano-7-hexadecene (6). The methanethiol adduct[8] of this cyclopropene, formed in 98% yield, was homogeneous according to gas–liquid chromatographic assay. Replacing the chloro group with cyano by heating with sodium cyanide in dimethyl

(1) Sterculynic acid, as reported by A. W. Jevans and C. Y. Hopkins, *Tetrahedron Lett.*, 2167 (1968), and 2-hydroxysterculic acid, as reported by L. J. Morris and S. W. Hall, *Chem. Ind.* (London), 32 (1967), and by J. A. Recourt, G. Jurriens, and M. Schmitz, *J. Chromatogr.*, **30**, 35 (1967).

(2) F. L. Carter and V. L. Frampton, *Chem. Rev.*, **64**, 497 (1964).

(3) W. J. Gensler, M. B. Floyd, R. Yanase, and K. W. Pober, *J. Amer. Chem. Soc.*, **91**, 2397 (1969); **92**, 2472 (1970).

(4) M. M. Schlosser, A. J. Longo, J. W. Berry, and A. J. Deutschman, Jr., *J. Amer. Oil Chem. Soc.*, **46**, 171 (1969).

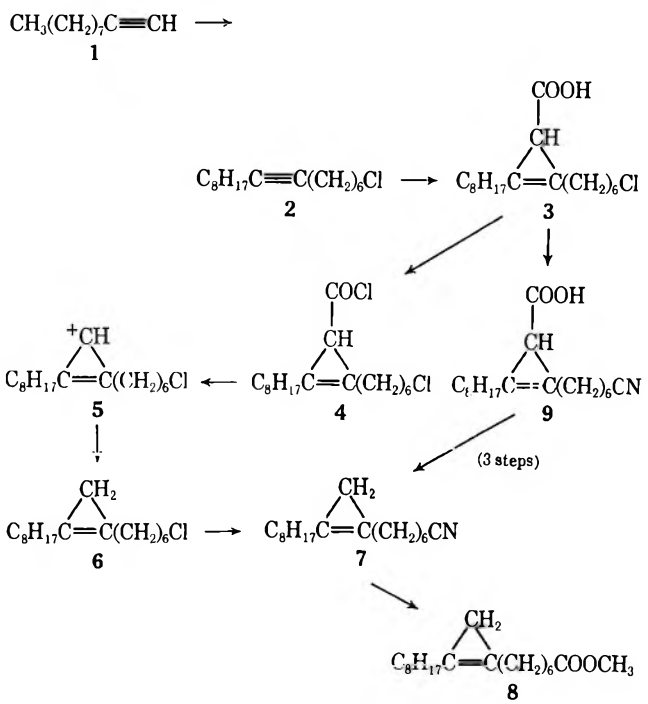
(5) The structure of methyl malvalate has been defined by J. J. Macfarlane, F. S. Shenstone, and J. R. Vickery, *Nature*, **179**, 830 (1957); B. Craven and G. A. Jeffrey, *ibid.*, **183**, 676 (1959); A. C. Fogerty, A. R. Johnson, J. A. Pearson, and F. S. Shenstone, *J. Amer. Oil Chem. Soc.*, **42**, 885 (1965).

(6) *Cf.*, H. H. Schlubach and K. Repenning, *Justus Liebigs Ann. Chem.*, **614**, 37 (1958); G. Grimmer and J. Kracht, *Chem. Ber.*, **96**, 3370 (1963).

(7) *Cf.* R. Breslow and P. Dowd, *J. Amer. Chem. Soc.*, **85**, 2729 (1963); H. E. Nordby, Doctoral Dissertation, University of Arizona, 1963; R. Breslow, P. Gal, H. W. Chang, and L. J. Altman, *J. Amer. Chem. Soc.*, **87**, 5139 (1965); S. D. McGregor and W. M. Jones, *ibid.*, **90**, 123 (1968).

(8) *Cf.*, H. W. Kircher, *J. Amer. Oil Chem. Soc.*, **41**, 4 (1964); P. K. Raju and R. Reiser, *Lipids*, **1**, 10 (1964); N. K. Hooper and J. H. Law, *J. Lipid Res.*, **9**, 270 (1968). A longer reaction period than that originally called for was found to be beneficial.

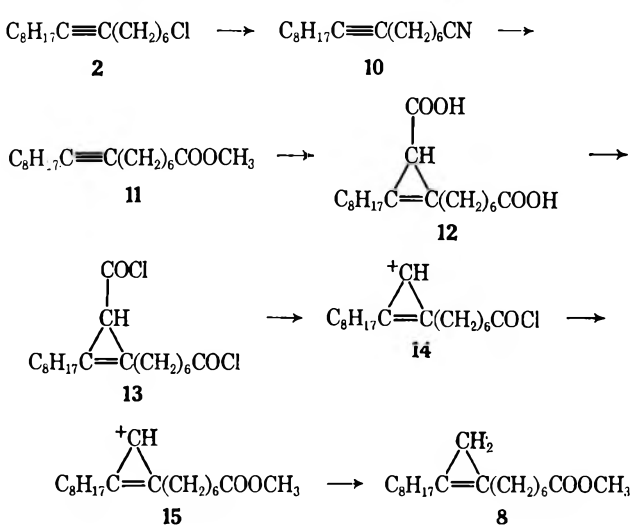
sulfoxide yielded malvalonitrile (**7**), and finally, saponification and esterification with diazomethane led to the desired methyl malvalate (**8**). The yield of



methyl malvalate from 1-chloro-7,8-methano-7-hexadecene (**6**) was 72% and from 1-chloro-7-hexadecyne (**2**) was 23%. The ester was homogeneous as judged by thin layer chromatography as well as by the gas–liquid chromatographic behavior of its methanethiol adduct. The nuclear magnetic resonance and infrared absorption curves were consistent with the assigned structure.

Methyl 5,6-methano-5-undecenoate was similarly synthesized by starting with 1-chloro-4-decyne and proceeding through an analogous series of intermediates, all well characterized. The decarbonylation step in this series made use of aluminum chloride instead of zinc chloride.

Two alternate pathways for synthesis of methyl malvalate were also explored. Instead of first removing the unwanted carboxyl group from the cyclopropene ring of intermediate **3** to give **6** and then attaching the necessary carbon atom (**6** to **7**), the steps were reversed, so that the chain in **3** was first extended by one carbon (**3** to **9**) and only then was the ring carboxyl removed (**9** to **7**). Although successful, this sequence offered no advantages and was not pursued. Another pathway was modeled after the earlier synthesis of methyl sterculate from methyl 9-octadecynoate.[3] The starting ester, methyl 8-heptadecynoate (**11**), came from the corresponding nitrile **10**, which in turn was obtained either from 1-chloro-7-hexadecyne (**2**) or 1-iodo-7-hexadecyne. Dibasic acid **12**, prepared in 72% yield from the copper-catalyzed reaction of diazoacetic ester with methyl 8-heptadecynoate (**11**) followed by saponification, was converted to its diacid chloride **13**. Decarbonylation with the help of zinc chloride removed the carboxyl carbon from the ring (as in **14**) but did not attack the terminal group. Aluminum chloride and ferric chloride were also effective in selectively and rapidly decarbonylating the ring carboxyl. The cyclopropenium ion–acid chloride **14** was esterified with 1 mol of methanol to give the ion–ester **15**, and this was reduced with sodium borohydride to the final product, methyl malvalate (**8**). The overall yield from dibasic acid **12** was in the order of 40%.



The reagent pair, diethylzinc and methylene iodide, by inserting a methylene group into an olefinic bond, can develop a cyclopropane.[9a] If the method were applicable to acetylenes, methyl 8-heptadecynoate (**11**) could be transformed in one step to methyl malvalate (**8**). Trial of this possibility unfortunately gave no sign of cyclopropene material.

The syntheses realized here open the way to preparing methyl malvalate labeled at specific positions with radioactive carbon.[9b]

Experimental Section[10]

1-Chloro-7-hexadecyne (2).[6]—A mixture of white powdery lithium amide (1.15 g, 0.050 mol) and 6.9 g (0.050 mol) of freshly distilled 1-decyne (**1**) in 50 ml of dioxane that had been distilled from lithium aluminum hydride directly into the reaction flask was stirred and heated in a bath at 125–130°. To control the initial vigorous forthing, the bath temperature had to be lowered for short periods. Then the vigorously stirred brown mixture was boiled for 7.5 hr. Redistilled 1,6-dichlorohexane (23.3 g, 0.15 mol) was added in one portion to the slightly cooled dioxane suspension, which was then heated and stirred further for 2 days. More lithium amide was added (0.23 g, 0.010 mol) and the reaction was continued for another 14 hr.

The cooled mixture was treated carefully with 85 ml of water and then extracted with several portions of ether. The extracts were washed twice with water and once with saturated salt solution, and then were dried with sodium sulfate. Distillation through a 16-in. spinning-band column afforded several fractions, of which the second was recovered 1,6-dichlorohexane [12.1 g, bp 90–91° (19 mm)], and the fourth was water-white 1-chloro-7-

(9) (a) J. Furakawa, N. Kawabata, and J. Nishimura, *Tetrahedron*, **24**, 53 (1968). (b) See W. J. Gensler, K. W. Pober, D. W. Solomon, R. Yanase, and M. B. Floyd, *Chem. Comm.*, 287 (1970).

(10) Infrared absorption curves were taken with double-beam recording spectrophotometers. Nuclear magnetic resonance curves were taken on a 60-MHz instrument purchased with funds made available by National Science Foundation under Grant GP 3618. Chemical shifts are reported in parts per million downfield from tetramethylsilane. Boiling points and melting points are uncorrected. Analyses for elementary composition were performed by S. M. Nagy, Microchemical Laboratory, Belmont, Mass.; Galbraith Laboratories, Inc., Knoxville, Tenn.; and Chemalytics, Inc., Tempe, Ariz. For thin layer chromatography, silica gel on glass plates or in the form of flexible strips were purchased from Eastman Kodak Co. Gelman Instrument Co., and Brinkman Instruments, Inc. Iodine vapor proved convenient and effective in making the spots visible. In most of the preparations the glassware used was scrupulously dry, and prepurified nitrogen blanketed the reaction mixture.

hexadecyne [bp 115–118° (0.11 mm), n^{25}D 1.4602]. Both materials were 99% homogeneous according to gas–liquid chromatography on a 6-ft neopentyl–glycol–succinate isothermal column at 140 and 195°, respectively. The yield of chlorohexadecyne (**2**) was 8.4 g (65% based on decyne or 45% based on 1,6-dichlorohexane not recovered). Another run on a double scale and with an 80-hr reaction period gave the product in 72% yield (50% based on dichlorohexane).

A sample was prepared for analysis by chromatography through a column of silica gel with hexane as the eluting solvent. The colorless material, carefully freed of solvent, showed a single spot on a thin layer plate (hexane solvent).

Anal. Calcd for $C_{16}H_{29}Cl$: C, 74.81; H, 11.38. Found: C, 74.83; H, 11.05.

The infrared absorption curve was not particularly informative, although a C–Cl band was noted around 725 cm^{-1}; nmr (50% in CCl_4) δ 0.88 (poor triplet, CH_3), 1.29 (complex), 2.07 (complex, CH_2's at 6 and 9), 3.42 (t, J = 6 Hz, CH_2 at position 1). The integration ratio of the 3.42-ppm signal to all the others was close to the required 2:27.

1-Iodo-7-hexadecyne could be prepared by starting with 0.43 mol of lithium amide, 0.40 mol of 1-decyne, and 0.45 mol of 1,6-diiodohexane and following essentially the above procedure. The iodohexadecyne was obtained as a faintly yellow liquid, bp 140–143° (0.01 mm), homogeneous according to gas–liquid chromatography, in 64% yield: nmr δ 0.88 (diffuse triplet, CH_3), 1.2–1.6 (multiplet), 1.9–2.2 (multiplet, CH_2's at positions 6 and 9), 3.15 (t, J = 7 Hz, CH_2I). The integration ratio of the 3.15-ppm signal to all the others was 2:27.

1-Chloro-7,8-carboxymethano-7-hexadecene (3).—In a three-necked flask fitted with a vertical condenser, a magnetically stirred mixture of 1-chloro-7-hexadecyne (**2**, 5.15 g or 0.020 mol) plus 0.46 g of copper–bronze was brought to 130°. Distilled ethyl diazoacetate (4.56 g or 0.040 mol) was added in small portions directly onto the stirred mixture. The nitrogen sweep was interrupted just before the first addition, and thereafter the evolving gases were led from the top of the condenser to a receiver over water. The bubbling observed after each addition of reagent lasted 3–4 min, after which time another portion was introduced. When all the diazoacetate had been added (25 min), heating was continued for another 10 min. The gas that evolved corresponded to 91% of the expected 0.040 mol.

The reaction mixture plus a solution of 2.7 g (0.048 mol) of potassium hydroxide in 4 ml of water and 24 ml of methanol was boiled in a nitrogen atmosphere for 5.5 hr. Water (100 ml) and hexane (50 ml) were added, and the separated aqueous phase was extracted with several 25-ml portions of 1:1 hexane–ether. According to its infrared absorption curve, the extracted material contained much ester; saponification of this portion, freed of solvent (1.3 g), was repeated using 0.2 g of potassium hydroxide in aqueous methanol.

Acidification of the alkaline layer from the first saponification at ice-bath temperatures to pH 5 with 4 N hydrochloric acid was followed without delay by ether extraction. The extracts were washed, dried, and then stripped of solvent to leave 4.7 g of a viscous brown oil. Similar treatment of the aqueous layer from the second saponification afforded an additional 0.5 g.

The combined organic acids (5.0 g) were chromatographed on a column of active silica gel (58 g) with 1 l. of 8:1 hexane–ether as developing solvent. After careful removal of all volatile material from the eluate, the oil remaining weighed 3.4 g (55%). From its thin layer chromatogram (hexane–ether–acetic acid 100:40:1), which showed one dominant spot accompanied by two faint spots, this material was accepted as practically pure 1-chloro-7,8-carboxymethano-7-hexadecene (**3**). It was suitable for use in the next stages.

In another similar preparation, the chloro acid product **3** was chromatographed over silica gel containing some water (5%) and with a solvent of 6:1 hexane–ether with gradually increasing proportions of ether. After removing volatiles, the chloro acid was pumped at room temperature (10^{-4} mm).

Anal. Calcd for $C_{18}H_{31}ClO_2$: C, 68.65; H, 9.92; Cl, 11.26. Found: C, 68.80; H, 9.76; Cl, 11.09.

This material on thin layer chromatography (hexane–ether–acetic acid 100:20:1) showed only one spot, R_f 0.87; ir (CCl_4) 1690 (C=O), 1900 cm^{-1} (cyclopropene); nmr (25% in CCl_4) δ 0.88 (ill-defined triplet, CH_3), 1.30 and 1.45 (broad singlets, CH_2's at positions 2–5 and 10–16), 1.95 (s, cyclopropene H), 2.42 (m, CH_2 at positions 6 and 9), 3.45 ppm (t, J = 7 Hz, CH_2 at position 1). Integration showed a ratio of 2:28 for the signal at 3.45 ppm relative to all the rest. No signal for the carboxylic H was seen.

In another 0.020-mol run, saponification was effected by heating the crude adduct in a bath at 98° for 2 hr with a solution of 0.08 mol of sodium hydroxide in 225 ml of 2-propanol and 4.5 ml of water. Chromatography of the acid fraction over silica gel deactivated with water (5%) and with 8:1 hexane–ether as eluting solvent afforded a faintly yellow oil (63%), which according to thin layer chromatography and infrared absorption consisted of practically pure chloro acid **3**.

1-Chloro-7,8-methano-7-hexadecene (6).—A mixture of 3.8 g (0.012 mol) of homogeneous 1-chloro-7,8-carboxymethano-7-hexadecene (**3**) and 3.1 g (0.024 mol) of oxalyl chloride was stirred at room temperature for 5.25 hr. After removing most of the volatile material, the viscous residual oily acid chloride **4** was pumped at 0.15 mm for a day: ir (neat), 1775 (but not at 1690), 1905, 980 cm^{-1}. Use of ether solvent gave about the same results, as did replacing oxalyl chloride with thionyl chloride, or using a threefold instead of a twofold excess of oxalyl chloride.

To the clear stirred solution of the acid chloride (0.012 mol) in 25 ml of azeotropically dried methylene chloride was added 1.72 g (0.013 mol) of granular zinc chloride. The mixture, which frothed and very soon changed from orange to purple, was stirred for 4.5 hr. At this time most of the solid had dissolved[11] and the bubbling had stopped.

The decarbonylation mixture was added over 10 min to a stirred, −80° solution of lithium aluminum hydride (0.57 g or 0.015 mol) in about 60 ml of ether that had been distilled from lithium aluminum hydride. The color was discharged instantaneously. After another 20 min at −80°, the cooling bath was removed, and water (0.6 ml), 0.6 ml of 15% aqueous sodium hydroxide, and more water (1.8 ml) were added. Filtration through diatomaceous earth (Celite) removed the gelatinous solids, which were rinsed on the funnel with fresh ether. After washing the combined yellow ethereal filtrates several times with saturated aqueous salt solution, the ether solution was dried with sodium sulfate. Removal of all volatile material left 3.1 g of dark crude product **6**.

Chromatography through a 2 × 121 cm column containing 90–95 g of fresh silica gel with hexane as developing solvent was effective in resolving the mixture. After a fast moving component (0.1 g, R_f >0.9 on silica thin layer plates with hexane solvent) had been removed with the first 200 ml of solvent, 1.6 g (50%) of the desired colorless 1-chloro-7,8-methano-7-hexadecene (**6**), homogeneous by thin layer chromatography (R_f 0.64), came through in the next 160 ml. An intermediate two-spot fraction (0.33 g) emerged in the following 340 ml, after which 0.26 g of faintly yellow 1-chloro-7-hexadecyne (**2**) appeared, with R_f 0.13 (a second very faint spot was also visible). The yields given here are based on constant weights determined after long exposure to vacuum.

The slow moving recovered actylene **2** was identified by direct thin layer chromatographic comparison with authentic material as well as by gas–liquid chromatography through a 10% silicone oil column (SF-96) at 210–212°.

In another preparation, the decarbonylated mixture was added to excess sodium borohydride in methanol containing 2 mol of sodium hydroxide for every mole of starting acid chloride. The temperature was kept at −33 to −38°. The yield of homogeneous 1-chloro-7,8-methano-7-hexadecene (**6**) was about 30%; some 1-chloro-7-hexadecyne (**2**) was obtained here, too. The cyclopropene product **6** was identical with the same material produced from the lithium aluminum hydride reduction, as shown by identical ir and nmr absorption curves, as well as by the same results with the methanethiol adducts (see below).

1-Chloro-7,8-methano-7-hexadecene (**6**) showed the following properties: ir (neat) 725 (C–Cl), 1010, 1872 cm^{-1} (the absence of any absorption peak at 1773 cm^{-1} supported the absence of any 1,3-disubstituted cyclopropene[12]); nmr (30% in CCl_4) δ 0.75 (s, cyclopropene CH_2), 0.91 (m, terminal CH_3), 1.29 (m,

(11) Speculation on the nature of the decarbonylation product is interesting. If a cyclopropenium salt is formed, the anion would be expected to be $ZnCl_4^-$, since zinc(II) tends to coordinate with four ligands. If so, the experimental 1:1 ratio of acid chloride to zinc chloride would provide too much zinc chloride and, contrary to observation, the excess zinc chloride would remain undissolved. The fact that 1 mol of zinc chloride dissolves as well as the development of a deep color suggests the possibility of a tetrahedral π complex, possibly (π-cyclopropenium)$ZnCl_3$ [*cf.* D. L. Weaver and R. M. Tuggle, *J. Amer. Chem. Soc.*, **91**, 6506 (1969)].

(12) G. L. Closs, *Advan. Alicycl. Chem.*, **1**, 74 (1966).

CH_2's at positions 2–5 and 10–15), 2.39 (m, CH_2's at positions 6 and 9), 3.48 (t, J = 6.5 Hz, CH_2Cl). The ratio of the area under the last signal to all the others corresponded closely to the required 2:29.

Anal. Calcd for $C_{17}H_{31}Cl$: C, 75.38; H, 11.54. Found: C, 75.18; H, 11.41.

The methyl mercaptan adduct[8] was prepared by allowing 0.1142 g of the cyclopropene **6** to stand stoppered for 7 days at room temperature in *ca.* 2.9 ml of an ether solution previously saturated with dry methyl mercaptan at 10° or below. A jet of pure nitrogen was directed to the surface of the reaction mixture until the weight no longer decreased (0.1319 g or 98.1%). The colorless liquid adduct on gas–liquid chromatography on a 10% silicone oil (SF-96) column at 235° gave a single symmetrical peak.

Methyl Malvalate (8) from 1-Chloro-7,8-methano-7-hexadecene (6).—A slurry of 0.108 g (2.2 mmol) of dry sodium cyanide in 1 ml of dimethyl sulfoxide that had been dried with calcium hydride was stirred at 96° for a short time. 1-Chloro-7,8-methano-7-hexadecene (0.45 g, 1.66 mmol) was injected from a syringe, and the magnetic stirring and heating (90°) was continued for 1.5 hr. Water (4 ml) was added to the cooled reaction mixture, and the two-phase system was extracted with hexane. The extracts, washed first with water and then with saturated salt solution, were dried with sodium sulfate. The yellow malvalonitrile (**7**), freed of all volatiles, weighed 0.42 g (97%).

A solution of this nitrile (1.6 mmol) with sodium hydroxide (0.37 g, 9.2 mmol), water (0.3 ml), and 95% alcohol (2.4 ml) was stirred and boiled for 7.5 hr and then was allowed to stand overnight. The clear orange solution was diluted with 5–7.5 ml of water plus 8–10 ml of methanol and then was shaken with 4 ml of hexane. The two lower layers of the resulting three-phase system were mixed with 10 ml of 1:1 hexane–ether and then were treated at 0° with 3 ml of 4 *N* hydrochloric acid. With no unnecessary delay, the acid aqueous phase was further extracted with hexane–ether, and the combined organic extracts were washed with several small portions of water, dried with sodium sulfate, and then carefully freed of all volatile material. The residual orange malvalic acid, pumped at 0.1 mm, weighed 0.44 g (97%): ir (neat) 1710 and 2300–3400 (COOH), 1870, and 1005 cm^{-1}.

This crude acid in 2 ml of ether was added in portions at 0° to 20–25 ml of an ethereal solution of diazomethane prepared from 14 mmol of N-nitroso-N-methyltoluenesulfonamide.[13] Low-boiling materials were removed first by evaporation in a jet of pure nitrogen and then by exposure to reduced pressure in a rotary evaporator. The residual crude methyl malvalate (**8**, 0.45 g) was fractionated by chromatography on a 2.4 × 30 cm column containing 35 g of silica gel deactivated with 1.75 ml of water. The developing solvent was 15:1 hexane–ether. After the first 100 ml had been collected, methyl malvalate (**8**), homogeneous according to thin layer chromatography, emerged in the next 40 ml. Most of the solvent was removed, and the clear, colorless residual oil was then kept under reduced pressures until the weight held constant at 0.35 g (72% from 1-chloro-7,8-methano-7-hexadecene).

This methyl malvalate spotted on a silica plate together with the same material obtained from methyl 8-heptadecynoate (**11**) and developed with hexane–ether–acetic acid (100:40:1) showed a single spot moving exactly the same as the other product. The neat material gave an infrared absorption curve identical with the one from the alternative route, ir (neat) 1748 (C=O) and 1870 and 1005–1010 cm^{-1}; nmr (CCl_4) δ 0.72 (s, cyclopropene CH_2), 0.88 (distorted t, CH_2CH_3), 1.29 (complex), 2.11 (m, CH_2 at 2), 2.36 (m, CH_2's at positions 7 and 10), 3.59 (s, OCH_3). Integration showed a ratio for the ester methyl group signal to all others of 3:31, as required.

The methyl mercaptan adduct,[8] formed as described below in 100.4% yield, showed a single symmetrical peak at 21.2 min on gas–liquid chromatography through a silicone oil column (10% SF-96) at 225° plus a faster moving blip (≪1%) at 9.2 min.

Additional information on the properties and purification of methyl malvalate is given below. When purified malvalonitrile (**7**), prepared as described below, was hydrolyzed and esterified, essentially the same results were obtained.

Ethyl Diazoacetate with Dodecyl Chloride.—Diazoacetic ester (13.7 g or 0.12 mol) was added dropwise over a 3.75-hr period to a stirred 145° mixture of dodecyl chloride (20.5 g or 0.10 mol) plus copper bronze (0.05 g). The crude reaction mixture was mixed with a solution of 9.75 g (0.17 mol) of potassium hydroxide in 140 ml of methanol plus 24 ml of water, and the two-phase system was stirred and boiled for 3 hr. The recovered nonacidic material was a practically colorless oil (17.6 g, 86%) which, according to its infrared absorption curve, was unchanged starting material. The small quantitity of acidic material, a mixture, was not investigated.

1-Chloro-4,5-(ethoxycarbonylmethano)-4-decene.—According to the same general procedure as described above, ethyl diazoacetate (11.4 g, 0.10 mol) was added over a period of 4.5 hr to 17.3 g (0.10 mol) of 1-chloro-4-decyne plus 0.15 g of copper–bronze. The bath temperature was 150–155°. After another 20 min of heating, the liquid was fractionated through a spinning-band column to give 6.4 g (37%) of unchanged 1-chloro-4-decyne, bp 33–35° (0.01–0.0001 mm). A portion of the residual oil heated in a bath at 65° was evaporatively distilled (10^{-4} mm) in a short-path apparatus over a 12-hr period. The distillate was taken as the desired ester: ir 1720 (C=O) and 1900 cm^{-1}; nmr (CCl_4) δ 0.97 (distorted t, distal CH_3), 1.18 (t, J = 7 Hz, OCH_2CH_3), 1.4–2.8 (m's, chain CH_2's), 2.00 (s, cyclopropene H), 3.60 (t, J = 7 Hz, CH_2Cl), 4.03 (q, J = 7 Hz, OCH_2CH_3). A sample of the ester was sent for analysis after two more distillations.

Anal. Calcd for $C_{14}H_{23}ClO_2$: C, 64.97; H, 8.96; Cl, 13.70. Found: C, 65.15; H, 8.95; Cl, 13.65.

1-Chloro-4,5-carboxymethano-4-decene.—A double-sized preparation of the above ester was performed essentially as described above. The crude reaction mixture, dissolved in 200 ml of methanol and 40 ml of water containing 13.5 g (0.24 mol) of potassium hydroxide was boiled for 3 hr. Considerable 1-chloro-4-decyne (12.9 g, 37%) could be recovered from the nonacidic fraction. The dark oily acidic fraction (30.5 g) was chromatographed on a 3.7 × 27 cm column containing 200 g of silica gel deactivated with 10 g of water; 2.5 l. of solvent was used, starting with 5:1 hexane–ether and ending with 1:1 hexane–ether. Fractions were combined on the basis of thin-layer chromatographic evidence. Faintly yellow 1-chloro-4,5-carboxymethano-4-decene (22.5 g, 49%) was obtained from the early fractions as one-spot material. A sample was evaporatively distilled at 90° (10^{-4} mm).

Anal. Calcd for $C_{12}H_{19}ClO_2$: C, 62.64; H, 8.28; Cl, 15.39. Found: C, 62.64; H, 8.42; Cl, 15.52.

The acid in carbon tetrachloride showed ir absorption peaks at 1695 (C=O), 2300–3500 (OH), and 1905 cm^{-1}; nmr (CCl_4) δ 0.92 (distorted t, CH_3), 1.43–2.8 (broad signals, CH_2's), 2.00 (s, cyclopropene H), 3.57 (t, J = 7 Hz, CH_2Cl). The nmr curves taken before and after distillation were identical.

A slower moving minor product (2.6 g), homogeneous according to thin layer chromatography, was tentatively taken as 1-methoxy-4,5-carboxymethano-4-decene on the basis of its nmr curve: δ 0.90 (t, terminal CH_3), 1.42 and 2.45 (m's, CH_2's), 1.96 (s, cyclopropene H), 3.26 (s, OCH_3), 3.38 (t, CH_2OCH_3).

1-Chloro-4,5-(chlorocarbonylmethano)-4-decene.—A mixture of 2.3 g (0.010 mol) of 1-chloro-4,5-carboxymethano-4-decene with colorless thionyl chloride (2.4 g, 0.020 mol) was shaken occasionally during a 45-min period. After removing volatiles, the black residue was evaporatively distilled in a cold-finger apparatus at 60° (10^{-4} mm) to give 2.0 g (81%) of the pale yellow acid chloride.

Anal. Calcd for $C_{12}H_{18}Cl_2O$: C, 57.84; H, 7.28; Cl, 28.46. Found: C, 58.11; H, 7.39; Cl, 28.74.

The acid chloride darkens on standing at room temperature, becoming black after 2 days.

1-Chloro-4,5-methano-4-decene.—The cyclopropene acid (19.7 g or 0.085 mol) plus thionyl chloride (20 g or 0.17 mol) in 25 ml of ether was shaken for 1 hr. After most of the volatiles had been removed, the red-brown oily acid chloride was pumped at 0.1 mm for 1 hr.

Aluminum chloride (14.2 g or 0.11 mol) was rapidly weighed and then added in several portions over a 10-min period to a stirred solution of the crude acid chloride in 85 ml of dry methylene chloride at room temperature. After 0.5 hr, the dark, almost opaque, solution was added dropwise over 20 min to a vigorously stirred mixture of 4.1 g (0.11 mol) of lithium aluminum hydride and 425 ml of ether. Ice-bath cooling was employed. After an additional 5 min, ether (25 ml) mixed with water (4 ml) was cautiously introduced, followed by 85 ml of 2.5 *M* sodium hydroxide solution. Crude dark-red product (14.5 g) was isolated essentially as described above in the preparation of the higher analog **6**.

(13) See L. F. Fieser and M. Fieser, "Reagents for Organic Syntheses," John Wiley & Sons, Inc., New York, N. Y., 1967, p 191.

Distillation through a spinning-band column allowed two water-white fractions to be collected. According to gas–liquid chromatography, the first fraction (0.93 g), bp 65–70° (1.8 mm), was a 3:2 mixture of 1-chloro-4-decyne (retention time 7.0 min, the same as authentic material) and 1-chloro-4,5-methano-4-decene (retention time 8.0 min). Use of a 6-ft Apiezon M column at 151° evidently caused little if any decomposition of the cyclopropene. The second fraction (6.9 g), bp 72–74° (1.5 mm), still showed a very small peak for 1-chloro-4-decyne but was essentially all 1-chloro-4,5-methano-4-decene.

Anal. Calcd for $C_{11}H_{19}Cl$: C, 70.75; H, 10.26; Cl, 18.99. Found: C, 70.48; H, 9.99; Cl, 18.85.

The yield could be estimated as over 40%: ir (CCl_4) 1870 and 1010 cm^{-1}; nmr (25% in CCl_4) δ 0.78 (s, cyclopropene methylene) 0.90 (t, terminal CH_3), 1.40 (m), 1.8–2.9 (m, CH_2's at positions 3 and 6), 3.48 (t, J = 7 Hz, CH_2Cl). The integration ratio of the δ 3.48 triplet to all the other signals was close to the correct 2:17.

Methyl 5,6-Methano-5-undecenoate.—A slurry of 1-chloro-4,5-methano-4-decene (3.7 g or 0.020 mol), dried sodium cyanide (1.2 g, 0.025 mol), and dimethyl sulfoxide (6 ml) that had been exposed to calcium hydride was stirred in a bath at 100–110° for 1 hr. Processing the mixture essentially according to the corresponding preparation of malvalonitrile (**7**) gave 3.3 g (93%) of 1-cyano-4,5-methano-4-decene as a pale yellow liquid: ir (CCl_4) 2250 (C≡N), 1870 and 1015 cm^{-1}. The nitrile, spotted on a silica plate and developed with hexane, produced a single spot at R_f 0.51; no sign of any material appeared at R_f 1, the value determined on the same plate for the starting chloride.

A solution of the nitrile (2.4 g or 0.013 mol) and sodium hydroxide (3.0 g) in 18 ml of 95% alcohol plus 2.2 ml of water was boiled for 11 hr. The 2.1 g of 5,6-methano-5-undecenoic acid isolated from this reaction mixture was dissolved in 8 ml of ether, and this solution was added slowly and with stirring to an ice-cold solution of *ca.* 1.5 g (0.036 mol) of diazomethane in 100 ml of ether. The product (2.3 g) from this reaction was evaporatively distilled at 80° (0.02 mm) in a short-path cold-finger apparatus to give 1.8 g (59% from the chloride) of faintly yellow methyl 5,6-methano-5-undecenoate.

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.55. Found: C, 74.10; H, 10.50.

Thin layer chromatography on a silica plate with hexane solvent produced only a single spot, R_f 0.79; nmr (25% in CCl_4) δ 0.77 (s, cyclopropene CH_2), 0.90 (distorted t, CH_2CH_3), 1.40 (complex), 1.7–2.9 (complex, CH_2's at positions 2, 4, and 7), 3.58 (s, $COOCH_3$). The integration ratio of the ester methyl group to all other protons was exactly 3:19. No signals corresponding to any kind of olefinic hydrogen could be detected at $\delta > 4$. Gas–liquid chromatography on a 6-ft Apiezon column at 151° indicated a single component; a 6-ft neopentylglycol succinate column at 159° gave a main peak as well as two small shoulders on the long-retention-time side of the main peak. We believe that the shoulders, rather than indicating minor impurities in the product, originate in the partial decomposition of the cyclopropene on the column.[14]

1-Cyano-7,8-carboxymethano-7-hexadecene (9).—Sodium cyanide (0.91 g, 19 mmol) that had been dried at 100° (reduced pressures) was stirred for a short time with dry dimethyl sulfoxide (5.5 ml) at 96°. 1-Chloro-7,8-carboxymethano-7-hexadecene (**3**, 2.5 g or 8.0 mmol) was introduced with the help of 1 ml of rinse dimethyl sulfoxide, and the stirred slurry was heated for 1.75 hr. Shaking the cooled mixture with 20 ml of hexane plus 35 ml of 1.3% hydrochloric acid produced a troublesome emulsion (pH <2) that could be broken by adding small portions of salt, methanol, and ether. The organic layer was washed several times with saturated salt solution, dried with sodium sulfate, and stripped of volatiles to leave 2.4 g of a dark brown residue. This was chromatographed on a 3.8 × 46-cm column of 150 g of silica gel deactivated with 7.5 g of water. Hexane–ether (3:1) was used to condition the column as well as for the initial eluting solvent (1.2 l.); the hexane–ether ratio was then reduced to 2:1 (2.3 l.) and finally to 1.5:1 (1.4 l.). The desired nitrile product 9 (1.34 g after long pumping, 55%), homogeneous according to thin layer chromatography (hexane–ether–acetic acid 100:85:1), was collected in several fractions in the last 2.4 l. of eluate.

Anal. Calcd for $C_{19}H_{31}NO_2$: C, 74.71; H, 10.23; N, 4.59. Found: C, 74.50; H, 10.35; N, 4.38.

The neat material showed ir absorption peaks at 3500–2400, 1685 (small shoulder at 1720), 2250, 1900, 990 cm^{-1}; nmr (CCl_4) δ 0.89 (t, CH_3), 1.30 (multiplet), 1.95 (s, cyclopropene H), 2.28 (poor t, CH_2CN), 2.42 (m, CH_2 at 7 and 10).

Appreciable amounts of product 9 were found in the earlier eluate fractions, but as two-spot material.

Malvalonitrile (7) from 1-Cyano-7,8-carboxymethano-7-hexadecene (9).—A solution of 1.1 g (3.6 mmol) of carboxymethano derivative 9 in 10 ml of dry ether containing 1.1 g (9.0 mmol) of thionyl chloride was stirred in a dry atmosphere for 1.5 hr. Removal of volatiles followed by pumping at 0.15 mm for 16 hr left 1.2 g of the orange acid chloride; ir (neat) 2250, 1900, 1775, and 1720 (w), 980 cm^{-1}. Decarbonylation was effected by stirring a mixture of this acid chloride with zinc chloride (0.50 g, 3.6 mmol) in dry methylene chloride (13 ml) for 3.75 hr. The color soon became dark red, and all but traces of the solid dissolved. The decarbonylation mixture was added over a 15-min period to a vigorously stirred solution of 0.68 g (18 mmol) of sodium borohydride in 16 ml of anhydrous methanol containing 0.31 g (7.8 mmol) of sodium hydroxide. The temperature was −45 to −50° or lower. A small amount of methylene chloride helped to complete the transfer. The resulting yellow two-phase mixture was stirred without cooling for 20 min.

After adding 35 ml of water, the stirred mixture at −15° was treated with 10.5 ml of 10% hydrochloric acid. The resulting frothing called for care. With no unnecessary delay, ether was added so that the organic phase was the upper one. The lower aqueous layer was extracted further with ether, and the combined organic extracts were washed with 5% sodium bicarbonate solution, twice with water, and finally with saturated salt solution. The dried solution, freed of all solvent, left a clear yellow-orange residual oil of crude malvalonitrile (**7**).

Chromatography on a 2.1 × 45-cm column of silica gel (45 g) deactivated with 2.75 ml of water with 10:1 hexane–ether as developing solvent furnished a series of fractions that were combined on the basis of monitoring by thin layer chromatography (hexane–ether–acetic acid 100:40:1). Removal of solvents first in a rotary evaporator and then by exposure to a 0.1-mm vacuum for 12 hr gave very faintly colored one-spot malvalonitrile (**7**, 0.19 g or 20%).

Anal. Calcd for $C_{18}H_{31}N$: C, 82.69; H, 11.95. Found: C, 82.94; H, 11.68.

The neat malvalonitrile absorbed in the infrared at 2250, 1870, 1725 (weak), 1010 cm^{-1}; nmr (CCl_4) δ 0.75 (s, cyclopropene CH_2), 0.90 (ill-defined t, CH_3), 1.30 (complex), 2.19–2.29 (poor t, CH_2 at 2), 2.42 (m, CH_2 at 7 and 10).

Although additional amounts of the nitrile could be detected in all the other chromatography fractions, no attempt was made to isolate more of the homogeneous product.

1-Cyano-7-hexadecyne (10).—Pure dimethyl sulfoxide (500 ml) that had been dried with calcium hydride was poured into a three-necked flask containing sodium cyanide (19.6 g, 0.40 mol) previously held at 100° *in vacuo*. 1-Chloro-7-hexadecyne (76.8 g, 0.30 mol) was added dropwise to the stirred suspension heated in a 90° bath. Some tendency for the inside temperature to rise was noted. The mixture was stirred and heated at 105–115° for 2.5 hr. The cooled mixture was poured into 1 l. of cold water, and the separated aqueous phase was extracted several times with ether. After washing the ether extracts with water, they were combined with the original dimethyl sulfoxide phase and dried with magnesium sulfate. Removal of low-boiling materials followed by fractionation in a short-path still gave water-white 1-cyano-7-hexadecyne (**10**), bp 130–132° (0.01 mm), in 93% yield. Gas–liquid chromatography (6-ft silicone oil SF 96 column at 218°) indicated a purity of 98%.

A small amount of the product was further purified by preparative gas–liquid chromatography.

Anal. Calcd for $C_{17}H_{29}N$: C, 82.52; H, 11.81. Found: C, 82.37; H, 11.69.

This material revealed only a single peak on analytical gas–liquid chromatography through the silicone oil column at 218° or a 4-ft silicone rubber column at 227°; $n^{25}D$ 1.4578; ir (neat) 2260 cm^{-1}; nmr (20% in CCl_4) δ 0.88 (skew triplet, CH_3), 1.2–1.8 (multiplet), 2.0–2.4 (m, CH_2's at position 2, 7, and 10). The integration ratio of the 2.0–2.4-ppm signal to the others was 6:23, as required.

(14) *Cf.* H. W. Kircher, *J. Amer. Oil Chem. Soc.*, **41**, 4 (1964); **42**, 899 (1965). F. G. Magne, *ibid.*, **42**, 332 (1965). A. C. Fogerty, *et al.*, ref 5. T. W. Hammonds and G. G. Shone, *Analyst*, **91**, 455 (1966). M. M. Hassan, *J. Chem. U. A. R.*, **9**, 217 (1966). Some factors influencing gas–liquid chromatography results have been examined. See Recourt, *et al.*, ref 1, as well as I. A. Wolff and T. K. Miwa, *J. Amer. Oil Chem. Soc.*, **42**, 208 (1965).

When essentially the same directions were followed with 85 ml of dimethyl sulfoxide, 3.8 g (0.080 mol) of sodium cyanide, and 18.0 g (0.052 mol) of 1-iodo-7-hexadecyne, the yield of distilled nitrile, bp 125–129° (0.1–0.03 mm), was 93%. Gas–liquid chromatography showed less than 1% impurity. Alcohol was also used successfully as the reaction solvent.

Methyl 8-Heptadecynoate (11).—A mixture of 98–99% 1-cyano-7-hexadecyne (**10**, 11.1 g or 0.045 mol), sodium hydroxide (9.0 g or 0.23 mol), 95% ethanol (115 ml), and water (10 ml) was boiled for 17 hr. The cooled solution was diluted with 275 ml of water and then washed with *ca.* 100 ml of hexane. Acidification of the stirred and cooled solution by dropwise addition of 12 *N* hydrochloric acid to pH 3 was followed by dilution with water to about 700 ml and then extraction with ether. The extracts were washed several times with water, dried with sodium sulfate, and stripped of volatile solvents at room temperature. The faintly yellow residual solid was dissolved in 30 ml of dry ether and was treated with stirring and cooling with diazomethane (estimated 3 g or 0.07 mol) by distilling diazomethane plus ether directly into the reaction flask. After a short time, excess reagent was swept out in a stream of nitrogen. Distillation of the remaining material through a Claisen head gave 11.8 g (94%) of water-white methyl 8-heptadecynoate (**11**), bp 125–128° (0.03 mm).

Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50. Found: C, 77.24; H, 11.50.

This product gave a single spot on thin layer chromatography (silica gel, with 8:1 hexane–ether) and a single peak on gas–liquid chromatography (6-ft silicone oil SF-96 column at 220°). In a similar run, the same product, analyzed on a 6-ft neopentylglycol succinate (10%) column at 197° or on a 6-ft silicone rubber column (SE-30, 10%) at 218°, showed a purity of 99+%. Methyl 8-heptadecynoate (**11**) had the following properties: mp −11 to −13°; n^{26}D 1.4524; ir (CCl_4) 1740 cm^{-1}; nmr (CCl_4) δ 0.88 (t, CH_2CH_3), 1.32–1.42 (complex), 2.08 (m, CH_2's at positions 2, 7, and 10), 3.60 (s, $COOCH_3$). The integration ratio of the methyl ester signal to the others was 3:29. Raman absorption spectra were taken on a sample obtained by preparative gas liquid chromatography through a 10-ft Carbowax 20M column at 205°. The pure neat ester **11** in a laser-based Raman spectrophotometer showed absorption peaks at 2237 and 2295 cm^{-1} with an intensity ratio of approximately 3:1. A pure sample of 4-octyne showed exactly the same kind of absorption, attributable to the disubstituted C≡C grouping.

8,9-Carboxymethano-8-heptadecenoic Acid (12).—According to the general directions described above, ethyl diazoacetate (20.6 g, 0.18 mol) was added over a 6.5-hr period to 40.6 g (0.145 mol) of methy 8-heptadecynoate (**11**) mixed with 0.1 g of powdered copper–bronze. The temperature was kept at 145–150°. When arrangements were made to measure the evolved nitrogen, it became clear that even at 140° the diazoacetic ester decomposition occurred smoothly, rapidly, and quantitatively. Saponification of the red-brown reaction mixture was effected with potassium hydroxide (40.5 g, 0.72 mol) in boiling 95% alcohol (180 ml) and water (20 ml) for 4.5 hr. Isolation of acidic material afforded 50.2 g of a viscous orange oil, which was chromatographed on a column (3.7 × 80 cm) of silica gel (360 g) deactivated with about 15% of its weight of water. Untreated silica (or Florisil) was not satisfactory, since the diacid moved much too slowly. The developing solvent at first was hexane alone and then hexane with gradually increasing amounts of ether until the hexane–ether ratio was 2:3. About 4.25 l. was used. Some 8-heptadecynoic acid (5.0 g or 13%), mp 29–32°, was recovered in the earlier fractions. On a thin layer chromatography plate (hexane–ether–acetic acid 40:10:1), this acid showed a single spot with the same R_f value as authentic 8-heptadecynoic acid. Later fractions, combined on the basis of thin layer chromatography results, provided 34.3 g (73%) of single-spot 8,9-carboxymethano-8-heptadecenoic acid (**12**) as a faintly yellow oil, n^{25}D 1.714.

Anal. Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94; neut equiv, 162.2. Found: C, 70.55; H, 10.15; neut equiv, 165, 161.

Although the above directions gave the best yield of diacid **12** (73%, 84% corrected for recovered starting acid), a more reproducible yield of 65% (69% corrected) was realized with a 2:1 instead of a 1.25:1 molar ratio of diazoacetic ester to acetylenic ester and with a tenfold greater ratio of copper–bronze to diazoacetic ester. In almost all of the additions, a slow moving component emerged after the desired diacid **12**. This could have been the corresponding bicyclo[1.1.0]butane triacid product,[15] but the point was not pursued. Subsequent work showed that thin layer chromatography using Brinkmann silica plates with 1:1 hexane–ether containing 5–10% (v/v) of 1:1 acetone–acetic acid differentiated well between the acetylenic acid, the desired cyclopropene diacid **12**, and the suspected triacid.

The homogeneous product **12**, which crystallized (mp 42–45°) after some time in the refrigerator, gave ir absorption maxima at 1700 (C=O) and 1900 cm^{-1} (cyclopropene); nmr (CCl_4) δ 0.88 (t, CH_3), 1.3–1.43 (m, CH_2's at positions 3–7 and 11–16), 1.97 (s, cyclopropene H), 2.32–2.42 (m, CH_2's at positions 2, 7, and 10), 12.18 (s, COOH).

Methyl Malvalate (8) from 8,9-Carboxymethano-8-heptadecenoic Acid (12).—A solution of diacid **12** (3.9 g, 0.012 mol), oxalyl chloride (5.0 g, 0.040 mol), and 45 ml of dry ether was stirred at room temperature for 1.5 hr. After most of the volatile materials had been removed, the residual light brown oily diacid chloride **13** was pumped at 10^{-3} mm to a constant weight of 4.3 g (99%): ir (neat) 1785 (poorly resolved carbonyls) and 1905, but nothing at 3100–3600 cm^{-1}.

The subsequent decarbonylation, esterification, and borohydride reduction in its essentials followed the procedure developed for the corresponding synthesis of methyl sterculate.[3] After purification by column chromatography, the colorless product **8**, homogeneous according to thin layer chromatography, weighed 1.5 g (34%); other fractions (6%) which were largely methyl malvalate but with additional spots were also obtained. In other preparations, yields up to 43% were realized. All fractions from chromatography give an immediate positive Halphen test.[16] For the main fraction the following properties were noted: n^{26}D 1.4545, n^{30}D 1.4515; ir (neat) 1745 (C=O), 1875 (weak), and 1005 (medium) cm^{-1}; nmr (20% in CCl_4) δ 0.75 (s, cyclopropene CH_2), 0.88 (distorted t, CH_2CH_3), 1.1–1.8 (complex), 2.20 (t, J = *ca.* 7 Hz, CH_2 at position 2), 2.35 (m, t, J = *ca.* 7 Hz, CH_2's at positions 7 and 10), 3.55 (s, OCH_3). The integrations for the cyclopropene CH_2, ester OCH_3, and all the remaining protons were in the ratio of 2 (estimated):3:29, as required for methyl malvalate (**8**).

Anal. Calcd for $C_{19}H_{34}O_2$: C, 77.50; H, 11.64. Found: C, 77.57; H, 11.47.

Methyl malvalate (**8**), on attempted gas–liquid chromatography through a silicone fluid (SF-96) column at 222°, produced two peaks, with an 85:15 ratio of the faster to the slower moving component.[14] No new thin layer chromatography spots were developed when methyl malvalate was stored under nitrogen for 4 days at −17°. For longer storage periods, the solid material in sealed ampoules was held at −78°. Samples that had become yellow on standing could be purified by chromatography through silica gel or Florisil. Purification of the crude product could be accomplished satisfactorily though less conveniently by reverse phase chromatography.[3] Attempted fractional crystallization in acetone at −70° gave little sign of separation. Urea adduction from methanol solvent at −5, −30, or −50° gave precipitates, but the material in the adduct and in the mother liquor differed but little in composition.[17] Chromatography through a column of powdered urea with 50:1 hexane–methanol as eluting solvent gave no separation. Short-path distillation involving a 5-min exposure to 160° gave distillate showing distinct olefinic proton signals in the nmr curve at δ 4.8 and 5.33–6.3. Although evaporative distillation in a wide bore bulb-to-bulb apparatus at 110° (5 × 10^{-4} mm) did not introduce olefinic impurities and appeared promising, the method was not developed. Exposure to temperatures greater than 120° is to be avoided.

When anhydrous ferric chloride or aluminum chloride was substituted for zinc chloride in the decarbonylation, evolution of carbon monoxide was more rapid. When ferric chloride was used, mixing with borohydride in the reduction step produced a black precipitate (iron boride?) possibly effective in the catalytic decomposition of the borohydride;[18] the yield of methyl malvalate here was 10–30%. In general, aluminum chloride gave yields in the order of 20–30%, although in one exceptional case in the analogous synthesis of methyl sterculate, the yield was 45% from the corresponding diacid.

(15) *Inter alia*, I. A. D'yakanov, V. V. Razin, and M. I. Komendantov, *Tetrahedron Lett.*, 1127 (1966); P. F. Wolf, Doctoral Dissertation, Columbia University, 1964; *Dissertation* Abstr., **26**, 4251 (1966); T. Shimadate and Y. Hosoyama, *Bull. Chem. Soc. Jap.*, **40**, 2971 (1967).

(16) F. C. Magne, *J. Amer. Oil Chem. Soc.*, **42**, 332 (1965).

(17) See R. E. Feuge, *et al.*, ref 8.

(18) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p 60.

The Methanethiol Adduct[8] from Methyl Malvalate (8).—A sample of homogeneous methyl malvalate (0.333 g or 1.13 mmol) was allowed to stand away from air for 8 days at room temperature with 15 ml of a 10% benzene solution of methyl mercaptan. After volatiles were blown off in a stream of pure nitrogen, the residue was pumped in a high vacuum to a constant weight of 0.389 g (100.5%). This methyl mercaptan adduct was colorless though faintly milky. It showed the same single spot on thin layer chromatography and the same single peak on gas–liquid chromatography as the sample obtained after further purification. Preparative gas–liquid chromatography, using an 8-ft 10% silicone oil (SE-30) column at 230° with helium as the carrier, provided approximately 0.3 ml of water-white product.

Anal. Calcd for $C_{20}H_{38}O_2S$: C, 70.12; H, 11.18. Found: C, 70.12; H, 11.32.

The adduct gave one spot on thin layer chromatography on a silica plate with 8:1 hexane–ether as developing solvent. Gas–liquid chromatography through a 6-ft silicone oil (SF-96) column at 230° produced a single symmetrical peak. The adduct showed $n^{25}D$ 1.4702; ir (neat) 3060 (cyclopropane), but no peaks at 1875 or 1005 cm^{-1}; nmr (20% in CCl_4) δ 0.3–0.85 (complex, cyclopropane H's), 0.90 (distorted t, CH_3 at position 17), 1.1–1.8 (complex), 2.0 (s, SCH_3), 2.2 (distorted t, CH_2COOCH_3), 3.60 (s, OCH_3). The ratio of the area under the 3.60-ppm signal to all others was very close to the expected 3:35.

Registry No.—**2**, 24471-13-4; **3**, 24471-14-5; **6**, 24471-15-6; **7**, 24471-16-7; **8**, 5026-66-4; **9**, 24471-18-9; **10**, 24471-19-0; **11**, 24471-20-3; **12**, 24471-23-6; 1-chloro-4,5-(ethoxycarbonylmethano)-4-decene, 24471-24-7; 1-chloro-4,5-carboxymethano-4-decene, 24471-25-8; 1-chloro-4,5-(chlorocarbonylmethano)-4-decene, 24471-26-9; 1-chloro-4,5-methano-4-decene, 24471-27-0; methyl 5,6-methano-5-undecenoate, 24471-28-1; 1-cyano-4,5-methano-4-decene, 24471-29-2.

Acknowledgment.—We gratefully acknowledge the help of Southern Regional Research Laboratory, U. S. Department of Agriculture [Research Grant No. 12-14-100-7992 (72)], that made this work possible.

Compounds Derived from 1-Methyl-4-phosphoraninone. A Wittig Reaction with Retention of Phosphorus

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1-Methyl-4-phosphoraninone was condensed with a series of arylmagnesium bromides. The resulting alcohols were converted to a series of derivatives including 1,2,3,6-tetrahydro-4-aryl-1,1-dimethylphosphorinium iodides. These latter were allowed to react *via* their ylides with aromatic aldehydes to afford 3,6-diaryl-3,5-hexadienyldimethylphosphine oxides. The reaction of these ylides with ketones also gave the corresponding dienes.

Though innumerable nitrogen heterocyclic compounds have been prepared as potential medicinal agents, their phosphorus counterparts remain largely unknown. Recent reports on the preparation and biological activity of the phosphorus analogs of a series of phenothiazines[1] and the finding that 4-phosphoraninones[2] prepared from bis(2-cyanoethylalkyl)phosphines[3] readily add Grignard reagents[4] led us to use 1-methyl-4-phosphoraninone (**1**) as the key intermediate for the present work.

Reaction of ketone **1** with a series of arylmagnesium bromides afforded the corresponding alcohols (Scheme I). Because of the conformational stability of trivalent phosphorus,[5] these products would be expected to be mixtures of the geometrical isomers about phosphorus and C-4. Indeed, each of the oily alcohols exhibited a pair of P–CH_3 doublets in the nmr in a roughly 1:1 ratio. Reaction of these phosphines with methyl iodide afforded the quaternary salts; since this last reaction removes one of the centers of isomerism by symmetrizing the phosphorus, each alcohol mixture gave a single crystalline methiodide (**2**–**7**) (Table I).

Alternately, the center of isomerism at C-4 was removed by conversion of the alcohol to the olefin. These last products, though often crystalline, proved too labile to air to characterize as the free bases. Conversion to either the *p*-toluenesulfonate (**8**, **9**) or methiodide (**10**–**13**) gave a series of stable, easily characterized compounds. In the case of the *m*-trifluoromethylphenyl derivative, one of the isomers of the alcohol was isolated as its *p*-toluenesulfonate salt (**14**); attempts to dehydrate this last compound were unavailing.

The Wittig reaction has come to be one of the most versatile of methods for the elaboration of carbon chains; modifications of the reaction are legion.[6,7] Since this reaction involves in its first stages the generation of a carbanionoid center, the phosphonium salt chosen usually contains but one group with hydrogens α to phosphorus. In the course of the reaction reorganization of the bonding in the intermediate betaine results in the loss of phosphorus as a phosphine oxide.[8,9]

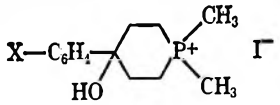
The quaternary salts **10**–**13** contain structural features which suggest a novel modification of the Wittig reaction: first, though there are three sets of α hydrogens, the allylic ring proton should be removed in preference to the others; and, second, collapse of the betaine (Scheme II), as in the generally accepted mechanism, should lead to a product in which the phosphorus is retained.

Treatment of a suspension of the quaternary salt **11** in THF with butyllithium followed by benzaldehyde gave upon work-up and chromatography a crystalline compound (**15**). The nmr spectrum of this material showed the presence of two aromatic rings (multiplets from δ 6.9 to 7.7; 9 H), the three vinyl protons as multi-

(1) R. A. Wiley and J. H. Collins, *J. Med. Chem.*, **12**, 146 (1969).
(2) R. P. Welcher, G. A. Johnson, and V. P. Wystrach, *J. Amer. Chem. Soc.*, **82**, 4437 (1960).
(3) M. Grayson, P. T. Keough, and G. A. Johnson, *ibid.*, **81**, 4803 (1959).
(4) H. E. Shook, Jr., and L. D. Quin, *ibid.*, **89**, 1841 (1967).
(5) L. D. Quin and H. E. Shook, Jr., *Tetrahedron Lett.*, 2193 (1965).
(6) S. Trippett, *Quart. Rev.* (London), **17**, 406 (1963).
(7) H. J. Bestman, *Angew. Chem. Int. Ed. Engl.*, **4**, 583 (1965).
(8) A. J. Speziale and D. E. Bissing, *J. Amer. Chem. Soc.*, **85**, 2790 (1963).
(9) M. E. Jones and S. Trippett, *J. Chem. Soc., C*, 1090 (1966).

TABLE I

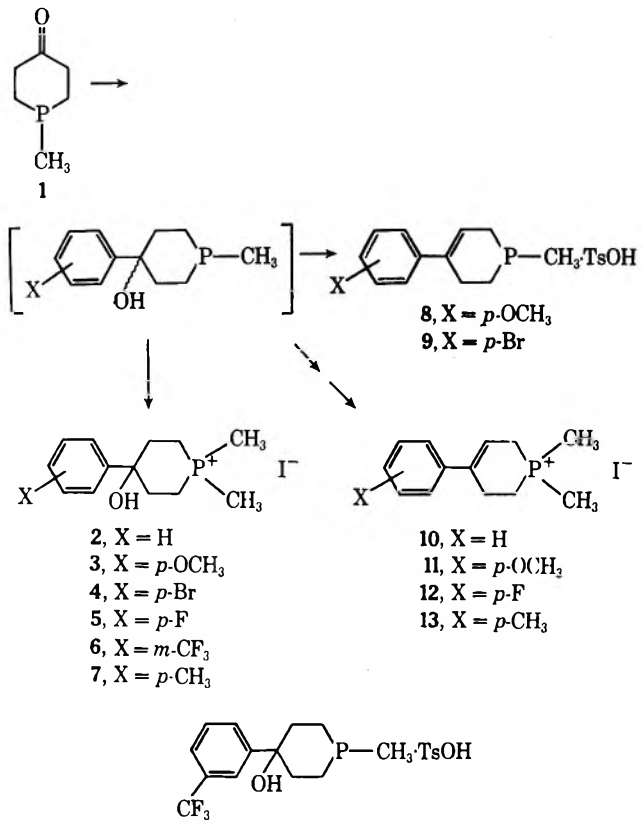
4-HYDROXY-1,1-DIMETHYL-4-ARYLPHOSPHORANINIUM IODIDES



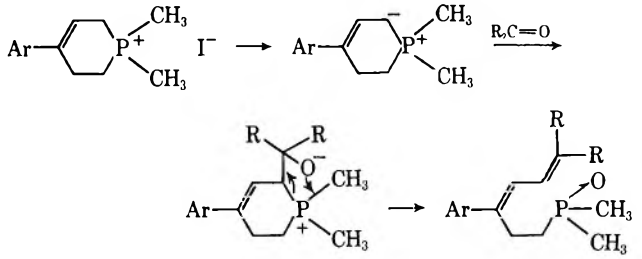
Compd no.[a]	X	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % I	Found, % C	Found, % H	Found, % I
2	H	228–230	41	44.59	5.76		44.66	5 81	
3	*p*-CH_3O	212–214	58	44.22	5.83	33.38	44.21	5.72	33.40
4[b]	*p*-Br	233–235.5	45	36.39	4.46	29.58	36.54	4.30	29.26
5	*p*-F	227.5–229	47	42.58	5.20		42.58	5.29	
6	*m*-CF_3	142–148	28	40.21	4.58		40.75	4.72	
7	*p*-CH_3	182–183	44	46.17	6.09		45.94	6.12	

[a] Compound recrystallized from acetonitrile–ether. [b] Recrystallized from acetonitrile.

SCHEME I

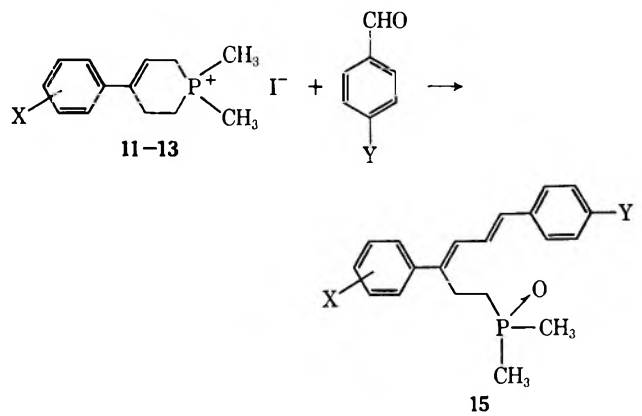


SCHEME II



plets (δ 6.4 to 6.9), the methoxyl as a three-proton singlet at δ 4.9, the ethylene carrying the phosphorus as an A_2B_2 pattern of multiplets centered at δ 1.85 and 3.1, and finally the two methyl groups on phosphorus as a six-proton doublet (J = 13 Hz) centered at δ 1.5. The double bond adjacent to the ring has perforce the *trans* configuration; since only a single isomer was isolated, the geometry of the newly generated double bond cannot be assigned unambiguously. The uv spectrum of the product [λ_{max} 330 mμ (ϵ 53,000)] suggests it to be the *trans,trans* compound.[10] As can be seen from Table II this reaction can be applied quite generally to the preparation of substituted 3,6-diaryl-3,5-hexadienyldimethylphosphine oxides by the choice of the appropriate salt and aromatic aldehyde. Though a single isomer was isolated in most cases we consider this a consequence of the purification procedure rather than a stereoselective reaction, particularly in view of the less than 50% yields. It is of note in this regard that, in the case of the tolyl compound (**15h**, **15i**) (Table II), both possible isomers were obtained in pure form.

SCHEME III



The reaction of the cyclic ylides with representative ketones similarly afforded the phosphorus-containing dienes. Both benzophenone and cyclohexanone gave the condensation products in workable yields. Though the product from the condensation with acetone was obtained in good yield as a crude material, this product (**18**) proved difficult to handle; the yield of pure material was consequently quite low.

Experimental Section[11]

1-Methyl-4-(*p*-methoxyphenyl)-4-phosphoraninol.—To the ice-cooled Grignard reagent prepared from 11.0 g (0.059 mol) of

(10) The corresponding uv spectra for *trans,trans*- and *cis,trans*-1,4-diphenylbutadiene are λ_{max} 330 mμ (ϵ 50,000) and λ_{max} 312 mμ (ϵ 30,000): J. Dale, *Acta Chem. Scand.*, **11**, 971 (1957).

(11) All melting points are uncorrected and reported as obtained on a Thomas–Hoover capillary melting point apparatus. Nmr spectra were obtained in deuteriochloroform on a Varian A-60A spectrometer. The author is indebted to the Department of Physical and Analytical Chemistry of The Upjon Co. for spectral determinations and elemental analyses.

TABLE II

3,6-DIARYL-3,5-HEXADIENYLDIMETHYLPHOSPHINE OXIDES

$$p\text{-}XC_6H_4C(CH_2CH_2PO(CH_3)_2)=CHCH=CH-(p\text{-}C_6H_4Y)$$

Compd no.	X	Y	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Found, % C	Found, % H
15a	CH_3O	H	135–137	50	74.09	7.40	73.72	7.49
15b	CH_3O	CH_3O	147–149	50[a]	70.67[b]	7.57	70.73	7.67
15c	F	CH_3O	167–169	41[a]	70.38	6.75	70.26	6.77
15d	F	F	122–125	21	69.35	6.11	69.02	6.51
15e	F	CH_3[c]	141–143	51	73.66	7.07	73.41	7.05
15f	F	CH_3[d]	117–119.5	20	73.66	7.07	73.42	7.68
15g	F	NO_2[e]	177–179	13	64.33	5.67	63.97	5.91
15h	CH_3	H	130–132	45	77.77	7.77	77.27	8.21
15i	CH_3	F	129–131	43	73.66	7.07	73.44	7.15

[a] Isolated without chromatography. [b] Nmr shows presence of 0.5 mol of acetone; calcd for $C_{22}H_{27}O_3P \cdot 0.5Me_2CO$. [c] *trans,trans*, λ_{max} 323 (ϵ 37,950). [d] *trans,cis*, λ_{max} 323 (ϵ 36,000). [e] Recrystallized from aqueous methanol.

anisyl bromide and 1.45 g (0.06 g-atom) of magnesium in 50 ml of THF (tetrahydrofuran) there was added 5.0 g (0.036 mol) of 1-methyl-4-phosphoraninone in 50 ml of THF. The mixture was allowed to stand overnight at room temperature, cooled in ice, and treated with 50 ml of saturated ammonium chloride. Ether was then added and the organic layer was washed with water. The ether was extracted several times with 2.5 *N* hydrochloric acid. The gum which precipitated when the acid extracts were made basic was taken up in ether. This last extract was washed with water and brine, percolated through sodium sulfate, and taken to dryness. There was obtained 7.73 g (98%) of the crude alcohols as a viscous syrup.

Proceeding exactly as above, but using the Grignard reagents from *p*-dibromobenzene, *p*-fluorobromobenzene, and *p*-bromotoluene, respectively, there was obtained 1-methyl-4-(*p*-bromophenyl)-4-phosphoraninol (98%), 1-methyl-4-(*p*-fluorophenyl)-4-phosphoraninol (98%), and 1-methyl-4-(*p*-tolyl)-4-phosphoraninol. All these products were obtained as viscous oils and were not characterized.

1-Methyl-4-(*m*-trifluoromethyl)-4-phosphoraninol *p*-Toluenesulfonate (14).—To the Grignard reagent prepared from 22.5 g (0.10 mol) of *m*-trifluorobromobenzene and 2.45 g of magnesium in 250 ml of THF there was added 5.20 g of the ketone in 50 ml of THF. The alcohol was obtained in the same manner as those above. A solution of that oil in 200 ml of xylene was treated with 8.40 g of *p*-toluenesulfonic acid and the precipitated solid was collected on a filter. A small sample was recrystallized from acetonitrile–ether to mp 201–205°.

Anal. Calcd for $C_{20}H_{24}F_3O_4PS$: C, 53.56; H, 5.34. Found: C, 53.86; H, 5.07.

The remaining solid was reconverted to the free base to afford 8.47 g (86%) of oil.

1-Methyl-1,2,3,6-tetrahydro-4-(*p*-methoxyphenyl)phosphorin Tosylate (8).—A mixture of the crude alcohol obtained from 5 g of the phosphoraninone and 8.0 g of *p*-toluenesulfonic acid in 200 ml of benzene was heated at reflux under a Dean–Stark trap overnight. The mixture was then extracted in turn with water and two portions of 2.5 *N* hydrochloric acid. The aqueous layer was then made basic under a blanket of nitrogen. The precipitated oil was taken up in ether and washed with water and brine. A solution of 6.4 g of *p*-toluenesulfonic acid in 10 ml of acetone was then added and the precipitated solid was collected on a filter. The solid was recrystallized several times from acetonitrile–ether to afford 6.25 g (48%) of solid, mp 161–162°.

Anal. Calcd for $C_{20}H_{25}O_4PS$: C, 61.21; H, 6.42. Found: C, 61.00; H, 6.69.

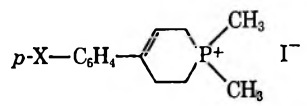
1-Methyl-1,2,3,6-tetrahydro-4-(*p*-bromophenyl)phosphorin Tosylate (9).—A mixture of 4.79 g of the crude alcohol obtained above and 3.40 g of *p*-toluenesulfonic acid in 100 ml of xylene was heated under a Dean–Stark trap overnight. The mixture was allowed to cool and the solvent was decanted from the oily solid. The latter was washed with ether and recrystallized twice from methanol. There was obtained 1.92 g (25.5%) of the salt, mp 210–215°.

Anal. Calcd for $C_{19}H_{22}BrO_3PS$: C, 51.71; H, 5.03. Found: C, 51.99; H, 5.27.

1,2,3,6-Tetrahydro-1,1-dimethyl-4-arylphosphorinium Iodides (Table III).—A solution of the crude alcohol and 2 equiv of *p*-toluenesulfonic acid in 200 ml of xylene was heated at reflux under a Dean–Stark trap for 8 hr. The mixture was allowed to cool and extracted thoroughly with water. The aqueous layer was made strongly basic (under nitrogen) and extracted with ether. The extracts were worked up in the normal way and converted to their methiodides.

TABLE III

1,2,3,6-TETRAHYDRO-1,1-DIMETHYL-4-ARYLPHOSPHORINIUM IODIDES



Compd no.	X	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Found, % C	Found, % H
10	H	186–189	81	47.00	5.46	47.44	5.68
11	CH_3O	217–219	48	46.42	5.57	46.58	5.67
12	F	222–224	72	44.54	4.89	44.85	4.95
13	CH_3	184–185.5	43	48.57	5.82	48.63	5.87

3,6-Diaryl-3,5-hexadienyldimethylphosphine Oxides (Table II).—In a typical experiment, 6.4 ml of 1.6 *N* butyllithium in pentane was added to a well-stirred ice-cooled suspension of 0.01 mol of the appropriate finely powder quaternary salt in 60 ml of THF. At the end of 10–15 min a solution of 0.011 mol of the appropriate aldehyde in 20 ml of THF was added to this. The mixture was then stirred for 30 min at room temperature and 5 hr at reflux. After cooling, 50 ml of saturated ammonium chloride in ether was added. The organic layer was separated, washed in turn with water and brine, and taken to dryness under vacuum. The residue (except when crystalline; see Table II) was chromatographed on Florisil[12] (elution with 1 l. of 20% acetone–Skellysolve B,[13] then 100% acetone). The crystalline fractions were combined and recrystallized from acetone–Skellysolve B.

[3-(*p*-Fluorophenyl)-6,6-diphenyl-3,5-hexadienyl]dimethylphosphine Oxide (16).—The salt **12** (3.50 g) was converted to its ylide and allowed to react with 1.83 g of benzophenone. Following 18 hr of heating at reflux the mixture was worked up and chromatographed as in the general procedure. The product was recrystallized from ethyl acetate to afford 2.67 g (66%) of **16**, mp 173–176°.

Anal. Calcd for $C_{26}H_{26}FOP$: C, 77.21; H, 6.48. Found: C, 77.19; H, 6.58.

[3-(*p*-Fluorophenyl)-5-cyclohexylidene-3-pentenyl]dimethylphosphine Oxide (17).—Cyclohexanone (1 ml) in 10 ml of THF was added to a solution of the ylide prepared from 3.50 g of the salt **12**. The mixture was heated at reflux overnight and worked up as above (chromatography omitted). The product was re-

(12) A synthetic magnesia–silica gel absorbent manufactured by the Floridin Co., Warren, Pa.

(13) Skellysolve B, a petroleum fraction, bp 60–70°, sold by the Skelly Oil Co.

crystallized twice from acetone–Skellysolve B to afford 2.42 g (76%) of oxide, mp 125–127°, λ_{max} 282 (ϵ 26,200).

Anal. Calcd for $C_{15}H_{26}FOP$: C, 71.22; H, 8.18. Found: C, 71.26; H, 8.21.

[3-(*p*-Fluorophenyl)-6-methyl-3,5-heptadienyl]dimethylphosphine Oxide (18).—The ylide prepared from 3.50 g of the salt **12** was allowed to react with 0.8 ml of acetone. There was obtained on work-up 2.48 g of crude oxide, mp 81–95°. A sample was rechromatographed and recrystallized from moist Skellysolve B to give a sample (320 mg): mp 90–96°; ν_{max} 3300 cm^{-1}; nmr four aromatic protons (multiplets δ 6.8–7.6), two vinyl protons (multiplets δ 5.9–6.7), allylic methyl (three-proton singlets at δ 2.82 and 2.9), P–CH_3 (6 H, doublet about δ 1.5, J = 13 Hz).

Anal. Calcd for $C_{16}H_{22}FOP \cdot H_2O$: C, 64.48; H, 8.12. Found: C, 64.61; H, 8.00.

Registry No.—**2**, 24699-83-0; **3**, 24728-08-3; **4**, 24699-84-1; **5**, 24699-85-2; **6**, 24699-86-3; **7**, 24699-87-4; **8**, 24699-88-5; **9**, 24699-89-6; **10**, 24699-90-9; **11**, 24699-91-0; **12**, 24699-92-1; **13**, 24699-93-2; **14**, 24699-94-3; **15a**, 24691-52-9; **15b**, 24691-53-0; **15c**, 24691-54-1; **15d**, 24691-55-2; **15e**, 24691-56-3; **15f**, 24728-09-4; **15g**, 24691-57-4; **15h**, *trans,trans*, 24691-58-5; **15h**, *trans,cis*, 24691-60-9; **15i**, *trans,trans*, 24691-59-6; **15i**, *trans,cis*, 4728-00-5; **16**, 24699-95-4; **17**, 24728-96-5; **18**, 24699-96-5.

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Synthesis of 2,6,7-Trioxa-4-phosphabicyclo[2.2.2]octane Systems

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The formation of $P(CH_2O)_3P$ from $P(CH_2OH)_3$ and $P(OMe)_3$ is shown to be highly dependent on the manner in which the triol is prepared. Neutralization of $[P(CH_2OH)_4]Cl$ with NaOH produces 1 mol of H_2O which is difficult to remove and leads to extensive hydrolysis of the $P(OMe)_3$ when transesterification is attempted. Treating the salt with an equimolar quantity of NaOMe, although eliminating the hydrolysis problem, results in appreciable isomerization of $P(OMe)_3$ to $Me(O)P(OMe)_2$. In neither case does $P(CH_2O)_3P$ form in consistent or reasonable yields. The isomerization side reaction is shown to be due to small amounts of unneutralized phosphonium salt. A 20% molar excess of NaOMe over salt results in 20–30% yields of $P(CH_2O)_3P$ and only a trace of $Me(O)P(OMe)_2$ side product. The synthesis and characterization of the new compounds $P(CH_2O)_3As$, $OP(CH_2O)_3As$, $P(CH_2O)_3SiMe$, and $MeC(CH_2O)_3SiMe$ are also reported.

In 1965 we reported[2] what appeared at the time to be a straightforward synthesis of $P(CH_2O)_3P$ by the transesterification of $P(CH_2OH)_3$ with trimethyl phosphite in tetrahydrofuran. Since then we have experienced little success in consistently repeating the synthesis. Moreover, it has come to our attention that several other investigators have had similar difficulties, although there is one published report[3] in which the compound was successfully prepared by our method. We thought it appropriate, therefore, to examine the synthesis more closely in an effort to elucidate the nature of the side products in the reaction of $P(CH_2OH)_3$ with $P(OMe)_3$. Moreover, it was highly desirable to determine the conditions necessary for a more reliable preparation of $P(CH_2O)_3P$ since this difunctional nonchelating ligand has been found to exhibit interesting coordination properties.[4]

It is not obvious *a priori* why the transesterification of $P(CH_2OH)_3$ with $P(OMe)_3$ should be more difficult than the analogous reaction with $RC(CH_2OH)_3$ or *cis*-1,3,5-cyclohexanetriol. These latter triols with $P(OMe)_3$ afford $P(OCH_2)_3CR$ and $P(OCH)_3(CH_2)_3$, respectively, in high yields and numerous reports in the literature from other laboratories[5] as well as ours[6] on the use of these bicyclic phosphites in other reactions attest to the reliability of our syntheses[7] of these compounds.

We show in the present report that the formation of $P(CH_2O)_3P$ is very sensitive to the manner in which the $P(CH_2OH)_3$ is prepared from the commercially available $[P(CH_2OH)_4]Cl$. It is also demonstrated that $P(OMe)_3$ undergoes deleterious hydrolysis and rearrangement reactions whereas $As(OMe)_3$ and $MeSi(OMe)_3$ are quite stable to rearrangement. The arsenic and silicon esters with $P(CH_2OH)_3$ lead to the new bicyclic compounds $P(CH_2O)_3As$ and $P(CH_2O)_3SiMe$, respectively. Also reported for the first time are $OP(CH_2O)_3As$ and $MeC(CH_2O)_3SiMe$.

Experimental Section

Elemental analyses were carried out by Chemalytics, Inc., Tempe, Ariz., or Galbraith Laboratories, Inc., Knoxville, Tenn. Molecular weights were obtained on an atlas CH-4 single-focusing spectrometer at 70 eV. Infrared spectra were obtained on a Perkin-Elmer Model 21 double-beam spectrometer using sodium chloride optics. Proton nmr spectra were obtained on a Varian Associates A-60 spectrometer using tetramethylsilane as an internal standard. Melting points were taken in capillaries and are uncorrected.

$P(CH_2OH)_3$.—To a well-stirred solution of 19.05 g (0.1 mol) of $[P(CH_2OH)_4]Cl$ in 75 ml of anhydrous methanol, 65 ml of methanolic $NaOCH_3$ containing 1 g of $NaOCH_3$ in 10 ml of MeOH was added all at once, the latter being in about a 20% excess of the equimolar amount. The mixture was allowed to stir for 15 min during which time the NaCl precipitated. A small amount of dry ether (about 15 ml) was then added to precipitate the last traces of NaCl, which was subsequently removed by filtration.

(1) NSF Undergraduate Research Participant, 1969.

(2) K. J. Coskran and J. G. Verkade, *Inorg. Chem.*, **4**, 1655 (1965).

(3) W. McFarlane and J. A. Nash, *Chem. Commun.*, 127 (1969).

(4) R. D. Bertrand, D. A. Allison, and J. G. Verkade, *J. Amer. Chem. Soc.*, **92**, 71 (1970).

(5) See, for example, F. Basolo and H. G. Schuster-Woldan, *ibid.*, **88**, 1657 (1966); C. S. Krainanzel and P. K. Maples, *Inorg. Chem.*, **7**, 1806 (1968).

(6) See, for example, A. C. Vandenbroucke, D. G. Hendricker, R. E. McCarley, and J. G. Verkade, *ibid.*, **7**, 1825 (1968), and references therein.

(7) J. G. Verkade, T. J Huttemann, M. K. Fung, and R. W. King, *ibid.*, **4**, 83 (1965).

The resulting solution of $P(CH_2OH)_3$ was strongly basic when tested with moist pH paper and gave no further precipitate upon introduction of a few additional drops of $NaOCH_3$ solution. Removal of the solvent by evaporation gave the triol as a clear viscous liquid.

$P(CH_2O)_3P$.—Freshly prepared $P(CH_2OH)_3$ (0.1 mol) was slowly added with constant stirring to a solution containing 24 ml (0.2 mol) of $P(OMe)_3$, an equal volume of methanol, and 1 ml of 10% methanolic $NaOCH_3$. The methanol permits a homogeneous reaction mixture but can be omitted giving a two-phase reaction which gives $P(CH_2O)_3P$ in yields identical with those obtained from the homogeneous reaction mixture. Upon completion of the addition of $P(CH_2OH)_3$, the reaction mixture was heated to 90° and held at this temperature for several hours. Methanol, formed as the result of the transesterification reaction

$$P(OCH_3)_3 + P(CH_2OH)_3 \rightleftharpoons P(CH_2O)_3P + 3CH_3OH$$

slowly distils from the reaction mixture. When no more methanol was collected, the excess $P(OMe)_3$ was swept out of the reaction with the aid of a slow N_2 flush. Upon allowing the reaction to cool, a crystalline but oily mass of crude product was obtained. The oily nature of the crude product makes difficult the isolation of pure $P(CH_2O)_3P$. Nonetheless, two dissimilar purification procedures have been found to give satisfactory results.

In the first method the crude product was stirred for about 1 hr with 50 ml of dry benzene while the mixture was kept at 70°. After decanting the benzene, the extraction process was repeated three more times. Evaporation of the extracts gave a liquid which solidified on standing. The solid mass was dissolved in 25 ml of benzene and the clear solution was decanted from the oily, insoluble droplets that were also present. Final crystallization was effected by bubbling a slow stream of N_2 through the slightly warmed (30–35°) benzene solution until crystallization commenced, whereupon it was cooled to 0°. The crystalline solid was then separated from the small amount of remaining solvent by rapid filtration. The last traces of solvent were removed under vacuum to give pure $P(CH_2O)_3P$ in the form of large, clear but soft crystals. The absence of any significant impurities was confirmed by nmr spectroscopy, the spectrum being identical with that previously recorded of pure $P(CH_2O)_3P$.[2]

Alternately, purification was accomplished by stirring the crude reaction product in three or four separate portions with excess ice water whereupon the oil dissolved almost immediately, leaving the solid ester behind. The water was quickly drawn off through a coarse frit and the solid was washed with benzene into a stirred mixture of benzene and anhydrous magnesium sulfate (approximately 200 g of $MgSO_4$ in 400 ml of benzene). These operations were performed quickly as $P(CH_2O)_3P$ dissolves with hydrolysis quite rapidly in water. The exposure of $P(CH_2O)_3P$ to water has not been allowed to exceed 30 sec and even minimal exposure to H_2O undoubtedly has resulted in some loss of yield. *Caution: Allowing $P(CH_2O)_3P$ moist with water to stand has occasionally caused the material to burst into flames.* After filtration of the benzene to remove $MgSO_4$, evaporation of the benzene gave $P(CH_2O)_3P$ as a dry, crystalline powder which exhibited the expected nmr spectrum.

The purities and yields of $P(CH_2O)_3P$ have been found to be nearly identical for the two purification procedures but the second method described can be completed in much less time and has been most often, albeit cautiously, used. Consistent yields of 20–30% of the theoretical have been obtained. Calcd: mol wt, 152. Found: mol wt, 152. *Caution: In this synthesis it is essential that the $P(CH_2OH)_3$ used be strongly basic. It has been found in the ^1H nmr spectrum of triol which is nearly neutral or even slightly basic (as in the case when the stoichiometric amount of $NaOCH_3$ is used) that considerable amounts of $[P(CH_2OH)_4]^+Cl^-$ are present and will, when added to $P(OCH_3)_3$, give rise to a violent, exothermic reaction which occasionally takes fire or explodes and from which no $P(CH_2O)_3P$ can be isolated.*

$P(CH_2O)_3As$.—To 12.4 g (0.100 mol) of $P(CH_2OH)_3$ was added, with stirring under nitrogen flush at room temperature, 16.9 g (0.100 mol) of $As(OCH_3)_3$ prepared as reported previously.[8] The mixture immediately formed a solid crystalline mass of crude product. Rapid nitrogen flush was continued for 15 min to remove most of the methanol. Benzene was added and the mixture was stirred until only a small amount of oil remained undissolved. After filtration of the solution, the solvent was removed and the remaining product was sublimed at 40° (2 mm). A 61.2% yield of product as colorless crystals (mp 91–92°) was realized. The very hygroscopic crystals were stored under dry nitrogen in a desiccator. The dipole moment of 1.58 D in benzene at 25.0° was measured as described previously.[9] Because of a small amount of decomposition noted after the measurements, the experimental moment is probably precise to only ±0.15 D. *Anal.* Calcd for $PC_3H_6O_3As$: C, 18.38; H, 3.09; mol wt, 196. Found: C, 18.39; H, 2.98; mol wt, 196.

$OP(CH_2O)_3As$.—To a solution of 3.92 g (20.0 mmol) of $P(CH_2O)_3As$ in 100 ml of benzene was added 4.64 g (20.0 mmol) of benzoyl peroxide and the mixture was refluxed under nitrogen flush for 2 hr. A yield of 85.5% of product as colorless needles decomposing at 175° separated from the solution. A strong infrared absorbance at 1195 cm^{-1} in $CDCl_3$ revealed the presence of a P=O link in the compound. Calcd for $PC_3H_6O_4As$: mol wt, 212. Found: mol wt, 212.

$P(CH_2O)_3SiCH_3$.—To 12.4 g (0.100 mol) of $P(CH_2OH)_3$ was added under nitrogen flush 13.6 g (0.100 mol) of $CH_3Si(OCH_3)_3$ prepared as described previously.[10] The reaction was carried out in a 250-ml flask equipped with a mechanical stirrer, distillation condenser, and nitrogen inlet. The mixture was heated with stirring at 90° for 3 hr with a gentle nitrogen flush to remove methanol. After the reaction period the mixture was transferred to a sublimation apparatus and colorless crystals were sublimed from the mixture at 80° (2 mm). Purification was achieved by resublimation under vacuum at room temperature. There was obtained a 41.9% yield of crystals (mp 61–62°). The extremely hygroscopic crystals could be stored for long periods only under vacuum. *Anal.* Calcd for $PC_4H_9O_3Si$: C, 29.25; H, 5.52; mol wt, 164. Found: C, 29.02; H, 5.46; mol wt, 164.

$CH_3Si(OCH_2)_3CCH_3$.—This bicyclic compound was prepared in the same manner as the previous compound except that 12.0 g (0.100 mol) of $CH_3C(CH_2OH)_3$ was used in place of $P(CH_2OH)_3$ and 0.50 g of $NaOCH_3$ was added to catalyze the reaction. The product was sublimed from the reaction mixture at 250° (2 mm). Purification was achieved by resublimation of the colorless crystals at 60°. A 9.75% yield of colorless crystals (mp 106–108°) was obtained. The extremely hygroscopic solid was stored under vacuum. *Anal.* Calcd for $C_6H_{12}O_3Si$: C, 44.98; H, 7.56; mol wt, 160. Found: C, 46.11; H, 7.83; mol wt, 160.

Results and Discussion

The course of the reaction between $P(CH_2OH)_3$ and $P(OMe)_3$ was followed by observing changes in the ^1H nmr spectrum in *t*-butyl alcohol as a solvent. Because the $P(CH_2OH)_3$ used in our earlier synthesis[2] of $P(CH_2O)_3P$ was prepared after the manner of Grayson[11] rather than by the procedure given in the Experimental Section, our initial nmr studies were made with $P(CH_2OH)_3$ obtained by the reaction

$$P(CH_2OH)_4Cl + NaOH \xrightarrow{EtOH} P(CH_2OH)_3 + NaCl + H_2CO + H_2O$$

The reaction mixture was prepared by adding slightly more than an equimolar amount of $P(OMe)_3$ to a solution of the triol in *t*-butyl alcohol[12] and the ^1H nmr spectrum of the mixture was periodically scanned.

If the major reaction is the transesterification, then the ^1H spectra of the appropriate compounds in Table I

$$P(CH_2OH)_3 + P(OMe)_3 \longrightarrow P(CH_2O)_3P + 3MeOH$$

would show that (a) the integrated area of the $P(OMe)_3$ peaks would decrease 1.5 times as fast as the area of the $P(CH_2OH)_3$ methylene proton peaks, and (b) the

(8) K. Moedritzer, *Inorg. Syn.*, **11**, 182 (1968).

(9) A. C. Vandenbroucke, R. W. King, and J. G. Verkade, *Rev. Sci. Instrum.*, **39**, 558 (1968).

(10) D. Seyferth and E. G. Rochow, *J. Org. Chem.*, **20**, 250 (1955).

(11) M. Grayson, German Patent 1151255; *Chem. Abstr.*, **60**, 554*g* (1964).

(12) Not quite all of the triol dissolves in *t*-butyl alcohol regardless of the preparation used. Thus insoluble side products in minor quantities may form. Indeed $P(CH_2OH)_3$ has been found [W. J. Vulbo, *J. Org. Chem.*, **33**, 3665 (1968)] to react with the CH_2O formed in the NaOH neutralization reaction to give $HOCH_2OCH_2P(CH_2OH)_2$.

TABLE I

^{1}H NMR SPECTRAL DATA[a]

Compd	Registry no.	δ ^{1}H (resonance)	J (nuclei)	Solvent
$P(CH_2O)_3P$	4579-03-7	4.54 (CH_2)	8.8 (PCH)	$CDCl_3$[b]
			2.8 (POCH)	
$P(CH_2O)_3As$	24647-30-1	4.61 (CH_2)	9.4 (PCH)	$CDCl_3$
$OP(CH_2O)_3As$	24647-31-2	4.64 (CH_2)	7.4 (PCH)	$CDCl_3$
$P(CH_2O)_3SiCH_3$	24647-32-3	4.66 (CH_2)	8.9 (PCH)[c]	$CDCl_3$
		0.11 (CH_3)		
H_3C–$Si(OCH_2)_3CCH_3$	24647-52-7	3.98 (CH_2)		$CDCl_3$
		0.66 (CCH_3)		
		0.20 ($SiCH_3$)		
$(CH_3)_3COH$	75-65-0	1.22 (CH_3)		*d*
		4.64 (OH)		
$P(CH_2OH)_3$	2767-80-8	4.07 (CH_2)	3.0 (PCH)	$(CH_3)_3COH$
$P(OCH_3)_3$	121-45-9	3.44 (CH_3)	10.6 (POCH)	$(CH_3)_3COH$
CH_3OH	67-56-1	3.31 (CH_3)		$(CH_3)_3COH$
$H(O)P(OCH_3)_2$	868-85-9	3.75 (CH_3)	11.5 (POCH)	$(CH_3)_3COH$
		6.75 (PH)	698 (PH)	
$CH_3(O)P(OCH_3)_2$	756-79-6	3.66 (OCH_3)	11.0 (POCH)	Neat
		1.44 (PCH_3)	17.0 (PCH)	
$[P(CH_2OH)_4]Cl$	16980-25-9	4.73 (CH_2)	2.0 (PCH)	D_2O

[a] δ ^{1}H and *J* values are in parts per million with respect to TMS and in hertz, respectively. [b] See ref 2. [c] ^{29}Si chemical shifts and couplings will be reported later. [d] The data are for a $(CH_3)_3COH$ solution saturated with $P(CH_2OH)_3$. The OH proton absorption is broadened compared with that in the pure solvent.

methyl proton area of MeOH would grow at twice the rate that either member of the $P(OMe)_3$ proton doublet is decreasing. Using $P(CH_2OH)_3$ prepared by Graysons method,[11] however, it was found that 80% of the $P(OMe)_3$ disappeared after 1 hr while the $P(CH_2OH)_3$ concentration decreased only about 10%. Three new peaks appeared at the expense of the $P(OMe)_3$ protons: a singlet (δ 3.31) due to methanol (OCH_3) and an OCH_3 doublet (δ 3.75, J = 11.5 Hz) shown to arise from $H(O)P(OMe)_2$ by addition of an authentic sample. The intensity ratio (1:2) of the methanol peak to that of the new doublet showed that only 1 mol of methanol was formed from each mole of reacting $P(OMe)_3$. At this point it was suspected that substantial water contamination of the $P(CH_2OH)_3$ stemming from its mode of preparation was hydrolyzing the $P(OMe)_3$ and that $H(O)P(OMe)_2$ was the source of the new doublet.

Although the liquid $P(CH_2OH)_3$ was subjected to prolonged evacuation in an effort to remove water, the strong hydrogen bonding undoubedtly present in $P(CH_2OH)_3$–H_2O solutions retains the H_2O in most cases. It is to be noted, however, that $P(CH_2O)_3P$ obviously has been obtained[2] in poor to moderate yield from $P(CH_2OH)_3$ prepared according to Grayson's method,[11] although the vast majority of attempts since have ended in failure. These successes may indicate that sufficient water can be removed in some instances such as in the case of rotary evacuation where a large and changing surface of water-containing material is exposed to the vacuum.

The most straightforward solution to this problem was to prevent the formation of water by the preparation of $P(CH_2OH)_3$ according to the equation

$$[P(CH_2OH)_4]Cl + NaOCH_3 \longrightarrow P(CH_2OH)_3 + NaCl + CH_2O + CH_3OH$$

The reaction of $P(OMe)_3$ with dry $P(CH_2OH)_3$ was performed under the same conditions as the reactions just described in which hydrolysis was noted. The absence of water was confirmed by the complete lack of dimethyl phosphite in spectra of the reaction mixture. It was found, however, that anhydrous conditions were not a sufficient condition for formation of $P(CH_2O)_3P$. In a typical experiment, a violent, exothermic reaction yielding a viscous oil would occur upon mixing the two reactants neat. The gas in the reaction spontaneously inflamed in air indicating the presence of phosphines. Since completely aliphatic triols under the same conditions undergo facile transesterification with $P(OMe)_3$ to give bicyclic phosphite esters, it was of interest to determine the cause of the uncontrollable exothermic reaction. New features in the ^{1}H nmr spectra of the viscous product of the reaction included a doublet (J = 17 Hz) at 1.44 ppm and a doublet (J = 11 Hz) of twice the intensity at 3.66 ppm. Moreover, the $P(OMe)_3$ doublet was absent while the $P(CH_2OH)_3$ methylene proton absorption remained relatively unchanged. These doublets were found to be superimposable with a spectrum of a pure sample of $Me(O)P(OMe)_2$, and it is quite reasonable that in the exothermic reaction sufficiently high temperatures were reached (210°)[13] to isomerize $P(OMe)_3$ thermally to $Me(O)P(OMe)_2$.[14] It was also suspected that perhaps unneutralized $[P(CH_2OH)_4]Cl$ might catalyze this reaction since small amounts of unreacted phosphonium salt were detected in the nmr spectrum of the reaction mixture even when the mole ratio of NaOMe to salt was 1.05. Indeed a 1:1 mol ratio of $[P(CH_2OH)_4]Cl$ and $P(OMe)_3$ in methanol produced an exothermic reaction in which all of the phosphite reacted. About 40% of the phosphite is converted to $Me(O)P(OMe)_2$ as shown by the nmr spectrum.

Apparently there are two likely ways in which this isomerization reaction can arise. It is possible that the $[P(CH_2OH)_4]^+$ cation is directly responsible, since it has been observed that $P(OMe)_3$ behaves similarly in the presence of $[MeP(OMe)_3]BPh_4$.[13] Although the

(13) L. V. Nesterov and A. Ya. Kessel, *Zh. Obsch. Khim.*, **37**, 1171 (1967); *Chem. Abstr.*, **67**, 54215a (1967).

(14) J. R. Van Wazer, "Phosphorus and its Compounds," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1958.

mechanism of this reaction is unknown, the phosphonium salt may provide a nucleophilic site for phosphite attack *via* a phosphorus or an oxygen lone pair. The nucleophilic site in the phosphonium salt could be the phosphorus or a released methylene proton. House[15] notes that the Ph_3P^+ substituent will enhance the acidity of an adjacent methylene hydrogen to a greater extent than a carbonyl function. The $[P(OMe)_3]^+$ moiety may have a similar effect on the methyl protons in the $[MeP(OMe)_3]^+$ cation. Similar arguments might apply to the $[P(CH_2OH)_3]^+$ group and its effect on the methylene protons in the remaining CH_2OH moiety. Although protons do effectively bring about the isomerization of $P(OMe)_3$,[16] a more likely source of these species in the present reaction stems from the dissociation of $[P(CH_2OH)_4]Cl$ to $P(CH_2OH)_3$, CH_2O, and HCl.[17] In any case, a large excess of neutralizing base is to be avoided in the preparation of $P(CH_2O)_3P$, however, inasmuch as $P(CH_2OH)_3$ is destroyed under these conditions.[17] The presence of excess phosphonium salt in the reactions carried out with $P(CH_2OH)_3$ prepared by Grayson's method[11] could also account for the extensive hydrolysis of $P(OMe)_3$ since this reaction is known[18] to be acid catalyzed.

In sharp contrast to the difficulties encountered in the reaction of $P(OMe)_3$ with anhydrous $P(CH_2OH)_3$, the formation $P(CH_2O)_3As$ took place rapidly at room temperature and in high yield. Trimethyl arsenite hydrolyzes more readily than $P(OMe)_3$ to give solid As_2O_3 and MeOH; so the preparation of anhydrous triol is essential. The difference in the two reactions undoubtedly lies in the tendency for $P(OMe)_3$ to isomerize to $Me(O)P(OMe)_2$ and the absence of this property in $As(OR)_3$ compounds. The greater strength of the O=P link compared with the O=As bond is very likely responsible as the driving force for the $P(OMe)_3$ isomerization. Supporting chemical evidence for this reasoning is found in the ease of peroxide oxidation of $P(CH_2O)_3As$ to $OP(CH_2O)_3As$. The formulation of the latter compound as shown was deduced from the presence of an infrared band at 1195 cm^{-1} assigned to $\nu_{P=O}$ which was absent in the reduced form and which appeared at 1200 cm^{-1} in $OP(CH_2O)_3CCH_3$.[19]

Group dipole moments in polycyclic molecules are quite additive owing to the rigidity and symmetry of the molecules.[20] It is therefore possible to compare the experimental moments of $P(CH_2O)_3As$ (1.58 D) and $P(CH_2O)_3P$ (3.10 D)[21] with those obtained by considering the appropriate vectorial sums of the $P(CH_2)_3$, O_3As, and O_3P group contributions. The $P(CH_2)_3$ contribution is taken as 1.19 D, the dipole moment of $P(CH_3)_3$,[22] while the O_3PAs and O_3P moments of 2.68[23] and 4.13 D,[21] respectively, are the dipole moments of the $CH_3C(CH_2O)_3As$ and $CH_3(CH_2O)_3P$ molecules.[24] Taking appropriate differences (inasmuch as the two group contributions are opposed along the C_3 axis of the cages), values of 1.49 and 2.94 D are calculated for $P(CH_2O)_3As$ and $P(OCH_2)_3P$, respectively. The reasonable agreement with the experimental values further substantiates the indicated structures of these polycycles.

Polycyclic systems of the type $P(CH_2O)_3CCH_3$[19,25] and $CH_3C(OCH_2)_3CCH_3$[25] have been studied previously, and it is therefore not surprising that the silicon analogs $P(CH_2O)_3SiCH_3$ and $CH_3Si(OCH_2)_3CCH_3$ could be synthesized. The relative ease of formation of $P(CH_2O)_3SiCH_3$, however, again attests to the normal behavior of $P(CH_2OH)_3$ toward transesterification except with $P(OMe)_3$.

Registry No.—$CH_3Si(OCH_2)_3CCH_3$, 24647-57-2.

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(15) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965.

(16) The adverse effect of protons in some triester formations is seen when MeOH is treated with PCl_3 in a 3:1 mol ratio in CH_2Cl_2. Only $H(O)P(OMe)_2$ and MeCl in 1:1 mol ratio was produced as shown by ^1H nmr spectroscopy. It is well known in fact (ref 14) that $P(OMe)_3$ in the presence of gaseous HCl gives excellent yields of these products. In the presence of 3 mol of pyridine, however, 3MeOH + 1PCl_3 gives only $P(OMe)_3$ as shown from the ^1H nmr spectrum.

(17) A. Hoffman, *J. Amer. Chem. Soc.*, **43**, 1684 (1921).

(18) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley & Sons, Inc., New York, N. Y., 1950.

(19) E. J. Boros, R. D. Compton, and J. G. Verkade, *Inorg. Chem.*, **7**, 165 (1968).

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Prostaglandins. III.[1] Synthesis of Methyl Esters of 15-Dehydro-PGB$_1$, 15-Dehydro-PGE 237, and DL-PGE 237

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The stereochemistry of bicyclo[2.2.1]hept-5-ene-3-*n*-hexanoyl-2-carboxylic acid (**1**) was elucidated and the chloro ketone (**12**) was prepared. The methyl ester of 15-dehydro-PGB$_1$ (**23**) was synthesized in 10% overall yield from the chloro ketone (**12**) as described in Scheme I. Also presented are the unequivocal proof of structure **23** and evidence for the erroneous structural assignment to the free acid of **23** in the literature. Compound **23** was converted into the methyl esters of 15-dehydro-PGE 237 (**25**) and racemic PGE 237 (**26**).

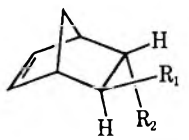
Methyl bicyclo[2.2.1]hept-5-ene-3-*n*-hexanoyl-2-carboxylate and the corresponding free acid have been described in the literature,[2] although the stereochemistry remained unknown. The free acid, prepared easily from the readily available 5-norbornene-2,3-*endo*-dicarboxylic anhydride, seemed to be a good starting material for the chloro ketone (**12**), the key intermediate for the synthesis of the prostaglandins.[3]

The objectives of this work were to elucidate the stereochemistry of these bicycloheptenes and to convert them into the properly functionalized prostanoic acid[3a] derivatives.

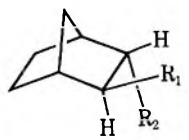
Fraser[4] described a method for determining the configuration of 2- and 3-substituted bicyclo[2.2.1]hept-5-enes. Upon hydrogenation of the double bond, the 2- or 3-*exo* hydrogen exhibited an upfield shift, whereas the *endo*-hydrogen resonance exhibited a downfield shift. This behavior was attributed to the magnetic anisotropy of the double bond. It is also known[4,5] that the 2- and 3-*endo* hydrogens of bicyclo[2.2.1]hept-5-enes are generally found 0.47–0.67 ppm upfield from the *exo*-proton resonances. To simplify our presentation we have used the correct configurations throughout the following discussion.

Bicyclo[2.2.1]hept-5-ene-3-*n*-hexanoyl-2-carboxylic acid (**1**) prepared by Walton's procedure,[2] was hydrogenated to **8** and subsequently both **1** and **8** were esterified to give **3** and **9**, respectively. The pmr data (summarized in Table I) indicated that **1** and **3** must have one *exo* and one *endo* hydrogen at C-2 and C-3; that is **1** and **3** must be the *trans* isomers. However, the pmr data presented in Table I fit equally well for the alternative *trans* configuration (**2** for the acid, **4** for the ester). To determine which *trans* structure is correct, the corresponding hydroxy acid (**5**), prepared by borohydride reduction of **1**, was esterified with diazomethane to give **6**. The pmr spectra (see Table I) of **6** and the hydrogenation product (**10**) were compatible only with **6** and **10**, but not with the alternative *trans* structures.

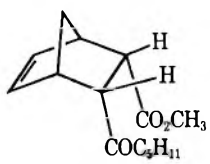
The methyl ester **7**, from which **1** was prepared[2] by saponification, was different from the methyl ester **3** prepared from **1** with diazomethane. Taking into account the method of preparation, **7** must be the *cis*,-



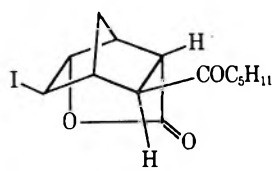
1, $R_1 = COC_5H_{11}$; $R_2 = CO_2H$
2, $R_1 = CO_2H$; $R_2 = COC_5H_{11}$
3, $R_1 = COC_5H_{11}$; $R_2 = CO_2CH_3$
4, $R_1 = CO_2CH_3$; $R_2 = COC_5H_{11}$
5, $R_1 = CHOHC_5H_{11}$; $R_2 = CO_2H$
6, $R_1 = CHOHC_5H_{11}$; $R_2 = CO_2CH_3$



8, $R_1 = COC_5H_{11}$; $R_2 = CO_2H$
9, $R_1 = COC_5H_{11}$; $R_2 = CO_2CH_3$
10, $R_1 = CHOHC_5H_{11}$; $R_2 = CO_2CH_3$



7



11

TABLE I
NMR SIGNALS[c] OF C-2 AND C-3 HYDROGENS

	2-*exo* H chemical shift[b] (multiplicity, *J* in Hz)	3-*endo* H chemical shift[b] (multiplicity, *J* in Hz)
1	6.62 (t, 4.5)	7.22 (d, 4.5)
↓ H_2		
8	6.62 (t, 4.5)	7.15[c] (d, 5.5)
3	6.62 (t, 4.5)	7.22 (d, 4.5)
↓ H_2		
9	6.72[d] (t, 4.5)	7.12[c] (d, 5)
6	7.46 (t, 4)	In envelope region
↓ H_2		
10	7.60[a] (t, 4)	In envelope region

[a] Reference 16a. [b] Given in τ. [c] A typical downfield shift for *endo* H. [d] A typical upfield shift for *exo* H.

(1) For a preliminary communication of some of these results, see M. Miyano, *Tetrahedron Lett.*, 2771 (1969).

(2) H. M. Walton, *J. Org. Chem.*, **22**, 308 (1957).

(3) (a) P. W. Ramwell, J. E. Shaw, G. B. Clarke, M. F. Grostic, D. G. Kaiser, and J. E. Pike, *Progr. Chem. Fats Other Lipids*, **9** (2), 231 (1968); (b) S. Bergström, *Science*, **157**, 382 (1967); (c) S. Bergström, L. A. Carlson, and J. R. Weeks, *Pharmacol. Rev.*, **20**, 1 (1968); (d) S. Bergström and B. Samuelsson, Editors, Nobel Symposium, 2, Prostaglandins, Almqvist and Wiksell, Stockholm, and Interscience Publishers, Inc., New York, N. Y., 1967; (e) U. S. von Euler and E. Eliasson, "Medicinal Chemistry Monographs," Vol. 8, Academic Press Inc., New York, N. Y., 1967; (f) V. R. Pickles, *Nature*, **224**, 221 (1969).

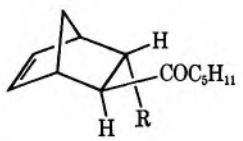
(4) R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).

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

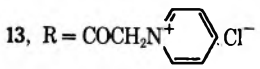
endo isomer. It was not possible to confirm the expected upfield shifting of the *exo* hydrogen of **7** upon hydrogenation of the double bond, because isomerization to a *trans* isomer took place during the hydrogenation (see Experimental Section).

Chemical evidence supported the pmr data; that is the keto acid **1** was converted into the iodo lactone **11** by the well-known iodolactonization procedure.[6]

It was reported[2] that the pyrolysis of **7** (without regard to stereochemistry) gave methyl 4-oxo-2-nonenoate (**18**, without statement of the geometry), mp 48.5°, in about 75% yield. A reverse Diels–Alder

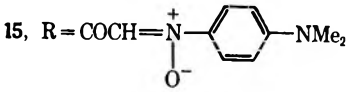


12, R = $COCH_2Cl$

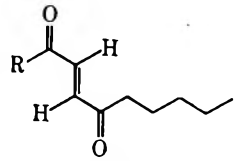


13, R = $COCH_2N^+$ Cl^-

14, R = $COCH_2OAc$



15, R = $COCH{=}N^+(O^-)$–NMe_2



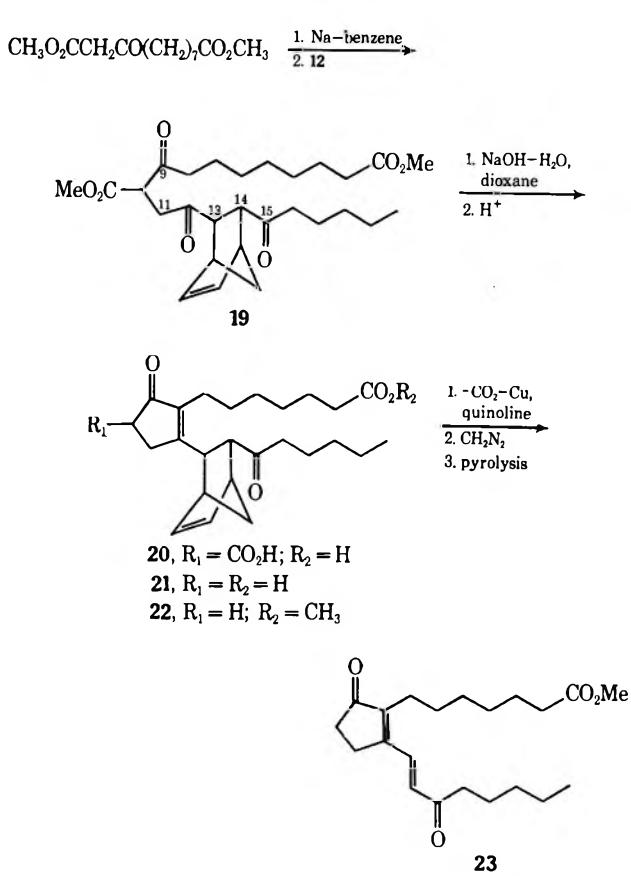
16, R = CH_2Cl
17, R = CH_2OAc
18, R = OCH_3

mechanism suggests that the nonenoate is probably *cis* if the starting material is *endo,cis*. Repetition of Walton's procedure[2] gave only one crystalline product, mp 49°, in only 19.7% yield. The pmr spectrum (typical AB-type olefinic protons, J = 16 Hz) demonstrated, however, that this was the *trans* olefin. The noncrystalline portion was found to be the *cis* olefin (major component, J = 12 Hz) contaminated by the *trans* olefin, suggesting that the *cis* alkene, the primary pyrolysis product, was partially isomerized to the more stable geometric isomer.

Bicyclo[2.2.1]hept-5-ene-3-*exo*-*n*-hexanoyl-2-*endo*-carboxylic acid (**1**) was converted into the chloro ketone (**12**) by successive treatment with oxalyl chloride, excess diazomethane, and finally with hydrogen chloride. The chloro ketone (**12**) was a poorly characterized, low melting compound slightly contaminated by **16** (see Experimental Section). However, crude **12** gave good yields of pyridinium chloride (**13**, further characterized as the crystalline nitrone **15**) and the acetoxy ketone (**14**). The latter was pyrolyzed to the *trans*-enedione (**17**) *via* a reverse Diels–Alder mechanism.

The chloro ketone (**12**) was condensed with the sodium derivative of dimethyl 3-oxoundecane-1,11-dioate[7] to afford the triketo diester (**19**) which was cyclized to the diketo diacid (**20**) (Scheme I). It must be emphasized that the cyclopentenyl-protecting group possesses many unique advantages. The bicyclo system makes only one mode of condensation (**19** → **20**) possible, although **19** contains three ketonic groups and several active methylenes or methines in the same molecule. More specifically, the rigid system in **19** holds the C-13-*endo* and C-14-*exo* substituents far enough apart to eliminate certain undesirable condensations (for example, between C-11 and C-15). The bicyclo

SCHEME I



system makes the C-13 and C-14 carbons tertiary ones, thus preventing undesirable condensations, for example, between C-9 and C-14 (no dehydration can take place). The keto acid **20** was decarboxylated smoothly in quinoline to **21**, which was then esterified with diazomethane to **22**, and the ester was finally pyrolyzed to afford methyl 9,15-dioxoprosta-8(12),13-*trans*-dienoate (**23**, 15-dehydro-PGB_1 methyl ester) in 10–15% overall yield from crude **12**. The geometry of the 13,14 double bond in **23** can be predicted to be *trans* provided that the C-13 and C-14 substituents in **22** are *trans*. The structure of **23** was well supported by the spectral data. The expected uv maximum[8] was 202 (five-membered enone) + 30 (γ,δ double bond) + 10 (α substituent) + 12 (β substituent) + 18 (δ substituent) + x. Since the increment (x) of the fully transoid ketone[9] is about 26, the expected value for **23** should be about 298 mμ. The actual uv (methanol) of 296 mμ (ϵ 22,800) was in good agreement with the calculated value. In addition, the two olefinic protons formed a typical AB pattern (J = 15.5 Hz, suggesting *trans*) and **23** was further characterized as the crystalline dioxime (**24**).

The free acid of structure **23** was incorrectly assigned to another compound by Änggård and Samuelsson.[10] The Swedish workers treated **27** [uv in ethanol 230 mμ (ϵ 8450)] with 0.5 *N* sodium hydroxide in 50% ethanol and observed the shift of the uv absorption to a longer wavelength (280 mμ, no extinction coefficient or any

(6) E. E. van Tamelen and M. Shamma, *J. Amer. Chem. Soc.*, **76**, 2315 (1954).

(7) K. E. Arosenius, G. Ställberg, E. Stenhagen and B. Tägtström-Eketorp, *Ark. Kemi, Mineral., Geol.*, **26A**, No. 19, 20 (1948).

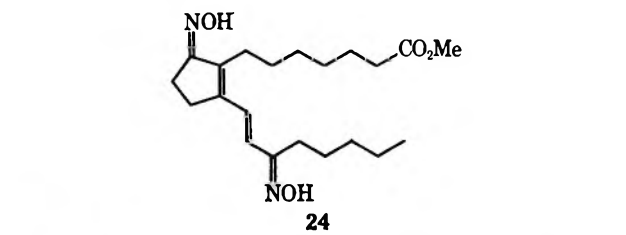
(8) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," a Pergamon Press Book, The Macmillan Co., New York, N. Y., 1964, pp 58, 61, and 69.

(9) Taking into account the dipole repulsion between C-9 and C-15 carbonyl groups, the full transoid conformation (**23**) is a good one.

(10) (a) E. Änggård and B. Samuelsson, *J. Biol. Chem.*, **239**, 4097 (1964); (b) B. Samuelsson, *Angew. Chem.*, **77**, 445 (1965).

other physical data were given). They stated that the shift was probably due to the formation of **23** (the free acid instead of methyl ester). However, the uv maximum is different from **23** (uv in methanol 296 mμ) and it seems unlikely to ascribe the shift of 16 mμ to the difference of the free carboxylic acid and its ester, because the carboxyl function is far removed from the chromophore. Saponification of **23** with methanolic alkali at room temperature resulted in total destruction of the chromophore demonstrating that **23** is very unstable to alkali while Samuelsson's compound was supposedly formed by an alkaline treatment. More careful saponification of **23** with 0.1 *N* methanolic sodium hydroxide at room temperature indicated that the disappearance of the chromophore was about 3 to 10 times as fast as saponification of the ester group. The half-life of the chromophore in 0.1 *M* potassium carbonate solution in 50% aqueous dioxane at 25° was 8 hr. We next tried pyrolysis of **21** in an attempt to prepare the free acid directly. The pyrolysis product, which was not purified completely, showed a uv maximum at 296–297 mμ (not at 280 mμ), and could be converted to **23** by treatment with diazomethane.

Additional chemical and spectral evidence supporting structure **23** are presented below. The formation of **25** by zinc reduction is excellent evidence that the two



double bonds in **23** are located between two carbonyl groups.[11] The structure **25** was substantiated by the spectral evidence. The uv (methanol) of 238 mμ (ε 13,400) was in agreement with the calculated value (236 mμ)[8] and the extinction coefficient was also in accordance with the known examples.[12] The pmr spectrum showed no olefinic proton, but a "sharp" singlet at τ 7.32 representing the four protons of C-13 and C-14 which happen to exhibit equal chemical shifts. Catalytic hydrogenation of **23**, on the other hand, gave rise to two products **25** and **26** in almost equal amount. The spectral data of the more polar substance (**26**) were in good agreement with authentic[13] optically active PGE 237 as summarized in Table II.

An additional proof of structure **23** was obtained later by comparison of the spectral data with **28** and **29** (prepared by another totally independent synthesis[14]) as summarized in Table III.

(11) See among others (a) P. Karrer and C. H. Eugster, *Helv. Chim. Acta*, **32**, 1934 (1949); (b) D. H. R. Barton, *J. Chem. Soc.*, 3830 (1963).

(12) B. Samuelsson and G. Ställberg, *Acta Chem. Scand.*, **17**, 810 (1963).

(13) S. Bergström, R. Ryhage, B. Samuelsson, and J. Sjövall, *J. Biol. Chem.*, **238**, 3555 (1963).

(14) To be published elsewhere.

TABLE II

UV AND IR SPECTRA OF AUTHENTIC AND SYNTHETIC **26**

PGE 237[a]	PGE 237 methyl ester[a]	Synthetic **26**
237 mμ (ε 14,200)[b]	5.75 μ	237.5 mμ (ε 15,600)[c]
	5.90 μ	5.76 μ (ester)
	6.11 μ	5.90 μ (ketone)
		6.105 μ (olefin)

[a] Reference 13. [b] In ethanol. [c] In methanol.

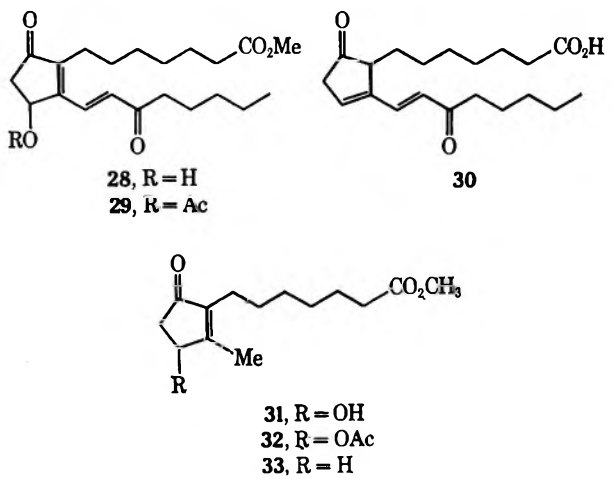
TABLE III

UV (IN METHANOL) AND NMR SPECTRA[a] OF **23**, **28** AND **29**

	Uv, mμ (ε)	C-11 H	C-13 H	C-14	$J_{13,14}$, Hz
23	296 (22,800)	None	2.22[b]	3.32[c]	15.5
		downfield	2.48	3.58	
28	291.5[d] (24,600)	4.84[f]	2.30[b]	2.92[c]	16.0
			2.56	3.19	
29	288[g] (27,200)	3.94[f]	2.35[b]	3.35[c]	16.0
			2.62	3.62	

[a] Reference 16a. [b] A little broadened doublet owing to coupling either with the C-11 or more likely with the C-7 H. [c] Doublet. [d] A hypsochromic shift of about 4–5 mμ by the 11-OH is expected.[e] [e] For example, uv values (methanol) for **31** and **32** are 231.5 mμ (ε 12,000) and 229.5 mμ (ε 13,900), respectively, while the calculated value[8] for **33** is 236 mμ. For the preparation of **31** and **32** see Experimental Section. [f] A doublet of multiplets. [g] A hypsochromic shift of about 6–7 mμ by the 11-OAc is expected.[e]

After this work had been completed, the methyl ester of **30** was synthesized by another group of investigators[15] and the identity of **30** with Samuelsson's compound was suggested.



Experimental Section[16]

Methyl Bicyclo[2.2.1]hept-5-ene-3-*endo*-*n*-hexanoyl-2-*endo*-carboxylate (7).—This material was prepared by a known procedure[2] and the stereochemistry was determined by the pmr spectral evidence as well as the chemical transformations (see text).

Bicyclo[2.2.1]hept-5-ene-3-*exo*-*n*-hexanoyl-2-*endo*-carboxylic Acid (1).—This material was prepared by Walton's procedure[2] and recrystallized from hexane and the stereochemistry was elucidated by means of the pmr spectrum and the chemical evi-

(15) R. B. Morin, D. O. Spry, K. L. Hauser, and R. A. Mueller, *Tetrahedron Lett.*, 6023 (1968).

(16) (a) All pmr spectra were determined in deuteriochloroform on Varian A-60 using tetramethylsilane as an internal reference. (b) Melting points given in the Experimental Section represent the highest value obtained after successive recrystallizations unless otherwise stated and were obtained on Thomas–Hoover apparatus (uncorrected).

dence (see text): mp 90.5–92° (lit.[2] 85°); nmr ($CDCl_3$) τ 6.54 (t, J = 4.5 Hz, C-2-*exo* H), 7.22 (d, J = 4–4.5 Hz, C-3-*endo* H), 6.72 and 6.98 (bridgeheads).

Bicyclo[2.2.1]heptane-3-*exo*-*n*-hexanoyl-2-*endo*-carboxylic Acid (8).—The unsaturated acid 1 was hydrogenated in the presence of palladium on carbon in ethanol. The distilled product, bp 148° (0.08 mm), crystallized spontaneously: mp 53.5–55°; nmr ($CDCl_3$) τ 6.62 (t, J = 5 Hz, C-2-*exo* H), 7.15 (d, J = 5.5 Hz, C-3-*endo* H). *Anal.* Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.30; H, 9.33.

Methyl Bicyclo[2.2.1]hept-5-ene-3-*exo*-*n*-hexanoyl-2-*endo*-carboxylate (3).—The free acid 1 was esterified with diazomethane in the usual manner (94.5%): bp 108° (0.3 mm); nmr ($CDCl_3$) τ 6.62 (t, J = 4.5 Hz, C-2-*exo* H), 7.22 (d, J = 4.5 Hz, C-3-*endo* H), 6.75 and 7.02 (s, bridgeheads). *Anal.* Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.68; H, 8.76.

Methyl Bicyclo[2.2.1]heptane-3-*exo*-*n*-hexanoyl-2-*endo*-carboxylate (9).—The free acid 8 was esterified with diazomethane in the usual manner: bp 110° (0.3 mm); nmr ($CDCl_3$) τ 6.72 (t, J = 4.5 Hz, C-2-*exo* H), 7.12 (d, J = 5 Hz, C-3-*endo* H). *Anal.* Calcd or $C_{15}H_{24}O_3$: C, 71.39; H, 9.95. Found: C, 71.48; H, 9.33.

Attempted Synthesis of Methyl Bicyclo[2.2.1]heptane-3-*endo*-*n*-hexanoyl-2-*endo*-carboxylate.—The unsaturated ester 7 was hydrogenated in ethanol in the presence of 5% palladium on carbon (4 hr at room temperature). The product, bp 124° (0.4 mm), was found to have partially isomerized during the hydrogenation to 3-*exo*-*n*-hexanoyl compound 9. Judging from the height of the methoxy signals (3-*exo* at τ 6.31, 3-*endo* at 6.37), the *exo*/*endo* ratio was about 3/4.

Bicyclo[2.2.1]hept-5-ene-3-*exo*-(1-hydroxy-*n*-hexyl)-2-*endo*-carboxylic Acid (5).—The keto acid 1 was suspended in 150 ml of 33% methanol and neutralized with sodium hydroxide. To the clear solution was added 3 g of sodium borohydride, and the mixture was kept in a refrigerator overnight and then at room temperature for 6 hr, acidified with hydrochloric acid, filled with water to 400 ml, and again refrigerated overnight. The crystals were collected, dried, and recrystallized first from benzene and then from ethyl acetate, mp 164–165°. *Anal.* Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.60; H, 9.24.

Methyl Bicyclo[2.2.1]hept-5-ene-3-*exo*-(1-hydroxy-*n*-hexyl)-2-*endo*-carboxylate (6).—The free acid 5, dissolved in a minimum amount of ethyl acetate, was esterified with ethereal diazomethane and distilled: bp 131° (0.3 mm); nmr ($CDCl_3$) τ 7.46 (t, J = 4 Hz, C-2-*exo* H), 6.86 and 6.99 (2, bridgeheads), 6.57 (C-1′ H). *Anal.* Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.44; H, 9.53.

Methyl Bicyclo[2.2.1]heptane-3-*exo*-(1-hydroxy-*n*-hexyl)-2-*endo*-carboxylate (10).—The unsaturated hydroxy ester 6 was hydrogenated in ethanol in the presence of 5% palladium on charcoal and the product was recrystallized from cyclohexane–pentane: mp 62–63°; nmr ($CDCl_3$) τ 7.60 (t, J = 4 Hz, C-2-*exo* H overlapped with others), 6.70 (C-1′ H). *Anal.* Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 71.08; H, 10.22.

Bicyclo[2.2.1]heptane-3-*exo*-*n*-hexanoyl-5-*exo*-iodo-6-*endo*-hydroxy-2-*endo*-carboxylic Acid Lactone (11).—To a solution of 23.6 g (0.1 mol) of 1 in 200 ml (0.2 mol) of 10% potassium bicarbonate solution was added dropwise under ice cooling potassium iodide–iodine solution, which had been prepared from 63.5 g (0.4 g-atom) of iodine, 166 g (1.0 mol) of potassium iodide, and 500 ml of water. Soon the oily iodo lactone started to separate. About 100 ml of ether was added to the reaction mixture. After 180 ml of the iodine solution had been consumed, decoloration of the iodine on addition of the reagent slowed remarkably. More ether was added and the organic layer was washed successively with water, with thiosulfate solution, and again with water, dried over sodium sulfate, concentrated, and dried at 60° (0.1 mm): 35.6 g (0.98 mol, 98%); ir ($CHCl_3$) 5.58 (lactone), 5.81 μ (ketone); nmr ($CDCl_3$) τ 4.86 (d, of m, J = 4.5 and 1.0 Hz, C-6-*exo* H), 6.05 (d, J = 2.5 Hz, C-5-*endo* H). *Anal.* Calcd for $C_{14}H_{19}IO_3$: C, 46.42; H, 5.29; I, 35.04. Found: C, 46.66; H, 5.35; I, 35.29.

Methyl 4-Oxo-2-nonenoate (18).—Compound 18 was prepared by Walton's procedure:[2] mp 49° (lit.[2] 48.5°); yield 19.7%; nmr ($CDCl_3$) τ 2.88 (d, 1, J = 16 Hz), 3.37 (d, 1, J = 16 Hz). The noncrystalline portion of the pyrolysis product was a mixture of two compounds. One (about 45% deduced from the methoxy signal at τ 6.18) was the *trans*-nonenoate (18) and the other (about 55%, the methoxy at 6.25) was the *cis*-nonenoate as shown by the AB-type olefinic protons at τ 3.49 (d, J = 12 Hz) and 4.00 (d, J = 12 Hz).

2-*endo*-Chloroacetyl-3-*exo*-*n*-hexanoylbicyclo[2.2.1]hept-5-ene (12).—To a solution of 27 g (0.114 mol) of 1 in 100 ml of benzene was added 30 g (0.236 mol) of oxalyl chloride. The mixture was refluxed for 10 min, concentrated, dissolved in benzene, and added gradually to 1 l. of cold ethereal diazomethane, prepared from 28 g (0.30 mol) of nitrosomethylurea and dried over potassium hydroxide. After 2 hr, the reaction mixture was treated with dry hydrogen chloride gas, set aside for 1.5 hr, and then washed twice with water, with bicarbonate solution, and with water, dried over sodium sulfate, and distilled giving 22.8 g of crude 12: bp 146–147° (0.2 mm); ir ($CHCl_3$) 5.76 ($COCH_2Cl$), 5.83 (ketone); nmr ($CDCl_3$) τ 5.84 (s, 2, $COCH_2Cl$), 6.29 (t, J = 4 Hz, C-2-*exo* H), 2.91 (s, impurity 16), 5.72 (s, impurity 16). *Anal.* Calcd for $C_{15}H_{21}O_2Cl$: C, 67.03; H, 7.82; Cl, 13.19. Found: C, 65.89; H, 7.73; Cl, 10.77.

Pyridinium Chloride (13).—The chloro ketone 12 prepared from 40 g (0.169 mol) of acid was dissolved in 100 ml of anhydrous pyridine. After 48 hr, the crystals were collected, washed with dioxane, and recrystallized from ethanol–dioxane giving 35.3 g (0.101 mol, 60%) of 13: mp 186°; nmr ($CDCl_3$) τ 6.11 (t, J = 4 Hz, C-2 *exo* H), 6.95 (C-3-*endo* H overlapped with a bridgehead), 6.35 (another bridgehead), 3.19 (s, $NCH_2C{=}O$). *Anal.* Calcd for $C_{20}H_{26}O_2NCl$: C, 69.05; H, 7.53; N, 4.03; Cl, 10.19. Found: C, 68.99; H, 7.60; N, 3.79; Cl, 10.33.

Nitrone 15.—To a solution of 24.6 g (70.8 mmol) of 13 in 50 ml of ethanol was added a solution of 10.6 g (70.7 mmol) of *p*-dimethylaminonitrosobenzene in 200 ml of ethanol. The stirred mixture was cooled in an ice bath and treated with 70 ml of 1 *N* sodium hydroxide solution. The greenish solution turned to deep red brown and crystals soon separated. The flask was stored in a refrigerator overnight. The crystals were collected, washed with cold aqueous ethanol, dried (15 g), and dissolved in acetone. Sodium chloride was removed by filtration and the filtrate was concentrated. Crystallization was accomplished by addition of aqueous ethanol: mp 125°; nmr ($CDCl_3$) τ 0.47 (s, N=CHCO), 7.10 (s, NMe). *Anal.* Calcd for $C_{23}H_{30}O_3N_2$: C, 72.22; H, 7.91; N, 7.32. Found: C, 72.29; H, 8.06; N, 7.49.

2-*endo*-Acetoxyacetyl-3-*exo*-*n*-hexanoylbicyclo[2.2.1]hept-5-ene (14).—A solution of 24.8 g (92 mmol) of 12 and 32 g (326 mmol) of potassium acetate in 240 ml of ethanol was refluxed for 1.5 hr, concentrated, diluted with water, and extracted with ether. The ether solution was washed with water, dried over sodium sulfate, concentrated, and distilled, giving 18.1 g (62 mmol, 67.3%) of oil: bp 158° (0.35 mm); nmr ($CDCl_3$) τ 3.75 (m, 1, olefinic), 4.00 (t, of d, 1, olefinic), 5.28 (broad s, 2, $AcOCH_2CO$), 6.68 and 7.0 (bridgeheads), 7.85 (s, 3, acetoxy); ir ($CHCl_3$) 5.70 ($-CO-CH_2OAc$), 5.76 (OAc), 5.83 μ (hexanoyl). *Anal.* Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.78; H, 8.28.

1-Acetoxy-2,5-dioxo-3-*trans*-decene (17).—Pyrolysis of 14 (12.0 g, 41.3 mmol) at a bath temperature of 230–240° under reduced pressure (12 mm) gave 7.0 g of distillate which was recrystallized from hexane giving 2.9 g (12.8 mmol, 31%) of pure substance: mp 79.5°; ir ($CHCl_3$) 5.69, 5.87–5.90 μ; uv (in methanol) 229.5 mμ (ϵ 12,600); nmr ($CDCl_3$) τ 3.04 (s, 2, olefinic), 5.11 (s, 2, $AcOCH_2CO$), 7.82 (s, 3, acetoxy), 7.35 (t, 2, J = 7 Hz, $BuCH_2CO$).

Methyl 9,15-Dioxoprosta-8(12),13-dienoate (23).—To 8 g (0.348 g-atom) of sodium sand in 400 ml of benzene was added 93 g (0.36 mol) of dimethyl 3-oxoundecane-1,11-dioate[7] in several portions. To the clear solution of the soldio derivative was added 48.7 g (0.181 mol) of the chloro ketone (12, about 75% pure) dissolved in 50 ml of benzene. The mixture was stirred at room temperature for 0.5 hr and refluxed for 3.5 hr. After cooling, the reaction mixture was treated with iced hydrochloric acid, washed with dilute sodium chloride solution, dried over sodium sulfate, and concentrated. The residue was dissolved in 3.8 l. of 50% aqueous dioxane containing 127 g of sodium hydroxide, stirred under nitrogen for 2 hr, set aside overnight, stirred at 65° for 3 hr, cooled, poured onto ice and 350 ml of concentrated hydrochloric acid, and extracted with ether and the ether extract was washed twice with sodium chloride solution, dried over sodium sulfate, and concentrated. The residue was dissolved in 500 ml of quinoline containing 0.8 g of copper powder, heated to 120–126° for 5 hr under nitrogen stream, cooled, poured into iced hydrochloric acid, and extracted with ether. The extract was washed with sodium chloride solution and esterified in the usual manner with excess diazomethane prepared from 100 g

of nitrosomethylurea. The solvent was removed *in vacuo* (15 mm) at 100° and the residue (126.4 g) was further concentrated at 200° (0.5–1.0 mm[17]). About 45 g of mobile liquid, bp 130° (0.5–1.0 mm), was distilled with decomposition (strong odor of cyclopentadiene). The residue (78.0 g) was pyrolyzed in eight portions as mentioned below. About one-fourth (22.8 g) of the total residue was further concentrated in a short-pass flask to remove 1.161 g of mobile liquid, bp 160° (0.05 mm), no uv maximum at ~296 mμ. The residue was divided into two equal portions, each one thus corresponding to about one-eighth of the total product. This material was transferred to a short-pass (3 cm) still equipped with a magnetic stirrer and distilled slowly with concomitant liberation of cyclopentadiene. The first batch gave 3.622 g of pale yellow distillate, bp 155–172° (0.03 mm), uv (in methanol) 296 mμ (ε 8050), purity about 35%, followed by 0.614 g of amber oil, bp 172–185° (0.04 mm), uv (in methanol) 296 mμ (ε 2900), purity about 13%), during 8 hr. The second batch gave 4.083 g of pale yellow oil, bp 160–175° (0.04 mm), uv (in methanol) 296.5 mμ (ε 7600), purity about 33%, followed by 0.953 g of brown distillate, bp 175–185° (0.04 mm), uv (in methanol) 295 mμ (ε 3000), purity about 13%. The pyrolysis product of the two batches amounted to 10.4 g which corresponded to 2.85 g of the pure material (15.4% of the calculated amount based upon the chloro ketone[18]). The whole pyrolysis product, amounting to 33.5 g, was purified by dry column chromatography using silica gel containing 8% water as adsorbent and benzene containing ethyl acetate (5:1, v/v) as a solvent. The desired material was recovered by elution with ethyl acetate containing methanol as a pale yellow oil (6.4 g, 18.4 mmol, or 10.1% of the calculated amount based upon **12**): uv (in methanol) 296 mμ (ε 22,800); nmr (see Table II). *Anal.* Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.20; H, 9.22.

Beside the pure material mentioned above, an additional 1.8 g of slightly impure product was recovered from the dry column chromatogram.

Methyl 9,15-Dioximinoprosta-8(12),13-*trans*-dienoate (24).—The hydroxylamine solution used in this experiment was prepared as follows: a solution of 16.4 g of sodium acetate and 6.95 g of hydroxylamine hydrochloride were diluted with 40 ml of methanol, set aside, and decanted from the precipitate (NaCl). A solution of 271 mg of **23**, 5 ml of the hydroxylamine solution, and 3 ml of ethanol was heated on a steam bath for 1 hr. Most of the solvent was removed and the residue was taken up in ether. The ethereal extract was washed with bicarbonate, dried over sodium sulfate, concentrated, and refrigerated overnight. The crystals were triturated with benzene, filtered, washed with benzene, and recrystallized from benzene giving 140 mg of **24**: mp 120.5°; uv (in methanol) 308 mμ (ε 38,400), 317 (38,300); nmr (warm $CDCl_3$) 2.99 (d, 1, J = 16 Hz), 3.63 (d, 1, J = 16 Hz), 6.34 (s, 3), 7.28 (broad s, 4, C-9 and C-10 protons). *Anal.* Calcd for $C_{21}H_{34}O_4N_2$: C, 66.63; H, 9.05; N, 7.40. Found: C, 66.60; H, 9.04; N, 7.39.

Methyl 9,15-Dioxoprost-8(12)-enoate (25).—A solution of 1.4 g of **23** in 50 ml of acetic acid was stirred with 2 g of zinc powder for 2 hr at room temperature. The reaction mixture was filtered to remove inorganic material, diluted with ether, washed twice with water, washed with bicarbonate solution, dried over potassium carbonate, concentrated, and purified by dry column chromatography on silica gel containing 8% water and 2% acetic acid as adsorbent and 20% ethyl acetate in benzene as solvent. The major fraction (894 mg, 59%, colorless oil) was **25**: ir ($CHCl_3$) 5.76–5.87 (carbonyls), 6.09 μ (C=C); uv (in methanol) 238 mμ (ε 13,400); nmr ($CDCl_3$) τ 7.32 (s, 4, C-13 and C-14 protons). *Anal.* Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.14; H, 9.66.

Methyl DL-15-Hydroxy-9-oxoprost-8(12)-enoate (26, PGE 237 Methyl Ester).—Compound **23** (417 mg) was hydrogenated in 50 ml of 95% ethanol in the presence of 0.1 g of 5% palladium on carbon and 32 ml of hydrogen was taken up in 15 min. The catalyst was removed and the filtrate was concentrated *in vacuo* giving 371 mg of residue which was separated into two components (**25** and **26**) by preparative tlc on silica gel using 25% ethyl acetate in benzene. The less polar product (75 mg) was **25** and the more polar product (83 mg) was identified as **26** based upon the spectral data: ir ($CHCl_3$); uv (in methanol), see Table I; nmr ($CDCl_3$) τ 6.32 (s, 3, OMe), 6.44 (m, 1, C-15 H). *Anal.* Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.40; H, 10.10.

Methyl 2-Methyl-3-hydroxy-5-oxo-1-cyclopentene-1-heptanoate (31).[19]—Dimethyl 3-oxoundecan-1,11-dioate[7] (76.4 g, 92% pure) was dissolved in 400 ml of cold 10% potassium hydroxide solution, refrigerated for 4 days, and neutralized to pH 8 with solid carbon dioxide. An aqueous solution (132 ml, pH was adjusted to 8 just before use) containing 0.296 mol of pyruvaldehyde was added and the mixture was set aside under nitrogen for 53 hr. The reaction mixture was washed with ether, acidified with hydrochloric acid, satuated with sodium chloride, and extracted with ether. The ethereal extract was washed twice with saturated salt solution, concentrated, dissolved in 560 ml of cold 5% sodium hydroxide solution, kept under nitrogen at room temperature for 4 hr, made acidic with 70 ml of concentrated hydrochloric acid, saturated with salt, and extracted with ether. The ethereal extract was washed with saturated salt solution, esterified with diazomethane in the usual manner, and distilled giving 35.9 g (52%) of the crude ester **31** (estimated to be 85–96% pure by gas chromatography), bp 180–205° (0.5 mm). The purification was carried out by redistillation, bp 175–185° (0.025 mm), or better by chromatography on silica gel using chloroform containing increasing amounts (up to 5%) of ethyl acetate: ir ($CHCl_3$) 2.72 (OH), 2.83 (broad, OH), 5.73 (ester), 5.82 (ketone), 6.02 (C=C); uv (in methanol) 231.5 mμ (ε 12,000); nmr ($CDCl_3$) τ 5.27 (broad d, J = 5.5 Hz, C-3 H), 6.33 (s, 3, OMe), 7.90 (s, CMe). *Anal.* Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.26; H, 8.90.

2-Methyl-3-hydroxy-5-oxo-1-cyclopentene-1-heptanoic Acid.—The methyl ester (**31**, 2.5 g) was saponified with 0.5 g of sodium hydroxide in 50 ml of 90% methanol at room temperature overnight. The reaction mixture was diluted with water, washed with ether, made acidic with hydrochloric acid, and extracted with ether, and the ethereal extract was washed twice with salt solution, dried over sodium sulfate, and concentrated (1.2 g): ir ($CHCl_3$) 5.82 (broad, carboxyl and ketone), 6.05 μ (C=C); uv (in methanol) 231.5 mμ (ε 11,700); nmr ($CDCl_3$) τ 5.27 (broad d, 1, J = 5.5 Hz), 7.91 (s, CMe). *Anal.* Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.04; H, 8.33.

Methyl 2-Methyl-3-acetoxy-1-cyclopentene-5-one-1-heptanoate (31).—The hydroxy ester (**31**, 16.1 g) was dissolved in 14 g of acetic anhydride and 30 g of pyridine and set aside for 2 days. The reaction mixture was decomposed with ice and taken up with ether. The ethereal extract was washed successively with dilute hydrochloric acid, water, and potassium carbonate solution, dried over sodium sulfate, and distilled giving 8.1 g of **32**: bp 157–159° (0.04 mm); ir ($CHCl_3$) 5.76 (broad, carbonyls), 6.02 (C=C); uv (MeOH) 229.5 mμ (ε 13,900); nmr ($CDCl_3$) τ 4.31 (broad d, J = 6 Hz, C-3 H), 6.41 (s, 3, OMe), 7.89 (s, 3, acetoxy), 7.99 (s, 3, CMe). *Anal.* Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.10. Found: C, 64.65; H, 8.10.

Registry No.—**3**, 24694-56-2; **5**, 24694-57-3; **6**, 24694-58-4; **8**, 24694-59-5; **9**, 24694-60-8; **10**, 24694-61-9; **11**, 24694-62-0; **12**, 24692-63-1; **13**, 24728-15-2; **14**, 24694-64-2; **15**, 24710-84-7; **17**, 24704-23-2; **23**, 24710-85-8; **24**, 24710-86-9; **25**, 24716-17-4; **26**, 20106-43-8; **28**, 24716-18-5; **29**, 24716-19-6; **31**, 24716-20-9; **32**, 24716-21-0; 2-methyl-3-hydroxy-5-oxo-1-cyclopentene-1-heptanoic acid, 24716-22-1.

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(17) All boiling points shown in this paragraph are bath temperatures.

(18) Taking into account the purity (75%) of the chloro ketone, this yield (15.4%) can be evaluated as 20.5%.

(19) Similar condensations of pyruvic aldehyde and various β-keto acids are very well known: M. S. Schechter, N. Green, and F. B. LaForge, *J. Amer. Chem. Soc.*, **71**, 3165 (1949).

Halo Sugar Nucleosides. I. Iodination of the Primary Hydroxyl Groups of Nucleosides with Methyltriphenoxyphosphonium Iodide[1]

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Reactions of the 5′-hydroxyl group of suitably substituted pyrimidine nucleosides with methyltriphenoxyphosphonium iodide (1) in DMF are very rapid and give the corresponding 5′-deoxy-5′-iodo nucleosides in high yield. Selective iodination of only the primary hydroxyl function in a series of unprotected pyrimidine nucleosides can also be achieved in a number of cases. Iodination of 2′,3′-O-isopropylideneuridine can also be accomplished in pyridine, but in the presence of N,N-diisopropylethylamine there is also formation of 2′,3′-O-isopropylidene-O²,5′-cyclouridine. The reaction of thymidine with an excess of 1 in pyridine gives 5′-deoxy-5′-iodo-O²,3′-cyclothymidine, which is an intermediate in the formation of 3′,5′-dideoxy-3′,5′-diiodothymidine *via* a similar reaction in DMF. In certain cases, the formation of phenyl methylphosphonate esters of secondary hydroxyl groups is also observed. The reactions of 2′,3′-O-isopropylidene derivatives of purine nucleosides, or of free adenosine, with 1 gives the corresponding N³,5′-cyclonucleosides in high yield and only in the case of 2′,3′-O-isopropylideneinosine was any 5′-deoxy-5′-iodo derivative isolated.

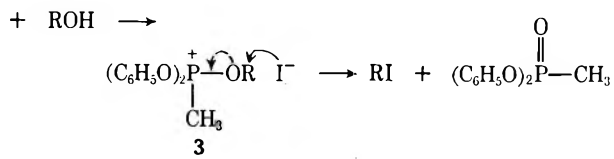
Halodeoxy sugars, and in particular the iodo compounds, have been widely used as intermediates in the synthesis of deoxy sugars, unsaturated sugars, amino sugars, etc.[2] Traditionally the conversion of the primary hydroxyl function of a sugar into the corresponding iodide has been accomplished in a two-step process *via* preliminary conversion into a suitable sulfonate ester[3] followed by heating with sodium iodide in a solvent such as acetone. In most cases, displacement of secondary tosylates in this way proves to be considerably more difficult although certain 4-tosylpyranosides have been found to react quite satisfactorily.[2] Iodo sugars have also been prepared *via* reaction of epoxides with Grignard reagents[4] or with salts[5] and by oxidation of hydrazine derivatives with iodine.[6]

In 1953 Rydon and his colleagues published the first of a significant series of papers on methods for the halogenation of alcohols using quasiphosphonium halides.[7] The major reagents developed were methyltriphenoxyphosphonium iodide (1) and iodotriphenoxyphosphonium iodide (2) which were prepared as crystalline

1 2

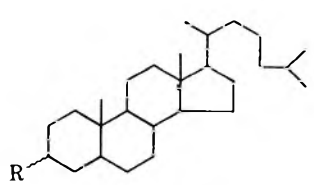
compounds through reaction of triphenyl phosphite with methyl iodide and with iodine respectively.[8] While 1 and 2 are depicted as ionic species, the contributions of pentacovalent forms, especially in nonpolar solvents should not be excluded.[8] Physical studies on the related triphenylphosphine dihalides have indicated that the extent of ionic behavior is a function of solvent polarity.[9]

The reaction of 1 with alcohols is assumed to proceed *via* nucleophilic attack on phosphorus with expulsion of phenol and formation of the alkoxyphosphonium salt 3 which then collapses to the alkyl iodide and diphenyl methylphosphonate.



3

Such a concerted mechanism requires that the conversion of an alcohol into the corresponding iodide should be accompanied by an inversion of configuration. Early work[7a,b] showed that reaction of optically active octan-2-ol with either 1 or 2 gave iodides with low optical rotations indicative of net inversion accompanied by extensive racemization. Since these experiments were done at elevated temperatures, racemization is not surprising in view of the well-known ease of nucleophilic attack by iodide ion upon alkyl iodides.[10] It has recently been shown that the iodination of cholestanol **4a** with triphenylphosphine diiodide does indeed proceed with inversion of configuration giving the axial 3α-iodo compound **4b**.[11] Subsequent treatment of **4b** with



4a, R = β-OH
b, R = α-I
c, R = β-I

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(8) See, *e.g.*, C. S. L. Baker, P. D. Landor, S. R. Landor, and A. N. Patel, *J. Chem. Soc.*, 4348 (6519).

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(10) (a) E. D. Hughes, F. Juliusburger, S. Masterman, B. Topley, and J. Weiss, *J. Chem. Soc.*, 1525 (1935); (b) C. L. Stevens, K. G. Taylor, and J. A. Valicenti, *J. Amer. Chem. Soc.*, **87**, 4579 (1965).

(11) A. V. Bayless and H. Zimmer, *Tetrahedron Lett.*, 3811 (1968).

sodium iodide in hot acetone led to epimerization of the iodo function giving the thermodynamically more stable equatorial 3β-iodo derivative **4c**. The same situation occurs during iodination of cholestanol with the Rydon reagent (**1**), crystalline 3α-iodocholestane being obtained in 57% yield. No evidence for the presence of the 3β-iodo isomer was found under the mild reaction conditions.

Other evidence for inversion of configuration during halogenation of alcohols with triphenylphosphine dihalides has been presented,[12] and isolation of the intermediate alkoxyphosphonium salts has been achieved.[12,13]

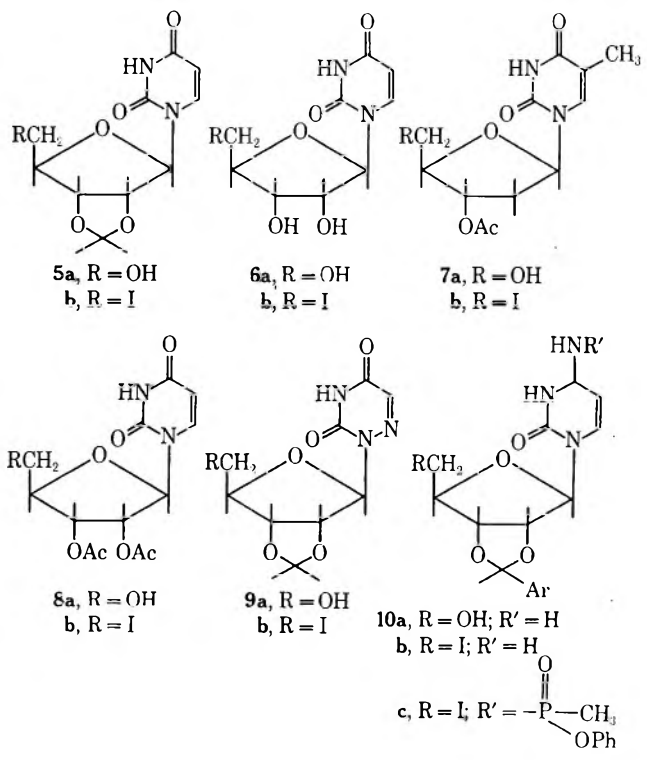
The first applications of the Rydon reagent (**1**) in the carbohydrate field were reported in 1960 by Kochetkov, *et al.*,[14] and by Lee and El Sawi.[15] The work of both groups has pointed out that caution must be used in interpreting the reactions of **1** with substituted sugars in boiling benzene. Thus, the reaction of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose with **1** did not give the expected 3-deoxy-3-iodo derivative as originally reported[15] but rather 6-deoxy-6-iodo-1,2:3,5-di-O-isopropylidene-α-D-glucofuranose with migration of an acetal group.[16] Also it has recently been shown[17] that the major product from reaction of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside with **1** is a 5-deoxy-5-iodoallofuranoside rather than the expected 4-deoxy-4-iodoallopyranoside.[18] In spite of these problems, the Rydon reagent has provided a valuable, but not often used, method for the preparation of iodo sugars.

As part of a general program on the synthesis of nucleosides containing modified sugars, we have undertaken a broad study of methods suitable for the direct halogenation of hydroxyl functions in the sugar moiety of nucleosides. In this and paper II[19] we describe the reactions of a wide range of nucleosides with the Rydon reagent while in a forthcoming paper we will discuss similar reactions using other mechanistically related reagents.

The preparation of methyltriphenoxyphosphonium iodide (**1**) was carried out essentially as described by Rydon[7a] except that a smalller excess of methyl iodide and a shorter reaction time were employed. An oil bath was also found to be preferable to a heating mantle in order to avoid local overheating and coloration (see Experimental Section).

While most previous iodinations using **1** have been carried out in hot benzene, the low solubility of many nucleoside derivatives, and of pure **1** itself in this solvent, have led us to use dimethylformamide (DMF) in our studies. Dimethyl sulfoxide seems less satisfactory since there is rapid coloration of the reaction mixture presumably due to oxidation of iodide ion to iodine in this solvent.[20] The use of DMF appears to promote the iodination reaction which occurs at room temperature and is frequently extremely fast. In general, the iodination of the primary hydroxyl group of a suitably protected pyrimidine nucleoside is found to be complete within 10 min at 20–25°. For example, 2′,3′-O-isopropylideneuridine (**5a**) was allowed to react with 2 equiv of **1** in DMF for 15 min and, after destruction of excess reagent by addition of methanol,[21] pure 5′-deoxy-5′-iodo-2′,3′-O-isopropylideneuridine (**5b**)[22] was isolated by direct crystallization in 96.5% yield. Subsequent acidic hydrolysis then gave 5′-deoxy-5′-iodouridine (**6b**) identical with a sample prepared according to Brown, *et al.*[23]

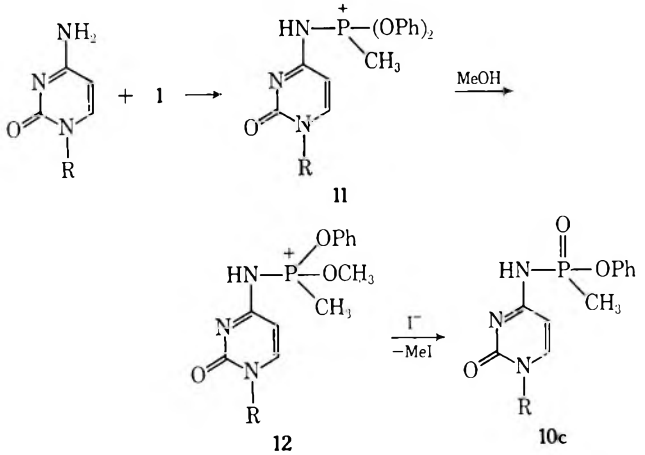
In very similar ways the reactions of 3′-O-acetylthymidine (**7a**) and of 2′,3′-di-O-acetyluridine (**8a**) with **1** in DMF rapidly led to the formation of the corresponding 5′-deoxy-5′-iodo derivatives **7b** and **8b** in isolated yields of 88 and 84%, respectively. The reaction with 2′,3′-O-isopropylidene-6-azauridine (**9a**)[24] was more troublesome, and in spite of an apparently clean reaction as judged by thin layer chromatography, the isolated yield of crystalline 5′-deoxy-5′-iodo-2′,3′-O-isopropylidene-6-azauridine (**9b**) was only 48%. In this case, it was necessary to purify the product by preparative thin layer chromatography in order to obtain crystalline material. The same iodo compound (**9b**) has recently been obtained in somewhat lower yield by displacement of the corresponding 5′-mesylate by iodide ion.[25]



In the cytidine series it becomes clear that the presence of a free amino function on the pyrimidine ring can lead to complications. Thus, reaction of 2′,3′-O-benzylidenecytidine (**10a**) with **1** in DMF led to the

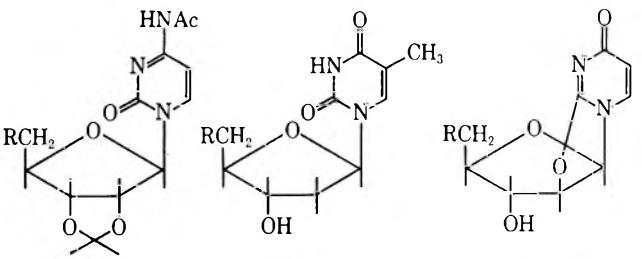
(12) J. P. Schaefer and D. S. Weinberg, *J. Org. Chem.*, **30**, 2635 (1965).
(13) L. Kaplan, *ibid.*, **31**, 3454 (1966).
(14) N. K. Kochetkov, L. I. Kudryashov, and A. I. Usov, *Dokl. Akad. Nauk SSSR*, **133**, 1091 (1960).
(15) J. B. Lee and M. M. El Sawi, *Chem. Ind.* (London), 839 (1960).
(16) N. K. Kochetkov and A. I. Usov, *Tetrahedron*, **19**, 973 (1963).
(17) E. Kefurt, J. Jary, and Z. Samek, *J. Chem. Soc., D*, 213 (1969).
(18) K. S. Adamyanto, N. K. Kochetkov, and A. I. Usov, *Izv. Akad. Nauk SSSR*, 1311 (1967).
(19) J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, in press.
(20) R. A. Strecker and K. K. Andersen, *ibid.*, **33**, 2234 (1968).
(21) Addition of methanol prior to other work-up is recommended since otherwise hydrogen iodide is released upon addition of water, and partial loss of acid labile protecting groups can result.
(22) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **106**, 113 (1934).
(23) D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 868 (1957).
(24) J. Smrt, J. Beránek, and F. Šorm, *Collect. Czech. Chem. Commun.*, **25**, 130 (1960).
(25) J. Zemlička and F. Šorm, *ibid.*, **32**, 576 (1967).

formation of two strongly ultraviolet-absorbing products which were separated by preparative thin layer chromatography. The more polar of these was shown to contain the desired 2′,3′-O-benzylidene-5′-deoxy-5′-iodocytidine (**10b**) which was obtained in 45% yield as a homogeneous syrup and in 34% yield as the crystalline material. The less polar product was unstable and partially decomposed to **10b** on attempted rechromatography or storage. While this substance has not been isolated in pure form, it was shown to contain phosphorus and its nmr spectrum showed both aromatic protons and a roughly 3-proton doublet (J = 17 Hz) at 1.86 ppm which is consistent with the presence of a methylphosphonate moiety. We tentatively suggest that this material is the phenyl methylphosphonate derivative of the 4-amino function of **10b** (**10c**). As will be seen later, phenyl methylphosphonate esters can arise during iodination of secondary hydroxyl groups under certain conditions. The formation of **10c** could involve reaction of the 4-amino group with **1** giving a phosphonium derivative (**11**) which is relatively stable toward iodide ion. Upon addition of methanol, however, phenol could be displaced with formation of a methoxyphosphonium compound (**12**) which can undergo rapid dealkylation by iodide ion giving the observed product (**10c**). If water, rather than methanol, were to attack **11**, direct expulsion of phenol would also give **10c**.



Treatment of a methanolic solution of the crude reaction mixture from iodination of **10a** with a slight excess of hydrochloric acid led to immediate hydrolysis of the 4-amino substituent and crystallization of the hydrochloride of **10b** in 90% yield. Subsequent treatment of the latter with sodium bicarbonate then gave crystalline **10b** as the free base in 89% yield. As might be expected, acylation of the cytosine amino group eliminated this problem, and iodination of N^4-acetyl-2′,3′-O-isopropylidenecytidine (**13a**) gave the corresponding crystalline 5′-deoxy-5′-iodo derivative (**13b**) in 91% yield.[26]

While it can be seen from the accompanying paper[19] that secondary hydroxyl groups of nucleosides also react with **1**, it is possible to effect selective iodination of only the primary hydroxyl function. Thus, brief reaction of thymidine (**14a**) with 1.1 equiv of **1** in DMF gave crystalline 5′-deoxy-5′-iodothymidine (**14b**)[27] in 63% yield, and in a similar way direct reaction of uridine (**6a**) gave the 5′-deoxy-5′-iodo derivative (**6b**) in 65% yield, the latter compound being identical with that obtained by acidic hydrolysis of **5b**. In a somewhat more demanding test it proved possible to effect fairly selective iodination of the 5′-hydroxyl group of O^2,2′-cyclouridine (**15a**)[28] without excessive cleavage of the rather labile anhydro linkage. After 10-min reactions in DMF, thin layer chromatography showed complete disappearance of the starting material and formation of a major, less polar product. Isolation of this material by preparative thin layer chromatography gave an 80% yield of somewhat impure material, and rechromatography was accompanied by considerable decomposition, crystalline 5′-deoxy-5′-iodo-O^2,2′-cyclouridine (**15b**)[29] being obtained in 31% yield.



Since **1** decomposes in the presence of traces of moisture to release hydrogen iodide, care must be taken to avoid loss of acid labile protecting groups. Since the iodination of primary hydroxyl groups is so rapid, loss of isopropylidene groups has not proved to be a problem, but, during the slower reactions of secondary hydroxyls, some loss of trityl groups is evident.[19] It was thus of interest to see whether the iodination reaction could be conducted in the presence of a base to neutralize any acidic by-products. Indeed, it was found that reaction of 2′,3′-O-isopropylideneuridine (**5a**) with **1** gave the 5′-deoxy-5′-iodo derivative (**5b**) essentially quantitatively within 15 min in various mixtures of DMF and pyridine or in pyridine alone. Upon more prolonged reactions there was a gradual accumulation of the 5′-deoxy-5′-pyridinium derivative (**16**) which was characterized by its electrophoretic mobility and ultraviolet spectrum, both of which were identical with an authentic sample.[30] After a 2-hr reaction only about 10% **16** had been formed. Attempts to use a small excess of the relatively nonnucleophilic base N,N-diisopropylethylamine in place of pyridine led to the formation of brown impurities and to the isolation of a 16% yield of 2′,3′-O-isopropylidene-O^2,5′-cyclouridine (**17**)[23] in addition to **5b**. It is not clear whether the formation of **17** is a consequence of base-catalyzed displacement of iodide ion from **5b** or of an increased nucleophilicity of the 2-carbonyl group toward displacement of the phosphonium moiety in the intermediate **18**. Some evidence in favor of the latter route comes from the isolation of the cyclonucleoside **17** in 21% yield following reaction of **5a** with methyltriphenoxyphosphonium perchlorate and N,N-diisopropylethyl-

(26) This reaction is part of a separate study and will be reported in detail later: J. P. H. Verheyden, J. Smejkal, and J. G. Moffatt, unpublished results.

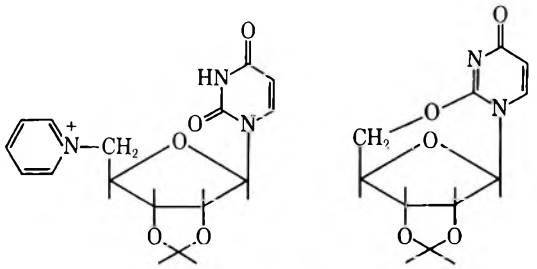
(27) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955).

(28) A. Hampton and A. W. Nicol, *Biochemistry*, **5**, 2076 (1966).

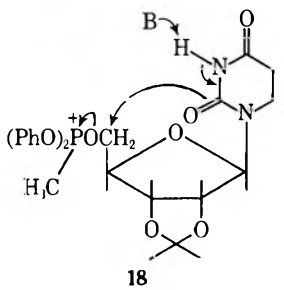
(29) D. M. Brown, W. Cochrane, E. H. Medlin, and S. Varadarajan, *J. Chem. Soc.*, 4873 (1956).

(30) H. Peter and J. G. Moffatt, unpublished experiments.

amine. The perchlorate salt was prepared *in situ* from **1** and silver perchlorate in DMF, and its use led only to **17** and unreacted **5a** with formation of no observable iodo compounds.



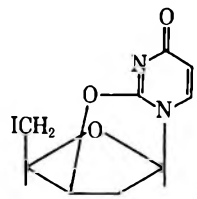
16 **17**



18

While the addition of bases has relatively minor effect upon the iodination of primary hydroxyl groups, the reaction with secondary hydroxyls in pyrimidine nucleosides is markedly changed. While, as will be seen in the accompanying paper,[19] the reaction of thymidine with excess **1** in DMF gives 3′,5′-dideoxy-3′,5′-diiodothymidine in high yield, the comparable reaction in pyridine gives mainly 5′-deoxy-5′-iodo-O^2,3′-cyclothymidine (**19**) which was isolated in crystalline form in 43% yield. The structure of (**19**) is based upon its typical O^2,3′-cyclothymidine ultraviolet spectrum and upon its elemental analyses and nmr spectrum. It has been shown[19] that iodination of the 3′-hydroxyl group of pyrimidine deoxynucleosides with **1** involves initial formation of the O^2,3′-cyclonucleoside which subsequently undergoes nucleophilic attack by iodide ion giving the 3′-iodo nucleoside with overall retention of configuration. Since nucleophilic opening of cyclonucleosides is known to be an acid-catalyzed process,[31] such reactions in pyridine are blocked at this stage thus explaining the accumulation of **19**.

While selective iodination of O^2,2′-cyclouridine (**15a**) with 1.4 equiv of **1** in DMF gave the 5′-iodo derivative (**15b**) in quite good yield, the use of a larger excess of Rydon reagent in the presence of N,N-diisopropylethylamine or pyridine led to an unexpected result. After a brief reaction time the starting material had completely disappeared with formation of two major products and a considerable number of minor products all showing the typical ultraviolet spectra of O^2,2′-cyclouridine. The two major products, which had very similar chromatographic mobilities, were isolated together in 42% yield and shown to be an almost equal mixture of the phosphorus diastereoisomers of 5′-deoxy-5′-iodo-O^2,2′-cyclouridine 3′-O-(phenyl methylphosphonate) (**22**), both of which were obtained in crystalline form. In the accompanying paper[19] further examples of the formation of phenyl methylphosphonate esters are to be found and in general, it appears that their formation is favored when the displacement of the phosphonium moiety in the intermediate **3** is sterically hindered. In the present case, there is presumably rapid formation of the 3′,5′-di-O-(methyldiphenoxyphosphonium) intermediate (**20**) and subsequent displacement of the 5′ group by iodide ion. Because of the existing O^2,2′-anhydro linkage, there is no opportunity for intramolecular displacement of the 3′ group by the uracil ring; owing to the rigid *syn* configuration in O^2,2′-cyclonucleosides, there is considerable hindrance to the approach of iodide ion from the β face of the ribose ring. This presumably leads to an accumulation of the 3′-oxyphosphonium intermediate (**21**) which undergoes reaction with either water or methanol, as previously outlined in the conversion of **11** to **10c**, giving the diastereoisomers (**22**). The isomers of **22** also appear to be the major by-products during the previously mentioned selective iodination of **15a** in the absence of amine.



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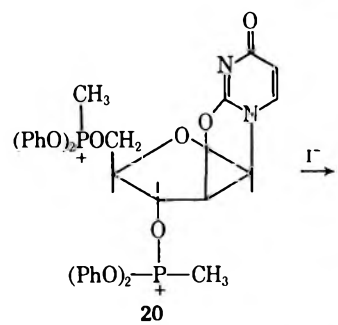

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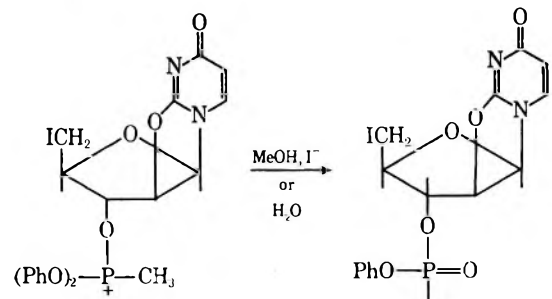


21 **22**

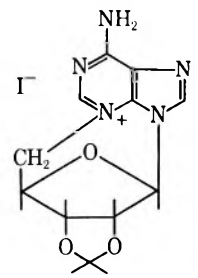
Direct application of the iodination reaction to purine nucleosides leads to cyclonucleosides. Thus, reaction of either 2′,3′-O-isopropylideneadenosine or 2′,3′-O-isopropylideneguanosine with **1** in DMF leads to very rapid and essentially quantitative formation of the N^3,5′-cyclonucleoside salts (**23** and **24**). Both compounds were obtained crystalline and characterized by their ultraviolet spectra and their electrophoretic and chromatographic mobilities, all of which were identical with those of **23**[32] and **24**[33] prepared by heating the

(31) J. J. Fox and N. C. Miller, *J. Org. Chem.*, **28**, 936 (1963).

(32) V. M. Clark, A. R. Todd, and J. Zussman, *J. Chem. Soc.*, 2952 (1951).

(33) (a) E. J. Reist, P. A. Hart, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 1577 (1961). (b) R. E. Holmes and R. K. Robins, *ibid.*, **28**, 3483 (1963). We thank Dr. R. K. Robins for samples of 2′,3′-O-isopropylidene-N^3,5′-cycloinosine and its tosylate salt.

appropriate 5′-tosylates with sodium iodide. A similar reaction with 2′,3′-O-isopropylideneinosine gave crystalline 2′,3′-O-isopropylidene-N³,5′-cycloinosine (**25**)[33b] in 76% yield along with 15% 5′-deoxy-5′-iodo-2′,3′-O-isopropylideneinosine (**26**). The latter compound was only recently obtained by displacement of the corresponding 5′-tosylate[34] and its formation, albeit in low yield, from our reaction with **1** is a further indication of the somewhat reduced tendency of inosine derivatives, relative to other purine nucleosides, to form N³,5′-cyclonucleosides.[33]



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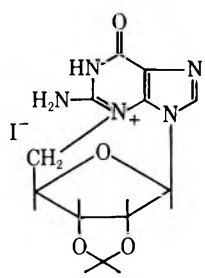

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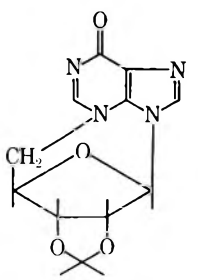

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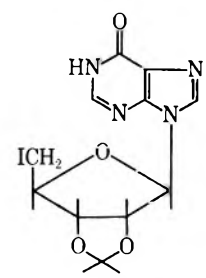

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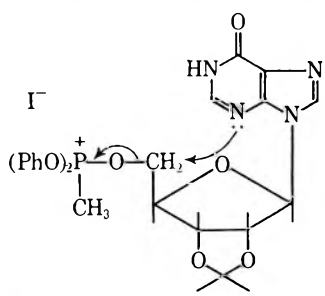
The formation of N³,5′-cyclonucleosides is clearly a consequence of the very facile attack by N³ of the purine ring upon C⁵′ of the phosphonium intermediate (**27**) with expulsion of diphenyl methylphosphonate. The reduced propensity for such an intramolecular displacement in the inosine series permits some competitive attack by iodide ion on **27** leading to the 5′-iodo derivative **26**. The intermediacy of an ionic cyclonucleoside **28**, similar to that isolated by Holmes and Robins,[33b] was detected by paper chromatography but only the nonionic form (**25**) was isolated following a work-up involving addition of pyridine.



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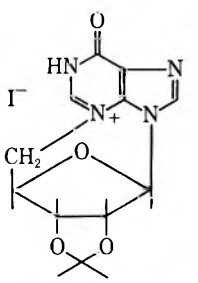

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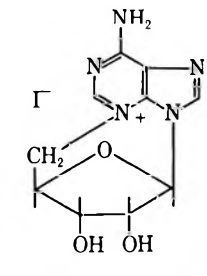

29

Treatment of unprotected adenosine with 1 equiv of **1** in DMF for 5 min gave a major, very polar material and two less polar, minor by-products. Following extraction into water crystalline N³,5′-cycloadenosine iodide (**29**) was obtained in 50% yield. Unprotected N³,5′-cycloadenosine salts have recently been obtained upon heating either 5′-O-tosyl- or 5′-O-sulfamoyladenosine in DMF at 100° but have not been characterized.[35] The two minor products appear from their nmr spectra to be phenyl methylphosphonate esters of adenosine but were not obtained in sufficient amounts for detailed study.

From the work described in this paper, it is clear that the Rydon reagent (**1**) provides a very efficient method for the iodination of the primary hydroxyl function of pyrimidine nucleosides. The reaction is very rapid and the overall yields are generally considerably higher than those obtained *via* the two-step tosylation and displacement route. In the accompanying paper[19] iodination of secondary hydroxyl groups is discussed.

Experimental Section

Methods.—Thin layer chromatography (tlc) was done on 0.25-mm layers of Merck silica gel HF and preparative tlc on 20 × 100 cm glass plates coated with a 1.3-mm layer of the same silica. Nuclear magnetic resonance (nmr) spectra were obtained using a Varian HA-100 spectrometer and chemical shifts are recorded in parts per million downfield from an internal standard of TMS. Mass spectra were obtained using an Atlas CH-4 instrument with a direct inlet system and optical rotatory dispersion (ORD) spectra using a Jasco ORD/UV-5 instrument. All instrumental analyses were performed by the staff of the Analytical Laboratory of Syntex Research, and elemental analyses were obtained from the laboratory of Dr. A. Bernhardt, Mülheim, Germany, or from the Analytical Laboratory of the University of California, Berkeley, Calif. We are particularly grateful to Dr. M. Maddox, Mr. J. Murphy, and Miss J. Tremble and to Dr. L. Tökes for their help with nmr and mass spectra, respectively.

Methyltriphenoxyphosphonium Iodide (1).[7a]—Triphenyl phosphite (52 ml, 0.2 mol) and methyl iodide (16 ml, 0.26 mol) were mixed in a 250-ml flask fitted with a very efficient 3-ft condenser and a thermometer well. The flask was placed in a 90° oil bath and the temperature of the bath was slowly raised to 125° over 8 hr while the pot temperature rose slowly from 70 to 85° and then rapidly to 115°.[36] This temperature was then maintained for 12–14 hr and, upon cooling and seeding, the mixture crystallized to a solid brown mass. Dry ether (100 ml) was added and the product was carefully broken up with a spatula. The resulting crystalline material was then repeatedly washed by decantation with fresh dry ethyl acetate until the washings were only light colored.[37] The amber crystals were then dried and stored *in vacuo* giving 80 g (90%) of **1** suitable for direct use: nmr (rigorously dry $CDCl_3$) 3.11 ppm (d, 3, $J_{P,H}$ = 16.5 Hz, PCH_3), 7.45 (m, 15, aromatic). If the sample was not prepared in a drybox appreciable amounts of diphenyl methylphosphonate were formed as indicated by a doublet ($J_{P,H}$ = 18 Hz) at 1.84 ppm. In all subsequent reactions **1** was always weighed and handled in a drybox under a nitrogen atmosphere.

3α-Iodocholestane (4b).[38]—Cholestanol (0.78 g, 2 mmol) and **1** (1.81 g, 4 mmol) were dissolved in anhydrous DMF (10 ml) and

(34) A. Hampton, M. Bayer, V. S. Gupta, and S. Y. Chu, *J. Med. Chem.*, **11**, 1229 (1968).

(35) D. A. Shuman, R. K. Robins, and M. J. Robins, *J. Amer. Chem. Soc.*, **91**, 3391 (1969).

(36) If the reaction is worked up as soon as the internal temperature reaches 115°, **1** is obtained in a very light-colored form but only in about 50% yield.

(37) Ethyl acetate is much preferable to ether for this purpose and a much lighter colored product is obtained. Compound **1** has recently become available from Eastman Kodak Co. in a dark-colored crystalline form that can be readily purified by treatment with ethyl acetate as above.

(38) We are grateful to Mr. E. K. Hamamura for this experiment.

stored for 2 hr at 25°. After addition of methanol (1 ml), the mixture was diluted with chloroform and extracted with dilute aqueous sodium thiosulfate followed by water. After drying (Na_2SO_4) the solvent was evaporated and the residue was chromatographed on a column of silicic acid using hexane. The major peak was evaporated giving 640 mg of **4b** which was crystallized from acetone giving 562 mg (57%) of pure product with mp 112–113°; $[\alpha]^{23}D$ +36.9° (lit.[11] mp 111.5–112.5°; $[\alpha]^{20}D$ +32.2°; and for β isomer mp 105.5–107°); nmr ($CDCl_3$) 0.65 ppm (s, 3, $C_{18}H_3$), 0.79 (s, 3, $C_{19}H_3$), 0.86 (d, 6, J = 6 Hz, $C_{26}H_3$ and $C_{27}H_3$), 0.90 (d, 3, J = 6 Hz, $C_{21}H_3$), 4.95 (m, 1, C_3H).

Iodination of 2′,3′-O-Isopropylideneuridine (5a). (A) In DMF Alone.—2′,3′-O-Isopropylideneuridine (10 g, 35.2 mmol) and **1** (32 g, 70 mmol) were dissolved in anhydrous DMF (140 ml) and after 15 min at 25° methanol (5 ml) was added. After 10 min the solvent was evaporated *in vacuo* and the residue was dissolved in chloroform. After extraction with aqueous sodium thiosulfate and then water, the chloroform layer was dried (Na_2SO_4) and evaporated giving a colorless syrup containing **5b**, phenol, and diphenyl methylphosphonate. Crystallization from chloroform by slow addition of hexane gave 13.4 g (96.5%) of pure **5b**: mp 165–166° (lit.[22] mp 164°); λ_{max}^{MeOH} 259 mμ (ε 10,500); nmr ($CDCl_3$) 1.34 ppm (s, 3, CMe_2), 1.55 (s, 3, CMe_2), 3.34 (q, 1, J_{gem} = 10 Hz, $J_{4',5'a}$ = 5 Hz, $C_{5'a}H$), 3.52 (q, 1, J_{gem} = 10 Hz, $J_{4',5'b}$ = 6.5 Hz, $C_{5'b}H$), 4.25 (hex, 1, $J_{3',4'}$ = 3.5 Hz, $J_{4',5'}$ = 6 Hz, $C_4'H$), 4.79 (q, 1, $J_{2',3'}$ = 6.5 Hz, $J_{3',4'}$ = 3.5 Hz, $C_3'H$), 5.03 (q, 1, $J_{1',2'}$ = 2 Hz, $J_{2',3'}$ = 6.5 Hz, $C_2'H$), 5.63 (d, 1, $J_{1',2'}$ = 2 Hz, $C_1'H$), 5.75 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 7.35 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Treatment of **5b** (788 mg, 2 mmol) with 80% acetic acid (18 ml) at 100° for 90 min gave 620 mg (87.5%) of 5′-deoxy-5′-iodouridine (**6b**) of mp 184–185° after crystallization from ethanol (see below).

(B) In the Presence of N,N-Diisopropylethylamine.—A solution of **5a** (142 mg, 0.5 mmol), **1** (250 mg, 0.5 mmol), and N,N-diisopropylethylamine (260 mg, 2 mmol) in DMF (3 ml) was kept overnight at 25° and then evaporated to dryness *in vacuo* after addition of methanol (1 ml). Upon addition of ethyl acetate a brown precipitate (60 mg) separated and was discarded. After extraction with water, the organic phase was dried (Na_2SO_4) and purified by preparative tlc using acetone–methanol (9:1) which gave **5b**, unreacted **5a**, and a slow moving band. Elution of the latter and crystallization from ethanol gave 21 mg (16%) of 2′,3′-O-isopropylidene-O²,5′-cyclouridine (**17**) which decomposed from 228 to 280° (lit.[23] decomposition above 190°): λ_{max}^{MeOH} 236 mμ (ε 13,900); ORD (MeOH) negative Cotton effect with minimum at 245 mμ (Φ −16, 100°) and zero rotation at 233 mμ; nmr (d_6-DMF) 1.33 ppm (s, 3, CMe_2), 1.43 (s, 3, CMe_2), 4.27 (d, 1, J_{gem} = 12 Hz, $C_{5'a}$), 4.67 (q, 1, J_{gem} = 12 Hz, $J_{4',5'b}$ = 2 Hz, $C_{5'b}H$), 4.77 (br s, 1, $C_4'H$), 5.0 (s, 2, $C_2'H$ and $C_3'H$), 5.85 (s, 1, $C_1'H$), 5.98 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 8.12 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

(C) In the Presence of Silver Perchlorate.—Silver perchlorate (230 mg, 1.1 mmol) and **1** (500 mg, 1.1 mmol) were dissolved in DMF (3 ml) giving a yellow precipitate of silver iodide. N,N-Diisopropylethylamine (3 ml) and **5a** (284 mg, 1 mmol) were added, and after 10 min methanol (1 ml) was added to the dark mixture. After filtration through Celite, the solvent was evaporated and the residue was separated by preparative tlc using acetone–methanol (9:1). In addition to a band of unreacted **5a** a major band of **17** was observed and eluted. Crystallization from ethanol gave 55 mg (21%) of **17** identical with that above.

3′-O-Acetyl-5′-deoxy-5′-iodothymidine (7b).—A solution of 3′-O-acetylthymidine (4.26 g, 15 mmol) and **1** (10.0 g, 22 mmol) in DMF (50 ml) was kept at 25° for 1 hr and then evaporated to dryness after addition of methanol (5 ml). The residue was dissolved in chloroform, washed with thiosulfate and water, dried, evaporated, and crystallized from chloroform–hexane giving 5.20 g (88%) of **7b** with mp 132–132.5° (lit.[39] mp 131°); nmr ($CDCl_3$) 1.95 ppm (d, 3, $J_{allylic}$ = 1 Hz, C_5Me), 2.10 (s, 3, OAc), 2.1–2.4 (m, 2, $C_2'H_2$), 3.4–3.7 (AB of ABC, 2, J_{gem} = 11 Hz, $J_{4',5'a}$ = 3.5 Hz, $J_{4',5'b}$ = 3 Hz, $C_5'H_2$), 3.9 (m, 1, $C_4'H$), 5.1 (m, 1, $C_3'H$), 6.32 (q, 1, $J_{1',2'a}$ = 5 Hz, $J_{1',2'b}$ = 7.5 Hz, $C_1'H$), 7.57 (q, $J_{allylic}$ = 1 Hz, C_6H).

2′,3′-Di-O-acetyl-5′-deoxy-5′-iodouridine (8b).—A solution of 2′,3′-di-O-acetyluridine (6.4 g, 19.5 mmol) and **1** (13 g, 30 mmol) in DMF (100 ml) was kept at room temperature for 2 hr. After addition of methanol (10 ml) the solvent was evaporated and a chloroform solution of the residue was washed with aqueous thiosulfate and water. After drying (Na_2SO_4) the solvent was evaporated and the residue crystallized from chloroform (20 ml) by slow addition of hexane giving 7.2 g (84%) of **8b** with mp 162–164°. An analytical sample had mp 163–164°; λ_{max}^{MeOH} 259 mμ (ε 10,400); ORD (MeOH) positive Cotton effect with a peak at 272 mμ (Φ +2800°), zero rotation at 252 mμ, and a minimum at 232 mμ (Φ −2400°); nmr ($CDCl_3$) 2.11 ppm (s, 3, OAc), 2.15 (s, 3, OAc), 3.54 (d, 2, $J_{4',5'}$ = 4 Hz, $C_5'H_2$), 4.11 (q, 1, $J_{3',4'}$ = $J_{4',5'}$ = 4 Hz, $C_4'H$), 5.22 (q, 1, $J_{3',4'}$ = 4 Hz, $J_{2',3'}$ = 6 Hz, $C_3'H$), 5.40 (t, 1, $J_{1',2'}$ = $J_{2',3'}$ = 6 Hz, $C_2'H$), 5.85 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.08 (d, 1, $J_{1',2'}$ = 6 Hz, $C_1'H$), 7.58 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Anal. Calcd for $C_{13}H_{16}N_2O_7I$: C, 35.64; H, 3.45; N, 6.39. Found: C, 35.89; H, 3.49; N, 6.29.

5′-Deoxy-5′-iodo-2′,3′-O-isopropylidene-6-azauridine (9b).—A solution of **9a** (285 mg, 1 mmol) and **1** (1 g, 2 mmol) in DMF (5 ml) was stored for 30 min at 25° and worked up as above using ethyl acetate in place of chloroform. The dried organic phase was purified by preparative tlc using two successive developments with chloroform–ethyl acetate (3:2). Elution of the major band with acetone gave 190 mg (48%) of crystalline **9b** which was recrystallized from chloroform–hexane with mp 178–181° (lit.[25] mp 176–181); λ_{max}^{MeOH} 261 mμ (ε 6700); nmr ($CDCl_3$) 1.36 and 1.56 ppm (s, 3, CMe_2), 3.24 (d, 2, $J_{4',5'}$ = 7.5 Hz, $C_5'H_2$), 4.43 (hex, 1, $J_{4',5'}$ = 7.5 Hz, $J_{3',4'}$ = 3 Hz, $C_4'H$), 4.81 (q, 1, $J_{3',4'}$ = 3 Hz, $J_{2',3'}$ = 6 Hz, $C_3'H$), 5.07 (q, 1, $J_{2',3'}$ = 6 Hz, $J_{1',2'}$ = 1 Hz, $C_2'H$), 6.38 (d, 1, $J_{1',2'}$ = 1 Hz, $C_1'H$), 7.51 (s, 1, C_6H).

Anal. Calcd for $C_{11}H_{14}N_3O_5I$: C, 33.43; H, 3.57. Found: C, 33.60; H, 3.55.

2′,3′-O-Benzylidene-5′-deoxy-5′-iodocytidine (10b). (A).—A solution of **10a** (662 mg, 2 mmol)[40] and **1** (2 g, 4 mmol) in DMF (10 ml) was reacted overnight and worked up as usual using ethyl acetate. The resulting syrup (2.86 g) was purified by preparative tlc on 4 plates using acetone–chloroform (1:1). In addition to fast bands of phenol and diphenyl methylphosphonate two intense ultraviolet-absorbing bands were obtained. Elution of the slower band with acetone gave 400 mg (45%) of **10b** as a chromatographically homogeneous syrup from which 300 mg (34%) of crystalline material with mp 175–180° was obtained from ethanol. An analytical sample from acetone had mp 176.5–177.5°; λ_{max}^{MeOH} 278 mμ (ε 12,800); nmr ($CDCl_3$) showing a mixture of benzylidene diastereoisomers with 3.3–3.8 ppm (m, 2, $C_5'H_2$), 4.45 (m, 1, $C_4'H$), 5.0–5.4 (m, 2, $C_2'H$ and $C_3'H$), 5.63 (s, 1, $C_1'H$), 5.80 (br d, 1, $J_{5,6}$ = 7 Hz, C_5H), 5.94 and 6.06 (2s, 1, $ArCHO_2$), 7.45 (m, 6, Ar and C_6H).

Anal. Calcd for $C_{16}H_{16}N_3O_4I$: C, 43.55; H, 3.66; N, 9.53. Found: C, 43.28; H, 3.70; N, 9.79.

Elution of the faster band gave a phosphorus-containing syrup that could not be crystallized and that partially decomposed to **10b** upon storage: λ_{max}^{MeOH} 280 mμ, $\lambda_{max}^{OH^-}$ 270 mμ; nmr (d_5-pyridine) was poor but showed a sharp doublet at 1.86 ppm ($J_{P,H}$ = 17 Hz) and an overabundance of aromatic protons. Brief treatment with methanolic hydrochloric acid gave **10b** (see below).

(B).—A reaction was carried out exactly as in A. After evaporation of the ethyl acetate solution the resulting syrup was dissolved in methanol (4 ml) and upon addition of concentrated hydrochloric acid (0.2 ml) white crystals separated. After 15 min the crystals were removed by filtration, washed with ethanol, and dried *in vacuo* over sodium hydroxide giving 855 mg (90%) of the hydrochloride of **10b**, λ_{max}^{MeOH} 278 mμ. This material (755 mg) was partitioned between ethyl acetate and 0.2 *M* sodium bicarbonate and the organic phase was dried (Na_2SO_4) and evaporated. The resulting syrup was crystallized from acetone giving 770 mg (89%) of **10b** identical with that above.

Iodination of Thymidine with 1. (A) In DMF.—Thymidine (1.94 g, 8 mmol) and **1** (4.35 g, 9.6 mmol) reacted in DMF (20 ml) at room temperature for 10 min. After addition of methanol (10 ml) the mixture was worked up in the usual way giving a syrup that was crystallized from methanol giving 1.61 g (57%) of pure 5′-deoxy-5′-iodothymidine (**14b**) with mp 173–174° (lit.[27] mp 172–173°). Chromatography of the evaporated mother liquors on four preparative plates using carbon tetrachloride–acetone (1:1) gave a further 170 mg (total yield 63%) of **14b**: λ_{max}^{MeOH} 263 mμ (ε 9600); nmr (d_5-pyridine) 1.94 ppm (d, 3, $J_{allylic}$ = 1.5 Hz, C_5Me), 2.54 (q, 1, $J_{1',2'a}$ = 7 Hz, $J_{2'a,3'}$ = 2.5

(39) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 951 (1953).

(40) J. Baddiley, J. G. Buchanan, and A. R. Sanderson, *ibid.*, 3107, (1958).

Hz, $C_{2'a}H$), 2.60 (d, 1, $J_{1',2'b}$ = 7 Hz, $J_{2'b,3'}$ = 0 Hz, $C_{2'b}H$), 3.68 (br d, 2, $J_{4',5'}$ = 6 Hz, $C_{5'}H_2$), 4.24 (hex, 1, $J_{3',4'}$ = 3 Hz, $J_{4',5'}$ = 6 Hz, $C_{4'}H$), 4.7 (m, 1, $C_{3'}H$), 6.86 (t, 1, $J_{1',2'}$ = 7 Hz, $C_{1'}H$), 7.67 (q, 1, $J_{allylic}$ = 1.5 Hz, C_6H).

During tlc purification of **14b** a minor, slower moving band was also eluted giving 60 mg of a chromatographically homogeneous product tentatively identified as thymidine 3',5'-cyclic methylphosphonate. The product could not be crystallized and was contaminated with silica so as to give an unsatisfactory elemental analyses: λ_{max}^{MeOH} 262 mμ; nmr ($CDCl_3$) 1.77 ppm (d, 3, $J_{P,H}$ = 18 Hz, PCH_3), 1.91 (d, 3, $J_{allylic}$ = 1 Hz, C_5Me), 2.78 (q, 2, $J_{1',2'}$ = 7 Hz, $J_{2',3'}$ = 5 Hz, $C_{2'}H_2$), 3.61 (d, 2, $J_{4',5'}$ = 6 Hz, $C_{5'}H_2$), 4.27 (m, 1, $C_{4'}H$), 5.45 (m, 1, $C_{3'}H$), 6.72 (t, 1, $J_{1',2'}$ = 7 Hz, $C_{1'}H$), 7.46 (br s, 1, C_6H); mass spectrum *m/e* 303 (M^+, weak), 287 (M − CH_3, weak), 173, 94, 81.

(B) In Pyridine.—Thymidine (484 mg, 2 mmol) and **1** (2.6 g, 5.5 mmol) were dissolved in pyridine (15 ml) and kept at 25° for 1 hr. After addition of methanol (5 ml) the solvent was evaporated, and the residue was coevaporated several times with methanol. Chromatography of the residue on three preparative tlc plates using ethyl acetate–methanol (1:1) gave a major band (R_f ~0.5) which was eluted and crystallized from acetone giving 340 mg of crude product that still contained an impurity. Rechromatography using two developments with chloroform–methanol (9:1) gave a sharp band that was eluted and crystallized from methanol–ethyl acetate giving 294 mg (43%) of 5'-deoxy-5'-iodo-O²,3'-cyclothymidine (**19**) with mp 192–192.5°; λ_{max}^{MeOH} 247 mμ (ε 9100); ORD (MeOH) negative Cotton effect with trough at 248 mμ (Φ −24,100°), zero rotation at 226 mμ and a peak at 217 mμ (Φ +5800°); nmr (d_6-DMSO) 1.75 ppm (d, 3, $J_{allylic}$ = 1 Hz), 2.45–2.65 (m, 2, $C_{2'}H_2$), 3.12 (q, J_{gem} = 10 Hz, $J_{4',5'a}$ = 8 Hz, $C_{5'a}H$), 3.27 (q, J_{gem} = 10 Hz, $J_{4',5'b}$ = 7 Hz, $C_{5'b}H$), 4.51 (hex, 1, $J_{3',4'}$ = 2 Hz, $J_{4',5'}$ = 7–8 Hz, $C_{4'}H$), 5.29 (br d, 1, $J_{3',4'}$ = 2 Hz, $C_{3'}H$), 5.92 (d, 1, $J_{1',2'}$ = 3 Hz, $C_{1'}H$), 7.56 (q, $J_{allylic}$ = 1 Hz, C_6H).

Anal. Calcd for $C_{10}H_{11}N_2O_3I$: C, 35.94; H, 3.32. Found: C, 36.07; H, 3.43.

On prolonged reaction a spot of increasing intensity appeared near the origin during tlc with ethyl acetate–methanol (1:1). Elution of this material with methanol gave a syrup with λ_{max}^{MeOH} 260 mμ and shoulders at 255 and 265 mμ. Paper electrophoresis at pH 7.5 showed the product to be a cation with a mobility identical with that of an authentic salt of **16**.[30]

5'-Deoxy-5'-iodouridine (6b).—Uridine (244 mg, 1 mmol) and **1** (640 mg, 1.5 mmol) were allowed to react for 1 hr at 25° in DMF (5 ml). After the usual work-up using chloroform, the product was found in the aqueous phase and was recovered by continuous extraction into ethyl acetate. Evaporation of the solvent left 230 mg (65%) of crystalline **6b** that was recrystallized from methanol giving 140 mg of analytically pure product with mp 184–185° (lit.[23] mp 182–183°); λ_{max}^{MeOH} 260 mμ (ε 10,400); nmr (d_5-pyridine) 3.67 ppm (q, 1, J_{gem} = 10 Hz, $J_{4',5'a}$ = 5 Hz, $C_{4'}H$), 3.81 (q, 1, J_{gem} = 10 Hz, $J_{4',5'b}$ = 5 Hz, $C_{5'b}H$), 4.35 (q, 1, $J_{3',4'}$, $J_{4',5'a}$, $J_{4',5'b}$ = 5 Hz, $C_{4'}H$), 4.51 (t, 1, $J_{2',3'}$, $J_{3',4'}$ = 5 Hz, $C_{3'}H$), 4.81 (t, 1, $J_{1',2'}$, $J_{2',3'}$ = 5 Hz, $C_{2'}H$), 5.85 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.64 (d, 1, $J_{1',2'}$ = 5 Hz, $C_{1'}H$), 7.95 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Iodination of O²,2'-Cyclouridine (15b). (A) In DMF.—O²,2'-Cyclouridine (451 mg, 2 mmol) and **1** (1.8 g, 4 mmol) were allowed to react in DMF (10 ml) for 10 min at 25°. After addition of methanol the reaction was evaporated to dryness and directly chromatographed on two preparative plates using acetone. The major band was eluted giving 450 mg of a syrup containing one major spot and two close moving impurities (**22**). Rechromatography using two successive developments with acetone led to considerable decomposition and crystallization of the major band from ethanol gave 175 mg (31%) of 5'-deoxy-5'-iodo-O²,2'-cyclouridine (**15b**) with mp 194–195° (lit.[29] mp 194–195°); λ_{max}^{MeOH} 245 mμ (ε 8050), 223 (9,250); ORD (MeOH) positive Cotton effect with a peak at 260 mμ (Φ +12,000°), zero rotation at 247 mμ and a trough at 226 mμ (Φ −31,000°); nmr (d_6-DMSO) 2.97 ppm (q, 1, J_{gem} = 11 Hz, $J_{4',5'a}$ = 7.5 Hz, $C_{5'a}H$), 3.20 (q, 1, J_{gem} = 11 Hz, $J_{4',5'b}$ = 6.5 Hz, $C_{5'b}H$), 4.15 (rough hex, 1, $J_{4',5'}$ = ~7 Hz, $J_{3',4'}$ = 2 Hz, $C_{4'}H$), 4.35 (m, 1, $C_{3'}H$), 5.26 (q, 1, $J_{1',2'}$ = 5.5 Hz, $J_{2',3'}$ = 1 Hz, $C_{2'}H$), 5.88 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.14 (d, 1, $J_{H,OH}$ = 4.5 Hz, $C_{3'}OH$), 6.37 (d, 1, $J_{1',2'}$ = 5.5 Hz, $C_{1'}H$), 7.81 (d, 1, $J_{5,6}$ = 8 Hz, C_6H); mass spectrum *m/e* 336 (M^+), 254 (I_2^+), 192, 127 (I^+), 112 (uracil).

(B) In the Presence of N,N-Diisopropylethylamine.—O²,2'-Cyclouridine (1.13 g, 5 mmol), **1** (6.4 g, 14 mmol), and N,N-diisopropylethylamine (2.6 g) were allowed to react for 15 min at 25° in DMF (50 ml). After addition of methanol (1 ml) and evaporation to dryness, ethyl acetate was added giving 1.0 g of a precipitate which contained at least seven very polar spots all with λ_{max} 247 and 225 typical of O²,2'-cyclouridine. The ethyl acetate supernatant was extracted with saturated aqueous sodium chloride, decolorized with charcoal, and evaporated to dryness. Addition of ether (150 ml) gave 1.01 g (42%) of white crystals which contained equal amounts of the diastereoisomers of **22**. Preparative tlc using acetone cleanly separated these compounds. The slower isomer was crystallized from methanol: mp 222–224°: λ_{max}^{MeOH} 225 mμ (ε 9800), 247 (8800); ORD (MeOH) positive Cotton effect with peak at 260 mμ (Φ +10,600°), zero rotation at 247 mμ and a trough at 227 mμ (Φ −26,000°); nmr (d_6-DMSO) 1.82 ppm (d, $J_{P,H}$ = 18 Hz, PCH_3), 2.92 (q, 1, J_{gem} = 11 Hz, $J_{4',5'a}$ = 8 Hz, $C_{5'a}H$), 3.2 (m, 1, $C_{5'b}H$), 4.32 (m, 1, $C_{4'}H$), 5.19 (q, 1, $J_{3',4'}$ = 3 Hz, $J_{P,H}$ = 8 Hz, $C_{3'}H$), 5.62 (d, 1, $J_{1',2'}$ = 6 Hz, $C_{2'}H$), 5.90 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.45 (d, 1, $J_{1',2'}$ = 6 Hz, $C_{1'}H$), 7.1–7.6 (m, 5, Ar), 7.95 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Anal. Calcd for $C_{16}H_{16}N_2O_6IP$: C, 39.20; H, 3.29; N, 5.72. Found: C, 39.19; H, 3.27; N, 5.87.

The faster moving isomer was crystallized from ethanol: mp 196–197°: λ_{max}^{MeOH} 225 mμ (ε 9800), 247 (8600); ORD (MeOH) positive Cotton effect with a peak at 265 mμ (Φ +4100°), zero rotation at 252 mμ and a trough at 227 mμ (Φ −26,000°); nmr (d_6-DMSO) almost identical with that of the slower isomer.

Anal. Calcd for $C_{16}H_{16}N_2O_6IP$: C, 39.20; H, 3.29; N, 5.72. Found: C, 38.95; H, 3.31; N, 6.08.

2',3'-O-Isopropylidene-N³,5'-cycloadenosine Iodide (23).—2',3'-O-Isopropylideneadenosine (307 mg, 1 mmol) and **1** (1.4 g, 3 mmol) were allowed to react overnight in DMF (15 ml). After addition of methanol the solvent was evaporated and upon addition of ethyl acetate 400 mg (96%) of pure **23** separated as a white precipitate. Crystallization from ethanol gave colorless crystals with mp 280–282° dec (lit.[32] mp 277° dec); $\lambda_{max}^{H_2O}$ 273 mμ (ε 15,400), 220 mμ (ε 20,700); ORD (H_2O) negative Cotton effect with a trough at 272 mμ (Φ −4600°), zero rotation at 257 mμ, a shoulder at 232 mμ (Φ +10,000°), and a peak at 212 mμ (Φ +35,000°);[41] nmr (d_5-pyridine) 1.35 and 1.55 (s, 3, CMe_2), 3.39 (q, 1, J_{gem} = 14 Hz, $J_{4',5'a}$ = 2 Hz, $C_{5'a}H$), 3.83 (q, 1, J_{gem} = 14 Hz, $J_{4',5'b}$ = 3 Hz, $C_{5'b}H$), 4.67 (d, 1, $J_{2',3'}$ = 6 Hz, $C_{3'}H$), 4.84 (m, 1, $C_{4'}H$), 5.01 (d, 1, $J_{2'3'}$ = 6 Hz, $C_{2'}H$), 6.04 (s, 1, $C_{1'}H$), 7.86 (s, 1, C_8H), 9.56 (s, 1, C_2H). The spectrum in d_6-DMSO gave less resolution of the sugar protons and led to a large solvent shift of the C_2H and C_8H protons which appeared at 8.60 and 8.76 ppm.

N³,5'-Cycloadenosine (29).—Adenosine (267 mg, 1 mmol) and **1** (500 mg, 1.1 mmol) were allowed to react for 5 min in DMF (5 ml) and after addition of methanol (1 ml) the mixture was evaporated to dryness. Addition of ethyl acetate gave a white crystalline residue that was dissolved in water and repeatedly extracted with ethyl acetate to remove two relatively nonpolar byproducts. Evaporation of the aqueous phase and crystallization of the residue from methanol gave 189 mg (50%) of **29** which melted with decomposition at 215–230°: $\lambda_{max}^{H_2O}$ 220 mμ (ε 21,700), 273 (13,500); ORD (H_2O) negative Cotton effect with a trough at 272 mμ (Φ −7970°), zero rotation at 237 mμ and a peak at 235 mμ (Φ +615°); nmr (d_6-DMSO) 3.99 ppm (d, 1, $J_{2',3'}$ = 6 Hz, $C_{2'}H$), 4.30 (m, 1, $C_{3'}H$), 4.69 (br s, 2, $C_{5'}H_2$), 4.90 (br s, 1, $C_{4'}H$), 6.41 (s, 1, $C_{1'}H$), 8.49 (s, 1, C_2H or C_8H), 8.72 (s, 1, C_2H or C_8H).

Anal. Calcd for $C_{10}H_{12}N_5O_3I$: C, 31.84; H, 3.21; N, 18.57. Found: C, 32.02; H, 3.38; N, 18.45.

2',3'-O-Isopropylidene-N³,5'-cycloguanosine Iodide (24).—2',3'-O-Isopropylideneguanosine (323 mg, 1 mmol) and **1** (640 mg, 1.4 mmol) were allowed to react overnight in DMF (10 ml). After addition of methanol, evaporation to dryness, and addition of ethyl acetate, 375 mg (87%) of crystalline **24** was obtained. Recrystallization from aqueous acetone gave needles with mp above 300°; $\lambda_{max}^{H_2O}$ 219 mμ (ε 37,800), 265 (11,000); $\lambda_{max}^{pH\ 2}$ 228 mμ (ε 18,500), 260 (sh, 11,000); $\lambda_{max}^{pH\ 12}$ 220 mμ (ε 36,400), 260 (9800) all in agreement with earlier reports;[33] nmr (d_6-DMSO) 1.24 and 1.46 ppm (s, 3, CMe_2), 3.99 (q, 1, J_{gem} = 14 Hz, $J_{4',5'a}$ = 2 Hz, $C_{5'a}H$), 4.55 (d, 1, $J_{2',3'}$ = 6 Hz, $C_{3'}H$), 4.77 (q, 1, J_{gem} = 14

(41) These data are in agreement with those of others: (a) A. Hampton and A. W. Nichol, *J. Org. Chem.*, **32**, 1688 (1967); (b) D. W. Miles, R. K. Robins, and H. Eyring, *Proc. Nat. Acad. Sci. U. S.*, **57**, 1138 (1967).

Hz, $J_{4',5'b}$ = 2 Hz, $C_{5'b}H$), 4.93 (m, 1, $C_{4'}H$), 5.00 (d, 1, $J_{2',3'}$ = 6 Hz, $C_{2'}H$), 6.53 (s, 1, $C_{1'}H$), 8.10 (s, 1, C_8H).

Iodination of 2',3'-O-Isopropylideneinosine.—2',3'-O-Isopropylideneinosine (616 mg, 2 mmol) and I (1.7 g) were allowed to react overnight in DMF (10 ml) containing pyridine (0.8 ml). After addition of methanol and evaporation of the solvent, the residue was partitioned between water and chloroform. Pyridine (0.5 ml) was added to the aqueous phase and the solvent was evaporated leaving a crystalline residue that was recrystallized from ethanol giving 470 mg (76%) of 2',3'-O-isopropylidene-N^3,5'-cycloinosine (**25**) with mp 265–268° (lit.[33b] mp 266–269°); $\lambda_{max}^{H_2O}$ 252 mμ (ε 6500); $\lambda_{max}^{pH\ 2}$ 253 mμ (ε 7300); $\lambda_{max}^{pH\ 12}$ 253 mμ (ε 6700) and changing to λ_{max} 269 mμ (ε 11,300) within 2 hr; nmr (d_5-pyridine) 1.23 and 1.46 ppm (s, 3, CMe_2), 3.04 (q, 1, J_{gem} = 14 Hz, $J_{4',5'a}$ = 1.5 Hz, $C_{5'a}H$), 4.83 (m, 1, $C_{4'}H$), 4.93 (s, 1, $J_{2',3'} = J_{3',4'}$ = 0 Hz, $C_{3'}H$ or $C_{2'}H$), 4.95 (s, 1, $C_{3'}H$ or $C_{2'}H$), 5.10 (q, 1, J_{gem} = 14 Hz, $J_{4',5'}$ = 2.5 Hz, $C_{5'a}H$), 6.39 (s, 1, $C_{1'}H$), 8.02 (s, 1, C_2H or C_8H), 8.91 (s, 1, C_2H or C_8H).

Anal. Calcd for $C_{13}H_{14}N_4O_4 \cdot H_2O$: C, 50.64; H, 5.23; N, 18.18. Found: C, 50.61; H, 5.40; N, 18.34.

Evaporation of the chloroform phase left a syrup (1.04 g) that was crystallized from ethanol giving 65 mg of 5'-deoxy-5'-iodo-2',3'-O-isopropylideneinosine (**26**) as needles of mp 195–197° dec (lit.[34] mp 203–204° dec). Chromatography of the mother liquors on a column of silicic acid using a gradient (0–30%) of methanol in chloroform gave a further 70 mg (total yield 15%) of **26**: λ_{max}^{MeOH,H^+} 249 mμ (ε 11,600); $\lambda_{max}^{MeOH/OH^-}$ 254 mμ (ε 12,200); nmr (d_6-DMSO) 1.52 and 1.32 ppm (s, 3, CMe_2), 3.41 (m, 2, $C_{5'}H_2$), 4.35 (h, 1, $J_{3',4'}$ = 3 Hz, $J_{4',5'}$ = 6.5 Hz, $C_{4'}H$), 4.99 (q, 1, $J_{3',4'}$ = 3 Hz, $J_{2',3'}$ = 6 Hz, $C_{3'}H$), 5.45 (q, 1, $J_{2',3'}$ = 6 Hz, $J_{1',2'}$ = 2.5 Hz, $C_{2'}H$), 6.24 (d, 1, $J_{1',2'}$ = 2.5 Hz, $C_{1'}H$), 8.16 (s, 1, C_2H or C_8H), 8.36 (s, 1, C_2H or C_8H); ORD (H_2O) negative Cotton effect with a trough at 285 mμ (Φ −3300°) and a peak at 255 mμ (Φ −580°).

Anal. Calcd for $C_{13}H_{15}N_4O_4I$: C, 37.33; H, 3.62; N, 13.40. Found: C, 37.55; H, 3.82; N, 13.71.

Registry No.—**1**, 17579-99-6; **5a**, 362-43-6; **8b**, 14842-09-2; **10b**, 24498-13-3; **15b**, 24453-27-8; **19**, 24453-28-9; **22**, 24453-29-0; **29**, 24453-30-3; **14a**, 50-89-5.

Nucleosides. LXV. Synthesis and Reactions of Some Pyrimidine 2',6-Anhydronucleosides[1]

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The synthesis of a series of 4-substituted 2-oxo-6-hydroxypyrimidine 2',6-anhydronucleosides (4-oxo, 4-thio, 4-methylthio, 4-hydroxylamino, and 4-amino) is described, and their chemical properties are compared with certain 5',6-anhydronucleosides. These 2',6-anhydro compounds undergo facile ring opening in aqueous base to give the corresponding 6-oxo-1-β-D-arabinofuranosylpyrimidines, but unlike the 5',6-anhydronucleosides they are exceedingly stable in dilute aqueous acid. Treatment of either 4-amino- or 4-methylthio-1-β-D-arabinofuranosylpyrimidine-2,6-dione with aqueous acid gives 2',6-anhydro-1-(β-D-arabinofuranosyl)barbituric acid as the major product. In anhydrous base the 4-amino- and 4-methylthio-2',6-anhydro compounds undergo rearrangement to their 2',2-anhydro isomers. A plausible mechanism for this rearrangement is given.

Although pyrimidine nucleosides containing a 5',6-anhydro linkage (for example **1**) are now well known,[2-4] only one example (**2**) of the corresponding 2',6-anhydro system has been reported.[5,6] This study deals with the synthesis of a series of 2',6-anhydronucleosides and demonstrates that their chemical properties differ in several important respects from those of the 5',6-anhydro compounds.

The 2',6-anhydronucleoside **2**, which is readily prepared by treatment of arabinosyl-5-bromouracil with sodium methoxide in methanol,[5,7] was converted into a series of 4-substituted derivatives as outlined in Scheme I. These transformations involve the 4-thione **7**, a key intermediate that was prepared in 78% yield by thiation of the dibenzoate **4** with P_2S_5 in refluxing 1,4-dioxane.[8] Attempts to prepare the 4-amino nucleoside **9** by treatment of the 4-thione **7** with alcoholic ammonia under a variety of conditions resulted in either no reaction or in considerable degradation with very low yields (<10%) of the desired product **9**. Similarly, treatment of the 4-methylthio nucleoside **8** with either liquid or alcoholic ammonia failed to give acceptable yields of **9**. As will be shown later, the low yields of **9** obtained in these amination reactions are due in part to unexpected rearrangements of the 4-methylthio nucleoside **8** and of **9** itself.

A satisfactory synthesis of the 4-amino nucleoside **9** was achieved *via* the 4-hydroxylamino nucleoside **12**. The 4-methylthio derivative **8** (obtained *via* **10**) reacted with an excess of hydroxylamine in methanol to give **12** directly. Under the same conditions, however, the 4-thione **10** afforded an intermediate bishydroxylamino compound[9] **11** which underwent acid-catalyzed elimination of hydroxylamine to give **12** in 66% yield. Reduction of **12** using palladium–charcoal catalyst gave the 4-amino nucleoside **9**. Attempts to deaminate **9** with nitrous acid, as part of the structural proof, failed

(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).

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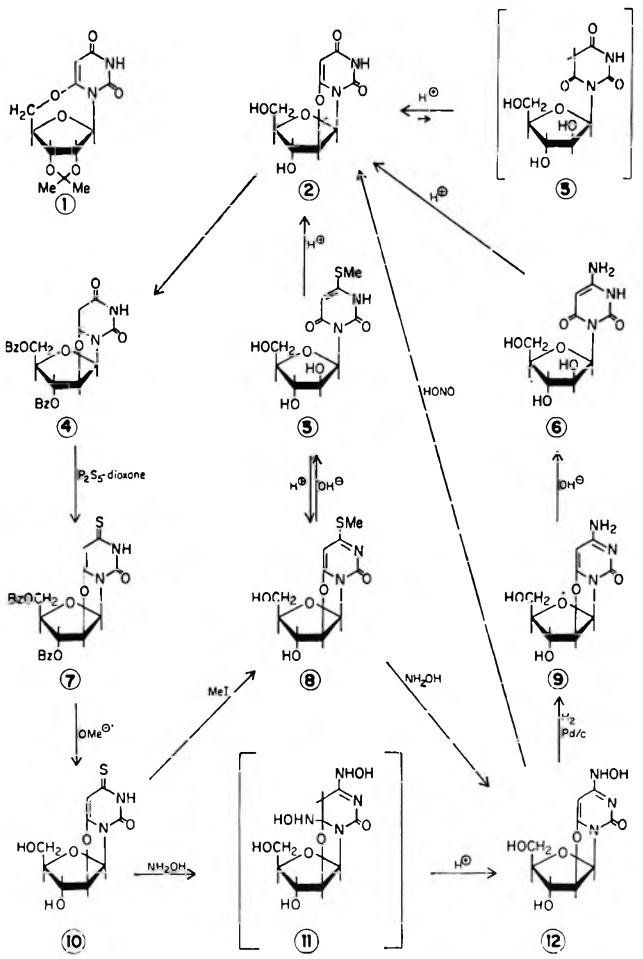
(7) Compound **2** has also been prepared[6] by reductive dehalogenation of the corresponding 5-iodo nucleoside. The latter compound was isolated (yield unstated) from a mixture of products obtained by iodination of 1-β-D-arabinofuranosylcytosine.

(8) This reagent combination (P_2S_5–dioxane) affords higher yields of 4-thiones in a shorter reaction time than the conventional P_2S_5–pyridine system (R. S. Klein, *et al.*, manuscript in preparation) for the thiation of nucleosides. With the conventional system **7** was obtained in only ~50% yield after a 24-hr reaction period. The authors are indebted to Dr. M. P. Kotick of this institute for suggesting the applicability of the P_2S_5–dioxane reagent to nucleosides.

(9) An intermediate bishydroxylamino compound has also been observed in the hydroxylamination of 4-thiouridine; see I. Wempen, N. Miller, E. A. Falco, and J. J. Fox, *J. Med. Chem.*, **11**, 144 (1968), and references therein.

SCHEME I



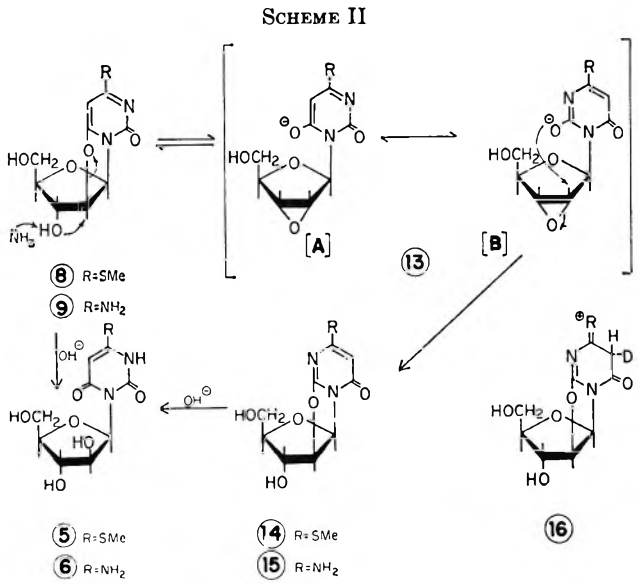
to give any **2** and **9** was recovered unchanged. However, the 4-hydroxylamino compound **12**, the immediate precursor of **9**, could be converted into **2** by treatment with nitrous acid, thereby confirming the 2′,6-anhydro structure.

Acid–Base Stability of the 2′,6-Anhydro Linkage.—The 2′,6-anhydronucleosides are in general unstable in aqueous alkali and in this regard they resemble their 5′,6-anhydro counterparts.[2,3] Thus treatment of **9** with 1 *N* sodium hydroxide at room temperature afforded 4-amino-1-(β-D-arabinofuranosyl)pyrimidine-2,6-dione (**6**) in excellent yield. The structure of **6** was demonstrated by the similarity of the ultraviolet spectral and acidic (pK_a = 8.52) data to that of 4-aminopyrimidine-2,6-dione (pK_a = 8.25) and its 1-β-D-ribofuranosyl derivative.[10] Similarly, the 4-methylthio nucleoside **8** underwent rapid anhydro ring opening in 1 *N* sodium hydroxide to give the 4-methylthiopyrimidine-2,6-dione nucleoside **5**, which was identified by comparison of its ultraviolet spectrum with that of the corresponding ribonucleoside.[10,11] As expected, the 4-oxo nucleoside **2** is relatively stable in 1 *N* sodium hydroxide at 25°, presumably because it can exist as a monoanion which is not readily attacked by hydroxide ion. However some ring opening does occur as shown by a 25% decrease in concentration of **2** over a 1-week period under the above conditions. 1-β-D-Arabinofuranosylbarbituric acid (**3**) was not detected in the reaction mixture probably because this compound, like the corresponding ribonucleoside,[2] would be unstable in aqueous base.

Unlike the seven-membered 5′,6-anhydro ring of **1**, the five-membered 2′,6-anhydro ring of **2** is remarkably stable in acidic media. Thus **2** was recovered unchanged after refluxing in 1 *N* hydrochloric acid over a 24-hr period; in 12 *N* hydrochloric acid at room temperature, **2** is stable for at least 4 days. This behavior contrasts to that of **1** which is completely hydrolyzed within 8 hr by 0.1 *N* hydrochloric acid at 50° to give 1-β-D-ribofuranosylbarbituric acid.[2] That any equilibrium between **2** and **3** is almost exclusively in favor of the ring-closed form **2** is shown by the following data. Treatment of the 4-amine **6** with 1 *N* hydrochloric acid at 48° resulted in the quantitative formation of **2**. This reaction *must* proceed *via* the barbituric acid nucleoside **3** rather than the 2′,6-anhydro-4-amino compound **9**, because compound **9** is itself stable under these reaction conditions. Ring closure of **3** would then involve addition of the 2′-hydroxy group across the 6-carbonyl function followed by acid-catalyzed elimination of water from the resulting dihydro intermediate. In a similar manner, acid treatment of the 4-methylthio nucleoside **5** afforded predominately **2** together with a small amount of the 2′,6-anhydro 4-methylthio nucleoside **8**. Since compound **8** is stable under the reaction conditions, the major product **2** is again formed *via* **3**.

Rearrangement of 2′,6-Anhydronucleosides.—It was pointed out earlier that treatment of the 4-methylthio nucleoside **8** with ethanolic ammonia (105°, 5 hr) afforded only small amounts of the 4-amino derivative **9**. Instead, **8** undergoes rearrangement to the isomeric 2′,2-anhydro-1-(β-D-arabinofuranosyl)-2-hydroxy-4-methylthiopyrimidin-6-one (**14**, Scheme II), a crystalline compound which was isolated in 27% yield. The structure assigned to **14** rests on the following data: base-catalyzed hydrolysis of **14** afforded the same product (**5**) as was formed by hydrolysis of **8**, thus establishing that **14** is an *arabino* nucleoside containing an anhydro bridge at either the 5′ or 2′ position. That the 5′ position is not involved in the anhydro linkage

SCHEME II



(10) M. W. Winkley and R. K. Robins, *J. Chem. Soc. C*, 791 (1969).

(11) Attempts to displace the 4-methylthio group of **5** with liquid ammonia (50°), ethanolic hydroxylamine (108°), or anhydrous hydrazine (25°) were unsuccessful and in each case **5** was recovered unchanged.

of **14** follows from the nmr spectrum which showed the H-5′ signals as a narrow multiplet at δ 3.30. In a 5′-anhydro structure the H-5′ signals would appear at lower field (for example[2] δ 4.08, 4.73 for compound **1**) as a widely spaced quartet with $J_{5',5'} \cong 13$ Hz.[2] In fact, except for the H-5 signal at δ 5.81, the nmr spectrum of **14** is almost identical with that of starting material **8** (H-5, δ 6.07). The similarity of the nmr spectra of **8** and **14** means that both compounds have the same conformation and, therefore, contain anhydro rings of the same size. This requirement is met only by a 2′,2-anhydro structure for **14**. Further support for this assignment is that H-5 of **14** undergoes slow exchange for deuterium in DMSO-d_6–DCl. This exchange is consistent with a 4-methylthio-6-oxo system where the cation **16** can be formed by deuteration at C-5. This type of ion clearly cannot be formed in a 4-methylthio-2-oxo system such as **8**, and, in fact, no measurable incorporation of deuterium at C-5 was observed when **8** was treated with DMSO-d_6–DCl over a 24-hr period.

A mechanism that accounts for the formation of **14** from **8** involves displacement of the 2′-anhydro linkage by the 3′-hydroxyl group to form the *ribo*-epoxide **13**. Attack of the initially formed C-6 oxygen anion (structure A) on C-2′ would regenerate **8** but attack by the C-2 oxygen anion (structure B) would lead to **14**. Ammonia functions only as a base in this mechanism and this is supported by the observed formation of **14** when **8** is treated with hot ethanolic triethylamine. The mechanism is also consistent with the observation that the 4-oxo nucleoside **2** is stable in ethanolic ammonia (105°, 24 hr). In this case dissociation of the N-3 hydrogen occurs and the monoanionic form predominates, a fact which we have determined spectrophotometrically.[12] Displacement of the anhydro linkage of **2** by attack of the C-3′ substituent (to form a *ribo*-epoxide) would be less favored because the negatively charged aglycon would be a poor leaving group.

As with compound **8**, treatment of **9** with ethanolic ammonia (108°, 24 hr) afforded a crystalline product (**15**) with analytical and spectroscopic data consistent with the 2,2′-anhydro structure. The basic pK_a of **9** (4.22) and **15** (<1) are in the expected order and may be compared with those of 1-methylcytosine (pK_a = 4.57)[13] and 1-methyl-4-aminopyrimidin-6-one (pK_a = 0.98),[14] respectively. Compound **15** underwent rapid exchange of H-5 for deuterium when treated with DMSO-d_6–DCl, probably *via* the cation **16**, and formed a blue, crystalline nitroso compound when treated with nitrous acid. In contrast, the 4-amino 2′,6-anhydronucleoside **9** did not undergo deuterium exchange and failed to react with nitrous acid.

General Considerations.—The phenomenon of anhydro bond migration has been observed previously. It has been shown that 2,3′-anhydro-1-(2,5-di-*O*-benzoyl-β-D-xylofuranosyl)uracil undergoes thermal rearrangement to the 2,2′-anhydro isomer *via* a 2′,3′-benzoxonium ion intermediate.[15] The isomerization of a 2,5′-anhydro-*arabino*-nucleoside to the 2,2′ isomer[16] and of a 2,5′-anhydro-*xylo*-nucleoside to a 2,3′ isomer[17] have also been recorded. In these cases, however, anhydro migration resulted from attack by an "up" sugar hydroxyl on the C-2 position of the anhydro linkage.

That a 2′,3′-*ribo*-epoxide **13** is involved in the conversion of a 2′,6-anhydronucleoside into its 2,2′ isomer is supported by several studies[18] which attest to the extreme susceptibility of such epoxides to attack by nucleophiles including the 2-carbonyl of the aglycon. It is reasonable to expect that suitable derivatives of the as yet unknown 3′,6-anhydronucleosides will also undergo rearrangement to the 2,2′ isomers *via* the same epoxide intermediate **13**.

Experimental Section

General Procedures.—Melting points were determined with a Thomas–Hoover apparatus (capillary method) and are uncorrected. Ultraviolet spectra were recorded on a Cary Model 15 spectrometer and nuclear magnetic resonance spectra were measured with a Varian A-60 spectrometer using DMSO-d_6 as a solvent and tetramethylsilane as an internal standard. Values given for coupling constants (hertz) and chemical shifts (δ) are first order. Preparative chromatographic separations were carried out on 20 × 20 cm plates coated with thin layers (0.25 mm) of silica gel GF_{254} or thick layers (2 mm) of silica gel PF_{254}. In each case separated materials were detected with uv light and recovered by extraction of the silica with hot ethanol. Apparent pK_a values were determined spectrophotometrically and are accurate to ± 0.05 pH unit unless otherwise specified. Evaporations were carried out under reduced pressure with bath temperatures kept below 45°. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and by Galbraith Laboratories, Inc., Knoxville, Tenn.

2′,6-Anhydro-1-(3,5-di-*O*-benzoyl-β-D-arabinosyl)-6-hydroxypyrimidine-2,4-dione (4).—Benzoyl chloride (8.1 g, 58 mmol) was added dropwise to a stirred solution of **2** (7.0 g, 29 mmol) in 200 ml of dry pyridine. The solution was kept at room temperature overnight, concentrated to ~100 ml, and then poured into ice water. The resulting solid (11.3 g, 87%) was washed well with water, and a portion was crystallized from methanol to give an analytical sample: mp 158–160°; nmr, 10.9 (1, broad s, NH), 8.2–7.3 (10, m, benzoyl protons), 6.45 (1, d, H-1′, $J_{1',2'}$ = 5.0 Hz), 5.73 (2, m, H-2′, H-3′), 5.11 (1, s, H-5), 4.82 (1, m, H-4′), 4.45 (2, m, H-5′, H-5′), 3.32 (1, s, 0.5 H_2O).

Anal. Calcd for $C_{23}H_{18}N_2O_8 \cdot {}^1/_2H_2O$: C, 60.15; H, 4.13; N, 6.10. Found: C, 59.80; H, 4.15; N, 5.97.

2′,6-Anhydro-1-(3,5-di-*O*-benzoyl-β-D-arabinosyl)-6-hydroxy-2-oxopyrimidine-4-thione (7).—Phosphorus pentasulfide (6.44 g, 29 mmol) was dissolved in a hot solution of **4** (13.2 g, 29 mmol) in dioxane (200 ml) and the solution was refluxed for 35 min. A further charge of P_2S_5 (6.44 g) was added and refluxing was continued for a further 40 min. The cooled solution was concentrated to ~50 ml and poured into ice water. The aqueous mixture was extracted with chloroform (700 ml), sodium chloride was added to facilitate dispersal of the resulting emulsion, and the chloroform layer was washed with aqueous sodium chloride. The chloroform solution was dried (Na_2SO_4) and then concentrated to dryness. The residue was dissolved in ethyl acetate (50 ml), and the solution was diluted with methanol (200 ml) and set aside to crystallize. The yield of pure **7** was 7.6 g (56%). A second crop, obtained by concentration, was recrystallized to give a further 3.0 g (total yield 78%): mp 114–115°; nmr, 12.3 (1, broad s, NH); 8.2–7.4 (10, m, benzoyl protons), 6.50 (1, d, H-1′, $J_{1',2'}$ = 5.5 Hz), 6.00 (1, s, H-5), 5.75 (2, m, H-2′,

(12) Compound **2** exhibits spectral shifts in aqueous solution between pH 7 and 12.[5,6] Similar spectral shifts are observed in ethanol *vs.* ethanolic ammonia.

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H-3'), 4.85 (1, m, H-4'), 4.47 (2, m, H-5', H-5'), 3.31 (1, s, 0.5 H_2O).

Anal. Calcd for $C_{23}H_{18}N_2O_7S \cdot {}^1/_2H_2O$: C, 58.11; H, 4.00; N, 5.89; S, 6.73. Found: C, 58.12; H, 4.28; N, 5.76; S, 6.57.

2',6-Anhydro-1-(β-D-arabinofuranosyl)-6-hydroxy-2-oxopyrimidine-4-thione (10).—Compound **7** (5 g, 10.5 mmol) was dissolved in methanol (200 ml) containing sodium (200 mg), and the solution was kept at room temperature for 4 hr. Water (20 ml) was added and the solution neutalized with ~2 g of Dowex 50 (H^+). The filtrate was concentrated to dryness, and the residue (2.09, 87%) was crystallized from 95% ethanol to give needles: mp 223–224° dec; $\lambda_{max}^{pH\ 1}$ 320 mμ (ε 36,700) and 250 (3600), $\lambda_{min}^{pH\ 1}$ 273 (520), $\lambda_{max}^{pH\ 14}$ 306.5 mμ (ε 31,250) and 274 (9600), $\lambda_{min}^{pH\ 14}$ 281 (8800); nmr, 12.1 (1, broad s, NH), 6.24 (1, d, H-1', $J_{1',2'}$ = 5.5 Hz), ~5.80 (2, H-5, s at 5.85 overlapped by 3'-OH), 5.24 (1, d, H-2'), 4.95 (1, t, 5'-OH), 4.33 (1, narrow m, H-3'), 4.05 (1, sextet, H-4', $J_{3',4'}$ = 2 Hz, $J_{4',5'}$ = 5 Hz), 3.3 (2, m, H-5', H-5').

Anal. Calcd for $C_9H_{10}N_2O_5S$: C, 41.86; H, 3.88; N, 10.85; S, 12.40. Found: C, 41.88; H, 3.88; N, 10.77; S, 12.40.

2',6-Anhydro-1-(β-D-arabinofuranosyl)-6-hydroxy-4-methylthiopyrimidin-2-one (8).—Methyl iodide (1 ml) was added to a stirred solution of **10** (516 mg, 2 mmol) in 40 ml of methanol, and 1 *N* sodium hydroxide was added dropwise to keep the solution at pH ~9. After 2 hr of stirring at room temperature the reaction mixture was neutralized with 1 *N* HCl, and the solution was concentrated to remove the methanol. Water (10 ml) was added and the solution was passed through a column (2.5 × 12 cm) of Dowex 50 (H^+). The column was washed with 250 ml of water, and then the product was eluted with 0.7 *N* aqueous ammonia. The eluate was concentrated to dryness and the residue (440 mg, 81%) crystallized from 35 ml of ethanol to give colorless needles: mp 200–203° (sinters 193°); $\lambda_{max}^{pH\ 1}$ 304 mμ (ε 29,400) and 256 (5700), $\lambda_{min}^{pH\ 1}$ 270 (4350), $\lambda_{max}^{pH\ 10}$ 294 (ε 19,000) and 263 (11,960), $\lambda_{min}^{pH\ 10}$ 272 (11,150) basic pK_a ~2; nmr, 6.30 (1, d, H-1', $J_{1',2'}$ = 5.5), 6.07 (1, s, H-5), 5.87 (1, d, 3'-OH, $J_{3',OH}$ = 4.5), 5.27 (1, d, H-2'), 4.91 (1, t, 5'-OH, $J_{5',OH}$ = 5.0), 4.37 (1, m, H-3'), 4.04 (1, m, H-4'), 3.25 (2, m, H-5', H-5'), 2.45 (s, overlapped by solvent signal, SCH_3).

Anal. Calcd for $C_{10}H_{12}N_2O_5S$: C, 44.12; H, 4.41; N, 10.29; S, 11.76. Found: C, 44.02; H, 4.44; N, 10.25; S, 11.82.

2',6-Anhydro-1-(β-D-arabinofuranosyl)-4-hydroxylamino-6-hydroxypyrimidin-2-one (12).—A solution of hydroxylamine (58 mmol) in methanol [freshly prepared by adding sodium (1.3 g) in methanol (200 ml) to a solution of hydroxylamine hydrochloride (4.05 g) in methanol and then removing the precipitated sodium chloride] was added to 1.5 g (5.8 mmol) of compound **10**. The solution was kept at 48° for 19 hr, at which time an aliquot showed loss of uv absorption at 320 mμ. The reaction mixture was concentrated to 50 ml and water (100 ml) was added. The solution was adjusted to pH 1 with 12 *N* HCl, and the appearance of absorption at 269 mμ (at pH 1) was monitored. After 1 hr the reaction mixture was passed through a column (2.5 × 15 cm) of Dowex 50 (H^+), and the resin was washed with 250 ml of water. Elution with 0.7 *N* aqueous ammonia then afforded 1 g (66%) of **12** which crystallized from 95% ethanol as colorless rods: mp 211–212° dec; $\lambda_{max}^{pH\ 1}$ 269 mμ (ε 21,450), $\lambda_{min}^{pH\ 1}$ 235 (2700); nmr, 9.6 (2, broad peak, NHOH), 6.08 (1, d, H-1', $J_{1',2'}$ = 5.0 Hz), ~5.7 (1, broad peak, 3'-OH), ~5.0 (3, m, H-5, H-2', 5'-OH), 4.24 (1, m, H-3'), 3.95 (1, m, H-4'), 3.30 (2, m, H-5', H-5').

Anal. Calcd for $C_9H_{11}N_3O_6$: C, 42.02; H, 4.28; N, 16.34. Found: C, 42.00; H, 4.36; N, 16.34.

4-Amino-2',6-anhydro-1-(β-D-arabinofuranosyl)-6-hydroxypyrimidin-2-one (9).—A solution of **12** (538 mg, 2.1 mmol) in water (25 ml containing 3 drops of 12 *N* HCl) was hydrogenated at atmospherric pressure over 10% palladium–charcoal catalyst (150 mg). When the theoretical amount of hydrogen had been taken up, the catalyst was removed and the filtrate was passed through a column (2.5 × 10 cm) of Dowex 50 (H^+). The resin was washed with water until the eluate was neutral, and then the product was eluted with 0.7 *N* aqueous ammonia. Concentration of the eluate afforded 320 mg (63%) of **9** which crystallized from 95% ethanol as micaceous plates, mp 278–279° eff; $\lambda_{max}^{pH\ 7}$ 261 mμ (ε 14,260), $\lambda_{min}^{pH\ 7}$ 240 (5260), $\lambda_{max}^{pH\ 0}$ 265 (ε 22,320), $\lambda_{min}^{pH\ 0}$ 233 mμ (2340); basic pK_a = 4.22; nmr, 7.06 (2, broad s, NH_2), 6.14 (1, d, H-1', $J_{1',2'}$ = 5.2 Hz), 5.77 (1, d, 3'-OH, $J_{3',OH}$ = 4.5 Hz), ~5.1 (2, H-5 s at 5.11 overlapped by H-2' d at 5.14), 4.89 (1, t, 5'-OH, $J_{5',OH}$ = 5.5 Hz), 4.28 (1, m, H-3'), 3.95 (1, m, H-4'), 3.27 (2, m, H-5', H-5').

Anal. Calcd for $C_9H_{11}N_3O_5$: C, 44.81; H, 4.56; N, 17.42. Found: C, 44.75; H, 4.58; N, 17.41.

4-Methylthio-1-(β-D-arabinofuranosyl)pyrimidine-2,6-dione (5).—A solution of **8** (1 g) in 5 ml of 1 *N* sodium hydroxide was kept at room temperature for 1 hr. The solution was then neutralized with an excess of Dowex 50 (H^+) and the filtrate was concentrated to dryness. The residue (1.02 g, 98%) crystallized from methanol as a monomethanolate which melted indistinctly (foams ~110–120°). Drying *in vacuo* at 100° for 24 hr failed to remove the methanol: uv $\lambda_{max}^{pH\ 0}$ 225 mμ (ε 9800), (shoulder at 236), and 283 (15,600), $\lambda_{min}^{pH\ 0}$ 250 (2900); $\lambda_{max}^{pH\ 14}$ 231 (ε 11,400), 248 (12,800) and 295 (12,800), $\lambda_{min}^{pH\ 14}$ 238 (11,300), and 268 (3700); nmr, 11.3 (1, broad s, NH), 6.41 (1, d, H-1', $J_{1',2'}$ = 7.5 Hz), 5.41 (1, s, H-5), ~5.16 (2, broad peak, 2'-OH, 3'-OH), ~4.2 (4, m, H-2', H-3', 5'-OH and methanol OH), ~3.6 (3, m, H-4', H-5', H-5'), 3.18 (3, s, CH_3OH), 2.45 (s, overlapped by solvent signal, SCH_3).

Anal. Calcd for $C_{10}H_{14}N_2O_6S \cdot CH_3OH$: C, 40.99; H, 5.59; N, 8.70; S, 9.94. Found: C, 40.93; H, 5.59; N, 8.73; S, 9.91.

4-Amino-1-(β-D-arabinofuranosyl)pyrimidine-2,6-dione (6).—A solution of **9** (482 mg) in 10 ml of 1 *N* NaOH was kept at room temperature until the change in uv absorption from 262.5 to 272 mμ (as determined with aliquots at pH 11) was complete (~72 hr). The solution was neutralized with excess Dowex 50 (H^+) and the filtrate was concentrated to dryness. The residue (320 mg, 62%) was recrystallized from a small volume of water to give colorless crystals: mp 231–232° dec; $\lambda_{max}^{pH\ 2-7}$ 266 mμ (ε 22,970), $\lambda_{min}^{pH\ 2-7}$ 237 (2600), $\lambda_{max}^{pH\ 12}$ 272 (ε 16,100), $\lambda_{min}^{pH\ 12}$ 245 (1570); acidic pK_a = 8.52; nmr, 10.2 (1, broad s, NH), 6.25 (3, broad peak, NH_2 and H-1'), 5.0 (2, broad, 2'-OH, 3'-OH), ~4.1 (4, H-5 s at 4.50 overlapped by H-2', H-3' and 5'-OH), ~3.5 (3, m, H-4', H-5', H-5').

Anal. Calcd for $C_9H_{13}N_3O_6$: C, 41.72; H, 5.01; N, 16.21. Found: C, 41.76; H, 4.89; N, 16.22.

2,2'-Anhydro-1-(β-D-arabinofuranosyl)-2-hydroxy-4-methylthiopyrimidin-6-one (14).—A solution of **8** (252 mg) in 50 ml of anhydrous ethanolic ammonia (saturated at 0°) was heated in a sealed tube at 105° for 5 hr. The cooled solution was concentrated to dryness, and the residue was separated into three components (R_f ~0, 0.5, and 0.6) by thick layer chromatography in methanol–chloroform (1:10). The material with R_f 0.5 (20 mg) was identical (uv, ir, melting point) with starting material **8**. The material with R_f 0.6 was recrystallized from ethyl acetate to give pure **14** (63 mg, 27%): mp 194–196°; $\lambda_{max}^{pH\ 1-10}$ 285 mμ (ε 13,000), 248 (11,300), and 232 (11,310); $\lambda_{min}^{pH\ 1-10}$ 239.5 mμ (ε 10,150) and 261 (6100); basic pK_a <0; nmr, 6.34 (1, d, H-1', $J_{1',2'}$ = 5.8 Hz), ~5.8 (s, H-5 s at 5.81 overlapped by 3'-OH d at 5.84), 5.18 (1, d, H-2'), 4.92 (1, t, 5'-OH, $J_{5',OH}$ = 5.2 Hz), 4.39 (1, m, H-3'), 4.05 (1, m, H-4'), 3.30 (2, m, H-5', H-5'), 2.45 (s, overlapped by solvent signal, SCH_3).

Anal. Calcd for $C_{10}H_{12}N_2O_5S$: C, 44.12; H, 4.41; N, 10.29; S, 11.76. Found: C, 44.16; H, 4.28; N, 10.18; S, 11.64.

The material with R_f ~0 was separated into two fractions on thin layer chromatography in chloroform–methanol (4:1). These trace components were identified from their uv spectra as compounds **9** and **15**.

4-Amino-2,2'-anhydro-1-(β-D-arabinofuranosyl)-2-hydroxypyrimidin-6-one (15).—Treatment of **9** (30 mg) with alcoholic ammonia for 24 hr, as described above in the preparation of **14**, and fractionation of the crude residue by thin layer chromatography [triple development in chloroform–methanol (4:1)] gave unchanged starting material (9 mg) and 16.7 mg (80%) of **15** recrystallized from methanol: mp 217–218° (sinters at 193°); $\lambda_{max}^{pH\ 1}$ 264 mμ (ε 11,330) and 209 (23,000); $\lambda_{min}^{pH\ 1}$ 232 (2200); $\lambda_{max}^{pH\ 7}$ 264.5 mμ (ε 11,800) and 210 (24,100); $\lambda_{min}^{pH\ 7}$ 232 (1320); basic pK_a <1; nmr 6.60 (2, broad s, NH_2), 6.25 (1, d, H-1, $J_{1',2'}$ = 5.7 Hz), 5.78 (1, d, 3'-OH, $J_{3',OH}$ = 4.5 Hz), 5.15 (1, d, H-2'), 4.92 (1, t, 5'-OH, $J_{5',OH}$ = 5.5 Hz), 4.72 (1, s, H-5), 4.33 (1, m, H-3'), 3.97 (1, m, H-4'), 3.28 (2, m, H-5', H-5').

Anal. Calcd for $C_9H_{11}N_3O_6$: C, 44.81; H, 4.56; N, 17.42. Found: C, 44.33; H, 4.77; N, 17.09.

Acid-Catalyzed Conversion of 4-Substituted 1-(β-D-Arabinofuranosyl)-pyrimidine-2,6-diones into 2. From 5.—A solution of **5** (100 mg) in 50 ml of 1 *N* hydrochloric acid was heated at 48° for 19 hr. Periodic examination of aliquots (diluted to 1 × 10^{-4} with water and adjusted to pH 1) showed a gradual loss of absorption at 283 mμ together with appearance of peaks at 252 mμ (corresponding to ~80% yield of **2**) and 306 mμ (corresponding to ~7% yield of **8**). The reaction mixture was passed through a column containing excess Amberlite IR-45, and the effluent

and washings were concentrated to dryness. A portion of the residue was fractionated by thin layer chromatography (chloroform–methanol, 5:1) to give crystalline material identical (uv, ir, melting point) with authentic **2**. A faster moving component was identified as **8** from its uv spectrum and chromatographic properties.

From 6.—A solution of **6** (10 mg) in 10 ml of 1 *N* hydrochloric acid at 48° was monitored (at pH 12) in the ultraviolet. The initial absorption at 272 mμ shifted over a 50-min period to give a peak at 252 mμ having a final ε value corresponding to a quantitative yield of **2**. Concentration of the reaction mixture and isolation of the product by thin layer chromatography (chloroform–methanol, 5:1) afforded a single component which gave uv and ir spectra identical with those of authentic **2**.

Registry No.—**4**, 24704-26-5; **5**, 24704-27-6; **6**, 24704-28-7; **7**, 24710-89-2; **8**, 24710-90-5; **9**, 24704-29-8; **10**, 24710-91-6; **12**, 24710-92-7; **14**, 24710-93-8; **15**, 24710-94-9.

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Nucleosides. LXVII. The Chemistry of 4-Methyl-2-pyrimidinone Ribonucleosides[1]

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The synthesis of 4-methyl-2-pyrimidinone and 4,5-dimethyl-2-pyrimidinone ribonucleosides **3a** and **3b** is described. The site of glycosylation is determined by two independent routes. Nitrosation of the 4-methyl group converts **3a** and **3b** into their corresponding oxime derivatives (**7a** and **7b**) which, by treatment with acetic anhydride, afford the corresponding nitriles (**8a** and **8b**). The nitrile groups are easily displaced by a variety of nucleophiles. Reduction of oxime **7a** followed by acetylation gives the N-acetylated aminomethyl derivative (**10**) which undergoes facile air oxidation to the 4-carboxymethyl derivative (**11**). In model studies, the structure of **11** is established by an unambiguous synthesis of 1-methyl-2-oxo-4-pyrimidinecarboxylic acid methyl ester (**16**) from 3-methylorotic acid. 1-Methyl-2-oxo-4-pyrimidinecarboxaldehyde oxime (**14**) is also shown to undergo reduction, acetylation, and autoxidation to **16**.

As part of a program directed toward the syntheses of nucleosides of potential biological interest, we have investigated the chemistry of the hitherto unknown ribofuranosyl derivatives of 4-methyl-2-pyrimidinones. Such nucleosides containing a basic aglycon may be viewed as isosteres of cytidine and, since they also contain a potential enamine system, may undergo reactions at the allylic position with electrophilic reagents leading to new types of nucleoside analogs.

Condensation of 4-methyl-2-pyrimidinone (**1a**) or its 5-methyl derivative (**1b**) with tri-*O*-benzoyl-D-ribofuranosyl chloride by the mercuric cyanide–nitromethane procedure[2] gave the blocked nucleosides **2** which were isolated as their hydrochloride salts in good yields (Scheme I). After debenzoylation of **2**, the unblocked nucleosides **3a** and **3b** were obtained as the crystalline hydrochloride salts.

The site of ribosylation (N-1) was established for nucleosides **3** as follows. Condensation of 6-methyluracil (**4**) with the halogenose by the generalized mercuric cyanide–nitromethane procedure[2b] afforded crystalline 3-(tri-*O*-benzoyl-β-D-ribofuranosyl)-6-methyluracil (**5**) in 70% yield, which exhibited an nmr spectrum with values identical with those reported for this product (as a syrup) by Winkley and Robins,[3] and by Prystaš and Šorm.[4] Debenzoylation of **5** followed by acetylation afforded the known[3] crystalline tri-*O*-acetate. Treatment of tri-*O*-benzoate **5** with phosphorus pentasulfide in pyridine, a widely used method for thiation of nucleosides,[5] was accompanied by extensive decomposition. When dioxane instead of pyridine was used as solvent in this reaction, a facile conversion of **5** to 4-thione **6** in above 70% yield occurred.[6] Assignment of the thioxo group to the 4 position of **6** rests on analogy with the thiation of 3-methyluracil (which gave the 4-thione exclusively)[7] and from subsequent reactions of **6**. Reductive desulfurization of **6** with various preparations of Raney nickel under a variety of conditions was complicated by excessive ring reduction. Partial reduction of **6** under mild conditions with activated Raney nickel prepared according to Brown[8] allowed at least the isolation by column chromatography of **2a** from the reaction mixture. Compound **2a**, thus obtained, was identical with that prepared by direct condensation from **1** and afforded the same crystalline picrate. These results establish unambiguously both the site of glycosylation in **2a** at N-1 and the 4-thioxo structure for **6**. Since nucleosides **3** derived from **2** exhibited very similar ultraviolet absorption spectral properties, both **3a** and **3b** are 1-substituted ribosyl derivatives.

Compound **1a** has been shown[9] to undergo nitrosa-

(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) N. Yamaoka, K. Aso, and K. Matsuda, *J. Org. Chem.*, **30**, 149 (1965); (b) K. A. Watanabe and J. J. Fox, *J. Heterocycl. Chem.*, **6**, 109 (1969).

(3) M. W. Winkley and R. J. Robins, *J. Org. Chem.*, **33**, 2822 (1968).

(4) M. Prystaš and F. Šorm, *Collect. Czech. Chem. Commun.*, **34**, 331, 2316 (1969).

(5) J. J. Fox, I. Wempen, A. Hampton, and I. L. Doerr, *J. Amer. Chem. Soc.*, **80**, 1669 (1958).

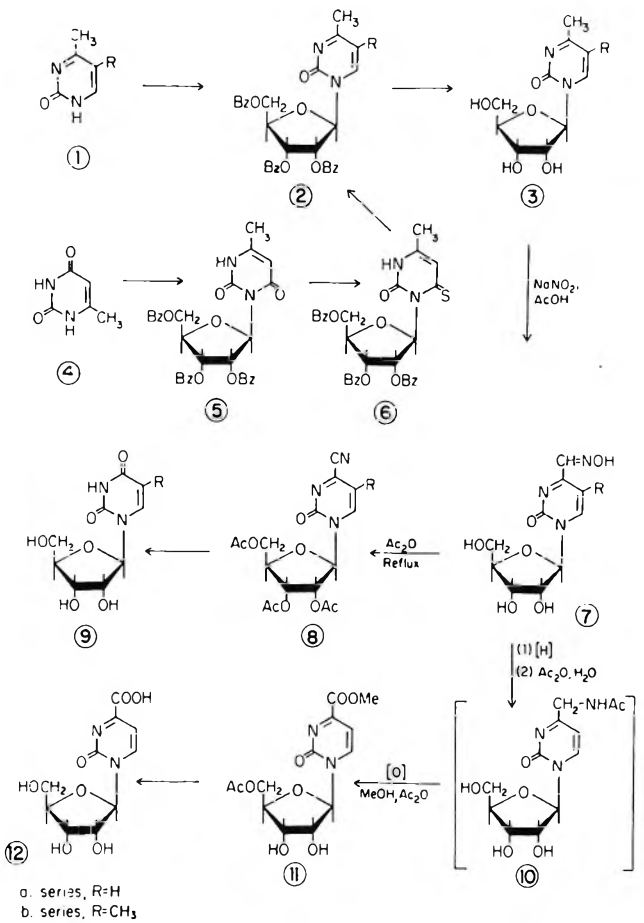
(6) The use of phosphorus pentasulfide in dioxane as a thiating reagent combination has since been applied in our laboratory (E. A. Falco, B. A. Otter, and J. J. Fox, manuscript in preparation) to other nucleosides which are thiated with difficulty in pyridine as solvent. This reagent combination (P_2S_5–dioxane) is described by L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 333, and should have wide application in the nucleoside area.

(7) T. Ueda and J. J. Fox, *J. Amer. Chem. Soc.*, **85**, 4024 (1963); K. A. Watanabe, H. A. Friedman, R. J. Cushley, and J. J. Fox, *J. Org. Chem.*, **31**, 2942 (1966).

(8) D. J. Brown, *J. Soc. Chem. Ind., London*, **69**, 353 (1950).

(9) G. D. Daves, Jr., D. E. O'Brien, L. R. Lewis, and C. C. Cheng, *J. Heterocycl. Chem.*, **1**, 130 (1964).

SCHEME I



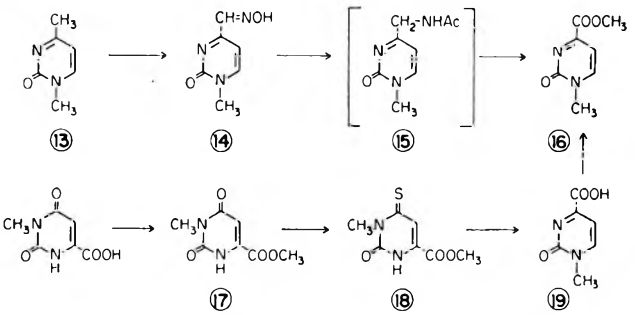
tion on the methyl group. Similar treatment of nucleosides **3** gave crystalline aldoximes **7** in good yields. These were readily converted to the tri-*O*-acetylated carbonitriles (**8**) by refluxing with acetic anhydride. Treatment of **8** with hydrochloric acid in methanol at ambient temperature resulted in displacement of the cyano function to afford crystalline uridine (**9a**) and 5-methyluridine (**9b**), respectively.[10] The exclusive formation of nucleosides **9** from **8** is best explained in this case[11] by initial protonation at N-3 followed by nucleophilic attack by water at C-4 to afford a cyanohydrin-like intermediate which eliminates hydrogen cyanide. The conversion of nucleosides **8** into **9** is also consistent with the 1-β-D-ribofuranosyl structures assigned to nucleosides **2** → **8** and suggests that the cyano derivatives **8** may serve as versatile intermediates for the introduction of other functional groups into the 4 position, thus leading to new nucleoside analogs.[11]

Attempts to tritylate selectively the 5′-hydroxyl function of **3a** resulted in the isolation by column chromatography of the expected 5′-tritylate along with a ditrityl derivative. Nmr spectroscopy (loss of methyl resonance) revealed that the second trityl function had affixed to the methyl group thus reflecting the susceptibility of this group to electrophilic substitution. This susceptibility is supported by the nmr spectrum of **3a** in DMSO-d_6 (methyl resonance at δ 2.28) which shows fairly rapid loss of the methyl resonance upon addition of D_2O. This exchange is catalyzed by acid. A similar situation obtains with the hydrochloride salt in which the protons of the 4-methyl substituent undergo exchange by deuterium. A similar type of exchange has been observed with **1a**.[12]

Attempts to obtain the aminomethyl derivative from **7a** by catalytic hydrogenation were unsuccessful owing to the propensity of the pyrimidine ring to reduction. If the reaction was stopped after the theoretical uptake of hydrogen and the aqueous solution treated with acetic anhydride, the problem of overreduction was partially alleviated. However, the reaction still developed some color and isolation of a product was unsuccessful. It was noted that the uv spectrum of the reaction shifted from that for the oxime ($\lambda_{max}^{pH\,7}$ 330 mμ) to 303 mμ akin to the $\lambda_{max}^{pH\,7}$ for **3a** which indicated that compound **10** had formed. The N-acetylation in methanol was monitored spectrophotometrically. Unexpectedly, a further shift on standing of λ_{max} from 303 to 335 mμ (pH 7.0) was observed. This second reaction was accelerated by bubbling oxygen in the mixture thus indicating an autoxidation process.[13] Acetamide was obtained as a by-product of this reaction. The major product, obtained by column chromatography, was shown to have structure **11** by nmr and by comparison of its uv spectrum with that for model compound **16** (see below).

In order to confirm the structure of nucleoside **11**, model studies were carried out with 1,4-dimethyl-2-pyrimidinone (**13**, Scheme II) which was converted into

SCHEME II



the oxime **14** with nitrous acid. When the same reduction and acetylation procedures were applied to this oxime, a crystalline compound identified as the methyl ester of 1-methyl-2-pyrimidinone-4-carboxylic acid (**16**) was obtained. Structure **16** was assigned on the basis of nmr and ir spectra and elemental analysis. In order to confirm its structure, compound **16** was also prepared by an unambiguous route from the methyl ester (**17**) of 3-methylorotic acid.[14] This ester was thiated to **18** then desulfurized with Raney nickel to **19** and esterified to **16** with diazomethane.

The ultraviolet characteristics of **16** were similar to those exhibited by nucleoside **11** obtained by autoxidation of **10** thus establishing the structure of the aglycon moiety of **11**. This product **11** was shown to be acetylated at position 5′ on the basis of its nmr spectrum and

(10) The conversion of 2-chloro-4-cyanopyrimidine to uracil by vigorous conditions had been demonstrated.[9]

(11) For example, reaction of nucleosides **9** with alcoholic ammonia affords cytidine and 5-methylcytidine. This reaction probably proceeds by direct displacement of the cyano group by the stronger nucleophile, ammonia.

(12) T. J. Batterham, D. J. Brown, and M. N. Paddon-Row, *J. Chem. Soc., B*, 171 (1967).

(13) When the reaction was performed under nitrogen, the spectral shift to 335 mμ did not occur.

(14) J. J. Fox, N. Yung, and I. Wempen, *Biochim. Biophys. Acta*, **28**, 295 (1957), and references therein.

by its positive reaction to a periodate–benzidine spray on tlc. Deesterification of **11** afforded the 4-carboxylic acid nucleoside (**12**) which was isolated as the crystalline cyclohexylamine salt.

The exocyclic methylene of **10** may be viewed as the β carbon of a potential enamine–imine system

$$-N{=}C{-}C{-}NHAc \rightleftharpoons NH{-}C{=}C{-}NHAc$$

The autoxidation of the β carbon in such systems has been noted[15] with certain indoles.

Experimental Section

General Procedures.—Melting points were determined on a Thomas–Hoover apparatus (capillary method) and are uncorrected. The nuclear magnetic resonance spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as internal reference. Chemical shifts are reported in parts per million (δ) and signals are described as s (singlet), d (doublet), 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[16] on silica gel G under positive pressure. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Spang Microanalytical Laboratory, Ann Arbor, Mich. The uv spectra of reactions monitored by changes in their absorbance were recorded on a Unicam SP 800 A spectrophotometer. The reported uv absorption spectral data were determined on a Cary Model 15 spectrophotometer; the apparent pK_a values were determined spectrophotometrically and are accurate to ± 0.05 pH unit unless otherwise indicated. All evaporations were carried out *in vacuo*.

4-Methyl-1-(tri-*O*-benzoyl-β-D-ribofuranosyl)-2-pyrimidinone Hydrochloride (2a).—A suspension of 2.44 g (0.0166 mol) of 4-methyl-2-pyrimidinone hydrochloride and 12.6 g (0.050 mol) of mercuric cyanide in 400 ml of nitromethane was refluxed and 100 ml distilled off. To the clear refluxing solution was added slowly a solution of 2,3,5-tri-*O*-benzoyl-D-ribosyl chloride [prepared from 10.5 g (0.0200 mol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose]. The red solution was refluxed for 20 min and cooled to room temperature. Any insoluble material was removed by filtration and the filtrate was evaporated. The residual syrup was dissolved in 200 ml of chloroform and the solution was filtered. The filtrate was extracted with 200 ml of 30% aqueous potassium iodide and with 200 ml of water, and the organic layer was dried over sodium sulfate. After filtration the solvent was removed and the residue was redissolved in 75 ml of dry benzene. The solution was cooled in ice and dry hydrogen chloride passed while stirring. Trituration of the precipitated gum gave a white semicrystalline solid which was removed by filtration from the dark red solution and was washed with ether. The procedure afforded 6.6 g (67%) of the crude hydrochloride. The neutralized product in chloroform was chromatographically pure. A small sample gave a picrate, mp 162–164°.

4-Methyl-1-β-D-ribofuranosyl-2-pyrimidinone Hydrochloride (3a).—The crude solid obtained above was partitioned between 100 ml of saturated aqueous sodium bicarbonate and 100 ml of chloroform. The organic layer was again washed with an equal volume of the sodium bicarbonate solution and finally with water. The organic layer was dried (sodium sulfate) and concentrated to a syrup. The residue was dissolved in 125 ml of warm methanol and was treated with 5 ml of alcoholic sodium methoxide (100 mg of sodium) overnight at room temperature. The reaction mixture was neutralized by stirring with 2.5 ml of wet Dowex AG 50 (H^+) resin and was then evaporated to 50 ml, diluted with 15 ml of ether, and dry hydrogen chloride was bubbled through the cold stirred solution. The crystalline precipitate was collected and a second crop was obtained from the mother liquor by further cooling and dilution with ether to give a total of 2.3 g of **3a**. Recrystallization from methanol gave an analytically pure sample: mp 164° dec; uv $\lambda_{max}^{0.1\ N\ HCl}$ 309 mμ (ϵ 9850); λ_{min} 250 mμ (ϵ 850); $\lambda_{max}^{pH\ 7-12}$ 297 mμ (ϵ 6300), sh 215 (8490); λ_{min} 235 mμ (ϵ 550); $pK_a = 2.77$; $[\alpha]^{26}D$ +132° (*c* 1.2, water); nmr (DMSO-d_6) δ 9.15 (1, d, H-6), 6.91 (1, d, H-5), 5.72 (broad s, H-1'), 2.58 (3, s, CH_3), $J_{5,6} = 6.5$, $J_{1',2'} = 1$ Hz.

Anal. Calcd for $C_{10}H_{14}N_2O_5 \cdot HCl$: C, 43.09; H, 5.42; N, 10.05; Cl, 12.72. Found: C, 43.24; H, 5.38; N, 10.08; Cl, 12.82.

4,5-Dimethyl-1-(tri-*O*-benzoyl-β-D-ribofuranosyl)-2-pyrimidinone Hydrochloride (2b).—Condensation of 6.7 g (0.042 mol) of **1b** hydrochloride[17] with 2,3,5-tri-*O*-benzoyl-D-ribosyl chloride [prepared from 22.7 g (0.045 mol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose] in the presence of 30 g (0.12 mol) of mercuric cyanide with 1500 ml of nitromethane as solvent was carried out essentially as outlined in the synthesis of **1a** above. The yield of the hydrochloride salt of **2b** was 19.3 g (76%), mp 173–175° eff. A second crop, 0.8 g (3%), was obtained from the mother liquor.

4,5-Dimethyl-1-β-D-ribofuranosyl-2-pyrimidinone Hydrochloride (3b).—The blocked nucleoside hydrochloride **2b** (18.5 g, 0.0306 mol) was debenzoylated to **3b** by a procedure essentially similar to that used in the synthesis of **3a** (*vide supra*). The unblocked nucleoside obtained as a syrup (7.7 g) was converted to the hydrochloride salt. The crude salt was obtained as a purple gummy precipitate which was triturated repeatedly with ether until solidification occurred, affording an amorphous reddish purple product, 4.0 g (45%), mp 152–155° dec. A further 2.45 g of a lower melting product was obtained from the mother liquor. The first crop was recrystallized from a minimum amount of hot ethanol. Crystallization of product was slow, affording 3.2 g of pale violet platelets: mp 157–158° dec; uv $\lambda_{max}^{1N\ HCl}$ 322 mμ (ϵ 9680); λ_{min} 265 mμ (ϵ 2260); $\lambda_{max}^{pH\ 7-12}$ 307 mμ (ϵ 6260); λ_{min} 242 mμ (ϵ 3980); $pK_a = 2.97$; nmr (DMSO-d_6) δ 9.13 (1, s, H-6), 5.76 (broad s, H-1'), 2.59 (3, s, 4-CH_3), 2.13 (3, s, 5-CH_3); $[\alpha]^{26}D$ +96° (*c* 0.3, water).

Anal. Calcd for $C_{11}H_{16}N_2O_5 \cdot HCl$: C, 45.13; H, 5.85; N, 9.57; Cl, 12.11. Found: C, 45.15; H, 5.81; N, 9.61; Cl, 12.05.

It was found unnecessary to use the isolated **3b** hydrochloride for subsequent conversion to the oxime **7b**. For this purpose the unblocked crude syrup was utilized directly.

6-Methyl-4-thio-3-(tri-*O*-benzoyl-β-D-ribofuranosyl)uracil (6).—A suspension of 1.90 g (0.0150 mol) of 6-methyluracil and 5.1 g of mercuric cyanide in 500 ml of nitromethane was heated to reflux and 100 ml distilled off. To the clear mixture was added *dropwise* a solution of 2,3,5-tri-*O*-benzoyl-D-ribosyl chloride (from 0.02 mol of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose) in 50 ml of nitromethane. The reaction mixture was heated for an additional 3 hr. After cooling and filtration from unreacted 6-methyluracil (300 mg), the solution was evaporated to a syrup, redissolved in 250 ml of chloroform, and filtered again from insoluble mercury salts. The chloroform layer was extracted with 250 ml of 30% aqueous potassium iodide and washed with 250 ml of water. The organic layer was dried over sodium sulfate and evaporated. The residue was chromatographed on 500 g of silica gel G (benzene–ethyl acetate 3:1) and 20-ml fractions were collected. Fractions containing the only nucleosidic product were collected and evaporated to give **5** as a brittle foam (6.0 g, 70%). It was crystallized from methanol to give 5.1 g of pure product: mp 164–167°; nmr ($CDCl_3$) δ 2.15 (3, s, CH_3), 4.50–4.90 (3, m, H-5' and H-4'), 5.55 (1, s, H-5), 6.00–6.40 (2, m, H-2' and H-3'), 6.70 (1, s, H-1'), 7.12–7.70, 7.82–8.20 (15, m, benzoate H's), 10.58 (1, broad s, 1-NH), $J_{1',2'} < 1$ Hz. The compound was further characterized by debenzoylation and acetylation[3] to give the crystalline acetate derivative with physical properties identical with those previously reported.[3] To a stirred solution of 3.62 g (0.00635 mol) of **5** in 150 ml of dioxane was added 1.55 g (0.0070 mol) of P_2S_5 and the mixture was refluxed for 30 min. A second charge (1.55 g) of P_2S_5 was then added and heating was resumed for another 30 min. The mixture was cooled to room temperature overnight and filtered to remove some unreacted P_2S_5. The filtrate was evaporated to a gum and heated on a steam bath with 5 ml of water while stirring for 10 min. The resulting mixture was partitioned between chloroform and saturated sodium bicarbonate, and the organic layer was washed with water and dried over sodium sulfate. The chloroform solution was evaporated and the residue was triturated with ethanol to afford a yellow crystalline mass. One recrystallization from 100 ml of ethanol afforded 2.69 g (72%) of **6** as yellow plates,

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mp 174–178°. A second recrystallization from methanol gave an analytical sample: mp 181–183°; nmr ($CDCl_3$) δ 2.10 (3, s, CH_3), 4.50–5.00 (3, m, H-4′ and H-5′), 5.95–6.37 (2, m, H-2′ and H-3′), 6.47 (1, s, H-5), 7.12–7.65, 7.75–8.14 (16, m, benzoate H's and H-1′), 10.25 (1, broad s, 1-NH).

Anal. Calcd for $C_{31}H_{26}N_2O_8S$: C, 63.47; H, 4.47; H, 4.77; S, 5.46. Found: C, 63.75; H, 4.39; N, 4.80; S, 5.59.

Reduction of 6 to 2a.—A solution of 1.17 g of **6** (0.0020 mol) in 100 ml of ethanol was refluxed and treated with 4 g of activated Raney nickel.[8] After 15 min another 2 g of Raney nickel was added and the reaction was stopped after 5 min. Thin layer chromatography (benzene–ethyl acetate 1:1) shows unreacted material (R_f 0.66) and two major products (R_f 0.16 and 0.30). After filtration through Celite the solution was evaporated to dryness and chromatographed on a column of 100 g of silica gel G (benzene–ethyl acetate 1:1). The slow moving component was collected and the eluent was evaporated to a syrup. It had the same mobility as 4-methyl-1-(tri-*O*-benzoyl-β-D-ribofuranosyl)-2-pyrimidinone in two solvent systems [benzene–ethyl acetate (1:1) and chloroform–methanol (20:1); R_f 0.16 and 0.63, respectively] and formed a crystalline picrate with the same melting point and mixture melting point (162–164°) as **2a**. Ir spectra (KBr) were identical.

2-Oxo-1-β-D-ribofuranosyl-4-pyrimidinecarboxaldehyde Oxime (7a).—To a solution of 1.87 g (0.0077 mol) of **3a** (as the free base) in 8 ml of 50% acetic acid cooled at 0° was added with rapid stirring 0.69 g (0.010 mol) of sodium nitrite. A pale yellow crystalline solid precipitated after *ca.* 10 min. The mixture was stirred for 30 min and the product was filtered, washed with ice water, and dried at room temperature. The crude oxime weighed 1.32 g (63%). Recrystallization of a 1.0 g sample from 110 ml of anhydrous methanol afforded 0.91 g of white prisms: mp 223–224° dec; nmr (DMSO-d_6) δ 3.53–4.18 (5, m, H-2′, H-3′, H-4′, and H-5′), 5.78 (1, d, H-1′), 6.77 (1, d, H-5), 7.80 (1, s, H-4), 8.47 (1, d, H-6), 5.5–7.7 (broad absorption band, sugar OH's), $J_{1',2'}$ = 1.7, $J_{5,6}$ = 6.8 Hz; uv $\lambda_{max}^{1\ N\ HCl}$ sh 223 mμ (ε 4420), 268 (8440), 348 (3090); λ_{min} 303 mμ (ε 3240); $\lambda_{max}^{pH\ 5}$ 225 mμ (ε 12,590), 252 (12,180), 330 (6380); λ_{min} 238 mμ (ε 9820), 293 (2900); $\lambda_{max}^{pH\ 12}$ 219 mμ (ε 10,060), 305 (16,910), 333 (18,050); λ_{min} 250 mμ (ε 1480), 314 (16,370); pK_{a_1} = 1.32, pK_{a_2} = 8.65.

Anal. Calcd for $C_{10}H_{13}N_3O_6$: C, 44.28; H, 4.83; N, 15.49. Found: C, 44.16; H, 4.79; N, 15.42.

2-Oxo-1-(tri-*O*-acetyl-β-D-ribofuranosyl)-4-pyrimidinecarbonitrile (8a).—A solution of 1.00 g (0.0037 mol) of **7a** in 10 ml of acetic anhydride was heated to reflux for 30 min. The mixture was then poured in 100 ml of ice water and stirred for 30 min. The product was extracted with 100 ml of chloroform and the organic layer was washed with aqueous sodium bicarbonate and water. The solution was dried over sodium sulfate and evaporated to dryness. The residue was dissolved in toluene and the solution evaporated again to remove residual acetic acid. The resulting gum was then chromatographed on 120 g of silica gel G (benzene–ethyl acetate, 1:1) and the fractions containing the major product were evaporated to afford 1.26 g (96%) of **8a** as a chromatographically homogeneous syrup: nmr ($CDCl_3$) 2.05–2.10 (9, m, acetate H's), 4.19–4.64 (3, m, H-4′, H-5′), 5.02–5.58 (2, m, H-2′, H-3′), 5.95 (1, d, H-1′), 6.74 (1, d, H-5), 8.33 (1, d, H-6), $J_{1',2'}$ = 2.6, $J_{5,6}$ = 6.8 Hz; $\lambda_{max}^{H_2O}$ sh 248 and 343 mμ. The product fails to give the characteristic nitrile absorption band at 2250 cm^{-1}. This is not without precedent[18] and is probably due to the strong electron-withdrawing effect of the two ring nitrogen atoms.

Hyrolysis of 8a to Uridine.—The product obtained from the acetic anhydride dehydration of 1.00 g (0.0037 mol) of **7a** was dissolved in 4 ml of methanol and treated with 0.4 ml of 12 *N* HCl. Hydrogen cyanide was detected immediately. After standing overnight at room temperature, the solution had an ultraviolet spectrum identical with that of uridine. Examination of a thin layer chromatogram of the mixture (1-butanol saturated with water) indicated the presence of only one product with the same mobility as uridine (R_f 0.35). After evaporation of the solution to dryness, the residue was azeotroped with toluene and after trituration with ethanol afforded a crystalline product. Two recrystallizations from ethanol–water (20:1) gave uridine (0.30 g, 33%) identical in all respects with an authentic sample.

5-Methyl-2-oxo-1-β-D-ribofuranosyl-4-pyrimidinecarboxaldehyde Oxime (7b).—A solution of 7.7 g (~0.03 mol) crude syrupy **3b** in 50 ml of 50% acetic acid was stirred and chilled to 0°. Sodium nitrite (2.4 g, 0.035 mol) was added in one portion. Precipitation started immediately and the reaction mixture became thick. A second 50-ml portion of 50% acetic acid was added and stirring of the suspension was continued for 10 min. The precipitate was filtered and washed with ice water. The damp solid was triturated with a cold methanol–ether solution, and the cream-colored solid was filtered and dried, 5.47 g (59%), mp 149–153° eff. A second crop, 1.0 g (11%), was obtained from the wash liquor. A small sample was recrystallized from methanol (charcoal) and afforded a white crystalline product: mp 150–151° dec; uv $\lambda_{max}^{1\ N\ HCl}$ 222 mμ (ε 6770), 277 (7760), 364 (14,160); λ_{min} 243 mμ (ε 3090), 315 (2680); $\lambda_{max}^{pH\ 4-7}$ 224 mμ (ε 11,270), 258 (9200), 346 (6260); λ_{min} 240 mμ (ε 7240), 300 (2360); $\lambda_{max}^{pH\ 12}$ sh 315 mμ (ε 13,620), 342 (16,450); λ_{min} 218 mμ (ε 12,320), 255 (1280); pK_{a_1} = 1.87, pK_{a_2} = 9.08; nmr (DMSO-d_6) δ 8.40 (1, s, H-6), 7.90 (1, s, 4-CH), 5.77 (1, d, H-1′), 2.20 (3, s, CH_3), $J_{1',2'}$ = 1.8 Hz. The presence of 1 mol of H_2O supports the analytical data.

Anal. Calcd for $C_{11}H_{16}N_3O_6 \cdot H_2O$: C, 43.56; H, 5.65; N, 13.85. Found: C, 43.50; H, 5.67; N, 13.73.

5-Methyl-2-oxo-1-(tri-*O*-acetyl-β-D-ribofuranosyl)-4-pyrimidinecarbonitrile (8b).—A solution of 1.0 g (0.0033 mol) of **7b** in 10 ml of acetic anhydride was refluxed for 30 min. Tlc (ethyl acetate–benzene 2:1) now showed the absence of starting material. The light brown solution was poured into ice water and stirred for 30 min. The product was extracted into methylene chloride which was washed with cold saturated sodium bicarbonate solution, then with water, and dried over sodium sulfate. The solvent was evaporated and the syrupy residue was reconcentrated several times with portions of toluene to remove residual acetic acid and finally with methanol to afford crude **8b** as a yellow syrup which was not further purified: uv $\lambda_{max}^{H_2O}$ 252.5 and 353 mμ; $\lambda_{max}^{pH\ 14}$ 267 mμ.

Hydrolysis of 8b to 5-Methyluridine (9b).—The crude nitrile **8b** was dissolved in methanol containing 1 ml of concentrated hydrochloric acid and was kept at room temperature overnight. The uv spectrum showed loss of the peak at ~355 mμ and the presence of a new peak at 265 mμ. The acid was neutralized with dilute ammonium hydroxide and the reaction mixture evaporated to a syrup. Tlc (butanol–ethanol–water, 40:11:19) of this crude material *vs.* an authentic sample of **9b** showed the same migration. The syrup was dissolved in hot methanol and ethyl acetate was added to incipient turbidity. Crystallization occurred after 4 days in the refrigerator. The precipitate was filtered and washed with cold methanol and ether. The cream-colored solid, 312 mg (37%), gave an undepressed mixture melting point with an authentic sample of **9b** and also an identical ir spectrum.

1-(5′-*O*-Acetyl-β-D-ribofuranosyl)-2-oxo-4-pyrimidinecarboxylic Acid, Methyl Ester (11).—A solution of 0.540 g (0.0020 mol) of **7a** in 100 ml of 0.02 *N* HCl was hydrogenated at atmospheric pressure over 40 mg of 10% Pd–C, and the reaction was stopped after theoretical uptake (0.004 mol). The solution was immediately treated with 10 ml of acetic anhydride for 45 min and then filtered with Celite. The filtrate was then left at 0° overnight. The uv spectrum of the solution exhibited maxima at 303 mμ (pH 7.0) and at 315 mμ (pH 1.0). The solution was treated with 2 ml of 1 *N* NaOH and evaporated to dryness. The residue was redissolved in 50 ml of methanol and 5 ml of acetic anhydride, and the solution was stirred vigorously in an open flask at room temperature overnight. The final uv spectrum of the solution had maxima at 333 mμ (pH 7.0), 315 (pH 12.0), and 328 (pH 1.0) corresponding to the ethyl ester, carboxylate anion, and free carboxylic acid, respectively. The solution was evaporated and the residue was chromatographed on 70 g of silica gel G (methanol–chloroform, 1:5). The major fractions were collected and evaporated to a syrup. The amount of **11** recovered was ~255 mg (calculated spectrophotometrically): nmr (D_2O) δ 1.97 (3, s, CH_3CO–), 3.97 (3, s, $COOCH_3$), 3.62–4.10 and 4.10–4.40 (5, m, H-2′, H-3′, H-4′, and H-5′), 5.84 (1, d, H-1′), 7.15 (1, d, H-5), 8.68 (1, d, H-6), $J_{1',2'}$ ~ 1, $J_{5,6}$ = 6.8 Hz.

2-Oxo-1-β-D-ribofuranosyl-4-pyrimidinecarboxylic Acid (12).—From a methanolic stock solution, 85 mg of **11** was dissolved in 2 ml of 0.5 *N* NaOH and left 3 hr at room temperature. The mixture was then passed through 4.5 ml (wet volume) of Dowex AG 50 (H^+) and eluted with distilled water. The uv absorbing fractions were collected and evaporated to a syrup. A solution of the residue in 1 ml of methanol was treated with 6 drops of freshly distilled cyclohexylamine. The solvent was slowly

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evaporated at room temperature, and the salt crystallized to give, after thorough washing with ethanol and drying (78°, 6 hr, high vacuum), 47 mg of a pure cyclohexylamine salt as a stable adduct, mp 160–163° eff, containing a second mole of cyclohexylamine: nmr (methanol-d_4) 0.80–2.20 (20, m, cyclohexylamine C-H), 3.61–4.26 (5, m, H-2′, H-3′, H-4′, H-5′, and OH), 5.91 (1, d, H-1′), 6.92 (1, d, H-5), 8.73 (1, d, H-6), $J_{1',2'} \sim 1$, $J_{5,6} = 7.0$ Hz. The adduct was hygroscopic and analyzed best for a hydrate: uv $\lambda_{max}^{pH\ 1}$ 213 mμ (ε 14,080), sh 250 (1690), 330 (8600); λ_{min} 272 mμ (ε 1170); $\lambda_{max}^{pH\ 7-12}$ 213 mμ (ε 13,090), 315 (6730); λ_{min} 260 mμ (ε 1380); p$K_a \sim 2.5$.[19]

Anal. Calcd for $C_{10}H_{12}N_2O_7 \cdot 2C_6H_{13}N \cdot {}^1/_2H_2O$: C, 53.10; H, 8.30; N, 11.26. Found: C, 53.02; H, 7.87; N, 11.39.

1-Methyl-2-oxo-4-pyrimidinecarboxaldehyde Oxime (14).—A solution of 1.07 g (0.0086 mol) of 1,4-dimethyl-2-pyrimidinone (**13**)[20] in 30 ml of 50% aqueous acetic acid was treated at 0° with 0.89 g (0.013 mol) of sodium nitrite with rapid stirring. After 30 min the crystalline product was filtered and a second crop was obtained by further evaporation and cooling of the filtrate. The procedure afforded 0.74 g (56%) of crude **14** which was recrystallized from methanol (dec pt 240°) to give an analytical sample: nmr (DMSO-d_6), δ 3.45 (3, s, NCH_3), 6.83 (1, d, H-5), 7.79 (1, s, H-4), 7.98 (1, d, H-6), $J_{5,6} = 6.5$ Hz.

Anal. Calcd for $C_6H_7N_3O_2$: C, 47.06; H, 4.61; N, 27.44. Found: C, 46.98; H, 4.54; N, 27.36.

1-Methyl-2-oxo-4-pyrimidinecarboxylic Acid Methyl Ester (16).

A. From 14.—A solution of 1.22 g of **14** (0.008 mol) in 150 ml of 0.053 *N* HCl was hydrogenated at atmospheric pressure over 40 mg of 10% Pd–C and the reaction was stopped after the theoretical uptake. The solution was filtered through Celite and treated with 25 ml of acetic anhydride. After stirring at room temperature for 40 min another 25 ml of acetic anhydride was added and the mixture was left overnight at 0°. The ultraviolet absorption spectrum showed a maximum at 300 mμ (pH 7.0) with a shift to 310 mμ in acid (pH 1.0). The solution was evaporated to dryness, dissolved in 100 ml of methanol, and neutralized with Amberlite IR-45 (OH^-). The filtrate was then treated with 20 ml of acetic anhydride and stirred at room temperature for 48 hr with ready access to the atmosphere. The ultraviolet maximum had then shifted to 335 mμ (pH 7.0). Thin layer chromatography (chloroform–methanol, 10:1) indicated the presence of one ultraviolet absorbing product (R_f 0.46). The residue after evaporation to dryness was chromatographed on 150 g of silica gel G (chloroform–methanol, 10:1). The major product crystallized on evaporation of the major fractions and was recrystallized from hot ethanol to yield 200 mg of **16**: mp 241–245° eff; nmr (DMSO-d_6) 3.51 (3, s, NCH_3), 3,89 (3, s, $COOCH_3$), 6.77 (1, d, H-5), 8.27 (1, d, H-6), $J_{5,6} = 6.0$ Hz; uv $\lambda_{max}^{pH\ 7}$ 332 mμ (ε 5090), sh 217 (780).

Anal. Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.42; H, 4.75; N, 16.74.

B. From 3-Methylorotic Acid Methyl Ester (17).—To a solution of 3-methylorotic acid[14] (9.3 g, 0.048 mol) in 35 ml of concentrated H_2SO_4 was added very slowly 65 ml of methanol. The hot solution was left for 1 hr and was diluted with 100 ml of methanol. The mixture was chilled and the white crystalline precipitate was filtered and washed with a cold methanol–ether mixture and then with ether. The crude product (**17**, 6.5 g, mp 203–210°) was used directly for the subsequent step. Recrystallization of a small amount of the crude product from methanol gave the analytical sample: nmr (DMSO-d_6) δ 3.15 (3, s, NCH_3), 3.88 (3, s, $COOCH_3$), 6.17 (1, d, H-5), 11.4 (1, broad s, NH), $J_{NH-5'} \sim 2$ Hz. The signal for H-5 collapses to a singlet with the addition of D_2O.

Anal. Calcd for $C_7H_8N_2O_4$: C, 45.65; H, 4.38; N, 15.21. Found: C, 45.41; H, 4.41; N, 15.02.

To a solution of 3.68 g (0.020 mol) of **17** in 120 ml of dioxane was added 5.55 g (0.025 mol) of P_2S_5; the mixture was refluxed for 1.5 hr. Another charge of 5.55 g of the reagent was added and heating was resumed for 30 min. The mixture was filtered after cooling to room temperature and the filtrate was evaporated to a small volume (*ca.* 20 ml). Methanol (100 ml) was added to the concentrated dioxane solution and the mixture was heated on the steam bath until homogeneous. The solution was chilled and the crude crystalline **methyl ester of 3-methyl-4-thioorotic acid** (4.0 g) was filtered and washed with cold methanol. The product was recrystallized from 600 ml of boiling methanol and afforded 2.7 g of **18** as a yellow crystalline solid: mp 234–235°; nmr (DMSO-d_6) 3.57 (3, s, NCH_3), 3.87 (3, s, $COOCH_3$), 6.83 (1, s, H-5), 11.95 (1, broad s, NH).

Anal. Calcd for $C_7H_8N_2O_3S$: C, 41.99; H, 4.02; N, 13.99; S, 16.01. Found: C, 41.92; H, 4.06; N, 13.82; S, 15.95.

A second crop (0.7 g, mp 226–231°) was obtained from the mother liquor (85% yield).

A solution of 1.0 g (0.010 mol) of **18** in 75 ml of a 10% solution of ammonium hydroxide was heated to reflux with vigorous stirring in the presence of 2.5 g of activated Raney nickel. After 25 hr the reaction was cooled to room temperature and filtered through Celite. The solid was washed several times with small portions of boiling water, and the filtrate and washings were evaporated to a small volume. The solution was put on 60 ml (wet volume) of Dowex AG-50 (H^+) and the product collected by elution with distilled water. The fractions containing ultraviolet absorbing material were evaporated to dryness to afford 0.30 g of crystalline **1-methyl-2-oxo-4-pyrimidinecarboxylic acid (19)**. A small sample was recrystallized from water to give the pure product which decomposes at 209–210° eff: nmr (DMSO-d_6) 3.49 (3, s, NCH_3), 5.12 (COOH), 6.79 (1, d, H-5), 8.39 (1, d, H-6), $J_{5,6} = 6.4$ Hz; uv $\lambda_{max}^{pH\ 1}$ 328 mμ (ε 6950); λ_{min} 272 mμ (ε 530); $\lambda_{max}^{pH\ 7-14}$ 312 mμ (ε 5035); λ_{min} 257 mμ (ε 845); p$K_a \sim 2.80$.[19]

A suspension of 260 mg (0.0016 mol) of crude **19** in 100 ml of methanol was treated with an ethereal solution of diazomethane (from 7.5 g of N-nitrosomethylurea) and stirred at 0° for 20 min. The excess of diazomethane was decomposed with acetic acid and the solution was filtered from unreacted acid. After neutralization of the solution with Amberlite IR-45 (OH^-), it was filtered from the resin and evaporated to dryness to yield 190 mg of **16** in crystalline form. Recrystallization from hot ethanol gave pure product (mp 241–245°) identical in all respects with **16** as obtained by method A.

Registry No.—**2a** hydrochloride, 24744-13-6; **2b** hydrochloride, 24744-14-7; **3a** hydrochloride, 24744-15-8; **3b** hydrochloride, 24744-16-9; **5**, 24744-17-0; **6**, 24744-18-1; **7a**, 24744-19-2; **7b**, 24744-20-5; **8a**, 24744-21-6; **8b**, 24744-22-7; **11**, 24744-23-8; **12**, 24744-24-9; **14**, 24766-53-8; **16**, 24766-54-9; **17**, 24766-55-0; **18**, 24766-56-1; **19**, 24806-53-9.

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(19) This "apparent" pK_a value is an approximation due to the overlap of the dissociation from pH 1–7 with a second "dissociation" in the extremely acidic region for which it was not possible to determine a pK_a value.

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The Addition of Diazomethane to 1,2-O-Isopropylidene-5-O-Trityl-α-D-*erythro*-pentos-3-ulose[1]

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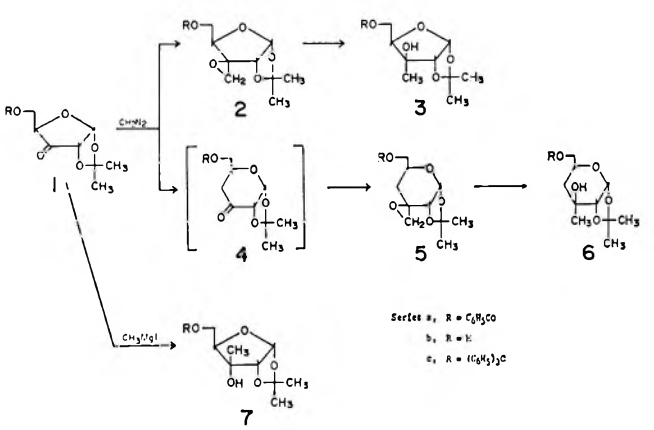
The reaction of 1,2-*O*-isopropylidene-5-*O*-trityl-α-D-*erythro*-pentos-3-ulose (**1c**) with excess diazomethane in methanol–ether affords a multicomponent mixture from which a tricyclic derivative and two epoxides, in addition to methyl trityl ether, were isolated on preparative tlc and identified. The structures of the epoxides were established from the corresponding products of reduction ($LiAlH_4$), 1,2-*O*-isopropylidene-3-*C*-methyl-5-*O*-trityl-α-D-xylofuranose (**3c**) and 4,5-dideoxy-1,2-*O*-isopropylidene-3-*C*-methyl-5-*O*-trityl-α-D-heptoseptanose (**10**). The presence of a seven-membered ring in **10** indicates that the homologation of **1c** first to a pyranos-3-ulose (**4c**) and then to a septanos-3-ulose (**8**) competes successfully with oxetane ring formation. The structure 3,5-anhydro-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-D-ribofuranose (**14a**), which was deduced from nmr spectral data, was assigned to the tricyclic derivative. It is proposed that **14a** arises from a cyclic oxonium ion (**13**), formed in turn by trityloxy-group participation in the expulsion of nitrogen from the initial addition intermediate (**12**) or as a two-step process involving prior loss of nitrogen. Attack of methanol on **13** provides **14a** and methyl trityl ether in about equal (35%) yield.

Overend and coworkers[3] obtained a mixture of two epoxides in 85% yield from the interaction of diazomethane and 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentos-3-ulose (**1a**) in methanol–ether (Scheme I). The major component (**5a**), a product of prior

Scheme I



ring expansion of **1a**, on treatment with excess lithium aluminum hydride in tetrahydrofuran, yielded a solid to which the structure 4-deoxy-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-*xylo*-hexopyranose (**6b**) was assigned. The minor epoxide (**2a**) (20% yield), which incidentally was obtained in 70% yield when the addition of diazomethane to **1a** was carried out in ether alone, gave 1,2-*O*-isopropylidene-3-*C*-methyl-α-D-xylofuranose (**3b**) on reduction with lithium aluminum hydride.

The failure to detect products of the *ribo* configuration[4] is perhaps somewhat surprising in view of the fact that the methyl 3,4-*O*-isopropylidene-β-(D and L)-*erythro*-pentosulopyranosides both give the isomeric oxetane derivatives on treatment with diazomethane.[5,6] Moreover, the "*ribo*-epoxide" is the preponderant isomer in both cases.

The present investigation was undertaken to examine more closely the apparent stereoselectivity of the reaction of **1** and diazomethane which leads (after reduction) to methyl branched chain sugars of a configuration opposite to those obtainable from corresponding reactions with methylmagnesium halides.[7,8] In the current study, 1,2-*O*-isopropylidene-5-*O*-trityl-α-D-*erythro*-pentos-3-ulose (**1c**)[9] was used rather than **1a** to avoid the loss of the blocking group at C-5 in the reduction step and thereby to facilitate the isolation of products.

The reaction mixture obtained following addition of excess diazomethane to **1c** in methanol–ether showed four spots[10a] on tlc (silica gel, ether–petroleum ether) with R_f values of ≅0 (A), 0.17 (B), 0.28 (C), and 0.61 (D). A separation of the four components was effected by preparative tlc (plc[10b]) using the same system. Substance D, obtained in 36% yield, was readily identified as methyl trityl ether on the basis of spectral (ir and nmr) evidence together with mixture melting point.

Of the remaining components, only B and C gave a positive Ross test[11] for an epoxide. Moreover, the nmr spectrum of C, which was isolated as a foam (11% yield), showed a well-resolved AB system at high field consistent with an exocyclic methylene epoxide.[12] Reduction of C with lithium aluminum hydride gave a product which, on the basis of the evidence outlined below, was assigned the structure 1,2-*O*-isopropylidene-3-*C*-methyl-5-*O*-trityl-α-D-xylofuranose (**3c**).

Walton and coworkers[7] have shown that the reaction of **1a** with methylmagnesium iodide is essentially stereospecific affording the 3-*C*-methyl-α-D-ribofuranose

(1) This investigation was supported in part by U. S. Public Health Service Research Grant No. CA-02624 and FR-05529 from the National Cancer Institute and in part by an institutional grant to the Detroit Institute of Cancer Research Division of the Michigan Cancer Foundation from the United Foundation of Greater Detroit.

(2) (a) To whom all inquiries should be addressed at the Michigan Cancer Foundation, 4811 John R. Street, Detroit, Mich. 48201. (b) Michigan Cancer Foundation Research Fellow.

(3) S. Nahar, W. G. Overend, and N. R. Williams, *Chem. Ind.* (London), 2114 (1967).

(4) It is conceivable that the direct precursor of the hexopyranos-3-ulose (**4a**) is an intermediate of the *ribo* configuration.

(5) W. G. Overend and N. R. Williams, *J. Chem. Soc.*, 3446 (1965).

(6) R. J. Ferrier, W. G. Overend, G. A. Rafferty, and N. R. Williams, *ibid.*, 1091 (1968).

(7) R. F. Nutt, M. J. Dickinson, F. W. Holly, and E. Walton, *J. Org. Chem.*, **33**, 1789 (1968).

(8) R. D. King, W. G. Overend, J. Wells, and N. R. Williams, *Chem. Commun.*, 726 (1967).

(9) W. Sowa, *Can. J. Chem.*, **46**, 1586 (1968).

(10) (a) The same reaction in ether alone gave rise to a multicomponent system, as judged by glpc, and was not further investigated. (b) Preparative layer chromatography.

(11) W. C. J. Ross, *J. Chem. Soc.*, 2257 (1950).

(12) L. J. T. Andrews, J. M. Coxon, and M. P. Hartshorn, *J. Org. Chem.*, **34**, 1126 (1969).

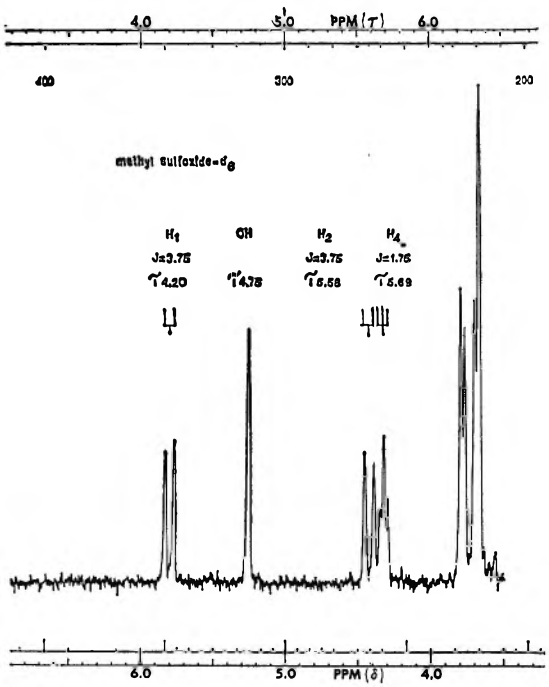


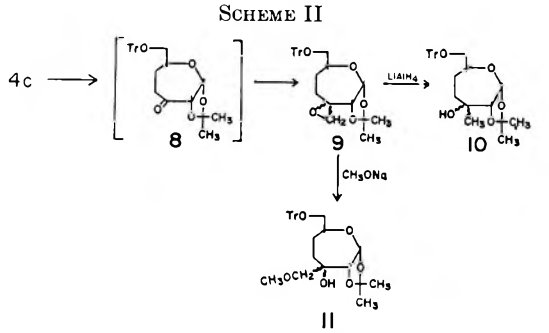
Figure 1.—A 60-MHz partial spectrum of substance A (**14a**) in methyl sulfoxide-d_6.

derivative, **7a**. Similarly, we observed that the action of the same Grignard reagent on **1c** produced a single 3-*C*-methyl derivative (**7c**) in high yield but with properties different from those of the reduction product (**3c**).

Debenzoylation of **7a** with sodium methoxide and tritylation of the resulting intermediate, **7b**, gave a product identical in every respect with **7c**. Accordingly, the reduction product (**3c**) and the precursory oxetane (**2c**, substance C) are both of the *xylo* configuration.

Reduction ($LiAlH_4$) of the slower moving epoxide B, which appeared to be the major product, gave a crystalline solid though in relatively low yield to which the structure 4-deoxy-3-*C*-methyl-1,2-*O*-isopropylidene-5-*O*-trityl-α-D-hexopyranose (**6c**) was tentatively assigned on the basis of elemental analysis and a nmr spectrum. However, a molecular ion peak of 474 in the mass spectrum precludes **6c** (mol wt 460) as a plausible structure. Moreover, an unambiguous (nmr) proton count of 34 exceeds by two the number required by **6c**. These findings indicate a further homologation of the initial product of ring expansion, **4c**, to a septanos-3-ulose (**8**, Scheme II) prior to oxetane formation (B, **9c**).

SCHEME II



Accordingly, the initial structural assignment (**6c**) was amended to a 4,5-dideoxy-1,2-*O*-isopropylidene-3-*C*-methyl-5-*O*-trityl-α-D-heptoseptanose (**10**) as the product of reduction of B.

The location of the site of branching at C_3, ascertained initially for **6c**, is consistent as well with **10**. Thus, the nmr ($CDCl_3$) of the reaction product showed (*inter alia*) doublets at τ 4.5 and 5.9 (J = 5.0 Hz) which were assigned to the bridgehead protons of C_1 and C_2, respectively. These data then locate the site of branching at C_3 but the exact configuration remains in question. A strong absorption at 3570 cm^{-1} for the hydroxyl group was seen in the ir spectrum (carbon tetrachloride, c 0.005 M) of **10** which suggests[13] possible hydrogen bonding with neighboring oxygen and therefore a *ribo* configuration at C-3. However, the present data on related structures are simply too limited to extend the method of Ferrier[13] for the assignment of configuration at the site of branching to **10**.

Additional evidence for the presence of a seven-membered ring in **10** was derived from alkaline methanolysis which afforded, though once more in low yield, a crystalline product with properties in accord with a 3-*C*-methoxymethyl-α-D-heptoseptanose (**11**). Again, the configuration at C-3 in **11** as well as the precursory oxetane **9** must remain unassigned.

Indirect support for structures **9**–**11** is derived from the findings of Overend and coworkers[14] who obtained a branched-chain methyl α-D-heptoseptanoside derivative on reduction of one of two epoxides isolated following the addition of diazomethane to methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose. The second epoxide, after treatment with lithium aluminum hydride, yielded methyl 4,6-*O*-benzylidene-2-deoxy-3-*C*-methyl-α-D-*arabino*-hexopyranoside.

While no epoxide derivative of the pyranos-3-ulose, **4c**, was isolated in the present work, glpc (Chromosorb W) indicated, contrary to tlc, that B was in fact a mixture of two minor components along with the principal spirooxetane **9**. This would explain, in part, the relatively low yield of reduction and hydrolysis products **10** and **11**, respectively.

The absence of an exocyclic methylene epoxide residue in the slowest moving component A was confirmed by nmr and ir spectra which revealed, in addition, the loss of the original trityl group. The latter observation, together with the isolation of methyl trityl ether, suggested the possibility of a prior detritylation of either **1c**, or the direct precursor of A, induced by diazomethane. However, 5-*O*-trityl-1,2-*O*-isopropylidene-α-D-xylofuranose was recovered unchanged after treatment with diazomethane in methanol.

Substance A, a crystalline solid of the composition $C_9H_{14}O_5$, afforded a monoacetate on treatment with acetic anhydride in pyridine at room temperature but attempts to tritylate the hydroxyl group under the usual conditions were unsuccessful. The alcohol proton in A appears (Figure 1) as a clearly resolved singlet at τ 4.7 ppm in methyl sulfoxide-d_6. The absence of spin–spin splitting of the hydroxyl proton together with the failure of A to tritylate point to the presence of a tertiary hydroxyl group. In fact, the structure of A was readily deduced by analysis of its nmr spectrum which is reproduced without the corresponding inte-

(13) R. J. Ferrier, W. G. Overend, G. A. Rafferty, H. M. Wall, and N. R. Williams, *Proc. Chem. Soc.*, 133 (1963).

(14) B. Flaherty, W. G. Overend, and N. R. Williams, *Chem. Commun.*, 434 (1966).

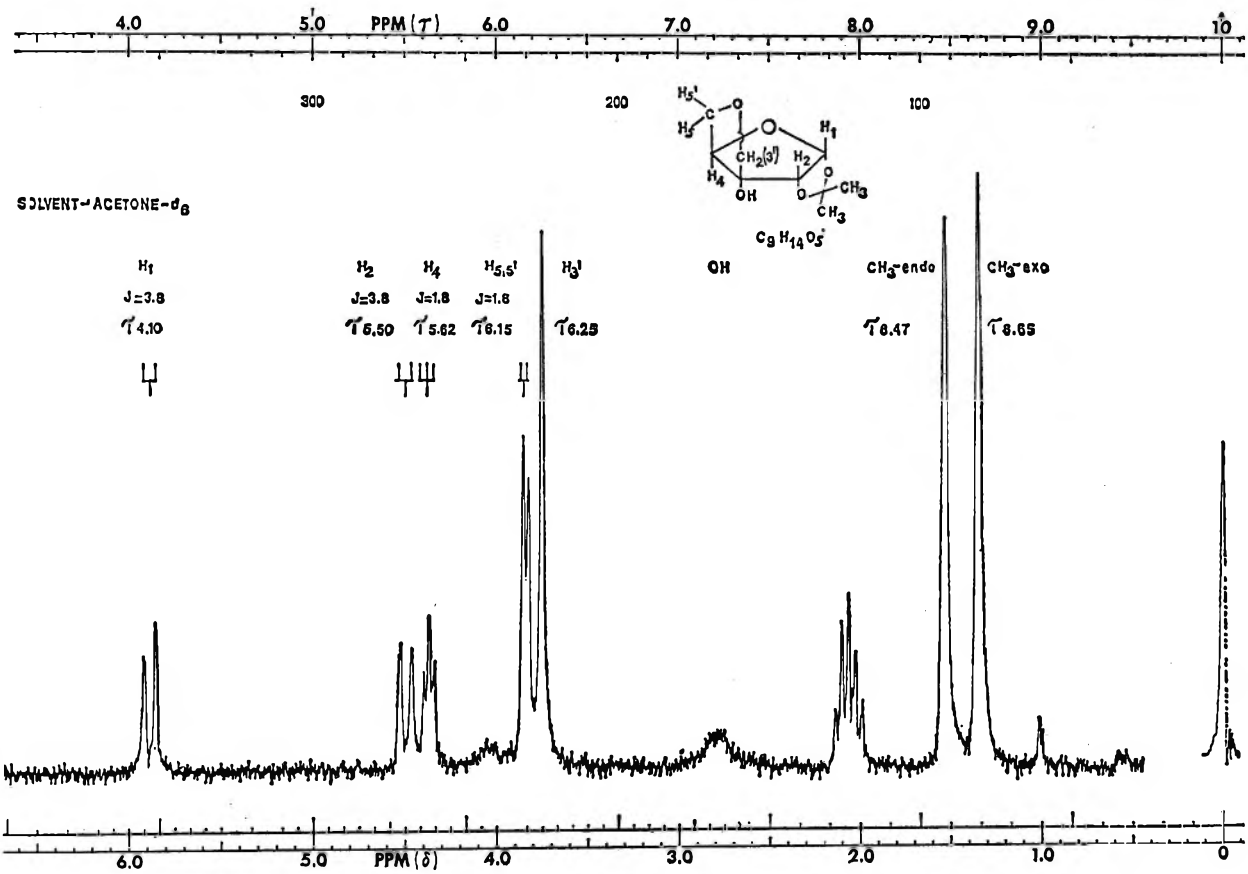


Figure 2.—The 60-MHz spectrum of substance A (**14a**) in $CDCl_3$.

gration curve in Figure 2. The three-proton singlets at τ 8.49 and 8.66 are ascribed to the *endo*- and *exo*-methyl groups, respectively, of an *O*-isopropylidene residue.[15] A pair of doublets that characterize the bridgehead hydrogen atoms H_1 and H_2 of the two *cis*-fused five-membered rings of a number of 1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose derivatives[16] are seen at τ 4.10 and 5.50 (J = 3.8 Hz), respectively. The one-proton triplet at τ 5.62 (J = 1.8 Hz) and the two-proton doublet at τ 6.15 (J = 1.8 Hz) are assigned to the protons at C_4 and C_5, respectively, which apparently comprise an AX_2 pattern in substance A.

The spectral patterns of H_4 and H_2 preclude the presence of a proton at C_3. In fact, the patterns locate both the site of the branch as well as the (tertiary) hydroxyl group at C_3 of the furanose derivative. Finally, the two-proton singlet at τ 6.25, together with the other data, indicate that the branch involves a methylene group which is linked through oxygen to C_5 as part of a second, *cis*-fused five-membered ring. Accordingly, the structure 3,5-anhydro-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-D-ribofuranose (**14a**) is assigned to substance A. The facile acetylation of the tertiary OH in **14a** (to **14b**) is in accord with the findings of Nutt, *et al.*,[7] who effected the benzoylation of **7a** under mild conditions.

The formation of **14a** requires that the addition of diazomethane to the furanos-3-ulose (**1c**) occurs at the side above the isopropylidene ring. The resulting intermediate (**12**) can lead to **14a** *via* the cyclic oxonium ion (**13**), formed by either trityloxy-group participation in expulsion of nitrogen or a two-step process involving prior loss of nitrogen. Attack of methanol on the cyclic oxonium ion (**13**) provides compound **14** together with methyl trityl ether which, incidentally, were isolated in virtually identical (35%) yields.

Investigations by Winstein and coworkers[17,18] as well as those by Capon[19] have established that methoxy-group participation in solvolytic displacement reactions is substantial where such anchimeric assistance leads to a five- or six-membered ring. Recently, examples of both methoxy[19-21] and benzyloxy[22,23] assisted solvolysis of a sulfonate have been recorded in the carbohydrate literature and, therefore, evidence of trityloxy participation is not surprising, though it is to our knowledge the first such case described.

It is evident that **12** (see Scheme III) is also the requisite precursor of a "*ribo*-oxetane" (**15**) derivative of **1c**. Moreover, the initial product of ring enlargement (**4c**) may, in part, evolve from **12**. However, the extent of cyclization of **12** to **15** remains in question, since the corresponding product of reduction, 1,2-*O*-isopropylidene-3-*C*-methyl-5-*O*-trityl-α-D-ribofuranose, (**7c**), if indeed generated, remained undetected.

(15) R. D. King and W. G. Overend, *Carbohyd. Res.*, **9**, 423 (1969).

(16) R. J. Abraham, L. D. Hall, L. Hough, and K. E. McLaughlan, *J. Chem. Soc.*, 3699 (1962).

(17) S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958).

(18) E. Allred and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 3991, 3998, 4008, 4012 (1967).

(19) B. Capon, *Quart. Rev.* (London), **18**, 45 (1964).

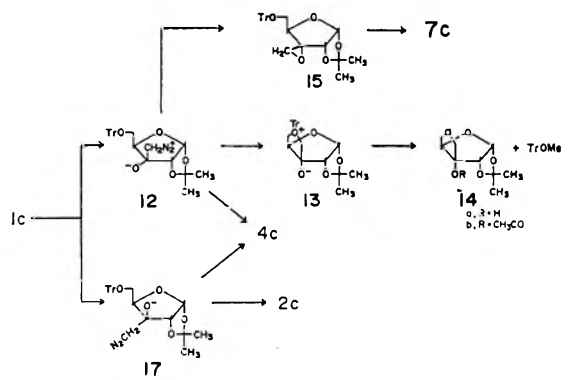
(20) J. S. Brimacombe and O. A. Ching, *Carbohyd. Res.*, **9**, 287 (1969).

(21) Examples of methoxy-group participation have been reported in the carbohydrate field (see ref 20) but all have involved the migration of a methoxy group of an acetal ring.

(22) (a) J. S. Brimacombe and O. A. Ching, *ibid.*, **5**, 239 (1967); (b) *J. Chem. Soc., C*, 1642 (1968).

(23) (a) G. R. Gray, F. C. Hartman, and R. Barker, *J. Org. Chem.*, **30**, 2020 (1965); (b) J. S. Brimacombe and O. A. Ching, *Carbohyd. Res.*, **8**, 376 (1968).

SCHEME III



The isomeric intermediate, **17**, which originates from the addition of diazomethane to **1c** at the side adjacent to the *O*-isopropylidene residue and which leads to the *xylo*-oxetane derivative, **2c**, could as well account for the hexopyranos-3-ulose (**4c**). The possibility that this same intermediate could lead to a cyclic oxonium ion comprised of *trans*-fused five-membered rings appears remote from examination of molecular models. The uncertainties as to origin of **4c** together with the failure to identify **15** preclude any firm conclusion as to the stereoselectivity attending the addition of diazomethane to **1c**.

Experimental Section

General Procedures.—Evaporations were carried out *in vacuo* at bath temperatures below 45°. Melting points were determined on a Thomas–Hoover apparatus (capillary method) and are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Thin layer chromatography (tlc) was performed on silica gel GF (Merck); separated materials were detected by spraying with a 6% solution of ammonium molybdate in 10% sulfuric acid followed by heating at 100°. Preparative tlc was carried out on 20 × 20 cm glass plates coated with 1-mm layers of the same adsorbent. Optical rotations were determined in chloroform with a Perkin-Elmer Model 141 polarimeter. The ir spectra were measured in a Perkin-Elmer Model 21 spectrophotometer. Nuclear magnetic resonance spectra were obtained using a Varian A-60A spectrometer with TMS as internal reference, and mass spectra using an A.E.I. MS-902 instrument with a direct inlet system and an ionizing voltate of 70 eV. Gas chromatography was carried out on a Barber–Colman Series No. 5000 with 6 ft × 1/8 in. glass U tubes packed with Chromosorb W (80–100 mesh) coated with 1.2% SE-30. Operation was isothermal at 225° with nitrogen as carrier gas and flame ionization detection. Petroleum ether used in recrystallizations was of a 30–60° range.

1,2-*O*-Isopropylidene-3-*C*-methyl-5-*O*-trityl-α-D-ribofuranose (7c).—To a stirred solution of methylmagnesium bromide, prepared from 0.243 g (0.01 g-atom) of magnesium shavings and 2.13 g (15 mmol) of methyl iodide in 10 ml of dry ether, and then cooled to 0°, was added, dropwise, a solution of 1.29 g (10 mmol) of **1c**[9] in 50 ml of dry ether. The addition complex, a heavy white precipitate, was carefully decomposed by addition of water. The water layer was separated and extracted with three 25-ml portions of ether. The extracts were combined, washed with 20 ml of saturated sodium chloride solution, and dried over magnesium sulfate. Evaporation of the solvent left a solid residue (1.29 g) which, on recrystallization from ether, gave 1.15 g (86% yield) of a crystalline solid: mp 152–153°; $[\alpha]^{27}D$ −14.7° (c 1.0); ir (CCl_4) 3660 cm^{-1} (OH); nmr ($CDCl_3$) τ 3.68 (m, 15, aromatic), 4.23 (d, 1, $J_{1,2}$ = 3.6 Hz, H-1), 5.96 (d, 1, H-2), 6.10 (m, 1, H-4), 6.73 (m, 2, H-5), 8.40 (s, 3, 3-CCH_3), 8.67 (s, 3, isopropylidene, CH_3-*endo*), 9.05 (s, 3, isopropylidene, CH_3-*exo*); mass spectrum *m/e* 446 (M^+).

Anal. Calcd for $C_{28}H_{30}O_5$: C, 75.31; H, 6.77. Found: C, 75.13; H, 6.80.

1,2-*O*-Isopropylidene-3-*C*-methyl-α-D-ribofuranose (7b).—A quantity (0.308 g, 1 mmol) of **7a**, prepared according to the procedure of Nutt, *et al.*,[7] was dissolved in 10 ml of ethanol containing 1 mequiv of sodium ethoxide and the solution was refluxed for 0.75 hr. The dark reaction mixture was evaporated to dryness and the residue was dissolved in 10 ml of water. The solution was carefully neutralized with dilute acetic acid and then extracted with four 25-ml portions of ether. The combined dried extracts were concentrated to *ca.* 10 ml and the product, 0.105 g (50% yield), crystallized as a mat of colorless, fine needles: mp 92.5–93.5°; $[\alpha]^{26}D$ +24.8° (*c* 0.5); nmr ($CDCl_3$) τ 4.18 (d, 1, $J_{1,2}$ = 3.7 Hz, H-1), 5.88 (d, 1, H-2), 8.40 (s, 3, 3-C-CH_3), 8.63 (s, 3, isopropylidene, CH_3-*endo*), 8.84 (s, 3, isopropylidene, CH_3-*exo*).

Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.9. Found: C, 53.02; H, 7.89.

To a solution of 25 mg (0.12 mmol) of **7b** in 0.5 ml of dry pyridine was added 40 mg (0.14 mmol) of trityl chloride and the mixture, protected from moisture, was held at room temperature for 1 week. The reaction mixture was evaporated to dryness and the pyridine-free residue crystallized on trituration with water. The solid was collected and the air-dried product was recrystallized from ether–petroleum ether to give 25 mg (56% yield) of crystalline solid, mp and mmp (with **7c**) 151–152°. The ir and nmr spectra of this material and the corresponding spectra of **7c** were essentially superimposable.

Addition of Diazomethane to 1,2-*O*-Isopropylidene-5-*O*-trityl-α-D-*erythro*-pentos-3-ulose (1c).—To a solution of 4 g (9.3 mmol) of **1c** in a mixture of 50 ml of dry ether and 50 ml of anhydrous methanol, cooled to 0°, was added, all at once, a solution of ~18 mmol of diazomethane in 50 ml of ether. The reaction mixture was gradually allowed to attain room temperature and then maintained at ambient temperatures for 2 days.[24] The colorless solution was evaporated to a syrup which amounted to *ca.* 4 g and which showed four spots on tlc [ether–petroleum ether, 2:5 (v/v)] with the following R_f values: (≅0 A), (0.17 B), (0.28 C), and (0.61 D). Preparative tlc was effected on a total of 20 plates using the same solvent system.

Methyl Trityl Ether (D).—The bands corresponding to the fastest moving spot were eluted with acetone and the combined filtered solutions on evaporation left a solid residue which crystallized from methanol: wt 0.890 g (35% yield), mp and mmp (with an authentic sample of methyl trityl ether) 82–84° (lit.[25] 82.6–82.9°). The ir and nmr spectra of D were identical in every respect with corresponding spectra of methyl trityl ether.

3,5-Anhydro-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-D-ribofuranose (14a).—The band corresponding to the slowest moving spot A was eluted from each plate with acetone and the combined, filtered eluents were evaporated to dryness. The residue crystallized from ether–petroleum ether as a colorless solid, wt 0.675 g (36% yield), mp 66–69°. An analytical sample, mp 72–73°, was obtained by sublimation of the recrystallized material at room temperature (5 × 10^{-2} mm): $[\alpha]^{22}D$ +51.4°, $[\alpha]^{22}_{365}$ +182° (*c* 0.5); nmr (see Figures 1 and 2); mass spectrum *m/e* ($M^+ - CH_3$) 187.

Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.93. Found: C, 53.58; H, 6.93.

To a solution of 0.2 g (1 mmol) of **14a** in 6 ml of dry pyridine was added 3 ml of acetic anhydride, and the reaction mixture was stirred at room temperature for 16 hr. The solution was then chilled to −20°, while 10 ml of methanol was added dropwise with stirring and, after 1 hr at room temperature, the solution was evaporated to dryness. The last traces of pyridine were removed by evaporation from toluene. The residue was taken up in ether, and the solution was washed first with water and then dried over magnesium sulfate. The filtered solution was evaporated to dryness and the residue (**14b**) was crystallized from ether–petroleum ether as a colorless solid (0.112 g, 50% yield): mp 122–124°; $[\alpha]^{24}D$ +78.8°, $[\alpha]^{27}_{365}$ +151.1° (*c* 1); nmr ($CDCl_3$) τ 4.03 (d, 1, $J_{1,2}$ = 4.0 Hz, H-1), 5.09 (d, 1, H-2), 5.27 (m, 1, H-4), 7.91 (s, 3, acetate, CH_3), 8.49 (s, 3, isopropylidene, CH_3-*endo*), 8.66 (s, 3, isopropylidene, CH_3-*exo*).

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.29; H, 6.71.

1,2-*O*-Isopropylidene-3-*C*-methyl-5-*O*-trityl-α-D-xylofuranose (3c).—Substance C (**2c**), which was isolated as a foam (0.443 g, 11% yield), showed the following properties: $[\alpha]^{24}D$ −2.4°, $[\alpha]^{24}_{364}$ −18.7° (c 1); ir (KBr) 1220 cm^{-1} (epoxy ring, sym

(24) The color of the diazomethane was not completely discharged until nearly 2 days had elapsed.

(25) J. F. Norris and A. Cresswell, *J. Amer. Chem. Soc.*, **55**, 4946 (1933).

stretch); nmr ($CDCl_3$) τ 2.73 (m, 15 (C_6H_5)$_3$C), 4.05 (d, 1, $J_{1,2}$ = 4.0 Hz, H-1), 5.47 (t, H-4), 5.72 (d, 1, H-2), 6.78, 6.99 (q, 2, J = 4.0 Hz, epoxy, CH_2AB), 8.44 (s, 3, isopropylidene, CH_3-*endo*), 8.66 (s, 3, isoproylidene, CH_3-*exo*). A quantity of **2c** (0.392 g, 0.9 mmol) and 0.190 g (5 mmol) of lithium aluminum hydride in 10 ml of dry ether was refluxed for 10 hr. Water (*ca.* 1.0 ml) was added dropwise to the reaction mixture, the ether layer was drawn off, and the aqueous phase was extracted with four 20-ml portions of ether. The combined extracts were dried over magnesium sulfate and the filtered solution was evaporated to dryness. The foamy residue (0.286 g) was judged to be *ca.* 90% pure on tlc (ethyl–acetate petroleum ether, (1:4) but could not be crystallized from the usual solvents. The material was applied to two plc plates and the mixture was resolved with the same solvent system. The major fraction (**3c**, 0.194 g) showed a single spot on tlc and readily crystallized from petroleum ether as a colorless solid: wt 0.130 g (33% yield); mp 130–131°; $[\alpha]^{23}D$ +70.4°, $[\alpha]^{25}_{365}$ +247.4° (c 1); ir (CCl_4) 3510 cm^{-1} (OH) 1380 (geminal CH_3); nmr (pyridine d_5) τ 3.96 (d, 1, $J_{1,2}$ = 3.7, H-1), 5.60 (d, 1, H-2), 5.67 (m, 1, H-4), 6.32 (m, 2, H-5, H-5′); mass spectrum *m/e* 446 (M^+).

Anal. Calcd for $C_{28}H_{30}O_5$: C, 75.31; H, 6.77. Found: C, 75.19; H, 6.83.

4,5-Dideoxy-1,2-*O*-isopropylidene-3-*C*-methyl-5-*O*-trityl-α-D-heptoseptanose (10).—Substance B, when subjected to glpc at a gas flow rate of 64.5 ml/min, was found to consist of one major and two minor components exhibiting retention times of 33, 27, and 23 min, respectively. A solution of 0.675 g of B in 10 ml of dry tetrahydrofuran containing 0.190 g (5 mmol) of lithium aluminum hydride was refluxed for 8 hr. The work-up of the reaction mixture was the same as that described for **3c**. The product, obtained as a foam (0.507 g), was applied to two plc plates which were developed in ethyl acetate–petroleum ether (1:4). The principal band was eluted with acetone and the filtered solution was evaporated to dryness. The residue crystallized from petroleum ether to give 0.205 g of a colorless solid: mp 129–130°; $[\alpha]^{23}D$ −44.6°, $[\alpha]^{23}_{365}$ −138.3° (c 1, $CHCl_3$); ir (KBr) 3420 (OH), 1380 cm^{-1} (geminal $-CH_3$); ir (CCl_4) 3570 cm^{-1} (OH); nmr ($CDCl_3$) τ 2.62 (m, 15, aromatic), 4.46 (d, 1, $J_{1,2}$ = 5.0 Hz, H-1), 5.95 (d, 1, H-2), 6.70–8.22 (m, 6, CH_2 envelope), 8.35 (s, 3, 3-CH_3–), 8.63 (s, 6, $(CH_3)_2$C–); mass spectrum *m/e* 474 (M^+), 416 ($M^+ - (CH_3)_2CO$).

Anal. Calcd for $C_{30}H_{34}O_5$ (mol wt 474):[26] C, 75.92; H, 7.22. Found: C, 75.77; H, 7.16.

4,5-Dideoxy-1,2-*O*-isopropylidene-3-*C*-methoxymethyl-5-*O*-trityl-α-D-heptoseptanose (11).—A solution of 0.309 g of B in 55 ml of methanol containing 6 ml of 10 *N* sodium hydroxide was refluxed for 3 hr. The cooled solution was neutralized (phenolphthalein) with dilute acetic acid and evaporated to dryness. The residue was dissolved in ether previously equilibrated with water and the ether layer was washed with a dilute solution of sodium bicarbonate, and then dried over magnesium sulfate. The filtered solution was evaporated to dryness and the residue was crystallized first from ether–petroleum ether and then from ethanol to give 0.253 g of the product: mp 145–147°; $[\alpha]^{23}D$ −47.2°, $[\alpha]^{23}_{365}$ −148° (*c* 0.25); ir (CCl_4) 3550 cm^{-1} (OH); nmr ($CDCl_3$) τ 2.68 (m, 15, aromatic), 4.46 (d, 1, $J_{1,2}$ = 5.0 Hz, H-1), 5.70 (d, 1, H-2), 6.60 (s, 3, CH_3O), 6.68–8.32 (m, 8, CH_2 envelope), 8.38 (s, 3, isopropylidene, CH_3-*endo*), 8.66 (s, 3, isopropylidene, CH_3-*exo*); mass spectrum *m/e* 504 (M^+), 489 ($M^- - CH_3$).

Anal. Calcd for $C_{31}H_{36}O_6$ (mol wt 504):[27] C, 73.78; H, 7.19. Found: C, 73.99, H, 6.90.

Registry No.—Diazomethane, 334-88-3; **1c**, 20590-54-9; **2c**, 24515-45-5; **3c**, 24467-32-1; **7b**, 24467-33-2; **7c**, 24467-36-5; **10**, 24467-39-8; **11**, 24467-40-1; **14a**, 24467-37-6; **14b**, 24467-38-7.

Acknowledgment.—The authors are indebted to Dr. Jiří Zemlička for his timely advice and criticisms during this work. We wish to thank Mr. Nikolai Cvetkov of this laboratory for assistance with ir and nmr spectra. We are also grateful to Professor Don C. DeJongh and Mr. David Brent, Department of Chemistry, Wayne State University, for mass spectral data.

(26) Calcd for $C_{29}H_{32}O_5$ (mol wt 460): C, 75.62; H, 7.00.
(27) Calcd for $C_{30}H_{34}O_6$ (mol wt 490): C, 73.44; H, 6.99.

The Synthesis and Birch Reduction of 2-Isoamyl-3-methyl-4-methoxy-2,3-dihydrobenzofurans and Related Compounds[1]

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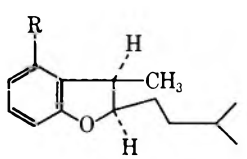
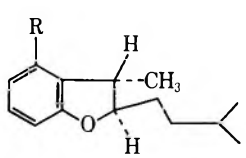
Conditions have been found by which Birch reduction, followed by hydrolysis of *cis*-2-isoamyl-3,4-dimethyl-2,3-dihydrobenzofuran (**1a**), gave 75% of α,β-unsaturated ketone. Stereospecific catalytic reduction of the carbon–carbon unsaturation could not be attained. 4-Methoxy-2-isoamyl-3-methyl-2,3-dihydrobenzofuran (**9b**) was prepared in good yield, and was converted into *cis*-2-isoamyl-3-methyl-4-keto-2,3,4,5,6,7-hexahydrobenzofuran in good yield. Mass spectral fragmentation patterns for perhydrobenzofurans and related compounds have been determined.

The synthesis and proof of configuration of *cis*- and *trans*-2-isoamyl-3,4-dimethyl-2,3-dihydrobenzofurans (**1a** and **2a**), which were needed for syntheses in the fumagillin series, were reported recently.[2] The present paper describes a study of the Birch reduction of the *cis* compounds **1a** as well as the synthesis and Birch reduction of the corresponding 4-methoxy compound **1b**; the *trans* compound **2b** was also prepared.



1a, R = CH_3
b, R = OCH_3

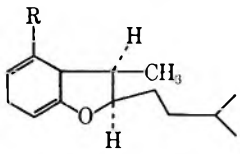


2a, R = CH_3
b, R = OCH_3

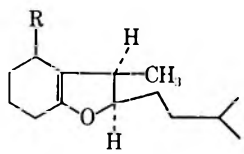
The *cis* compound **1a** was prepared by catalytic reduction of the corresponding 2-isoamyl-3,4-dimethylbenzofuran, using platinum and hydrogen in ethanol; the product, obtained in 92% yield, was 98% pure by vpc. Reduction of **1a** with 16 g-atoms of lithium in liquid ammonia, *t*-butyl alcohol, and ether,[3,4] followed by methanol, gave a product which showed no aromatic protons in the nmr, and showed a deficit of vinyl

(1) Aided by Grant AI-08424 from the National Institutes of Health.
(2) E. C. Hayward, D. S. Tarbell, and L. D. Colebrook, *J. Org. Chem.*, **33**, 399 (1968).
(3) A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.*, **75**, 5360 (1953); H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **26**, 3237 (1961).
(4) D. P. Brust and D. S. Tarbell, *ibid.*, **31**, 125 (1966).

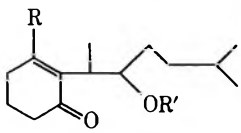
protons, indicting some overreduction. This was evidently a mixture of the expected tetrahydro compound **3a** (with possible double-bond isomers) and the hexahydro[5] compound **4a**. Hydrolysis of this mixture



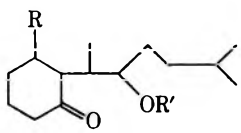
3a, R = CH_3
b, R = OCH_3



4a, R = CH_3
b, R = O=



5a, R = CH_3; R′ = H
b, R = CH_3; R′ = Ac

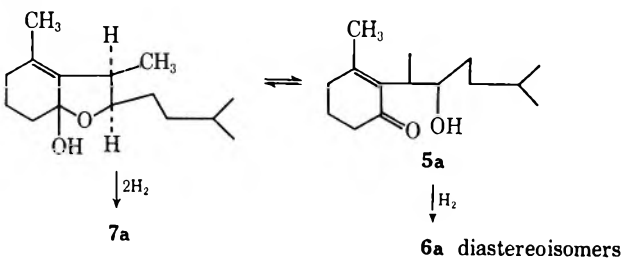


6a, R = CH_3; R′ = H
b, R = CH_3; R′ = Ac

with oxalic acid in aqueous dioxane, followed by chromatography on alumina, gave a mixture of hexahydrobenzofurans, such as **4a**, judging from the nmr spectrum; there was also obtained a smaller amount of saturated and α,β-unsaturated keto alcohols, such as **5a**, and the corresponding saturated keto alcohols **6a**.

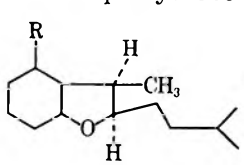
The Birch reduction using only 5 g-atoms of lithium gave a mixture containing, after hydrolysis with aqueous acid, about 75% of α,β-unsaturated ketone; acetylation, followed by chromatography on alumina, yielded 10% of starting material **1a**, and in addition a mixture containing about three parts of α,β-unsaturated keto acetate (such as **5b**) and one part of saturated keto acetate **6b**. The mixture of conjugated and unconjugated keto acetates was hydrogenated with 30% Pd–C as catalyst; the product, from its ir spectrum, consisted only of saturated keto acetates.

The keto alcohol **5a** could exist in equilibrium with the cyclic hemiketal. Hydrogenation of the double bond of the hemiketal form should give only one diastereoisomer of the corresponding **6a** cyclic tautomer, the direction of hydrogenation being controlled by the *cis* methyl and isoamyl groups.



7a **6a** diastereoisomers

Mass spectrometry[6] of the peaks from a vpc column allowed an identification of seven out of nine peaks. Three were stereoisomeric perhydrobenzofurans **7a**, one



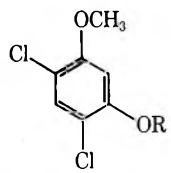
7a, R = CH_3
b, R = H

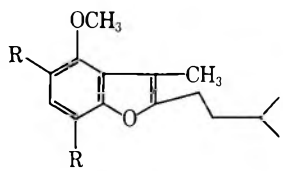
was a saturated keto alcohol, and three peaks (two major and one minor, ratio 3:3:1) were saturated keto acetates of structure **6b**.

When the procedure was varied by following the Birch reduction and hydrolysis by Pd–C catalytic reduction, and then by acetylating, the examination by vpc–mass spectrometry showed 17 peaks, of which 4 were perhydrobenzofurans (**7a**), 2 were saturated keto alcohols (**6a**), 3 were saturated keto acetates (**6b**), 2 were unsaturated keto acetates (**5b**) or double-bond isomers, and 2 were probably β,γ-unsaturated keto alcohols.

The procedure using 5 g-atoms of lithium, in which the acetylation precedes the Pd–C reduction, is obviously the best one, giving a more homogeneous product and only two major stereoisomeric products of the keto acetate formula **6b**. Repeated attempts to cyclize the keto alcohols **6a** to the cyclic ketal with methanol or to the analogous cyclic pyrrolidino compound, a reaction which goes well with less highly substituted compounds,[7] or to a cyclic hemiketal, were all unsuccessful. The formation of two diastereoisomeric keto alcohols (**6**) or acetates in roughly equal amounts by these procedures indicated that control of the stereochemistry was not promising in this series.

The 4-methoxy analog **1b** was investigated because it might lead to bicyclic products, *via* a cyanhydrin–lactone route, for example, in which R and OR′ in **5a** were in a lactone ring. This might give better control over the stereochemistry of the reduction of the double bond than could be achieved with **5a** or **5b**. Compound **1b**, *cis*-2-isoamyl-3-methyl-4-methoxy-2,3-dihydrobenzofuran, was therefore synthesized by methods similar to those described for **1a**. Chlorination of resorcinol monomethyl ether gave 3-methoxy-4,6-dichlorophenol (**8a**), which was converted to the keto ether **8b**; this was cyclized to 2-isoamyl-3-methyl-4-methoxy-5,7-dichlorobenzofuran, **9a**, and the chlorine





8a, R = H
b, R = $CH_3COCHCH_2CH_2CH(CH_3)_2$

9a, R = Cl
b, R = H

atoms were removed by catalytic reduction in acetic acid–sodium acetate with 10% Pd–C to yield 90% of the chlorine-free benzofuran **9b**, along with 10% of the correspondiug *cis*-2,3-dihydro compound **1b**. Catalytic reduction of the benzofuran **9b** with platinum gave mainly hydrogenolysis of the methoxyl group, with the formation of perhydrobenzofurans (**7b**), along with starting material. It was finally found that catalytic reduction of **9b** with 30% Pd–C in absolute alcohol gave a 60% yield of the *cis*-2,3-dihydro compound **1b**, along with 30% of the perhydro compound(s) **7b**.

Birch reduction of the *cis*-2,3-dihydro-4-methoxy compound **1b** gave the tetrahydro product **3b** (or double bond isomer), which, on hydrolysis with oxalic acid and purification by chromatography on alumina,

(5) "Tetrahydro" and "hexahydro" refer to the benzofuran nucleus as a whole; the starting material for the Birch reduction is the dihydrobenzofuran.

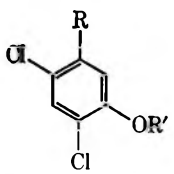
(6) Using the vpc attachment with an LKB 9000 mass spectrometer; spectra measured by Mr. C. T. Wetter and Mrs. Betty Fox.

(7) L. H. Brannigan, Ph.D. Thesis, Vanderbilt University, 1969.

gave a 79% yield of *cis*-2-isoamyl-3-methyl-4-keto-2,3,4,5,6,7-hexahydrobenzofuran (**4b**).

The *cis* configuration of the 4-methoxy-2,3-dihydro compound **1b** is assigned on the fact that it is prepared by catalytic reduction of the 2,3 double bond in **9b**. This is supported by the isomerization of **1b** to the corresponding *trans* compound **2b**, by the action of cold concentrated sulfuric acid.[8] Although the *trans* compound **2b** has a cracking pattern in the mass spectrometer almost identical with that of the *cis* compound **2a**, the 3-CH_3 is shifted in the nmr spectrum to 1.22 ppm, compared with 1.08 ppm for the 3-CH_3 in the *cis* compound **1a**. This is analogous to the relationships observed in the 3-CH_3 of the *cis–trans* pair **1a** and **2a**, where the configurations are established by several unequivocal methods.[2]

Another approach to introducing a functional group at position 4 involved the side-chain bromination of 3-methyl-4,6-dichlorophenyl acetate (**10a**); the benzyl bromide **10b** was converted to the methoxymethyl-



10a, R = CH_3; R′ = Ac
b, R = CH_2Br; R′ = Ac
c, R = CH_2OCH_3; R′ = H
d, R = CH_2OCH_3; R′ = $CH_3OCCHCH_2CH_2CH(CH_3)_2$

phenol **10c** by sodium methoxide, and from the latter was prepared the keto ether **10d**. This could not be cyclized to the corresponding benzofuran.

Experimental Section[9]

***cis*-2-Isoamyl-3,4-dimethyl-2,3-dihydrobenzofuran (1a).**—Platinum oxide (Englehard Industries, 100 mg) was added to a solution of 7.6 g (0.035 mol) of 2-isoamyl-3,4-dimethylbenzofuran in 200 ml of absolute ethanol, and the mixture was hydrogenated at atmospheric pressure. After 8 hr the uptake of hydrogen (0.035 mol) ceased. Platinum metal was removed by filtration and the alcohol was removed by evaporation under reduced pressure. Distillation through a Vigreux column gave 7.0 g (93% yield) of a colorless liquid, bp 148–150° (10 mm). Vapor phase chromatography on a 20% Apiezon column showed that this product was about 98% pure. Co-injection with authentic *cis*-2-isoamyl-3,4-dimethyl-2,3-dihydrobenzofuran showed only one peak. The nmr and ir spectra were identical with those reported by Hayward.[2,10]

Birch Reduction of *cis*-Isoamyl-3,4-dimethyl-2,3-dihydrobenzofuran (1a).—A solution of 2.18 g (0.01 mol) of the 2,3-dihydrobenzofuran **1a** in 23 ml of *t*-butyl alcohol and 100 ml of ethyl ether was added slowly to 50 ml of liquid ammonia. Lithium wire (1.13 g, 0.16 g-atom) was added over about 15 min to the solution in small pieces. The mixture was allowed to reflux with stirring for 2 hr; absolute methanol (20 ml) was added and the blue color disappeared. The ammonia was evaporated by gentle warming and 50 ml of ethyl ether was added, followed by 100 ml of ice water, added dropwise. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether solutions yielded an oil whose nmr spectrum (2.0 g) showed continuous complex absorption from 0.85 to 2.0 ppm, isoamyl, allylic, and ring protons; a multiplet at 2.65 ppm, tertiary allylic proton; a multiplet at 3.87 ppm, proton adjacent to the ether linkage; and a multiplet at 5.55 ppm, vinyl proton. The low integration of olefinic protons indicated the presence of over-reduced product. The lack of absorption above 6 ppm indicated the absence of starting material.

Hydrolysis of the Crude Birch Reduction Product.—The light yellow oil from the above Birch reduction of *cis*-2-isoamyl-3,4-dimethyl-2,3-dihydrobenzofuran was dissolved in 10 ml of 3% oxalic acid in 9:1 dioxane–water. After stirring at room temperature for 20 hr, 100 ml of water was added. The mixture was extracted with ether which was washed with 5% sodium carbonate and with distilled water; the combined washings were extracted twice with ether. The combined ether solutions were dried and the solvent was evaporated, yielding a yellow oil which was chromatographed on 90 g of neutral Woelm alumina, activity II. Elution with 180 ml of petroleum ether (bp 30–60°) gave 0.98 g of a clear colorless liquid, whose ir spectrum showed no hydroxyl or carbonyl absorption; the nmr spectrum showed continuous complex absorption from 0.8 to 2.0 ppm and weak, complex absorptions centered at 2.2 and 3.9 ppm, with no absorption in the aromatic region. These spectra indicated that this material was a mixture of hexahydrobenzofurans such as **4a** as reported by Hayward.[10] Elution with ether gave 0.340 g of a viscous slightly yellow oil. The ir spectrum showed a broad hydroxyl absorption at 3420 cm^{-1} and absorptions in the carbonyl region at 1710 and 1670 and a weak band at 1620 cm^{-1}; the 1670-cm^{-1} band was stronger than the 1710-cm^{-1} band. The second fraction was a mixture of the saturated and α,β-unsaturated keto alcohols. These mixtures are similar to those obtained by Hayward.[10]

Birch Reduction of *cis*-2-Isoamyl-3,4-dimethyl-2,3-dihydrobenzofuran (2a) Using a 3-g-atom Excess of Lithium.—A solution of 2.18 g (0.01 mol) of *cis*-2-isoamyl-3,4-dimethyl-2,3-dihydrobenzofuran in 25 ml of anhydrous ether and 6.5 ml of *t*-butyl alcohol was slowly added to 50 ml of liquid ammonia. Lithium (0.35 g, 0.05 g-atom) was added in small pieces over a period of about 20 min. The mixture was treated as above, and the nmr spectrum of the resulting oil (2.1 g) showed both olefinic and aromatic absorptions, indicating incomplete reduction.

Hydrolysis of the Birch Reduction Product in 3% Oxalic Acid in THF and Water.—The reduction product (2.1 g) from the above reaction was stirred in 10 ml of 3% oxalic acid in 9:1 THF:water for 2 hr at room temperature and diluted with 100 ml of water. It was worked up as above, and the resulting 2.0 g of oil was chromatographed on 90 g of neutral Woelm alumina, activity II. Elution with petroleum ether gave 0.5 g of a colorless oil, the nmr spectrum of which was identical with that of the 2,3-dihydrobenzofuran **1a**. Low integration of protons in the aromatic region of the spectrum indicated the presence of over-reduced products. Elution with ether gave 1.5 g of a viscous, yellow oil, whose ir spectrum had hydroxyl absorption at 3420 cm^{-1} and carbonyl absorptions at 1710 and 1670 cm^{-1}. The nmr spectrum showed no vinyl proton absorption, indicating that very little β,γ-unsaturated ketone was present. The mixture was about 75% α,β-unsaturated ketone, based on the relative intensities of the ir bands at 1710 (saturated carbonyl) and 1670 cm^{-1} (α,β-unsaturated carbonyl). Attempts to obtain the unsaturated ketone pure, by chromatography on alumina, silica gel, and alumina–silver nitrate (6%) failed. The above mixture was used for the following experiments.

***erythro*-2-(1,5-Dimethyl-2-acetoxyhexyl)-3-methylcyclohex-2-enone (6b).**—The mixture of saturated and unsaturated keto alcohols **5a** and **6a** (1.2 g, 0.005 mol), was dissolved in 4 ml of pyridine and 2 ml of acetic anhydride. The mixture was allowed to stand at room temperature for 24 hr and worked up as usual. The brown viscous product (1.1 g) was chromatographed on neutral Woelm alumina, activity II; elution with petroleum ether gave 100 mg of colorless oil, the ir spectrum of which was identical with the dihydrobenzofuran **1a**. Elution with ether gave 849 mg of a yellow oil, whose ir spectrum showed strong absorptions at 1742 (ester carbonyl), 1712 (saturated carbonyl), 1675 (α,β-unsaturated carbonyl), and 1244 cm^{-1} (ester C–O). This spectrum indicated that this material was a mixture of saturated and α,β-unsaturated ketoacetates in a ratio of about 1:3. These esters were not separable by column chromatography on alumina, silica gel, or alumina impregnated with 6% silver nitrate.

(8) D. P. Brust, D. S. Tarbell, S. M. Hecht, E. C. Hayward, and L. D. Colebrook, *J. Org. Chem.*, **31**, 2192 (1966).

(9) Microanalyses were done by the Galbraith Laboratories, Knoxville, Tenn.; all melting points and boiling points are uncorrected. Ir spectra were taken on a Beckman IR-10 spectrophotometer in KBr disks, solution or as liquid films, as indicated for each compound. Nmr spectra were recorded on a Varian A-60 spectrometer in $CDCl_3$ or CCl_4; chemicals shifts are reported in parts per million, with $(CH_3)_4Si$ as internal standard. Varian-Aerograph Model 90-P, A90-P or F & M Models 720 or 700 were used for vpc.

(10) E. C. Hayward, Ph.D. Thesis, University of Rochester, 1967.

erythro-2-(1,5-Dimethyl-2-acetoxyhexyl)-3-methylcyclohexanone (6b) from Hydrogenation of the Mixture of Saturated and Unsaturated Acetates.—The mixture of saturated and unsaturated ketoacetates obtained above (335 mg, 0.0014 mol, based on unsaturated keto ester) was dissolved in 15 ml of absolute methanol, and 75 mg of 30% palladium on carbon was added. The mixture was hydrogenated at atmospheric pressure. The uptake of hydrogen stopped after 14 hr, when 32.4 ml had been used. The ir spectrum of the crude product showed carbonyl bands at 1745 (ester) and 1710 cm^{-1} (carbonyl), with no absorption near 1670 cm^{-1}.

Vapor phase chromatography of the above mixture on a 6 ft × 0.25 in. 1% SE-30 column of the mass spectrometer (temperature program 3°/min starting at 110°) gave nine peaks. The first peak was small and was not identified. Minor peaks eluting at 130, 132, and 133° were identified by the cracking patterns as diastereoisomeric perhydrobenzofurans **7a**. A minor peak at 138° was the saturated ketoacetates **6b**. The last eluting peak, 166°, was minor and was not identified. The peaks identified as the desired saturated ketoacetates were present in an approximate ratio of 1:3:3, in order of their elution temperatures.

Hydrogenation of the Mixture of Saturated and Unsaturated Keto Alcohols Obtained from Birch Reduction of *cis*-2-Isoamyl-3,4-dimethyl-2,3-dihydrobenzofuran (1a). Acetylation of the Hydrogenation Mixture.—The keto alcohol mixture (1.13 g), in 15 ml of methanol with 100 mg of 30% palladium on carbon, was stirred at room temperature under hydrogen at 1 atm. After about 12 hr, hydrogen uptake ceased at 250 ml. The catalyst was removed by filtration and the solvent by reduced pressure evaporation. The resultant oil, about 1.0 g, was dissolved in 4 ml of pyridine and 2 ml of acetic anhydride was added. The mixture was allowed to stand at room temperature for 48 hr. The excess pyridine and acetic anhydride was removed by slow evaporation under reduced pressure. Vapor phase chromatography on the 6 ft × 0.25 in. 1% SE-30 column of the mass spectrometer (temperature program 3°/min starting at 110°) showed 17 peaks. Of these, 13 were identified on the basis of the mass spectra scans. They are, in order of their elution temperatures, 125, 126, 130, and 133°, diastereoisomers of the perhydrobenzofuran **7a**; 137 and 140°, saturated keto alcohols; 142, 143, and 156°, saturated ketoacetates **6b**; 160°, minor, and 162°, major, identified as the unsaturated ketoacetate **5b** and its double-bond isomer; 164°, minor, and 169°, massive, identified as unsaturated alcohols. The ratio of the saturated ketoacetate diastereoisomers, approximated by inspection, was 1:3:4 in order of eluting temperature. There were minor peaks eluting at 121, 154, 173, and 226°, which were not identified.

4,6-Dichloro-3-methoxyphenol (8a).—3-Methoxyphenol[11] (108 g) was chlorinated with 270 g of sulfuryl chloride at 0° over a 3-hr period; the reaction mixture was warmed on a steam bath for 30 min; and the product was distilled through an 8-in. Vigreux column. One fraction was collected [bp 82–85° (0.4 mm), 155 g, 80% yield], which crystallized completely on standing. Two recrystallizations from petroleum ether gave analytically pure 4,6-dichloro-3-methoxyphenol. The ir and nmr spectra were in complete agreement with the structure assigned.

Anal.. Calcd for $C_7H_6Cl_2O_2$: C, 43.55; H, 3.13. Found: C, 43.69; H, 2.95.

3-(4,6-Dichloro-3-methoxyphenoxy)-6-methyl-2-heptanone (8b).—This was prepared from the above phenol (100 g) and 3-bromo-6-methyl-2-heptanone[12] (113 g) in dry acetone with finely powdered potassium carbonate (70 g) and a few milligrams of potassium iodide. The product was 139 g (84% crude yield) of a cloudy yellow oil; a portion of this product (4.6 g) was chromatographed on 50 g of Woelm neutral alumina, activity I. Elution with 90 ml of petroleum ether gave 2.3 g of an oil; elution with a second 90-ml portion of petroleum ether gave 2.0 g of a clear yellow oil. The ir spectra of these two oils were identical. Vapor phase chromatography of the combined fractions on a 25% QF-1 column showed only one peak eluting at 10.3 min. An analytical sample was prepared by collection of this peak as a colorless quite viscous oil, followed by evaporative distillation (bath temperature 110°, pressure 0.025 mm). The ir spectrum (CCl_4) showed strong absorptions (cm^{-1}) at 1718, ketone; 1595, aromatic; 1450–1500, aliphatic; 1360, 1385, *gem*-dimethyl group; 1205, ether C–O; and 880, 1,2,4,5-tetrasubstituted aromatic ring. The nmr spectrum (CCl_4) showed a doublet at 0.9 ppm (6 H), *gem*-dimethyl protons; a complex envelope from 1.17 to 2.1 (5 H), chain protons; a singlet at 2.17 (3 H), methyl protons adjacent to carbonyl; a singlet at 3.78 (3 H), methoxyl protons; a triplet at 4.49 (1 H), tertiary proton adjacent to carbonyl and ether linkage; a singlet at 6.43 (1 H), aromatic proton; and a singlet at 7.32 (1 H), aromatic proton.

Anal. Calcd for $C_{15}H_{20}Cl_2O_3$: C, 56.43; H, 6.32. Found: C, 56.72; H, 6.27.

2-Isoamyl-3-methyl-4-methoxy-5,7-dichlorobenzofuran.—3-(4,6-Dichloro-3-methoxyphenoxy)-6-methyl-2-heptanone (122 g, 0.38 mol) was cooled in an ice bath, and similarly cooled concentrated sulfuric acid (150 ml) was added with rapid stirring during about 15 min. After the addition was complete, the dark red mixture was stirred at 0° for 15 min and poured over 400 g of ice. The dark oily precipitate which formed was extracted with ether; the combined extracts were washed with water, twice with 10% sodium carbonate, and again with water. The washings were back-extracted with ether. The combined ether solutions yielded 75 g of red oil, which was chromatographed on Woelm neutral alumina, activity I. Elution with 2 l. of petroleum ether provided 70 g (61% yield) of a colorless liquid. Vapor phase chromatography of this liquid on a 10 ft × 0.25 in. UCON Polar column showed one peak with a retention time of 14.5 min. This single peak was collected and the resulting clear colorless liquid was evaporatively distilled (bath temperature 90°, pressure 0.5 mm). The nmr spectrum had a doublet at 0.92 ppm (6 H), *gem*-dimethyl group protons; a multiplet at 1.58 (3 H), side-chain protons; a singlet at 2.22 (3 H), allylic methyl protons; a triplet at 2.67 (2 H), allylic side-chain protons; a singlet at 3.86 (3 H), methoxyl protons; and a singlet at 7.09 (1 H), aromatic proton.

Anal. Calcd for $C_{15}H_{18}Cl_2O_2$: C, 59.81; H, 6.02. Found: C, 59.69; H, 6.04.

2-Isoamyl-3-methyl-4-methoxybenzofuran (9b).—To a solution of 24 g (0.08 mol) of 2-isoamyl-3-methyl-4-methoxy-5,7-dichlorobenzofuran (9a) in 50 ml of absolute ethanol was added 13.1 g (0.16 mol) of anhydrous sodium acetate, 9.6 g (0.16 mol) of glacial acetic acid, and 0.5 g of 10% Pd–C (Matheson Coleman and Bell).

The mixture was shaken in a Parr apparatus under 50 psi of hydrogen; hydrogen uptake (0.16 mol) ceased after 20 hr. The catalyst and salts were removed by filtration through a Celite mat, the solvents by evaporation under reduced pressure, and the cloudy residual oil was taken up in ether; the ether solution was washed with water, 10% sodium carbonate, and again with water, and dried. The product, distilled through an 8-in. Vigreux column, yielded 18.0 g (96% yield) of a clear colorless liquid, bp 93–95° (0.3 mm). Vapor phase chromatography on a 25% FFAP column showed peaks at 16.0, 22.8, and 30 min. The peak at 22.8 min was about 90% of the mixture, and the peak at 16 min about 10%. The peak at 30 min was very small and was identified as starting material by co-injection with 2-isoamyl-3-methyl-4-methoxy-5,7-dichlorobenzofuran. The peak at 16.0 min was identified in later experiments as *cis*-2-isoamyl-3-methyl-4-methoxy-2,3-dihydrobenzofuran (1b). The peak at 22.8 min was collected and evaporatively distilled (bath temperature 80°, 0.05 mm). The nmr spectrum (CCl_4) showed a doublet at 0.92 ppm (6 H), *gem*-dimethyl protons; a complex multiplet at 1.55 (3 H), side-chain protons; a singlet at 2.26 (3 H), allylic methyl protons; a triplet at 2.58 (2 H), allylic side chain protons; a singlet at 3.70 (3 H), methoxyl protons; a multiplet at 6.37 (1 H), aromatic proton between two other protons; and a multiplet at 6.89 (2 H), aromatic protons adjacent to ether linkages.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.41; H, 8.72.

Hydrogenation of 2-Isoamyl-3-methyl-4-methoxybenzofuran (9b) with Platinum Catalyst. 2-Isoamyl-3-methylperhydrobenzofuran (7b).—To a solution of 11.6 g of 2-isoamyl-3-methyl-4-methoxybenzofuran (0.05 mol) in 50 ml of methanol was added 100 mg of platinum oxide (Engelhard Industries); the mixture was shaken under hydrogen at 50 psi. In less than 1 hr, 0.05 mol of hydrogen was taken up. The platinum metal was removed by filtration, the solvent was removed by reduced pressure evaporation; the colorless oil was distilled through a Vigreux column. Three fractions were collected. The first fraction (3.1 g), bp 59° (0.15 mm), showed no aromatic or allylic protons in the nmr spectrum, indicating that it was a perhydrobenzofuran. The two high-boiling fractions were shown by vapor phase

(11) W. H. Perkin, J. N. Ray and R. Robinson, *J. Chem. Soc.*, 945 (1926).

(12) *Cf.* D. S. Tarbell, S. E. Cremer, *et al.*, *J. Amer. Chem. Soc.*, **83**, 3112 (1961).

chromatography to be identical with the starting material. Hydrogenation over platinum catalyst at atmospheric pressure gave similar results.

Vapor phase chromatography of the fraction boiling at 59° (0.15 mm) on a 25% QF-1 column showed one peak with a retention time of 5.1 min. This peak was collected and evaporatively distilled (bath temperature, 60°; 0.5 mm). The ir spectrum (liquid film) had bands at 1390 and 1370, *gem*-dimethyl doublet, and 1080 cm^{-1}, C–O stretching of ether. The nmr spectrum (CCl_4) had two partially superimposed doublets centered at 0.9 ppm (9 H, total), methyl protons; a complex multiplet from 1.0 to 2.1 (15 H), ring and chain protons; and a multiplet at 3.72 (2 H), protons adjacent to ether linkages.

Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 80.12; H, 12.41.

Hydrogenation of 2-Isoamyl-3-methyl-4-methoxybenzofuran (9b) with 10% Palladium-on-Carbon Catalyst.—Palladium on carbon 10% (0.5 g) was added to a solution of 11.6 g (0.05 mol). of 2-isoamyl-3-methyl-4-methoxybenzofuran in 50 ml of methanol. The mixture was shaken under hydrogen at 50 psi; after 24 hr no hydrogen had been taken up. The catalyst was removed, 0.5 g of fresh catalyst was added, and the mixture was again shaken under hydrogen at 50 psi; after 24 hr no hydrogen had been taken up. The catalyst was removed by filtration and the solvent evaporated under reduced pressure. The liquid residue was dissolved in 40 ml of methanol and 10 ml of glacial acetic acid was added along with 0.5 g of 10% palladium on carbon. The mixture was shaken under hydrogen at 50 psi. After 12 hr, 0.05 mol of hydrogen had been taken up. The catalyst was removed by filtration, most of the solvent by evaporation under reduced pressure, and the residue was dissolved in ether, washed with water, 10% sodium carbonate, and again with water. The combined washings, basic to litmus, were back-extracted with ether. The combined ether solutions were dried, filtered, and concentrated under reduced pressure. Vapor phase chromatography on a 25% FFAP column showed peaks at 5.2, 20, and 23 min. The peak at 5.2 min, about 30% of the mixture, was shown by co-injection to be due to the perhydrobenzofuran **7b**. The peaks at 20 and 23.5 min were shown by co-injection to be the 2,3-dihydrobenzofuran **1b** and the benzofuran **9b** in approximately the same ratio as the starting material.

Hydrogenation of 2-Isoamyl-3-methyl-4-methoxybenzofuran (9b) with 30% Pd–C. *cis*-2-Isoamyl-3-methyl-4-methoxy-2,3-dihydrobenzofuran (1b).—To a solution of 23.2 g (0.1 mol) of 2-isoamyl-3-methyl-4-methoxybenzofuran (**9b**) in 20 ml of absolute ethanol was added 2.5 g of 30% Pd–C (Engelhard Industries). The mixture was stirred under hydrogen at atmospheric pressure; after 5 hr, 500 ml of hydrogen (about 20% of the theoretical amount) had been taken up. A few microliters of the reaction mixture was injected onto a 5 ft × 0.25 in. 3% SE-30 column (column temperature, 172°; flow rate, 60 ml of He/min). Two peaks were observed with retention times of 5.5 and 6.8 min. These were identified by co-injection as the same two peaks in the starting material. The relative concentration of the peak at 5.5 min had risen from about 5 to 20%. The hydrogenation was continued. After 13 hr a total of 900 ml of hydrogen had been taken up. Vapor phase chromatography (conditions above) at this point showed a third peak at 2.8 min, about 2% of the total mixture. This new peak was identified as the perhydrobenzofuran **7b** by co-injection. The peak at 5.5 min had risen to about 40%. After the theoretical amount of hydrogen had been taken up, the peak at 2.8 min had risen to about 20% and the peak at 5.5 min to 60%. Hydrogenation was continued until the peak at 6.8 min had decreased to 7%. This required 48 hr and 3900 ml of hydrogen (0.134 mol); the 2.8-min peak had increased to 28% and the 5.5-min peak to 65%. The catalyst was removed by filtration through a Celite mat and the solid mixture was washed thoroughly several times with absolute ethanol. The filtrate and washings were combined and the solvent removed by evaporation under reduced pressure. The residue was 23 g of a colorless cloudy liquid. The liquid was distilled through an 8-in. Vigreux column. Two fractions were collected: 6.5 g of colorless liquid, bp 63° (0.15 mm), and 16.0 g of a slightly cloudy colorless liquid, bp 97–105° (0.15 mm). The first was shown by vapor phase chromatography to be of more than 98% purity, and to be identical with the perhydrobenzofuran **7b** previously obtained. Vapor phase chromatography of the high-boiling fraction on a 20% Ucon Polar column gave three peaks with retention times 6.1, 11.0, and 17.0 min in a ratio of 1:40:4, respectively. The peaks at 11.0 and 17.0 min were identified by co-injection as the two components in the mixture before hydrogenation. The peak at 11.0 min was collected and evaporatively distilled (bath temperature 70°, 1 mm). Reinjection of the collected material showed that it was about 98% pure *cis*-2,3-dihydrobenzofuran **1b**; the nmr spectrum showed two close doublets at 0.92 and 1.08 ppm (total 9 H), *gem*-dimethyl and homobenzylic methyl protons; a complex envelope from 1.2 to 1.9 (5 H), side-chain protons; a multiplet at 3.28 (1 H), benzylic proton; a singlet at 3.69 (3 H), methoxy protons; a multiplet at 4.36 (1 H), proton adjacent to the ether linkage; two close doublets at 6.18 and 6.32 (total 2 H), aromatic protons; and a triplet at 6.81 (1 H), aromatic proton.

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.02; H, 9.53.

The high-boiling fraction (15.5 g) was redistilled on an 18-in. annular Teflon spinning-band column. Two fractions were collected: 14.0 g (60% yield) bp 122° (0.5 mm), and 1.3 g, bp 124° (0.5 mm). Vapor phase chromatography of the low-boiling fraction showed that it was more than 98% pure **1b**; co-injection with the above analytical sample showed that the fraction boiling at 122° (0.5 mm) was *cis*-2-isoamyl-3-methyl-4-methoxy-2,3-dihydrobenzofuran.

Attempts to reduce the benzofuran **9b** to the 2,3-dihydro compound **1b** by diimide failed.[13]

***trans*-2-Isoamyl-3-methyl-4-methoxy-2,3-dihydrobenzofuran (2b).**—To 2 g of *cis*-isoamyl-3-methyl-4-methoxy-2,3-dihydrobenzofuran was added 5 ml of ice-cold concentrated sulfuric acid; the mixture was kept in the refrigerator for 16 hr, after which it was poured over 50 g of ice. The product, after the usual procedures, was 0.54 g of a red liquid. Vapor phase chromatography on a FFAP column showed peaks at 5.2, 16.7, 19.8, and 23.5 min in a ratio of 1:60:40:1. The peaks at 5.2, 16.7, and 23.5 min were identified, by co-injection with the appropriate known compounds, as the perhydrobenzofuran **7b**, *cis*-2-isoamyl-3-methyl-4-methoxy-2,3-dihydrobenzofuran (**1b**), and 2-isoamyl-3-methyl-4-methoxybenzofuran (**9b**), respectively. The peak at 16.7 min was collected and evaporatively distilled (bath temperature 80°, 0.1 mm). The mass spectrum was identical with that of the *cis*-dihydrobenzofuran **1b**. The nmr spectrum of the collected peak was nearly identical with that of the *cis* compound, except that the absorption of the 3-methyl group protons was shifted to 1.22 ppm from 1.07 ppm for the *cis* compound.

***cis*-2-Isoamyl-3-methylketo-2,3,4,5,6,7-hexahydrobenzofuran (4b).**—A solution of 7.24 g (0.031 mol) of *cis*-2-isoamyl-3-methyl-4-methoxy-2,3-dihydrobenzofuran in 70 ml of anhydrous ethyl ether and 70 ml of *t*-butyl alcohol was added slowly to 150 ml of liquid ammonia. Lithium wire (0.75 g, 0.107 g-atom) was added with rapid stirring over a period of 20 min. After the mixture had refluxed for 30 min, a second portion of 0.75 g of lithium wire was added. The procedure for the reduction of **1a** was followed essentially, and 7.2 g of a slightly yellow mobile liquid was obtained. The nmr spectrum of this crude material showed no aromatic absorption, indicating complete reduction. A complex multiplet at 4.63 ppm and a singlet at 3.51 suggested the presence of the enol ethers (tetrahydrobenzofurans). The crude mixture in 75 ml of tetrahydrofuran was stirred with 25 ml of 12% aqueous oxalic acid at room temperature for 18 hr. The mixture was diluted with water, the tetrahydrofuran layer was separated, and the aqueous layer was extracted with ether. The combined tetrahydrofuran and ether solutions were washed with water, 10% sodium carbonate, and again with water. The basic washings were back-extracted with 50 ml of ether. The combined organic solutions were worked up as usual, and concentrated by evaporation under reduced pressure. The ir spectrum of the residual oil, 6.8 g, showed a hydroxyl band at 3440 cm^{-1} and a strong broad band from 1620 to 1680 cm^{-1}. The product was chromatographed on Woelm neutral alumina, activity I. Elution with petroleum ether produced 0.1 g of a colorless liquid with an ir spectrum identical with that of the starting material. Elution with ether gave 5.47 g of a light yellow oil, whose ir and nmr spectra showed that it was the deisired 4-keto compound **4b**. The ir spectrum had bands at 1640 and 1680 cm^{-1}, O—C=C—C=O; and 1195 and 1245, C—O. The nmr (CCl_4) had a multiplet centered at 4.51 ppm (1 H), proton adjacent to ether linkage; a multiplet centered at 3.09 (1 H),

(13) E. J. Corey, W. L. Mock, and D. J. Pasto, *Tetrahedron Lett.*, 347 (1961); S. Hünig, H. R. Muller, and W. Thier, *ibid.*, 353 (1961); R. S. Dewey and E. E. van Tamelen, *J. Amer. Chem. Soc.*, **83**, 3729 (1961); C. E. Miller, *J. Chem. Educ.*, **42**, 254 (1965).

tertiary allylic proton; 2.2 (4 H), a multiplet, allylic protons and protons adjacent to a carbonyl bond; a complex envelope from 1.1 to 1.8 (7 H), ring and side-chain protons; and two superimposed doublets at 0.95 (9 H), three sets of methyl group protons. Vapor phase chromatography of this liquid on a 5 ft × 0.25 in. UCON Polar column showed only one peak with a retention time of 31 min. This peak was collected and evaporatively distilled (bath temperature 90°, 0.05 mm).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.52; H, 9.92.

The yield of *cis*-2-isoamyl-3-methyl-4-keto-2,3,4,5,6,7-hexahydrobenzofuran (**4b**, 5.47 g) was 79%.

4,6-Dichloro-3-bromomethylphenyl Acetate (10b).—N-Bromosuccinimide (17.8 g, 0.1 mol), which had been freshly recrystallized from water and dried in a vacuum desiccator over phosphorus pentoxide, was refluxed in a solution of 21.8 g (0.1 mol) of 4,6-dichloro-3-methylphenyl acetate[14] in 200 ml of carbon tetrachloride, with the addition of 200 mg of benzoyl peroxide. Refluxing was continued for 4 hr and the mixture was allowed to stand overnight. The succinimide was removed by filtration and washed several times with carbon tetrachloride. The solvent was evaporated under vacuum at 35° and the resulting yellow oil was taken up in 100 ml of petroleum ether. After standing in the freezer overnight, the product crystallized, giving 18.4 g (mp 38–46°) of yellow oily crystals. Concentration of the mother liquor gave an additional 6.0 g of product. Recrystallization, with decolorization with activated charcoal, from petroleum ether gave 22.0 g (mp 51–53°, 74% yield). An analytical sample (mp 52.2–53°) was prepared by four recrystallizations from petroleum ether. The ir and nmr spectra were in agreement with those for the structure.

Anal. Calcd for $C_9H_7BrCl_2O_2$: C, 36.27; H, 2.37. Found: C, 36.28; H, 2.52.

4,6-Dichloro-3-methoxymethylphenol (10c).—The bromomethyl compound **10b** (19.6 g) was treated dropwise at room temperature with a solution of 4.8 g of sodium in 75 ml of dry methanol and was stirred overnight. Water (50 ml) was added carefully, and the mixture was refluxed for 2 hr. Conventional work-up gave an oil, which was distilled through a 4-in. Vigreux column. The main fraction was 10.6 g (74% yield) of a colorless liquid, bp 113–116° (0.6 mm), which crystallized, mp 61–64°. An analytical sample was prepared by three recrystallizations from petroleum ether and sublimation (bath temperature 60°, 0.5 mm). The pure sample of **10c** had mp 68–69.5°. The ir spectrum ($HCCl_3$) had bands at 3400 cm^{-1}, hydroxyl; 1080, 1170, and 1200, ether and phenol C–O stretching. The nmr spectrum (CCl_4) showed singlets at 3.43 ppm (3 H), methoxy protons; 4.42 (2 H), benzylic methylene protons; 6.59 (1 H), broad, phenolic protons; 7.02 (1 H) and 7.19 (1 H), aromatic protons.

Anal. Calcd for $C_8H_8Cl_2O_2$: C, 46.40; H, 3.89. Found: C, 46.51; H, 3.79.

3-(4,6-Dichloro-3-methoxymethylphenyl)-6-methyl-2-heptanone (10d) was prepared in the usual way from 9.0 g of the phenol, 8.9 g of 3-bromo-6-methyl-2-heptanone, 2.0 g of potassium carbonate, and a few milligrams of potassium iodide in 25 ml of dry acetone. Vapor phase chromatography of the resulting liquid on a 25% QF-1 column showed peaks at 1.7 and 8.3 min. The second peak, **10d**, about 90% of the mixture, was collected and evaporatively distilled (bath temperature 90°, 0.5). The ir spectrum (liquid film) had bands at 1720 cm^{-1}, carbonyl stretching; 1250, 1195, 1168, 1105, and 1080, ether stretching bands; and a doublet at 1360 and 1380, *gem*-dimethyl group. The nmr spectrum (CCl_4) had a doublet at 0.92 ppm (6 H), *gem*-dimethyl group; a complex envelope from 1.1 to 1.9 (5 H), aliphatic methylene and methine protons; a singlet at 2.23 (3 H), methyl ketone protons; a singlet at 3.40 (3 H), methoxyl protons; a singlet at 4.37 superimposed upon a multiplet at 4.50 (3 H, total), benzylic ether and ketone ether protons; a singlet at 6.95 (1 H), aromatic proton; and a singlet at 7.32 (1 H), aromatic proton.

Anal. Calcd for $C_{16}H_{22}Cl_2O_3$: C, 57.66; H, 6.65. Found: C, 57.59; H, 6.51.

Attempted Cyclization of 3-(4,6-Dichloro-3-methoxymethylphenoxy)-6-methyl-2-heptanone (10d).—3-(4,6-Dichloro-3-methoxymethylphenoxy)-6-methyl-2-heptanone (2.0 g, 0.006 mol), was cooled in an ice bath to 0°. Ice-cold sulfuric acid (5 ml) was added and the mixture was stirred for 12 min. The dark red mass was mixed thoroughly with 50 g of ice. The brown oily precipitate was extracted into five 25-ml portions of ethyl ether. The combined ether extracts were washed with water, 10% sodium hydroxide, and again with water and dried. The nmr and ir spectra of the viscous liquid residue were identical with those of the starting material. The experiment was repeated, replacing the sulfuric acid with polyphosphoric acid, at 0° for 2 hr, and at room temperature for 18 hr. When these mixtures were worked up as above, only starting material could be detected by nmr or ir spectra.

Registry No.—**1a**, 24099-57-8; **1b**, 24099-58-9; **2b**, 24099-59-0; **4b**, 24099-60-3; **6b**, 24099-61-4; **7b**, 24099-62-5; **8a**, 18113-13-8; **8b**, 24099-64-7; **9a**, 24099-65-8; **9b**, 24099-66-9; **10b**, 24099-67-0; **10c**, 24099-68-1; **10d**, 24099-69-2.

(14) S. E. Cremer and D. S. Tarbell, *J. Org. Chem.*, **26**, 3653 (1961).

Reaction of Hexaalkyl- and α,α'-Dichlorotetraalkyldistannoxanes with Cyclic Carbonates

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Hexaalkyldistannoxanes react with equimolar amounts of ethylene or propylene carbonate at 80–180° to give bis(trialkyltin) alkylene glycolates and/or 2-dialkylstanna-1,3-dioxolanes. However, α,α'-dichlorotetraalkyldistannoxane gives rise to 2-dialkylstanna-1,3-dioxolane exclusively. Formation of the stannadioxolanes was confirmed through a new cyclization reaction of bis(tributyltin) ethylene glycolates, $R_3SnOC_2H_4OSnR_3$, and their cyclizing tendencies were as follows: $ClEt_2Sn$, $Me_3Sn > Et_3Sn > n\text{-}Bu_3Sn$. Reactions of hexaethyl- and hexabutyldistannoxanes with ethylene monothiolcarbonate at higher temperature afford bis(trialkyltin) monothiolethylene glycolates, together with small amounts of 2-dialkylstanna-1-oxa-3-thialanes.

Davies and coworkers have reported the reaction of hexabutyldistannoxane with ethylene carbonate to afford bis(tributyltin) ethylene glycolate in a good yield.[1] In the course of our study on the reaction of distannoxane with cyclic carbonate, we obtained a cyclic organotin alkoxide, instead of the ethylene glycolate, for instance, 2-diethylstanna-1,3-dioxolane from hexaethyldistannoxane and ethylene carbonate. We investigated the similar reactions of four kinds of the distannoxanes with ethylene or propylene carbonate and ethylene thiolcarbonate at various temperature, which provided a new type of cyclization reaction of sterically less hindered bis(trialkyltin) alkylene glycolate

(1) A. G. Davies, P. R. Palan, and S. C. Vasishtha, *Chem. Ind.* (London), 229 (1967).

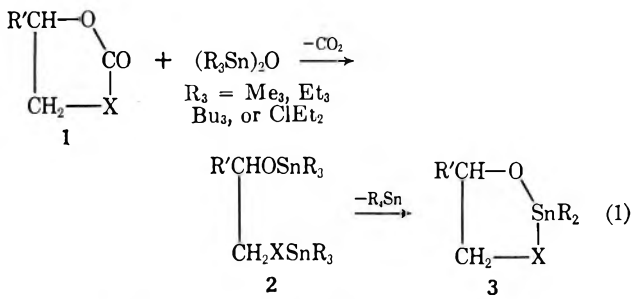
to 2-dialkylstanna-1,3-dioxolane.[2] The analogous reaction between ethylene thiolcarbonate and the above-mentioned distannoxanes was investigated.

Results and Discussions

A mixture of equimolar amounts of hexaethyldistannoxane and ethylene carbonate was heated under nitrogen at 100° to give 12% of bis(triethyltin) ethylene glycolate and an 85% yield of 2-diethylstanna-1,3-dioxolane, together with a quantitative yield of tetraethyltin. Results concerning the reactions of some hexaalkyldistannoxanes with ethylene or propylene carbonate are summarized in Table I.

It seems of interest that the reaction of ethylene carbonate with hexabutyldistannoxane at 100° gave a fairly good yield of linear dialkoxide, while, in the case of the reaction with hexamethyldistannoxane, cyclic dialkoxide was a only product. These results would suggest that the cyclization reaction of a linear dialkoxide to a cyclic product is sterically hindered by the bulky alkyltin group. However, at higher reaction temperature, such as 180°, the reaction between hexabutyldistannoxane and ethylene carbonate could give the cyclic dialkoxide **3c** in fairly good yield.

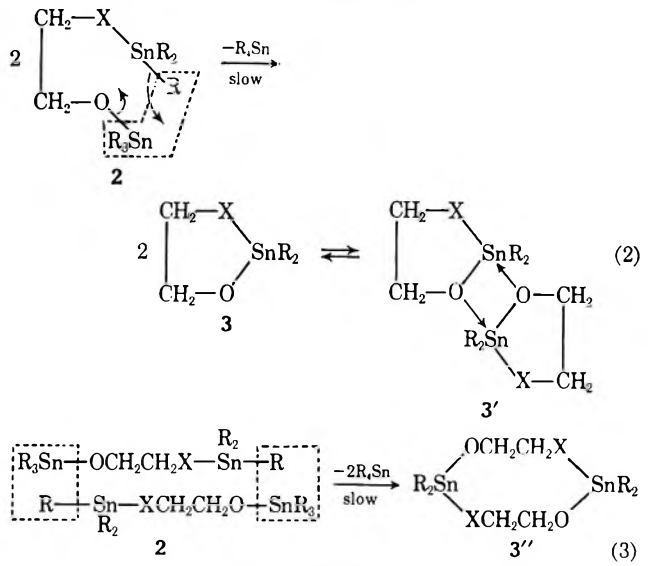
However, when bis(triethyltin) ethylene glycolate (**2b**) was heated at 100° for 3 hr, 2-diethylstanna-1,3-dioxolane (**3b**) and tetraethyltin were quantitatively obtained, supporting the reaction path **1** → **2** → **3** as shown in eq 1.



(1)

1		2			3		
R′	X	R′	R	X	R′	R	X
a H	O	a H	Me	O	a H	Me	O
b Me	O	b H	Et	O	b H	Et	O
c H	S	c H	Bu	O	c H	Bu	O
		d Me	Et	O	d Me	Et	O
		e Me	Bu	O	e Me	Bu	O
		f H	Et	S	f H	Et	S
		g H	Bu	S	g H	Bu	S

Even when di-*t*-butyl peroxide or diphenylpicrylhydrazyl was added in the reaction of hexaethyldistannoxane with ethylene carbonate at 100°, the yields of cyclic and linear dialkoxide were not affected, indicating a coordination mechanism (eq 2 or 3) as has been suggested for redistribution reactions of trialkyltin hydroxide[8] and methoxide,[9] rather than a free-radical mechanism. Equilibrium phenomena among **3**, **3′**, and **3″** were documented by Pommier and Valade[7] and the dimer form **3′** or **3″** was suggested to be stable.[10] By our experiment, the rate of the cyclization reaction of bis(triethyltin) ethylene glycolate at 137° in mixed xylene was followed by the first-order kinetics, and therefore, an intramolecular process (2) seems to be more preferable than intermolecular path (3).



(2)

(3)

Hexaethyldistannoxane was found to react with ethylene monothiolcarbonate (**1c**) at 150° for 2 hr, to yield 59% of bis(triethyltin) monothiolethylene glycolate (**2f**) and 12% of 2-diethylstanna-1,3-thioxolane (**3f**). The necessity of higher reaction temperature is indicative of the lower reactivity of the monothiolcarbonate than the carbonate, which would be affected by the electronegativity of heteroatom X in cyclic compounds. In spite of the higher reaction temperature, the low yield of cyclic thio compound **3f** and relatively high yield of **2f** could result from a smaller cyclization rate of the linear thio compound **2f** to **3f**, owing to the stable tin–sulfur bond.[11]

A mixture of hexabutyldistannoxane and monothiolcarbonate was heated at 150° for 2 hr, affording solely a linear product **2g**, probably because of steric hindrance on the cyclization reaction.

α,α'-Dichlorotetraethyldistannoxane makes a stable dimer[12] and was less reactive than hexaethyldistannoxane, which exists as monomer in solution. In the reaction with ethylene carbonate, the former required 2 days of heating at 80° to react quantitatively, while the latter reacted completely in only 2 hr. The dimeric distannoxane was less reactive than the monomeric one in the ring-opening reactions of cyclic esters.[13]

Reaction of α,α'-dichlorotetraethyldistannoxane with ethylene carbonate at 80° afforded cyclic dialkoxide **3b** in 88% yield and no linear dialkoxide **5** was isolated, suggesting the facile cyclization reaction of **5**

(2) Stannadioxolanes were also prepared by another methods from dibutyltin dichloride,[3] dibutyltin oxide,[4,5] and dibutyltin methoxide.[6,7]

(3) H. E. Remsden and C. K. Banks, U. S. Patent 2,789,994 (1957); *Chem. Abstr.*, **51**, 14786 (1957).

(4) J. Bornstein, B. R. La Liberter, T. M. Andrews, and J. C. Montermoso, *J. Org. Chem.*, **24**, 886 (1959).

(5) W. J. Considine, *J. Organometal. Chem.*, **5**, 263 (1966).

(6) R. C. Mehrota and V. D. Gupta, *ibid.*, **4**, 145 (1965).

(7) J. Pommier and J. Valade, *ibid.*, **12**, 433 (1968).

(8) C. A. Krauss and R. H. Bullard, *J. Amer. Chem. Soc.*, **51**, 3605 (1929).

(9) E. Amberger and M. Kula, *Chem. Ber.*, **96**, 2562 (1963).

(10) Cyclic butyltin compound **3** in eq 1 and eq 4 was shown conventionally as monomer, but the stable form seems to be dimer[7] in equilibrium among **3**, **3′**, or **3″**.

(11) K. Itoh, Y. Kato, and Y. Ishii, *J. Org. Chem.*, **34**, 459 (1969).

(12) R. Okawara and M. Wada, *J. Organometal. Chem.*, **1**, 84 (1963).

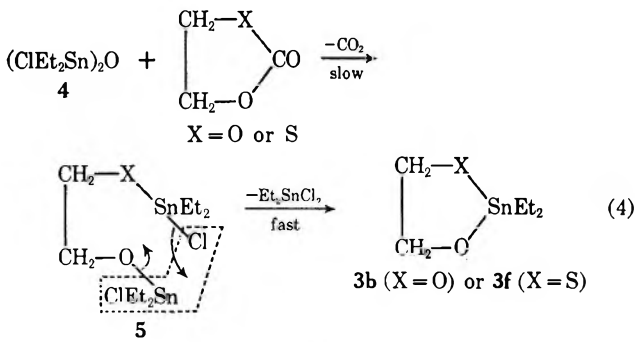
(13) S. Sakai, Y. Kiyohara, M. Kokura, K. Itoh, and Y. Ishii, unpublished work.

TABLE I

REACTIONS OF DISTANNOXANES WITH CYCLIC CARBONATES

Reactants		Reaction		Dialkoxides formed, %	
Carbonates	Distannoxanes	Temp, °C	Time, hr	2	3
Ethylene carbonate	$(Me_3Sn)_2O$	100	0.166	0 (2a)	64 (3a)
Ethylene carbonate	$(Et_3Sn)_2O$	80	2	60–70 (2b)	5–10 (3b)
Ethylene carbonate	$(Et_3Sn)_2O$[a]	80	2	64 (2b)	9 (3b)
Ethylene carbonate	$(Et_3Sn)_2O$	100	2	12 (2b)	85 (3b)
Ethylene carbonate	$(Et_3Sn)_2O$[b]	100	2	18 (2b)	80 (3b)
Ethylene carbonate	$(Bu_3Sn)_2O$	100	6	88 (2c)	3[c] (3c)
Ethylene carbonate	$(Bu_3Sn)_2O$	120	6	86 (2c)	5[c] (3c)
Ethylene carbonate	$(Bu_3Sn)_2O$	180	6	0	90 (3c)
Propylene carbonate	$(Et_3Sn)_2O$	100	2	0	78 (3d)
Propylene carbonate	$(Bu_3Sn)_2O$	120	6	75 (2e)	3[c] (3e)
Ethylene monothiolcarbonate	$(Et_3Sn)_2O$	150	2	59 (2f)	12 (3f)
Ethylene monothiolcarbonate	$(Bu_3Sn)_2O$	150	2	60 (2g)	1 (3g)
Ethylene carbonate	$(ClEt_2Sn)_2O$	80	48	0	88 (3b)
Ethylene monothiolcarbonate	$(ClEt_2Sn)_2O$	150	3	0	85 (3f)

[a] Dibenzoyl peroxide (0.3 wt %) was added. [b] Diphenylpicrylhydrazyl (0.3 wt %) was added. [c] Cyclic dialkoxide 3 was formed during high-temperature distillation up to 240°.



(4)

to 3b and the larger mobility of the chlorine atom in comparison with the ethyl group. Analogous phenomena were also observed in the reaction of dichlorotetraethyldistannoxane with ethylene monothiolcarbonate to give the cyclic thio compound 3f.

In the mass spectral inspections, all cyclic dialkoxides 3a–e, seem to show parent mass numbers of the dimer,[14,15] while 2-diethylstanna-1-oxa-3-thialane has that of monomer. Both stannadioxolane and stannaoxathialane would exist mainly as dimers in equilibrium, 3 ⇄ 3′ or 3″,[16] but the association of two molecules of stannaoxathialane would be weaker than that of the cyclic dialkoxide; so the former might show the parent mass number of monomer in mass spectral measurements.

Experimental Section

Boiling points and melting points have not been corrected. Infrared spectra were recorded on a JASCO Model IR-S spectrometer. Nmr spectra were measured on a Japan Electron Optics Laboratory Model JNM-MH 60, using tetramethylsilane (TMS, τ 10) as an internal standard. Mass spectral data (75 eV, calcd for ^{118}Sn) were obtained with a Japan Electron Optics Type JMS-OISG mass spectrometer. Microanalyses were done by the Analytical Center of Kyoto University, and the content of tin atom in the products was analyzed by Gilmans' method.[17]

Materials.—Ethylene thiolcarbonate (Aldrich Chemical Corp.), ethylene, and propylene carbonate were redistilled *in vacuo*. Hexaethyl-, hexabutyl-,[18] and hexamethyldistannoxane[19] were prepared by literature methods. Bis(triethyltin) ethylene glycolate was obtained by Lorberth and Kula's method.[20]

Reaction of Hexaethyldistannoxane with Ethylene Carbonate (General Procedure).—Hexaethyldistannoxane (15.9 mmol) and ethylene carbonate (16.0 mmol) were added to a 30-ml distillating flask which was heated at 80° for 2 hr under nitrogen; the reaction mixture was distilled, giving a 12% yield (based on the distannoxane used) of the linear dialkoxide 2b, bp 112–114° (0.1 mm), and an 85% yield of the cyclic dialkoxide 3b as distillation residue, mp 280° (recrystallized from $CHCl_3$). Tetraethyltin was condensed in a cold trap.

2b: ir (CCl_4) 1055, 1010 (C–O) and 880 cm^{-1}; nmr (CCl_4) τ 6.67 (s, 4) and ~9.2 (broad, 30); ir and nmr spectra coincided well with those of an authentic sample prepared from N,N-diethyltriethylstannylamine and ethylene glycol.[18]

3b: ir (KBr) 1120, 1068 (C–O), 965, 950, 895, and 680 cm^{-1}; nmr ($CHCl_3$) τ 6.48 (s, 4, CH_2O) and ~8.8 (broad, 10, Et–Sn); mass spectrum (*m/e*) 443 (calcd for $(3b)_2$–Et, 443). *Anal.* Calcd for $C_6H_{14}O_2Sn$: C, 30.43; H, 5.96; S, 50.11. Found: C, 30.39; H, 5.95; Sn, 49.76.

Reaction of Hexamethyldistannoxane with Ethylene Carbonate.—Hexamethyldistannoxane reacted with ethylene carbonate at 100° for 10 min analogously giving a 64% yield of 3a: mp <270°; ir (KBr) 1230, 1120, 1185, 1070 (C–O), 900, and 780 cm^{-1}; an nmr measurement could not be done owing to its poor solubility; mass spectrum (*m/e*) 403 (calcd for $(3a)_2$–Me, 403). *Anal.* Calcd for $C_4H_{10}O_2Sn$: C, 23.01; H, 4.83; Sn, 56.84. Found: C, 22.75; H, 5.05; Sn, 56.65.

Reaction of Hexabutyldistannoxane with Ethylene Carbonate.—Hexabutyldistannoxane reacted with ethylene carbonate at 180° for 6 hr, and the reaction mixture was recrystallized from carbon tetrachloride giving a 90% yield of 3c: mp 222–223° (lit.[7] 215–220°, lit.[5] 223–227°); ir (KBr) 1120, 1060, 895, and 710 cm^{-1}; nmr ($CHCl_3$) τ 6.51 (s, 4, CH_2O) and 8.60–9.20 (m, 18, Bu–Sn). Ir and nmr spectra were quite similar when compared with those of the authentic material.[7] Tetrabutyltin (86% yield) was condensed in a cold trap.

The reaction of hexabutyldistannoxane with ethylene carbonate at 100° gave an 88% yield of 2c: bp 175–180° (0.2 mm); ir (CCl_4) 1110, 1070, 1040, and 870 cm^{-1}; nmr (CCl_4) τ 6.57 (s, 4, CH_2) 8.85–9.37 (m, 54, Bu–Sn). 2c had the same ir and nmr spectra of authentic sample prepared from ethylene glycol and N,N-diethyltributylstannylamine.[19] A small amount of 3c,

(14) Maximum mass number observed was dimer of cyclic dialkoxide-alkyl group, as has been reported on the other organotin compounds by DeLidder, and Dijkstru.[15]

(15) J. J. DeLidder, and G. Dijkstru, *Recl. Trav. Chim. Pays-Bas*, **86**, 737 (1967).

(16) M. Wada, T. Okada, and R. Okawara (read at Symposium on Organometallic Compounds in Osaka, Oct 1969) suggested that the stannaoxathialane would be dimeric in solution from the ir and nmr data in carbon tetrachloride and chloroform solutions.

(17) H. Gilman and W. B. King, *J. Amer. Chem. Soc.*, **51**, 1213 (1929).

(18) G. S. Sasin, *J. Org. Chem.*, **18**, 1142 (1953).

(19) T. Harada, *Sci. Papers Inst. Phys. Chem. Res.* (Tokyo), **38**, 146 (1940).

(20) J. Lorberth and M. R. Kula, *Chem. Ber.*, **97**, 3444 (1964).

formed during high-temperature distillation up to 200°, was found in distillation residue.

Reaction of Hexaethyldistannoxane with Propylene Carbonate.—A mixture of equimolar amounts of two reagents was heated at 100° for 2 hr, and the reaction mixture was distilled, giving a 78% yield of **3d**: mp 255–257°; ir (KBr) 1140, 1050, 950, 930, 850, and 680 cm^{-1}; nmr ($CHCl_3$) τ 8.98 (d, 3, J = 6.0 Hz, CH_3CHO), ~8.8 (broad, 10, Et-Sn), and 6.45 (M, $ABCX_3$ pattern, 3, $OCH-CH_2$);[21] mass spectrum (m/e) 473 (calcd for $(3d)_2$-Et, 473). *Anal.* Calcd for $C_7H_{16}O_3Sn$: C, 33.51; H, 6.43; Sn, 47.31. Found: C, 33.70; H, 6.41; Sn, 47.20.

Reaction of Hexabutyldistannoxane with Propylene Carbonate.—A mixture of equimolar amounts of two reagents was heated at 120° for 6 hr. The distillation products were 75% **2e**: bp 155–160° (0.02 mm); ir (CCl_4) 1150, 1070, 1050, 960, 875, and 860 cm^{-1}; nmr (CCl_4) τ 6.64 (m, 3, CH_2CHO), and 8.5–9.1 (broad, Bu-Sn and CH_3-CHO). Spectra were the same as those of an authentic sample prepared by another method.[20] From the distillation residue, a 3% yield of **3e** was obtained, which was identified by the comparison with the ir and nmr spectra of an authentic sample prepared by Remsden and Bank's method:[3] mp 181–183°; ir (KBr) 1140, 1050, 930, 855, and 680 cm^{-1}.

Anal. Calcd for $C_{11}H_{24}O_2Sn$: C, 43.04; H, 7.88; Sn, 38.66. Found: C, 43.03; H, 8.03; Sn, 38.61.

Reaction of Hexaethyldistannoxane with Ethylene Monothiolcarbonate.—A mixture of equimolar amounts of the two reagents was heated at 150° for 2 hr and distilled to give a 59% yield of **2f**, bp 146–149° (0.3 mm), and 12% yield of **3f**, mp 205–207°.

2f: ir (CCl_4) 1180, 1050, 1010, 950, and 650 cm^{-1}; nmr (CCl_4) τ 6.39 (t, 2, J = 5.8 Hz, CH_2O), 7.51 (t, 2, J = 5.8 Hz, CH_2S), 8.9 (broad, 30, Et-Sn).

3f: ir ($CHCl_3$) 1280, 1220, 1175, 1165, 1055, 1010, 960, and 670 cm^{-1}; nmr ($CHCl_3$) τ 6.36 (t, 2, J = 5.4 Hz, CH_2O), 7.21 (t, 2, J = 5.4 Hz, CH_2S), and ~8.7 (broad, 10, Et-Sn); mass spectrum (m/e) 254 (calcd for **3f**, 254). *Anal.* Calcd for $C_6H_{14}OSSn$: C, 28.49; H, 5.58; Sn, 46.93. Found: C, 28.79; H, 5.79; Sn, 46.65.

Reaction of Hexabutyldistannoxane with Ethylene Monothiolcarbonate.—The two reagents reacted at 150° for 2 hr, giving trace amounts (<1%) of **3g** [bp 165–168° (0.5 mm); mp 89–90°; ir and nmr spectra ($CHCl_3$) were the same as those of the sample prepared from dibutyltin dimethoxide and mercaptoethanol], and 60% yield of **2g** [bp 180–185° (0.2 mm); ir (CCl_4) 1070, 1050, 1015, 950, and 870 cm^{-1}; nmr (CCl_4) τ 6.45 (t, 2, J = 6.0 Hz, CH_2O), 7.53 (t, 2, J = 6.0 Hz, CH_2S), and 8.6–9.1 (broad, 54, Bu-Sn); spectra identical with those of an authentic sample prepared from mercaptoethanol and N,N-diethyltributylstannylamine[20]].

(21) Ambiguous $ABCX_3$ pattern analogous to that of propylene carbonate was observed, but poor solubility of the product prevented analysis.

Reaction of α,α'-Dichlorotetraethyldistannoxane with Ethylene Carbonate.—A mixture of equimolar amounts of the two reagents was heated at 80° for 2 days in dry toluene, and the reaction mixture was recrystallized from a mixture of hexane and chloroform, giving an 81% yield of dibutyltin dichloride, mp 83–84° (lit.[22] 83–84), and an 88% yield of **3b**, mp >270°; ir and nmr spectra were the same as mentioned above.

Reaction of α,α'-Dichlorotetraethyldistannoxane with Ethylene Monothiolcarbonate.—A mixture of equimolar amounts of the two reagents was heated at 150° for 3 hr, and the reaction mixture was recrystallized from carbon tetrachloride, giving an 85% yield of **3f**, mp 206–208°. Dibutyltin dichloride was isolated from the mother liquor.

Thermal Decomposition of Bis(tributyltin) Ethylene Glycolate.—The ethylene glycolate was heated in a sealed glass tube at 100° for 3 hr, and the reaction mixture was recrystallized from carbon tetrachloride giving a 93% yield of **3b**; ir and nmr spectra were the same as those mentioned above. Tetraethyltin was isolated in 90% yield by distillation of the filtrate.

Kinetic Measurement on the Rate of Cyclization Reaction.—The solutions of bis(triethyltin) ethylene glycolate at the initial concentrations of 1.090 and 1.985 M in dry xylene were heated at 137.0 ± 0.5° in glass tube, and the tetraethyltin formed was analyzed by vapor phase chromatography with a column of Apiezon L. Table II shows the results.

TABLE II

THE RATE OF FORMATION OF TETRAETHYLTIN IN THE THERMAL DECOMPOSITION OF **2b** AT 137.0°

	Tetraethyltin formed (mol/l.)				
Initial concn, M	4.0[a]	8.0	12.0	16.0	20.0
1.090	0.042	0.081	0.120	0.150	0.190
1.985	0.130	0.227	0.290	0.320	0.390

[a] Reaction time in hours.

The plots of the data in Table II by the first-order rate law showed straight lines, and the rate constants of the cyclization reaction of **2b** were estimated to be 1.2×10^{-6} and 1.3×10^{-6} sec^{-1} for the initial concentrations of 1.090 and 1.985 mol/l., respectively.

Registry No.—**1a**, 96-49-1; **1b**, 108-32-7; **1c**, 3326-89-4; **2f**, 24471-68-9; **3a**, 24471-69-0; **3b**, 24471-70-3; **3d**, 24471-71-4; **3f**, 24471-72-5; $(Me_3Sn)_2O$ 1692-18-8; $(Et_3Sn)_2O$, 1112-63-6; $(Bu_3Sn)_2O$, 56-35-9; $(ClEt_2Sn)_2O$, 17973-82-9.

(22) A. C. Smith and E. G. Rochow, *J. Amer. Chem. Soc.*, **75**, 4103 (1953).

A Novel Synthesis of Cyclic Thioncarbonates and Spiro Orthocarbonates from Bis(tributyltin) Alkylene Glycolates and Carbon Disulfide

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Cyclic thioncarbonates and symmetrical spiro orthocarbonates were readily prepared in excellent yields from carbon disulfide and bis(tributyltin) alkylene glycolates having a C_2–C_4 glycol unit, together with bis(tributyltin) sulfide. Unsymmetrical spiro orthocarbonates were obtained by the reaction of alkylene thioncarbonates with other types of bis(tributyltin) alkylene glycolates. On the other hand, bis(tributyltin) alkylene glycolate having a bulky or longer glycol unit above C_5 reacted with carbon disulfide to form the insertion product to the tin–oxygen bond, but did not give any cyclic compound.

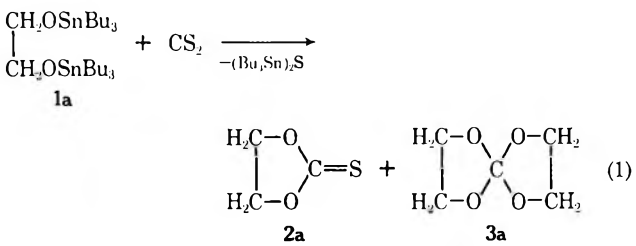
Hitherto, thioncarbonates were obtained by thiocarbonylation reactions of diols using thiocarbonylimidazole,[1] thiophosgene,[2] or carbon disulfide, butyllithium, and methyl iodide.[3] Orthocarbonates have been so far prepared from sodium alkoxide and chloropicrin[4] or thiocarbonyl perchloride (Cl_3CSCl).[5]

In this report, a novel synthetic method of cyclic thioncarbonates and spiro orthocarbonates by the

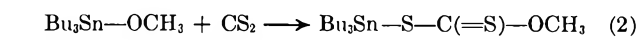
(1) H. A. Staab and G. Walther, *Ann.*, **657**, 98 (1962).
(2) F. N. Jones and S. Andreades, *J. Org. Chem.*, **34**, 3011 (1969).
(3) E. J. Corey and R. A. Winter, *J. Amer. Chem. Soc.*, **85**, 2677 (1963).
(4) J. D. Roberts and R. E. McMashon, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 200.
(5) H. Tieckelman and H. W. Post, *J. Org. Chem.* **13**, 265 (1948).

reaction of bis(tributyltin) alkylene glycolates with carbon diulfide is disclosed.

For a standard example, bis(tributyltin) ethylene glycolate (**1a**) reacted with excess amounts of carbon disulfide in dry nitrogen at room temperature, giving a 69% yield of ethylene thioncarbonate (**2a**), 26% yield of bis(ethylene) orthocarbonate (**3a**), and bis(tributyltin) sulfide. The cyclic thioncarbonate **2a** showed a $\nu_{C=S}$ band at 1155 cm^{-1} in the ir spectrum and a sharp singlet at τ 5.23 in the nmr spectrum, whereas **3a** had a strong ν_{C-O} band at 1050 cm^{-1}, a sharp singlet at τ 5.95, and the molecular peak at 132 (*m/e*) in the mass spectrum.



As has already been well established,[6-9] trialkyltin alkoxide can add across the A=B type unsaturated bond of acceptor molecules: tributyltin methoxide reacted exothermically with carbon disulfide at room temperature to give relatively stable methyl tributyltin xanthate as shown in eq 2.



It is interesting that monotributyltin alkoxide gave the xanthate, while bis(tributyltin) dialkoxide **1a** afforded the thion- and the orthocarbonates, **2a** and **3a**, in the reaction with carbon disulfide under the same reaction conditions. Now, we have established an excellent thiocarbonylation reaction of glycols and a new preparative method of some new spiro orthocarbonates by the reaction of bis(tributyltin)alkylene glycolate with carbon disulfide, since bis(tributyltin)alkylene glycolates, especially the ethylene glycolate, are easily prepared from glycols.[10] The results of the reaction of various glycolates, **1**, with carbon disulfide at room temperature are summarized in Table I.

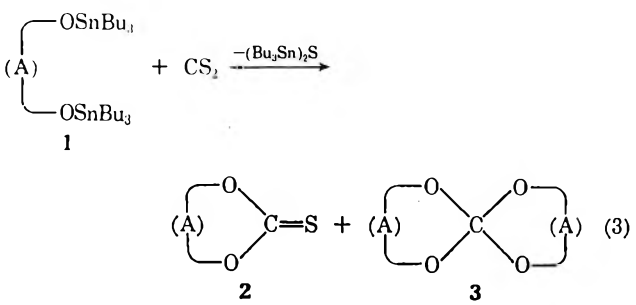


TABLE I

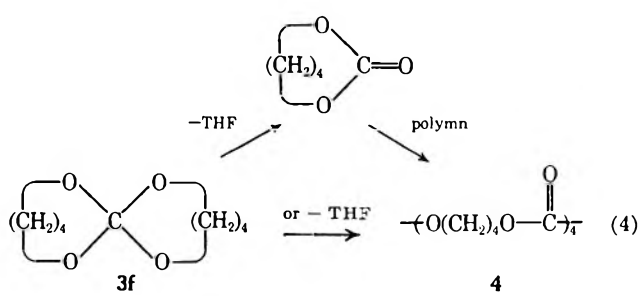
SYMMETRICAL SPIRO ORTHOCARBONATES AND CYCLIC THIONCARBONATES PREPARED FROM BIS(TRIBUTYLTIN) ALKYLENE GLYCOLATES AND CARBON DISULFIDE WITHOUT SOLVENT

No.	A in bis(tributyltin) glycolate used	Product yield, % 2	Product yield, % 3
1	$(CH_2)_2$ (**1a**)	69 (**2a**)	26 (**3a**)
2	$CH_2CH(CH_3)$ (**1b**)	6 (66)[a] (**2b**)	75 (25)[a] (**3b**)
3	$CH(CH_3)CH(CH_3)$ (**1c**)	56 (**2c**)	32 (**3c**)
4	$C(CH_3)_2C(CH_3)_2$ (**1d**)	0	0
5	$(CH_2)_3$ (**1e**)	0	65 (**3e**)
6	$(CH_2)_4$ (**1f**)	0	29[b] (**3f**)
7	$(CH_2)_5$ (**1g**)	0	0
8	$(CH_2)_2O(CH_2)_2$ (**1h**)	0	0

[a] Numbers in parentheses showed the yields in the reaction in toluene. [b] Poly(1,4-butylene carbonate) was also formed in 45% yield.

The results in Table I indicate that reaction 3 is generally applicable to sterically unhindered 1,2-glycol and α,ω-glycol derivatives having less than five carbon atoms. The 1,2-glycolates, except 2,3-dimethyl-2,3-butylene glycolate (**1d**), gave high yields of thioncarbonate and spiro orthocarbonate. Because reaction 3 consists of very fast two-step reactions as will be discussed later, the ratios of the yield of thioncarbonates to that of spiro orthocarbonates may be affected by the solvent used and other reaction conditions; *e.g.*, the yield of propylene thioncarbonate (**2b**) was improved by adding toluene to the reaction of bis(tributyltin) 1,2-propylene glycolate (**1b**) with carbon disulfide.

Contrary to the reaction of the 1,2-glycolates, the reactions of the 1,3- and 1,4-glycolate gave only spiro orthocarbonates. The reaction of 1,4-butylene glycolate (**1f**) with carbon disulfide gave a low yield (29%) of spiro orthocarbonate and 45% yield of poly(1,4-butylene carbonate), which will be formed by the decomposition of **3f** to tetrahydrofuran and 1,4-butylene carbonate and the subsequent polymerization of the latter, or by the direct polymerization of **3f**, as indicated in eq 4, because a small amount of tetrahydrofuran was detected in the reaction mixture by ir and vpc measurements.



The reaction mixture of bis(tributyltin) pentamethylene glycolate (**1g**) and carbon disulfide showed a strong $\nu_{C=S}$ band at about 1200 cm^{-1}, but **1g** was recovered

(6) A. J. Bloodworth and A. G. Davies, *J. Chem. Soc.*, 5238 (1965); *C*, 299 (1966).

(7) A. G. Davies and W. R. Symes, *ibid.*, *C*, 1009 (1967).

(8) A. J. Bloodworth, A. G. Davies, and S. C. Vasishtha, *ibid.*, 1309 (1967).

(9) A. G. Davies and P. G. Harrison, *ibid.*, 1313 (1967).

(10) Bis (tributyltin) ethylene or propylene glycolate solution prepared by heating ethylene or propylene carbonate with bis(tributyltin) oxide in toluene can be used as a starting material. Other preparation methods of bis(trialkyltin) alkylene glycolates from glycols were also reported.[11-16]

(11) J. Loberth and M. Kula, *Chem. Ber.*, **97**, 3444 (1964).

(12) R. C. Mehrotra and V. D. Gupta, *J. Organometal. Chem.*, **4**, 145 (1965).

(13) R. K. Ingham, S. D. Rosenberg, and H. Gilman, *Chem. Rev.*, **60**, 459 (1960).

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(15) D. L. Ailleston and A. G. Davies, *J. Chem. Soc.*, 2050 (1962).

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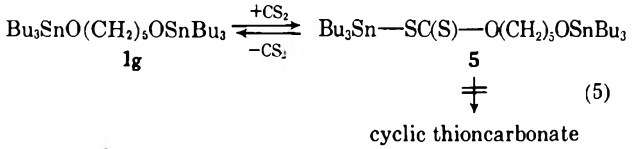
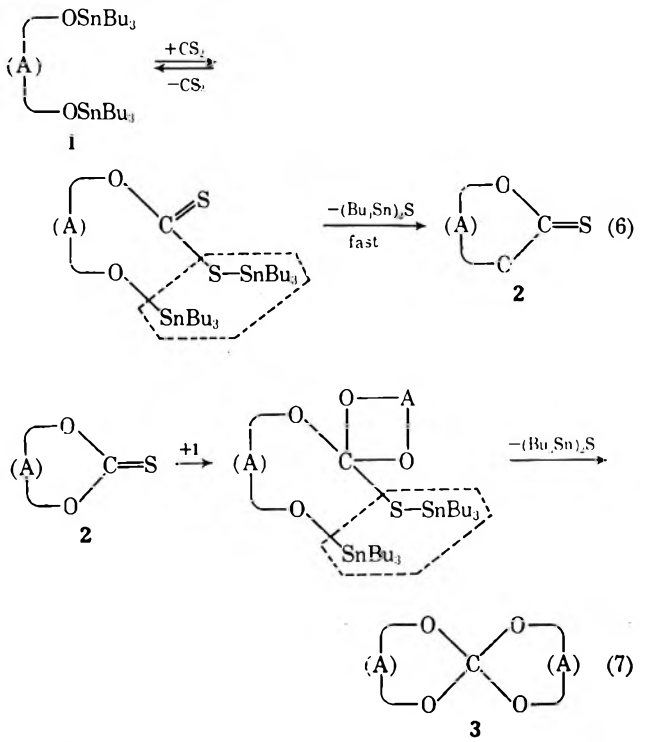
by distillation, suggesting the reversible insertion reaction of carbon disulfide to the tin–oxygen bond (eq 5).



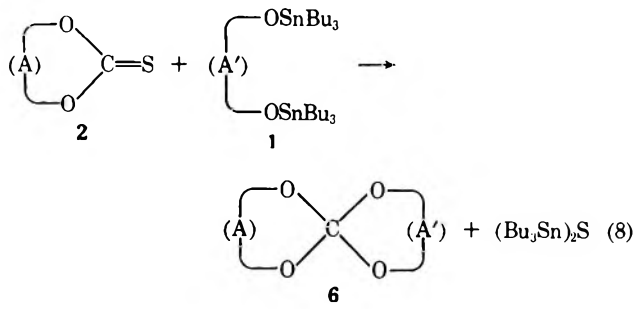
(5)

The same phenomena were observed in the reactions of tributyltin derivatives of pinacol and of diethylene glycol.

The above reaction (3) would be explained by addition–elimination mechanisms shown by eq 6 and 7. The formation of stable Sn–S–Sn bond might be a driving force in the reaction as in other desulfurization reactions,[17–19] and cyclization assisted by coordination would be an important factor, because 2 was formed only when carbon chain length in A was from two to four. The desulfurization reaction to give linear product did not occur at room temperature in the case of more than five-carbon chain length or bulky glycol unit in A.



This two-step mechanism in the formation of spiro orthocarbonates was confirmed by the fact that the reaction of ethylene or propylene thioncarbonate with another bis(tributyltin)alkylene glycolate in chloroform solution at room temperature afforded unsymmetrical spiro orthocarbonates in good yield, where thioncarbonate acted as a new type of acceptor molecule for the addition of organotin alkoxide, as was shown by eq 8. The results are listed in Table II.



(8)

TABLE II

UNSYMMETRICAL SPIRO ORTHOCARBONATES PREPARED BY THE REACTION OF CYCLIC THIONCARBONATE WITH BIS(TRIBUTYLTIN) ALKYLENE GLYCOLATE IN CHLOROFORM

No.	A in cyclic thioncarbonate	A in $Bu_3SnO(A)OSnBu_3$	Product yield, %
11	$(CH_2)_2$	$CH_2CH(CH_3)$	61 (**6a**)
12	$(CH_2)_2$	$(CH_2)_3$	82 (**6b**)
13	$(CH_2)_2$	$(CH_2)_4$	76 (**6c**)
14	$CH_2CH(CH_3)$	$(CH_2)_3$	86 (**6d**)
15	$CH_2CH(CH_3)$	$(CH_2)_4$	55 (**6e**)

Experimental Section

General.—Melting points and boiling points are uncorrected. Elementaly analyses were performed by the Analysis Center of Kyoto University. Ir and nmr (TMS as internal standard) were recorded on JASCO Model IR-S spectrometer, and on Japan Electron Optics Model JMN-MH6O spectrometer, respectively. Mass spectra were obtained by Japan Electron Optics Type JMS-OISG mass spectrometer. Vapor phase chromatography was carried out by a Yanagimoto Type GCG-5DH chromatograph with a column of Apiezon.

Materials.—All glycols and solvents were dried with sodium or calcium hydride and distilled before use. Tributyltin chloride, bis(tributyltin) oxide, and ethylene and propylene carbonates were commercially available and were distilled *in vacuo*.

Bis(tributyltin) Alkylene Glycolates (1). **Method A.**[16]—A mixture of ethylene carbonate (0.10 mol) and hexabutyldistannoxane (0.12 mol) in 60 ml of toluene was allowed to reflux for 5–15 hr under nitrogen. After evaporation of toluene and excess amounts of distannoxane, vacuum distillation gave a 92.5% yield of bis(tributyltin) ethylene glycolate (**1a**), bp 185–188° (0.3 mm), and a 5.5% yield of 2-dibutylstanna-1,3-dioxolane, mp 223–224° (lit.[20] 223–227°).[21] Bis(tributyltin) 1,2-propylene glycolate was also prepared by this method, yield 92%, bp 180–182° (0.1 mm).

Method B.—This is a modification of Kula[14] and Davies' methods.[5,22] Disodium alkylene glycolate was obtained by refluxing a mixture of the glycol and 2 equiv of sodium metal in toluene for 2–5 hr, followed by the reaction with 2 equiv of tributyltin chloride at the refluxing temperature. After dilution with dry toluene, sodium chloride was separated by centrifuge, and the solution was fractionally distilled. Yields and boiling points of bis(tributyltin) 1,3-propylene, 1,4-butylene, 2,3-butylene, 2,3-dimethyl-2,3-butylene, 1,5-pentamethylene, and diethylene glycolates were 49, 46, 57, 35, 50, and 55%, and 195° (0.1 mm), 212° (0.1 mm), 195–204° (0.1 mm), 199° (0.1 mm), 223° (0.1 mm), and 217–218° (0.1 mm), respectively.

Reaction of Bis(tributyltin) Ethylene Glycolate (**1a**) **with CS_2.**—Bis(tributyltin) ethylene glycolate (86 mmol) and CS_2 (170 mmol) were allowed to react in nitrogen at room temperature for 0.5–2 hr and distilled, giving 26% of bis(ethylene) orthocarbonate (**3a**) and 68.5% of ethylene thioncarbonate (**2a**).

(17) K. Itoh, I. K. Lee, I. Matsuda, S. Sakai, and Y. Ishii, *Tetrahedron Lett.*, 2640 (1967).

(18) K. Itoh, Y. Fukumoto, and Y. Ishii, *ibid.*, 3199 (1968).

(19) A. J. Bloodworth, A. G. Davies, and S. C. Vasishtha, *J. Chem. Soc., C*, 2640 (1968).

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(21) The stannadioxolane was formed during distillation.

(22) Distillation of the reaction product of trimethyltin chloride with sodium methoxide gave a mixture of trimethyltin methoxide and trimethyltin chloride,[15] while pure bis(tributyltin) alkylene glycolates were obtained by the distillation of the reaction mixture of tributyltin chloride with disodium alkylene glycolate, because the boiling points of **1a–1h** were much higher than that of tributyltin chloride.

3a: needle crystals, bp (subln) 60–70° (0.5 mm), mp (CCl_4) 143.0–143.5°; ir (CCl_4) 1356, 1245, 1200, 1060 (strong), 1019, and 945 cm^{-1}; nmr ($CDCl_3$) τ 5.95 (s, 4, CH_2O); mass spectrum (30 eV) *m/e* (relative intensity) 132 (92, molecular ion peak), 102 (100), 88 (86), 72 (89) 44 (91), and 30 (38). *Anal.* Calcd for $C_5H_8O_4$: C, 45.46; H, 6.10. Found: C, 45.46; H, 6.09.

2a: plate crystal; bp 99° (0.3 mm); mp ($CHCl_3$–CCl_4 1:10) 51–52°; ir ($CHCl_3$) 2985, 1375, 1155, 1015, and 955 cm^{-1}; nmr ($CHCl_3$) τ 5.23 (s, 4, CH_2O); mass spectrum (30 eV) *m/e* (relative intensity) 104 (100, molecular ion peak), 60 (85), and 44 (45). *Anal.* Calcd for $C_3H_4O_2S$: C, 34.61; H, 3.87; S, 30.79. Found: C, 34.89; H, 3.91; S, 30.69.

Reaction of Bis(tributyltin) 1,2-Propylene Glycolate (1b) with CS_2.—The glycolate **1b** (184 mmol) and CS_2 (920 mmol) were allowed to react in the same manner as mentioned above and distilled, giving 75% of bis(1,2-propylene) orthocarbonate (**3b**): bp 73° (2 mm); ir ($CHCl_3$) 1225, 1195, 1051, and 1030 cm^{-1}; nmr (CCl_4) τ 8.71 (d, 3, J = 6.6 Hz, CH_3–C), 5.5–6.7 ($ABCX_3$ pattern, 3, OCH_2CHO); molecular ion peak on mass spectrum (30 eV) *m/e* 160. *Anal.* Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.51; H, 7.56. High-vacuum distillation of the residue gave 6% of 1,2-propylene thioncarbonate (**2b**): bp 78° (0.1 mm); ir ($CHCl_3$) 1485, 1355, 1295, 1175, and 988 cm^{-1}; nmr ($CHCl_3$) τ 8.43 (d, J = 6.0 Hz, CH_3–C), 4.9–5.85 ($ABCX_3$ pattern, 3, OCH_2CHO); molecular ion peak on mass spectrum (30 ev) *m/e* 118. *Anal.* Calcd for $C_4H_6O_2S$: C, 40.66; H, 5.12. Found: C, 41.01; H, 5.27.

Reaction in Toluene.—A mixture of 0.2 mol of propylene carbonate, 0.25 mol of hexabutyldistannoxane, and 100 ml of dry toluene was refluxed for 10 hr with stirring; then an additional 100 ml of toluene and 1.05 mol of CS_2 were added and the mixture was stirred for 1 hr, and 66% of **2b** and 25% of **3b** were obtained by distillation.

Reaction of Bis(tributyltin) 2,3-Butylene Glycolate (1c) with CS_2.—The glycolate **1c** (41 mmol) and 200 mmol of CS_2 were allowed to react without solvent in the same manner, as mentioned above, giving 32% of bis(2,3-butylene) orthocarbonate (**3c**): bp 86° (3.5 mm): ir (CCl_4) 1380, 1200, 1080, and 1060 cm^{-1}; nmr (CCl_4)[23] τ 8.86 (d, 12 × 70%, J = 6.1 Hz, *cis*-CH_3CH), 8.76 (d, 12 × 30%, J = 6.1 Hz, *trans*-CH_3CH), 6.05–6.35 (m, 4 × 30%, *trans*-CH_3CH), and 5.62–5.87 (m, 4 × 70%, *cis*-CH_3CH); molecular ion peak on mass spectrum (30 eV) *m/e* 188; the sample was not analytically pure.[24]

Further distillation of the residue gave 56% of **2c**: bp 115° (3 mm); ir (CCl_4) 1460, 1320, 1280, 1185, 1135, 1060, and 913 cm^{-1}; nmr (CCl_4) τ 8.56 (d, 6 × 70%, J = 6.3 Hz, *cis*-CH_3CH), 8.46 (d, 6 × 30%, J = 6.3 Hz, *trans*-CH_3CH), *ca.* 5.35 (m, 2 × 30%, *trans*-CH_3CH), and 4.75–5.00 (m, 2 × 70%, *cis*-CH_3CH); molecular ion peak on mass spectrum (30 eV) *m/e* 132. *Anal.* Calcd for $C_5H_8O_2S$: C, 45.43; H, 6.10. Found: C, 45.70; H, 6.39.

Reaction of Bis(tributyltin) 1,3-Propylene Glycolate (1e) with CS_2.—The glycolate **1e** (49 mmol) was allowed to react with CS_2 (200 mmol), giving only one product, bis(1,3-propylene) orthocarbonate (**3e**): 65%; bp (subln) 90° (0.06 mm); mp (*n*-hexane) 132–133°; ir ($CHCl_3$) 1145, 1120, 1100, and 915 cm^{-1}; nmr ($CHCl_3$) τ 5.97 (t, 8, J = 5.4 Hz, CH_2O) and 8.24 (q, 4, J = 5.4 Hz, CH_2CH_2O); parent peak on mass spectrum (35 eV) *m/e* 160. *Anal.* Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.58; H, 7.44.

Reaction of Bis(tributyltin) 1,4-Butylene Glycolate (1f) with CS_2.—Carbon disulfide (198 mmol) and **1f** (46 mmol) were mixed, and distillation, at first, gave a trace of tetrahydrofuran in a cold trap, which was detected by the comparisons of the ir and vpc with the authentic sample; thereafter bis(1,4-butylene) orthocarbonate (**3f**) was isolated by vacuum distillation.

3f: yield 29%; bp (subln) 110° (0.1 mm); mp (*n*-hexane) 109–110°; ir (CCl_4) 1145, 1105, 1055, and 970 cm^{-1}; nmr (CCl_4) τ 6.38 (m, 8, OCH_2CH_2) and 8.40 (m, 8, OCH_2CH_2); molecular ion peak on mass spectrum (35 eV) *m/e* 188. *Anal.* Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.59. Found: C, 57.23; H, 8.60.

The distillation residue was diluted with *n*-hexane to precipitate the polymer, which was separated by filtration and showed a strong $\nu_{C=O}$ band at 1750 cm^{-1} in the ir spectrum; τ 5.83 (broad, 4, CH_2–O) and 8.24 (broad, 4, CH_2CH_2O) in the nmr spectrum; on the hydrolysis, 1,4-glycol and CO_2 were formed, suggesting the polycarbonate structure of **4**. The polymer yield was about 45%.

Evaporating *n*-hexane from the filtrate, bis(tributyltin) sulfide was obtained in 93% yield, which was identified by the comparison of the ir spectrum with that of an authentic sample.

Reaction of Bis(tributyltin) 1,5-Pentamethylene Glycolate (1g) with CS_2.—The glycolate **1g** reacted with excess CS_2 at room temperature in nitrogen, and the ir spectrum of the reaction mixture showed a band $\nu_{C=S}$ at 1200 cm^{-1}, suggesting the formation of the xanthate structure **5**. Thereafter the reaction mixture was refluxed for 90 min, and its ir spectrum had no band assigned to cyclic or linear thioncarbonate. Vacuum distillation of the product afforded **1g** in good yield.

Reaction of Bis(tributyltin) α,ω-Diethylene Glycolate (1h) with CS_2.—The glycolate **1h** was mixed with excess amounts of CS_2 at room temperature in nitrogen and showed a $\nu_{C=S}$ band at 1190 cm^{-1} in the ir spectrum and downfield shifts from τ 6.21 (t, 4, J = 5.0 Hz, $SnOCH_2$) and 6.57 (t, 4, J = 5.0, CH_2-OCH_2) to 5.43 (broad, 4, $SnSC(S)OCH_2$) and 6.19 (broad, 4, CH_2OCH_2) in the nmr spectrum, suggesting the insertion reaction of CS_2 into the Sn–O bond. Then the reaction mixture was refluxed for 1 hr and distilled; compound **1h** was recovered quantitatively.

Reaction of Bis(tributyltin) 2,3-Dimethyl-2,3-butylene Glycolate (1d) with CS_2.—The glycolate **1d** was refluxed in excess amounts of CS_2 for 1 hr and distilled, giving the starting material **1d** only.

Preparation of Unsymmetrical Spiro Orthocarbonates.—Bis(tributyltin) alkylene glycolate and an equimolar amount (20 mmol) of ethylene or propylene thioncarbonate (dissolved in dry chloroform) were mixed at room temperature in dry nitrogen and distilled to afford unsymmetrical spiro orthocarbonate.

Ethylene 1,2-propylene orthocarbonate (6a) was obtained in 61% yield from **2a** and **1b**: bp 87° (7 mm): ir (CCl_4) 2986, 2906, 1230, 1197, 1053, 1023, and 945 cm^{-1}; nmr (CCl_4) τ 6.00 (s, 4, OCH_2), 8.74 (d, 3, J = 6.1 Hz, CH_3CH), and 5.36–6.65 (m, 3, CH_2CHO). *Anal.* Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.30; H, 6.80.

Ethylene 1,3-propylene orthocarbonate (6b) was prepared in 82% yield from **2a** and **1e**: bp 68° (1.0 mm); ir ($CHCl_3$) 1155, 1080, 1028, 948, and 927 cm^{-1}; nmr (CCl_4) τ 6.04 (s, 4, OCH_2), 6.02 (t, 4, J = 6.0 Hz, $OCH_2CH_2CH_2O$), and 8.32 (quintet, 2, J = 6.0 Hz, $OCH_2CH_2CH_2O$). *Anal.* Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.01; H, 7.00.

Ethylene 1,4-butylene orthocarbonate (6c) was prepared in 76% yield from **2a** and **1f**: bp 76–77° (2.5 mm); ir (CCl_4) 2964, 2904, 1190, 1080, 994, and 945 cm^{-1}; nmr (CCl_4) τ 6.04 (s, 4, OCH_2), 6.27 (broad, 4, OCH_2CH_2), and 8.34 (broad, 4, OCH_2CH_2). *Anal.* Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.60; H, 7.71.

1,2-Propylene 1,3-propylene orthocarbonate (6d) was obtained in 86% yield from **2b** and **1e**: bp 70° (5 mm); ir (CCl_4) 2964, 2884, 1210 1160, 1075, 1042, and 930 cm^{-1}; nmr (CCl_4) τ 8.72 (d, 3, J = 6.1 Hz, CH_3CH) 8.34 (quintet, 2, J = 6.1 Hz, $CH_2CH_2CH_2$), 5.98 (t, 4, J = 6.1 Hz, OCH_2CH_2), and 5.48–6.59 ($ABCX_3$ pattern, 3, OCH_2CHO). *Anal.* Calcd for $C_7H_{12}O_4$: C, 52.48; H, 7.55. Found: C, 52.46; H, 7.69.

1,2-Propylene 1,4-butylene orthocarbonate (6e) was prepared in 55% yield from **2b** and **1f**: bp 83° (2.7 mm); ir (CCl_4) 2965, 1185, 1075, and 1005 cm^{-1}; nmr (CCl_4) τ 8.75 (d, 3, J = 6.2 Hz, CH_3C), 8.35 (broad, 4, OCH_2CH_2C), 6.30 (broad, 4, OCH_2CH_2C), and 5.67–6.67 ($ABCX_3$ pattern, 3, OCH_2CHO). *Anal.* Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.46; H, 8.31.

Registry No.—Carbon disulfide, 75-15-0; **1c**, 24471-92-9; **1d**, 24471-93-0; **1e**, 24471-90-7; **1f**, 24471-91-8; **1g**, 24471-94-1; **1h**, 24471-95-2; **2a**, 20628-59-5; **2b**, 13303-26-9; **2c**, 24471-98-5; **3a**, 24471-99-6; **3b**, 24472-00-2; **3c**, 24472-01-3; **3e**, 24472-02-4; **3f**, 24472-03-5; **6a**, 24472-04-6; **6b**, 24472-05-7; **6c**, 24472-06-8; **6d**, 24472-07-9; **6e**, 24472-08-0.

(23) The mixed 2,3-butylene glycol (*erythro*:*threo* = 7:3) was used in the preparation of **1c**, form which a mixture of *cis*- and *trans*-2,3-butylene thioncarbonate (**2c**) or spiro orthocarbonate **3c** was formed, giving a complex nmr spectrum.

(24) A weak band of carbonate at 1820 cm^{-1} was observed, as a spiro orthocarbonate having a tertiary alkoxyl group was found to be decomposed to cyclic carbonate and epoxide.

Enol Esters. XII.[1] C-Acylations with Enol Esters

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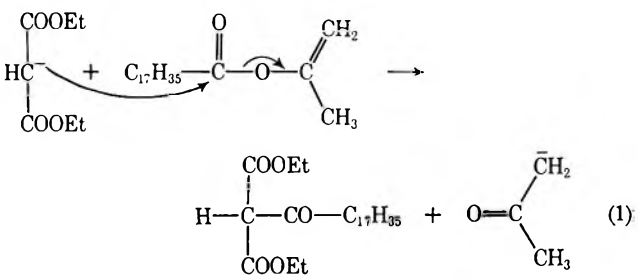
Isopropenyl esters under conditions of aluminum chloride catalysis provide a simple method of preparation of β-keto aldehydes and symmetrical β diketones. For example, isopropenyl stearate gives distearoylmethane. Under mild conditions vinyl stearate gives the β-keto aldehyde 3-oxoeicosanal, but on longer heating distearoylmethane results. With aromatic systems, isopropenyl stearate gives typical Friedel–Crafts acylation products in good yields. Palmitoyl chloride with aluminum chloride converts ethyl acetoacetate to ethyl palmitoacetate and ethyl dipalmitoacetate.

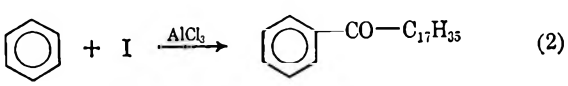
We have demonstrated in previous publications the usefulness of long-chain fatty acid enol ester derivatives in various types of chemical syntheses such as the acylation of OH, NH_2, RCONHR, Hal-H, SH, and SO_2NHR groups,[3,4] and also the formation of cyclic derivatives from alkylketene self-condensations.[5] In the present paper we wish to report the further utility of such enol esters (as exemplified by ispropenyl stearate and vinyl stearate) in carrying out acylations wherein the acyl group becomes attached to carbon. As a result of our experiences with enol esters, we might summarize by stating that isopropenyl stearate (I), in general, resembles stearoyl chloride in its reactions but bears little chemical resemblance[6] to its homolog, vinyl stearate. For example, isopropenyl esters are acylating agents whereas vinyl esters are not; compound I stearoylates succinimide at 170° whereas the vinyl homolog is totally inert under identical conditions. We do, however, report here that under conditions of aluminum chloride catalysis both isopropenyl and vinyl esters behave alike to form diacylmethanes (*i.e.*, β diketones).

In studying C-acylations we allowed the anion of diethyl malonate to react with I and obtained the C-stearoylated product shown in eq 1.



(1)

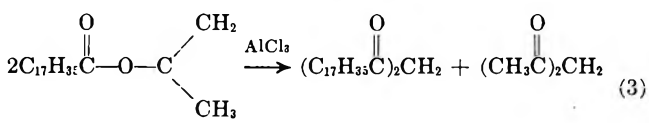
The versatility of I was further demonstrated by its ability to acylate benzene to form stearophenone in good yield in sharp contrast to saturated esters which do not[7] ordinarily succeed in the Friedel–Crafts reaction (eq 2).



(2)

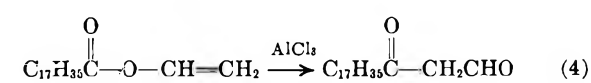
Aluminum chloride catalysis also enabled I to attack isolated olefinic bonds but gave low yields (35%) of α,β-unsaturated ketone. An interesting by-product, mp 77°, always accompanied the ketone, and, instead of pursuing the unsatisfactory olefinic ketone, we gave our attention to the crystalline by-product. The by-product was obtained from several different olefin acylation reactions so that we concluded that it arose solely from I. The compound showed unusual carbonyl absorption in the infrared in chloroform solution in the region where carbon disulfide is opaque. These bands are characteristic of β diketones, and elemental analysis, the nmr singlet at 5.58 ppm, strong ultraviolet absorption in isooctane at 274 mμ (E 10,000), together with the ability to form colored copper chelate complexes all led to the formulation of the side-reaction product as that of a diacylmethane.

By way of confirmation, it was found that solutions of isopropenyl esters in hexane in the absence of olefins on treatment with 0.25 to 1.0 mol of aluminum chloride also gave, after work-up with dilute acid, distearoylmethane[8] in typically 75% yield, eq 3. In view of the



(3)

fact that vinyl esters, as mentioned before, usually take reaction paths different[6] from those of the isopropenyl esters, we were interested to see what their behavior toward aluminum chloride would be. We found that the nature of the reaction product was strongly controlled by the length of reaction time. In a short reaction time, the product obtained was the expected β-ketoaldehyde,[9] eq 4; however, on somewhat longer re-



(4)

(1) For the previous paper in this series see E. S. Rothman, G. G. Moore, and A. N. Speca, *Tetrahedron Lett.*, 5205 (1969).

(2) Agricultural Research Service, U. S. Department of Agriculture.

(3) E. S. Rothman, S. Serota, and D. Swern, *J. Org. Chem.*, **29**, 646 (1964).

(4) E. S. Rothman, G. G. Moore, and S. Serota, *ibid.*, **34**, 2486 (1969).

(5) E. S. Rothman, *J. Amer. Oil Chem. Soc.*, **45**, 189 (1968).

(6) E. S. Rothman, S. Serota, T. Perlstein, and D. Swern, *J. Org. Chem.*, **27**, 3123 (1962).

(7) P. H. Gore in "Friedel-Crafts and Related Reactions," Vol. III, Part I, G. A. Olah, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 34.

(8) Two preliminary communications have been submitted concerning β dicarbonyl compounds: (a) E. S. Rothman and G. G. Moore, *Tetrahedron Lett.*, 2553 (1969); (b) ref 1.

(9) The β-keto aldehydes are stable compounds in the protected copper chelate form, but after removal of the metal atom (with dilute acid) are sensitive to chromatography on silica gel and Florisil. An intense red coloration quickly develops and rechromatography leads to the isolation of three products: (a) white, mp 86–87°; (b) yellow, mp 72–72.7°; (c) red, unstable. The first two appear to be aldol and bisaldol products; the third shows aromatic bands in the nmr. These same products are encountered in the preparation of β-keto aldehydes by the published methods[10a] involving the condensation of alkyl methyl ketones with ethyl formate using sodium metal catalyst.

(10) (a) V. Prelog, O. Metzler, and O. Jeger, *Helv. Chim. Acta*, **30**, 681 (1947); T. Kosuge, Japanese Patent 2171 (1954); *Chem. Abstr.*, **49**, P14800*f*, (1955). (b) *Cf.* A. Sieglitz and O. Horn, *Chem. Ber.*, **84**, 607 (1951).

fluxing, the product isolated was exclusively the same β diketone obtainable from the isopropenyl ester.

Under conditions of aluminum chloride catalysis we have obtained interesting reactions with acetoacetic ester–palmitoyl chloride mixture. The two products isolated are palmitoacetic ester and dipalmitoacetic ester, eq 5. The former forms a blue-green copper

$$CH_3COCH_2COOEt + C_{15}H_{31}COCl \xrightarrow{AlCl_3} C_{15}H_{31}COCH_2COOEt + C_{15}H_{31}CO{-}CH(CO{-}C_{15}H_{31}){-}COOEt \quad (5)$$

chelate and the latter a lilac-colored copper chelate. In occasional runs small amounts of dipalmitoylmethane were detected, presumably arising from hydrolytic decarboxylation of dipalmitoacetic ester.

Since these data, in particular those giving vinyl ester product change with time, show that acyl interchange can occur, one is alerted to the possibility, among others,[10b] that the formation of distearoylmethane from the aluminum chloride catalyzed reaction of isopropenyl stearate may occur *via* quasi-Fries rearrangement of isopropenyl stearate to form acetyl stearoylmethane as the proximate product which subsequently is converted to distearoylmethane.

Experimental Section

Diethyl 2-Stearoylmalonate.—To 8 g of diethyl malonate in 150 ml of toluene was added 1.15 g of finely divided sodium. After the sodium reacted, 16.2 g of isopropenyl stearate was added and the mixture refluxed for 2.5 hr. The cooled mixture was shaken with 4.5 ml of hydrochloric acid, the sodium chloride removed by filtration, and the toluene removed by evaporation *in vacuo*. The residue was dissolved in pentane, 1.3 g of stearic acid (insoluble) was removed by filtration, and the filtrate was chromatographed on a 45 × 4 cm silica gel column. Elution with pentane removed traces of toluene and unreacted isopropenyl stearate. Elution with 2–20% methylene chloride in pentane washed out 3.12 g of ethyl stearate. The product was eluted by 30–50% methylene chloride in pentane. (Further elution with methylene chloride removed an additional 1.4 g of stearic acid.) The product, recrystallized from ethanol, melted from 55.5 to 56.5°: ir 1758, 1721 to 1737 broad doublet cm^{-1} (CS_2); uv 245 mμ (E 6550) (ethanol), 272 mμ (E 18,800) (ethanol containing sodium hydroxide) (C-alkylation).

Anal. Calcd for $C_{35}H_{66}O_5$: C, 70.38; H, 10.89. Found: C, 70.60; H, 10.88.

Stearophenone from Isopropenyl Stearate.—Benzene (12 g, 0.15 mol), aluminum chloride (5.3 g, 0.04 formula wt), and isopropenyl stearate (6.48 g, 0.02 mol) were refluxed together for 10 min. The cooled mixture was poured onto iced dilute hydrochloric acid, and the ketone was isolated by extraction with ether. The residue, recrystallized from ether, gave 4.14 g (60%) of stearophenone, mp 62.5–63.5°, identical with an authentic sample.[11]

4-Methylstearophenone.—To toluene (6.5 g, 0.079 mol) and aluminum chloride (3.3 g, 0.024 formula wt) was added 3.0 g (0.0093 mol) of isopropenyl stearate. After 5 min of reflux and work-up as described just above, 2.65 g (83%) of 4-methylstearophenone, mp 67–67.7° (lit.[12] mp 67°), was obtained.

2,4-Dimethylstearophenone.—*m*-Xylene (9.5 g, 0.090 mol), aluminum chloride (2.66 g, 0.02 formula wt), and 3.24 g of isopropenyl stearate (0.01 mol) were stirred together at 30° for 10 min, refluxed for 10 min, and worked up as the above examples. Recrystallization from ethanol gave 2.35 g (63%) of ketone, mp 45.5–46.5° (lit.[13] mp 39°).

3,4-Dimethylstearophenone.—In like manner *o*-xylene gave a 66% yield of ketone: mp 51.0–51.5°, ir (CS_2) 685 cm^{-1} (C=O).

Anal. Calcd for $C_{26}H_{44}O$: C, 83.80; H, 11.90. Found: C, 83.96; H, 12.07.

8,10-Dioxoheptadecane (Dioctanoylmethane). Procedure A.—Isopropenyl octanoate, bp 65° (8 mm) (prepared by the sulfuric acid catalyzed exchange reaction between octanoic acid and isopropenyl acetate)[6] (18.4 g, 0.1 mol), in 60 ml of olefin-free hexane, was heated with a total of 14.3 g (0.11 mol) of aluminum chloride delivered in three equal portions at 5-min intervals. The mildly exothermic reaction mixture was cooled to maintain near room temperature. After 1 hr, the mixture was poured into dilute hydrochloric acid–methylene chloride mixture. The separated, washed, and dried (sodium sulfate) organic layer was evaporated to a small volume and chromatographed on Florisil to give a pale yellow oil freezing to a solid in the refrigerator. Recrystallization from pentane in the cold gave a 70% yield of colorless plates: mp 20–21°; uv 274 mμ (E 11,000) (isooctane); nmr 5.58, 3.56 ppm.

Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02; mol wt, 268.24022 g/mol. Found: C, 75.05; H, 11.92; mol wt, 268.24051 g/mol (CEC Model 21-110-B mass spectograph).

Copper Chelate Derivative.—Hot solutions in ethanol of curpic acetate and the dione were combined and let cool to deposit pale blue fibrous needles, mp 108.2–109.5°. Recrystallization from ethanol gave the analytical sample: mp 110.2–110.7°; ir 1350 (w), 1410 (s), 1458 (w), 1554 (s) $CHCl_3$.

Anal. Calcd for $C_{34}H_{62}O_4Cu$: C, 68.24; H, 10.44. Found: C, 68.27; H, 10.42.

18,20-Dioxoheptatriacontane (Distearoylmethane). Procedure B.—Isopropenyl stearate (19 g, 0.059 mol) in 25 ml of hexane, was treated with 8.5 g (0.06 mol) of aluminum chloride. After stirring at 40° for 0.5 hr the mixture was worked up as above (occasional emulsion problems were corrected by methanol). The product is exceedingly insoluble in methanol. Crystallization from hexane and from ether gave a 65% yield of the diketone: mp 77.3–77.8°, lit.[14] mp 75–76°; uv 273 mμ (E 12,000) (isooctane); ir 6.24 μ ($CHCl_3$); nmr 3.54, 5.41 ppm. When only 0.25 mol of aluminum chloride was used, the yield was 50%.

Anal. Calcd for $C_{37}H_{72}O_2$: C, 80.95; H, 13.22; mol wt, 548. Found: C, 80.93; H, 13.28; mol wt, 516 (thermistor, $CHCl_3$).

The dioxime melted at 92.5–93.5° (lit.[14] mp 90–92°).

Copper Chelate Derivative.—Hot solutions of aqueous cupric chloride and of the β diketone in ethanol were mixed, the pH was adjusted to about 7 with potassium carbonate, and the solution was allowed to cool to deposit lilac crystals of the chelate. These, separated and recrystallized from benzene and from chloroform, melted at 113.2–114.3°.

Anal. Calcd for $C_{74}H_{142}O_4Cu$: C, 76.65; H, 12.35. Found: C, 76.99; H, 12.31.

16,18-Dioxotritriacontane (Dipalmitoylmethane).—In an analogous manner (procedure B), isopropenyl palmitate gave dipalmitoylmethane, mp 71.8–72.1°.

Anal. Calcd for $C_{33}H_{64}O_2$: C, 80.40; H, 13.11. Found: C, 80.33; H, 13.50.

The copper chelate had mp 113.2–114.3°, lilac color.

Anal. Calcd for $C_{66}H_{126}O_4Cu$: C, 75.67; H, 12.15. Found: C, 75.50; H, 12.00.

12,14-Dioxopentacosane (Dilauroylmethane).—Analogously, isopropenyl laurate gave dilauroylmethane, mp 53° (lit.[15] mp 50°), copper chelate mp 110° (lit.[16] mp 102–104°).

Reaction of Vinyl Alkanoate with Aluminum Chloride to Form β-Keto Aldehyde. Procedure C. 3-Oxoeicosanal.—Vinyl stearate (15.45 g, 0.05 mol) in 50 ml of olefin-free hexane was heated with 6.7 g (0.05) of anhydrous aluminum chloride added in one portion. The mixture was then brought to reflux temperature, held there for 20 min, cooled, and poured into methylene chloride–iced dilute hydrochloric acid mixture. The organic layer was separated, dried (sodium sulfate), and evaporated under nitrogen to give 10.5 g (68%) of a crystalline residue of crude keto aldehyde, mp 42–47°. Recrystallization from ethanol gave erratic results. The analytical sample, recrystallized from pentane, melted at 60–61°: uv 269 mμ 269 mμ (E 6000) (isooctane); ir 1630, 1590, 1459, 1087 ($CHCl_3$); ir 720, 769 (CS_2); nmr 5.45 ppm doublet (J = 4.5 Hz), 7.89 ppm doublet (J = 4.5 Hz) (enols).

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Anal. Calcd for $C_{20}H_{38}O_2$: C, 77.36; H, 12.34; mol wt, 310.5. Found: C, 76.60; H, 12.48; mol wt, 314 (thermistor).

Copper Chelate.—Hot aqueous cupric acetate and an ethanolic solution of the keto aldehyde were combined and cooled to deposit blue-green crystals of the chelate: mp 128–129°; uv 245 mμ (*E* 7300), 302 (8900); ir, 1585, 1498, 1445, 1350 cm^{-1} ($CHCl_3$).

Anal. Calcd for $C_{40}H_{74}O_4Cu$: C, 70.39; H, 10.93. Found: C, 70.53; H, 10.94.

Dechelation.—A solution of the chelate in warm chloroform was shaken with 0.1 *N* hydrochloric acid, and the chloroform layer was washed with water, dried (sodium sulfate), and evaporated to yield a residue of the free keto aldehyde identical in properties with the sample described above.

3-Oxooctadecanal.—By a method analogous to procedure C, vinyl palmitate was converted to the C-18 3-keto aldehyde: mp 51.5–52.2° (lit.[10] mp 47°); ir and uv very like those of the C-20 compound; copper chelate, mp 125–126.5°.

3-Oxotetradecanal.—By a method analogous to procedure C, vinyl laurate was converted to the C-14 3-keto aldehyde: mp 32.5–33.0°; ir and uv very similar to those of the C-18 and C-20 homologs. The pure crystalline compound was not stable to storage.

The copper chelate had mp 126.8–127.4°.

Anal. Calcd for $C_{28}H_{50}O_4Cu$: C, 65.38; H, 9.82. Found: C, 65.38; H, 9.81.

Reaction of Vinyl Alkanoate with Aluminum Chloride to Form β Diketones. Procedure D. 18,20-Dioxoheptatriacontane (Distearoylmethane).—Vinyl stearate (23.4 g, 0.075 mol) in 200 ml of olefin-free hexane was treated with 10.15 g (0.075 mol) of aluminum chloride, and the mixture was refluxed for 2 hr, cooled, quenched by agitation with dilute hydrochloric acid, and dried (sodium sulfate), and the solvent was removed *in vacuo*. The residue weighed 8.5 g and more material (10 g) was recovered from the aqueous acid by methylene chloride–ether extraction.

The residues were combined, dissolved in hot 95% ethanol, and treated with an excess of hot aqueous curpic acetate to deposit a 73% yield of the lilac chelate identical with the preparation described above. [Where mixtures of the keto aldehyde and diketone were obtained as, for example, in intermediate reaction times (compare procedures C and D), separation was effected by chromatography of the mixed chelates on Florisil. Elution with hot benzene gave a forerun of the lilac chelated distearoylmethane followed by the blue-green chelated 3-oxoeicosanal. Additional chelated keto aldehyde was eluted with chloroform.]

16,18-Dioxotritriacontane (Dipalmitoylmethane).—In a manner analogous to the above (procedure D) vinyl palmitate was converted to dipalmitoyl methane.

12,14-Dioxopentacosane (Dilauroylmethane).—In a manner analogous to the above, vinyl laurate was converted to dilauroylmethane.

Ethyl Palmitoacetate and Ethyl Dipalmitoacetate.—Acetoacetic ester (3.6 ml, 0.028 mol) and 7.62 g of palmitoyl chloride (0.028 mol) in 50 ml of olefin-free hexane were treated with 3.7 g (0.028 formula wt) of aluminum chloride added in one portion. The pasty mixture was warmed for 2 hr at 70° during which time all solids dissolved. The mixture was cooled, poured into iced dilute hydrochloric acid, and extracted into ether. A little ethanol was used to break emulsions. The organic layer was dried (sodium sulfate), solvents were removed, and the product was chromatographed on Florisil. The first pentane eluates contained 1 g of dipalmitoylacetic ester purified by recrystallization of the copper chelate from ethanol: mp 91.9–92.3°; uv 297 mμ (*E* 26,000), 241 (18,000).

Anal. Calcd for $C_{72}H_{134}O_8Cu$: C, 72.58; H, 11.34. Found: C, 72.88; H, 11.34.

Dechelation with hydrochloric acid gave the free dipalmitoylacetic ester, mp 42–43°, uv 280 mμ (*E* 92000) (EtOH). Further elution of the column with methylene chloride gave palmitoacetic ester which, after recrystallization from hexane, melted from 38.7 to 39.2°, copper chelate mp 112–114° (lit.[16] mp 37–38 and 111°, respectively).

Registry No.—I, 6136-89-6; vinyl stearate, 111-63-7; diethyl 2-stearoylmalonate, 24514-82-7; 3,4-dimethylstearophenone, 24514-83-8; 8,10-dioxoheptadecane, 24514-84-9; copper chelate of 8,10-dioxoheptadecane, 24523-20-4; 18,20-dioxoheptatriacontane, 24514-85-0; copper chelate of 18,20-dioxoheptatriacontane, 24515-38-6; 16,18-dioxotritriacontane, 24514-86-1; copper chelate of 16,18-dioxotritriacontane, 24515-39-7; 3-oxoeicosanal, 24514-87-2; copper chelate of 3-oxoeicosanal, 24515-40-0; 3-oxotetradecanal, 24514-88-3; copper chelate of 3-oxotetradecanal, 24515-41-1; ethyl dipalmitoacetate, 24514-89-4; copper chelate of ethyl dipalmitoacetate, 24515-42-2.

Insertion of Ethylene Oxide into the Carbon–Chlorine Bond of Benzyl Chloride

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The synthesis of β-chloroethyl benzyl ethers from benzyl chlorides and ethylene oxide is described. Benzyl chlorides rapidly polymerize, releasing hydrogen chloride, in the presence of Friedel–Crafts catalysts or metal oxides. The chlorides, however, give only small quantities of polymer when N,N-dimethylformamide, N,N-dimethylacetamide, or acetonitrile is added to the system, and β-chloroethyl benzyl ethers can be prepared by adding ethylene oxide to the mixture. The reaction mechanism is discussed.

There are several reports describing the insertion reactions of epoxides into the carbon–chlorine bond.[1–5] Recently, Klamann and coworkers have shown that tetraethylammonium bromide and metallic copper are excellent catalysts for this reaction.[6] On the other hand, it has been reported that benzyl halides easily polymerize in the presence of Friedel–Crafts catalysts or certain metal oxides.[7,8]

We have now shown that the presence of certain solvents in a zinc chloride–benzyl chloride–ethylene oxide system depresses the condensation–polymerization reaction of benzyl chloride and permits the insertion of ethylene oxide into the carbon–chlorine bond to form β-chloroethyl benzyl ethers. This dramatic solvent effect is observed when N,N-dimethyl-

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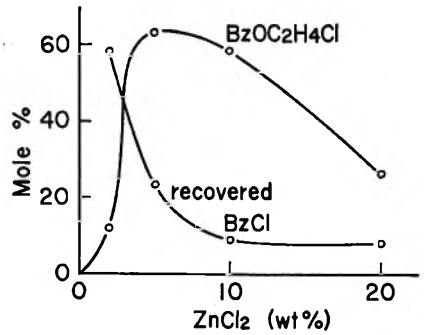


Figure 1.—Variation of generated $BzOC_2H_4Cl$ and recovered BzCl *vs.* $ZnCl_2$ amount. Reaction conditions: BzCl; 4.0 g of DMA; 2.0 g of EO; 50–55 ml/min, 140°, 1 hr. Bz = $C_6H_5CH_2$–, DMA = N,N-dimethylacetamide, EO = ethylene oxide.

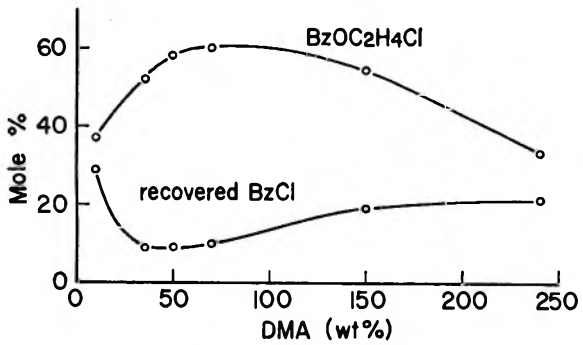


Figure 2.—Variation of generated $BzOC_2H_4Cl$ and recovered BzCl *vs.* DMA. Reaction conditions: BzCl; 4.0 g of $ZnCl_2$; 0.4 g of EO; 50–55 ml/min, 140°, 1 hr.

formamide, N,N-dimethylacetamide, or acetonitrile is used.

Results and Discussion

In the reaction of ethylene oxide and benzyl chlorides, condensation of benzyl chlorides, formation of ethylene chlorohydrin, or complicated reactions with solvent may occur. The various factors affecting this reaction were studied.

Catalysts.—Several Friedel–Crafts type catalysts were compared with each other using benzyl chloride in sealed-tube reactions. The results are shown in Table I. Zinc chloride and cupric chloride give the highest yields.

TABLE I
INSERTION OF ETHYLENE OXIDE INTO BENZYL CHLORIDE[a]

Catalyst	Yield, mol % of $C_6H_5CH_2OC_2H_4Cl$	Recovered benzyl chloride, mol %
$AlCl_3$	Trace	100
$FeCl_3$	5.2	81
$SnCl_4$	Trace	81
$BiCl_3$	3.7	54
$ZnCl_2$	14.7	33
$CuCl_2$	11.0	63
$CuCl_2$[b]	6.3	53

[a] Reaction conditions: catalyst, 0.001 mol; N,N-dimethylacetamide, 0.01 mol; benzyl chloride, 0.01 mol; ethylene oxide, 0.01 mol; 140°; 1 hr. [b] Without solvent.

As shown in Figure 1, when zinc chloride is used as the catalyst (5 wt % based on benzyl chloride), the maximum yield is 63 mol %). When more catalyst is used, the yield of both β-chloroethyl benzyl ether and the recovery of benzyl group[9] decrease owing to condensation polymerization.

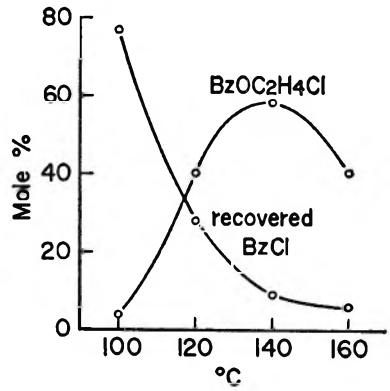


Figure 3.—Variation of generated $BzOC_2H_4Cl$ and recovered BzCl *vs.* temperature. Reaction conditions: BzCl; 4.0 g of DMA; 2.0 g of $ZnCl_2$; 0.4 g of EO; 50–55 ml/min, 1 hr.

Solvent.—N,N-Dimethylacetamide, N,N-dimethylformamide, acetonitrile, dimethyl sulfoxide, nitrobenzene, nitromethane, and nitroethane were examined. When either N,N-dimethylacetamide, N,N-dimethylformamide, or acetonitrile was used, the insertion reaction occured. Without the solvent, however, a glassy polymer is obtained on heating the mixture with or without ethylene oxide. The yield of β-chloroethyl benzyl ether under optimum conditions increases in the following order, acetonitrile < N,N-dimethylformamide < N,N-dimethylacetamide, with N,N-dimethylacetamide giving the least by-product.

Under the same reaction conditions as in Table I, the results in Table II are obtained.

TABLE II
INSERTION REACTION IN SEALED-TUBE REACTION[a]

Solvent	Yield of $C_6H_5CH_2OC_2H_4Cl$, mol %
Acetonitrile	7.6
N,N-Dimethylformamide	15.0
N,N-Dimethylacetamide	14.0

[a] Reaction conditions: same as in Table I.

Nitroalkanes, though effective solvents in Friedel–Crafts reactions, give no insertion product. This may be attributed to the poor solubility of the catalyst. Dimethyl sulfoxide gives various by-products but not the desired product.

The conversion of benzyl chloride, the recovery of benzyl group, and the yield of β-chloroethyl benzyl ether were also determined *vs.* the amount of N,N-dimethylacetamide. As shown in Figure 2, use of 50–70 wt % N,N-dimethylacetamide to benzyl chloride gives the maximum yield of β-chloroethyl benzyl ether. With more solvent, the recovery of benzyl group as well as the yield of the ether decreases.

Reaction Temperature.—As shown in Figure 3, the reaction starts at about 100°, and at 140° the maximum yield is obtained.

(9) Recovery of the benzyl group means the mole summation of β-chloroethyl benzyl ether and unreacted benzyl chloride.

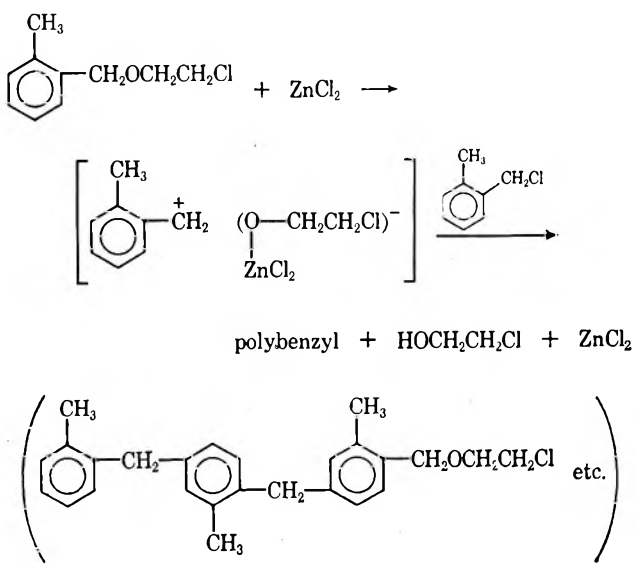
Water.[10]—The presence of water causes the formation of the by-product polyethylene glycol. Moreover, the appearances of reaction mixtures differ from each other owing to the amount of water. The reaction mixture is homogeneous when the solvent contains 0.07–0.4 wt % water. When the solvent is dehydrated as completely as possible (0.03 wt %) with calcium hydride or azeotropically, or when the solvent contains much more water (1.9 wt %), the mixture is heterogeneous.

As shown in Figure 4, the yield of the insertion product decreases to 37% when the system contains 1.9% water, and the recovery of the benzyl group decreases also. The formation of by-products as well as of polyethylene glycol is effected by water.

When the water content is as low as 0.03%, the yield of β-chloroethyl benzyl ether is 44%, and the recovery of benzyl group is 54%. This suggests that the reaction is depressed by low solubility of the catalyst in this system, and that a certain amount of water is necessary to promote the insertion reaction, since the recovery of benzyl group decreases also.

Substitution on the Benzene Ring.—In the reaction of ethylene oxide and benzyl chloride, the intermediate benzylcarbonium ion may form. Therefore, we examined several benzyl chlorides having alkyl, chloro, nitro, and methoxy group substituents. Reactivity of chloromethylated toluene with ethylene oxide increases in the following order as shown in Figure 5: *o*-CH_3 > *p*-CH_3 > *m*-CH_3.

This fact may be explained as follows. When the insertion reaction proceeds *via* a carbonium ion intermediate, the cation from the *meta* derivative may be less stable than that from the *ortho* or *para* derivative. Yields of *ortho* derivative product decrease after 70 min which may also be explained by assuming that the *ortho* derivative may be easily attacked sterically by a benzyl carbonium ion to become polybenzyl.



The yields of insertion products from other *para*-substituted benzyl chlorides are shown in Table III. Yields from *p*-methoxy, *p*-methyl (Figure 5), and *p*-nitro derivatives are comparable to their σ values.

(10) Water content in the solvent and benzyl chloride was determined by means of the Karl–Fisher titration.

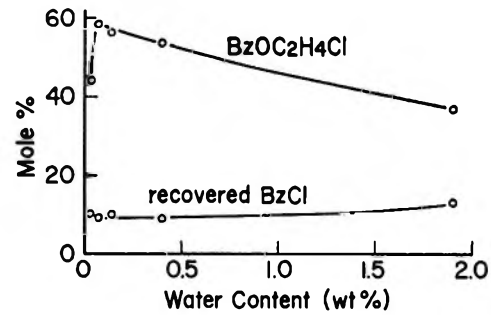


Figure 4.—Variation of generated $BzOC_2H_4Cl$ and recovered BzCl *vs.* water content. Reaction conditions: BzCl; 4.0 g of DMA; 2.0 g of $ZnCl_2$; 0.4 g of EO; 50–55 ml/min, 140°, 1 hr.

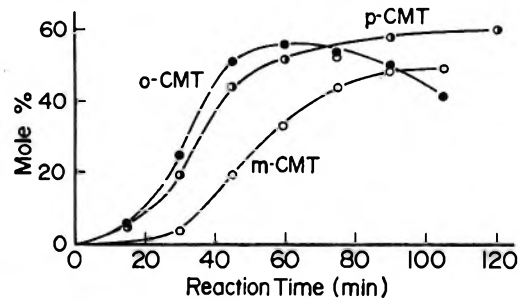


Figure 5.—Progress of insertion product of chloromethylated toluene. Reaction conditions: CMT; 8.0 g of DMA; 4.0 g of $ZnCl_2$; 0.8 g of EO; 55 ml/min, 140°.

The *p*-chloro derivative, however, shows a high yield despite its positive σ value, 0.226. This fact may be accounted for by its large resonance effect rather than its inductive effect.

TABLE III

INFLUENCE OF *para* SUBSTITUENTS[a]

Substituent, *p*-X	Yield of *p*-$XC_6H_4CH_2OC_2H_4Cl$, mol %	σ value
H	14.7	0
CH_3	24.9	−0.170
Cl	34.5	+0.226
CH_3O	39.3	−0.268
NO_2	0	+0.778

[a] Benzyl chloride–ethylene oxide = 1.0; zinc chloride, 10% by weight of benzyl chloride; 140°; 1 hr.

The insertion reaction is applied to higher alkyl derivatives. Thus, dodecylbenzyl chlorides were examined. Products were purified by vacuum distillation, but small amounts of contamination cannot be removed because of their high viscosities and molecular weights. Results are shown in Table IV.

TABLE IV

INSERTION PRODUCTS FROM *n*-DODEC-*Y*-YLBENZYL CHLORIDE[a]

Y	Yield of R-$C_6H_4CH_2OC_2H_4Cl$, %	Bp, °C (0.008 mm)	Analysis, % C	H	Cl[12]
1	41	160–170	73.96	10.86	10.0
2	45	159–165	74.17	10.94	10.6
6	51	153–157	74.14	10.54	9.8

[a] Calcd for $C_{21}H_{35}OCl$: C, 74.41; H, 10.41; Cl, 10.46.

Probable Mechanism of Insertion Reaction.—The insertion reaction may proceed through a free benzylcarbonium ion or a solvated or nearly σ-bonded ion[8]

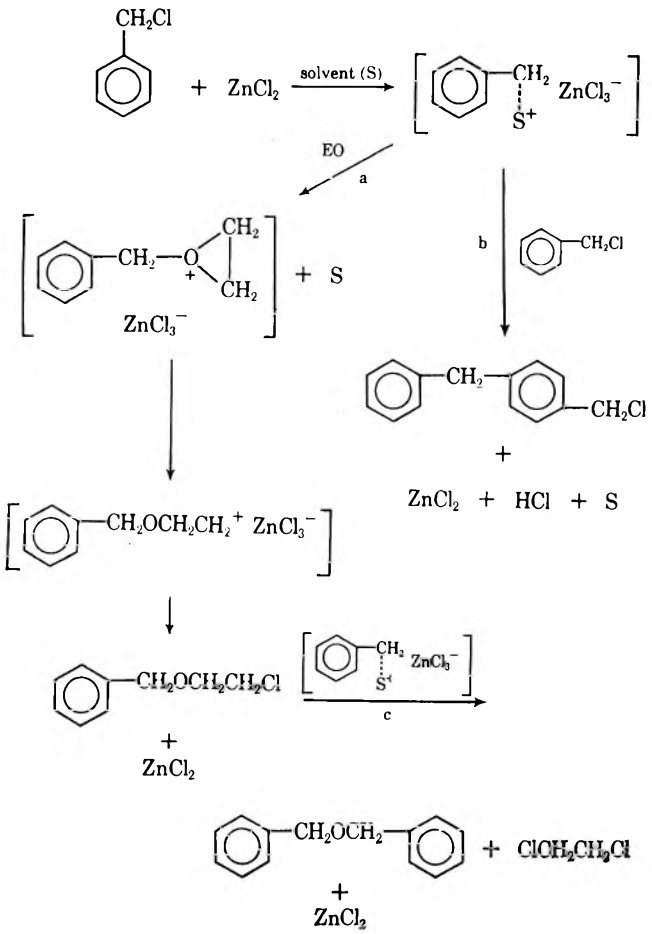
TABLE V

INSERTION PRODUCTS FROM SUBSTITUTED BENZYL CHLORIDES

Substrate X	Bp, °C (mm)	Calcd % C	Calcd % H	Calcd % Cl	Found % C	Found % H	Found % Cl[a]
o-CH_3	85–87 (3)	65.04	7.10	19.2	65.18	7.10	18.7
m-CH_3	96–97 (3)	65.04	7.10	19.2	65.20	7.31	19.3
p-CH_3	101–102 (3)	65.04	7.10	19.2	64.92	7.23	19.7
p-Cl	105 (1)	52.71	4.92	34.6	52.95	5.04	34.1
p-CH_3O	108–110 (1)	59.86	6.53	17.7	59.66	6.38	17.7

[a] Reference 12.

to the solvent. The intermediate, stabilized by solvation, may then react with ethylene oxide (route a) to form the ether. Another benzyl chloride may be attacked by the solvated cation to form polymer



(route b), since a small amount of polymer was detected in all experiments. Dibenzyl ether may be generated by attack of a benzyl cation on β-chloroethyl benzyl ether or benzyl alcohol (route c).

Experimental Section

Reaction of Ethylene Oxide (EO) and Benzyl Chloride.—In the typical run, 2.0 g of N,N-dimethylacetamide (DMA) was added to a vessel containing 0.4 g of freshly dried $ZnCl_2$. After dispersion of $ZnCl_2$ by warming, 4.0 g of benzyl chloride was added, and EO, 50–55 ml/min, was bubbled in at 140° for 1 hr. Products were separated by distillation after washing with 1 *N* HCl and H_2O. The main product, bp 52–53° (1 mm), showed a characteristic infrared band at 1115 cm^{-1} besides those owing to the phenyl group; nmr (15% CCl_4 solution) τ 6.47[11] (4 H), 5.57 (2 H), 2.87 (5 H). *Anal.* Calcd for $C_9H_{11}OCl$ C, 63.35; H, 6.50; Cl, 20.8. Found: C, 63.04; H, 6.64; Cl,[12] 20.8. Comparing with the authentic sample synthesized from benzyl alcohol and ethylene oxide in the presence of sodium benzyl alcoholate, followed by chlorination of the hydroxyl group by thionyl chloride, which showed the same ir, nmr spectrum, and boiling point, the main product was identified as β-chloroethyl benzyl ether.

The yield of β-chloroethyl benzyl ether was 63 mol % by glpc.[14] Ethylene chlorohydrin was detected by glpc from the crude product before washing with 1 *N* HCl. Small amounts of dibenzyl ether, benzyl alcohol, and benzyl formate (when N,N-dimethylformamide was used as a solvent) were also shown by glpc.

Reaction of Substituted Benzyl Chlorides.—To compare reactivities of benzyl chlorides, a mixture of $ZnCl_2$ (0.2 g), DMA (1.4 g), substituted benzyl chloride (0.016 mol), and EO (0.7 g, 0.016 mol) was heated in a sealed tube at 140° for 1 hr. These β-chloroethyl ethers were isolated by the same procedure as in the case of β-chloroethyl benzyl ether. The substituted β-chloroethyl ethers were also analyzed by glpc.[15]

Phenyldodecanes. 1-Phenyldodecane (I).[16]—I was prepared from lauroyl chloride and benzene by a Friedel-Crafts reaction[17] followed by Clemensen reduction:[18] bp 120–125° (1 mm); yield, 72% based on lauroyl chloride; nmr (neat) τ 9.17 (3 H), 8.73 (18 H), 8.35 (2 H), 7.57 (2 H), 2.96 (5 H). *Anal.* Calcd for $C_{18}H_{30}$: C, 87.73; H, 12.27. Found: C, 87.55; H, 12.20.

2-Phenyldodenane (II).—After dehydration of methyldecylcarbinol[16] (prepared from decyl bromide[19] and acetophenone) by refluxing with 90% formic acid for 20 hr, the olefin [bp 120–130° (1 mm), two components detected by glpc] was hydrogenated to II in ethanol in the presence of 5% Pd–carbon and 25–30 kg/cm^2 of hydrogen at room temperature for 4 hr: bp 115–118° (0.8 mm); yield, 52% based on decyl bromide; nmr (neat) τ 9.14 (3 H), 8.85 (3 H), 8.80 (16 H), 8.55 (2 H), 7.45 (1 H), 2.90 (5 H). *Anal.* Calcd for $C_{18}H_{30}$: C, 87.73; H, 12.27. Found: C, 87.54; H, 12.43.

6-Phenyldodecane (III).—III was prepared by a procedure similar to that used for II, with the olefins [bp 111–120° (0.8 mm), two components detected by glpc] through pentylhexylphenylcarbinol[16] prepared from hexyl bromide and pentyl phenyl ketone[17] obtained from caproyl chloride: bp 115–117° (1 mm); yield, 66% based on pentyl phenyl ketone; nmr (neat) τ 9.20 (6 H), 8.82 (14 H), 8.45 (4 H), 7.60 (1 H), 2.95 (5 H). *Anal.* Calcd for $C_{18}H_{30}$: C, 87.73; H, 12.27. Found: C, 87.75; H, 12.08.

Chloromethylated Dodecylbenzenes.—Phenyldodecanes were chloromethylated[20] with paraformaldehyde and hydrogen chloride. In the chloromethylation reaction of alkylbenzenes, mixtures of ring-position isomers are generally obtained. In the case of alkylbenzene having bulky alkyl moiety, the genera-

(11) This was considered to be the superimposed signal of four methylene protons in the β-chloroethyl group, because of the same chemical shifts of protons.

(12) Determined by modified semimicro butanol–Na method.[13]

(13) W. Kimura, *Kogyo Kagaku Zasshi*, **37**, 1310 (1934).

(14) Apiezon L grease 10% on Diasolid, 1 *m*, 140°, H_2 70 ml/min. By making a calibration curve between the isolated product and the internal standard, the yield based on benzyl chloride was determined (internal standard, N,N-diethylaniline).

(15) Triton X-305 10% on Diasolid L, 180°; internal standard methyl benzoate for $C_6H_5CH_2Cl$, lauryl acetate for *p*-$CH_3C_6H_4CH_2Cl$, $CH_3(OCH_2CH_2)_3CH$ for *p*-$CH_3OC_6H_4CH_2Cl$ and *p*-$ClC_6H_4CH_2Cl$.

(16) E. R. Lynch and E. B. McCall, *J. Chem. Soc.*, 1254, (1960).

(17) F. L. Breusch and M. Oguzer, *Chem. Ber.*, **87**, 1225 (1954).

(18) "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 444.

(19) Reference 18, Coll. Vol. I, 1941, p 30.

(20) S. K. Freeman, *J. Org. Chem.*, **26**, 212 (1961).

TABLE VI

PROPERTIES OF CHLOROMETHYLATED DODECYLBENZENES

Phenyldodecane	Bp, °C (1 mm)	Cl, % (calcd)
I	158–162	11.9 (12.0)
II	145–148	11.6 (12.0)
III	138–142	11.5 (12.0)

tion ratio of the *para* derivative becomes great, but the compositions of chloromethylated dodecylbenzenes for the insertion reaction cannot be determined by ir, nmr, or glpc. The yields of chloromethylated dodecylbenzenes are low[20] in every case; so raw dodecylbenzenes must be treated repeatedly to obtain chloromethylated compounds. Their properties are shown in Table VI.

Reactions of Chloromethylated Dodecylbenzenes.—The procedure was similar to the case of benzyl chloride, except for the reaction time, 3 hr, and the reactant ratio, dodecylbenzyl chloride:$ZnCl_2$:DMA = 10:1:10 by weight. The properties of the insertion products are shown in Table IV.

Registry No.—Ethylene oxide, 75-21-8; benzyl chloride, 100-44-7; *p*-methylbenzyl chloride, 104-82-5; *p*-chlorobenzyl chloride, 104-83-6; *p*-methoxybenzyl chloride, 824-94-2; *o*-methylbenzyl chloride, 552-45-4; *m*-methylbenzyl chloride, 620-19-9; *p*-nitrobenzyl chloride, 100-14-1.

Acknowledgment.—The authors wish to thank Professor D. Swern, Temple University, for advice and helpful discussion.

Bridged Polycyclic Compounds. LXI. Synthesis and Some Properties of Tribenzobicyclo[3.2.2]nonatriene (Homotriptycene) and Derivatives[1]

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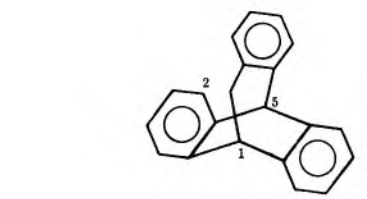
Received December 3, 1969

A preparation of homotriptycene (1) was conducted *via* ring expansion of tribenzobicyclo[2.2.2]octatrienylcarbinyl cation. Alkyl cations from 1 (*i.e.*, 2 and 7) do not rearrange to each other, but the 2-tribenzobicyclo[3.2.2]nonatrienyl cation (2) is an intermediate whose degeneracy was demonstrated with the aid of deuterium labeling. Pmr spectra of some homotriptycenes and triptycenes are recorded.

A natural extension of work in this laboratory on bridged polycyclic systems centered about tribenzobicyclo[3.2.2]nonatriene (1) and some of its derivatives, in particular, the carbonium ion 2. For reasons of simplicity 1 will be referred to as homotriptycene, as it



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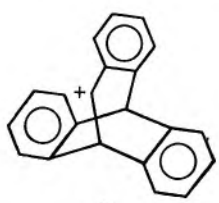

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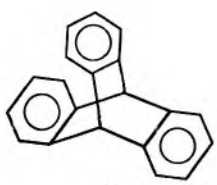

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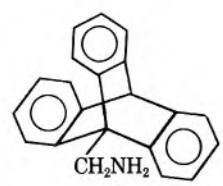
is the next higher homolog of 9,10-dihydro-9,10-*o*-benzenoanthracene, or triptycene (3). Within the last few years syntheses of bicyclo[3.2.2]nonatriene[2] and one of its mono-[3] and both of its dibenzo-substituted[4] derivatives have been described. We now describe another member of this bicyclic family, tribenzobicyclo[3.2.2]-nonatriene.

The key to the synthesis of the homotriptycene ring system appeared to us to be a ring expansion reaction of some derivative of 1-methyltriptycene. As 1-aminomethyltriptycene (4) was known,[5] this appeared to be a very reasonable precursor. In accord with our expectations, nitrous acid in glacial acetic acid converted 4 into a mixture representing a 42% yield of 1-tribenzobicyclo[3.2.2]nonatrienol (5-OH) and a 56%



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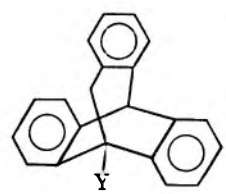

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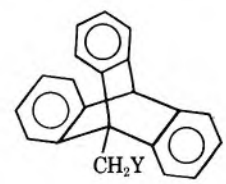

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yield of the corresponding acetate (5-OAc).[6] We did not find any alcohol or acetate with unrearranged carbon skeleton (*i.e.*, 6-OH or 6-OAc). Neither 5-OH nor 5-OAc seemed to be an ideal precursor of 1, as 5-OH

(1) Paper LX: S. J. Cristol, M. A. Imhoff, and D. C. Lewis, *J. Org. Chem.*, **35**, 1722 (1970).

(2) (a) M. J. Goldstein and A. H. Gevirtz, *Tetrahedron Lett.*, 4413 (1965); (b) M. Jones, Jr., and S. D. Reich, *J. Amer. Chem. Soc.*, **89**, 3935 (1967); (c) M. J. Goldstein and B. G. Odell, *ibid.*, **89**, 6356 (1967).

(3) J. Ciabattoni, J. E. Crowley, and A. S. Kende, *ibid.*, **89**, 2778 (1967).

(4) (a) S. J. Cristol, R. M. Sequeira, and C. H. DePuy *ibid.*, **87**, 4007 (1965); (b) S. J. Cristol, R. M. Sequeira, and G. O. Mayo, *ibid.*, **90**, 5564 (1968); (c) S. J. Cristol, G. O. Mayo, and G. A. Lee, *ibid.*, **91**, 214 (1969).

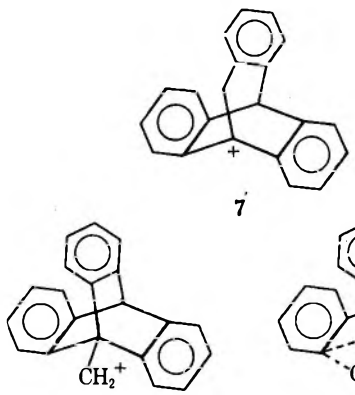
(5) E. C. Kornfeld, P. Barney, J. Blankley, and W. Faul, *J. Med. Chem.*, **8**, 342 (1965).

(6) The presence of large amounts of alcohols from diazotization reactions in acetic acid has been noted before.[7]

(7) (a) J. H. Ridd, *Quart. Rev.* (London), **15**, 418 (1961); (b) P. S. Bailey and J. G. Burr, Jr., *J. Amer. Chem. Soc.*, **75**, 2951 (1953); (c) A. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1957); (d) H. Felkin, *Bull. Soc. Chim. Fr.*, 1582 (1960); (e) J. R. Mohrig, Ph.D. Thesis, University of Colorado, 1963; (f) G. T. Tiedeman, Ph.D. Thesis, University of Colorado, 1964.

was converted only extremely slowly with thionyl chloride to **5**-Cl. However, the nitrous acid experiment suggested that the Demjanov ring expansion was useful for entry into the homotriptycene ring system.

Use of nitrosyl chloride[8] in methylene chloride with **4** gave rearranged (**5**-Cl) and unrearranged (**6**-Cl) chlorides in yields of 66 and 12%, respectively. The isolation of **6**-Cl in this experiment and the absence of **6**-OH and **6**-OAc in the acetic acid deamination described above raise some interesting questions. There is the possibility that at least a portion of the nitrosyl chloride reaction proceeds by a noncarbonium ion process, not utilized in the other deamination. Alternatively, chloride ion may trap some other carbonium ion precursor faster than it rearranges to **7**. This precursor may be the primary cation **8** or the ion **9**. Note that geometric requirements make **9** σ bonded, rather than a phenonium ion. Our data do not enable a choice to be made among these possibilities.



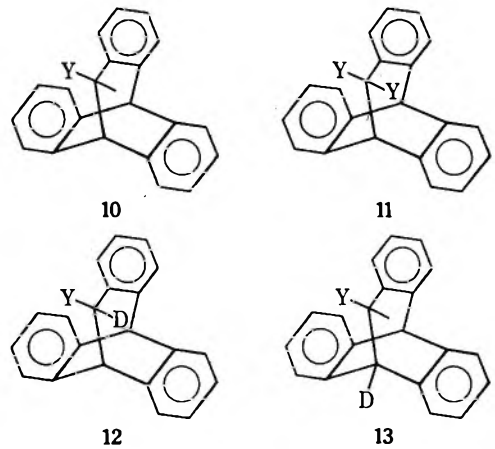
7 **8** **9**

Nitrosyl chloride and nitrous acid deaminations are susceptible to modifications to give a wide variety of substituents at the bridgehead (C-1 of **1**). As an example, when ethanol was a cosolvent with dichloromethane during nitrosyl chloride treatment of **4**, large amounts of ethyl 1-tribenzobicyclo[3.2.2]nonatrienyl ether (**5**-OEt) were formed. Proper choice of solvent or solute–solvent systems could supply many different bridgehead derivatives of **5**.

The success of the deamination procedure from **4** as the ring-expansion process was fortunate, as other **6** compounds did not react readily. For example, **6**-OAc was recovered unchanged after 2 hr of refluxing in 1 *M* $HClO_4$ in acetic acid and **6**-Cl was recovered unchanged after treatment with silver acetate in acetic acid at 210° for 24 hr.

Reduction of **6**-Cl with sodium in *t*-butyl alcohol gave 1-methyltriptycene (**6**-H).[9] In similar fashion, homotriptycene (**1**) was obtained from **5**-Cl.

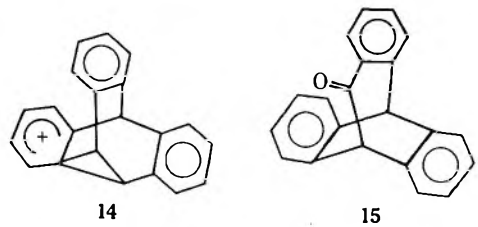
1 was transformed to a monobromo derivative (**10**-Br) by light-promoted treatment with N-bromosuccinimide. Chlorohomotriptycene (**5**-Cl) gave a similar reaction. Treatment of **1** with 2 mol of NBS gave the dibromo compound **11**-Br. Solvolyses of **10**-Br in 1:1 methanol–benzene and 1:1 ethanol–benzene at reflux were complete in less than 1 hr and gave the methyl (**10**-OCH_3) and ethyl (**10**-OEt) ethers, respectively and quantitatively. Silver acetate in acetic acid gave **10**-OAc quantitatively. Thus, in these experiments, ion **2** does not isomerize to **7**.



10 **11** **12** **13**

Ion **2**, if a classical ion, is triply degenerate (*via* Wagner–Meerwein rearrangement) and should demonstrate scrambling of one of the bridgehead atoms and the cationic carbon atom. To test this, **1** was converted with potassium *t*-butoxide and DMSO-d_6 to dideuteriohomotriptycene (**11**-D) and bromination of this led to **12**-Br. The pmr spectrum of **12**-Br indicated that no rearrangement occurred in the radical bromination. When **12**-Br was solvolyzed in methanol in the absence of base or in the presence of 0.02, 0.38, or 3.8 *M* sodium methoxide, it was converted cleanly to a mixture of methyl ethers (**12**-OCH_3 and **13**-OCH_3), which in each case appeared (by pmr analysis) to be an equimolar mixture. Thus, complete scrambling occurs in 2-homotriptycyl ion (**2**) before capture.

An alternative to the classical structure **2** for the ionic intermediate is the phenonium ion structure **14** which would also rationalize the observed scrambling. The completely delocalized structure for the unsubstituted bicyclo[3.2.2]nonatrienyl cation has been rejected by Goldstein and Odell,[10] and their objections would probably pertain as well to our system. A distinction could be made between **2** and **14**, if **14** is stable toward interconversion by Wagner shifts, by appropriate ring labeling. Possibly Olah's method[11] would also be applicable.



14 **15**

Hydrolysis of the dibromide **11**-Br with aqueous sodium acetate gave the ketone **15**. This was also prepared by oxidation of **1** and was readily reduced to the alcohol **10**-OH with lithium aluminum hydride and in analogous fashion to the deuterio analog **12**-OH.

Attempts to interconvert ions **2** and **7** were not successful. Both **5**-OAc and **10**-OAc were stable to 1–2 hr of refluxing in 1 *M* $HClO_4$ in acetic acid. While

(8) P. A. S. Smith, D. R. Baer, and S. N. Ege, *J. Amer. Chem. Soc.*, **76**, 4564 (1954).

(9) W. Theilacker, U. Berger-Brone, and K. H. Beyer, *Chem. Ber.*, **93**, 1658 (1960).

(10) M. J. Goldstein and B. G. Odell, *J. Amer. Chem. Soc.*, **89**, 6356 (1967); M. J. Goldstein, *ibid.*, **89**, 6357 (1967).

(11) G. M. Olah and A. M. White, *ibid.*, **91**, 3954, 3956 (1969).

it is possible that **7** was not in fact formed from **5**-OAc by this treatment, it is obvious that **10**-OAc gives **2** readily under these conditions. It seems certain[12] that treatment of **5**-OH with thionyl chloride, which leads to **5**-Cl, proceeds *via* **7**, and rearrangement did not occur in this experiment, nor did any **10** species form in the deamination of **4** which led to **5** species. Although **7** must be a highly unstable ion,[13] it seems clear that it must be substantially more stable than the primary ion **8**.

The lack of interconversion between **7** and **2** by a 1,2 hydride shift is reasonably rationalized on geometric grounds.[15] The carbon–hydrogen bonds which would be involved in migration are nearly orthogonal to the p orbital of the cationic center, and the energy barrier to such a migration must therefore be significantly greater than those for capture of each ion by nucleophile.

Structure and Pmr Spectra.—The structures of the compounds described above were generally ascertained by consideration of the interconversions among them and by pmr spectra. Like triptycene,[16] the 1-substituted triptycenes had bridgehead absorption in the τ 4.5–4.7 range, and had two distinct aromatic absorption bands, each representing six protons, presumably reflecting the shielding and deshielding effects of the aromatic rings. The homotriptycenes had broad aromatic absorptions but were generally not readily separable into low- and high-field bands on the 60-Mc instrument. With chlorine, hydroxy, and ethoxy at C-1 in homotriptycene (compounds **5**), two aromatic protons, presumably those *syn periplanar*, were significantly deshielded, and, with compound **15**, the hydrogen *ortho* to the keto group was, as expected,[17] significantly deshielded. Details of the pmr spectra are given in the Experimental Section.

Experimental Section

Elemental microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points are corrected. Except where otherwise stated, pmr spectra were taken in $CDCl_3$ on a Varian Associates Model A-60 spectrometer.

Deamination of 1-Aminomethyltriptycene (4) with Nitrous Acid–Acetic Acid.—Dry sodium nitrite, 2.12 g (31 mmol), was added to a solution of 1.02 g (3.1 mmol) of the hydrochloride of **4**[5] in 60 ml of anhydrous acetic acid (distilled from acetyl borate[18]) over a 1-hr period at 18–20°. On the next day the mixture was added to 50 ml of benzene and 50 ml of water. The water layer was separated and washed with three 25-ml portions of benzene. The combined benzene layers were washed with water, aqueous $NaHCO_3$, and saturated aqueous NaCl and dried ($MgSO_4$). After evaporation, the residue was crystallized from methanol to give 910 mg of a mixture; analysis (pmr) showed 530 mg (56%) of **5**-OAc and 380 mg (42%) of **5**-OH.

A solution of 1.34 g of a similar mixture (4.3 mmol) in 200 ml of anhydrous ether was added slowly to a solution of 1.0 g (26 mmol) of $LiAlH_4$ in 100 ml of anhydrous ether. The mixture was heated at reflux for 1 hr, cooled to 0°, and *cautiously*(!) decomposed with water. The ethereal layer was filtered, washed with dilute aqueous HCl, $NaHCO_3$, and saturated NaCl solution and dried ($MgSO_4$). The residue from solvent evaporation was recrystallized from benzene–Skellysolve B (petroleum ether, bp 60–70°) to give 1.22 g (85%) of **1-tribenzobicyclo[3.2.2]-nonatrienol** (**5**-OH), as small prisms, mp 150.5–151°; pmr (in CD_3COCD_3) τ 2.2 m, (2 aromatic H), 2.8 m, (10 aromatic H), 4.93, s (2, OH, H-5), and 6.66 s (2, H-2).

Anal. Calcd for $C_{21}H_{16}O$: C, 88.70; H, 5.67. Found: C, 88.45; H, 5.69.

This alcohol (200 mg, 0.70 mmol) was acetylated with acetyl chloride in N,N-dimethylaniline and chloroform using a standard procedure[19] to give, after recrystallization from aqueous methanol, 201 mg (88%) of **1-tribenzobicyclo[3.2.2]nonatrienyl acetate** (**5**-OAc), mp 153–154°; pmr τ 2.8 m (12 aromatic H), 5.13 s (1, H-5), 6.60 s (2, H-2), and 7.61 s (3, $OCOCH_3$).

Anal. Calcd for $C_{23}H_{18}O_2$: C, 84.64; H, 5.56. Found: C, 84.47; H, 5.68.

Preparation of 1-Chloro-tribenzobicyclo[3.2.2]nonatriene (5-Cl) and 1-Chloromethyltriptycene (6-Cl).—Gaseous nitrosyl chloride (5-ml liquid equiv at 0°) was passed over an ice–water-cooled solution of 5.00 g (0.0176 mol) of **4** in 100 ml of reagent grade dichloromethane until the yellow-brown nitrosyl chloride was no longer decolorized, following the general procedure of Smith.[8] Initial reaction produced a precipitate, gas evolution, and warming of the reaction mixture. Further addition led to less gas evolution and promoted solution of the earlier formed solid. After 2 hr of stirring, the solvent was removed by rotary evaporation; the residual solid was chromatographed on Merck 71707 neutral alumina. Elution with Skellysolve B gave 3.50 g (66%) of **5**-Cl; 25% benzene in Skellysolve B eluted 0.645 g (12%) of 1-chloromethyltriptycene (**6**-Cl), mp 231–232° (lit.[5] 229.5–236.5°); 75% benzene in Skellysolve B yielded 0.150 g of an unknown material, mp 180–182° (decomposition and gas evolution), which was not investigated.

Recrystallization of **5**-Cl from benzene–Skellysolve B deposited white needles: mp 157–157.5°; pmr τ 2.3 m (2 aromatic H), 2.8 m (10 aromatic H), 5.14 s (H-5), and 6.70 s (2, H-2).

Anal. Calcd for $C_{21}H_{15}Cl$: C, 83.30; H, 4.99. Found: C, 83.19; H, 5.02.

For **6**-Cl, the pmr spectrum was τ 2.6 m (6 aromatic H), 3.0 m (6 aromatic H), 4.64 s (H-5), 4.96 s (2, H-2).

Ethyl 1-tribenzobicyclo[3.2.2]nonatrienyl ether (**5**-OEt) was obtained in a nitrosyl chloride deamination of **4** as a side product when absolute ethanol was added to the methylene chloride solution before addition of NOCl. Recrystallization gave impure **5**-OEt, mp 152.5–158.5°; pmr τ 2.5 m (2 aromatic H), 2.9 m (10 aromatic H), 5.20 s (H-5), 6.22 q (2, J = 7.5 Hz, OCH_2CH_3), 6.73 s (H-2), and 8.66 t (3, J = 7.5 Hz, OCH_2CH_3).

Reduction of 6-Cl to 1-Methyltriptycene (6-H).—A solution of 156 mg (0.582 mmol) of **6**-Cl in 150 ml of *t*-butyl alcohol was treated with 7 g (0.3 g-atom) of sodium shot for 24 hr. Water was added (*caution!*) until solution was complete. Extraction with benzene, washing of the benzene layer with water, dilute HCl, and saturated NaCl, and drying (Na_2SO_4) gave, after evaporation of the benzene, chromatography on Merck 71707 alumina, and elution with Skellysolve B, 135 mg (97%) of **6**-H, mp (petroleum ether recrystallization) 258–259° (lit.[9] 253–254°); pmr τ 2.6 m (6 aromatic H), 3.0 m (6 aromatic H), 4.62 s (H-5), and 7.64 s (3, CH_3).

Reaction of 5-OH with Thionyl Chloride.—A solution of approximately 200 mg of **5**-OH in 10 ml of reagent grade thionyl chloride was heated at gentle reflux. After 15 hr the reagent–solvent was removed by distillation. Water (2 or 3 drops) was added to hydrolyze unreacted chlorosulfinate ester and the mixture was taken up in acetone. This solution was dried (Na_2SO_4) and the solvent removed by evaporation. Carbon tetrachloride was added to the residual solid and removed by evaporation. Integration of the peaks of the pmr spectrum showed that about 18% of the homotriptycene material was **5**-Cl.

The above sample was resubjected to the same treatment with

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(13) The relative instability of this bridgehead ion **7** may be inferred from the slow transformation with thionyl chloride of **5**-OH *via* **5**-OSOCl to **5**-Cl (half-life about 4 days) compared with the saturated analog 1-bicyclo-[3.2.2]nonanol, which is converted to its chloride in 1 hr.[14]

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(15) (a) J. S. Meek and W. R. Benson, private communication, have rationalized the lack of rearrangement,[15b] when 1-aminodibenzobicyclo-[2.2.2]octadiene is deaminated, on similar grounds: (b) W. R. Benson, Ph.D. Thesis, University of Colorado, 1958. (c) Similarly the 2-adamantyl cation does not rearrange[15d] to the more stable[15e] 1-adamantyl cation on acetolysis. (d) P. von R. Schleyer and R. D. Nicholas, *J. Amer. Chem. Soc.*, **83**, 182 (1961): (e) *ibid.*, **83**, 2700 (1961).

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thionyl chloride. After 70 hr (85 hr total) the isolated material was 50% 5-OH and 50% 5-Cl.

In a parallel experiment approximately 200 mg of 5-OH was set in refluxing thionyl chloride for 14 days. After work-up, a mixture of 17% 5-OH and 83% 5-Cl was separated by column chromatography, using Merck 71707 alumina and petroleum ether, to give 5-Cl, mp and mmp 155.5–156.5°.

Reduction of 5-Cl to Homotriptycene (Tribenzobicyclo[3.2.2]-nonatriene) (1).—A mixture of 3.63 g (0.0116 mol) of 5-Cl and 100 ml of dry *t*-butyl alcohol was stirred in a 250-ml round-bottom flask fitted with a condenser and drying tube. Enough benzene, 30 ml, was added to promote solution and 8.0 g (0.35 g-atom) of sodium metal shot was added in three portions, with dissolution of the sodium occurring between additions. After the sodium metal was completely consumed, the mixture was added to 150 ml of water. The benzene extract (two 150-ml portions) was dried (Na_2SO_4) and the solvent removed to give, after recrystallization from ethanol, 2.89 g (93%) of 1, mp 205.0–205.5°; pmr τ 2.8 m (12 aromatic H), 5.25 s (H-5), 5.82 t, (J = 3.8 Hz, H-1), and 6.80 d (2, H-2).

Anal. Calcd for $C_{21}H_{16}$: C, 93.99; H, 6.01. Found: C, 93.92; H, 6.08.

Preparation of 2-Bromotribenzobicyclo[3.2.2]nonatriene (10-Br).—A mixture of 2.46 g (0.00811 mol) of 1 and 1.44 g (0.00811 mol) of N-bromosuccimimide (NBS) in 150 ml of carbon tetrachloride was set under an unfrosted, 100-W tungsten bulb for 2 hr.[20] The flask and bulb were insulated in order to permit reflux. When the reaction mixture cooled, it was set into a refrigerator at −20° to allow complete crystallization of succimmide, which was removed by filtration. The solvent was distilled *in vacuo*. Four recrystallizations of the initially red-brown residue in benzene–petroleum ether deposited 2.93 g (92%) of 10-Br as thick prisms, mp 192–193.5°; pmr τ 2.8 m (12 aromatic H), 4.20 d (J = 4.5 Hz, H-2), 5.20 s (H-5), and 5.42 d (H-1).

Anal. Calcd for $C_{21}H_{15}Br$: C, 72.63; H, 4.35. Found: C, 72.85; H, 4.45.

In an alternate procedure the imide-free carbon tetrachloride product solution was passed through a pad of activated charcoal. Only one recrystallization was then needed.

Preparation of 2,2-Dibromotribenzobicyclo[3.2.2]nonatriene (11-Br).—Approximately 100 ml of carbon tetrachloride containing 212 mg (0.789 mmol) of 1 and 281 mg (1.58 mmol) of NBS was set under reaction conditions described for the synthesis of 10-Br. The resulting yellow solution was cooled and filtered through a pad of activated charcoal. Evaporation of the colorless solution yielded 248 mg (74%) of 11-Br, mp 217–220°; pmr τ 2.0 m (1 aromatic H), 2.4 m (2 aromatic H), 2.8 m (9 aromatic H), 4.79 s (H-1), and 5.22 s (H-5).

Anal. Calcd for $C_{21}H_{14}Br_2$: C, 59.19; H, 3.31. Found: C, 59.33; H, 3.22.

2-Bromo-1-chlorotribenzobicyclo[3.2.2]nonatriene was prepared from 500 mg (1.65 mmol) of 5-Cl and 332 mg (1.86 mmol) of NBS in 100 ml of CCl_4 as described for 10-Br. The product, after recrystallization from CCl_4, weighed 579 mg (92%), mp 182–185°; pmr τ 1.9 m (2 aromatic H), 2.8 m (10 aromatic H), 4.11 s (H-2), and 5.20 s (H-5).

Anal. Calcd for $C_{21}H_{14}ClBr$: C, 66.00; H, 3.70. Found: C, 66.00; H, 3.61.

Preparation of Methyl 2-Tribenzobicyclo[3.2.2]nonatrienyl Ether (10-OCH_3).—A solution of 106 mg (0.55 mmol) of 10-Br in 10 ml of 1:1 benzene–methanol was heated at reflux for 1 hr. Solvents were removed by rotary evaporation after charcoal filtration, giving 91 mg (100%) of 10-OCH_3, mp 210–214°, mp (after recrystallization from benzene–petroleum ether) 215–216°; pmr τ 2.8 m (12 aromatic H), 5.22 s (H-5), 5.42 d, 5.57 d (J = 4.5 Hz, H-1, H-2), and 6.30 s (3, CH_3).

Anal. Calcd for $C_{22}H_{18}O$: C, 88.56; H, 6.08. Found: C, 88.72; H, 5.91.

Preparation of Ethyl 2-Tribenzobicyclo[3.2.2]nonatrienyl Ether (10-OEt).—Treatment of the crude reaction product from 2.45 g (0.91 mmol) of 1 with 1.62 g (0.91 mmol) of NBS with ethanol gave 2.85 g (100%) of 10-OEt, mp 169–171°; pmr τ 2.8 m (12 aromatic H), 5.21 s (H-5), 5.42 s (2, H-1 and H-2), 6.01 q (2, OCH_2, J = 7.5 Hz), and 8.67 t (3, CH_3).

Anal. Calcd for $C_{23}H_{20}O$: C, 88.43; H, 6.45. Found: C, 88.26; H, 6.38.

(20) This is based upon a general procedure described by I. Koten and R. J. Sauer, *Org. Syn.*, **42**, 26 (1962).

This ether was readily converted to 10-Br by treatment with 50% aqueous HBr at reflux.

Preparation of 2-Tribenzobicyclo[3.2.2]nonatrienone (15).—After a 14-hr reflux, a solution of 213 mg (0.499 mmol) of dibromide 11-Br and 100 mg (1.22 mmol) of anhydrous sodium acetate in 16 ml of 80 vol % aqueous acetic acid was poured into 100 ml of cold water. Ether extraction was followed by washing with water, dilute aqueous Na_2CO_3, and saturated NaCl solutions and evaporation of the ether to give 169 mg of a yellow oil which deposited cubic prisms, 121 mg (86%) of 15, mp 175.5–176.0°, after washing with petroleum ether–benzene; pmr τ 2.0 m (1 aromatic H), 2.7 m (11 aromatic H), 4.77 s, and 4.95 s (H-1 and H-5).

Anal. Calcd for $C_{21}H_{14}O$: C, 89.34; H, 5.00. Found: C, 89.20; H, 5.03.

Preparation of 2-Tribenzobicyclo[3.2.2]nonatrienol (10-OH).—Lithium aluminum hydride (45 mg, 1.1 mmol) in 50 ml of absolute ether was cooled and stirred under a nitrogen blanket as 203 mg (0.723 mmol) of 15 in 100 ml of absolute ether was slowly (0.5 hr) added. After reflux for 1 hr, the reaction mixture was cooled and kept cool during the dropwise addition of water-saturated ether. When the gray solid had completely whitened, the ether solution was filtered.

Recrystallization from cyclohexane of the solid obtained from the above solution by solvent evaporation gave, in two crops, transparent prisms with occluded solvent. Vacuum desiccation for 24 hr was needed to bring the solid to constant weight, 199 mg (97%). Loss of solvent destroyed the prisms and left an opaque solid, mp 162–163°. Prior to the melting point this material liquefied and resolidified at approximately 100°. When the temperature was elevated slowly to 100°, liquefication was substituted by a softening with resolidification; pmr τ 2.8 m (12 aromatic H), 5.15 d (J = 4.5 Hz, H-2), 5.20 s (H-5), and 5.60 d (H-1).

Anal. Calcd for $C_{21}H_{16}O$: C, 88.70; H, 5.67. Found: C, 88.48; H, 5.54.

2-Tribenzobicyclo[3.2.2]nonatrienol-2-*d* (12-OH) was prepared in a similar manner with lithium aluminum deuteride and had initial mp 99–105° and mp 161–162°; pmr (in CCl_4) τ 2.8 m (12 aromatic H), 5.32 s (H-5), and 5.78 s (H-1).

Preparation of 4,4-Dideuteriotribenzobicyclo[3.2.2]nonatriene (11-D).—A pmr tube which contained 546 mg (2.03 mmol) of 1 and 1.5 ml of dimethyl sulfoxide-d_6 (99.5% D, Strohler Isotope Chemicals, Azusa, Calif.) was heated to 90° (variable-temperature controller) in the pmr cavity to maintain solution. After the spectrum of 1 was recorded, 10 mg (0.1 mmol) of potassium *t*-butoxide was added. Vigorous mixing was followed by development of a dark pink color. Deuteration at C-2 reached a constant level, 96%, after 4 hr.

Acetic acid-d_4 (2 drops) was used to neutralize the base. When the solution was added to 50 ml of water, a precipitate formed which was collected by filtration and washed with water. This solid was dried by vacuum desiccation and then dissolved in dichloromethane. The pale yellow solution was decolorized by activated charcoal filtration. Rotary evaporation yielded small prisms (546 mg, 99%). A small portion of this solid was recrystallized from absolute ethanol, mp 205.0–205.5°; pmr τ 2.8 m (12 aromatic H), 5.23 s (H-5), and 5.82 s (H-1).

Preparation of 2-Bromotribenzobicyclo[3.2.2]nonatriene-2-*d* (12-Br).—Bromination of 11-D was performed according to the procedure described for the synthesis of 10-Br. The reaction of 302 mg (1.12 mmol) of 11-D and 199 mg (1.12 mmol) of NBS produced 374 mg (95%) of 12-Br, mp 190–191.5°; pmr τ 2.8 m (12 aromatic H), 5.22 (H-5), and 5.44 (H-1).

Methanolysis of 12-Br.—When 171 mg (0.491 mmol) of 12-Br in 100 ml of absolute methanol was heated at reflux for 2 hr, a slight yellow color developed. The methanol was replaced by dichloromethane and this solution was filtered through activated carbon. Solids recovered from this solution, a 1:1 mixture (pmr) of 2-*d* (12-OCH_3) and 1-*d* (13-OCH_3), methyl 2-tribenzobicyclo-[3.2.2]nonatrienyl ether, were recrystallized from absolute methanol. The first crop, mp 212–213.5°, weighed 77 mg (53%). Subsequent crops totaled 44 mg (30%).

The following methanolyses with added base were also heated at reflux for 2 hr: 48.6 mg (0.140 mmol) of 12-Br in 100 ml of 0.02 M sodium methoxide in absolute methanol, 30.8 mg (0.089 mmol) of 12-Br in 100 ml of 0.001 M sodium methoxide in absolute methanol, 36.8 mg (0.106 mmol) of 12-Br in 20 ml of 0.38 M sodium methoxide in absolute methanol, and 36.8 mg (0.106

mmol) of 12-Br in 20 ml of 3.8 *M* sodium methoxide in absolute methanol.

The samples were treated in the manner described for the neutral methanolysis, but the recovered ethers were not recrystallized. Because the 3.8 *M* methoxide solution contained large amounts of dissolved solids, the solution was poured into water which was then extracted with dichloromethane. After the solution was dried over anhydrous magnesium sulfate, the ethers were isolated by vacuum evaporation. All products were 1:1 12-OCH_3 and 13-OCH_3 by pmr analysis. The pmr spectrum had absorbances at τ 2.8 m (12 aromatic H), 5.25 s (H-5), 5.45 s, and 5.57 s (0.5 proton each, H-1 and H-2).

Silver Ion Assisted Acetolysis of 10-Br.—Compound 10-Br (200 mg, 0.575 mmol) was added to 10 ml of glacial acetic acid which contained 111 mg (0.664 mmol) of silver acetate. The mixture was stirred and heated for 10 min. The reaction flask was cooled; silver bromide was collected by filtration and washed with several portions of ether. The combined filtrates were washed with water, 10% sodium carbonate solution, and saturated sodium chloride. The ether solution was dried ($MgSO_4$) and the ether evaporated to give 186 mg (99%) of 2-tribenzobicyclo[3.2.2]nonatrienyl acetate (10-OAc), mp 177–178°, after recrystallization from benzene–petroleum ether; pmr τ 2.8 m (12 aromatic H), 3.83 d (J = 4.5 Hz, H-2), 5.17 s (H-5) 5.44 d (H-1), and 7.93 s (3, $OCOCH_3$).

Anal. Calcd for $C_{23}H_{18}O_2$: C, 84.64; H, 5.56. Found: C, 84.83; H, 5.73.

Attempted Silver Ion Assisted Acetolysis of 5-Cl and 6-Cl.—A mixture of 202 mg (0.666 mmol) of 5-Cl and 120 mg (0.720 mmol) of silver acetate in 10 ml of glacial acetic acid was set under reflux for 50 hr. The organic solids were isolated according to the procedure outlined above. Only starting chloride was obtained. When the reaction was repeated at 210° for 48 hr, in a sealed tube, starting material was again isolated. Similar experiments with 6-Cl also led to recovery of starting material.

Treatment of Acetates with Perchloric Acid in Acetic Acid.—A solution of 100 mg of 10-OAc in 1 *M* perchloric acid in glacial acetic acid was heated at reflux for 1 hr. Work-up gave only recovered 10-OAc. When the experiment was conducted for 26 hr, the acetate was destroyed and no material could be recovered. Similar treatments of 5-OAc and 6-OAc for 2 hr gave recovery of starting materials.

Pmr Spectra of Some Triptycenes.—Some triptycene derivatives were prepared as synthetic intermediates and it seems reasonable to record their pmr spectra here. The spectrum of triptycene (3)itself has been recorded[16] and our data are consistent: τ 2.7 m (6 aromatic H), 3.1 m (6 aromatic H), and 4.62 s (2, H-9, H-10). New data include: **1-aminomethyltriptycene** (4),[5] τ 2.6 m (6 aromatic H), 3.1 (6 aromatic H), 4.64 s (H-10), and 5.69 broad s, (2, CH_2); **1-triptycenecarboxaldehyde**,[5] τ 2.5 m (6 aromatic H), 3.1 m (6 aromatic H), and 4.66 s (H-10); **1-hydroxymethyltriptycene**[5] (6-OH), τ 2.5 m (6 aromatic H), 3.1 m (6 aromatic H), 4.54 s (H-10), 4.82 d (2, J = 4 Hz, CH_2), and 5.61 t (OH); **1-acetoxymethyltriptycene** (6-OAc), mp 218–221°, prepared from 6-OH with acetic anhydride in pyridine, pmr τ 2.7 m (6 aromatic H), 3.1 m (6 aromatic H), 4.37 s (2, CH_2), 4.64 s (10-H), and 7.85 s ($OCOCH_3$) (*Anal.* Calcd for $C_{23}H_{18}O_2$: C, 84.64; H, 5.56. Found: C, 84.40; H, 5.58.); **1-ethylenedioxymethyltriptycene**,[5] τ 2.5 m (6 aromatic H), 3.0 m (6 aromatic H), 3.73 s (CH(–O)–O), 4.69 s (H-10), and 5.75 m (4, CH_2CH_2); **1-dimethoxymethyltriptycene**,[5] τ 2.6 m (6 aromatic H), 2.9 m (6 aromatic H), 4.14 s (CH(–O)–O), 4.64 s (H-10), and 5.92 s (6, OCH_3).

Registry No.—**1**, 24098-00-8; **4**, 4423-42-1; **5**-OH, 24098-02-0; **5**-OAc, 24098-03-1; **5**-Cl, 24098-04-2; **5**-OEt, 24098-05-3; **6**-Cl, 1469-58-5; **6**-H, 793-39-5; **6**-OH, 1469-57-4; **6**-OAc, 24098-09-7; **10**-Br, 24098-10-0; **10**-OCH_3, 24098-11-1; **10**-OEt, 24098-12-2; **10**-OH, 24098-13-3; **10**-OAc, 24098-14-4; **11**-Br, 24098-15-5; **11**-D, 24098-16-6; **12**-OH, 24098-17-7; **12**-Br, 24098-18-8; **12**-OCH_3, 24098-19-9; **13**-OCH_3, 24098-20-2; **15**, 24098-21-3; 2-bromo-1-chlorotribenzobicyclo[3.2.2]nonatriene, 24098-22-4; 1-triptycenecarboxaldehyde, 1469-54-1; 1-ethylenedioxymethyltriptycene, 1469-55-2; 1-dimethoxymethyltriptycene, 1469-56-3.

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Transition-State Conformations in the Reductive Opening of Cyclopropyl Methyl Ketones[1]

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The transition-state conformations in the lithium–ammonia reduction of three cyclopropyl methyl ketones, **1**–**3**, were determined through trapping of the enolates formed in the process. In the ketones studied, the cisoid conformer was found to predominate in the transition-state population distribution. The conformer population is more cisoid if the cyclopropane ring is unsubstituted or substituted in the 2 position than if it is substituted in the 1 position. The enolate trapping experiments show a similarity between ground-state (as calculated from nmr spectral data) and transition-state conformations in the lithium–ammonia reduction of cyclopropyl methyl ketones.

The importance of transition-state conformational preferences in photochemical excitation[2–4] or lithium–ammonia reductions[5–8] of various conjugated cyclopropyl ketones has been well documented. In the photochemical excitation or the lithium–ammonia reduction of fused-ring conjugated cyclopropyl ketones, fragmentation occurs with the cyclopropane bond that has the better orbital overlap with the adjacent carbonyl π system. The conformational geometry of these ring systems is fixed by the fusion of the two rings.

In acyclic conjugated cyclopropyl alkyl ketones the conformational restraints are removed and the ketone carbonyl is allowed to rotate freely over both bonds of the cyclopropane ring. The lithium–ammonia reduction of acyclic cyclopropyl ketones has also been shown to be a highly selective process[7,8] where the cyclopropane bond that cleaves is controlled by both steric and electronic factors. In the reductive cleavage of *cis*- and *trans*-2-methylcyclopropyl methyl ketone, rupture of the C-1–C-3 bond gives rise to a more thermody-

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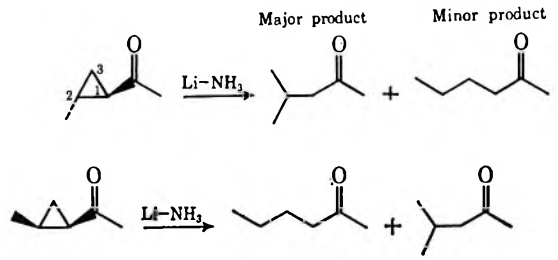
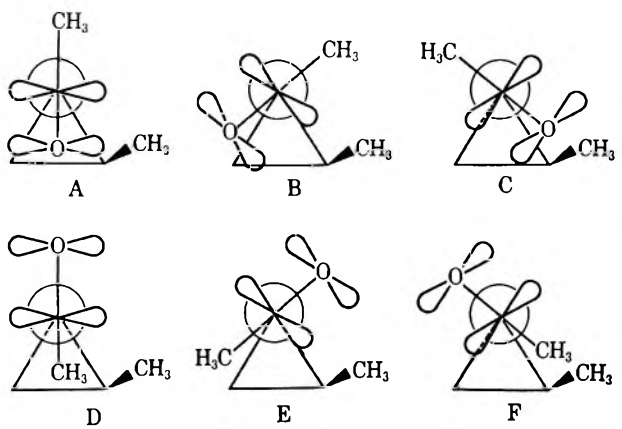
namically stable carbanion intermediate (primary carbanion) than does fragmentation of the C-1–C-2 bond (secondary carbanion). When no steric interaction occurs between the carbonyl group and the 2-methyl substituent (such as is the case with *trans*-2-methylcyclopropyl methyl ketone), ring opening occurs at the



C-1–C-3 bond in accord with relative carbanion stabilities. Reductive cleavage of *cis*-2-methylcyclopropyl methyl ketone, however, occurs with fragmentation of the C-1–C-2 bond leading to the less stable carbanion intermediate. This result suggests a conformational preference in the transition state of the reductive process where one of the cyclopropane bonds has a preferential overlap with the carbonyl π system. In the case of the *cis*-substituted cyclopropane, a steric element causes overlap control of the reaction to be in competition with electronic control. The contrasting ring-opening pattern of the isomeric cyclopropyl alkyl ketones can best be explained by the consideration of several conformers.

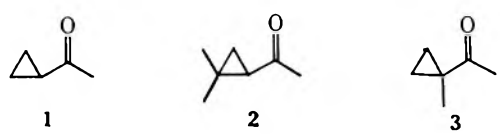


The "bisected conformers A and D represent the situation where both bonds of the cyclopropane ring have equal overlap with the carbonyl π cloud. Because of the high bond-breaking selectivity of the lithium–ammonia reduction it is felt that these conformers contribute little to the transition state at the moment of ring opening. Rather, it is more important to consider the cisoid (B and C) and transoid (E and F) *gauche* conformers. Transition states related to conformations B and E would be expected to lead to C-1–C-2 fragmentation whereas conformations C and F would be responsible for C-1–C-3 cleavage. In the absence of a steric element at C-2, either of the respective *gauche* conformers (B and C or E and F) has equal probability, and the electronic factor controls the reductive process. The rotation of the carbonyl is restricted when a *cis* substituent is present (for transition-state conformations C and F would be expected to be of higher energy). Transition state conformations B and E are preferred and the ring cleavage occurs at the C-1–C-2 bond.

As was previously reported,[8] the product ratio of the ring-opened ketones is insensitive to a variation of size in the reducing metal. This result suggested that the conformation of the transition state did not change significantly because of the increased size of the metal atom. This insensitivity could be due either to the fact that the lithium atom (the smallest atom of the series) was already large enough to establish the preferred conformation or that the transition state conformer was predominantly transoid. Although the high selectivity of the metal–ammonia reduction can be adequately explained by either the cisoid or transoid geometries, the study with various metals suggested a transoid preference, which is in opposition to the findings[9,10] that ground-state conformations of cyclopropyl methyl ketones are predominantly cisoid. The present work was initiated to settle this discrepancy.

The conformational distributions of several substituted cyclopropyl methyl ketones have been calculated from nmr spectral measurements.[9] Owing to the diamagnetic anisotropy of the cyclopropane ring[11] it has been possible to calculate relative ground-state conformer populations. From nmr and electron diffraction data[10] it has been reported that cyclopropyl methyl ketone exists predominantly as the *s-cis* conformer. By way of comparison, cyclopropylcarboxaldehyde is reported[12] to exist mainly as the *s-trans* conformer. These conformational preferences are thought to be owing to the size of the group attached α to the carbonyl carbon. It is conceivable that metal coordination with the carbonyl oxygen could cause a shift in conformational population from a cisoid distribution in the ground state to a transoid population in the transition state.

The compounds chosen for the present study were cyclopropyl methyl ketone (1), 2,2-dimethylcyclopropyl methyl ketone (2), and 1-methylcyclopropyl methyl ketone (3). The lithium–ammonia reduction of a conjugated cyclopropyl ketone can be viewed as an overall two-electron process to give a carbanion–enolate intermediate.[13] The carbanion generated is sufficiently basic ($pK_a > 50$)[14] to abstract a proton from ammonia ($pK_a \sim 34$), but the enolate that remains ($pK_a \sim 16$) is not basic enough to abstract a second proton from ammonia, and it will remain until a proton source is added



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(11) H. M. McConnell, *J. Chem. Phys.*, **27**, 226 (1957).

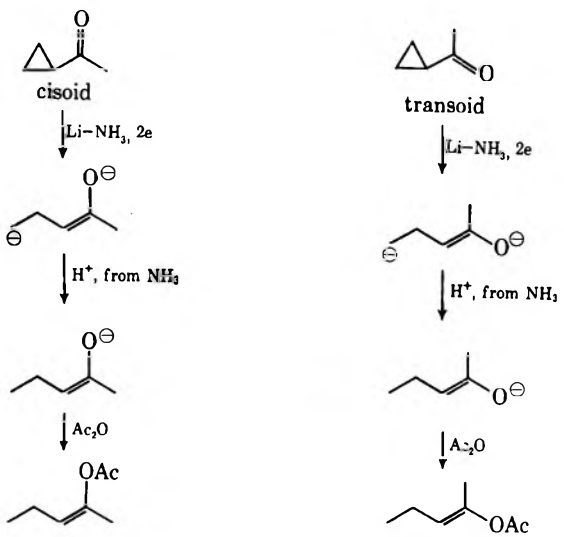
(12) G. J. Karabastos and N. Hsi, *J. Amer. Chem. Soc.*, **87**, 2864 (1965).

(13) Considerable evidence can be found in the literature to support the hypothesis that the β carbon of the cyclopropane ring acquires carbanion character during the reductive process. See (a) D. H. Williams, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **85**, 2091 (1963); (b) M. Fetizon and J. Gore, *Tetrahedron Lett.*, 471 (1966); (c) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, **87**, 275 (1965); (d) H. A. Smith, B. J. L. Huff, W. J. Powers, III, and D. Caine, *J. Org. Chem.*, **32**, 2851 (1967).

(14) H. Smith, "Organic Reactions in Liquid Ammonia," Vol. I, part 2, Interscience Publishers, Inc., New York, N. Y., 1963.

or it is trapped by a reagent such as acetic anhydride.[16] The geometry of the lithium enolate thus formed will be related to the original conformer of the cyclopropyl methyl ketone at the time of ring opening provided that no equilibration of the lithium enolate takes place during the trapping process. This sequence is represented in Scheme I.

SCHEME I



trans-enol acetate 4 *cis*-enol acetate 5

The trapping of enolate anions under kinetic and equilibrating conditions has undergone extensive investigation.[15-17] Lithium enolates are particularly resistant to isomeric equilibration under various trapping conditions and have been used to assess the extent of kinetic control in enolate alkylations.[15,18] The trapping of lithium enolates with acetic anhydride leads only to O-acylated products yielding the respective enol acetates. To demonstrate the slowness of isomeric equilibration relative to trapping with acetic anhydride, House and Trost[17] treated a specific enol acetate with methyl lithium to generate the corresponding lithium enolate. When this enolate was reacylated with acetic anhydride, no detectable interconversion to the other geometrical isomer was observed.

It is also of interest to note that House and coworkers[15-17] were able to separate and identify the structures of several enol acetates. The nmr spectra of the isomeric enol acetates show that the vinylic hydrogen β to the acetoxy function is deshielded in the *cis*-enol acetate relative to that of the *trans*-enol acetate.

With this information as background, it was felt that the lithium enolates formed from a lithium in liquid ammonia reduction would provide information about the transition-state conformational populations of various cyclopropyl methyl ketones. The procedure utilized for enolate trapping was essentially that described by House and Kramar.[15] Following the lithium in liquid ammonia reduction, the ammonia was evaporated and replaced with 1,2-dimethoxyethane. The resulting suspension was added to a cold, freshly distilled solution of acetic anhydride. The products were worked up in the usual manner[15] and identified by their nmr spectra in benzene.[15] The reaction products were contaminated with varying amounts of unreacted starting material and hydrolyzed enolate. The results of these experiments are shown in Table I.

TABLE I

ENOL ACETATE COMPOSITION FROM REDUCTIVE OPENING OF CYCLOPROPYL METHYL KETONES

Ketone	*trans*-Enol[a] acetate, %	*cis*-Enol acetate, %	% enol acetate[b] in product mixture
1	4, 82	5, 18	89
2	6, 88	7, 12	33–65[c]
3	10, 70	11, 30	46

[a] The *trans*-enol acetate corresponds to a cisoid conformation. The ratios are normalized to 100%. [b] The remainder of the product mixture included cyclopropyl ketone and hydrolyzed enolate. [c] The ratio of *trans*- to *cis*-enol acetate was calculated from the major bond-breaking path.

As shown in Scheme I the cleavage of cyclopropyl methyl ketone (1) can lead to two isomeric enol acetates **4** and **5**. The results of Table I show that the predominant conformer at the transition state is cisoid. This result is similar to the conformational preference of the ground-state molecule as found by nmr[9] and electron diffraction data[10] as shown in Table II.

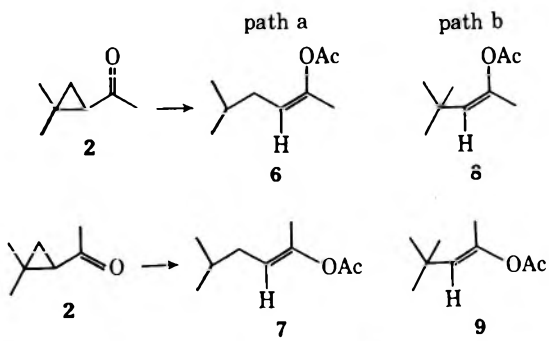
TABLE II

CONFORMATIONAL POPULATIONS OF CYCLOPROPYL METHYL KETONES AS DETERMINED BY VARIOUS METHODS[a]

Method	1	2	3
Electron diffraction[10]	80:20 ± 15%		
Nuclear magnetic resonance[9]	70:30	70:30	50:50
Enolate trapping	82:18	88:12	70:30

[a] The ratio is expressed as cisoid:transoid.

Reduction of 2,2-dimethylcyclopropyl methyl ketone (2) with lithium in liquid ammonia can provide four possible enol acetates **6**, **7**, **8**, and **9**. Enol acetates **6** and **7** are formed from the major reductive path whereas enol acetates **8** and **9** are produced *via* the minor reductive path. The enol acetates **6**, **7**, and **8** were separated on a vpc column (20% XF-1150 cyanosilicone) and were identified by spectral comparisons

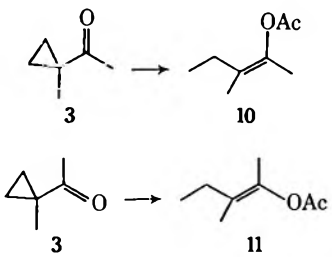


and vpc retention times to independently prepared samples. Enol acetate **9** was not detected in the product mixture, but because of the multiplicity of products its presence could not be ruled out. The result of this trapping experiment clearly shows that the cisoid conformers predominate the transition-state population distribution. Thus, in this case, the transition-state population distribution closely approximates

(15) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963).
(16) H. O. House and B. Trost, *ibid.*, **30**, 1341 (1965).
(17) H. O. House and B. Trost, *ibid.*, **30**, 2502 (1965); see also ref 10c and d.
(18) D. Caine, *ibid.*, **29**, 1868 (1964).

the results reported[9] for the ground-state molecule (see Table II). This fact suggests that the solvated electron-reductive process is very rapid and that little change occurs between the ground-state and transition-state conformations. The insensitivity of the product ratio to a change in the size of the reducing metal is apparently not owing to a transoid geometry.

It had been reported by Pierre and Arnaud[9] that 1-methylcyclopropyl methyl ketone (3) exists as a 50:50 mixture of *cis* and *trans* conformers. One might expect



that a nonbonded interaction between the 1-methyl substituent and the α-methyl group would cause a shift toward more transoid conformers in the ground state. The enolate-trapping results suggest this same trend in the transition state.

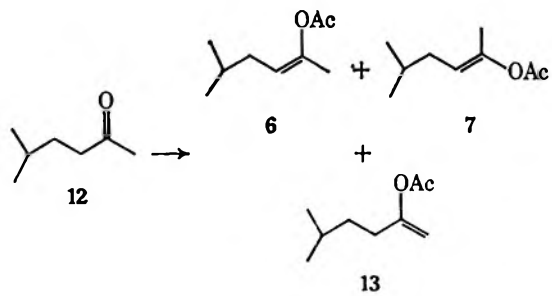
As mentioned earlier, the reductive cleavage of an unsymmetrically substituted cyclopropyl ketone (such as ketone 2) can lead to four isomeric enol acetates. If one examines the ratios of the *trans*-enol acetates **6** and **8**, which come from the same conformer *via* path a or path b cleavage, it is possible to evaluate whether one conformer is responsible for path a cleavage and the other conformer responsible for path b cleavage or whether both reductive paths come from the same conformational distribution. If a cisoid conformer were responsible for all path a type cleavage and a transoid conformer for fragmentation through path b, then one would expect to see a marked contrast in the ratios of the *trans*-enol acetates when compared with the overall reduction product ratio. If both cleavages were resulting from the same conformer distribution, then the *trans*-enol acetate ratios should reflect the overall product ratio. These results are summarized in Table III. From these data it is clear that both

TABLE III
RATIOS OF THE *trans*-ENOL ACETATES 6 AND 8 FROM PATH a OR PATH b CLEAVAGE IN THE LITHIUM–AMMONIA REDUCTION OF KETONE 2

Run	Path a	Path b	Overall product ratio Path a	Path b
1	73	27		
2	80	20		
3	69	31		
Average	77	23	76	24

reductive paths are proceeding from the same conformational equilibrium. The nearly identical ratio of the *trans*-enol acetates to the overall product ratio suggests that the rate of formation of either ring-cleaved product must be of the same order of magnitude.

In order to establish that the enol acetates obtained from this study were kinetic products and properly reflected the conformational equilibrium, the corresponding enol acetates related to isoamyl methyl ketone (12) were prepared under kinetic and equilibrating con-



ditions. The enol acetate ratios obtained under these conditions are compared to the ratios observed in the enolate trapping experiments in Table IV. The relative amounts of each enol acetate found under kinetic or equilibration conditions are in good agreement with the data reported by House[15] for similar compounds. If equilibration had occurred in the enolate-trapping experiments one would have to conclude that the cisoid conformer is even more predominant than indicated by the observed values. Based on the ground-state populations a completely cisoid conformer is unlikely.

TABLE IV
ENOL ACETATE RATIOS OBTAINED UNDER VARIOUS CONDITIONS FROM ISOAMYL METHYL KETONE (12)

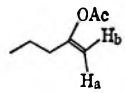
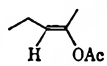
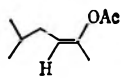
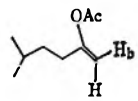
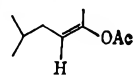
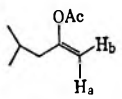
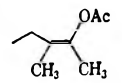
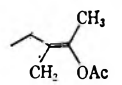
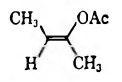
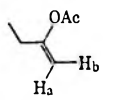
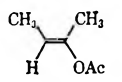
Procedure	6	7	13
Kinetic (isopropenyl acetate, H^+)	58	26	16
Equilibrium (acetic anhydride, H^+)	68	29	3
Enolate trapping	88	12	

The study of the conformational population of 1-methylcyclopropyl methyl ketone (3) presented some interesting complications. The enol acetates **10** and **11** could not be separated on any of the vpc columns at hand (XF-1150 cyanosilicone, SE-30 silicone, and Carbowax 20M). However, the presence of the two isomers was readily apparent when the nmr spectrum in benzene was examined. Two methyl triplets were observed at δ 0.92 and 0.88 in a ratio of 70:30, respectively. The product assignment was made, using the analogy similar to that of House[15] for the β-vinylic hydrogen, on the basis that the isomer with the methyl *cis* to the acetoxy function should be deshielded relative to the isomer with the *trans* methyl–acetoxy relationship. In addition, the vinylic methyl *cis* to the acetoxy group should appear downfield relative to the *trans* methyl. The larger peak (70%) was upfield. Using both peaks it was clear that the major isomer was the *trans*-enol acetate **10** and the minor isomer was *cis*-enol acetate **11**. Double resonance experiments were conducted with the enol acetate mixture. Irradiation of the vinylic methylene region caused a collapse of the two terminal methyl triplets into two singlets. The singlet ratio was 70% **10** to 30% **11**.

In summary, the enolate-trapping experiments clearly show the preference for a cisoid geometry in the transition state of the lithium–ammonia reduction of cyclopropyl methyl ketones. The high bond-breaking selectivity (in the cases where there is a *cis*-2-methyl substituent on the cyclopropane ring) of the process strongly suggests a cisoid *gauche* conformational

TABLE V

ENOL ACETATES. SPECTRAL CHARACTERISTICS

	Structure	Infrared spectrum, ν^{CCl_4} cm^{-1}	Nmr spectrum δ, (benzene) Vinyl H	Nmr spectrum δ, (benzene) Other
4		1750, 1695, 940	4.83	0.86 (t, 3, terminal CH_3, J = 7 Hz)
14		1755, 1665, 870	4.40 H_a 4.60 H_b	0.72 (distorted t, 3 Hz)
5		1750, 1692, 893	5.12	0.83 (t, 3, terminal CH_3, J = 7 Hz)
6		1750, 1692, 935	4.78	0.85 (d, 6, J = 6 Hz)
13		1750, 1660, 870	4.50 H_a 4.68 H_b	0.78 (d, 6, J = 6 Hz)
7		1750, 1690, 910	5.05	0.83 (d, 6, J = 6 Hz)
8		1750, 1695, 943	4.68	1.05 (s, 9)
15		1750, 1660, 870	4.46 H_a 4.75 H_b	0.87 (s, 9)
10		Could not be separated by vpc from the geometric isomer	1.47 (CH_3)	0.92 (t, 3, J = 7 Hz, CH_3–CH_2
11			1.52 (CH_3)	0.88 (t, 3, J = 7 Hz, CH_3–CH_2)
16		1750, 1698	4.78	1.39 (m, 3)
17		1750, 1660	4.50 H_a 4.65 H_b	0.90 (t, 3)
18		1750, 1695	5.06	1.37 (t, 3)

preference rather than a "bisected" geometry in the transition state. It is especially interesting to note the similarity between the transition-state and ground-state conformational populations. This similarity suggests little conformational change between these two states in the lithium–ammonia reduction.

Experimental Section[19]

Enol Acetate Preparations of Aliphatic Methyl Ketones under Kinetic and Equilibrium Conditions.—The procedures described by House and Kramar[15] were followed to prepare the kinetic and equilibrium mixtures of enol acetates from various ketones. The pertinent spectral data are shown in Table V, and the analytical and mass spectral data are tabulated in Table VI.

Kinetic Conditions. 2-Pentanone.—A mixture of 8.6 g (0.1 mol) of 2-pentanone, 20.4 g (0.2 mol) of isopropenyl acetate, and 100 mg of *p*-toluenesulfonic acid monohydrate was stirred at reflux for 27 hr. After the usual work-up[15] the mixture was bulb to bulb distilled under vacuum. The normalized product mixture was composed of 44% *trans*-enol acetate **4** (retention time 18.75 min, 20% XF-1150 cyanosilicone, 150°, 60 psi), 37% 2-acetoxy-1-pentene (**14**) (21 min), and 19% *cis*-enol acetate **5** (24.25 min). The structural assignments were based on the position of the vinylic hydrogen in the nmr spectrum in benzene.

(19) Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord or a 237 grating spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian Associates A-60 or HA-100 spectrometer. Mass spectra were recorded with either a Varian Associates M-66 or a modified Consolidated Electronics Corporations Type 21-103C mass spectrometer. An Aerograph A-90 gas chromatograph, equipped with a 10 ft × 0.375 in., 20% XF-1150 cyanosilicone column, was utilized for the separation of isomeric compounds unless indicated otherwise. Product percentages were determined from vpc trace analyses using either an Aerograph 204 or a Hewlett-Packard F & M Model 5720 gas chromatograph, both of which were equipped with a flame-ionization detector. All materials used were either reagent grade or were purified technical grades. The ammonia was dried by refluxing over sodium for a minimum of 30 min and was distilled directly into a flame-dried reaction vessel. The 1,2-dimethoxyethane was dried by distillation from lithium aluminum hydride. Combustion analyses were performed by the Microanalytical Department of the University of California, Berkeley, Calif.

TABLE VI
ENOL ACETATES. ANALYTICAL DATA

Structure	Molecular formula		% Analysis, Calcd	Found	Mol wt, mass spectrum
4	$C_7H_{12}O_2$	C	65.60	65.36	128
		H	9.44	9.62	
14	$C_7H_{12}O_2$	C	65.60	65.54	128
		H	9.44	9.48	
5	$C_7H_{12}O_2$	C	65.60	65.85	128
		H	9.44	9.70	
6	$C_9H_{16}O_2$	C	69.19	69.06	156
		H	10.32	10.52	
13	$C_9H_{16}O_2$	C	69.19	68.84	156
		H	10.32	10.18	
7	$C_9H_{16}O_2$	C	69.19	69.10	156
		H	10.32	10.61	
8	$C_9H_{16}O_2$	C	69.19	69.33	156
		H	10.32	10.40	
15	$C_9H_{16}O_2$	C	69.19	69.28	156
		H	10.32	10.62	
10 and 11	$C_8H_{14}O_2$	C	67.57	67.42	142
		H	9.22	10.11	

ously under a nitrogen atmosphere and was then pipetted into a flask containing 9.4 g (90 mmol) of cold, freshly distilled acetic anhydride (0–5°) which was also stirred under a nitrogen atmosphere. The suspension was stirred magnetically at room temperature for 4 hr. The product mixture, following the usual work-up, was bulb-to-bulb distilled, and the products were separated and identified by vpc and spectral comparisons to the independently prepared samples. The product distribution was as follows: 2% 2-pentanone, 75% *trans*-enol acetate **4**, 6% cyclopropyl methyl ketone (**1**), and 17% *cis*-enol acetate **5**.

Enol Acetates from 2,2-Dimethylcyclopropyl Methyl Ketone (2).—Following the general reduction and enolate-trapping procedure described for cyclopropyl methyl ketone (**1**) three runs were were made with ketone **2**. During the course of these runs it was observed that the 1,2-dimethoxyethane appeared to be reacting with the excess metal present. This reaction was evidenced by the appearance of the monomethyl ether of ethylene glycol and 1-acetoxy-2-methoxyethane in the product mixture. These two products were not included in the product distribution shown in Table VII.

The relative ratio of enol acetates from the major bond cleavage were 88% *trans*-enol acetate **6** and 12% *cis*-enol acetate **7**. The average of the *trans*-enol acetates **6** and **8** ratios were 73% *trans*-enol acetate **6** and 27% *trans*-enol acetate **8**.

TABLE VII
ANALYSIS OF REACTION MIXTURE FROM 2,2-DIMETHYLCYCLOPROPYL METHYL KETONES

Identification	Relative retention time, min	Relative %, Run 1[a]	Run 2[b]	Run 3[c]
Neopentyl methyl ketone (**19**)	4.8	2	10	3
2,2-Dimethylcyclopropyl methyl ketone (**2**)	6.5	11	20	22
trans-Enol acetate **8**	8.0	16	6	16
Isoamyl methyl ketone (**12**)	9.0	17	34	12
trans-Enol acetate **6**	11.8	43	24	36
Unknown	13	3	2	5
cis-Enol acetate **7**	16	6	3	5
Unknown	17	2	1	1

[a] Started with 1.12 g (10 mmol) of ketone **2**. [b] Started with 0.56 g (5 mmol) of ketone **2**. [c] Started with 1.68 g (15 mmol) of ketone **2**.

The vinylic hydrogen *cis* to the acetoxy function has been shown[15] to absorb at a lower field than the *trans* vinylic hydrogen.

Isoamyl Methyl Ketone (12).—Similar conditions were employed for the preparation of enol acetates as described for 2-pentanone. The product mixture composition was 27% ketone **12**, 43% *trans*-enol acetate **6**, 11% enol acetate **13**, and 19% *cis*-enol acetate **7**.

Neopentyl Methyl Ketone (19).—The product distribution from neopentyl methyl ketone (**19**) was 69% ketone **19** (retention time 12.25 min), 13% *trans*-enol acetate **8** (17.5 min), and 18% of 2-acetoxy-4,4-dimethyl-1-pentene (**15**) (22.5 min). None of the *cis*-enol acetate **9** could be isolated from the product mixture but when a large injection was made on the vpc column a trailing shoulder was observed on the peak of enol acetate **8**. The amount of this isomer **9** was judged to be less than 1%.

Thermodynamic Conditions.—A solution of 5.6 g (49 mmol) of isoamyl methyl ketone (**12**), 10.2 g (100 mmol) of acetic anhydride, and 55.3 mg of *p*-toluenesulfonic acid monohydrate were allowed to stir under reflux for 22 hr. After a similar work-up to that described for the kinetic procedure, the product distribution was found to be 62% ketone **12** (21 min), 26% *trans*-enol acetate **6** (24 min), 1% enol acetate **13** (29 min), and 11% *cis*-enol acetate **7** (32 min).

Enolate Trapping Experiments. Enol Acetates from Cyclopropyl Methyl Ketone (1).—To a 200-ml portion of ammonia was added 0.234 g (35 mg-atoms) of hexane-washed lithium wire. The blue solution was stirred for 30 min under a nitrogen atmosphere and a solution of 1.016 g (12.1 mmol) of cyclopropyl methyl ketone (**1**) in 5 ml of freshly dried 1,2-dimethoxyethane was added over a 5-min period. The blue color disappeared after 1 hr. An additional 0.03 g (4.6 mg-atom) portion of lithium was added to the flask. The blue color returned and persisted for 30 min. The ammonia was allowed to evaporate (4 hr) and to the white salt that remained was added 100 ml of dry 1,2-dimethoxyethane. The milky white suspension was stirred vigor-

Enol Acetates from 1-Methylcyclopropyl Methyl Ketone (3).—Following the procedure outline previously, 1.29 g (15 mmol) of 1-methylcyclopropyl methyl ketone (**3**) was reduced with 0.44 g (63 mg-atoms) of lithium in 200 ml of ammonia. The enolate suspension in 1,2-dimethoxyethane was added to 15.4 g (151 mmol) of cold acetic anhydride. The mixture was stirred for 2 hr and worked up as previously described. Five products were detected and identified as follows. Product A (1.8 min) was assigned the structure of 3-methyl-2-pentanone on the basis of the following data: ir (CCl_4) 1718 (C=O), 1460, 1355, and 1190 cm^{-1}; mass spectrum (prominant peaks) *m/e* 100, 85, 72, 57, and 43 (base peak). Product B (2.8 min) corresponded in retention time to ketone **3**, but the ir spectrum indicated the presence of a minor contaminant (1735, 1245, and 1045 cm^{-1}). No peaks above 98 were observed in the mass spectrum.

The structure of product C (3.3 min) could not be definitively established. The ir spectrum indicated the product to be a cyclopropyl alcohol (3600, 3440, and 3050 cm^{-1}).

Product D (3.7 min) was found to be a mixture of the *trans*- and *cis*-enol acetates **10** and **11**, respectively. They could not be separated on XF-1150 cyanosilicone, SE-30 silicone, or Carbowax 20M columns. When injected on a Carbowax–KOH column, the enol acetates were hydrolyzed to 3-methyl-2-pentanone, which had a retention time coincident with product A. The following data were obtained from the mixture of enol acetates **10** and **11**: ir (CCl_4) 1755, 1370, 1247, 1135, 1010, 915, and 850 cm^{-1}; mass spectrum (prominant peaks) *m/e* 142, 100 (B), 85, and 43.

The nmr spectrum of mixture D showed that the two enol acetates were present in a 70:30 ratio. The major product was assigned as *trans*-2-acetoxy-3-methyl-2-pentene (**10**) based on the following peak positions and relative heights: nmr (CCl_4) δ 1.47 (m, 3, $CH_3C{=}C$) and 0.92 (t, 3, J = 7 Hz, CH_3CH_2). The minor product was assigned the structure of *cis*-2-acetoxy-3-methyl-2-pentene (**11**) on these peaks: δ 1.52 (m, 3, $CH_3C{=}C$)

and 0.88 (t, 3, J = 7 Hz, CH_3CH_2). Irradiation of the methylene region, in a double resonance experiment, collapsed the two terminal methyl triplets (δ 0.92 and 0.88) into two singlets. The ratio of the two singlets was 70:30 as observed previously for the two triplets.

The structure of 1-methano-2-methyl-3-acetoxy-3-butene (4.3 min) was tentatively assigned to product E on the following data: ir (CCl_4) 1780 (C=O), 1670 (C=C), 1220, 1150, 1020, 965, 955, and 900 cm^{-1}. In the mass spectrum, peaks were observed at m/e of 140, 125, 112, 98 (B), and 83. Injection of the enol acetate on the Carbowax–KOH column (hydrolysis) gave a peak which corresponded to the retention time of the starting cyclopropyl ketone **3**.

Registry No.—**4**, 24471-77-0; **5**, 24471-78-1; **6**, 24471-79-2; **7**, 24471-80-5; **8**, 24471-81-6; **10**, 24471-82-7; **11**, 24471-83-8; **13**, 24471-84-9; **14**, 10499-83-9; **15**, 1541-05-5; **16**, 15984-03-9; **17**, 10500-08-0; **18**, 15984-02-8.

Cyclopentadienones from 1,2,4-Cyclopentanetriones, 2-Cyclopentene-1,4-diones, and 3-Cyclopentene-1,2-diones

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Cyclopentadienones may be prepared by enolization of 1,2,4-cyclopentanetriones, 2-cyclopentane-1,4-diones, and 3-cyclopentene-1,2-diones. 2,5-Diphenyl-1,2,4-cyclopentanetrione (**1b**) reacts with 1 and with 2 equiv of sodium hydride to give the corresponding mono- (**5b**) and dianions (**4b**). Dienolate **4b** is converted by benzoyl chloride into 3-benzoyloxy-2,5-diphenyl-2-cyclopentene-1,4-dione (**6**). 3,4-Dibenzoyloxy-2,5-diphenylcyclopentadienone (**10a**), 3,4-di-*p*-anisoyloxy-2,5-diphenylcyclopentadienone (**10b**), and 3,4-diacetoxy-2,5-diphenylcyclopentadienone (**10c**) result from reactions of **1b** with the appropriate acid chlorides in triethylamine. The structures of **10a–c** are established by reaction with N-phenylmaleimide and from the nmr of the resulting 2-norbornen-7-ones (**12a, d, e**). Cyclopentadienone **10b** and benzyne yield 2,3-di-*p*-anisoyloxy-1,4-diphenylnaphthalene (**18**). 3-Methoxy-2,5-diphenyl-2-cyclopentene-1,4-dione (**19**), prepared from **1b** and diazomethane, reacts with sodium hydride to give monoanion **20**, which with *p*-anisoyl chloride results in 4-*p*-anisoyloxy-3-methoxy-2,5-diphenylcyclopentadienone (**10d**). 3-Phenyl-1,2,4-cyclopentanetrione (**1c**), 3-methyl-1,2,4-cyclopentanetrione (**1d**), and 1,2,4-cyclopentanetrione (**1a**) are converted by diazomethane into their corresponding 3-methoxy-2-cyclopentene-1,4-diones (**21, 24,** and **25**). Acid- and base-catalyzed deuterium exchange into **19, 21, 24,** and **25** reveal that the 2-cyclopentene-1,4-diones are converted into hydroxycyclopentadienones and their conjugate bases. Enolization of 3-cyclopentene-1,2-diones has been investigated. Deuterium incorporation into 4-phenyl-3-cyclopentene-1,2-dione (**29a**), 3,4-diphenyl-3-cyclopentene-1,2-dione (**29b**), and 4-methyl-3-cyclopentene-1,2-dione (**29c**) in acid solution and into **29a** and **20b** in basic environments indicate that these systems are converted into their 2-hydroxycyclopentadienones (**31a–c**) and their cyclopentadienone enolates (**30a,b**). Dione **29b** has been prepared by nitrosation of 3,4-diphenyl-2-cyclopentene-1-one (**32**) to 1-oximino-4,5-diphenyl-3-cyclopentene-1,2-dione (**33**), conversion of **33** by formaldehyde in acid solution into 4,5-diphenyl-3-cyclopentene-1,2-dione (**34**), and isomerization of **34** by hot hydrochloric acid to **29b**. The previous structural assignment to 2-oximino-3,4-diphenyl-3-cyclopentene-1,2-dione is incorrect and **34** is a new cyclopentene-1,2-dione.

Cyclopentadienone is a highly reactive monomer whose isolation is yet to be accomplished.[2] Many tetraaryl- and tetraalkylcyclopentadienones[2c,d] and certain tri- and disubstituted cyclopentadienones such as 2,3,5-triphenylcyclopentadienone, 2,3,5-tri-*t*-butylcyclopentadienone,[3a] cyclooctatetraeno-4-methylcyclopentadienone,[3b] 2,5-diphenylcyclopentadienone,[3c] and 2,4-di-*t*-butylcyclopentadienone,[3d] cyclopentadienones containing delocalizing or bulky groups in 2 and/or 5 positions, are stable at 20–30° or may be generated at moderately elevated temperatures. 3-*t*-Butylcyclopentadienone has been prepared; it dimerizes rapidly, however, at −20°.[3d]

A variety of approaches have been used for synthesis or generation of cyclopentadienones.[2d] Of present interest is that cyclopentenediones and cyclopentanetriones are potentially capable of enolizing to substituted cyclopentadienones.[4,5] DePuy, *et al.*, reported on the synthesis and reactions of 2-cyclopentene-1,4-dione[5] and presented evidence for its enolization to 3-hydroxycyclopentadienone and its enolate.[5] Such enolizations to give cyclopentadienone derivatives have had little other study and, as a consequence, serve as the basis for the present investigation.

1,2,4-Cyclopentanetrione (**1a**)[6] exists as its monoenol (**2a**) and as such is a moderately strong acid (pK_a = 3.0), undergoing conversion into its monoenolate (**5a**). A second enolization would give 3,4-dihydroxycyclopentadienone (**3a**) and in a sufficiently basic environment its cyclopentadienone dianion **4a**. Strong electron-donating groups are expected to stabilize cyclopentadienones. Present attempts to demonstrate the existence of **3a** spectroscopically and of **4a** by reaction of **2a** with strong bases have been ambiguous (see Experimental Section). Additional experiments with this system have been deferred, and work with 3,4-diphenyl-

(1) (a) Abstracted in part from the Ph.D. dissertation of C. F. S., The Ohio State University, Columbus, Ohio, 1966. (b) This research was supported by grants from the Union Carbide Chemical Corp., the American Oil Co., the National Science Foundation, and The Ohio State University.

(2) (a) C. H. DePuy, M. Isaks, K. L. Eilers, and G. F. Morris, *J. Org. Chem.*, **29**, 3503 (1964). (b) For reviews of cyclopentadienones, see (c) C. F. H. Allen and S. A. VanAllan, *J. Amer. Chem. Soc.*, **72**, 5165 (1950); (d) M. A. Ogliaruso, M. G. Romanelli, and E. I. Becker, *Chem. Rev.*, **65**, 261 (1965).

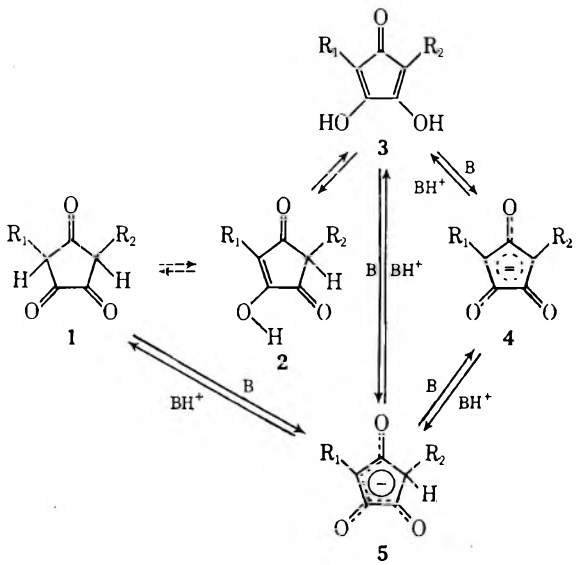
(3) (a) C. Hoogzand and W. Hübel, *Tetrahedron Lett.*, 639 (1961); (b) R. Breslow, W. Vitals, and K. Wandell, *ibid.*, 365 (1965); (c) V. Kruerke and W. Hübel, *Chem. Ber.*, **94**, 2829 (1961); (d) E. W. Garbisch and R. F. Sprecher, *J. Amer. Chem. Soc.*, **88**, 3433 (1966).

(4) (a) F. Kögl, H. Becker, G. deVoss, and E. Wirth, *Justus Liebigs Ann. Chem.*, **465**, 243 (1928); (b) C. F. Koelsch and T. A. Geissman, *J. Org. Chem.*, **3**, 480 (1938);

(5) C. H. DePuy and E. F. Zaweski, *J. Amer. Chem. Soc.*, **79**, 3923 (1957); C. H. DePuy and E. F. Zaweski, *ibid.*, **81**, 4920 (1959); C. H. DePuy and P. R. Wells, *ibid.*, **82**, 2909 (1960).

(6) J. H. Boothe, R. G. Wilkinson, S. Kushner, and J. H. Wilkinson, *ibid.*, **75**, 1732 (1953).

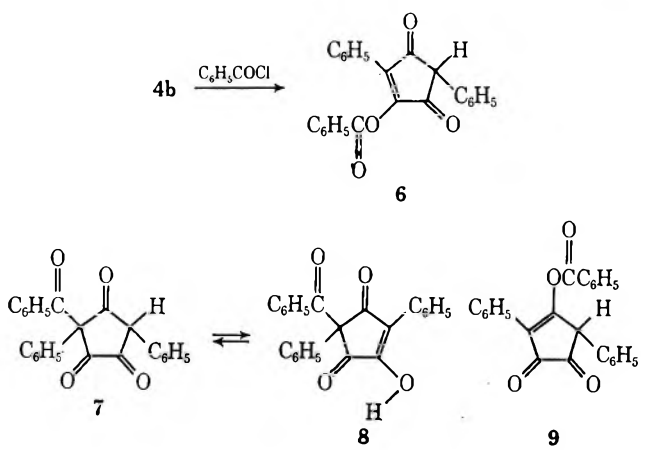
1,2,4-cyclopentanetrione (**1b**)[7] was initiated on the assumption that its phenyl substituents would confer



a, $R_1 = R_2 = H$
b, $R_1 = R_2 = C_6H_5$
c, $R_1 = C_6H_5$; $R_2 = H$
d, $R_1 = CH_3$; $R_2 = H$

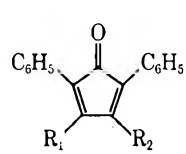
stability to dianion **4b**. It has been reported[7] that **1b** dissolves in aqueous sodium carbonate and in strong alkali to give yellow and deep blue solutions, respectively. It has now been established that these reactions correspond to removal of one and two active hydrogens from **1b**–**2b** to give **5b** and **4b**. The deep blue dianion **4b** is produced along with 1.96 equiv of hydrogen upon reaction of **1b**–**2b** with excess sodium hydride in anhydrous tetrahydrofuran. Acidification of **4b** results in generation of **1b**–**2b**.

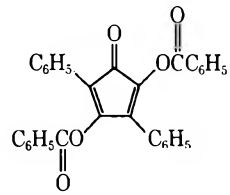
The chemistry of dianion **4b** has been studied. Reaction of **4b** with benzoyl chloride yields, after work-up, 3-benzoyloxy-2,5-diphenyl-2-cyclopentene-1,4-dione (**6**) rather than the desired 3,4-dibenzoyloxy-2,5-diphenylcyclopentadienone (**10a**). Monoester **6** is distinguished from its C-benzoyl isomeric possibilities, **7** and **8**, by its ester carbonyl absorption at 1750 cm^{-1},



the product isolated shows no enolic properties either by ferric chloride or by its infrared absorption (tetraketone **7** is expected to enolize strongly), and its pmr spectrum shows a sharp singlet of relative area 1 at τ 5.8 for a benzylic proton. The possibility that the product is **9** is excluded by experiments to be described.

Triketone **1b** undergoes reaction with excess benzoyl chloride and triethylamine in benzene. Immediately after the reactants are mixed at *ca.* 20°, the solution becomes deep purple, precipitation of triethylamine hydrochloride is rapid, and a material was isolated which crystallizes from ethyl acetate in deep purple needles. The product of dibenzoylation of **1b** is **10a** and not 2,4-dibenzoyloxy-3,5-diphenylcyclopentadienone (**11**) as subsequently proven. Reaction of **6** with





10a, $R_1 = R_2 = C_6H_5CO_2$
b, $R_1 = R_2 = p\text{-}CH_3OC_6H_4CO_2$
c, $R_1 = R_2 = CH_3CO_2$
d, $R_1 = CH_3O$; $R_2 = p\text{-}CH_3OC_6H_4CO_2$

11

benzoyl chloride and triethylamine also give **10a** and thus is consistent with its assigned structure. The infrared spectrum of **10a** shows a broad carbonyl band centered at 1740 cm^{-1} which is probably a composite of aromatic ester and substituted cyclopentadienone frequencies and conjugated carbonyl at 1705 cm^{-1}. The ultraviolet spectrum of **10a** in tetrahydrofuran exhibits maxima at 245 (ϵ 60,000) and 485 mμ (ϵ 7000). For comparison, 2,3,4,5-tetraphenylcyclopentadienone (tetracyclone) absorbs at 262 (ϵ 27,800), 342 (ϵ 6780), and 512 mμ (ϵ 1320).[8]

The pmr spectrum of **10a** shows only aromatic multiplets centered at τ 2.65, 2.35, and 2.0. In contrast, the pmr spectra of many other tetraarylcyclopentadienones exhibit a characteristic sharp singlet at *ca.* τ 2.76 which is attributed to the protons of the unsubstituted 2- and 5-phenyl groups.[9] The nature of the substituents on the phenyl groups at the 3 and 4 positions of a cyclopentadienone has little effect on this signal, even though the substituents may be varied from *p*-N,N-dicthylamino to *p*-nitro and *p*-cyano. The hypothesis has been advanced that electron depletion of the 2- and 5-phenyl groups is responsible for this singlet characteristic.[9] If this is correct, the inductive and/or resonance effects responsible for this electron depletion are radically altered by substitution of benzoyloxy for phenyl as in **10a**.

Substituted cyclopentadienones undergo Diels–Alder reactions as dienes to give norbornene derivatives.[10] Structural proof of **10a** was attempted *via* its addition to dienophiles. Attempts to condense excess tetracyanoethylene with **10a** or with tetracyclone for 4 days at 80° resulted in complete recovery of initial reactants. A possible explanation for the lack of reactivity of the cyclopentadienones is that the adducts suffer severe intramolecular strain. In contrast, both **10a** and tetracyclone react in refluxing benzene with N-phenyl-

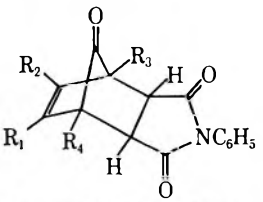
(7) L. Claisen and T. Ewan, *Justus Liebigs Ann. Chem.*, **284**, 245 (1885).

(8) S. B. Coan, D. E. Trucker, and E. I. Becker, *J. Amer. Chem. Soc.*, **75**, 900 (1953).

(9) Unpublished results as summarized in ref 2d.

(10) (a) C. F. H. Allen, R. W. Ryan, and J. A. VanAllan, *J. Org. Chem.*, **27**, 778 (1962); R. F. Doering, R. S. Miner, L. Rothman, and E. I. Becker, *ibid.*, **23**, 520 (1958).

maleimide, a good dienophile but usually less reactive than tetracyanoethylene, to give **12a** and **12b**. These reactions are easy to follow because of the gradual discharge of the intense purple color of the initial cyclopentadienones.

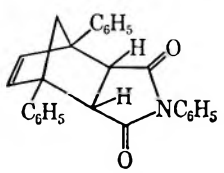


12a, $R_1 = R_2 = C_6H_5CO_2$; $R_3 = R_4 = C_6H_5$
b, $R_1 = R_2 = R_3 = R_4 = C_6H_5$
c, $R_1 = R_3 = C_6H_5CO_2$; $R_2 = R_4 = C_6H_5$
d, $R_1 = R_2 = p\text{-}CH_3OC_6H_4CO_2$; $R_3 = R_4 = C_6H_5$
e, $R_1 = R_2 = CH_3CO_2$; $R_3 = R_4 = C_6H_5$

The pmr spectrum of **12a** shows a sharp singlet of relative area 2 at τ 5.4 (2,3 protons) and multiplets at τ 2.9–2.2 (aromatic protons). The singlet character of the 2,3 protons of **12a** supports the symmetrical structure assigned. If the initial dibenzoyloxydiphenylcyclopentadienone possessed the unsymmetrical structure **11** and consequently gave the Diels–Alder adduct **12c**, the 2,3 protons would likely exhibit different chemical shifts and appear as a doublet.

Present data permit no definite assignment of the stereochemistry of **12a** or **12b**. The Alder rule[11] predicts the product to be *endo* (the 2,3 protons of **12a** and **12b** are thus *exo,exo*). However, *exo* additions of maleic anhydride to 6,6-dimethylfulvene and 6,6-diphenylfulvene have been observed.[12] The stereochemistry of these latter systems presumably results from isomerization of the initial labile *endo* adducts to the more stable *exo* products. A thermodynamic factor in the isomerization apparently involves overlap of the apical double bond with the succinic anhydride moiety in the adducts.

The model compounds possessing some of the steric aspects of **12a** and **12b** were prepared. 1,4-Diphenylcyclopentadiene reacts readily with N-phenylmaleimide and with tetracyanoethylene to form stable adducts (**13** and **14**). The stereochemistry of **13** is assigned as *endo* on the basis of the pmr spectrum shift of the 2,3



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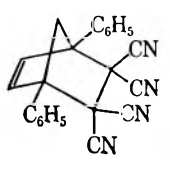

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protons of the succinimide moiety from τ 6.2 to 6.65 following hydrogenation of the norbornene double bond, whereas 2,3 *endo*-proton signals shift downfield.[13] These results thus indicate that in this system the 1,6-bridgehead phenyls do not lead to reaction in which the Alder rule of addition is flouted.

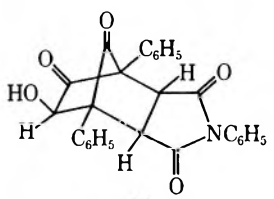
Adduct **14** exhibits the interesting property of reversible color change from colorless to intense blue[14] during recrystallization from ethyl acetate. In this system the phenyl groups at the 1,6-bridgehead positions do not impose sufficient steric strain on the 2,3-*endo,cis* cyano groups to prevent formation of the adduct.

Triketone **1b** reacts with excess *p*-anisoyl chloride and with acetyl chloride in triethylamine to give the substituted cyclopentadienones **10b** and **10c**. The pmr spectrum of **10b** exhibits a sharp singlet at τ 6.17 of relative area 6 (methoxy protons). Hydrogens *ortho* to the methoxy group appear as a doublet at τ 3.07 (J = 8.0 cps) and those *ortho* to the carboxyl group appear as a doublet at τ 1.92. Protons of the 2- and 5-phenyl groups occur as two sets of doublets at τ 2.63 and 2.25. The narrow singlet for the methoxy protons and the simple doublet character of the anisoxy ring protons support the symmetrical structure assigned as **10b**.

The pmr spectrum of **10c** shows a sharp singlet at τ 7.70 of relative area 6 (acetate methyls) and aromatic multiplets centered at τ 2.5. The singlet properties of the methyl protons are in agreement with the symmetrical structure of **10c** rather than the unsymmetrical possibility (the acetoxy analog of **11**).

Cyclopentadienones **10b** and **10c** react with N-phenylmaleimide to give adducts **12d** and **12e**. The pmr spectrum of **12e** shows acetate methyls as a sharp singlet at τ 8.0 of relative area 6 and the 2,3-succinimide protons as a singlet at τ 5.4 of relative area 2. The magnetic resonance of **12e** thus confirms the symmetrical diacetoxy structure assigned as **10c**. No definite stereochemistry is assignable as yet to **12d** and **12e**.

Saponification of adducts **12a**, **10b**, and **10c** is of interest as a possible source of ketol **15** and in particular dianion **16**. Dianion **16** is a homoanalog of deltic acid dianion, $C_3O_3^{2-}$ (**17**), an oxy anion calculated to be of real stability.[15] As yet, however, conversions of **12a**, **10b**, and **10c** into **15** and/or **16** have been unsuccessful.



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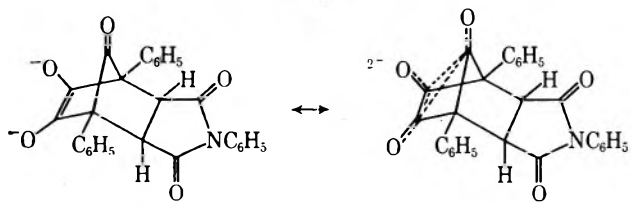
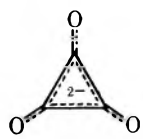


16 **16**

The structure of the blue product arising from saponification of the above Diels–Alder adducts remains to be determined.



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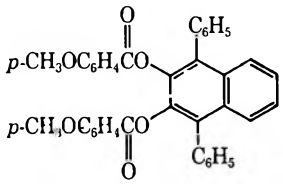
(11) K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937).
(12) J. A. Norton, *Chem. Rev.*, **31**, 319 (1942); (b) R. B. Woodward and H. Baer, *J. Amer. Chem. Soc.*, **66**, 645 (1944).
(13) R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).
(14) The nature of the chromophoric intermediate, possibly a charge-transfer complex, is unknown.
(15) R. West and D. L. Powell, *J. Amer. Chem. Soc.*, **85**, 2577 (1963).

Substituted cyclopentadienones react with benzyne with loss of carbon monoxide to yield naphthalene derivatives.[16] Cyclopentadienone **10b** behaves analogously to benzyne to give 2,3-di-*p*-anisoxy-1,4-diphenylnaphthalene (**18**, 90%). The structure of **18** is established by its elemental analysis and by its pmr and infrared spectra. The latter shows a very narrow carbonyl band at 1735 cm^{-1} (aromatic ester), substituted naphthalene bands at 770–700 cm^{-1}, and no bridged absorption. Saponification of **18** yields the known 1,4-diphenylnaphthalene-2,3-diol.[17]



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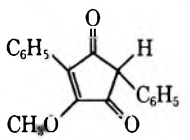
The cyclopentadienone **1b**–enol **2b** system is methylated by diazomethane to 3-methoxy-2,5-diphenyl-2-cyclopentene-1,4-dione[7] (**19**). The pmr spectrum of **19** exhibits a narrow singlet at τ 5.65 of relative area 3 (methoxy protons) and at τ 5.9 of relative area 1



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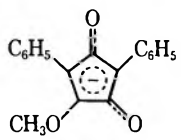
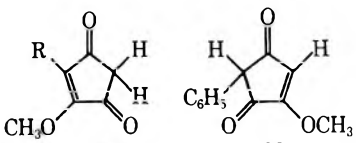


20

(benzyl proton). The infrared spectrum of **19** exhibits carbonyl absorption at 1750 and 1690 cm^{-1}, double-bond absorption at 1600 cm^{-1}, and vinyl ether absorption at 1200 cm^{-1}. It is of note that monoalkylation and acylation of **1b**–**2b** occur on oxygen at C-3 rather than C-1 of the cyclopentadienone.

Reaction of **19** with excess sodium hydride results in release of 1.09 equiv of hydrogen to form the blue monoanion **20**. Acylation of **20** with *p*-anisoyl chloride yields 4-*p*-anisoxy-3-methoxy-2,5-diphenylcyclopentadienone (**10d**) as scarlet needles. The pmr spectrum of **10d** shows a pair of narrow singlets of equal intensity, both of relative area 3, at τ 6.38 and 6.17, attributable to methoxy and to anisoxy protons, respectively. Protons of the 2- and 5-phenyl rings occur as a sharp singlet at τ 2.67 and a multiplet at τ 2.3. The ring proton of the *p*-anisoxy substituent gives the same pattern as that for **10b**; the overall pmr properties of **10d** are thus in agreement with the structural assignment.

Reactions of diazomethane with 1,2,4-cyclopentanetriones which are less substituted than **1b** have been investigated. The orientation in methylation of these systems and deuterium exchange of the products thereof are of present interest. 3-Phenyl-1,2,4-cyclopentanetrione (**1c**)[18] exists extensively as a yellow enol whose infrared absorption indicates that its hydroxyl group is highly intramolecularly hydrogen bonded. The principal enol of **1c** is apparently **2c** and it reacts with diazomethane to yield a yellow solid assigned as 3-methoxy-2-phenyl-2-cyclopentene-1,4-dione (**21**). The pmr spectrum of the product exhibits a narrow



21, R = C_6H_5
24, R = CH_3
25, R = H

22

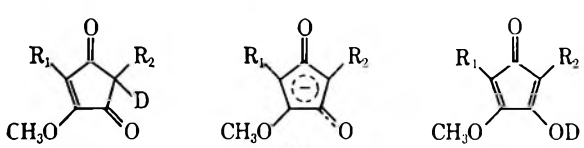
23

singlet at τ 7.05 of relative area 2 (methylene protons) and at τ 5.70 (methoxy protons), and two sets of multiplets centered at τ 2.6 and 2.1 (phenyl protons). The pmr results (vinyl protons are absent) discount **22** as the structure of the product. There is no direct evidence which eliminates **23** as the methylation product; however, on the basis of the structure of the parent enol (**2c**), possible minimum change during reaction of **2c**, and previous experience in methylation and acylation of **1b**–**2b**, it is very likely that the methyl ether is **22**.

3-Methyl-1,2,4-cyclopentanetrione (**1d**)[19] is also highly enolic and intramolecularly hydrogen bonded. Its enol is apparently principally **2d**. Diazomethane rapidly methylates the **1d**–**2d** system, yielding a white solid assigned as 3-methoxy-2-methyl-2-cyclopentene-1,4-dione (**24**). The pmr spectrum of **24** reveals methylene protons at τ 7.05 and methoxy protons at τ 5.65; there is no absorption for vinyl hydrogen. The structure is indicated as **24** rather than as 4-methoxy-3-methyl-3-cyclopentene-1,2-dione because of precedent with **19** (and **21**) and because of mechanistic considerations.

Methylation of the parent 1,2,4-cyclopentanetrione system, **1a**–**2a**, also occurs efficiently to give the white solid, presumably 3-methoxy-2-cyclopentene-1,4-dione (**25**). The infrared spectrum of the ether indicates carbonyl absorption at 1760 and 1695 cm^{-1}; olefinic absorption occurs at 1600 cm^{-1} and vinyl ether absorption occurs at 1220 cm^{-1}. The pmr spectrum of the product shows methylene protons at τ 7.05, methoxy protons at τ 6.0, and a vinyl proton at τ 3.6, all as sharp singlets. The possible structure, 4-methoxy-3-cyclopentene-1,2-dione, is eliminated for reasons cited previously for **23**.

Introduction of deuterium into the methoxy ethers **19**, **21**, **24**, and **25** from deuterium oxide has been examined in basic and in acidic environments. Rapid exchange of benzyl hydrogen occurs in **19** in mixtures of deuterium oxide, triethylamine, and tetrahydrofuran. The deuterium content in recovered **26a** is determined



26

27

28

a, $R_1 = R_2 = C_6H_5$
b, $R_1 = C_6H_5$; $R_2 = H$
c, $R_1 = CH_3$; $R_2 = H$
d, $R_1 = R_2 = H$

(16) F. M. Beringer and S. J. Huang, *J. Org. Chem.*, **29**, 445 (1964).

(17) M. S. Newman, personal communication of unpublished results and gift of comparison sample.

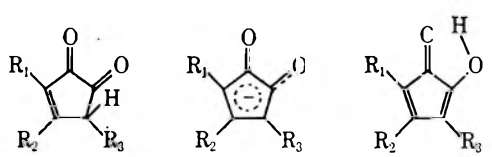
(18) W. Wislicenus and F. Melms, *Justus Liebigs Ann. Chem.*, **436**, 101 (1924).

(19) M. Orchin and L. W. Butz, *J. Amer. Chem. Soc.*, **65**, 2296 (1943).

from the residual benzyl pmr signal at τ 5.9. During the exchange experiment the tetrahydrofuran solution is dark violet. The color may be due to perceptible concentrations of its enolate **27a**. The ethers **21** and **24** exchange their methylene protons completely in deuterium oxide–triethylamine; pmr signals for methylene protons in recovered **26b** and **26c** are absent. It is thus clear that **19**, **21**, and **24** are converted into their cyclopentadienone-3-oxide anions **27a–c** and that the enolization behavior of these 2-cyclopentene-1,4-dione derivatives parallels that of the parent diketone.[5] Study of base-catalyzed deuterium incorporation in **26** is inconclusive as yet, because the diketone is rapidly destroyed in the alkaline environment.

Deuterium exchange into benzyl or methylene positions in **19**, **21**, **24**, aud **25** occurs extensively (>85%) in deuterium oxide containing catalytic quantities of hydrochloric acid. The deuterium content of the recovered diketones was determined by pmr methods. It is reasonable to infer that 3-deuterioxy-4-methoxycyclopentadienones (**28a–d**) are generated as intermediates in these experiments.

A study has been initiated of enolization of 3-cyclopentene-1,2-diones (**29a–c**) in the presence of bases and of acids. Such diones might be expected to undergo facile conversion into their cyclopentadienone monoanions (**30a–c**), because these enolates contain a powerful electron-donating group (O) in the 2 position and allow extended delocalization effects.[20] Enols (**31a–c**) derived from these diones also have the possible advantages of strong electron release at C-2 and of extended conjugation[21] along with contributions involving intramolecular hydrogen bonding.



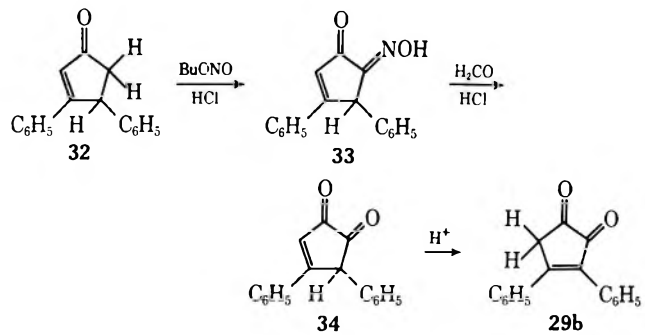
29 **30** **31**

a, $R_1 = R_3 = H$; $R_2 = C_6H_5$
b, $R_1 = R_2 = C_6H_5$; $R_3 = H$
c, $R_1 = R_2 = H$; $R_3 = CH_3$

4-Phenyl-3-cyclopentene-1,2-dione (**29a**)[21] undergoes deuterium exchange for its methylene hydrogens when suspended in deuterium oxide containing sodium acetate, and thus appears to involve enolate **30a** as an intermediate.[22] Deuterium is also exchanged for methylene hydrogens in **29a** in hot solutions of deuterium oxide and deuterioacetic acid containing traces of hydrochloric acid. The slow exchange of deuterium into **29a** presumably occurs *via* enol **31a** or its tautomer.

Study of enolization of 3,4-diphenyl-3-cyclopentene-1,2-dione (**29b**) then became of interest. This diketone has been previously reported[23] as the product of hydrolysis of 2-oximino-3,4-diphenyl-3-cyclopentene-1,2-dione as obtained from 3,4-diphenyl-3-cyclopentene-1-one,[24a] butyl nitrite, and hydrochloric acid. It later became apparent,[24b] on the basis of its ultraviolet absorption, that the initial cyclopentenone is 3,4-diphenyl-2-cyclopenten-1-one (**32**), and thus the structural assignment to **29b** is subject to question.

It has now been found that **32** reacts with butyl nitrite and hydrochloric acid to give 1-oximino-4,5-diphenyl-3-cyclopentene-1,2-dione (**33**). Exchange of **33** with formaldehyde in hydrochloric acid–glacial acetic acid at 30° yields 4,5-diphenyl-3-cyclopentene-1,2-dione (**34**). In refluxing hydrochloric acid–acetic acid **34** is converted into **29b**; similarly, **33** is deoximated and isomerized to **29b** by formaldehyde in hot hydrochloric acid–acetic acid. The previous structural assignment to **29b** is thus correct; however, that to 2-oximino-3,4-diphenyl-3-cyclopentene-1,2-dione is in error and **34** is a new diphenylcyclopentene-1,2-dione.[25]



32 **33** **34** **29b**

Dione **34** is refluxing deuterium oxide–deuterioacetic acid containing a trace of hydrochloric acid yields the rearranged diketone **29b** completely deuterated in the methylene position. Undeuterated **29b** under the same conditions also shows complete exchange of methylene protium for deuterium. These observations, along with the isomerization of **34** to **29b**, indicate that **34** and **29b** undergo enolization to **31b** and its enol isomer. The results, however, do not indicate whether **34** exchanges deuterium to give deuterated **34** prior to isomerization to deuterated **29b**.

4-Methyl-3-cyclopentene-1,2-dione (**29c**) is important to the development of the present theory of stabilized cyclopentadienones, since it is reported to give a ferric chloride test[26a] and is presumed to have enolic properties.[26b] It has been presently observed that **29c** does indeed give a positive ferric chloride reaction in aqueous solution and loses its protium in deuterium oxide containing traces of hydrochloric acid. The detailed chemistry of **29c** is not yet completely clear, particularly in alkaline solution. Study of **29c**, 3-cyclopentene-1,2-dione, and 1,2,3-cyclopentanetrione is in progress.

Experimental Section

Properties of 1a.—Solutions of **1a**[27] in water or methanol give positive ferric chloride tests and show strong broad enolic absorption (hydrogen bonded) at 3100 cm^{-1} and ultraviolet maxima at 305 and 225 mμ (ϵ 48,500). The triketone survives hot concentrated hydrochloric acid and reacts rapidly with aqueous sodium bicarbonate with evolution of carbon dioxide to give solutions, λ_{max} 308 mμ (ϵ 12,900). In excess 10% aqueous sodium

(20) Enolates and enols of 2-cyclopentene-1,4-diones are cross conjugated.

(21) S. Wawzonek and C. E. Morreal, *J. Amer. Chem. Soc.*, **82**, 439 (1960).

(22) In homogenous solution in deuterium oxide–tetrahydrofuran mixtures containing triethylamine, sodium carbonate, or sodium bicarbonate, **29a** is converted into products other than its simple deuterated analog.

(23) T. A. Geissman and C. F. Koelsch, *J. Org. Chem.*, **3**, 489 (1938).

(24) (a) F. R. Japp and E. Miller, *J. Chem. Soc.*, **47**, 27 (1885); (b) C. F. H. Allen and J. A. VanAllan, *J. Amer. Chem. Soc.*, **77**, 2315 (1955).

(25) For detailed evidence relative to the structures of **29b** and **32–34**, see Experimental Section. Reaction of **29b** with hydroxylamine yields an oxime (see Experimental Section) isomeric with **33**. It is likely that the oxime is 1-oximino-3,4-diphenyl-3-cyclopentene-1,2-dione.

(26) (a) E. Dane, J. Schmitt, and C. Rautenstrauch, *Justus Liebigs Ann. Chem.*, **532**, 29 (1937); (b) G. Singh, *J. Amer. Chem. Soc.*, **78**, 6109 (1956).

(27) Prepared by the method of ref 6.

hydroxide 1a has λ_{max} 261 mμ (ε 52,500); however, the chemistry of this system has not been elaborated. Solutions of 1a in dimethylformamide react sluggishly with sodium hydride with evolution of 1 equivalent of hydrogen and formation of an insoluble monosodium salt which resists further reaction with sodium hydride. Benzoyl chloride (2 equiv) and 1a in excess triethylamine give intractable products. Excess bromine in dioxane reacts with 1a at 0° to yield, after sublimation at 100° (0.3 mm), 2-bromo-1,3,4-cyclopentanetrione as white crystals: yield 0.40 g (44%); mp 152–153°; ir 3120 (enol), 1760, and 1700 cm^{-1} (C=O); pmr τ 6.83 (CH_2) and 0.00 (enol H). Efforts to dibrominate 1a with bromine or N-bromosuccinimide were unsuccessful.

Anal. Calcd for $C_5H_3BrO_3$: C, 31.35; H, 1.67; Br, 41.75. Found: C, 31.19; H, 1.87; Br, 41.62.

Reaction of the Dilithium Salt of 1b with Benzoyl Chloride.—A solution of 1b (1.00 g, 0.0076 mol), enol absorption at 3220 cm^{-1}, in tetrahydrofuran (25 ml) was treated under nitrogen with butyllithium (9 ml, 15% by weight in hexane, 0.015 mol). A solution of benzoyl chloride (2.2 g, 0.0157 mol) in tetrahydrofuran was added rapidly with stirring. The blue color was quickly discharged and a yellow solution resulted. The reaction mixture was refluxed for 4 hr, cooled, and poured over ice. The aqueous mixture was extracted with ether. A crystalline material began separating from the ether and was collected. The solvent was removed and the residue was combined with the precipitate. The product was recrystallized from benzene–hexane to give 6 as yellow needles: yield 1.2 g (43%); mp 161–161.5°; ir 1750, 1690, 1340, 1230, 1080 (split peak), 725, and 705 cm^{-1}; uv max ($CHCl_3$) 310 (ε 27,000) and 235 mμ (ε 34,5000).

Anal. Calcd for $C_{24}H_{16}O_4$: C, 78.30; H, 4.35. Found: C, 78.44; H, 4.19.

Reaction of 1b with Benzoyl Chloride.—A stirred suspension of 1b (6.35 g, 0.026 mol) in dry benzene (150 ml) upon addition of triethylamine (15 ml, 0.107 mol) gave a violet solution. Benzoyl chloride (10 g, 0.076 mol) in benzene (30 ml) was added (10 min), and a dark purple solution formed. The solution was stirred at room temperature for 12 hr and filtered free of amine salts. The filter cake was washed with benzene and the filtrates were combined. The solvent was removed to give a pasty red solid which was recrystallized from ethyl acetate–hexane to give 10a as large, purple needles: yield 5.75 g (47%); mp 182–184°; uv max (tetrahydrofuran) 245 (ε 60,000) and 485 mμ (ε 43,000).

Anal. Calcd for $C_{31}H_{20}O_5$: C, 78.80; H, 4.27. Found: C, 79.14; H, 4.27.

Reaction of 6 with Benzoyl Chloride.—A solution of 6 (0.39 g, 0.00106 mol), benzoyl chloride (0.23 g, 0.00165 mol), and triethylamine (2.5 ml, 0.0175 mol) in tetrahydrofuran (15 ml) was refluxed for 8 hr. The solution was filtered and the solvent was removed to give a dark red residue. Recrystallization from ethyl acetate–hexane resulted in dark needles of 10a, yield 0.25 g (50%), mp 180–182°, identical with that described previously.

Reaction of 10a and N-Phenylmaleimide.—A solution of 10a (2.01 g, 0.0043 mol) and N-phenylmaleimide (1.50 g, 0.0087 mol) in dry benzene (100 ml) was refluxed for 14 hr. At the end of this time, the intense purple color of 10a had disappeared and a clear, yellow solution resulted. Filtration and removal of solvent yielded a fluffy, amorphous product, mp 175–197°. Chromatography on silica gel (120 g, British Drug House) and elution with benzene (120 ml) led to recovery of N-phenylmaleimide (0.638 g). Elution of the column with methylene chloride (150 ml) and removal of solvent gave 12a as white needles: yield 2.19 g (67%); mp 208–208.5° from ethyl acetate–hexane.

Anal. Calcd for $C_{41}H_{27}NO_7$: C, 76.27; H, 4.20; N, 2.18. Found: C, 76.37; H, 4.28; N, 2.28.

Reaction of Tetracyclone and N-Phenylmaleimide.—Tetracyclone (3.00 g, 0.0072 mol) and N-phenylmaleimide (2.70 g, 0.0157 mol) was refluxed in dry benzene (100 ml) for 10 hr. The yellow solution was filtered and the solvent was removed. Recrystallization of the yellow glass from ethyl acetate–hexane gave 12b as white needles: yield 2.6 g (64%); mp 215–216.5°; ir 1760, 1710, 1480, 1360, 1180, 770, and 690 cm^{-1}; pmr multiplet (aromatic) and τ 5.3 (s, N-phenylsuccinimide moiety protons).

Anal. Calcd for $C_{39}H_{27}O_3N$: N, 2.51. Found: N, 2.46.

Reaction of 1,4-Diphenylcyclopentadiene and N-Phenylmaleimide.—1,4-Diphenylcyclopentadiene[28] (2.00 g, 0.0092 mol) and N-phenylmaleimide (1.85 g, 0.011 mol) were refluxed in dry benzene (20 ml) for 14 hr. Removal of the solvent resulted in yellow oil which crystallized. Recrystallization from ethyl acetate–hexane gave 13 as white needles: yield 2.2 g (60%); mp 165.5–166.2°; ir 1712 (C=O) and 1770 cm^{-1} (imide); pmr τ 7.7 (s, apical CH_2), 6.25 (s, N-phenylsuccinimide protons), and 3.45 (s, vinyl).

Anal. Calcd for $C_{27}H_{21}O_2N$: C, 82.92; H, 5.38; N, 3.58. Found: C, 83.09; H, 5.49; N, 3.55.

A solution of 13 (0.61 g, 0.00156 mol) in ethyl acetate (25 ml) was shaken with Pd–C catalyst (*ca.* 10 mg) and hydrogen (40 psi) for 2 hr. Filtration of the hot solution and removal of solvent left off-white crystals. Recrystallization (charcoal) from ethyl acetate–hexane gave the 5,6-dihydro adduct of 13: yield 0.52 g (85%); mp 210.8–212.0°; ir 1735, 1510, 1395, 1200 (split peak), 770 (split peak), 740, and 700 cm^{-1}; pmr τ 7.85 (s, apical CH_2), 7.58 (q, J = 10 cps, apparently the 5,6 CH_2), 6.55 (s, succinimide moiety protons), and 2.8 and 2.3 (m, phenyl protons). Comparison with the pmr spectrum of 13 shows a shift of 17 cps (from τ 6.25) of the succinimide moiety protons, indicating their probable *exo* configuration.[13]

Reaction of 1,4-Diphenylcyclopentadiene and Tetracyanoethylene.—Tetracyanoethylene (0.62 g, 0.0004 mol) and 1,4-diphenylcyclopentadiene were refluxed in benzene (25 ml) for 20 min. The precipitate from the cooled reaction mixture was washed with cold 50% benzene in hexane. Recrystallization from ethyl acetate–hexane gave 14 as white needles, yield 0.90 g (59%), mp 164.5–165.4° dec. Adduct 14 gives deep blue solutions in hot ethyl acetate. The color quickly fades as the crystals deposit during cooling. Identical behavior results during recrystallization of 14 from ethanol, with the exception that the supernatant liquid retains its blue color.

Anal. Calcd for $C_{23}H_{14}N_4$: C, 79.83; H, 3.95; N, 16.20. Found: C, 79.95; H, 4.00; N, 15.96.

Reaction of 1b with *p*-Anisoyl Chloride.—A solution of 1b (4.0 g, 0.0157 mol) and triethylamine (7.15 g, 0.071 mol) in benzene (100 ml) was stirred with *p*-anisoyl chloride (10.0 g 0.059 mol) for 24 hr and filtered, and the solvent was removed. Recrystallizations of the product from ethyl acetate yielded 10b as red needles: yield 5.6 g (65%); mp 169–171°; ir 1715 cm^{-1} (C=O); uv max (tetrahydrofuran) 482 (ε 4000) and 265 mμ (ε 61,000).

Anal. Calcd for $C_{33}H_{24}O_7$: C, 74.60; H, 4.45. Found: C, 74.77; H, 4.68.

Reaction of 1b with Acetyl Chloride.—To 1b (2.0 g, 0.079 mol) and triethylamine (4.0 g, 0.028 mol) in dry benzene (100 ml) was added acetyl chloride (2.5 g, 0.032 mol) in benzene (20 ml) during 20 min. The solution was stirred for 2 hr and filtered, and the solvent was evaporated. Recrystallization of the solid from absolute ethanol resulted in 10c as dark red needles: yield 0.79 g (30%); mp 165–168° dec; ir 1770 (acetate C=O) and 1712 cm^{-1} (cyclopentadienone C=O); uv max 485 (ε 1570) and 254 mμ (ε 40,000).

Anal. Calcd for $C_{21}H_{16}O_5$: C, 70.52; H, 4.47. Found: C, 70.65; H, 4.70.

Reaction of 10b and N-Phenylmaleimide.—A mixture of 10b (1.61 g, 0.003 mol) and N-phenylmaleimide (0.911 g, 0.0053 mol) in benzene (40 ml) was refluxed for 22 hr. Removal of solvent gave a tacky solid which was extracted with boiling ethyl acetate to yield 12d as white needles, yield 1.60 g (75%), mp 225–227.50°, recrystallized from benzene–hexane, mp 226–227.5°.

Anal. Calcd for $C_{41}H_{31}O_9N$: C, 69.00; H, 4.35; N, 1.96. Found: C, 69.17; H, 4.21; N, 2.10.

Reaction of 10c and N-Phenylmaleimide.—A mixture of 10c (0.600 g, 0.00168 mol) and N-phenylmaleimide (0.4 g, 0.0023 mol) in benzene (20 ml) was refluxed for 25 hr. The yellow solution was filtered and the solvent was removed. Recrystallization of the light tan product from ethyl acetate–hexane gave 12e as white crystals, yield 0.60 g (68%), mp 225–226°.

Anal. Calcd for $C_{31}H_{23}O_7N$: C, 71.21; H, 4.41; N, 2.68. Found: C, 71.41; H, 4.49; N, 2.57.

Reaction of 10b with Benzyne.—A mixture of 10b (4.0 g, 0.0075 mol) and isoamyl nitrite (2.3 g, 0.0196 mol) in dry tetrahydrofuran (100 ml) was brought to reflux. Anthranilic acid (2.6 g, 0.0190 mol) in tetrahydrofuran (15 ml) was added during 1 hr. Filtration and removal of solvent gave a brown oil which crystallized overnight. Extraction with hot ethanol gave tan crystals, mp 217–276°. Recrystallizations from benzene–hexane (charcoal) gave 18 as white needles: yield 3.96 g (91%); mp 283–

(28) S. G. Cohen, R. Zand, and C. Steel, *J. Amer. Chem. Soc.*, **83**, 2895 (1961).

285°; ir 1735–1740 cm^{-1} (ester C=O) but no bridge C=O); pmr τ 6.28 (s, 6, OCH_3) and 3.40–2.16 (m, 22, aromatic protons).

Anal. Calcd for $C_{38}H_{28}O_6$: C, 78.60; H, 4.86. Found: C, 78.75; H, 4.89.

Saponification of 18.—A solution of **18** (0.318 g, 0.00055 mol) in 5% ethanolic potassium hydroxide (10 ml) was refluxed for 7 hr. The cooled mixture was poured into cold 10% hydrochloric acid (25 ml). The yellow precipitate was filtered, washed free of acid, stirred for 2 hr with 5% potassium carbonate (5 ml), filtered, washed, and dried. Recrystallization from benzene (charcoal) gave **19**, yield 0.12 g (70%), mp 239–240° (lit.[17] mp 241–242°). A mixture of **19** with authentic 2,3-dihydroxy-1,4-diphenylnaphthalene has a melting point of 238–239°. The infrared spectra of the two materials are superimposable.

Reaction of 1b and Diazomethane.—A suspension of **1b** (3.0 g, 0.0113 mol) in ether (70 ml) was stirred with an ether solution of diazomethane until evolution of nitrogen ceased. Excess diazomethane was removed by evaporation of half the ether; addition of an equal volume of petroleum ether (bp 30–60°) and chilling at 0° gave yellow crystals, mp 90–92°. Recrystallization from cyclohexane resulted in 2.3 g (73%) of **19**: mp 94.0–94.8° (lit.[7] mp 94–95°); ir 1750, 1690 (split peak), 1590, 1450, 1350, 1320, 950, 782, and 735 cm^{-1}; uv max 320 (ϵ 11,500) and 238 mμ (ϵ 14,000).

Reaction of 19 with *p*-Anisoyl Chloride.—A solution of **19** (2.00 g, 0.0072 mol) and triethylamine (5 ml, 0.035 mol) in benzene (80 ml) was added to *p*-anisoyl chloride (2.0 g, 0.0117 mol) in benzene (20 ml) in 20 min. The mixture was stirred for 12 hr and filtered, and the solvent was removed. Attempts to recrystallize a small portion of the red oil from absolute ethanol resulted in decomposition of the product. The material showed similar instability to steam. Recrystallization from ether–pentane at −10° gave silky, scarlet needles of **10d**: yield 0.95 g (32%); mp 130–130.8°; uv max (tetrahydrofuran) 482 (ϵ 6700) and 260 mμ (ϵ 30,000).

Anal. Calcd for $C_{26}H_{20}O_5$: C, 75.71; H, 4.88. Found: C, 76.00; H, 5.01.

Reaction of 1c and Diazomethane.—A suspension of **1c** (2.1 g, 0.0114 mol) in ether (70 ml) was stirred with excess diazomethane in ether at 0°. Concentration of the mixture and sublimation (60°, 0.3 mm) of the product yielded **21** as yellow needles: yield 0.80 g (35%); mp 56.0–56.8° (lit.[19] mp 54–55°); ir 1750 and 1690 (conjugated C=O), 1605 (C=CC_6H_5), and 1200 cm^{-1} (vinyl ether); uv max (tetrahydrofuran) 235 (ϵ 13,000) and 305 mμ (ϵ 11,000).

Reaction of 1d and Diazomethane.—A suspension of **1d**[20] (2.22 g, 0.0716 mol) in ether (30 ml) was stirred with excess diazomethane in ether at 0°. Removal of the solvent gave a clear residue which solidified on cooling. Sublimation at 50° (0.3 mm) gave **24** as white needles: ir 1050 and 1170 (vinyl ether) and 1710 and 1760 cm^{-1} (C=O); uv max (tetrahydrofuran) 270 mμ (ϵ 24,200).

Anal. Calcd for $C_7H_8O_3$: C, 60.00; H, 5.71. Found: C, 60.11; H, 5.80.

Reaction of 1a and Diazomethane.—A suspension of **1a** (2.25 g, 0.02 mol) in ether was stirred with excess diazomethane in ether at 0° until evolution of nitrogen ceased. Removal of the solvent and sublimation at 75° (0.3 mm) of the residue gave **25**: yield 2.05 g (81%); mp 84. 5–86.0°; uv max 262 mμ (ϵ 25,000).

Anal. Calcd for $C_6H_6O_3$: C, 57.14; H, 4.80. Found: C, 57.24; H, 4.77.

Hydrogen Evolution in Reactions of Sodium Hydride with 1b, 6, and 19.—Solutions of **1b**, **6**, and **19** in tetrahydrofuran were treated with sodium hydride in wax dispersions and the hydrogen evolved was measured.

In a typical determination, a weighed quantity of reactant in tetrahydrofuran (10 ml) was added, *via* a pressure-equalizing funnel, to a stirred, heterogeneous mixture of excess sodium hydride in dry tetrahydrofuran (10 ml). The hydrogen evolved was collected over water in a gas burette separated by a Drierite tube; corrections were made for the vapor pressure of water and for the pressure of the measurement. Three experiments were conducted with each of the ketones studied. The number of moles of hydrogen evolved per mole in reaction of **1b**, **6**, and **19** was 1.93–2.01, 1.04–1.07, and 1.07–1.1, respectively. In independent experiments, **1b**, **6**, and **19** were each recovered in acidification of solutions of their anions.

Structure of 32.—Ketone **32** was prepared from anhydroacetone benzil, red phosphorus, and hydriodic acid in refluxing acetic acid as yellow crystals: mp 108.5–111.0° (lit. mp 108–110° (procedure of ref 25a)]; ir 1680 (conjugated C=O), and 890 and 860, and 700 and 690 cm^{-1} (*two* monosubstituted phenyls); pmr τ (ABX) pattern) 7.10 (d), 7.75 (J = 7.0 cps, nonequivalent CN_2), 5.4 (d, J = 7.0 cps), and 3.3 (d, J = 1.5 cps, vinyl protons).

Nitrosation of 32 to 33.—A solution of **32** (15.0 g, 0.055 mol), butyl nitrite (12.3 g, 0.12 mol), and concentrated hydrochloric acid (4 ml) in absolute ethanol (70 ml) was warmed to 65°. The mixture was stored for 3 hr and filtered to give **33**, yield 13.2 g (88%), mp 214.5–215.5° (lit.[24] mp 215–216°).

Hydrolysis of 33 to 34.—A solution of **33** (13 g, 0.048 mol), 37% formaldehyde (75 ml), and concentrated hydrochloric acid (12 ml) in glacial acetic acid (75 ml) was warmed to 30° and stirred overnight at room temperature. The orange-yellow product was washed with water, dried, and recrystallized from benzene–hexane to give **34** as deep orange crystals: yield 5.0 g (44%); mp 152–155°; ir 1750 (C=O) and 1700 cm^{-1} (conjugated C=O); uv max (tetrahydrofuran) 298 (ϵ 27,500) and 215 mμ (ϵ 20,000); pmr τ 5.2 (d), 2.8 (s), and 2.75–2.50 (m), no distinct vinyl proton is observed, ratio of aromatic to aliphatic protons is 11.1:1.0.

Anal. Calcd for $C_{17}H_{12}O_2$: C, 82.26; H, 4.84. Found: C, 82.32; H, 4.75.

Hydrolysis of 34 to 29b.—A solution of **34** (0.320 g, 0.0013 mol), concentrated hydrochloric acid (1.0 ml), and glacial acetic acid (4.0 ml) was refluxed for 2 hr. Removal of solvent under vacuum and crystallization of the residue from benzene–hexane resulted in **29b**: yield 0.21 g (66%); mp 182–183° (lit.[24] mp 185–187°; ir 1760 and 1700 (C=O) and 1570 cm^{-1} (split peak, conjugation); pmr τ 6.55 (s, CH_2), and 2.7 and 2.67 (pair of s, phenyl protons), ratio of aliphatic to aromatic protons is 1:5.

Hydrolysis of 33 to 29b.—A solution of **33** (5.0 g, 0.02 mol), 37% formaldehyde (30 ml), and concentrated hydrochloric acid (5 ml) in glacial acetic acid (30 ml) was refluxed for 45 min. After 15 hr, the precipitate formed was washed with water, dried, and recrystallized from benzene to give **29b** as yellow needles, yield 1.7 g (35%), mp 186–188°, identical with previous **29b**.

Reaction of 29b and Hydroxylamine.—Diketone **29b** (0.40 g, 0.0016 mol) in ethanol was warmed with a neutralized solution of hydroxylamine hydrochloride in water (5 ml). The derivative formed was crystallized from ethyl acetate–acetic acid to give the oxime of **29b**, possibly 1-oximino-3,4-diphenyl-3-cyclopentene-1,2-dione, yield 0.31 g (73%), mp 241–242° dec. This oxime depresses the melting point of **33**.

Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.72; H, 4.94; N, 5.32. Found: C, 77.86; H, 5.11; N, 5.51.

Deuterium Exchange Experiments.—The various ketones were stirred with deuterium oxide in the presence of acids or bases. After a stated period of time, solvent was removed and the ketone were recovered by crystallization or sublimation. Identity with original, nondeuterated compounds was established by comparison of infrared spectra and by mixture melting point. The pmr spectra of recovered compounds were compared with the original spectra to determine the extent of deuterium exchange.

A. 19, D_2O, and Et_3N.—To a solution of **19** (0.26 g, 0.0097 mol) and deuterium oxide (1.0 ml) in dry tetrahydrofuran (12 ml) was added triethylamine (*ca.* 0.01 ml). The mixture was stirred for 1 hr and the solvent was removed to yield a dark purple solid which recrystallized as yellow needles identical with original **31**. The pmr spectrum at 4.2 ppm showed 80% disappearance of benzylic protons.

B. 19, D_2O, and HCl.—A solution of **19** (0.26 g, *ca.* 0.001 mol), deuterium oxide (1.0 ml), and concentrated hydrochloric acid (0.01 ml) in tetrahydrofuran (10 ml) was stirred for 4 hr. Removal of solvent and crystallization of the residue from cyclohexane gave **19**, whose melting point (93–95°) is identical with that of initial material. The pmr spectrum indicated complete disappearance of the benzylic proton at 4.2 ppm.

C. 21, D_2O, and Et_3N.—A mixture of **21** (0.23 g, 0.00114 mol), deuterium oxide (0.80 ml), and triethylamine (*ca.* 0.01 ml) in dry tetrahydrofuran (8 ml) was stirred for 6 hr and concentrated. The residue was sublimed at 60° (0.3 mm) to give **21**, yield 0.18 g, whose pmr spectrum at τ 7.05 revealed complete exchange of methylene protium for deuterium.

D. 21, D_2O, and HCl.—Stirring of **21** (0.20 g, 0.001 mol), deuterium oxide (0.80 ml), concentrated hydrochloric acid (*ca.* 0.02 ml), and tetrahydrofuran (8 ml) for 14 hr, removal of solvent, and sublimation of the residue at 60° (0.3 mm) resulted in **21**

whose pmr spectrum showed 85–87% exchange of methylene protium for deuterium.

E. 24, D_2O, and Et_3N.—A mixture of 24 (0.20 g, 0.00141 mol), deuterium oxide (0.80 ml), dry tetrahydrofuran (10 ml), and triethylamine (*ca.* 0.01 ml) resulted in some decomposition of 24 in 6 hr. Sublimation led to 24, yield 0.12 g, whose pmr spectrum revealed complete disappearance of the 2.95-ppm signal for methylene protium.

F. 24, D_2O, and HCl.—Sublimed 24 (0.19 g), obtained from a mixture of 24 (0.22 g, 0.00157 mol), deuterium oxide (0.80 ml), and hydrochloric acid (*ca.* 0.01 ml) in tetrahydrofuran (10 ml) for 10 hr, contained only 10% methylene protium.

G. 25, D_2O, and Et_3N.—Diketone 25 is extensively decomposed in less than 15 min in deuterium oxide–tetrahydrofuran containing small amounts of triethylamine.

H. 25, D_2O, and HCl.—In neat deuterium oxide containing a trace of hydrochloric acid, 25 undergoes 90% exchange of its methylene protium for deuterium in 20 hr.

I. 29a, D_2O, and Sodium Acetate.—A suspension of 29a (0.30 g, 0.00175 mol) in deuterium oxide (1.2 ml) containing sodium acetate (10 mg) was stirred for 12 hr. Examination of 29a after removal of solvent showed no decomposition to have occurred. The infrared spectrum and melting point of the 29a recovered were the same as of initial 29a. The pmr spectrum of the recovered 29a showed that 40% of its methylene protium, τ 6.6, has been exchanged.

J. 29a, D_2O, and HCl.—A solution of 29a (0.25 g, 0.0145 mol), deuterium oxide (1.0 ml), and concentrated hydrochloric acid (0.01 ml) in deuterioacetic acid (4.0 ml) was refluxed for 2 hr and then kept at 50° for 9 hr.

Registry No.—6, 22837-57-6; 10a, 22837-58-7; 10b, 22837-59-8; 10c, 22837-60-1; 10d, 22837-61-2; 12a, 22837-62-3; 12b, 20142-93-2; 12d, 22837-64-5; 12e, 22837-65-6; 13, 22837-66-7; 5,6-dihydro adduct of 13, 22837-67-8; 14, 22837-68-9; 18, 22837-69-0; 24, 7180-62-3; 25, 22837-71-4; 34, 22837-73-6; 1-oximino-3,4-diphenyl-3-cyclopentene-1,2-dione, 22837-72-5; 2-bromo-1,3,4-cyclopentanetrione, 22922-42-5.

A New Synthesis of 2-Hydroxy-3-methylcyclopent-2-en-1-one. II[1]

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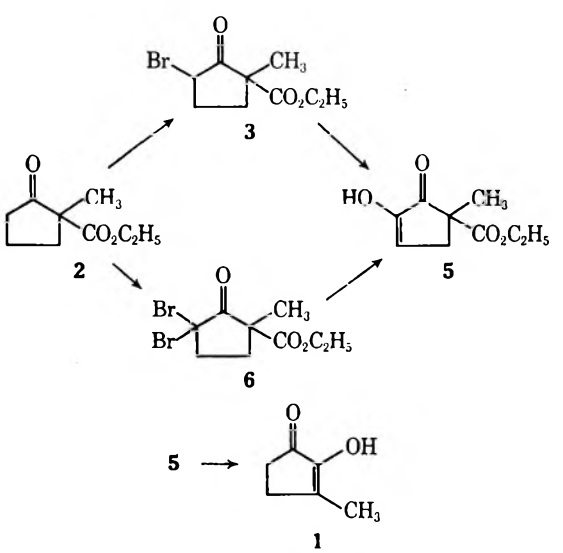
The synthesis of 2-hydroxy-3-methylcyclopent-2-en-1-one (1) was accomplished by the DMSO oxidation of 5-bromo-2-carbethoxy-2-methylcyclopentanone (3), the side reaction of which was prevented by the addition of epichlorohydrin (7). The two-step hydrolysis of 5,5-dibromo-2-carbethoxy-2-methylcyclopentanone (6) using morpholine gave 1 in a pure state. On the other hand, the reaction of 2,5-dibromocyclopentanone (9) with morpholine gave 2-morpholino-2-cyclopentenone (10), while 2,6-dibromocyclohexanone (11), when subjected to similar conditions, was converted into 1-cyclopentene-1-carboxymorpholide (12).

An earlier paper in this series[1] described a synthesis of 2-hydroxy-3-methylcyclopent-2-en-1-one (1) following two synthetic routes from 2-carbethoxy-2-methylcyclopentanone (2). Both procedures involved the oxidation of 2 with selenium dioxide and the nitrosation of 2 with *n*-butyl nitrite, respectively. In addition, it has been found[1] that the dimethyl sulfoxide (DMSO) oxidation of 5-bromo-2-carbethoxy-2-methylcyclopentanone (3) gave 3-bromo-5-carbethoxy-2-hydroxy-5-methylcyclopent-2-en-1-one (4).

In this paper, we aim to elucidate such an abnormal oxidation of cyclic α-bromo ketones as described above, and accomplish the preparation of 1 from the intermediate 2, *via* two routes containing 5-carbethoxy-2-hydroxy-5-methylcyclopent-2-en-1-one (5) as the key precursor: the DMSO oxidation of 3 and the hydrolysis of 5,5-dibromo-2-carbethoxy-2-methylcyclopentanone (6).



The DMSO oxidation of 2-bromocyclopentanone and 2-bromocyclohexanone gave 3-bromo-2-hydroxycyclopent-2-en-1-one and 3-bromo-2-hydroxycyclohex-2-en-1-one, respectively. Accordingly, this series of reactions was confirmed to be a characteristic one of cyclic α-bromo ketones. Since Hunsberger and Tien[2] have reported that dimethyl sulfoxide oxidizes hydrogen bromide to bromine, it appeared that a normal reaction could occur when hydrogen bromide liberated in the reaction was captured by such a neutral base as an epoxide. The DMSO oxidation of 3 in the presence of epichlorohydrin (7) gave a normal product 5 (58.5%) along with 1-bromo-3-chloro-2-propanol (8). Expected α diketone was also obtained by the DMSO oxidation of 2-bromocyclohexanone using phenyl glycidyl ether as the epoxide. From these results, the extraordinary reaction mentioned above is interpreted as follows. The existence of 7 prevents the produced α-diketone from subsequent bromination, because epoxides react with hydrogen bromide formed in the reaction. This process of the DMSO oxidation gave 1 in an overall yield of 29% based upon the diethyl adipate. This is a satisfactory result, compared with the two procedures[1] already described.

The bromination of ketone 2 gave 6 in 85% yield. Compound 1 could be prepared merely by the hydrolysis

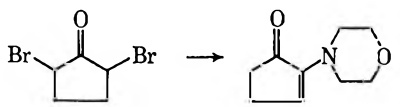
(1) For previous paper, see K. Sato, S. Suzuki, and Y. Kojima, *J. Org. Chem.*, **32**, 339 (1967).

(2) I. M. Hunsberger and J. M. Tien, *Chem. Ind.* (London), 88 (1967).

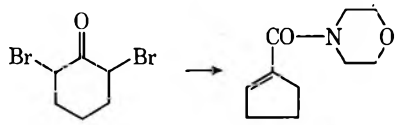
of **6** in aqueous potassium hydroxide. However, the basic hydrolysis of **6** brought about a ring fission mainly and gave crystals (mp 108–109°) which seemed to be 2,2-dibromo-5-carbethoxycaproic acid. When the hydrolysis of **6** was carried out in dilute basic solution, the cleavage was predominant even at a suitable temperature in which **1** was obtainable.

On the other hand, the treatment of **6** with morpholine, followed by the acid hydrolysis, afforded **5** in 49% yield. Compound **1** was synthesized from **6** without the isolation of **5**. This process utilizing morpholine not only gave **1** in a total yield of 30% equal to that of the DMSO oxidation, but also had the advantage of being easy to work with.

In addition, we have examined the reaction of cyclic α,α'-dibromo ketones with morpholine. The bromination of cyclopentanone with 2 mol of bromine has been shown[3,4] to give 2,5-dibromocyclopentanone (**9**). The reaction of **9** with morpholine at 20° afforded a new typified compound, 2-morpholino-2-cyclopentenone (**10**) together with morpholine hydrobromide. The structure of **10** was assigned on the basis of its ir and uv spectra. The ir spectrum showed conjugated carbonyl absorption at 1690 cm^{-1}, and the uv spectrum indicated that **10** possessed a 2-cyclopentenone containing a 2-substituent [uv max (EtOH) 285 mμ (ε 20,000)].



9 **10**



11 **12**

The inference concerning the present reaction mechanism was based on facts that, although the treatment of **9** with silver acetate gives a monoacetoxy derivative,[3] diacetoxide cannot be obtained from **9**.[4] It is supposed that morpholine may remove hydrogen bromide from molecule after the monodisplacement of **9** by 1,4 elimination through enolization. Consequently, **9** affords **10** without producing a dimorpholino derivative.

On the other hand, it was found out that the reaction of 2,6-dibromocyclohexanone (**11**) with morpholine was different from that of **9**. Compound **11** afforded 1-cyclopentene-1-carboxymorpholide (**12**), which was converted to 1-cyclopentenecarboxylic acid on acid hydrolysis. However, when 2-bromocyclohexanone was produced in the same way, only a substitution occurred without suffering from a ring contraction. These results of the two reactions show a new fact that the Favorskii rearrangement depends on the basicity and nucleophilicity of the basic reagent and may be considerably influenced by the steric effect of the reactants.

The above-stated results have revealed an interesting relationship between product and ring size. It is supported that each bromo derivative of five- and six-membered cyclic ketones takes a quite different action in the reaction with morpholine possessing both a strong basicity and nucleophilicity.

(3) P. Y. Yeh, H. C. Hsiu, and P. K. Chang, *Chemistry* (Taiwan), 315 (1955).

(4) I. V. Machinskaya and A. S. Podberezina, *Zh. Obshch. Khim.*, **28**, 1501 (1958).

Experimental Section[5]

Reaction of 2-Bromocyclopentanone with DMSO.—Freshly distilled 2-bromocyclopentanone (8.2 g, 0.05 mol) was dissolved in 50 ml of DMSO and stirred at 70° for 2 hr. After cooling, the reaction mixture was poured into 100 ml of ice water and extracted with ether. Removal of the ether and recrystallization from benzene gave 2.9 g (32%) of 3-bromo-2-hydroxycyclopent-2-en-1-one, mp 152.5–154.0°, lit.[6] mp 152.0–154.0°.

5-Carbethoxy-2-hydroxy-5-methylcyclopent-2-en-1-one (5) from 5-Bromo-2-carbethoxy-2-methylcyclopentanone (3).—A solution of 8.5 g (0.034 mol) of **3** and 3.2 g (0.034 mol) of epichlorohydrin in 100 ml of DMSO was stirred at 70° for 7 hr. The reaction mixture was cooled, poured into water, and extracted with chloroform. After drying, the chloroform was evaporated and the residual oil was distilled to yield 1.3 g (20.7%) of **5**.

Alternatively, DMSO was removed at reduced pressure from the reaction mixture, and the reulting oil was distilled to give 4.8 g (80%) of 1-bromo-3-chloro-2-propanol [bp 66–70° (1 mm), lit.[7] bp 92° (20 mm)] and 5.6 g of the crude oil [bp 98–103° (1 mm)]. Redistillation of the latter oil gave 3.7 g (58.5%) of **5**, bp 97–99° (1 mm), lit.[1] bp 97–99° (1 mm).

Basic Hydrolysis of 5-Carbethoxy-2-hydroxy-5-methylcyclopent-2-en-1-one (5).—A mixture of 3.7 g (0.02 mol) of **5** and 20 ml of 2 *N* potassium hydroxide was stirred for 30 min at room temperature. The resulting mixture was acidified and extracted with chloroform. The chloroform was distilled off and crude solids were then obtained. Recrystallization from water gave 1.4 g (63%) of 2-hydroxy-3-methylcyclopent-2-en-1-one (**1**), mp 104–106° [a mixture melting point with an authentic sample from natural sources (mp 106–107°) showed no depression].

2-Hydroxycyclohex-2-en-1-one.—A solution of 28.3 g (0.16 mol) of freshly distilled 2-bromocyclohexanone and 24.0 g (0.16 mole) of phenyl glycidyl ether in 150 ml of DMSO was stirred at 80° for 4 hr. After cooling, the reaction mixture was poured into ice water and repeated by extracting with chloroform. The extract was dried and concentrated yielding 33.3 g of dark oil. Distillation of this oil gave 8.1 g (45%) of 2-hydroxycyclohex-2-en-1-one [bp 75–76° (23 mm), lit.[8] bp 83° (20 mm)], which was identified on gas chromatography by comparing the retention times of peaks with those of an authentic sample obtained by selenium dioxide oxidation[8] of cyclohexanone.

2-Carbethoxy-5,5-dibromo-2-methylcyclopentanone (6).—To a solution of 10.0 g (0.055 mol) of 2-carbethoxy-2-methylcyclopentanone (**2**) in 150 ml of carbon tetrachloride was added 20.0 g (0.125 mol) of bromine at room temperature, dropwise and with stirring. After stirring and refluxing for 20 hr, the reaction mixture was poured into water and the organic layer was separated. After drying and removal of the solvent, distillation of the residual oil gave 16.3 g (85%) of **6**: bp 115–117° (2 mm); $n^{20}D$ 1.4909; d^{20}_4 1.0260; ir (film) 1735 (ester C=O), 1710 cm^{-1} (C=O).

Anal. Calcd for $C_9H_{12}Br_2O_3$: C, 32.95; H, 3.65. Found: C, 32.88; H, 3.98.

Basic Hydrolysis of 2-Carbethoxy-5,5-dibromo-2-methylcyclopentanone (6).—A mixture of 6.6 g (0.02 mol) of **6** and 50 ml of 2*N* potassium hydroxide was stirred at 100° for 1 hr. The resulting mixture was acidified and extracted with chloroform. The chloroform was evaporated and the residue was poured onto a column of silica gel; the column was eluted with 20:1 benzene–ethanol mixture. After removal of solvents, there remained 0.5 g (24%) of **1**, mp 100–103°, and 2.5 g of crystal, mp 108–109°.

2-Hydroxy-3-methylcyclopent-2-en-1-one (1) from 2-Carbethoxy-5,5-dibromo-2-methylcyclopentanone (6).—To 17.4 g (0.2 mol) of morpholine was added 6.6 g (0.02 mol) of **6**, dropwise and with stirring. The reaction mixture was stirred at 35° for

(5) Melting points are corrected and boiling points are uncorrected. Infrared spectra were determined with a Hitachi Model EPI-S2 spectrophotometer fitted with a sodium chloride prism. Ultraviolet spectra were recorded with a Hitachi Model EPS-3T spectrophotometer. The nmr spectra were determined with a JEOL Model C-60H spectrometer.

(6) J. D. Knight and D. J. Cram, *J. Amer. Chem. Soc.*, **73**, 4136 (1951).

(7) L. Blanchard, *Bull. Soc. Chim. Fr.*, **41**, 824 (1927).

(8) C. C. Hach, C. V. Banks, and H. Diehl, *Org. Syn.*, **4**, 229 (1963).

2.5 hr. The removal of morpholine under reduced pressure gave white crystals and 5.4 g of red oils. The crystals were filtered, and recrystallization from ethanol gave 6.1 g (91%) of morpholine hydrobromide, mp 202°, lit.[9] mp 202°.

The filtrate was stirred with 2 *N* potassium hydroxide solution for 1 hr at room temperature. The solution was then acidified with hydrochloric acid and extracted with chloroform. After drying, the chloroform was evaporated to dryness and the residue was recrystallized from water to yield 1.1 g (49%) of 1, mp 104–105.5°.

Reaction of 2,5-Dibromocyclopentaone (9) with Morpholine.—To a stirred solution of 21.7 g (0.25 mol) of morpholine in 100 ml of dry ether, 12.1 g (0.05 mol) of 9 was added dropwise with an ice–water bath cooling. The mixture was stirred for several hours at room temperature. The precipitated morpholine hydrobromide was filtered and the removal of ether and surplus morpholine under reduced pressure gave 8.1 g of viscous oils. The oils were crystallized after standing for a few days at −70°. The crystals that formed were recrystallized from a small amount of methanol, affording 4.8 g (57.5%) of 2-morpholino-2-cyclopentenone (10): mp 63°; uv max (*n*-hexane) 285 mμ (ε 20,000); ir (KBr) 1690 (C=O), 1613 (C=C), 1110 cm^{-1} (C–O–C); nmr ($CDCl_3$) δ 6.42 (broad s, 1), 3.81 (m, 4), 3.09 (m, 4), 2.47 (almost s, 1).

Anal. Calcd for $C_9H_{13}O_2N$: C, 64.65; H, 7.84. Found: C, 64.61; H, 8.02.

Reaction of 2,6-Dibromocyclohexanone (11) with Morpholine.—To a solution containing 28.0 g (0.11 mol) of 11 in 100 ml of absolute ether, 47.6 g (0.55 mol) of morpholine was added at room temperature, dropwise and with stirring. After standing overnight, the deposited morpholine hydrobromide was filtered off, and the resulting oil was distilled to yield 5.1 g (25.5%) of 1-cyclopentene-1-carboxymorpholide (12): bp 113–114° (0.07 mol); $n^{20}D$ 1.5254; d^{20}_4 1.1326; uv max (EtOH) 213 mμ (ε 10,000); ir (film) 1620 (C=O), 1120 cm^{-1} (C–O–C); nmr (CCl_4) δ 5.80 (broad s, 1), 3.57 (sharp s, 8), 2.48 (m, 4), 1.86 (m, 2).

Anal. Calcd for $C_{10}H_{15}O_2N$: C, 66.27; H, 7.73. Found: C, 66.04; H, 7.58.

A solution of 1.4 g (0.0077 mol) of 12 in 12 ml of 2 *N* hydrogen chloride was stirred at 80° for 2 hr. The reaction mixture was then cooled and filtered, affording 0.4 g (80%) of 1-cyclopentene-1-carboxylic acid, mp 124°, lit.[10] mp 120–121°.

Reaction of 2-Bromocyclohexanone with Morpholine.—To a solution of 9.8 g (0.055 mol) of 2-bromocyclohexanone in 50 ml of dry ether, 14.7 g (0.17 mol) of morpholine was added with an ice–water bath cooling. After standing overnight at room temperature, the reaction mixture was then filtered and the resulting oil was distilled to yield 5.1 g (50.5%) of 2-morpholinocyclohexanone, bp 114–115° (3 mm), lit.[11] bp 148° (20 mm).

Anal. Calcd for $C_{10}H_{17}O_2N$: C, 65.54; H, 9.39; N, 7.64. Found: C, 65.40; H, 9.49; N, 7.53.

Registry No.—**1**, 80-71-7; **6**, 24454-32-8; **10**, 24454-33-9; **12**, 24454-34-0.

(9) J. Gilbert and H. Gault, *Bull. Soc. Chim. Fr.*, 2975 (1965).

(10) H. Sletter and K. Kiehs, *Ber.*, **98**, 2099 (1965).

(11) M. Mousseron, J. Jullien, and Y. Jolchine, *Bull. Soc. Chim. Fr.*, 757 (1952).

Mechanism of the Cationic Addition-π,π-Transannular Cyclization of Disubstituted Methanes with 1,5-Cyclooctadiene

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The reaction of 1,5-cyclooctadiene with methoxymethyl acetate, dimethoxymethane, or chloromethyl methyl ether (Lewis acid catalysis) afforded mainly addition-π,π-transannular cyclization products, *cis*-bicyclo[3.3.0]-octane derivatives which exclusively consisted of *endo*-2-methoxymethyl isomers, and bicyclo[3.2.1]octane derivatives. The stereochemistry of the products and the high tendency of cyclization showed that attack of methoxymethyl cation was from the outside of the boat 1,5-cyclooctadiene with a simultaneous nucleophilic attack of the Δ^3 double bond on the transient carbonium ion, which was followed by a partially concerted attack of an anion moiety (Scheme VII).

The well-documented double-bond participation in carbonium ion solvolyses[1] suggests that unconjugated dienes of appropriate configuration and conformation should form cyclized products upon reaction with cationic species.[2] A suitable system for investigating this cationic addition-π,π-transannular cyclization is *cis,cis*-1,5-cyclooctadiene [1,5-COD]. A model indicates that its boat form, shown to be the stable conformer by dipole measurements,[3] affords the close proximity necessary for orbital overlap. In addition, double-bond participation has previously been shown to be important in the solvolysis of the related compounds, Δ^4-cyclooctenyl tosylate and brosylate.[4,5]

In the present paper, reactions of several disubstituted methane–Lewis acid combinations and 1,5-COD are described which afford predominately cyclic products.[6] This high proportion of cyclic products agrees with the previously reported results from the reaction of 1,5-COD with formic acid[7] and acetyl chloride.[8]

However, the stereochemistry of the product reported from the latter reaction is quite contrary to our findings. Results more similar to ours were reported for the reaction of *cis,cis*-1,6-cyclodecadiene with Br_2 in methanol[9] although even these results differ in a significant manner.

The following paper describes the reaction of 1,5-COD with methoxymethylacetate, dimethoxymethane, and chloromethyl methyl ether (Lewis acid catalysis). From careful analysis of the stereochemistry of the products, a mechanism for the cationic addition–cyclization reaction is presented. The discussion of this mechanism includes a comparison with results on similar

(1) P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, Inc., New York, N. Y., 1965.

(2) Cationic addition cyclizations are also known in some instances [*e.g.*, H. F. Tiemann and F. W. Seemler, *Chem. Ber.*, **26**, 2708 (1893); L. Ruzicka, *Helv. Chim. Acta*, **6**, 483 (1923)], but detailed mechanistic investigations are rather scarce [*e.g.*, W. S. Jonnson, A. van der Gen, and J. J. Swoboda, *J. Amer. Chem. Soc.*, **89**, 171 (1967)].

(3) J. D. Roberts, *ibid.*, **72**, 3300 (1950).

(4) W. D. Closson and G. T. Kwiatkowski, *Tetrahedron Lett.*, 6435 (1966).

(5) A. C. Cope, J. M. Crisar, and P. E. Peterson, *J. Amer. Chem. Soc.*, **82**, 4299 (1960).

(6) Preliminary reports have been presented on the subject: I. Tabushi, K. Fujita, and R. Oda, *Tetrahedron Lett.*, 3815, 3755 (1967).

(7) A. C. Cope and P. E. Peterson, *J. Amer. Chem. Soc.*, **81**, 1643 (1959).

(8) T. S. Cantrell, *J. Org. Chem.*, **32**, 1669 (1967); only formation of the cyclized product was described.

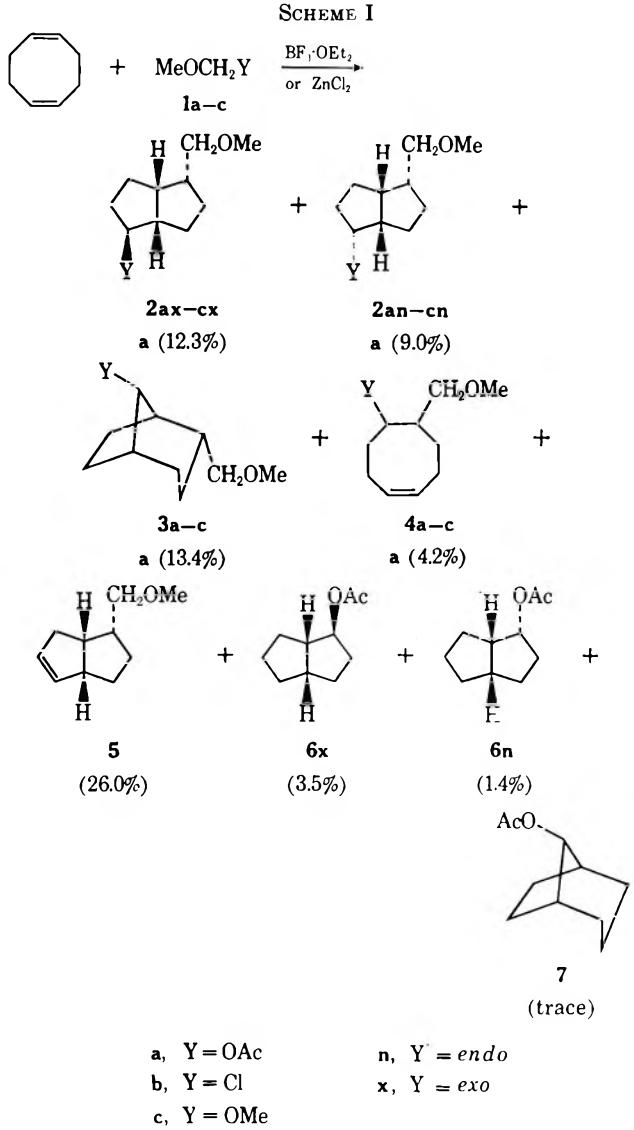
(9) F. M. Gipson, H. W. Guin, S. H. Simonsen, C. G. Skinner, and W. Shive *J. Amer. Chem. Soc.*, **88**, 5366 (1966).

systems and an interpretation of the correlations and discrepancies.

Results and Discussion

Reaction of 1,5-COD with Methoxymethyl Acetate.—The reaction gave the products shown in Scheme I.

SCHEME I



a, Y = OAc
b, Y = Cl
c, Y = OMe
n, Y = *endo*
x, Y = *exo*

The skeletal structure, *endo*-2-methoxymethyl-*cis*-bicyclo[3.3.0]octane, was determined for **2ax** and **2an** by the chemical conversion shown in Scheme II. Saponification of the isomeric acetates **2ax** and **2an** gave the alcohols **8ax** and **8an** which were converted to the tosylates, **9x** and **9n**, and reduced with lithium aluminum hydride. The main product **10n** was identified by comparison with an authentic sample prepared as shown in Scheme III. Further, the brosylates **11x** and **11n** from the mixture of alcohols **8x** and **8n** were treated with trifluoroacetic acid and then hydrogenated on PtO_2 to give **10n** as the major product.

Oxidation of the mixture of alcohols **8n** and **8x** with the chromic oxide–pyridine complex gave a single ketone, **12**, indicating that the acetates **2ax** and **2an** were stereoisomers. The two were distinguished by comparison of nmr spectra of the alcohols. By analogy to the nmr absorptions of the known *exo*- and *endo*-*cis*-bicyclo[3.3.0]oct-2-yl alcohols,[10] the absorption in **8n** at τ 5.95 (broader) was assigned to the *exo* proton, α to the hydroxyl, and the absorption in **8x** at τ 6.40 to the *endo* proton.

The assignment of the structure for **3a** was based mainly on spectroscopic evidence. The infrared spectrum of **3a** showed the presence of methoxyl (1100 cm^{-1}) and acetoxyl (1700 and 1245 cm^{-1}). The nmr spectrum showed a singlet for the α proton to the acetoxyl group, very similar to the absorption reported in the spectrum of *anti*-bicyclo[3.2.1]oct-8-yl acetates, **7**.[6] Hydrolysis of **3a** produced the alcohol **13**. Oxidation of alcohol **13** to the corresponding ketone was much slower than oxidation of alcohol **8**, a fact consistent with the assigned structure for **13**.[11]

The acetates **6x**, **6n**, and **7** were not soluble in aqueous silver nitrate and were unreactive toward Br_2–CH_2Cl_2. These saturated acetates were identified by comparison of their vapor phase chromatographs and infrared spectra with those of authentic samples.

The olefin **5** was soluble in aqueous silver nitrate and reacted readily with Br_2–CH_2Cl_2. Hydrogenation on PtO_2 converted the olefin to **10n**, identical with the authentic sample from Scheme III.

Contrary to the previous report of a single product **17b**,[12] dehydration of cyanohydrin **16** produced two cyanides **17a** and **17b** in a ratio of 55:45 as determined by analysis of either the nmr spectrum or the vapor phase chromatograph. This mixture of products is more reasonable since simple *trans* elimination should lead to both isomers. The mixture of cyanides was hydrolyzed to a mixture of isomeric carboxylic acids **18a** and **18b** present in a ratio of 56:44; hydrogenation of this mixture quantitatively produced a single saturated carboxylic acid **19n**. Completion of the reaction scheme produced a mixture of saturated ethers **10n** and **10x**, the latter compound also being synthesized by another reaction sequence shown in Scheme IV.

Reaction of 1,5-COD with Chloromethyl Methyl Ether or Dimethoxymethane.—The reactions gave the products shown in Scheme I.

Comparison of the product composition for these two reactions and the previously discussed reaction with methoxymethylacetate are shown in Table I. Product determinations were made by chemical conversions to appropriate derivatives and by nmr measurements.

TABLE I
PRODUCT COMPOSITION (PER CENT)

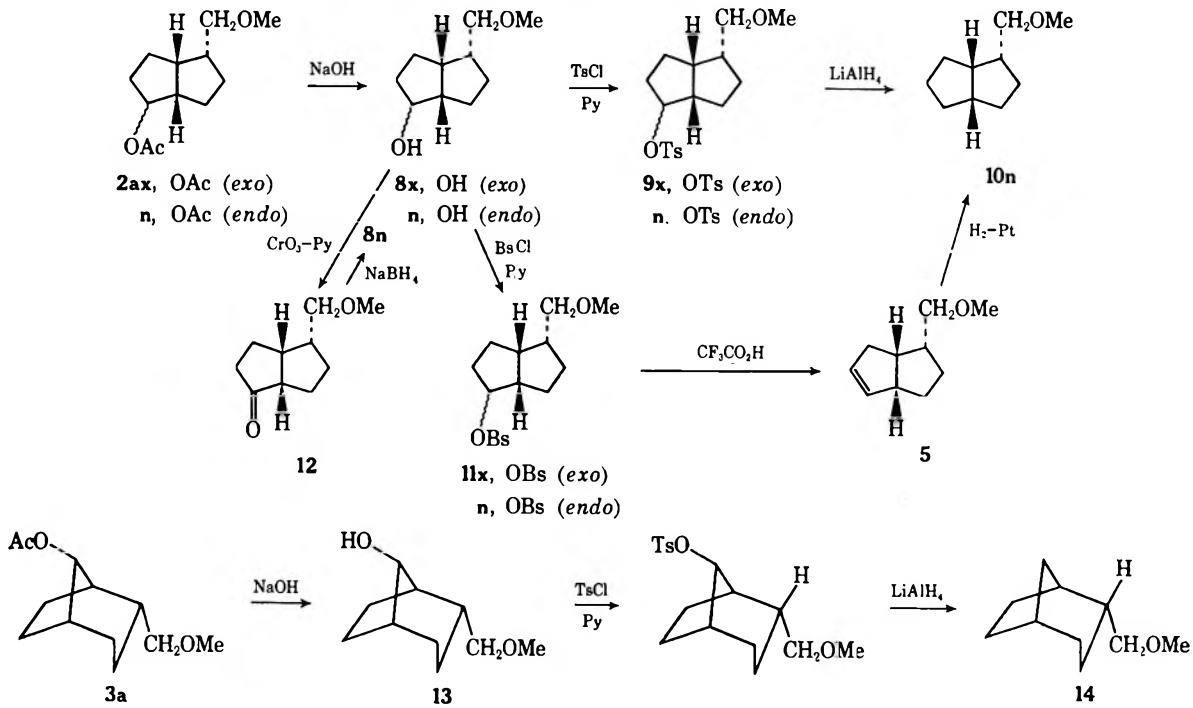
Product	2x	2n	3	4
a	31.6	23.9	34.4	10.8
b	22.6	26.4	12.2	38.8
c	15.2	24.2	17.9	42.7

(10) E. W. C. Wong and C. C. Lee, *Can. J. Chem.*, **42**, 1245 (1964); the α proton to the hydroxyl group in *exo*-*cis*-bicyclo[3.3.0]oct-2-yl alcohol absorbs at τ 6.27; the absorption for the corresponding proton in the *endo* isomer is broader and is at τ 5.91.

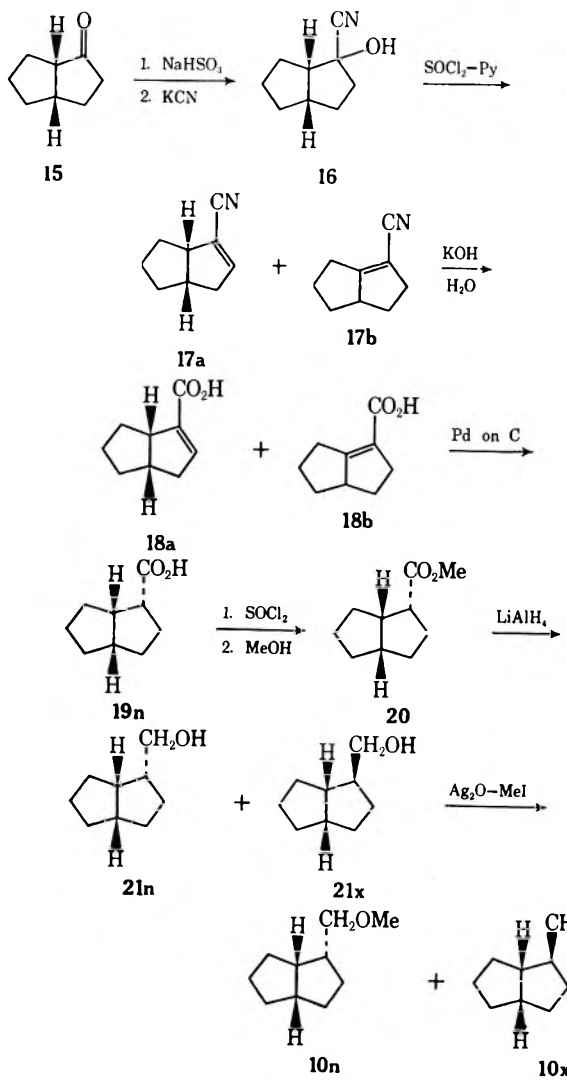
(11) The hydroxyl function on the highly strained bridge of the bicyclic compound (*e.g.*, bicyclo[3.2.1]oct-8-yl alcohol) is reasonably expected to be oxidized more slowly than that of relatively less strained compounds (*e.g.* *cis*-bicyclo[3.3.0]oct-2-yl alcohol), because oxidation to ketone increases bond angle strain. *syn*-Bicyclo[3.2.1]oct-8-yl alcohol is oxidized 16.1 times faster than the *anti* isomer (ref 5). Therefore, it is reasonable that **13** was recovered under the reaction condition where **2ax** and **2ax** were completely oxidized.

(12) A. C. Cope and M. Brown, *J. Amer. Chem. Soc.*, **80**, 2859 (1958).

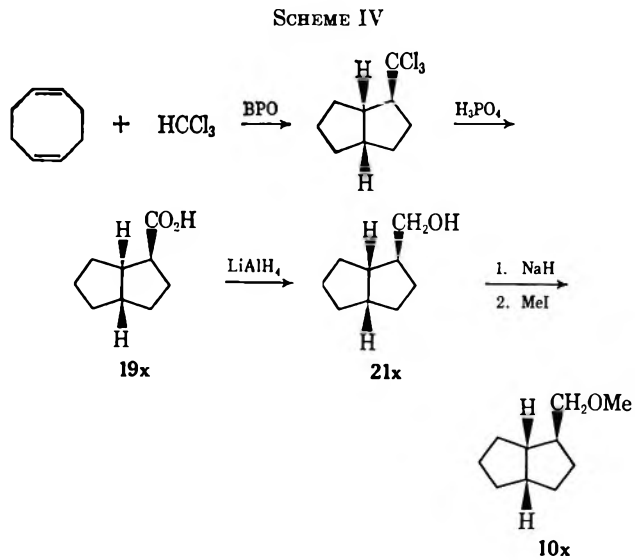
SCHEME II



SCHEME III



SCHEME IV



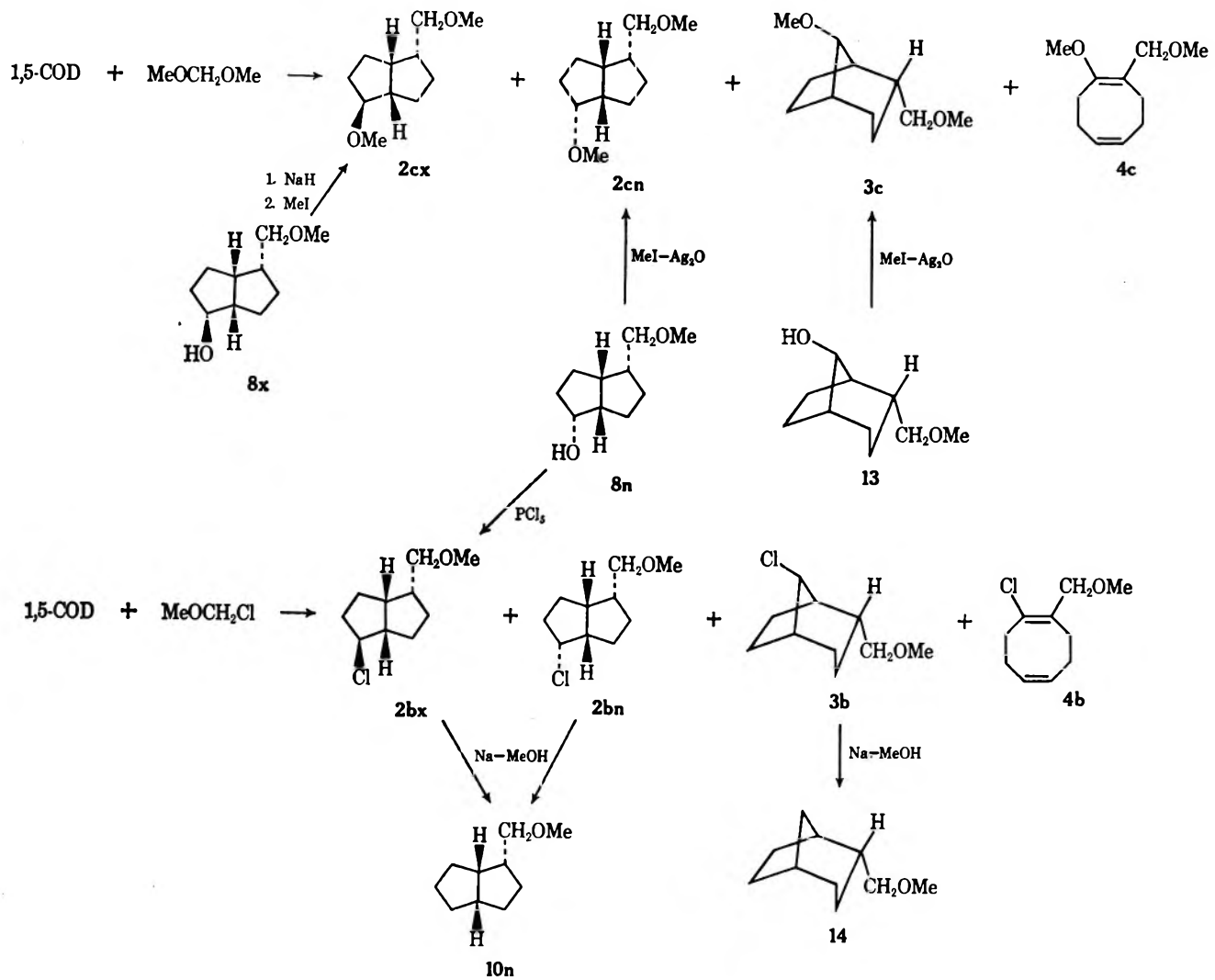
The chemical conversions and interconversions are summarized in Scheme V.

Mechanism of the Reaction.—The formation of the methoxymethyl cation from methoxymethyl acetate and a Lewis acid and its attack on a double bond have been previously reported.[13]

After the attack of methoxymethyl cation on one double bond, the resultant carbonium ion was attacked competitively by an anion to give the noncyclized product or by Δ^5 double bond to give the cyclized product. Therefore, the amount of the cyclized product formed in the reactions of 1,5-COD with CH_3OCH_2Y depends on the nucleophilicity of the anions: BF_3–$AcOCH_2OCH_3$, 89.8%; $ZnCl_2$–$ClCH_2OCH_3$, 61.2%; and BF_3–$(CH_3O)_2CH_2$, 57.3%. As the nucleophilicity

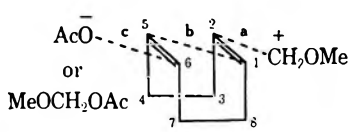
(13) R. Oda, K. Fujita, and I. Tabushi, *J. Chem. Soc. Jap., Pure Chem. Sect.*, **87**, 756 (1966).

SCHEME V



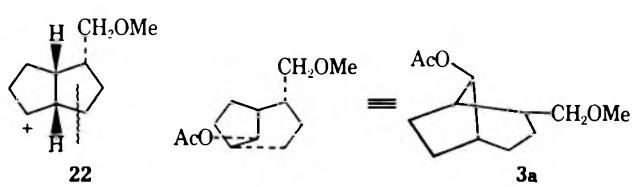
of Y^- increases, $OAc^- < Cl^- < OMe^-$, the cyclization tendency (cyclizability) of 1,5-COD decreases. This is consistent with the idea that the stronger nucleophile competes more effectively with the Δ^5 dcuble bond, resulting in decreased cyclizability. In the attack of methoxymethyl cation on one double bond of 1,5-COD, exclusive formation of the *endo*-methoxymethyl isomer results despite its expected thermodynamic instability[14] relative to the *exo* isomer. Thus, the product is kinetically controlled, and attack by the methoxymethyl cation is from the outside of the preferred boat form of 1,5-COD with a simultaneous nucleophilic attack of the Δ^5 double bond on the transient carbonium ion (step b), leading to new bond formation between C_1 and C_5 as shown in Scheme VI.

SCHEME VI



The stereochemistry of the acetoxyl group shows that step c, the attachment of the acetate ion, is not completely concerted with steps a and b. If step c were concerted with a and b, the acetate ion should attack the *endo* position of C_6 (as shown in step c of Scheme VI); if step c is nonconcerted, the thermodynamically favored *exo* product should predominate. The observed *exo/endo* ratio of 1.37 to 1.00 indicates that step c is only partially concerted with a and b. Also supporting this contention by indicating the formation of free *endo*-6-methoxymethyl-*cis*-bicyclo[3.3.0]oct-2-yl cation, (**22**) is the isolation of **3a** and **5**. The latter, a bicyclic olefin, is the result of loss of a proton from this carbonium ion **22**. The former, a bicyclo[3.2.1] derivative, results from the breaking of the C_8–C_1 bond of the carbonium ion **15** with subsequent formation of a bond from C_8–C_2 and concerted attack of acetate ion at the C_1 position (see Scheme VII).

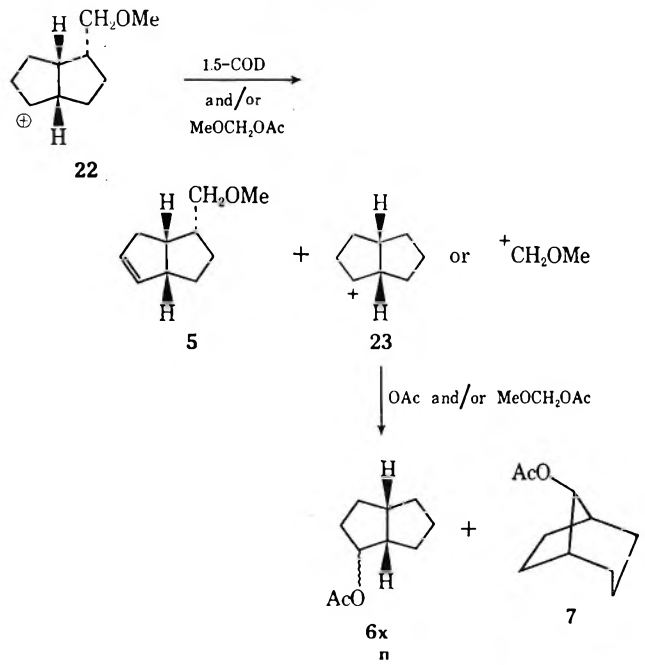
SCHEME VII



(14) *endo-cis*-Bicyclo[3.3.0]oct-2-yl alcohol gave a mixture of 61% *exo* alcohol and 39% *endo* alcohol upon refluxing with aluminum isopropoxide in isopropyl alcohol. Also, *endo-cis*-bicyclo[3.3.0]octane-2-carboxylic acid was readily converted to the *exo* isomer on treatment with hot alcoholic base: A. C. Cope, M. Brown, and H. E. Petree, *J. Amer. Chem. Soc.*, **80**, 2852 (1958).

The remaining products isolated, **6x**, **6n**, and **7**, arise from a secondary reaction in which the elements of acetic acid are added to 1,5-COD. The best rationalization of this is that it involves proton transfer from carbonium ion **22** to 1,5-COD, resulting in olefin **5** and a new carbonium ion, bicyclo[3.3.0]oct-2-yl cation (**23**), which reacts with acetic acid to give **6x**, **6n**, and **7** (see Scheme VIII).[6]

SCHEME VIII

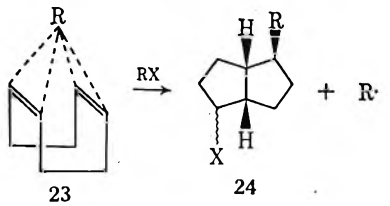


The *exo/endo* ratio of the bicyclic esters 2a also depends on the nucleophilicity of the anion in the system. Thus, the addition of methoxymethyl acetate (BF_3–OEt_2 catalyzed) gives the acetates **2a** with an *exo/endo* ratio of 1.37. For acetic acid addition (BF_3–OEt_2 catalyzed), this ratio is 1.67,[6] while for formic acid addition (perchloric acid catalyzed) it is 2.26. This increasing *exo/endo* ratio reflects a decreasing amount of concerted character of step c.

The outside cationic attack on a cyclic diene system (step a) with concerted cyclization (step b) is similar to that reported recently for the addition of Br_2 in methanol to *cis,cis*-1,6-cyclodecadiene.[9] The isolation of only *endo*-2-bromo-*endo*-7-methoxymethyl-*cis*-bicyclo[4.4.0]decane, indicating a concerted step c, is contrary to expectation based on our results; it is quite possible that only the major product was isolated and reported. A more serious discrepancy exists in the finding of Cantrell[8] that *exo*-2-acetyl-6-chloro-*cis*-bicyclo[3.3.0]octane was formed in the reaction of 1,5-COD with acetyl chloride under $AlCl_3$ catalysis. Two possibilities may explain this contradiction: (1) heterogeneity of the reaction or (2) isomerization from *endo* to *exo* isomer in his procedure for the replacement of chlorine with hydrogen using sodium in *t*-butyl alcohol.

An interesting difference exists in the free-radical addition of $CHCl_3$, $HCNMe_2$, and $CH_3\overset{O}{\overset{\|}{C}}H$ to 1,5-COD as reported by Dowbenko.[15] The isolation of *exo*-2-substituted *cis*-bicyclo[3.3.0]octanes indicates that the radical attacked the boat form of 1,5-COD from the inside of the double bonds, just the opposite of cationic attack (Scheme IX). In the cationic addition, the

SCHEME IX



outside attack of the cation with concerted intramolecular participation of the double bond seems to decrease remarkably the energy of the transition state relative to that of the nonconcerted process. In the radical reaction, on the other hand, the energy decrease of the transition state in the concerted addition is less important; instead, the free-radical intermediate is best stabilized when it is on the π-electron cloud.

In contrast to the high cyclizability of 1,5-COD in reaction with methoxymethyl acetate, 1,5-hexadiene shows little cyclization (<10.3%) under the same conditions. The marked difference in their cyclizabilities may be ascribed to differences in their entropies of activation. In order to achieve π overlap with the carbonium ion, the open-chain diene loses 2 degrees of internal rotational freedom, resulting in a considerable decrease in the preexponential factor. The importance of this entropy factor may be seen in the amount of cyclized product of the following solvolyses: formolysis of Δ^4-pentenyl nosylate, 0%,[16] compared with Δ^4-cyclooctenyl brosylate, 89%;[5] acetolysis of Δ^5-hexenyl nosylate, 73%,[16] compared with ω-(Δ^2-cyclopentenyl)-propyl-1 brosylate, 100%;[17] acetolysis of Δ^4-cycloheptenyl-methyl brosylate, 90%,[18] compared with Δ^5-cyclodecenyl nitrobenzoate, 100%.[19]

Experimental Section[20]

Reaction of *cis,cis*-1,5-Cyclooctadiene with Methoxymethyl Acetate.—A solution of 10.8 g (0.1 mol) of 1,5-COD in 20 g of 1,2-dichloroethane was added over 1 hr at 68° to a mixture of 10.4 g (0.1 mol) of methoxymethyl acetate, 2.8 g (0.02 mol) of boron trifluoride–ether complex (47 wt %), and 20 g of 1,2-dichloroethane. After refluxing for 12 hr, the reaction mixture was poured into saturated sodium bicarbonate and extracted with ether. The ether layer was washed with water, dried (Na_2SO_4), and concentrated. Upon distillation, 3.0 g of a mixture of *endo*-6-methoxymethyl-*cis*-bicyclo[3.3.0]oct-2-yl acetates (**2ax** and **2an**) and *endo*-2-methoxymethyl-bicyclo[3.2.1]oct-*anti*-8-yl acetate (**3a**) was obtained at 91–92° (3 mm). The lower boiling distillate (5.0 g), bp 66° (15 mm) and 94° (12 mm), contained *endo*-6-methoxymethyl-*cis*-bicyclo[3.3.0]oct-2-ene (**5**), *cis*-bicyclo[3.3.0]oct-2-yl acetates (**6x** and **6n**), and *anti*-bicyclo[3.2.1]oct-

(15) R. Dowbenko, *Tetrahedron*, **20**, 1843 (1964).

(16) W. D. Johnson, D. M. Bailey, R. Owyang, R. A. Bell, B. Jaques, and J. K. Crandall, *J. Amer. Chem. Soc.*, **86**, 1959 (1964).

(17) W. D. Closson and G. T. Kwaitkowsky, *ibid.*, **86**, 1887 (1964).

(18) G. LeNy, *C. R. Acad. Sci., Paris*, **251**, 1526 (1961).

(19) P. D. Bartlett and S. Bank, *J. Amer. Chem. Soc.*, **83**, 2591 (1961).

(20) Analyses were by the Microanalytical Laboratory, Department of Pharmaceutical Sciences, University of Kyoto, Japan. Boiling points are uncorrected. Nmr spectra were determined with a JMN-3H-60 recording spectrometer. Ir spectra were determined with a Nihon Bunko Model IR-S spectrometer. For vpc, columns (210 cm, 3.0-mm i.d.) packed with silicone DC 550, PEG 20M, or Apiezon L were used. In the descriptions of nmr absorptions, s, d, t, m, and b correspond to singlet, doublet, triplet, multiplet, and broad, respectively.

8-yl acetate (7) together with many minor unknown products. The products were identified by comparison with the vapor phase chromatographs, infrared spectra, and nmr spectra of authentic samples. The infrared spectrum of the mixture of **2ax**, **2an**, and **3a** had strong bands at 1740, 1245, and 1100 cm^{-1}. The nmr spectrum (CCl_4) of the mixture exhibited absorptions at τ 6.87 (s, OCH_3), 6.67–7.25 (b, OCH_2), 8.14 (s, CH_3CO_2), and 7.25–9.0 (b, other protons). The absorption for the H α to the acetoxy group varied: **2ax** τ 5.35 (b, *endo*-H), **2an** 4.95 (b, *exo*-H), **3a** 5.44 (singlet, *syn*-H).

Anal. Calcd for $C_{12}H_{20}O_3$ (mixture of **2ax**, **2an**, and **3a**): C, 67.89; H, 9.50. Found: C, 67.72; H, 9.47.

Hydrolysis of *endo*-6-Methoxymethyl-*cis*-bicyclo[3.3.0]oct-*exo*- and -*endo*-2-yl Acetates (2ax and 2an) and *endo*-2-Methoxymethylbicyclo[3.2.1]oct-*anti*-8-yl Acetate (3a).—One gram of the mixture of the acetates **2ax**, **2an**, and **3a** was hydrolyzed with methanolic sodium hydroxide (5 g of sodium hydroxide, 25 g of methanol, and 5 g of water) to give 0.8 g of the corresponding alcohols, bp 90–97° (7 mm). The infrared spectrum of this mixture **8x**, **8n**, and **13** exhibited strong bands at 3360 and 1100 cm^{-1}. The nmr spectrum (CCl_4) of each acetate isolated from the mixture by the following procedures exhibited absorptions at τ 6.85 (s, OCH_3), 6.60–7.15 (b, OCH_2), and 7.3–9.3 (b, other protons). The absorption of the H α to the hydroxy function varied: **8x** τ 6.40 (b, *endo*-H), **8n** 5.95 (b, *exo*-H), **13** 6.47 (singlet, *syn*-H).

Oxidation of the Mixed Alcohols 8x, 8n, and 13 with Chromic Oxide in Pyridine.—A solution of 3.7 g of the mixed alcohols in 37 ml of pyridine was stirred with a mixture of 5.94 g of chromic oxide in 74 ml of pyridine at room temperature for 8 hr. The reaction mixture was poured into ice–water and extracted with ether. The ether extract was washed with 6 *N* hydrochloric acid and saturated sodium bicarbonate and was dried ($MgSO_4$). Distillation afforded the following: fraction A, bp 85–109° (7 mm), 1.28 g; fraction B, bp 109–111° (7 mm), 0.47 g; fraction C, pb 111° (7 mm), 0.19 g. Fraction A was shown by vpc on PEG 20M and Apiezon L to be a single ketone, *endo*-6-methoxymethyl-*cis*-bicyclo[3.3.0]octan-2-one (**12**): ir (neat) 2940, 1738, and 1100 cm^{-1}; nmr (CCl_4) τ 6.85 (s, OCH_3), 6.5–7.1 (b, OCH_2), 7.1–9.0 (b, other protons). Fraction C was unreacted *anti*-bicyclo[3.2.1]oct-8-yl alcohol (**3a**) of which nmr spectrum is cited above.

Reduction of *endo*-6-Methoxymethyl-*cis*-bicyclo[3.3.0]octan-2-one (12) with Sodium Borohydride.—A solution of 1.0 g of the ketone **12** in 7.5 ml of methanol was stirred with 0.9 g of sodium borohydride in 19 ml of methanol at room temperature for 3 hr. After removal of the methanol under reduced pressure, the residue was carefully acidified with 2 *N* hydrochloric acid. This solution was extracted with ether. The ether extract was dried ($MgSO_4$) and evaporated to give 0.8 g of an alcohol **8n**. The infrared spectrum of the product showed complete conversion of the ketone to the alcohol **8n**. This alcohol, distilled at 90–97° (7 mm), was determined as **8n** by analysis of nmr spectrum (*vide supra*). The structural assignment is supported by the fact that the hydride reduction of *cis*-bicyclo[3.3.0]octan-2-one gives mainly *endo-cis*-bicyclo[3.3.0]oct-2-yl alcohol.[21]

Reduction of the Tosylates of the Mixed Alcohols 8x, 8n, and 13, with Lithium Aluminum Hydride.—A solution of 5 g of the mixed alcohols **8x**, **8n**, and **13** in 24.5 ml of pyridine was added dropwise to 11.5 g of *p*-toluenesulfonyl chloride in 24.5 ml of pyridine at 0°. After standing at room temperature overnight, 150 ml of water was added, and the mixture was extracted with ether. The ether extract was washed with 6 *N* hydrochloric acid and aqueous saturated sodium bicarbonate and was dried. Removal of the ether at reduced pressure produced a pasty oil. Its infrared spectrum showed complete conversion of the alcohols to their tosylates (from the disappearance of the OH stretching band). Dissolution of the oil in ether and reduction with 0.1 g of lithium aluminum hydride gave two hydrocarbons, neither of which reacted with Br_2–CH_2Cl_2. These were tentatively identified as *endo*-2-methoxymethyl-*cis*-bicyclo[3.3.0]octane (**10n**) and *endo*-2-methoxymethylbicyclo[3.2.1]octane (**14**). The product composition was determined by vapor phase chromatography (silicone DC 550): **10n** (53.2%), **14** (13.7)%, starting alcohols (11.9%), and two unknown products (5.0%). **10n** was identical with an authentic sample (*vide infra*) by vapor phase chromatography (PEG 20 M, silicone DC 550, and Apiezon L) and infrared spectroscopy.

Trifluoroacetolysis of the Brosylates of the Mixed Alcohols, 8x, 8n, and 13.—A solution of 1.02 g of the mixed alcohols **8x**, **8n**, and **13** in 4.9 ml of pyridine was added dropwise at 0° to 3.05 g of *p*-bromobenzenesulfonyl chloride in 4.9 ml of pyridine. After stirring for 16 hr, water was added, and the reaction mixture was extracted with ether. The ether extract was washed with 6 *N* hydrochloric acid and saturated aqueous sodium bicarbonate and was dried ($MgSO_4$). Evaporation of the ether gave a viscous oil, a mixture of the *p*-bromobenzenesulfonates. This oil was added at 0° to a mixture of 1.08 g of sodium acetate and 27.36 g of trifluoroacetic acid, and the mixture was stirred at 0° for 2 hr. Water was added and the mixture was extracted with ether. The oil obtained by evaporation of the ether was hydrolyzed with 1.2 g of sodium hydroxide, 12 ml of water, and 20 ml of methanol at 50° for 1 hr. The hydrolysis mixture was extracted with ether, and the extract was dried ($MgSO_4$). Evaporation of ether gave an oily residue which contained 16.1% mixed alcohols **8x**, **8n**, and **13** and 70.4% (combined) two olefinic products which readily reacted with Br_2–CH_2Cl_2. The olefinic products were hydrogenated over PtO_2 catalyst at atmospheric pressure to give 2-*endo*-methoxymethyl-*cis*-bicyclo[3.3.0]octane (**10n**) as one of the major products.

***endo*-2-Methoxymethyl-*cis*-bicyclo[3.3.0]octane (10n).**—The cyanohydrin **16** was prepared from the sodium bisulfite adduct of *cis*-bicyclo[3.3.0]octan-2-one (**15**) with potassium cyanide by Cope's procedure.[22] To a stirred solution of 5.5 g of the cyanohydrin **16** in 10 g of pyridine and 20 ml of ether was added 7.9 g of thionyl chloride with ice cooling. After refluxing for 2 hr, the mixture was poured onto 100 g of ice. The ether layer was separated, washed with water and saturated aqueous sodium bicarbonate, and was dried ($MgSO_4$). Distillation at 80–90° (5 mm) produced 2.7 g of a mixture of two cyanides **17a** and **17b**.

The nmr spectrum (CCl_4) of the mixed cyanides exhibited absorptions at τ 3.80 (t, with an intensity corresponding to 55.4% of olefinic protons) and 6.05–9.20 (b, other protons). Thus the ratio **17a**:**17d** was determined as 55.4:44.6 from nmr, which was supported by vpc (54.8:45.2).

The mixture of cyanides (5.3 g) was refluxed with 4.5 g of potsssium hydroxide, 0.85 g of water, and 22 ml of diethylene glycol for 48 hr. The solution was poured into 140 ml of water which was washed with benzene. After acidification with 6 *N* hydrochloric acid, the aqueous layer was again extracted with benzene. The benzene extract was washed with saturated sodium chloride and dried ($MgSO_4$). Distillation at 112.5–114.0° (0.65 mm) gave 2.8 g of a mixture of the two acids **18a** and **18b**.

The nmr spectrum (CCl_4) of the mixed acids exhibited absorptions at τ 2.11 (s, COOH), 3.35 (d, olefinic proton, with an intensity corresponding to 56% of olefinic protons), and 6.20–9.00 (b, other protons). Thus the ratio **18a**:**18b** was determined as 56:44 from nmr.

The mixture of the two acids (1.2 g) was hydrogenated over 0.14 g of 10% Pd-on-Norit catalyst in 13 ml of absolute ethanol at atmospheric pressure to give 1.1 g of the saturated *endo*-carboxylic acid **19n**.

One gram of this acid was refluxed for 3 hr with 19 ml of thionyl chloride. After removal of the thionyl chloride *in vacuo*, 2 ml of methanol was added to the residue with ice cooling and stirring. Ether was added, and the solution was washed with water and saturated aqueous sodium bicarbonate and was dried ($MgSO_4$). On distillation, the methyl ester **20** was obtained at 79–80° (3 mm) together with a small amount of an unknown ester. The ester was used in the following reaction without further purification.

A solution of 0.7 g of **20** in 20 ml of ether was added below −10° to a suspension of 0.095 g of lithium aluminum hydride in 20 ml of ether, and the mixture was stirred at room temperature overnight. After the usual work-up, a mixture of the alcohols **21n** and **21x** (in ratio of 70.0:30.0 as determined by vpc) was obtained. These alcohols were treated with 0.6 g of methyl iodide and 1.5 g of silver oxide to give the methyl ethers **10n** and **10x**, bp 70° (17 mm) and 65° (10 mm), in a ratio of **10n**:**10x** of 68.2:31.8 (determined by vapor phase chromatography with PEG 6000 column). The spectral data on the mixed ethers follow: ir (neat) 1100 cm^{-1}; nmr (CCl_4) τ 6.75 (superposition of the singlet from CH_3O and the multiplet from OCH_2) and 7.3–9.2

(21) H. C. Brown and W. J. Hammar, *J. Amer. Chem. Soc.*, **89**, 6378 (1967).

(22) A. C. Cope and W. R. Schmitz, *ibid.*, **72**, 3056 (1950).

(other protons). **10x** was identical with authentic ether as shown by vpc (PEG 6000, silicone DC 550, and Apiezon L).

exo-2-**Methoxymethyl-*cis*-bicyclo[3.3.0]octane (10x).**—The *exo*-carboxylic acid **19x** was obtained from hydrolysis of *exo*-2-trichloromethyl-*cis*-bicyclo[3.3.0]octane by Dowbenko's procedure.[15] A solution of 3.4 g of this acid in 20 ml of tetrahydrofuran was added to a suspension of 4.3 g of lithium aluminum hydride in 20 ml of tetrahydrofuran with stirring and cooling in an ice bath. The mixture was then stirred at 40° for 22 hr. After the usual work-up, the *exo* alcohol **21x** which was obtained, was dissolved in 20 ml of ether and stirred with 0.28 g of sodium hydride overnight at room temperature. A solution of 39.7 g of methyl iodide in 50 ml of tetrahydrofuran was added to the reaction mixture, and the mixture was heated at reflux overnight. After addition of water, the mixture was extracted with ether. The ether layer was dried ($MgSO_4$), concentrated, and distilled to give the *exo*-methyl ether **10x**, bp 90–93° (42 mm). This was shown to be a single product by vpc (PEG 8000, silicone DC 550, and Apiezon L). The spectral data follow: ir (neat) 2860, 1455, 1385, 1260, 1190, and 1100 cm^{-1}; nmr (CCl_4) τ 6.75 [superpositon of singlet (OCH_3) and multiplet (OCH_2)] and 7.3–9.2 (other protons).

exo-cis-**Bicyclo[3.3.0]oct-2-yl Acetate (6x).**—*exo-cis*-Bicyclo-[3.3.0]oct-2-yl alcohol was prepared by the reductive cleavage of *cis*-bicyclo[3.3.0]oct-2-ene oxide with lithium aluminum hydride.[23] A mixture of 0.5 g of the alcohol and 2.1 g of acetic anhydride was maintained at 60° overnight. The mixture was poured into saturated sodium bicarbonate and extracted with ether. The ether layer was washed with water, dried (Na_2SO_4), and concentrated to give the practically pure acetate (shown by vpc analysis).

endo-cis-**Bicyclo[3.3.0]oct-2-yl Acetate (6n).**—*cis*-Bicylco-[3.3.0]octan-2-one (**15**) was reduced with sodium borohydride to give *endo-cis*-bicyclo[3.3.0]oct-2-yl alcohol.[21] The acetate was obtained as described above for **6x**.

anti-**Bicyclo[3.2.1]oct-8-yl Acetate (7).**—Addition of formic acid to 1,5-COD (perchloric acid catalysis) followed by hydrolysis gave a mixture of alcohols.[7] 4-Cyclooctenol-1 was removed from the mixture as previously described.[7] A solution of 15 g of the remaining alcohols in 200 ml of pyridine was added to a mixture of 32 g of chromic oxide in 400 ml of pyridine. The reaction mixture was stirred at room temperature for 4 days. The mixture was poured into ice–water and extracted with ether, the extract being washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated. Distillation gave a first fraction composed of a mixture of oxidized products, bicyclo-[3.3.0]octan-2-one (**15**) and bicyclo[3.2.1]octan-8-one and a second fraction, bp 60° (5 mm), of unoxidized *anti*-bicyclo-[3.2.1]oct-8-yl alcohol. This solid alcohol had the following nmr spectrum (CCl_4): τ 6.47 (s, C_8-H), 7.50–8.75 (b, other protons). The corresponding acetate **7** was obtained from the reaction of the alcohol with acetic anhydride as described for **6x**.

Reaction of 1,5-COD with Chloromethyl Methyl Ether.—A solution of 25.9 g of 1,5-COD in 25 g of 1,2-dichloroethane was added at room temperature over 2 hr to a solution of 19.2 g of chloromethyl methyl ether and 1.5 g of zinc chloride in 25 g of 1,2-dichloroethane. The reaction mixture was stirred at room temperature for 38 hr after which it was poured into saturated aqueous sodium bicarbonate and extracted with ether. The ether layer was washed with water, dried ($MgSO_4$), and concentrated. Distillation at 121–169° (10 mm) produced 14.3 g of a mixture of the *endo*-6-methoxymethyl-*cis*-bicyclo[3.3.0]oct-2-yl chlorides (**2bx**[24] and **2bn**), *endo*-2-methoxymethyl-bicyclo[3.2.1]-oct-*anti*-8-yl chloride (**3b**), and an olefinic product **4b** which was removed from the mixture by extraction with aqueous silver nitrate. The mixture of **2bx**, **2bn**, and **3b** had the following spectral properties: nmr (CCl_4) of α proton to chlorine, τ 5.6 (m, **2bx**), 5.9 (m, **2bn**), and 6.06 (s, **3b**); ir (neat) 1100, 755, and 725 cm^{-1}.

Anal. Calcd for $C_{10}H_{17}OCl$: C, 63.83; H, 9.04; Cl, 18.62. Found: C, 63.36; H, 9.19; Cl, 18.24.

The skeletons of **2bx** and **2bn** were ascertained by the reduction to **1On**. The stereochemistry and the product composition of **2bx**, **2bn**, and **3b** were determined by the nmr measurement of the α proton to chlorine. The chloride **2bx** was shown by vpc (Apiezon L and PEG 20M) to be identical with an authentic sample obtained from the chlorination of **8n** with phosphorus pentachloride.[24]

Reduction of 2bx, 2bn, and 3d with Sodium in Methanol.—To a solution of 1.9 g of the mixture of chlorides **2bx**, **2bn**, and **3d** in 6.4 g of methanol was added 2.3 g of sodium metal in small portions with stirring. After the spontaneous refluxing ceased, the mixture was heated to maintain reflux until the sodium disappeared. The mixture was neutralized with dilute hydrochloric acid with ice cooling and was extracted with ether. After evaporation of the ether, the residue was shown by vpc (silicone DC 550) to consist of two products (53.3 and 46.7%). One was identical with an authentic sample of **10n** as demonstrated by vpc (PEG 20M and silicone DC 550), and the other was assumed to be **14**.

Reaction of 1,5-COD with Dimethoxymethane.—A solution of 21.6 g of 1,5-COD in 30 g of dichloromethane was added to a solution of 15.6 g of dimethoxymethane and 5.6 g of boron trifluoride–ether complex (47 wt %) in 30 g of dichloromethane with stirring at 31–41° over 7 hr. Stirring was continued for 93 hr at 35–37°. Then the mixture was poured into saturated aqueous sodium bicarbonate and was extracted with ether. The ether extract was washed with water, dried ($MgSO_4$), and concentrated. Distillation at 112–114° (10 mm) afforded 4.93 g of a mixture of the *endo*-6-methoxymethyl-*cis*-bicyclo[3.3.0]oct-2-yl methyl ethers (**2cx** and **2cn**), *endo*-2-methoxymethyl-bicyclo[3.2.1]oct-*anti*-8-yl methyl ether (**3c**), and an olefin **4c**, which was removed from the mixture by extraction with aqueous silver nitrate. The nmr spectrum (CCl_4) of the mixture of isomers exhibited absorptions at τ 6.55–7.20 (b, OCH and OCH_2), 6.75 (s, OCH_3), and 7.20–9.20 (b, other protons). Since the nmr absorptions of OCH were not separated from those of OCH_2, the nmr measurement did not define the stereochemistry of 6-methoxyl group.

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.43; H, 10.85.

By comparison of the infrared spectra and vapor phase chromatographs (Apiezon L and PEG 20M), the products were shown to be identical with the ether from the hydrolysis products of **2ax**, **2an**, and **3a** obtained in the reaction of 1,5-COD with methoxymethyl acetate.

endo-6-**Methoxymethyl-*cis*-bicyclo[3.3.0]oct-2-yl Methyl Ethers (2cx and 2cn) and *endo*-2-Methoxymethyl-bicyclo[3.2.1]oct-*anti*-8-yl Methyl Ether (3c) from 8x, 8n, and 13.**—To a solution of 1.7 g of the mixture of **8x**, **8n**, and **13** (obtained from the hydrolysis of **2ax**, **2an**, and **3a**) in 20 ml of tetrahydrofuran was added 2.4 g of sodium hydride (50%). After the mixture was stirred at reflux for 5 hr, the mixture was cooled in an ice bath, and 14.2 g of methyl iodide was added. After reflux for 24 hr, water was added to the mixture, and the mixture was extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated to give the methyl ethers **2cx**, **2cn**,[25] and **3c**.[26] Vapor phase chromatography (PEG 20M) showed complete conversion of the alcohols to their methyl ethers.

Registry No.—*cis,cis*-1,5-COD, 1552-12-1; methoxymethyl acetate, 4382-76-7; chloromethyl methyl ether, 107-30-2; dimethoxymethane, 109-87-5.

Acknowledgment.—The authors are grateful to Dr. Elva Mae Nicholson for stimulating discussions.

(23) I. Tabushi, K. Fujita, and R. Oda, unpublished data.

(24) **2bx** from **8n**. A solution of 0.2 g of **8n** in 2 ml of dichloromethane was heated to reflux for 2 hr with 0.3 g of phosphorus pentachloride. The mixture was poured into water and extracted with dichloromethane. The dichloromethane extract was washed with saturated aqueous sodium bicarbonate and was concentrated to give the chloride **2bx**. The product was contaminated by a small amount of impurity as shown by vpc (PEG 20M and Apiezon L).

(25) **2cn** from **8n**. A mixture of 0.5 g of **8n**, 1 ml of methyl iodide, and 0.1 g of silver oxide was refluxed for 4 hr. Ether (six washings) was used to dissolve the organic product from the precipitate, and the ether extracts were dried ($MgSO_4$). Evaporation of ether gave practically pure *endo* methyl ether **2cn**, as demonstrated by vpc (PEG 20M).

(26) **3c** from **13**. A mixture of 0.19 g of **13**, 1 ml of methyl iodide, and 0.1 g of silver oxide was refluxed for 4 hr. The procedure described above for the conversion of **2cn** to **8n** produced practically pure methyl ether, **3c** (shown by vpc on PEG 20M).

Nuclear Magnetic Resonance Chemical Shifts of *exo*- and *endo-cis*-Bicyclo[3.3.0]oct-2-yl and -3-yl Derivatives

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exo- and *endo-cis*-bicyclo[3.3.0]oct-2- and -3-ols and their acetates were prepared in a stereoselective fashion and the nmr chemical shifts of the proton α to hydroxyl and acetoxyl were measured. The *endo*-2 proton was found to be more shielded than the *exo*-2 proton, as expected, but the *exo*-3 proton was found to be considerably more shielded than the *endo*-3 proton, quite contrary to previous predictions. This unusual shielding effect was interpreted by calculations (using McConnell's equation) based on probable conformations of bicyclooctane. The best fit to the observed chemical shifts was obtained when the "W" conformation was adopted except for the 2-*exo*-ol or -acetate, which were assumed to be in the "S" conformation because of the conformational energies of the hydroxyl or acetoxyl groups.

The stereochemistry of the *cis*-bicyclo[3.3.0]octane (hereafter abbreviated as the *3.3.0*) system, substituted in the 2 and 3 positions, has been defined by certain reactions of the system.[1,2] Hydroboration of the *3.3.0*-2-ene (I) gave mainly two alcohols, the *exo-3.3.0*-2-ol (IIx) and the *3.3.0*-3-ol (IIIx), assumed to be the *exo* isomer (IIIx).[3] Lithium aluminum hydride or sodium borohydride reduction of the *3.3.0*-2-one (V) yielded predominately the *endo-3.3.0*-2-ol (IIn), contaminated by a small amount of the *exo* isomer;[3,4] reduction of the *3.3.0*-3-one (VI) also gave two alcohols in a 4:1 ratio,[4] the major of which was assumed to be the *endo* alcohol and the minor to be the *exo* isomer (IIIx). This stereochemistry is reasonable on the basis of steric approach control where the *exo* side of the *3.3.0* system is less hindered than the *endo* side.

Using this defined stereochemistry, we unexpectedly found that the nmr chemical shift required that the 3-*exo* proton of the *3.3.0* is more shielded than the 3-*endo* proton, contrary to the previous prediction.[5] This suggests the possibility that the often assumed hypothesis of the greater shielding of *endo* protons might be incorrect, and that in some cases, the *endo* side is actually less hindered.

In the present paper, we present the observed chemical shifts of isomeric *3.3.0* alcohols and their acetate derivatives, the absolute configurations of which were ascertained independently. Calculation of the nmr shielding effects for each *3.3.0*-2- and 3-ol using various conformational models is presented and a comparison with the observed shifts is made.

Results and Discussion

Preparation and Stereochemical Identification of the *3.3.0* Alcohols and Their Acetates.—The *exo* and *endo* isomers of the 2- and 3-hydroxybicyclo[3.3.0]octanes were prepared as shown in Scheme I. This series of reactions in conjunction with the previously determined stereochemistry of IIx and IIn[6] defined the stereochemistry of each of the four alcohols. See Table I for a summary of product composition.

TABLE I

PRODUCT COMPOSITION OF THE REACTIONS 1–6

	Product, %					
Reaction	IIx	IIn	IIIx	IIIn	IVx	IVn
1	44	t[a]	56	t		
2a					90	10
2b	83	t	17	t		
3	20	80				
4			20	80		
5					14	86
6		77		23		

[a] t = trace.

Worthy of note is the relatively low stereoselectivity in the reduction reactions. Reduction of the epoxide IVx gave a 5:1 ratio of IIx:IIIx. This is consistent with Brown's report of reduction of an asymmetrically hindered epoxide giving both isomers.[7] We also found that hydride reduction of VI gave a 4:1 ratio of IIIn:IIIx, contrary to a previous report of exclusive formation of the *endo* isomer IIIn.[4]

Nmr Chemical Shift and Conformation.—Nmr measurements were carried out in carbon tetrachloride with δ values determined from a TMS–chloroform double reference standard. In addition to the measurement on each pure alcohol, nmr spectra were run on each possible combination of alcohols in order to avoid error from slight changes in the conditions of measurement. The observed δ (and $\Delta\delta$ values) are shown in Table II.

TABLE II

OBSERVED δ VALUES OF PROTONS α TO HYDROXYL AND ACETOXYL GROUPS

	2n H	3x H	2x H	3n H
OH	3.73	3.93	4.09	4.16
AOc	4.73	4.92	5.09	5.18

The most interesting finding was that the α *endo* proton of the *3.3.0* 3-alcohol or acetate is less shielded than the corresponding α *exo* proton. This is contrary to the previous prediction that the *endo* proton should be more shielded than the *exo* proton, a prediction which was based on shielding calculations in which the

(1) I. Tabushi, K. Fujita, and R. Oda, *Tetrahedron Lett.*, 3755, 3815 (1967).

(2) For example, A. C. Cope, M. Brown, and H. E. Petree, *J. Amer. Chem. Soc.*, **80**, 2852 (1958).

(3) H. C. Brown, W. J. Hammar, J. H. Kawakami, I. Rothberg, and D. L. V. Jagt, *ibid.*, **89**, 6381 (1967).

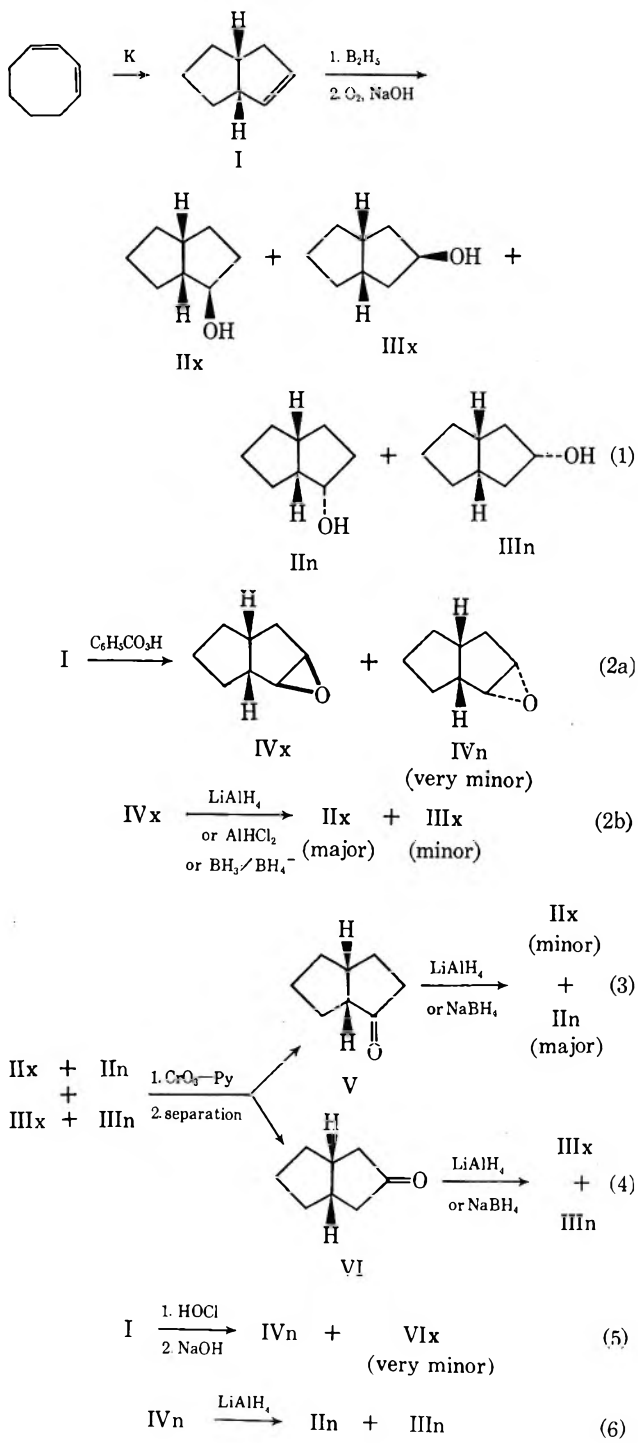
(4) Only the *endo* alcohol IIIn was reported as the product of the hydride reduction of the *3.3.0*-3-one (VI): R. Granger, P. Nau, and J. Nau, *C. R. Acad. Sci., Paris*, **247**, 2016 (1958).

(5) The previous calculation was made by assuming that the *3.3.0* was constructed of two planar cyclopentane rings: W. B. Moniz and J. A. Dixon, *J. Amer. Chem. Soc.*, **83**, 1671 (1961).

(6) IIx and IIn were obtained by the acid-catalyzed addition of formic acid to *cis,cis*-1,5-cyclooctadiene followed by hydrolysis: A. C. Cope and P. E. Peterson, *ibid.*, **81**, 1643 (1959).

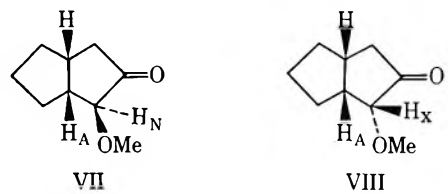
(7) H. C. Brown and N. M. Yoon, *ibid.*, **90**, 2686 (1968).

SCHEME I



"V" model containing two planar cyclopentane rings was assumed. This assumed "V" conformation seemed to offer a source of the disagreement, especially in conjunction with the fact that the *3.3.0*-3-one was reduced by hydride less stereospecifically than expected, suggesting a "W" rather than a "V" conformation. Therefore, we recalculated the expected shielding on the basis of other possible conformations. The best agreement between the observed and the calculated chemical shifts occurs by assuming a "W" conformation for both the *endo*- and *exo-3.3.0*-3-ol and for the *exo-3.3.0*-2-ol and an "S" conformation for the *endo-3.3.0*-2-ol. This shows that for the 3-alcohol, the skeletal stability ("W" shaped) determines the conformation, but for the 2-alcohol, the need for the 2-hydroxy to remain equatorial alters the conformation of the *3.3.0* skeletal system. This is consistent with the recent finding[8] that the J value of the α proton of 2-*endo*-ethyl-*3.3.0*-2,3-*cis*-diol indicates it to be "S" shaped with the larger ethyl group adopting an equatorial configuration and thus determining the conformational stability.

Actually, both of the "W" and "S" conformers seem to twist somewhat in order to avoid torsional strain; the extent should not, however, be large since the "T-U," "T-W," and "C_2" conformers give unsatisfactory calculated shielding. Our present assumption of concurrent contribution of "W" and "S" conformers can also explain τ and J values of some other *3.3.0* derivatives. For example, the following values were reported: δ 3.18, J_{A-N} = 3.6 Hz for VII; and δ 3.72, J_{A-X} = 5.0 Hz for VIII.[9] These J values cannot be interpreted on the basis of the assumption that either the "W" or "S" conformer alone is present (from the Karplus equation, J_{A-X} = 5.0 Hz corresponds to $\angle H_AH_X \sim 35°$; it then follows that J_{A-N} is larger than 7 Hz).



Experimental Section

Preparation of I.—I was prepared from 1,3-cyclooctadiene by isomerization with potassium.[10]

Preparation of IVx.—To 8.4 g (77.8 mmol) of I in 200 ml of chloroform was added dropwise 18 ml of a chloroform solution of perbenzoic acid (1.03 *N*). During the addition, the temperature was maintained below 25°; then the reaction mixture was stirred at room temperature for 2.5 hr. The mixture was washed with 10% aqueous NaOH solution three times, dried (Na_2SO_4), and concentrated. Distillation afforded 7.4 g of IVx, bp 83–87° (43 mm), $n^{30.0}D$ 1.4740. Vpc analysis (Apiezon Grease L, silicone DC-550 and PEG 6000) showed that IVx was accompanied by a small amount of IVn which was identified with the authentic sample (*vide infra*). Pure IVx, obtained by preparative vpc, had the following spectral values: nmr (CCl_4) τ 6.72 (t, C_3 **H**, J = 2.2 Hz), 6.85 (d, C_2 **H**, J = 2.2 Hz), and 7.0–9.2 (b, ring methylene and methine); ir (neat) 833 cm^{-1} (characteristic absorption of oxirane). *Anal.* Calcd for $C_8H_{12}O$: C, 77.42; H, 9.67. Found: C, 77.58; H, 9.74.

Preparation of IIx *via* Reaction 2b.—A solution of 1.0 g of IVx in 15 ml of ether was added dropwise to a suspension of 0.092 g of lithium aluminum hydride in 10 ml of ether with stirring. The temperature was kept below 5° during the addition and then the mixture was stirred at room temperature for 17 hr. Dilute hydrochloric acid was added to the reaction mixture with ice cooling and the mixture was extracted with ether. The ether layer was dried (Na_2SO_4) and concentrated. Distillation, bp 73° (8 mm), gave 0.5 g of a mixture of alcohols IIx and IIIx (83.4 and 16.6%, respectively, on the basis of vpc analysis on Apiezon Grease L and PEG 6,000 of the corresponding acetates and ketones).

Preparation of IIn *via* Reaction 3.—IIn was prepared *via* the reduction of V with sodium borohydride.[11]

Preparation of IIIx *via* Reaction 1.—At room temperature under nitrogen a solution of 10.0 g of boron trifluoride–ether complex (47 wt %) in 12 ml tetrahydrofuran was added dropwise

(8) E. Ghera, *J. Org. Chem.*, **33**, 1042 (1968).
(9) R. Noyori and M. Katō, *Tetrahedron Lett.*, 5075 (1968).
(10) P. R. Stapp and R. F. Kleinschmidt, *J. Org. Chem.*, **30**, 3006 (1965).
(11) A. C. Cope, M. Brown, and H. E. Petree, *J. Amer. Chem. Soc.*, **80**, 2852 (1958).

TABLE III

INDIVIDUAL SHIELDING EFFECT OF EVERY C–C BOND (σ_{av}) ON THE *3.3.0*-2 AND -3 PROTONS

	W				S		
σ_{av}	H_{2x}	H_{2n}	H_{3x}	H_{3n}	H_{2x}	H_{3n}	H_{3x}
C_1–C_2	−0.330	−0.330	+0.094	−0.076	−0.330	+0.094	−0.084
C_2–C_3	−0.330	−0.330	−0.330	−0.330	−0.330	−0.330	+0.019
C_3–C_4	−0.072	+0.090	−0.330	−0.330	+0.090	−0.330	+0.019
C_4–C_5	+0.053	+0.085	+0.094	−0.076	+0.085	+0.094	−0.084
C_5–C_6	−0.017	+0.032	−0.083	−0.019	−0.046	+0.097	+0.094
C_6–H_7	+0.022	+0.040	+0.009	+0.003	+0.021	+0.031	−0.330
C_7–C_8	−0.042	−0.053	+0.009	+0.003	−0.015	+0.031	−0.330
C_8–C_1	−0.016	+0.141	−0.083	−0.019	−0.093	+0.097	+0.094
C_1–C_5	−0.075	+0.023	+0.109	+0.053	+0.023	+0.109	+0.109
$\Sigma\sigma_{av}$	−0.81	−0.30	−0.55	−0.79	−0.60	−0.113	−0.49

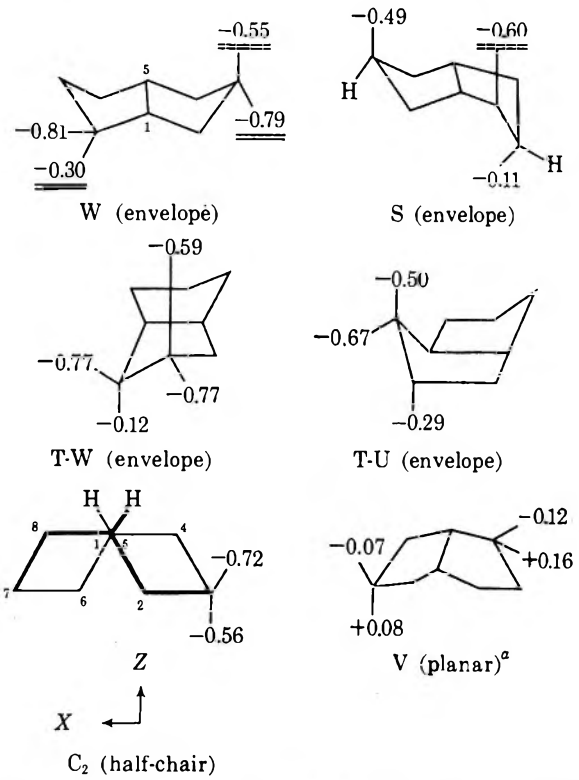


Figure 1.—Calculated overall shielding effect on the *3.3.0*-2 and −3 protons for every possible confomer. Calculated shielding in parts per million. [a] Previously predicted (ref 5).

with stirring to a mixture of 19.2 g of I, 2.0 g of sodium borohydride, and 300 ml of tetrahydrofuran. After 3 hr of stirring, the mixture was cooled in an ice bath and addition of 16 ml of 30% aqueous sodium hydroxide was followed by dropwise addition of 16 ml of 30% hydrogen peroxide over 2 hr. The mixture was extracted with ether; the ether extract was dried (Na_2SO_4) and concentrated. On distillation, 14.1 g of the mixture of IIx and IIIx was obtained at 90–95° (10 mm) together with a very small amount of IIn and IIIn. Pure IIIx was obtained by preparative vpc.

Preparation of IVn *via* Reaction 5.—A mixture of 2.1 g of I, 5 g of cracked ice, 1 ml of acetic acid, and 8 ml of an aqueous solution of monochlorourea[12] (containing 3.2 g of monochlorourea) was stirred with ice cooling for 2 days. After saturation with sodium chloride, the mixture was extracted three times with ether and the ether layers were combined and concentrated. The residue was added to a solution of 1.6 g of sodium hydroxide in 3 ml of water, and the mixture was stirred at room temperature overnight. The mixture was extracted with ether, and ether solution extracted was dried ($MgSO_4$) and concentrated. Distillation gave 0.6 g of IVn at 68–70° (27 mm). The nmr and ir spectra and the vpc showed that IVn was accompanied with a small amount of IVx. Pure IVn was obtained by preparative vpc. Spectral data follow: ir (neat) 843 cm^{-1} (characteristic absorption of oxirane); nmr (CCl_4), τ 6.67 (C_3 **H**), 6.77 (C_2 **H**, the coupling constant was observed much smaller than that of IVx), and 7.25–9.20 (ring methylene and methine).

Preparation of IIIn.—With stirring and ice-cooling a solution of 0.6 g of IVn in 10 ml of ether was added to a suspension of 0.1 g of lithium aluminum hydride in 10 ml of ether; then the mixture was stirred at room temperature for 20 hr. Hydrolysis was effected at 0° with a small amount of water and then 3 *N* hydrochloric acid, and the mixture was extracted with ether. Following drying ($MgSO_4$) and concentration of the ether extracts distillation afforded 0.2 g of a mixture of IIn and IIIn, bp 52° (7 mm), ~49° (4 mm).

General Procedure for Chromic Oxide–Pyridine Complex Oxidation of a Bicyclo[3.3.0]octyl Alcohol.—Chromic oxide (30 g) was added in small portions to 380 ml of pyridine with stirring and with ice-cooling. This solution was stirred for 12 hr with a solution of 14 g of a *3.3.0*-octyl alcohol dissolved in 190 ml of pyridine at room temperature. The mixture was poured onto cracked ice and extracted with eight 200-ml portions of ether. The ether extracts were combined and washed with 6 *N* hydrochloric acid, saturated aqueous sodium bicarbonate solution, and water. Following drying (Na_2SO_4) and concentration of the ether, 8.8 g of the corresponding ketone was distilled.

Calculations.—In order to calculate the nmr frequency shifts on the basis of bond anisotropy, plausible models of the *3.3.0* system were investigated. The *3.3.0* structure was constructed from two fused cyclopentane rings which were assumed to be either envelopes or half-chairs.[13] Thus the "W," "S," "T," "T-U," and "C_2" conformers were taken as models for the calculation. In each conformer, the bond between carbon 1 and 5, C_5C_1, was defined as the *Y* axis, with the midpoint of the bond defined as the origin O. The plane bisecting the dihedral angle $H_1C_1(C_5)H_5$ was defined as *ZY* plane (except in conformers "S" and "W" where the dihedral angle was zero; here the plane $H_1C_1C_5H_5$ was taken *ZY* plane).

The "S" and "W" conformers were constructed from two envelopes. Carbons 1, 2, 4, and 5 were placed on one plane with carbons 1, 5, 6, and 8 on another plane. Bond lengths of C–C, 1.54 Å, and C–H, 1.09 Å, were adopted. The angles were assumed to be $\angle C_2C_1H = \angle C_8C_1H = \angle C_4C_5H = \angle C_6C_5H$; other ∠CCH, 109° 28′; and $\angle C_2C_1C_8 = \angle C_4C_5C_6$, 109° 28′. The "T-W" and "T-U" conformers were also constructed from two envelopes but in these cases, carbons 1, 5, 4, and 3 were placed on one plane with carbons 5, 1, 8, and 7 on another. The "C_2" conformer was constructed from two half-chairs. Thus C_3–O or C_7–O was the C_2 axis of the orginal cyclopentane and the *Z* axis was the molecular C_2 axis of the *3.3.0* system.

By means of vector analyses, the positions of all of the carbons and of the necessary protons in the above models were ascertained in order to obtain values for γ and θ; γ is a distance between the proton in question and a midpoint (M) of a C_i–C_j bond, and θ is

(12) H. B. Donakoe and C. A. Vanderwerf, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 157.

(13) Pitzer showed that the envelope conformer was the most stable; later Brutcher and Hoffmann agreed that the half-chair conformer was more stable than the envelope conformer: K. S. Pitzer and W. E. Donath, *J. Amer. Chem. Soc.*, **81**, 3213 (1959); F. V. Brutcher, Jr., and W. Bauer, Jr., *ibid.*, **84**, 2232 (1962); R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963). In the present calculations, the evelope model of Pitzer and the half-chair model of Brutcher were used. One of the referees pointed out that a torsional angle of about 45° at the ring junction is probably the safest and the equilibrium conformations of the half-chair and the envelope are now believed to be equivalent in energy for cyclopentane itself.

an angle between HM and C_i–C_j. The frequency shifts were calculated according to the McConnell's equation[14]

$$\sigma_{av} = \frac{(3\cos^2\theta - 1)(X_L - X_T)}{3r^3}$$

where the magnetic susceptibility term, $X_L - X_T$, was taken to be -5.5×10^{-30} cm³/molecule.[15]

Examples of such calculations for the individual shielding effects of each C–C bond on the *3.3.0*-2 and -3 protons in the "W" and in the "S" conformation are given in Table III. These individual shielding effects are summed to give the frequency shift, $\Sigma\sigma_{av}$, of the proton. The frequency shifts of each significant proton in each model conformer are summarized in Figure 1.

Comparison of these calculated frequency shifts with the observed ones (Table IV) suggest that the *exo-3.3.0*-2-ol, the *exo-3.3.0*-3-ol, and the *endo-3.3.0*-3-ol are in the "W" conformation, while the *endo-3.3.0*-2-ol is in the "S" form. The observed frequency shifts of the *3.3.0* acetates are also in good agreement with the calculated values on the basis of similar conformational considerations.

(14) H. M. McConnell, *J. Chem. Phys.*, **27**, 226 (1957).
(15) A. A. Bothner-By and C. Naar-Colin, *Ann. N. Y. Acad. Sci.*, **70**, 833 (1958).

TABLE IV
NMR ABSORPTIONS OF THE 3.3.0-OLS AND -ACETATES. COMPARISON OF CALCULATED AND OBSERVED [δ_{rel} (2n H standard)]

	2n H	3x H	2x H	3n H
Obsd OH	0	0.20	0.36	0.43
Obsd OAc	0	0.19	0.36	0.45
Present calcd	0	0.22	0.30	0.49
Previous calcd (V model)	0	0.23	0.28	0.08

Registry No.—IIx, 23359-88-8; IIn, 24454-38-4; IIIx, 24454-39-5; IIIn, 24454-40-8; IVx, 24454-41-9; IVn, 24454-42-0.

Acknowledgment.—The authors are grateful to Dr. Elva Mae Nicholson for stimulating discussions.

Synthesis of 2-Oxabicyclo[2.2.2]octane

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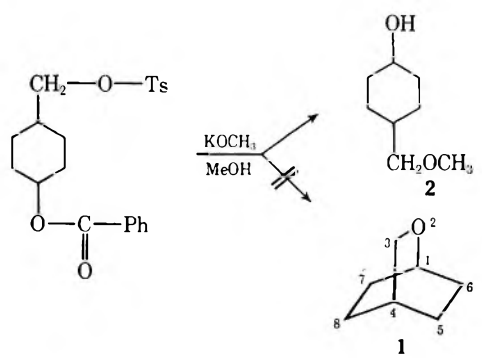
The synthesis of 2-oxabicyclo[2.2.2]octane (1) is described. Its structure was confirmed by mass spectrometry and nmr. Three different methods (I, II, III) for its preparation were investigated. Two of these involved a 1,4 transannular elimination; the other (II) was a dehydration procedure. Compound 1 was synthesized and isolated by all three methods; however, method I was shown to be superior. The *cis–trans* mixture of 4-hydroxycyclohexane-1-carboxylic acid (**4** + **5**) was obtained by hydrogenation of **3** over 5% Rh–Al_2O_3. The *cis* isomer was cyclized to the bicyclic lactone **6**, which was then reduced to the *cis*-diol **7**. Dehydration of **7** over Al_2O_3 gave 1 and the unsaturated alcohol **9** side product. Chlorination of **7**, followed by a 1,4 elimination, also gave 1. The best procedure involved the formation of the *cis* tosylate **8** and its intramolecular alkoxide ion elimination to give 1.

At least two attempts to synthesize the 2-oxabicyclo[2.2.2]octane (1) system have appeared in the literature.[3,4] The first attempt was made by Owen using an isomeric mixture of *cis*- and *trans*-4-tosyloxymethylene-1-benzoyloxycyclohexane according to Scheme I.

SCHEME I



This synthetic route did not give 1; rather it seems to have involved intramolecular tosyl elimination by methoxide ion, concurrent with ester hydrolysis to give 4-methoxymethylene-1-cyclohexanol (2). Wittbecker and coworkers[4] reported that the dehydration of *cis*-4-hydroxycyclohexanemethanol (7) gave products other than the expected bicyclic ether; none of the reaction products was isolated or characterized.

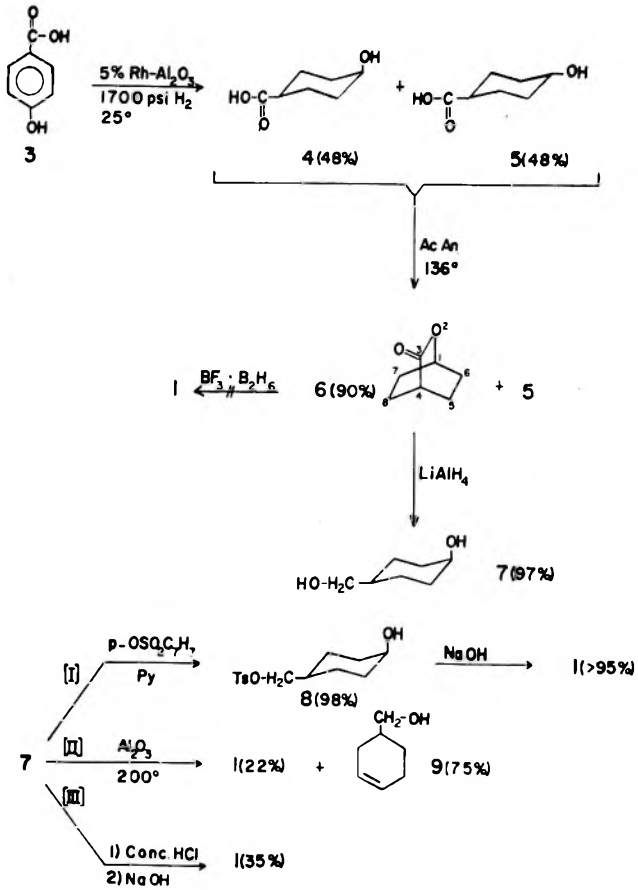
In this paper we report some of the physical properties and the synthesis of 2-oxabicyclo[2.2.2]octane (1) which was prepared by three different methods (Scheme II), one of which (method II) is a reinvestigation of the alumina dehydration of the *cis*-diol 7, as attempted by Wittbecker. Method III is similar to the approach used by Clarke to synthesize the 2-oxabicyclo[3.2.1]-octane system.[5] The synthetic methods are summarized in Scheme II (the isomers are shown in their expected favored conformations).

Results and Discussion

Hydrogenation.—The reduction of 4-hydroxybenzoic acid (3) to the isomeric mixture of *cis*- and *trans*-4-hydroxycyclohexane-1-carboxylic acid (**4** and **5**) has been accomplished previously.[6] Alternately the ethyl ester of **3** has been reduced at elevated pressure (270 atm) and temperature (220°).[7–9]

(1) Postdoctoral Fellow, Department of Chemistry, University of California at Santa Barbara.
(2) To whom inquiries should be addressed.
(3) L. N. Owen and P. A. Robins, *J. Chem. Soc.*, 326 (1949).
(4) E. L. Wittbecker, H. K. Hall, Jr., and T. W. Campbell, *J. Amer. Chem. Soc.*, **82**, 121 (1960).
(5) M. F. Clarke and L. N. Owen, *J. Chem. Soc.*, 2108 (1950).
(6) R. H. Levin and J. H. Pendergrass, *J. Amer. Chem. Soc.*, **69**, 2436 (1947).
(7) H. E. Unguade and F. V. Morriss, *ibid.*, **70**, 1898 (1948).
(8) W. Schneider and A. Huttermann, *Arch. Pharm. (Weinheim)*, **298**, 226 (1965).
(9) C. V. Banks, J. P. La Plante, and J. J. Richard, *J. Org. Chem.*, **23**, 1210 (1958).

SCHEME II

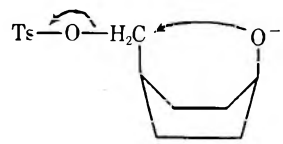


In our experience the procedure using PdO catalyst[6] gave unacceptably low yields (<25%) of the reduced product. The alternate methods, although reported to give good yields of **4** and **5**, involve the synthesis of additional intermediates. A more facile synthesis was desirable and we investigated the reduction with 5% Rh–Al_2O_3, a catalyst known to promote ring hydrogenation of aromatic phenols under relatively mild conditions.[10] At 110 atm and at ambient temperature, the reduction of **3** in the presence of a small amount of 5% Rh–Al_2O_3 proceeded smoothly and nearly quantitatively.

Cyclization of the Isomeric Mixture of 4 and 5.—The *cis* conformational isomer **4** lactonized readily and the 2-oxabicyclo[2.2.2]octan-3-one (**6**) was isolated by sublimation of the reaction mixture. Crystalline **6** was obtained in excellent yield after extraction with petroleum ether. The melting characteristics of this compound depend on the heating rate, indicating the existence of polymorphic forms. A change in the crystal structure occurs between 82 and 85°. The new structure shows a higher temperature transition (127–128°) where liquefaction is finally observed. The *trans* isomer **5** (mp 148°)[11,12] remained in the sublimator. The ir spectrum of **6** shows the absence of the OH band at 3400 cm^{-1} and an intense carbonyl band at 1740 cm^{-1}. We assigned the nmr absorption at δ 4.46 to the bridgehead proton at the 1 position. The δ 2.38 absorption was assigned to the other bridgehead proton at the 4 position. At the concentration employed, both of these absorptions appeared as broad singlets and did not show any multiplicity. The integration of the peaks gave the correct relative number of hydrogens 1:1:8, consistent with structure **6**.

The direct synthesis of **1** from **6** using BF_3–B_2H_6 according to the procedure of Pettit[13,14] failed; however, we did not make an extensive investigation of this approach. The direct reduction of **6** to **1** was attempted by Wittbecker without success.[4] An alternate scheme for the synthesis of **1** had to be employed. The reduction of **6** to **7** with $LiAlH_4$ was accomplished without problems. The *cis*-diol was obtained as a clear syrup and its physical properties were in agreement with those reported in the literature.[8] The tosyl derivative of **7** was prepared by the usual methods. Under the conditions employed, the primary alcohol function of **7** was tosylated predominantly. The ir of the product **8** exhibited the expected hydroxyl, aromatic, and sulfonate absorptions of a tosyl intermediate.

1,4 Transannular Elimination (Methods I, II, and III).—Three different ring closure reactions were investigated. Two of these involve the formation of the alkoxide ion which then undergoes intramolecular displacement of the tosyl (or chlorine) leaving group as shown in **10** for intermediate **8**, presumably in the boat conformation. Preliminary experiments indicated



10

that these methods would give acceptable results if the problems inherent in the isolation of the highly volatile bicyclic ether could be solved. A loss of **1** >70% was incurred if the usual procedures of extraction and solvent evaporation were applied during work-up. Samples of **1** could not be successfully separated by fractional distillation from any of the eluting solvents nor could **1** be recrystallized from a number of solvents without excessive loss of material.

To obviate these problems the elimination reaction was accomplished in the solid state without the use of solvents at any stage of the synthesis. (For apparatus, see Figure 1 in the Experimental Section.) Using this approach, a near-quantitative yield of **1** was achieved by method I. Method III involved the synthesis of the monochloromethyl derivative of the *cis*-diol and its cyclization to **1**. Compound **8** was obtained as a yellow oil containing additional components, and because of the excellent outcome of method I, this product was not investigated in greater detail. The dehydration of **7** over alumina (method II) was accomplished in low yield (22% estimated, 6.7% actually isolated). The predominant component of the reaction mixture was a clear liquid identified as 1-hydroxymethyl-4,5-cyclohexene (**9**) by its ir spectrum (–OH at 3300 cm^{-1} and C=C at 1650 cm^{-1}) and by its retention time when cochromatographed with an authentic sample.[15] The minor component was characterized as the bicyclic ether **1** by its retention time and ir and nmr spectra.

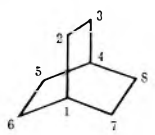
(10) Louis F. Fieser and Mary Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 979.
(11) H. Batzer and G. Fritz, *Makromol. Chem.*, **4**, 213 (1954).
(12) N. R. Campbell and J. H. Hunt, *J. Chem. Soc.*, 1379 (1950).
(13) G. R. Pettit and D. M. Piatak, *J. Org. Chem.*, **27**, 2127 (1962).
(14) G. R. Pettit and T. R. Kasturi, *ibid.*, **26**, 4557 (1961).
(15) We are deeply grateful to Professor Bruce Rickborn for providing a sample of **9** and for the use of his vpc instruments.

The melting characteristics of compound **1** closely parallel those of the lactone **6**. The volatile solid undergoes a crystal structure transition at approximately 42°; then the new crystal form rapidly vaporizes at the higher temperature range. The ir showed a strong absorption in the 1025–1035-cm^{-1} range. These intense bands are indicative of a cyclic ether and are within the range assigned by Rosowsky to a series of bicyclic oxetanes and to those assigned to a series of cyclic ethers.[16,17]

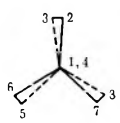
We assigned the nmr absorption at δ 3.65 to the tertiary bridgehead proton at position 1 and that at δ 3.46 to the methylene protons at position 3. Analogous to the lactone **6** case, the proton at position 1 in the bicyclic ether did not exhibit any multiplicity but gave only a broad unresolved singlet. The bridge methylene protons also appear as a broad singlet and not as a doublet. The nonequivalence of the methylene protons of the almost rigid cyclohexane boat conformation is further demonstrated by the unresolved doublet at δ 1.72–1.57. It is probable that the absorption at δ 1.92 is due to the tertiary bridgehead proton at the 4 position.

The protons at the 1 and 3 positions ($\delta_1 - \delta_2 = 11$ cps) did not integrate in a 1:2 ratio [found 1:3 = 1.4:1]; however, the integral sum of these two peaks showed a 3:9 hydrogen ratio in accord with structure **1**. It is conceivable that a contribution of the upfield methylene absorption coalesces into the absorption signal of the bridgehead proton. A similar absorption behavior, leading to incorrect integration, has been reported before, and it is encountered in analogous cases where the observed chemical shift is small.[18]

Recently the conformation of bicyclo[2.2.2]octane (**11**) was determined by single-crystal X-ray analysis.[19] It was shown that the carbon bond angles do not deviate markedly from the tetrahedral value. In the crystal-



11



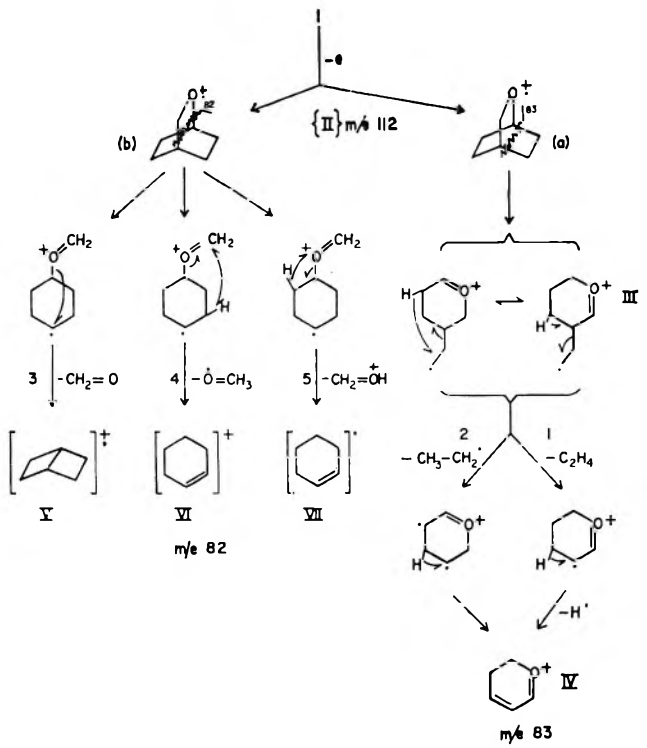
12

line state **11** is believed to exist in a slightly staggered conformation **12** rather than a fully eclipsed one, resulting in a torsional angle of the C(2)–C(3), C(5)–C(6), and C(7)–C(8) bonds of 5°. An analogy may be drawn between this system and the similar 2-oxabicyclo[2.2.2]octane structure. The heteroatom in **1** would not be expected to cause a great deviation from the tetrahedral value in the carbon–carbon bonds. In structure **11** the slightly staggered conformation is assumed to relieve or optimize the nonbonded hydrogen interactions. The relatively strain-free structure of **1** would be expected to show similar angular dependencies in the crystalline state.

Mass Spectrum of 1.—The structure assigned to the bicyclic ether was further supported by its mass spectrum. The intensity of the observed parent peak [M^+ (10)] m/e 112 is small; however, such behavior has been observed with many aliphatic ethers.[20] The existence of an oxygen atom in the fragmentation pattern is apparent from the intense mass peaks at m/e 31, 45, and 59; these could be considered to be homologous fragments of the $H_2C{=}OH$ structure.

The favored decomposition mode of **1** would be expected to involve β cleavage. This could occur at two different positions [Scheme III, steps a and b] in the parent molecular ion (II).

SCHEME III



The peak at m/e 83, could arise from a concerted β cleavage of the bicyclic ether *via* (a) and a concomitant α-ring cleavage of the ensuing cyclic alkyl oxonium ion (III). This ion could eliminate the molecule ethylene concurrent with the expulsion of a vicinal proton as H°, to give the (M − 29) cyclic oxonium ion fragment (IV) (Scheme III, path 1). Alternately, structure III could undergo intramolecular rearrangement of a hydrogen atom transferred *via* a six-membered cyclic intermediate concurrent with the migration of a vicinal proton (Scheme III, path 2). The expulsion of an ethyl radical could give the same cyclic oxonium ion (IV) postulated for path 1. Similar modes of H-atom transfer in molecules containing heteroatoms have been invoked to rationalize the observed fragmentation patterns of alkylated tetrahydrofuran and tetrahydropyran rings.[21,22] The postulated six-membered hydrogen transfer scheme is not an absolute requirement, because similar transfers can occur through smaller, cyclic transition states.[23] In either case the proposed ion fragment would be resonance stabilized in the form of the cyclic oxonium ion (IV).

(16) A. Rosowsky and D. S. Tarbell, *J. Org. Chem.*, **26**, 225 (1961).
(17) G. M. Barrow and S. Searles, *J. Amer. Chem. Soc.*, **75**, 1175 (1953).
(18) J. D. Roberts, "Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 32.
(19) A. F. Cameron, G. Ferguson, and D. G. Morris, *J. Chem. Soc., B*, 1249 (1968).
(20) F. W. McLafferty, *Anal. Chem.*, **29**, 1782 (1957).
(21) G. Ohloff, U. H. Schulte-Elte, and W. Willhalm, *Helv. Chim. Acta.*, **47**, 602 (1964).
(22) R. E. Wolff and M. Lenfant, *Bull. Soc. Chim. Fr.*, 2470, (1965).
(23) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 229.

β cleavage could also occur *via* (b) and at least three modes of fragmentation are possible. From the parent ion (II), paths 3 and 4 involve an α-ring cleavage by heterolysis of the carbon–oxygen bond. In path 3 the molecule of formaldehyde could be eliminated with formation of the bicyclo[2.2.0]hexane radical ion (V). In path 4 a methoxyl radical could be generated concomitant with the cyclohexenyl carbonium ion (VI). Similar modes have been demonstrated in the fragmentation of cyclic ethers.[24]

Path 5 invokes a H-atom migration to the oxygen, concurrent with homolytic α cleavage of the carbon–oxygen bond giving the protonated form of formaldehyde and the cyclohexenyl radical (VII). Such a migration has been proposed for the fragmentation of vinyl ethers.[25]

Only a low-intensity ($\ll$10%) (M − 30) peak is observed in the mass spectrum of the bicyclic ether, indicating that β cleavage as in (b) may not be a favored mode of fragmentation in this case. It is then assumed that cleavage, most likely occurs *via* (a) and probably by path 1. The peak at *m/e* 83 would then be due to the formation of the cyclic oxonium ion (IV). Without additional data a more valid selection of fragmentation modes is not possible and the conclusions reached here are only tentative.

Experimental Section

Materials and Equipment.—Reagent grade 4-hydroxybenzoic acid was recrystallized twice from ethanol–ether. High-pressure hydrogenation was carried out in a Parr Series 4000 hydrogenator using Engelhard 5% Rh–Al_2O_3 catalyst. All analytical vpc was done using a Varian Aerograph Series 200 with (a) an 18 ft × 1/8 in. copper column packed with 10% 20M Carbowax on Chromsorb W, 60–80 mesh, (b) a 12 ft × 0.25 in. copper column packed with 18% 6000 Carbowax on Chromsorb W, 60–80 mesh. The helium carrier gas flow rate was 46 cc/min for both columns. Preparative vpc was done on an Aerograph Model A-90-P with (c) a 25 ft × 0.25 in. copper column packed with 20% 20M Carbowax on Chromsorb W 60–80 mesh and a helium flow rate of 55 cc/min. The ir spectra, unless otherwise stated, were obtained as films or KBr disks on a Perkin-Elmer Model 137 spectrophotometer calibrated with polystyrene film. The nmr spectra were obtained with a Varian Associates A-60 spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given on the δ scale in parts per million relative to TMS. The mass spectrum was obtained from an Associated Electrical Industries MS902 double-focusing instrument. A special apparatus was built to facilitate the sublimation and quantitative collection of highly volatile solids (Figure 1). Melting points are uncorrected. The elemental analysis were performed by Galbraith Laboratories Inc., Knoxville, Tenn.

***cis*- and *trans*-4-Hydroxycyclohexane-1-carboxylic Acid (4 + 5).**—Recrystallized *p*-hydroxybenzoic acid (3), 100 g (0.724 mol), was dissolved in 150 ml of warm glacial acetic acid and transferred to the steel cylinder of a Parr high-pressure hydrogenator. After the solution cooled to ambient temperature, 1.2 g of 5% Rh–Al_2O_3 catalyst was introduced, and 1500-psi H_2 pressure at 20°, was applied. After 24 hr the required volume of hydrogen was absorbed and the hydrogenation was discontinued. The catalyst was removed by filtration over Celite and the clear solution was distilled under vacuum until all the solvent was removed. A clear viscous liquid was obtained; it readily crystallized on addition of dry ethyl ether. The *cis–trans* mixture of 4-hydroxycyclohexanecarboxylic acid (4 + 5) was recrystallized from ethanol–ethyl ether to give a 96% yield of a white crystalline compound having a melting point range of 120–125° (lit.[12] 120°). The ir spectrum (KBr) of 4 + 5 showed bands at 3400 (s), 2400, 2600 (broad), 1700 (s), 1055, 1020 (s), 955 (s), 740 (m) cm^{-1}; no bands were present in the 1600- and 800–850-cm^{-1} range.

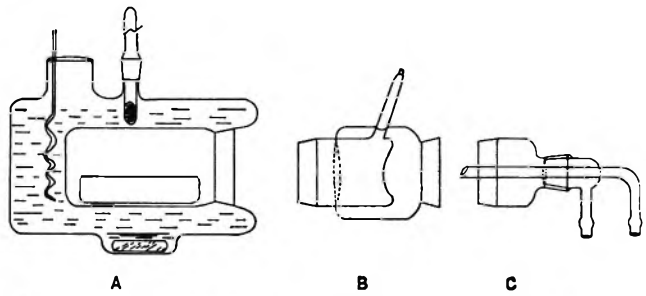


Figure 1.—Sublimation apparatus for a highly volatile component: (A) silicon oil vessel fitted with a magnetic stirring bar, glass boat, heating coil, and thermometer; (B) water-jacketed collection apparatus with a leur-tipped side arm and a 29/12 ⅋ joint; (C) condenser attachment with a 29/12 ⅋ joint.

2-Oxabicyclo[2.2.2]octan-3-one (6).—The isomeric mixture of 4-hydroxycyclohexanecarboxylic acids (4 + 5), 29 g (0.2012 mol), was dissolved in 300 ml of acetic anhydride and refluxed for 6 hr under anhydrous conditions; then it was left for 24 hr at ambient temperature. The acetic anhydride was removed by vacuum distillation and a viscous liquid was obtained. The crude mixture of lactone 6 and *trans* isomer 5 was introduced into a 1-l. sublimator. At a pressure of 2.0 mm and at a silicon oil bath temperature range of 100–115° the lactone 6 was collected (over a 3-hr period) as a crystalline semisolid. The crystalline residue was predominantly the *trans*-4-hydroxycyclohexylcarboxylic acid (5) isomer. The crude compound isolated in a 55% yield was further purified by extraction with petroleum ether (bp 20–60°) in a Soxhlet apparatus during a 10-hr period. The bicyclic lactone 6 crystallized from petroleum ether in needle-shaped crystals with mp 126–127° (lit.[12] mp 127–128°) and gave a 90% yield (12.0 g) as calculated for the cyclization of the *cis* isomer 4. A sample of 6 dissolved in ethyl ether was analyzed by vpc (column A, temperature 178°, isothermal) and was found to be homogeneous (retention time 24.5 min). Infrared analysis (KBr) showed bands at 1740 (s), 1065 (s), 1000 (s), 955 (m), 878 (m), 770 (m) cm^{-1}; no bands at 3550 cm^{-1} were obtained. The nmr spectrum of 6 in CCl_4 exhibited the following absorptions: δ 4.60 (broad 5, 1 H), 2.50 (broad, 1 H), 1.87 (broad, 8 H); signals in the range of δ 12.0–10.4 were not present. The sample for elemental analysis was sublimed a second time and had mp 127–128°.

Anal. Calcd for $C_7H_{10}O_2$: C, 66.62; H, 8.00. Found: C, 66.53; H, 8.07.

***cis*-4-Hydroxymethylcyclohexanol (7).**—Under anhydrous conditions and a nitrogen atmosphere, a suspension of 6.0 g (0.1581 mol) of $LiAlH_4$ in dry ethyl ether was treated dropwise with a solution of 15 g (0.1189 mol) of 6 dissolved in 200 ml of dry ethyl ether. The addition was continued for 40 min; then after the exothermic reaction subsided, the mixture was refluxed for an additional 4 hr and left overnight at ambient temperature. Excess hydride was destroyed by the dropwise addition of 6 ml of a 10% KOH solution followed by 6 ml of water. The suspension was filtered over Celite and the residue was washed with ethyl ether. The ethereal phase was separated and dried over $MgSO_4$. The solvent was removed by vacuum distillation and a clear viscous liquid (10.22 g) was obtained. An additional amount (4.9 g) of 7 was obtained by continuous extraction of the residual salts in a Soxhlet apparatus using ethyl ether as the solvent. The combined yield was 15.10 g (97.6%): ir (film) 3300 (s), 1040, 1025 (s), 978 (s), 935 (m) cm^{-1}; the band at 1750 cm^{-1} was not present. A solution of this material in *p*-dioxane was examined by vpc (column A, temperature 178°) and found to be homogeneous (retention time 46.7 min). A sample of 7 was distilled at 0.2 mm; the major fraction had a vapor temperature of 120–122° and $\mu^{20}D$ 1.4935. These values are in agreement with those reported for 7 when isolated from the reduction products of the *cis–trans* mixture of ethyl 4-hydroxycyclohexane-1-carboxylate.[8]

***cis*-4-Tosyloxymethylene-1-cyclohexanol (8).**—A solution of 11.95 g (0.0918 mol) of 7 in 50 ml of dry pyridine was cooled to −5°. A solution of *p*-toluenesulfonyl chloride (19.14 g, 0.1004 mol) in 35 ml of dry *p*-dioxane was then added dropwise over a

(24) A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 2920 (1965).

(25) S. Meyerson and J. D. McCollum, *Advan. Anal. Chem. Instrum.*, **2**, 202 (1963).

2-hr period while the temperature was maintained at −5°. After the addition, the reaction mixture was allowed to remain at −5° for another 3-hr period; then it was left overnight at ambient temperature. The mixture was rapidly poured into a a stirred slurry consisting of 100 ml of 6 *N* HCl and ice. A clear oily layer was formed. The aqueous phase was decanted and the residue was extracted with two 150-ml portions of chloroform. The organic layer was separated and dried with $MgSO_4$. The solvent was removed by vacuum distillation and a light yellow, viscous oil 25.38 g (98% yield) was obtained. After 2 weeks at room temperature, **8** solidified to a semicrystalline compound: ir (film) 3550, 3400 (broad), 1600 (m), 1250 (s), 1175, 1190 (s), 815, 843 (s) cm^{-1}.

2-Oxabicyclo[2.2.2]octane (1). Method I.—The apparatus represented in Figure 1 was utilized for this step. Under anhydrous conditions and a nitrogen atmosphere, NaOH, 2.0 g (0.050 mol), was finely powdered and transferred to a glass boat containing 2.0 g (7.083 mmol) of **8**. The reactants were thoroughly mixed, and then the container was placed in the sublimator maintained at atmospheric pressure. The temperature of the surrounding silicon oil was gradually raised to a maximum of 150° and maintained for 1.5 hr. Clusters of white, needle-shaped crystals formed on the cooled surface of the collector. The apparatus was allowed to slowly cool to room temperature, then the collector was quickly removed and sealed. Compound **1** was obtained in a quantitative yield (0.795 g) and had a camphor-like odor: mp 76–77° (sublimation); ir ($CHCl_3$) 2900 (s), 1190 (s), 1025–1035 (s), 955 (s), 865 (s), 810 (m) cm^{-1}; nmr (CCl_4) δ 3.65 (fairly sharp singlet), 3.46 (fairly sharp singlet), 3 H, 1.93 (broad singlet, not fully resolved), 1.72, 1.57 (unresolved broad doublet) 9 H; mass spectrum (70 eV) (70°) *m/e* (relative intensities) 112 (M^+, 10), 83 (M − 29, 11), 74 (63), 73 (13), 59 (97), 56 (13), 55 (16), 45 (80), 44 (12), 43 (29), 42 (10), 41 (29), 39 (13), 31 (100), 29 (97) (only those absorbances with a relative intensity of 10% or greater are listed). Crystallization of **1** from ethyl ether, methanol, and *p*-dioxane failed. A sample of the crystalline material dissolved in ethyl ether was analyzed by vpc and shown to be homogeneous: (column A, temperature 130°, isothermal) retention time 4.2 min, (178°) 2.17 min; (column B, temperature 130°, isothermal), 24.0 min. A sample for elemental analysis was further purified by a second sublimation at 50 mm and at a silicon oil bath temperature range of 48–58°. *Anal.* Calcd for $C_7H_{12}O$: C, 74.95; H, 10.77. Found: C, 74.74; H, 10.97.

Method II.—An apparatus was built to facilitate the short-path distillation and fraction collection of small volumes of distillate. Under anhydrous conditions, 2.01 g (0.0154 mol) of **7** and 2.0 g of activated alumina[26] were heated with a silicon oil bath to 220–230° at atmospheric pressure. During the initial phase of the dehydration a biphasic liquid collected on the condenser and gradually formed a semicrystalline deposit. The condensed material was heterogeneous during the entire course of the dehydration. Heating was discontinued when all of **7** had been dehydrated over the alumina bed. The semisolid product (1.36 g) was collected, and an aliquot dissolved in ethyl ether was examined by vpc (column A, temperature 130°) and found to contain the following compounds: (a) retention time 1.4 min, one or more unresolved highly volatile, low-molecular-weight compounds which were not investigated further; (b) 4.2 min, a highly volatile white crystalline compound identified as **1** by ir, nmr, and mass spectra; (c) 15.5 min, unidentified; (d) 24.1 min, isolated as a viscous clear liquid and characterized as **9** by ir 3300 (s), 1650 (w), 1025, 1035 (s), and 970 (m) and by comparison with the retention time of an authentic sample.[25] Compound **7** was not detected using this column at a temperature of 178°. The relative ratios of the peak areas of a:b:c:d were 0.64:1:0.14:1.14 (indicating approximately a 22% yield of the bicyclic ether). The combined fractions of **1** collected by preparative vpc, weighed 129.5 mg, an actual yield of 6.7%.

Method III.—The *cis*-diol **7** (0.50 g, 3.84 mmol) was dissolved in 1 ml of concentrated HCl and sealed in a vial under nitrogen. The vial was heated in a silicon oil bath at a temperature range of 115–120° for 5.5 hr. During this period the solution became heterogeneous and a yellow-colored upper phase appeared. The reaction mixture was gradually cooled to room temperature; then the vial was opened, and a saturated $NaHCO_3$ solution (2 ml) was added. The mixture was extracted twice with 3 ml of chloroform; the organic layer was separated, washed with water, and dried over $MgSO_4$. The solvent was removed by vacuum distillation at 30° and a yellow viscous liquid (0.40 g) was obtained in a 57% yield. It was stored in a vacuum desiccator over KOH. An aliquot, dissolved in ethyl ether was found to be heterogeneous when analyzed by vpc (column A, temperature 175°) with the following major components: (a) retention time 7.9 and 8.4 min, an unresolved doublet; (b) 25.5 and 26.4 min, an unresolved doublet. The *cis*-diol was not present. The relative ratio of the peak areas of a:b was 1:10.

The crude oil (0.183 g) was treated with 0.183 g of powdered NaOH, mixed into a slurry, and placed into a microsublimator. The temperature of the silicon oil bath was maintained at 130–140° for 1 hr. Gradually the temperature was raised to 200° to expel all the volatile fractions from the solid residue. A biphasic liquid collected on the condenser; it was dissolved in ethyl ether, analyzed by vpc (column A, temperature 175°, isothermal), and found to contain the following components: (a) retention time 2.0 min, the most volatile component which was collected and identified as **1** by ir and nmr; (b) 7.8 and 8.3 min, unresolved doublet; (c) 25.5 and 26.3, min, unresolved doublet. The relative ratio of peak areas b:c (comparable with the previous a:b ratio) was ~5.6. The estimated yield of a = **1** (assuming a:b:c = 100%) was 35%.

Registry No.— **1**, 280-39-7; **4**, 3685-22-1; **5**, 3685-26-5; **6**, 4350-84-9; **7**, 3685-24-3; **8**, 24472-55-7.

Acknowledgment.—This work was supported by a grant from the National Institutes of Health.

(26) Alcoa activated alumina (F 6¼ 8).

Condensation of Unsymmetrical Aliphatic Ketones with Formaldehyde in Trifluoroacetic Acid

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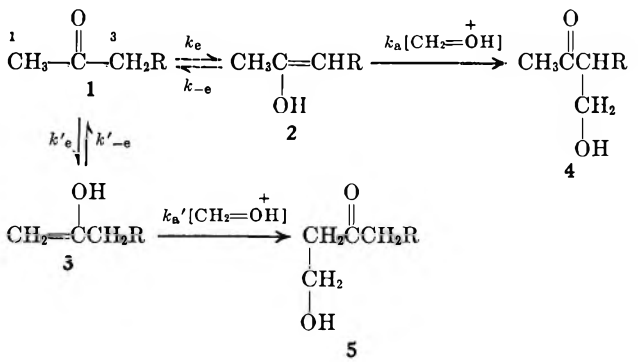
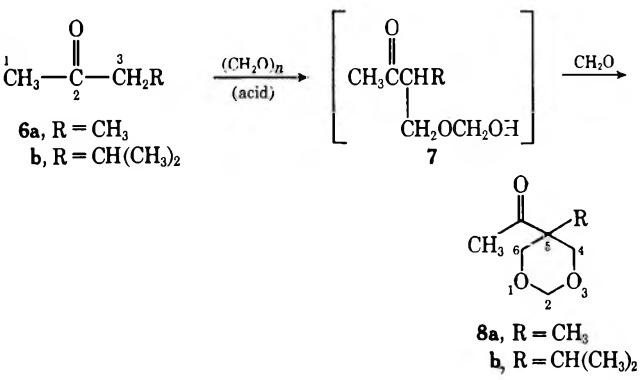
It is shown that methyl ethyl, methyl isopropyl, and methyl isobutyl ketones and 2-methylcyclohexanone condense with paraformaldehyde in trifluoroacetic acid predominantly at the more substituted α-carbon atom. Methylene positions condense with 3 mol of formaldehyde forming 1,3-dioxanes whereas methine positions condense with 1 mol irreversibly, forming β-ketols which trifluoroacetylate faster than they are formed.

Several generalizations regarding the mechanism and scope of the acid-catalyzed condensation of nonenolizable aldehydes with ketones are to be found in a recent review of the aldol reaction.[1] Important steps in the acid-catalyzed condensation of formaldehyde with unsymmetrical aliphatic ketones (**1**) are summarized in Scheme I.

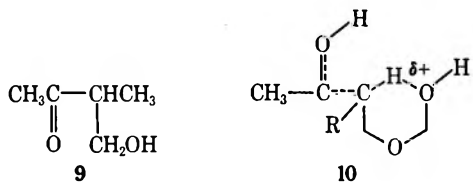
SCHEME I



Recently three very important studies of the acid-catalyzed condensation of trioxane with aldehydes and ketones have appeared.[2] No α-disubstituted ketones were studied but methyl ethyl (**6a**) and methyl isobutyl ketones (**6b**) were found to condense with 3 mol of formaldehyde predominantly at the methylene position forming 1,3-dioxanes (**8**) with selectivity that varied with the choice of catalyst.[2a] Aluminum chloride and



boron trifluoride etherate gave nearly equal amounts of 1 and 3 condensation with **6b** whereas sulfuric acid led to a 6:1 preference for the 3 position. Selectivity was not due to preferential enolization of ketol **9** in the 3 position but was attributed to intramolecular catalysis of enolization in hemiformal **7** *via* a six-membered-ring transition state **10**. Dioxane **8a** is also formed selectively in acetic acid with sulfuric acid catalyst, conditions under which the condensation step is rate limiting.[2c]



Prior to the reports of Wesslen and coworkers,[2] we had begun a study of the aldol reaction in trifluoroacetic acid, primarily because of its high solvent power, volatility, and suitability as an nmr solvent. The results of part of this study are reported in the next section.

Results and Discussion

Condensation at a Methylene Position.—In the present study condensation of 0.1 mol of methyl ethyl (**6a**) and methyl isobutyl ketones (**6b**) with paraformaldehyde (0.4 mol of CH_2O) in trifluoroacetic acid at 60–75° gave dioxanes **8a** and **8b** in yields of 23.2 and 47.7%, respectively (Table I; see Experimental Section).

TABLE I

OPTIMAL CONDENSATION EXPERIMENTS

	Ketone, mol	$(H_2CO)_n$, mol	Time, hr	Temp,[a] °C	Product, (% yield)
6a	0.1	0.4	24	60	**8a** (23.2)[a]
6b	0.1	0.4	24	75	**8b** (47.7)[a]
12a	0.1	0.13	24	25	**14a** (72.8)
12b	0.1	0.13	24	60	**14b** (77.8)

[a] These yields are minimal since the dioxanes proved to be quite water soluble and difficult to extract.

The reactions were followed by nmr[3] for a decrease in the signal for the $CH_3C(=O)-$ group at δ 2.30 for **6a** and 2.32 for **6b**. It was thus observed qualitatively that the former ketone was much more reactive than the latter. In the case of **6a**, the signals for starting material were replaced by AB quartets centered at δ 5.30 (2 H, J = 6.5 Hz, $\Delta\nu$ = 32 Hz) and 4.19 (4 H, J = 12 Hz, $\Delta\nu$ = 76 Hz) expected[2a] for the 1,3-dioxane ring positions 2, 4, and 6, respectively, in addition to signals for the 5-methyl and $CH_3C(=O)-$ substituents (δ 1.07 and 2.44, respectively).

(1) A. T. Nielsen and W. J. Houlihan, *Org. React.*, **16**, 1 (1968).

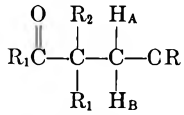
(2) (a) B. Wesslen and L. O. Ryrfors, *Acta Chem. Scand.*, **22**, 2071 (1968); (b) B. Wesslen, *ibid.*, **22**, 2085 (1968); (c) B. Wesslen, *ibid.*, **23**, 1017 (1969).

(3) Determined at 100 MHz in TFA at room temperature unless otherwise noted.

Support for the 100 MHz nmr spectrometer from National Science Foundation Grant No. GP-8510 is gratefully acknowledged.

TABLE II

PHYSICAL DATA OF MONOCONDENSATION PRODUCTS

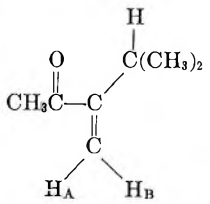


12, 13, 14, 16

Compd (R)	Bp (mm) or mp, °C	$\nu_{C=C}^{CHCl_3}$, cm^{-1}	$COCF_3$	δ_{AB} ($\Delta\nu$)[a]	J_{AB}, Hz	δ_{R_2}	δ_{R_1}
13a (H)	50–55 (0.004)	1690		3.51 (~0)[b]		1.18	
13b (H)		1685		3 57 (~0)		1.16[b]	2.17[b]
14a ($COCF_3$)	58–62 (0.01)	1700	1775	4.44 (22)[c]	11	1.34[c]	
14b ($COCF_3$)	28–30 (0.01)	1700	1780	4.46 (~0)[c]		1.33[c] (R_1)	2.35
16a (Ts)		1710		3.92 (~0)[d]		1.10[d]	
16b (Ts)	54.5–55.5	1705		3.90 (~0)[d]		1.11[d] (R_1')	2.05

[a] Separation in hertz between an inner and outer line of the AB quartet. [b] In $CDCl_3$. [c] In TFA. [d] In CCl_4.

Condensation of **6b** could not be carried to completion since prolonged heating resulted in elimination to form the α,β-unsaturated ketone **11**,[4] as evidenced by the

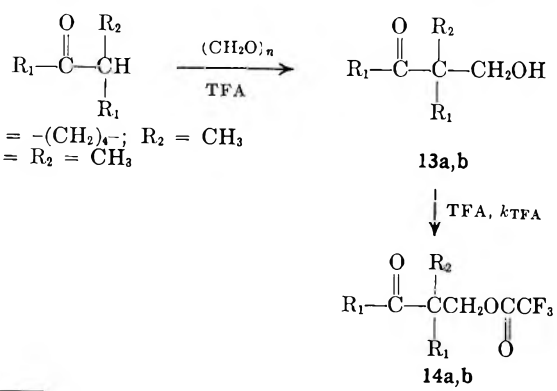


11

appearance of a singlet at δ 6.26 and doublet at δ 5.99 for H_A and H_B, respectively. Condensation with more than 3 mol of formaldehyde per mol of **6b** seemed to be more prevalent than competing dioxane formation at the 1 position, since consumption of the starting ketone (singlet at δ 2.30) was incomplete after 4 equiv of CH_2O [singlet at δ 5.3 for $(CH_2O)_3$] had been consumed. The formation of an isomeric dioxane at the 1 position is unlikely also in view of the fact that dioxane **8b** could be isolated in greater than 95% purity (by vpc) by partial fractional distillation of the crude product.

In contrast, methyl ethyl ketone (**6a**) reacted completely to give a crude product containing only minor impurities by nmr, even when 1 equiv of CH_2O in excess was used. No unreacted starting material could be detected.

Condensation at Methine Positions.—Condensation of 2-methylcyclohexanone (**12a**) with formaldehyde has apparently not been previously studied under acidic conditions (excepting, of course, the Mannich reaction[5]). Reaction of this ketone with paraformaldehyde in TFA under a variety of conditions (Table I summarizes optimal conditions) produced moderate yields of 2-trifluoroacetoxymethyl-2-methylcyclohexanone (**14a**) which was characterized by its nmr spectrum (Table II, Experimental Section) and infrared carbonyl bands at 1700 and 1775 cm^{-1}.

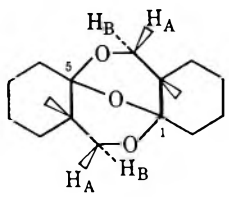


12a, $R_1 = -(CH_2)_4-$; $R_2 = CH_3$
b, $R_1 = R_2 = CH_3$

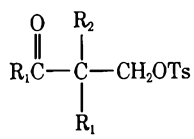
13a,b

14a,b

Hydrolysis of **14a** with aqueous methanolic 2 *N* sodium hydroxide gave ketol **13a**[6] which underwent dehydrative dimerization (see Experimental Section) forming **15**. The structure of **15** followed readily from elemental analysis and lack of hydroxyl and carbonyl absorption in the infrared. Moreover, the nmr spectrum of **15** was uniquely simple, showing, besides methylene absorption, a 6 H singlet at δ 0.91 (in $CDCl_3$) and 4 H AB quartet centered at δ 3.79 (J = 11.5 Hz, $\Delta\nu$ = 89 Hz). Structure **15** has a C_2 axis of symmetry through the bridge oxygen and perpendicular to the plane of atoms 2,4,6, and 8 in the chair–chair or boat–boat conformation of the 2,6,9-trioxabicyclo[3.3.1]-octane ring system, as required for equivalence of the methyl groups and methylene hydrogens H_A and H_B in pairs. Because of dimerization it was preferable to characterize ketol **13a** as the previously reported tosylate **16a**.[7]



15



16a, $R_1 = (CH_2)_4$; $R_2 = CH_3$
b, $R_1 = R_2 = CH_3$

Analysis of the condensation of ketone **12a** after low conversion at room temperature revealed the presence of singlets at δ 1.34, 1.29, and 1.24. After complete conversion additional weak singlets appeared at δ 1.38 and 0.90 (±0.01). The origin of the δ 1.24 singlet is undetermined, but singlets at δ 1.34 and 1.29 are assigned to trifluoroacetate **14a** and dimer **15**, respectively, on the following basis.

Nmr spectra of crystalline **15** and freshly distilled ketol **13a** in TFA were essentially identical after *ca.* 0.5 hr at room temperature (6 H singlet at δ 1.29 and 2 H AB, $\Delta\nu$ = 0, at δ 3.77) indicating rapid conversion of

(4) T. A. Spencer, D. S. Watt, and R. J. Friary, *J. Org. Chem.*, **32**, 1234 (1967).

(5) H. O. House and B. M. Trost, *ibid.*, **29**, 1339 (1964).

(6) J. Colonge, J. Dreux, and H. Delplace, *Bull. Soc. Chim. Fr.*, 1635 (1956).

(7) E. Wenkert and P. D. Strike, *J. Org. Chem.*, **27**, 1883 (1962).

the latter to the former. The spectra of these same solutions showed trace amounts of trifluoroacetate **14a** after 30 min, but the spectra became identical with one another and to that of freshly distilled **14a** after *ca.* 18 hr at room temperature. The absence of doublet at δ 1.09 for starting ketone **12a** indicates that no reverse aldol reaction takes place. Furthermore, the absence of methyl doublets other than for **12a** during the course of the condensation requires that positional selectivity for the methine position be >95%.

In summary, the condensation of ketone **12a** appears to be irreversible in TFA and the initial ketol **13a** is trifluoroacetylated far faster than it is formed. This method offers an opportunity for further study of the aldol reaction under what should be completely kinetically controlled conditions. The convenient synthesis of tosylate **16a**, compared with the previous method,[7] requiring several lengthy steps, attests to the synthetic utility of the method.

Similar condensation of ketone **12b** gave ketol trifluoroacetate **14b** as the only detectable product in the nmr spectra of crude condensation mixtures. The trifluoroacetate was characterized as a crystalline ketol tosylate **16b** following basic hydrolysis. Analysis of the mixture after low conversion by nmr revealed only two singlets at δ 2.35 and 2.30 in the region for methyl groups next to a carbonyl group. This fact and the absence of CH_3 doublets, except for starting ketone **12b** at δ 1.17 (J = 7 Hz), require >95% positional selectivity for the methine position.

Experimental Section

Melting points and boiling points are uncorrected and the former were measured in an electrically heated Thiele–Dennis tube. Infrared spectra were recorded on a Beckman IR-5A or Perkin-Elmer 457 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian HA 100 spectrometer in the frequency sweep mode, and chemical shifts were reported in δ units in either $CDCl_3$ or trifluoroacetic acid. Vpc analyses and purifications were performed on a Varian Aerograph Model A 90-P3 or 700 instrument using helium carrier gas at 80–100 ml/min and a thermal conductivity detector. Analyses were performed by Galbraith Laboratories, Inc.

Materials.—Trifluoroacetic acid was redistilled Eastman highest purity grade. Paraformaldehyde was Fisher Certified grade. Toluenesulfonyl chloride was Eastman practical grade, recrystallized according to Pelletier.[8] Ketones were commercially available materials used without redistillation.

Condensations in TFA.—Typically the ketone (0.100 mol) and paraformaldehyde (0.130 equiv for methine condensation, 0.400 equiv for methylene condensation) were dissolved in five times the weight of ketone of TFA and stirred in a preheated bath. Aliquots were withdrawn periodically and the reaction was followed by nmr to maximum ketone consumption. Identical reaction mixtures were obtained whether the paraformaldehyde was added all at once or 1 equiv at a time.

Excess TFA was removed with an aspirator vacuum at 25° and the crude product was freed of residual TFA by dissolving in ether and washing with saturated sodium bicarbonate solution until neutal. Drying of the ether layer with anhydrous magnesium sulfate, filtration, and evaporation of solvent *in vacuo*, followed by vacuum distillation, gave liquid trifluoroacetates **14a,b** (Table I) and 1,3-dioxanes **8a,b** (purified by fractional distillation[9] followed by preparative vpc; 8 ft × 0.25 in. column of 20% SE-30 on Chromosorb P).

2-Methyl-2-trifluoroacetoxymethylcyclohexanone (**14a**) (**Table II**).—*Anal.* Calcd for $C_{10}H_{13}O_3F_3$: C, 50.42; H, 5.50; F, 23.93. Found: C, 50.39; H, 5.59; F, 23.87.

3,3-Dimethyl-4-trifluoroacetoxy-2-butanone (**14b**) (**Table II**). —*Anal.* Calcd for $C_8H_{11}O_3F_3$; C, 45.28; H, 5.23; F, 26.86. Found: C, 45.44; H, 5.29; F, 27.11.

5-Methyl-5-acetyl-1,3-dioxane (**8a**): bp 32–27° (0.007 mm); lit.[2a] bp 74–76° (2.4 mm); $\nu_{max}^{CHCl_3}$ 2850, 1700, 1350, 1155, 1085, 1025, 930 cm^{-1}; nmr ($CDCl_3$) 4.81 (2 H, q, J = 6 Hz, $\Delta\nu$ = 20 Hz), 3.92 (4 H, q, J = 11 Hz, $\Delta\nu$ = 78 Hz), 2.27 (3 H, s), 0.98 (3 H, s).

5-Isopropyl-5-acetyl-1,3-dioxane (**8b**): bp 50–54° (0.007 mm); lit.[2a] bp 66–67° (0.9 mm); $\nu_{max}^{CHCl_3}$ 2840, 1695, 1346, 1158, 1028, 922 cm^{-1}; nmr ($CDCl_3$) 4.79 (2 H, q, J = 6 Hz, $\Delta\nu$ = 34 Hz), 4.06 (4 H, q, J = 11 Hz, $\Delta\nu$ = 89 Hz), 2.32 (3 H, s), 1.74 (1 H, J = 7 Hz), 0.88 (6 H, J = 7 Hz).

Hydrolysis of Ketol Trifluoroacetates 14a,b.—The trifluoroacetates were stirred at 0° with a 10% excess of 2 *N* sodium hydroxide and sufficient methanol to provide a homogeneous mixture for 2 hr. The ketos were isolated in nearly quantitative yield by ether extraction and distillation.

3,3-Dimethyl-4-hydroxy-2-butanone (**13b**): bp 83–85° (15 mm); lit.[10] bp 85–86° (14 mm); $\nu_{max}^{CHCl_3}$ 3400, 2900, 1685, 1355, 1110, 1030 cm^{-1}; nmr ($CDCl_3$) 3.57 (2 H, d, J = 6 Hz), 2.80 (1 H, broad t, J = 6 Hz), 2.17 (3 H, s), 1.16 (6 H, s).

2-Methyl-2-hydroxymethylcyclohexanone (**13a**): bp 50–55° (0.004 mm); lit.[6] bp 107–108° (11 mm); $\nu_{max}^{CHCl_3}$ 3450, 2586, 1690, 1432, 1310, 1035 cm^{-1}; nmr ($CDCl_3$) 3.51 (2 H, s), 2.66 (1 H, broad s), 2.38 (1 H, m) 1.79 (7 H, m), 1.18 (3 H, s).

***exo*-4,7-Dimethyl-2,6,9-trioxatetracyclo[3.3.1.4^{1,8}.4^{4,5}]heptadecane** (**Dimer 15**).—Addition of water to a methanol solution of ketol **13a** and a trace of *p*-toluenesulfonic acid which had been standing for 1 week at room temperature gave white crystals: mp 95–96° (after recrystallization from ether); $\nu_{max}^{CHCl_3}$ 2940, 1450, 1166, 1080, 967 cm^{-1}; nmr ($CDCl_3$) 3.78 (4 H, q, J = 11 Hz, $\Delta\nu$ = 98 Hz), 1.56 (16 H, m), 0.91 (6 H, s). *Anal.* Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.07; H, 9.56.

Preparation of Ketol Tosylates 16a,b.—The tosylates were prepared from 1.5 to 2 equiv of tosyl chloride in pyridine and crude or short-path distilled ketols, according to the procedure given by Fieser.[11] Crude tosylates **16a** and **16b** were obtained in yields of 76.5 and 100%, respectively.

3,3-Dimethyl-4-hydroxy-2-butanone tosylate (**16b**): $\nu_{max}^{CHCl_3}$ 1705, 1354, 1172, 972 cm^{-1}; nmr (CCl_4) 7.52 (4 H, q, J = 8 Hz, $\Delta\nu$ = 42 Hz), 3.90 (2 H, s), 2.45 (3 H, s), 2.05 (3 H, s), 1.11 (6 H, s). *Anal.* Calcd for $C_{13}H_{18}O_4S$: C, 57.76; H, 6.71; S, 11.86. Found: C, 57.76; H, 6.66; S, 12.01.

2-Methyl-2-hydroxymethylcyclohexanone Tosylate (**16a**).—The crude tosylate **16a** could not be crystallized even after repeated column chromatograph on silicic acid using benzene–ethyl acetate and ether–hexane eluents. This compound tends to form an oil after initial crystallization:[12] $\nu_{max}^{CHCl_3}$ 2940, 1710, 1360, 1170, 970 cm^{-1} (lit.[9] ir 1710, 1360, 1175 cm^{-1}); nmr (CCl_4) 7.50 (4 H, q, J = 8 Hz), 3.92 (2 H, s), 2.44 (3 H, s), 2.24 (1 H, m), 1.74 (7 H, m), 1.10 (3 H, s).

Registry No.—Formaldehyde, 50-00-0; **13a**, 10316-61-7; **13b**, 1823-90-1; **14a**, 24706-86-3; **14b**, 24706-87-4; **16a**, 13756-93-9; **16b**, 24706-89-6; **15**, 24694-65-3.

(8) S. W. Pelletier, *Chem. Ind.* (London), 1034 (1953).

(9) Trifluoroacetylated materials contaminated **8a,b** after fractionation; these were not investigated.

(10) J. Decombe, *Compt. Rend. H.*, **203**, 1077 (1936).

(11) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 1179.

(12) Private communication from Professor E. Wenkert whom we thank for a helpful discussion.

The Reformatsky Reaction. II. The Nature of the Reagent

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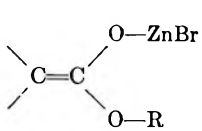
The chemical behavior of the immediate 1,4-addition product of phenylmagnesium bromide and methyl cinnamate has been compared with that of the reaction product of zinc with methyl 2-bromo-3,3-diphenylpropanoate. In each instance completely analogous behavior was observed: direct work-up afforded methyl 3,3-diphenylpropanoate; reaction with benzoyl chloride afforded the enol–benzoate of methyl 3,3-diphenylpropanoate; fluorenone afforded methyl 3,3-diphenyl-2-(9-hydroxy-9-fluorenyl)propanoate; and prolonged standing or heating afforded a "dimeric" reagent which upon work-up yielded methyl 5,5-diphenyl-2-diphenylmethyl-3-oxopentanoate, or a readily explained derivative thereof. The experimental data are interpreted as compelling evidence in support of describing the Reformatsky reagent as the bromozinc enolate of an ester and as providing support for describing the "dimerized" Reformatsky reagent as the bromozinc derivative of a hemiketal of an unsymmetrical (β-lactone) ketene dimer.

In a previous paper[4] a preliminary study of the preparation of the discrete Reformatsky reagent from zinc and ethyl α-bromoisobutyrate in solution was reported. Two types of organic compounds associated with zinc were shown to be present in solution: reagent A, which is formed first and which behaves as expected for the so-called Reformatsky reagent; and reagent B, which is inactive toward a reference ketone (fluorenone) and which can, most simply, be viewed as a "dimeric" compound derived from 2 mol of reagent A with the elimination of the elements of 1 mol of ethoxyzinc bromide. The present research was designed to provide experimental evidence for a choice between the two simplest alternatives for the structure of reagent A, the discrete Reformatsky reagent in solution: an α-bromozinc ester (*i.e.*, the classical Grignard formulation); or a bromozinc enolate of an ester (as suggested by comparison of its behavior with that of the Ivanov reagent,[5] *e.g.*, $RR'C{=}C(OMgX)_2$ from $RR'CHCO_2H$ + 2 *i*-PrMgX. The former structure is supported by the obvious parallels in its reactions with carbonyl compounds[6] with those of Grignard reagents, and the latter for its resemblance to the Ivanov reagent as well as by the slowness with which it appears to "dimerize"[4] and the apparent reluctance with which it adds to the ester carbonyl of unreacted α-bromo ester in the course of its formation. The possibility that the suggested "dimeric" product is formed principally by addition of reagent A to unreacted α-bromo ester is excluded by the fact that reagent A can be prepared in high yield virtually without concurrent production of presumed dimer, which can then be formed directly from reagent A by standing or heating.[4]

If reagent A is to be formulated as the second alternative, one must ask whether or not the zinc–ozygen bond



reagent A

is not equally well pictured as $-O^-\ {}^+ZnBr$, which after all is a necessary contributor to the resonance hybrid. Such a formulation suggests that the organic moiety might better be considered a discrete ester enolate anion. In the case of ethyl isobutyrate, this question may be answered by pointing to the nature of the tritylsodium-induced self-condensation of the ester which has been shown to proceed to completion only if the desired product, ethyl isobutyrylisobutyrate is removed from the solution by tritylsodium-induced γ enolization.[7] One must conclude that a highly unfavorable equilibrium exists for the reaction between ethyl isobutyrate anion and ethyl isobutyrate to give ethyl isobutyrylisobutyrate and ethoxide ion. Thus there is little tendency for the discrete ethyl isobutyrate anion to react with its parent ester carbonyl group. In contrast, the Reformatsky reagent adds to ester carbonyls,[6] albeit slowly. Consequently, it is reasonable to infer that there is a fundamental difference between reagent A and a sodium enolate. The latter, most simply pictured, involves a truly ambident ion[8] with sodium as the counterion, and the former, most simply, is better considered as an essentially covalent system. That one may expect a difference between anions with sodium as counterion and halozinc, halomagnesium, and lithium as counterions has been demonstrated by Hauser[9] and specifically for the "reverse Reformatsky"[6] by one of us.[4]

It has been pointed out by Fuson[10] that acid chlorides react with sodium enolates to give C-acylation, except under special conditions. However, the benzoyl chloride acylation of the bromomagnesium enolate of methyl 3,3-diphenylpropanoate leads to the O-benzoyl derivative *without* the aid of pyridine,[11] an observation which supports the argument favoring covalent character for the O–metal bond in a bromomagnesium enolate, which, if anything, should be less covalent than a corresponding bromozinc enolate. Whatever the exact situation may be, the discrete Reformatsky metal reagent and a corresponding sodio enolate *behave* respectively like "covalent enolate" and discrete enolate anions.

It is clear from the earliest reported synthesis of ethyl

(1) To whom inquiries should be addressed: The University of Connecticut.

(2) Work supported in part by a grant from The University of Connecticut Research Foundation.

(3) Abstracted from the Ph.D. Dissertation of H. P. Knoess, The University of Michigan, 1968.

(4) W. R. Vaughan, S. C. Bernstein, and M. E. Lorber, *J. Org. Chem.*, **30**, 1790 (1965).

(5) H. E. Zimmerman and M. D. Traxler, *J. Amer. Chem. Soc.*, **79**, 1920 (1957).

(6) R. L. Shriner, *Org. React.*, **1**, 1 (1942).

(7) C. R. Hauser and W. B. Renfrow, Jr., *J. Amer. Chem. Soc.*, **59**, 1823 (1933).

(8) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *ibid.*, **77**, 6275 (1955).

(9) C. R. Hauser and W. H. Puterbaugh, *ibid.*, **75**, 4756 (1953).

(10) R. C. Fuson, "Reactions of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1962, p 481.

(11) E. P. Kohler and G. Heritage, *Amer. Chem. J.*, **33**, 21 (1905).

isobutyrylisobutyrate from ethyl α-bromoisobutyrate and magnesium[12] that there may be parallels between the behavior of the Reformatsky reagent and the analogous bromomagnesium reagent which are closer than the suggested analogy[5] between the Reformatsky and Ivanov reagents. Consequently, it was decided to compare the chemical behavior of a bromomagnesium enolate formed by 1,4-Grignard addition to an α,β-unsaturated ester with that of the analogous Reformatsky reagent (*i.e.*, reagent A) formed from the corresponding α-bromo ester. If identical or strikingly similar behavior is encountered, the case for formulating reagent A as shown above (*i.e.*, as a bromozinc enolate of an ester) is greatly strengthened, if not completely settled.

Grignard reagents react with α,β-unsaturated esters by both 1,2 and 1,4 addition.[13] In 1905 Kohler and Heritage studied the reactions of phenylmagnesium bromide with methyl cinnamate[11] (**1a**) and phenyl cinnamate[14] (**1b**). With both esters 1,4 addition was observed. In both cases, treatment with water

$$\underset{\textbf{1a,b}}{C_6H_5CH{=}CHCO_2R} + C_6H_5MgBr \longrightarrow$$

$$(C_6H_5)_2CH{-}CH{=}C(OMgBr)(OR)$$

2a, R = CH_3
b, R = C_6H_5

afforded 3,3-diphenylpropanoate ester (**3a,b**) and with benzoyl chloride, the enol benzoate of the ester (**4a,b**).

In addition to confirming the observations of Kohler and Heritage with the methyl ester, the Reformatsky (**5**) reagent was prepared from methyl 2-bromo-3,3-diphenylpropanoate and zinc and allowed to react with water and with benzoyl chloride, whereupon the same products were obtained, **3a** and **4a**, respectively.

Next, **5** was allowed to react with fluorenone to give the typical Reformatsky product, methyl 3,3-diphenyl-2-(9-hydroxy-9-fluorenyl)propanoate (**6**). It was then shown that the same product (**6**) could be obtained from **2a**, prepared according to Kohler and Heritage's instructions, albeit in lower yield. Thus **5** and **2a** have three reactions in common: hydrolysis to **3a**, O-benzoylation to **4a**, and reaction with fluorenone to give **6**.

Besides the formation of **2a** and **2b**, Kohler and Heritage observed formation of "complex products derived from two molecules of the unsaturated compound" on reaction with phenylmagnesium bromide. Among these were the following: **7b**, phenyl 5,5-diphenyl-2-(diphenylmethyl)-3-oxopentanoate; **8**, 1,1,5,5-tetraphenyl-2-benzoyl-3-pentanone; and **9**, 1,1,5,5-tetraphenyl-2-diphenylhydroxymethyl-3-pentanone.

$(C_6H_5)_2CHCH_2COCH[CH(C_6H_5)_2]CO_2R$
7a, R = CH_3
b, R = C_6H_5

$(C_6H_5)_2CHCH_2COCH(COC_6H_5)CH(C_6H_5)_2$
8

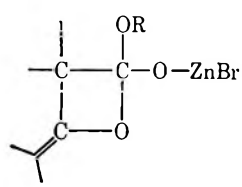
$(C_6H_5)_2CHCH_2COCH[C(OH)(C_6H_5)_2]CH(C_6H_5)_2$
9

The foregoing compounds were characterized by molecular weights, elemental analyses, and degradative experiments. In addition, the formation of **7a** was reported along with **8** and **9** from methyl cinnamate and phenylmagnesium bromide; but for **7a** only the elemental analysis was reported, no molecular weight being determined.

The dimerization of reagent A (**5**), as in the case of isobutyrate, was readily realizable for the reaction between zinc and methyl 2-bromo-3,3-diphenylpropanoate, the product isolated being **7a** which was independently synthesized *via* the Claisen condensation of methyl 3,3-diphenylpropanoate. However, our **7a** corresponded in no way with that reported by Kohler and Heritage which we, too, were able to obtain under their conditions. Mass spectrometric analyses on the Kohler and Heritage compound strongly suggest that it is a "trimeric" β,δ-diketo ester probably containing tightly bound solvent molecules sufficient to account for the observed elemental analyses which varied somewhat on prolonged vacuum drying. Conventional molecular weight determination for this supposed **7a** came within 4.5% of the calculated value for the "trimeric" compound, and nmr analysis provided support for the trimeric structure through integration for aromatic, methylene + methine, and methyl protons. A very similar product was detected as a minor product in the "dimerization" of **5**. However, the effective "dimerization" of bromomagnesium enolates is clearly evident in the formation of **7b** and in the synthesis of ethyl isobutyrylisobutrate.[12]

That no **8** or **9** is formed in the Reformatsky case follows from the absence of phenylmagnesium bromide under the usual conditions. However, it is surprising that, when the Grignard reagent is added to fully "dimerized" **5** (reagent B), compounds **8** and **9** still fail to appear. This would appear to be evidence that reagent B has no readily accessible carbonyl group. Infrared spectroscopy provides support for this inference (see below).

It has been suggested by one of us, with supporting arguments,[4] that "dimerization" of reagent A to reagent B proceeds by elimination of the elements of an alkoxyzinc bromide, leaving a ketene to which residual reagent A then adds, leading to



reagent B

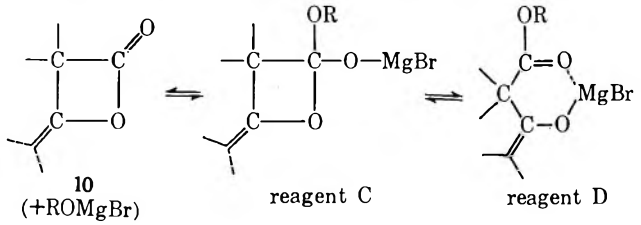
This clearly can yield **7a** on acidification,[4] and, provided only that the oxygen–zinc bond is sufficiently covalent, it need not react with Grignard reagent. The related ketene dimer (*e.g.*, **10**) would have a distinctive, high-frequency carbonyl absorption, which is totally lacking in the infrared spectra of samples of reagent B in solution (see below). If **2a**, the bromomagnesium analog of **5**, affords a reagent C (the bromomagnesium analog of reagent B) as a precursor to **8** and **9**, the only substantive difference between reagents B and C must reside in the oxygen–metal bond, which for magnesium

(12) Y. Salkind, *J. Russ. Phys. Chem. Soc.*, **38**, 97 (1906); J. Zeltmer, *Ber.*, **41**, 589 (1908).

(13) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, New York, N. Y., 1954, pp 564 ff.

(14) E. P. Kohler and G. Heritage, *Amer. Chem. J.*, **34**, 568 (1905).

is less covalent than for zinc.[15] This difference can facilitate either or both of the following reactions.



10 (+ROMgBr) reagent C reagent D

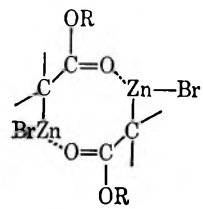
Reagent D has the ester carbonyl required for the production of **8** and **9** by reaction with 1 or 2 mol of phenylmagnesium bromide, and **10** is a β-lactone of the unsymmetrical ketene dimer type which has been shown to afford analogs of **8** and **9**.[16] Failure to obtain similar products from phenylmagnesium bromide and reagent B may be attributed to the greater covalent stability of the oxygen–zinc bond.[15]

To be sure, Kohler and Heritage proposed an alternative route to **7**, **8**, and **9** which involved first a Claisen-type reaction between **2** and unreacted cinnamate ester, but this postulate is seriously to be questioned, since the essential intermediate is a 2-cinnamoyl-3,3-diphenylpropanoate ester (**11**) which could not be isolated. Further, the only derivative of **11** whose intermediacy could reasonably be inferred was the 1,4-phenylmagnesium bromide adduct across the α,β-unsaturated ketone system of **11**, which is in fact D, whose genesis we have formulated *via* an entirely different route.

In summary, the chief difference between **2a** and **5** appears to be a greater propensity for **2a** to "dimerize" (and "trimerize") which seems to be more characteristic of magnesium enolates than of zinc enolates.[12] This, too, is reasonably attributed to lesser covalency in the oxygen–magnesium bond; however, one may wish to formulate the "dimerization" reaction.

In the preceding paragraphs we have presented evidence for three types of chemical reactions: O-benzoylation, addition to the fluorenone carbonyl group, and "dimerization," each of which is realizable with both the 1,4-phenylmagnesium bromide adduct of methyl cinnamate (**2a**) and the reaction product of zinc with methyl 2-bromo-3,3-diphenylpropanoate (**5**). These taken in concert with earlier evidence[4,5] establish a formal identity for the two reagents (**2a** and **5**) in solution, and the mode of formation of **2a** leaves little or no room for doubt as to the simplest compatible formulation for it and, therefore, for **5** (reagent A), the discrete Reformatsky reagent in solution. The case for formulating the Reformatsky "dimer" (reagent B) as a covalent bromozinc derivative of a hemiketal of the unsymmetrical (β-lactone) ketene dimer is strengthened by the failure of reagent B to afford **8** and **9** with added phenylmagnesium bromide. This failure would appear to rule out *any* appreciable equilibria involving a free ketene dimer (*e.g.*, **10**) and/or a chelated ester carbonyl (*e.g.*, the bromozinc analog of reagent D).

Finally a few words concerning infrared spectra are appropriate. At best it is extremely difficult to obtain good spectra of the Reformatsky reagent (A and/or B) in solution,[4] and the complexity of products from the 1,4-Grignard additions effectively rules out meaningful spectra in that system. However, we did examine a few cases of the Reformatsky reagent from methyl 2-bromo-3,3-diphenylpropanoate with results completely analogous to those obtained from the Reformatsky reagent derived from ethyl α-bromoisobutyrate. The only identifiable carbonyl absorption is clearly attributable to residual unreacted α-bromo ester; there is no high-frequency carbonyl stretching or still higher frequency-ketene absorption; and there is (in reagent A) a relatively strong absorption at 1555 cm^{-1} analogous to that at 1525 cm^{-1} in the simpler Reformatsky reagent.[4] That this is *not* to be attributed to a chelated carbonyl group (*e.g.*, the bromozinc analog of reagent D) or to



follows from the failure to obtain appropriate reaction products from the reagent solution and phenylmagnesium bromide.

Experimental Section[17–21]

Reformatsky–Zinc.—A 110-g portion of 20 mesh (Baker, granular, 99.8%) zinc was covered with concentrated sulfuric acid containing a few drops of nitric acid and was heated to 100° for 20 min with occasional stirring. Then the mixture was cooled to room temperature, suction filtered through a sintered-glass funnel, and washed with three 50-ml portions of water, three 50-ml portions of acetone, and three 50-ml portions of ether. The treated zinc was then stored in a vacuum desiccator over phosphorus pentoxide.

Methyl 2-Bromo-3,5-diphenylpropanoate.—A mixture of 24.3 g (107 mmol) of 3,3-diphenylpropionic acid, 1.3 g (43 mmol) of red phosphorus, and 25 ml of benzene was treated dropwise and with mechanical stirring with 35.2 g (217 mmol) of bromine. Stirring was continued with heating on the steam bath overnight, after which excess bromine and hydrogen bromide were removed by a water aspirator. The red upper layer was decanted from the phosphoric acid into cooled (0°) 80 ml of absolute methanol, and the resultant red solution was stirred for 45 min with intermittent warming on the steam bath. Next it was concentrated, dissolved in 100 ml of benzene, and washed with three 100-ml portions of water, two of 5% sodium carbonate solution, three of sodium thiosulfate solution, and one of saturated sodium chloride solution. Then the organic layer was dried over anhydrous magnesium sulfate, concentrated, and allowed to stand overnight, whereupon it partially solidified. The crystals were collected by filtration and washed with petroleum ether (bp 30–60°) leaving 13.11 g of crude product which was dissolved in 200 ml of cyclohexane, refluxed with Norit, filtered, and concentrated to give two crops of white crystals (7.23 and 1.48 g, 21.9% yield). An analytical sample was recrystallized from cyclohexane, mp 106.5–107.0°.

Anal. Calcd for $C_{16}H_{15}BrO_2$: C, 60.20; H, 4.74; Br, 25.04. Found: C, 60.28; H, 4.74; Br, 25.16.

The infrared and nmr spectra are consistent with the assigned structure.

(15) H. Gilman [in H. Gilman, "Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1943, p 489 ff.

(16) D. V. Nightingale and R. H. Turley, Jr., *J. Org. Chem.*, **26**, 2656 (1961).

(17) The molecular weight determination and all microanalyses were done by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(18) The mass spectra were recorded on a AEI-MS 12 mass spectrometer at The University of Connecticut by O. W. Norton.

(19) All melting points and boiling points are uncorrected.

(20) The vapor phase chromatography (vpc) was done on an Autoprep 705 instrument using a 5 ft × 1/8 in. column of 4% SE-30 on Chromosorb 6, a nitrogen flow rate of 5 ml/min, and a column temperature program of 50–200° with a 15°/min temperature rise.

(21) The silica gel used for all thin layer chromatography (tlc) was Brinkmann S. G. PF_{254} with 5% calcium sulfate.

Preparation of Reagent 2a.—Preparation of phenylmagnesium bromide was carried out in the usual manner and in a nitrogen atmosphere. Upon completion of the reaction, the solution of the Grignard reagent from 2.0 g (82 mg-atoms) of magnesium and 13.5 g (86 mmol) of bromobenzene in 40 ml of ether in one run was cooled in ice water and treated with 1.77 g (~15 mol %) of dry cuprous bromide; however, no readily observable difference in results was obtained if this step was omitted. Addition dropwise of 10.0 g (63 mmol) of methyl cinnamate in 40 ml of absolute ether over a 1.5-hr period with stirring for an additional hour provided the solution of reagent **2a**.

Preparation of Reagent 5.—This reaction was also conducted in a nitrogen atmosphere. Zinc, 295 mg (4.5 mg-atoms), and a small crystal of iodine were covered with 5 ml of 1:1 (v/v) absolute ethyl ether–dry benzene (called "solvent" in the sequel). The zinc–solvent mixture was stirred and warmed to effect reflux, and a few drops of a solution of methyl 2-bromo-3,3-diphenylpropanoate ("ester") (1.60 g, 5.00 mmol) in 12.5 ml of solvent was added. If needed, a few drops of methylmagnesium iodide solution was also added to initiate the reaction. The whole amount of the ester solution was added dropwise over a 3-hr period, but at 1.25 hr there was added an additional 197 mg (3.00 mg-atoms) of zinc, and at the end of ester addition there was added 154 mg (2.0 mg-atoms) of zinc, after which the mixture was refluxed for 2.25 hr. The resulting solution was used for experiments requiring reagent **5**.

1-Methoxy-2-benzhydrylvinyl Benzoate (4a). (a) *Via* **1,4-Grignard Addition.**—To the full amount (above) of reagent **2a** solution was added a solution of 11.55 g (82 mmol) of benzoyl chloride in 20 ml of absolute ether over a 10-min period. The resulting solution was refluxed for a few minutes and then was transferred with the aid of a little acetone into a beaker containing 200 ml of ether. Upon addition of 100 ml of 1% hydrochloric acid, the black tar dissolved leaving a precipitate of crude benzoate which was collected by filtration, washed with ether, dissolved in acetone, hot-filtered, and allowed to crystallize. The light green crystals were washed white with acetone, and two additional crops were obtained from the concentrated mother liquor: total yield, 3.38 g, 15.4%. An analytical sample was twice recrystallized from benzene–petroleum ether (bp 30–60°), mp 155–156° (lit.[11] 130–133°).

Anal. Calcd for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85. Found: C, 80.27; H, 5.92.

The infrared and nmr spectra are consistent with the assigned structure.

(b) *Via* **the Reformatsky Reaction.**—To the full amount (above) of reagent **5** was added 703 mg (5.00 mmol) of benzoyl chloride in 10 ml of 1:1 ether–benzene over a 15-min period. Reflux was continued for 5 hr. The reaction mixture was hydrolyzed with 50 ml of half-saturated ammonium chloride solution, and the aqueous phase was extracted with 25 ml of benzene. The combined organic layers were washed with 25 ml of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated to a yellow oil which partially crystallized on standing. The crystals were collected by filtration, washed with petroleum ether (bp 30–60°), and dried: 171.5 mg of crude **4a**, mp 144.0–144.5°. Purification as before afforded white crystals, mp 154.5–155.5° with no depression in mixture melting point. The infrared spectrum was identical with that of the previous sample.

Methyl 2-(9-Hydroxy-9-fluorenyl)-3,3-diphenylpropanoate (6). (a) *Via* **1,4-Grignard Addition.**—Using half of the solution of reagent **2a** prepared from 1.22 g (50.0 mg-atoms) of magnesium, there was added a solution of 3.6 g (20 mmol) of fluorenone in 30 ml of absolute ether, and the reaction mixture was refluxed for 2 hr. It was then poured into 50 ml of ice water and was treated with saturated ammonium chloride solution until the magnesium salts dissolved. The separated aqueous layer was extracted with two 25-ml portions of ether, and the combined ether layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to give 6.69 g of a six-component oil (thin layer chromatography): biphenyl, 3,3-diphenylpropiophenone, fluorenone, 9-phenylfluorenol, methyl cinnamate (trace), and the product, **6**. Two successive chromatographs on Florisil (100–200 mesh) afforded from 6.07 g of the oil, respectively, 1.11 g (29.2%)[22] and 340 mg of relatively pure **6**[23] which was recrystallized twice from carbon disulfide: mp 143–145°; ir (CS_2 solution) 3560 and 1735 cm^{-1}.

Anal. Calcd for $C_{29}H_{24}O_3$: C, 82.83; H, 5.75. Found: C, 82.87; H, 5.71.

The nmr spectrum is consistent with the assigned structure. Treatment of a colorless ethanol solution of **6** with a little dilute sodium hydroxide immediately produced a yellow color, fluorenone from a "reverse Reformatsky," as observed elsewhere.[4]

(b) *Via* **the Reformatsky Reaction.**—A solution prepared from 3.19 g (10 mmol) of the bromo ester was treated with 1.80 g (10 mmol) of fluorenone in 15 ml of the "solvent" and refluxing was continued for 2 hr. The reaction mixture was then hydrolyzed with 20 ml of saturated ammonium chloride solution, the aqueous layer was separated and extracted with 10 ml of benzene, and the organic layers were combined and dried over anhydrous magnesium sulfate. Filtration and concentration afforded 4.43 g of a yellow oil. As in the previous procedure chromatography on Florisil yielded **6**,[24] which was recrystallized from carbon disulfide–petroleum ether (bp 30–60°), in two crops: 0.91 g, mp 147.5–149.0°, and 0.38 g, mp 146.5–148.5°. The total yield was 34%. The melting point was not depressed by the previous sample, and the infrared spectra of the samples from both procedures were identical. The present product behaved identically with sodium hydroxide.

Methyl 5,5-Diphenyl-2-diphenylmethyl-3-oxopentanoate (7a). (a) *Via* **the Claisen Condensation.**—A solution of 48.1 g (200 mmol) of methyl 3,3-diphenylpropanoate in 50 ml of *o*-xylene (freshly distilled from calcium hydride) was treated under nitrogen with 9.6 g (200 mmol in 50% oil dispersion) of sodium hydride. Stirring was started and the gray mixture was slowly warmed to reflux in an oil bath. After 3.25 hr of refluxing, the dark brown mixture was cooled and hydrolyzed with 100 ml of 50% acetic acid. The solvents were removed in a rotary evaporator leaving a yellow solid which was triturated with hot chloroform and filtered. The filtrate was concentrated, diluted with absolute ethanol, and allowed to crystallize. Two crops of white crystals were obtained, 29.1 g (61.8%). An analytical sample was recrystallized from 2:1 (v/v) ethanol–acetone: mp 152.5–153.2°; ir (KBr) 1735 and 1710 cm^{-1}.

Anal. Calcd for $C_{31}H_{28}O_3$: C, 83.01; H, 6.29. Found: C, 83.12; H, 6.19.

The nmr spectrum is consistent with the assigned structure.

(b) *Via* **the Reformatsky Reaction.**—A solution of reagent **5** was prepared from 3.19 g (10 mmol) of bromo ester and then was refluxed for 24 hr. The reaction mixture was hydrolyzed with 50 ml of half-saturated ammonium chloride solution, the aqueous layer was separated and extracted with 25 ml of ether, and the combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to give 2.24 g of yellow oil. Trituration of the oil with ether left a white solid which was washed with ether and recrystallized from ethanol and then from 2:1 (v/v) ethanol–acetone to give 321 mg of satin-white needles of **7a**, mp 154.0–154.5° with no depression on mixture with product from Claisen condensation whose infrared spectrum was identical with that of the present product. A number of complex products were isolated from the mother liquors from recrystallization and trituration of which only dimethyl 2,3-dibenzhydrylsuccinate was identified: 210 mg; mp 188.5–190.0°; ir (KBr) 1755 cm^{-1}; nmr ($CDCl_3$) 7.20 (s, 11.4) 7.12 (s, 8.6), 4.05 (m, 3.9), 2.99 (s, 6.1); mass spectrum (70 eV) *m/e* 478 (parent ion).

Anal. Calcd for $C_{32}H_{30}O_4$: C, 80.31; H, 6.32. Found: C, 80.22; H, 6.28.

An additional 25.8% yield of **7a** was isolated from the mother liquors by column and thin layer chromatography.

The infrared spectrum of reagent **5** during the above dimerization was taken at the end of ester addition and at the end of 3 hr of refluxing. The first spectrum shows residual bromo ester (1750 cm^{-1}, strong) and a weak band at 1555 cm^{-1}; the second spectrum shows residual ester (1750 cm^{-1}, moderate) and a mod-

(22) Using 319 g of Florisil in a 4.5-cm-o.d. column, 200-ml fractions; no. 1–25, benzene; no. 26, 1:3 ether–benzene; no. 27, 1:1 ether–benzene; no. 28–39, ether. Crude **6** was found in fraction no. 25–35 (1.4 g).

(23) Using 32.9 g of Florisil in 20-mm-o.d. column, 75-ml fractions: no. 1–6, benzene; no. 7–19, 1:19 ether–benzene; no. 20–24, 1:1 ether–benzene. Compound **6** was found in fraction no. 7–12 (340 mg).

(24) Using 90 g of Florisil in 30-mm-o.d. column, 250-ml fractions: no. 1–8, benzene; no. 9–10, 5% ether–benzene; no. 11–14, 25% ether–benzene. Product **6** was obtained from fraction in no. 4–6. Preparative tlc (20 × 20 cm^2 × 1.25 mm silica gel, five benzene elutions) afforded 44.7 mg of **6** from an aliquot. This corresponds to 132 mg in the total eluate from no. 4–6. More product was obtained from later fractions, and **6** was isolated by recrystallization.

erately intense band at 1555 cm^{-1}. No other carbonyl bands were observed nor was there any absorption between the carbon–hydrogen stretching region and 1750 cm^{-1}.

2-Diphenylhydroxymethyl-1,1,5,5-tetraphenyl-3-pentanone (9).—A 15.4% yield of this compound was isolated, following the procedure of Kohler and Heritage,[11,14] mp (fast) 154–155°, lit.[11] 153°. The infrared spectrum is compatible with the assigned structure. Refluxing with 10% sodium hydroxide solution for 2 hr followed by ether extraction afforded 1,1,5,5-tetraphenylpentanone-3, mp 125.5–127.0° (lit.[14] 130°). On heating in a *kugelrohr* at 30° (11 mm) two pure products condensed on the cooler parts of the tube: the white solid was the above pentanone, and the liquid proved to be benzophenone by tlc (silica gel–benzene) comparison with authentic samples.

Attempts to prepare **9** from reagent **5** by addition of phenylmagnesium bromide solution were fruitless, only **7a** being isolated in 41.5% yield (crude). A considerable variety of unidentified products was obtained by chromatographic procedures and each, which could be isolated relatively pure (tlc), was checked by tlc for identity with **9** and its two decomposition products, none of which was detected.

Kohler's 7a.—The crude product had mp 200.5–206.5° and was recrystallized from ethanol–chloroform to give satin-white needles [dried over phosphorus pentoxide at 80° (5 mm)], mp 209.2–210.7°. A second recrystallization with 3 days of drying as before gave mp 216.0–217.5° (lit.[14] 211–213°); ir (KBr) 1760 1720, and 1665 cm^{-1}; nmr chemical shifts nearly identical with those for authentic **7a**. The integrated nmr peaks fit methyl 2,4-dibenzhydryl-3,5-dioxo-7,7-diphenylheptanoate: mass spectrum (70 eV) *m/e* 656 (parent ion); isotopic abundance ratios at *m/e* 656 (Calcd: 100, 51.65, 14.10. Found: 100, 51.5, 14.3.); conventional mol wt (vapor pressure[1] in chloroform) 680.

Registry No.—Methyl 2-bromo-3,3-diphenylpropanoate, 24689-50-7; dimethyl 2,3-dibenzhydrylsuccinate, 24728-01-6; **6**, 24689-51-8; **7a**, 24647-01-6.

Enthalpy, Entropy, and Free-Energy Changes in the Equilibration of *cis*- and *trans*-Ethyl 3-*t*-Butylcyclobutanecarboxylate and 3-*t*-Butylcyclobutanol

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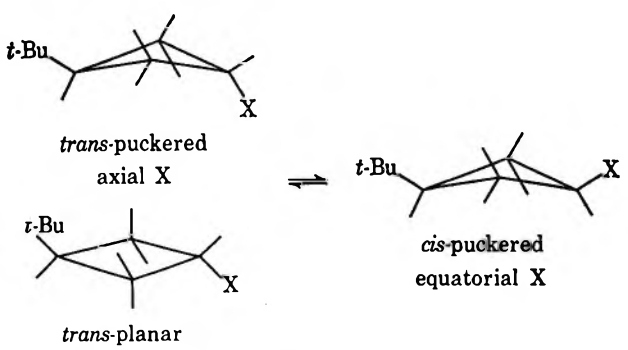
The *cis*- and *trans*-3-*t*-butylcyclobutanols have been prepared and equilibrated with aluminum isopropoxide in isopropyl alcohol at different temperatures. The thermodynamic parameters (*trans* to *cis*) are $\Delta H = -1.6$ kcal/mol, $\Delta S = -1.1$ cal/(deg mol), and $\Delta G_{100} = -1.15$ kcal/mol. The equilibration of ethyl 3-*t*-butylcyclobutanecarboxylate with sodium ethoxide in ethanol at different temperatures gives $\Delta H = -0.8$ kcal/mol, $\Delta S = -0.7$ cal/(deg mol), and $\Delta G_{100} = -0.58$ kcal/mol. The *cis* isomers are enthalpically favored while the *trans* isomers are entropically favored. The results have been explained on the basis of a relatively rigid puckered *cis* isomer and a somewhat flexible *trans* isomer.

The free-energy change in the equilibration of ethyl *cis*- and *trans*-3-*t*-butylcyclobutanecarboxylate has been previously reported.[1] The *cis* isomer predominates at equilibrium in support of the idea that the ring is puckered leading to the groups being placed in equatorial positions similar to those in cyclohexane (Chart I, X = CO_2Et). The *trans* isomer, on the other hand, would have an equatorial *t*-butyl and an axial carbethoxyl group provided that the ring is puckered to the same extent as in the *cis* isomer (Chart I, X = CO_2Et). The argument commonly used in conformational studies in cyclohexane would indicate that the enthalpy of the *trans* isomer would be higher than that of the *cis* one due to a 1,3 interaction. However, it is possible that this interaction may be great enough to result in a planar ring (Chart I, X = CO_2Et). Either way, the *trans* isomer should have the higher enthalpy since the puckered form would have a greater 1,3 interaction, increased angle strain, and better torsional angles, while the planar form would have a reduced 1,3 interaction, decreased angle strain, and poorer torsional angles. The actual structure for the *trans* isomer may be somewhere between the extremes.[1]

Experimental evidence supports conformations of rings varying between significantly puckered to planar ones for substituted cyclobutanes. For example, the *cis* isomers of methyl 3-methylcyclobutanecarboxylate,[2]

CHART I

EQUILIBRATION OF PLANAR AND NONPLANAR 3-*t*-BUTYLCYCLOBUTYL DERIVATIVES



X = CO_2Et, OH

3-isopropylcyclobutyl alcohols and amines,[3] methyl 3-isopropylcyclobutanecarboxylate,[4] 2,2,4,4-tetramethylcyclobutane-1,3-dinitrile,[5] 1,3-dibromocyclobutane,[6] and 1,3-cyclobutanedicarboxylic acid[7] all have been shown to be puckered, and calculations on 1,3-dimethylcyclobutane indicate that this should be expected.[8] On the other hand, conformations of the

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trans isomers of the above compounds vary from planar or nearly planar for methyl 3-isopropylcylcobutanecarboxylate[4,9] and 1,3-cyclobutanedicarboxylic acid[10] to significantly puckered 2,2,4,4-tetramethylcyclobutane-1,3-dinitrile[5] and 1,3-dibromocyclobutane.[6] Solid-state forces play an important role in determining the structure of *trans*-1,3-cyclobutanedicarboxylic acid since when alone in the crystal the ring is planar,[10] while the diacid is puckered in the sodium salt, $Na_2C_4H_6(CO_2^-)_2 \cdot 2C_4H_6(CO_2H)_2$.[11] Thus, it is not known whether the diacid would be puckered or planar in solution.

In this paper, the ethyl *cis*- and *trans*-3-*t*-butylcyclobutanecarboxylates synthesized previously[1] have been equilibrated at different temperatures in order to obtain ΔH and ΔS. In addition, the synthesis and equilibration of the *cis*- and *trans*-3-*t*-butylcyclobutanols (Chart I, X = OH) at different temperatures is reported. An independent report of the synthesis of the alcohol appeared while this work was in progress,[12] but no equilibrium studies were made. A comparison of the thermodynamic parameters for the two equilibrations would be of interest in order to help clarify the conformation situation indicated in Chart I. Although the conformational situation in cyclobutane is not completely analogous to cyclohexane, there are some similarities, and the enthalpies and entropies of the carbethoxyl[13] and hydroxyl[14] groups in cyclohexane have recently been reported.

The 3-*t*-butylcyclobutanols were synthesized starting from a mixture of *cis*- and *trans*-3-*t*-butylcyclobutanecarboxylic acids (**1**).[1] The acid **1** was converted to the acid chloride **2** and then to methyl 3-*t*-butylcyclobutyl ketone (**3**) with dimethylcadmium. The ketone **3** was converted to 3-*t*-butylcyclobutyl acetate (**4**) with perbenzoic acid. The acetate **4** was hydrolyzed to give 3-*t*-butylcyclobutanol (**5**) which was separated into the *cis* and *trans* isomers.[15] Peak one, the largest component in a chromatogram of the alcohols, corresponded to the *cis* isomer as was found with the esters.[1] The *cis* acid **1** predominated in the starting material and by about the same amount found in the alcohols. The nuclear magnetic resonance (nmr) spectra of the alcohols are consistent with the generalization found in cyclohexane[16,17] that an equatorial proton is less shielded than the corresponding axial one. The axial proton next to hydroxyl appears at τ 6.0 in the *cis* isomer while the resonance for the equatorial proton is at τ 5.7 in the *trans* isomer. A similar relationship was observed in the ethyl 3-*t*-butylcyclobutanecarboxylates[1] and in the 3-isopropylcyclobutanols.[3] While the *trans* alcohol is probably not so puckered as the *cis* alcohol, the qualitative argument would probably still hold.

The alcohol **5** was oxidized to 3-*t*-butylcyclobutanone (**6**) by means of ruthenium tetroxide. Lithium aluminum hydride reduction of the ketone **6** gave a mixture composed of 91% *cis* alcohol **5**. If one assumes a planar ring as in the case of cyclobutanone itself,[18] it seems reasonable that steric approach control may operate to give predominately the *cis* isomer.

The ethyl *cis*- and *trans*-3-*t*-butylcyclobutanecarboxylates were equilibrated at five different temperatures from 80 to 151° with sodium ethoxide in absolute alcohol in sealed ampoules. Each isomer and a mixture were equilibrated at 80 and 151° and only a mixture for the other temperatures. Previously, the time found adequate for complete equilibration was 450 hr[1] at 80°, and as seen in Table I this has been exceeded by more than a factor of 2. In addition, tubes were removed from the bath at two different times. The equilibrium constants, recorded in Table I, are the averages obtained from 9 to 18 chromatograms and indicate that the *cis* isomer predominates at all temperatures.

TABLE I

EQUILIBRIUM CONSTANTS AS A FUNCTION OF TEMPERATURE

Compound	Temp, °C	Time, hr	K = *cis*/*trans*
Ethyl 3-*t*-butylcyclo-	80.1 ± 0.1	1052, 1269	2.33 ± 0.11
butanecarboxylate	100.0 ± 0.1	1139, 1218	2.19 ± 0.05
(X = CO_2Et in	110.3 ± 0.5	1139, 1288	2.12 ± 0.02
Chart I)	134.8 ± 0.9	1139, 1288	1.97 ± 0.05
	150.8 ± 0.7	1139	1.92 ± 0.04
3-*t*-Butylcyclo-	100.1 ± 0.3	165, 207, 355	4.77 ± 0.07
butanol (X = OH	137.4 ± 0.3	184, 208	3.91 ± 0.07
in Chart I)	154.2 ± 1.2	138, 184, 208	3.64 ± 0.07

The equilibrium constants for 3-*t*-butylcyclobutanol shown in Table I were obtained at the temperatures indicated by reaction of 3-*t*-butylcyclobutanone with aluminum isopropoxide in isopropyl alcohol. The ketone was shown by gas chromatography to reduce rather quickly, followed by the equilibration of the resulting alcohols. As a check, mixtures rich in the *cis* and *trans* alcohols were each equilibrated at 100 and 154°, and the same equilibrium constants were found as those given in the table (well within experimental error). Tubes were removed from the bath at two or three different times in order to ensure that equilibrium had been attained. Seven to ten chromatograms were analyzed to obtain the constants given in Table I. Again, the *cis* isomer predominates at all temperatures as with the esters. Raney nickel[19,20] has been used for equilibrating alcohols in the cyclohexane series. Although the method is somewhat more convenient, particularly in solvents other than alcohol,[20] the cyclobutane ring may undergo cleavage at higher temperatures. Thus, the method was not employed. In any case, the aluminum isopropoxide and Raney nickel methods give similar results for the conformational free energy of the hydroxyl group in the cyclohexane ring.[20] Since the presence of aluminum alkoxide does not change the position of the equilibrium, presumably both methods involve the free alcohol, or

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TABLE II

THERMODYNAMIC PARAMETERS FOR EQUILIBRATION OF CYCLOBUTYL AND CYCLOHEXYL ESTERS AND ALCOHOLS

Compound	ΔH, kcal/mol	ΔS, cal/(deg mol)	ΔG_{100}, kcal/mol
Ethyl 3-*t*-butylcyclobutanecarboxylate (*trans* → *cis*; axial → equatorial in Chart I)	−0.8 ± 0.2	−0.7 ± 0.5	−0.58 ± 0.02
3-*t*-Butylcyclobutanol (*trans* → *cis*; axial → equatorial in Chart I)	−1.6 ± 0.2	−1.1 ± 0.5	−1.15 ± 0.01
Ethyl 4-*t*-butylcyclohexanecarboxylate (axial → equatorial)	−1.09[a]	+0.4[a]	
4-*t*-Butylcyclohexanol (axial → equatorial)	−1.09[b]	−0.46[b]	

[a] Reference 13. [b] Reference 14.

nearly so, at least in the cyclohexane ring. This may also be the situation in the present work.

Log K was plotted against $1/T$ resulting in excellent visual fits to straight lines in both cases. From the slopes of the lines, the enthalpies were obtained (slope $= -\Delta H/2.3R$), and this together with the equations $\Delta G = \Delta H - T\Delta S$ and $\Delta G = -RT \ln K$ gave the entropies and free energies. The thermodynamic parameters obtained for the cyclobutyl esters and alcohols are shown in Table II together with comparison data for the corresponding cyclohexanes. The error limits for the cyclobutyl compounds given in Table II were calculated in the following manner.[13] The equilibrium constants at the higher temperatures were increased and the ones at the lower temperatures decreased by the amounts of the standard deviations given in Table I. After a line was drawn through the new points, ΔH was recalculated. The procedure was repeated so that the constants at the higher temperatures were now lowered, the values at the lower temperatures were increased by the standard deviations, and the value of ΔH was calculated. The new values of ΔH were used to set the error limits. Thus, it is felt that the values given represent the extreme confidence limits of the thermodynamic parameters calculated in this study.

As expected, the enthalpies in each of the equilbrations of the cyclobutyl compounds were negative in keeping with the explanation given above and the situation in Chart I where the *cis* isomer is favored enthalpically. Before discussing the difference in magnitude between the enthalpies of the alcohols and esters, note should be made of the signs and magnitude of the entropy values. In both cases the *trans* isomers are favored entropically. This result might be expected in the case of the alcohols since it has been shown that the more accessible equatorial hydroxyl in a cyclohexane ring is solvated more strongly than the hindered axial group.[14] Using this analogy, it seems reasonable that the hydroxyl in the *cis* cyclobutyl alcohol would be more strongly solvated (lower entropy) than the *trans* alcohol (higher entropy) in either of the extreme puckered or planar conformations in Chart I. Therefore, a negative entropy change (*trans* → *cis*) is observed as is found in the cyclohexane ring (a → e) as given in Table II.

In explaining the negative entropy change for the esters, it would again be of interest to look at data given in Table II for the carbethoxyl group in the cyclohexane ring. The isomer with the equatorial carbethoxyl[13,21,22] and carbomethoxyl[23,24] group has the higher entropy in both the 3- and 4-*t*-butylcyclohexanecarboxylates. This result, inconsistent with a solvation argument, is explained on the basis of the axial group being subjected to greater rotational restrictions (lower entropy) than the equatorial group which can occupy a larger number of populated rotational conformations (higher entropy). The entropy change (a → e) recorded in Table II for carbethoxyl is therefore found to be positive in contrast to compounds with groups such as hydroxyl[14] and carboxyl[13] where the change (a → e) is negative.

It seems unlikely that the negative entropy change observed in the cyclobutyl esters would be caused by a solvation effect as apparently this is unimportant for esters in the cyclohexane ring.[13] Thus, it may appear that the carbethoxyl group in the *trans* isomer actually has more rotational freedom (higher entropy) than one would predict on the basis of the cyclohexane analogy, in comparison with the *cis* isomer (lower entropy). Perhaps, one of the methyls on the *t*-butyl group extends over the ring to some extent and thereby restricts the rotation of the carbethoxyl group in the *cis* isomer relative to the situation in the *trans* one. However, any large measure of interaction of the *t*-butyl group with the functional group would tend to increase the enthalpy of the *cis* isomer and reduce its concentration at equilibrium.

The most reasonable explanation might be in the flexibility of the cyclobutane ring itself. It is known that the difference in energy between a puckered and planar cyclobutane ring[25] is small. Thus, at the temperatures used in the equilibrations, the *trans* isomer might be undergoing continuous conformational change (higher entropy) leading to a number of conformers with nearly equal energies. On the other hand, the *cis* isomer might be expected to be more rigid (lower entropy) since moving toward a planar ring would create an increased interaction between the *t*-butyl and carbethoxyl, and more puckering would increase angle strain. Part of the entropy change observed with the alcohols could also be due to greater flexibility of the *trans* isomer as compared with the *cis* one, although

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(22) N. L. Allinger and L. A. Freiberg, *ibid.*, **31**, 894 (1966).
(23) B. J. Armitage, G. W. Kenner, and M. J. T. Robinson, *Tetrahedron*, **20**, 747 (1964).
(24) M. Tichý and J. Sicher, *Collect. Czech. Chem. Commun.*, **33**, 68 (1968).
(25) G. W. Rathjens, Jr., N. K. Freeman, W. D. Gwinn, and K. S. Pitzer, *J. Amer. Chem. Soc.*, **75**, 5634 (1953).

solvation effects are probably more important as discussed previously.

Returning to the difference in magnitude of the enthalpy changes in the alcohols and esters, it is seen in Table II that the *cis* cyclobutyl alcohol is favored enthalpically ($\Delta H = -1.6$) to a greater extent than the *cis* ester ($\Delta H = -0.8$). In the cyclohexane ring, a large solvent effect on the enthalpy change has been observed for the hydroxyl group probably because of the added stability given to the equatorial isomer due to hydrogen bonding.[14,20] For example, ΔH can vary from -0.62 to -1.09 as the solvent is changed from cyclohexane to isopropyl alcohol, the latter value being essentially the same as that found for the carbethoxyl group[13,21,22] (Table II). It is possible that a much greater solvent effect is being observed in the present case than seen in the cyclohexane ring. However, it appears somewhat more likely that the larger carbethoxyl group may be closer to the *t*-butyl group than the hydroxyl in the *cis* isomers. Thus, the effect might be to decrease the enthalpy difference between the *cis* and *trans* esters below that of the alcohols.

It seems reasonable to assume that the thermodynamic parameters ΔH, ΔS, and ΔG, for other 3-*t*-butylcyclobutyl derivatives (*trans* → *cis*) may also be negative. Thus, it would be of interest to investigate other groups such as the carboxyl and acetyl and to investigate hydroxyl in other solvents.

Experimental Section

3-*t*-Butylcyclobutanecarbonyl Chloride (2).—A mixture of 15.0 g (0.096 mol) of 3-*t*-butylcyclobutanecarboxylic acid[1] (1) and 21.2 g (0.179 mol) of freshly distilled thionyl chloride was allowed to stand at room temperature for 0.5 hr and then was heated at reflux for an additional 1.5 hr. The excess thionyl chloride was removed under reduced pressure, and the residue was distilled to give 16.0 g (96%) of *cis*- and *trans*-3-butylcyclobutanecarbonyl chloride, bp 86–87° (15 mm).

Methyl 3-*t*-Butylcyclobutyl Ketone (3).—A 250-ml three-necked flask containing 60 ml of anhydrous ether was fitted with an inlet tube dipping below the surface of the ether and an outlet protected with a drying tube. The ether was cooled in an ice–salt bath and weighed, and methyl bromide from a gas cylinder was added through the inlet tube until the gain in weight was 11.4 g (0.12 mol). Into a 1-l. three-necked flask, equipped with a stirrer, reflux condenser, and an addition funnel with a tube extending to the bottom of the flask, were placed 2.8 g (0.115 g-atom) of magnesium turnings, 40 ml of anhydrous ether, and a crystal of iodine. The cold solution of methyl bromide was transferred to the addition funnel and added with stirring over a 25-min period during which time the mixture refluxed spontaneously. The magnesium had completely reacted after a total of 30 min.[26] The flask was then cooled, and 11.3 g (0.061 mol) of cadmium chloride (dried to constant weight at 110°) was added over a period of 7 min. The ice bath was removed and the mixture was stirred for 15 min and then heated under reflux with stirring for an additional hour. Ether (50 ml) was distilled until a viscous residue remained. Dry benzene (80 ml) was added and the distillation continued until an additional 50 ml of distillate was obtained. Dry benzene (100 ml) was again added and the mixture refluxed with stirring for 15 min. The heating bath was removed and 16.0 g (0.092 mol) of 2 dissolved in 30 ml of dry benzene was added dropwise over a 5-min period with stirring. After the addition of the acid chloride was completed and spontaneous refluxing had stopped, the mixture was stirred and heated under reflux for an additional hr. To the cooled mixture was added 100 ml of ice water followed by sufficient 20% sulfuric acid to give two phases. The aqueous phase was separated and extracted with 25 ml of benzene. The combined organic layers were washed successively with 40 ml of water, 40 ml of dilute sodium bicarbonate, and 20 ml of saturated salt solution. The benzene was flask distilled after drying over anhydrous sodium sulfate.[27] The residue was distilled to give 9.2 g (65% based on the acid chloride) of *cis*- and *trans*-methyl 3-*t*-butylcyclobutyl ketone: bp 85–87° (16 mm); nmr (CCl_4) τ 7.1 (m, 1, CHCO), 7.94 and 7.98 (s, 3, $COCH_3$), 8.08 (m, 5, ring), 9.15 and 9.20 [s, 9, $C(CH_3)_3$]. Analysis by gas chromatography (12-ft 35% diethylene glycol succinate on 45–60 Chromosorb W column at 100° at 30 psi) gave retention times of 28 and 31 min for the *cis* and *trans* isomers, respectively. The order of elution and the composition was the same as previously found.[1] *Anal.* Calcd for $C_{10}H_{18}O$: C, 77.9; H, 11.8. Found: C, 77.9; H, 12.0.

3-*t*-Butylcyclobutyl Acetate (4).—To 290 ml of 0.38 *M* perbenzoic acid (15.2 g, 0.11 mol) in chloroform[28] contained in a 500-ml flask was added 9.2 g (0.060 mol) of 3. The flask was wrapped to exclude light and allowed to stand at room temperature for 48 hr. At this time, 0.063 mol of perbenzoic acid had been consumed as determined iodimetrically.[28] The remaining perbenzoic acid was decomposed with an excess of sodium iodide dissolved in water, followed by addition of a solution of sodium thiosulfate until colorless. The chloroform layer was then extracted with aqueous sodium carbonate to remove benzoic acid and dried over magnesium sulfate, and the chloroform was distilled.[29] The residue was distilled to give 7.2 g (71%) of *cis*- and *trans*-3-*t*-butylcyclobutyl acetate: bp 101–105° (30 mm); nmr (CCl_4) τ 5.1 (m, 1, CHOAc), 7.8 and 8.3 (m, 5, ring), 8.00 and 8.03 (s, 3, $COCH_3$), 9.13 and 9.17 [s, 9, $C(CH_3)_3$]. Analysis by gas chromatography under the conditions above gave retention times of 25 and 27 min for the *cis* and *trans* isomers, respectively. The composition was about the same as the original ketone mixture. *Anal.* Calcd for $C_{10}H_{18}O_2$: C, 70.6; H, 10.7. Found: C, 70.6; H, 10.8.

3-*t*-Butylcyclobutanol (5).—To 3.2 g (0.057 mol) of potassium hydroxide dissolved in 29 ml of methanol was added 7.2 g (0.0424 mol) of 4. The resulting solution was heated under reflux for 3 hr. The cooled solution was diluted with 60 ml of water and extracted four times with 30-ml portions of ether. The combined extracts were dried over magnesium sulfate and the ether was removed by distillation. The residue was distilled to give 4.05 g (75%) of *cis*- and *trans*-3-*t*-butylcyclobutanol, bp 99–100° (19 mm). A sample was purified by gas chromatography. *Anal.* Calcd for $C_8H_{16}O$: C, 74.9; H, 12.6. Found: C, 74.6; H, 12.5. The product was analyzed by gas chromatography and indicated a composition of 70% *cis* and 30% *trans*. The retention times on a 20-ft 30% SE-30 on 45–60 Chromosorb W column at 100° at 200 ml/min were 33 and 37 min and on a 11-ft 30% dioctyl phthalate on 45–60 Chromosorb W column at 130° at 30 psi were 39 and 42 min for the *cis* and *trans* isomers, respectively: nmr *cis* (CCl_4) τ 6.0 (m, 1, CHOH), 5.9 (s, 1, OH), 7.88 (m, 2, CH_2), 8.40 (m, 3, CH_2, CH), 9.17 (s, 9, $C(CH_3)_3$); *trans* (CCl_4) τ 5.7 (m, 1, CHOH), 6.2 (s, 1, OH), 7.90 (m, 5, ring), 9.15 [s, 9, $C(CH_3)_3$].

3-*t*-Butylcyclobutanone (6).—Sodium periodate (4.2 g, 0.020 mol) and 0.011 g of ruthenium trichloride hydrate were dissolved in 30 ml of water and added to 1.32 g (0.0103 mol) of 5 in 5 ml of carbon tetrachloride. The resulting mixture was stirred vigorously with a magnetic stirrer for 24 hr.[30] The layers were separated, and the aqueous layer was extracted with two 15-ml portions of chloroform. The combined organic layers were dried over magnesium sulfate, and the solvent was removed by distillation. The residue was distilled to give 0.90 g (68%) of 3-*t*-butylcyclobutanone: bp 85° (20 mm); nmr (CCl_4) τ 7.2 (m, 4, CH_2), 7.7 (m, 1, CH), and 9.06 [s, 9, $C(CH_3)_3$]. Analysis by gas chromatography on the above columns indicated one component. The ir spectrum showed the typical cyclobutanone carbonyl stretch at 5.6 μ. *Anal.* Calcd for $C_8H_{14}O$: C, 76.1; H, 11.2. Found: C, 76.2; H, 11.1.

Reduction of 3-*t*-Butylcyclobutanone with Lithium Aluminum Hydride.—To 0.187 g (4.92 mmol) of lithium aluminum hydride dissolved in 4 ml of anhydrous ether in a 50-ml flask was added 0.45 g (3.60 mmol) of 6 dissolved in 4 ml of ether over a 10-min period, with magnetic stirring. The mixture was then allowed to reflux for 30 min. To the cooled mixture was added 3.5 ml of 30 wt % aqueous potassium sodium tartrate until the gray solid was replaced by a white solid and an aqueous layer. The layers

(26) J. Colonge and R. Marey, "Organic Syntheses," Coll. Vol IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 601.

(27) J. Cason and F. S. Prout, ref 26, Coll. Vol. III, 1955, p 601.

(28) G. Braun, ref 26, Coll. Vol. I, 1941, p 431.

(29) S. L. Friess and R. Pinson, Jr., *J. Amer. Chem. Soc.*, **74**, 1302 (1952).

(30) J. A. Caputo and R. Fuchs, *Tetrahedron Lett.*, 4729 (1967).

were separated, and the aqueous layer was extracted twice with 4-ml portions of ether. The combined extracts were dried over magnesium sulfate, and the ether was distilled to give 0.38 g (85%) of 3-*t*-butylcyclobutanol as a residue that was not further purified. This residue was analyzed by gas chromatography on the 20-ft SE-30 column which indicated a composition of 91% *cis* and 9% *trans*. No other components were observed.

Equilibration of 3-*t*-Butylcyclobutanol.—A 0.6 *M* solution of aluminum isopropoxide in isopropyl alcohol was prepared by refluxing 3.28 g of aluminum and 0.16 g of mercuric chloride in 200 ml of isopropyl alcohol (reagent grade, heated at reflux over calcium oxide for 7 hr) for 8 hr.[31] There was a small amount of black precipitate formed that was removed by centrifuging and decanting the clear solution. Enough solution for 5 ampoules was obtained by dissolving 0.125 g of 3-*t*-butylcyclobutanone (6) in 1.65 ml of the above solution, yielding a solution approximately 0.6 *M* in each reactant. The solutions were distributed into test tubes, flushed with dry nitrogen, sealed, and immersed in baths at the temperatures indicated in Table I. The baths consisted of various liquids in flasks which were brought to reflux and maintained at their boiling points. The temperatures were found to remain constant within the limits given in Table I and were corrected with a National Bureau of Standards thermometer. The ampoules were removed at the times indicated in Table I, cooled in ice water, and opened immediately. To the contents was added 1 ml of 6 *N* HCl, and this solution was then extracted with two 1-ml portions of ether. After removal of the ether, the residue was analyzed by gas chromatography on the 20-ft 30% SE-30 column used above for separation of the alcohols. The equilibrium constants were calculated from the ratio of the peak areas obtained by the height times half band width method. Each value in Table I is the average of seven to ten chromatograms from at least two different tubes. Analysis of a mixture of known composition indicated that repsonse corrections were unnecessary.

As a check on the use of the ketone 6 for obtaining the equilibrium constants, mixtures rich in the *cis* and *trans* alcohols 5 were each equilibrated separately. A solution of 0.125 g of 3-*t*-butylcyclobutanol, rich in either the *cis* or *trans* isomer, 0.31 g of ketone 6, and 1.65 ml of 0.6 *M* aluminum isopropoxide–isopropyl alcohol was prepared and equilibrated as above. At 100°, the initial *cis* and *trans* rich mixtures gave equilibrium constants of 4.83 ± 0.14 and 4.75 ± 0.13, respectively. At 154°, the initial *trans* rich mixture gave an equilibrium constant of 3.62 ± 0.07.

Equilibration of Ethyl 3-*t*-Butylcyclobutanecarboxylate.—The procedure used to equilibrate the esters was described previously.[1] Sealed ampoules were immersed in the baths described above at the temperatures indicated in Table I and removed at the times given. The ampoules were cooled in ice water, opened, and worked up as before.[1] The concentrate was analyzed by gas chromatography on the 20-ft 30% column used above. The retention times on this column at 130° and 200-ml/min pressure were 51 and 56 min for the *cis* and *trans* esters, respectively. The equilibrium constants were obtained by the method above, and the averages of from 9 to 18 chromatograms are given in Table I. A 50:50 mixture was used to obtain the constants at 100, 110, and 135°. As a check on the use of this mixture, pure *cis* and *trans* isomers were each independently equilibrated at 80 and 151°. The equilibrium values thus obtained from both sides were identical and have been included in the averages in Table I. Tubes were removed at several times and the compositions were found to be identical. No correction factor was necessary for calculation of the equilibrium constants, as shown by gas chromatogaphic analysis of a known mixture prepared from weighed samples of the pure esters.

Registry No.—*cis*-1 ethyl ester, 14924-51-7; *trans*-1 ethyl ester, 14924-52-8; *cis*-2, 24165-52-4; *trans*-2, 24165-53-5; *cis*-3, 24122-09-6; *trans*-3, 24122-10-9; *cis*-4, 24122-12-1; *trans*-4, 24122-13-2; *cis*-5, 20588-76-5; *trans*-5, 20476-25-9; 6, 20614-90-8.

Acknowledgment.—This work was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this fund.

(31) W. G. Young, W. H. Hartung, and F. S. Crossley, *J. Amer. Chem. Soc.*, **58**, 100 (1936).

Studies of Benzonorbornene and Derivatives. IV.[1] Bridgehead and 1-Carbinyl Derivatives[2,3]

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Benzonorbornenyl-1-carbinyl tosylate (1) is investigated as a possible model for a non-π-participatory neophyl system. Its solvolysis compared with that of the nonbenzo analog 9 is retarded 47-fold in acetic acid at 133° and 14-fold in 80% acetone at 25°. No evidence for anchimeric assistance by the aromatic ring was found. Under the vigorous conditions of refluxing hydrobromic acid containing zinc bromide, benzonorbornenyl-1-carbinol (8) still failed to allow aromatic migration, although both methano and ethano bridge-migrated products were detected. Benzonorbornenyl-1-carbinyl radical, produced by radical-promoted decarbonylation of the aldehyde **22**, did not rearrange. The absence of rearrangement illustrates the necessity of twist in the aromatic ring during rearrangement. From benzonorbornene-1-carboxylic acid (2) synthetic prodedures to a number of the title compounds are described.

Recently our interest in benzonorbornene chemistry coincided with other interests in homoallylic π-electron systems[4] and ring-size effects in the neophyl rearrangements.[5] All three of these interests led to the present investigation of benzonorbornenyl-1-carbinyl derivatives. Incidental to this work was the synthesis of a number of heretofore unknown bridgehead-substituted benzonorbornenes.[6]

(1) Paper III: J. W. Wilt and P. Chenier, *J. Org. Chem.*, **35**, 1571 (1970).

(2) Taken from the dissertations of C. A. S., 1964, and H. F. D., Jr., 1969, and the M.S. Thesis of J. P. B., 1966.

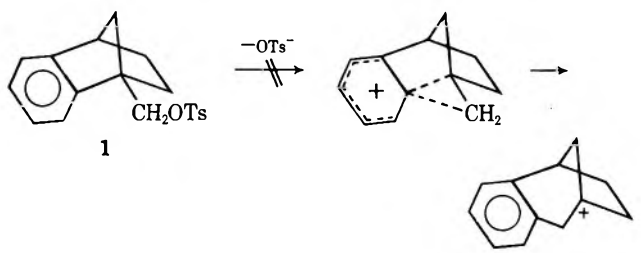
(3) Some of the material has appeared in preliminary form: J. W. Wilt and C. A. Schneider, *Chem. Ind.* (London), 951 (1963); J. W. Wilt, C. A. Schneider, J. P. Berliner, and H. F. Dabek, Jr., *Tetrahedron Lett.*, 4073 (1966).

(4) J. W. Wilt, C. F. Parsons, C. A. Schneider, D. G. Schultenover, and W. J. Wagner, *J. Org. Chem.*, **33**, 694 (1968).

(5) J. W. Wilt, L. L. Maravetz, and J. F. Zawadzki, *ibid.*, **31**, 3018 (1966).

(6) Of the known synthetic routes to benzonorbornene and derivatives which follow, we felt only one could be developed for bridgehead substitution: (a) G. Wittig and E. Knauss, *Chem. Ber.*, **91**, 895 (1958); (b) J. Meinwald and G. A. Wiley, *J. Amer. Chem. Soc.*, **80**, 3667 (1958); (c) K. MacKenzie, *J. Chem. Soc.*, 43 (1960); (d) P. D. Bartlett and W. P. Giddings, *J. Amer. Chem. Soc.*, **82**, 1240 (1960); (e) H. Rakoff and B. H. Miles, *J. Org. Chem.*, **26**, 2581 (1961); (f) A. F. Plate and N. A. Belikova, *Zh. Obshch. Khim.*, **30**, 3945 (1960); (g) A. F. Plate, N. A. Belikova, and S. Y. Kirichenko, *Neftekhimiya*, **1**, 494 (1961); *Chem. Abstr.*, **57**, 58166 (1962); (h) K. Alder and M. Fremery, *Tetrahedron*, **14**, 1960 (1961); (i) P. Bruck, *Tetrahedron Lett.*, 449 (1962); (j) H. Tanida, *Accounts Chem. Res.*, **1**, 239 (1968). See also ref 1.

Synthesis and Solvolysis of Benzonorbornenyl-1-carbinyl Tosylate (1).—Tosylate **1** has its aromatic ring so positioned that π participation at the carbinyl site should be precluded geometrically. The rigid nature of the bicyclic system simply prevents the twist required of the aromatic ring to achieve the phenonium ion geometry of the transition state. It therefore

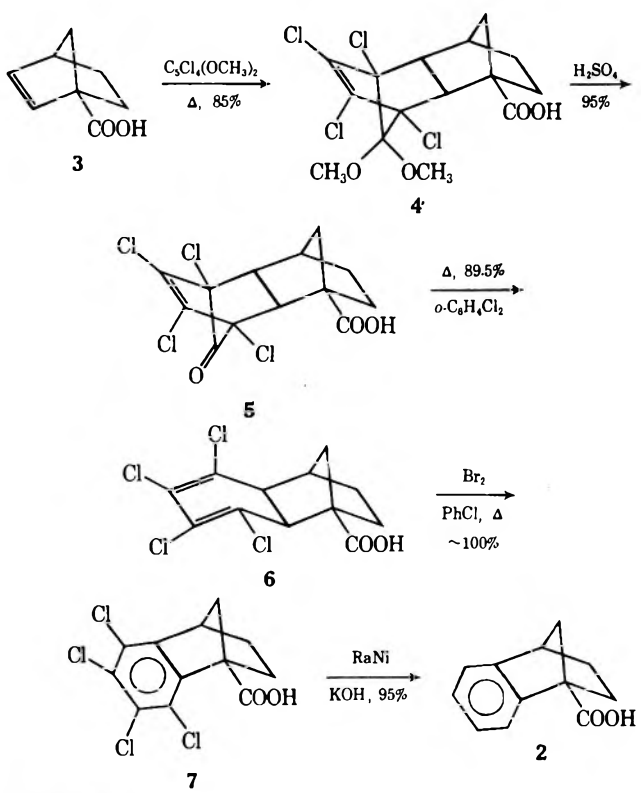


1

seemed worthwhile to measure the effect of the aromatic ring in the solvolysis of this constrained neophyl-like tosylate. It is well recognized that the aromatic ring retards solvolysis by induction (−I effect), but the real magnitude of the effect is normally masked by the accelerating influence of the aromatic ring *via* π participation.[7] The calculated value of *ca.* eightfold given by Streitwieser[8] is commonly used for this effect, but little direct experimental evidence is available.[9]

Benzonorbornene-1-carboxylic acid (**2**) was synthesized from norbornene-1-carboxylic acid[4] *via* the sequence shown below in Chart I. The sequence was modeled after that of Mackenzie.[6c]

CHART I



3 4 5 6 7 2

Tosylate **1** was then made by the usual method *via* the carbinol **8**. The solvolysis rate data for **1** and other selected tosylates are gathered in Table I. In acetic acid **1** is somewhat slower than neopentyl tosylate or **9** and much slower than neophyl tosylate. As this last is generally considered a model for π-assisted acetolysis,[10] it appears that π participation in **1** has been precluded. However, σ participation (principally by the *ethano* bridge) is unfortunately still possible; so it is difficult to ascribe a value for the −I effect of the aromatic ring on the *completely unassisted* process. In any event, based on neopentyl tosylate and **9**, the aromatic ring reduced reactivity 12- and 47-fold at 133°. Based on neophyl tosylate, reactivity was reduced 800-fold at this temperature.

TABLE I

SOLVOLYTIC RATE DATA

Tosylate[a,b]	Temp, °C[c]	$10^5 k_1$, sec^{-1}
1[d]	132.0	1.18 ± 0.04
	139.0	2.07 ± 0.13
	156.0	6.66 ± 0.14
	25	(8.0×10^{-11})[e]
11	139.0	~0.3
9[f]	109.0	2.24 ± 0.10
	120.0	6.30 ± 0.19
	130.0	14.0 ± 0.04
	25	(1.1×10^{-9})[e]
Tosylate[a,g]		
1[h]	110.0	0.102 ± 0.01
	131.0	0.553 ± 0.04
	154.0	5.57 ± 0.48
9	99.5	1.13 ± 0.12[i]
	133.0	27.0 ± 1.0
Neopentyl	133.0	6.8[e,i]
Neophyl	133.0	470[e,k]

[a] *Ca.* 0.03 *M* tosylate solutions were used, except for **11** which was 6×10^{-3} *M*. [b] In 80% acetone-20% water (v/v) containing *ca.* 0.033 *M sym*-collidine. [c] ±0.05°. [d] $\Delta H^* = 25.8 \pm 0.2$ kcal mol^{-1}, $\Delta S^* = -17.9 \pm 0.2$ eu. [e] Extrapolated from data at other temperatures. [f] $\Delta H^* = 26.0 \pm 0.3$ kcal mol^{-1}, $\Delta S^* = -12.4 \pm 0.3$ eu. $k_{rel}^{25°}$ for **1**, 1; **9**, 14. [g] In glacial acetic acid containing acetic anhydride (0.3%) and excess sodium acetate (1.5 mmol/mmol of tosylate). [h] $\Delta H^* = 27.9 \pm 0.2$ kcal mol^{-1}, $\Delta S^* = -13.7 \pm 0.5$ eu. $k_{rel}^{133°}$ for **1**, 1; neopentyl-OTs, 12; **9**, 47; neophyl-OTs, 800. [i] Lit. value, 1.17×10^{-5} sec^{-1} at 99.7°: R. L. Bixler and C. Niemann, *J. Org. Chem.*, **23**, 742 (1958). [j] S. Winstein and H. Marshall, *J. Amer. Chem. Soc.*, **74**, 1120 (1952). [k] S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *ibid.*, **74**, 1113 (1952).

In 80% acetone at 25° the retardation observed with **1** is 14-fold relative to **9**.[11] This 14-fold value compares well with the value of 16 obtained in an earlier study[4] in 60% acetone for the retardation caused by a homoallylic double bond. The comparison emphasizes the inductive similarity of the two π systems, the aromatic

(7) E. Kosower, "An Introduction to Physical Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1968, p 125.

(8) A. Streitwieser, Jr., *Chem. Rev.*, **56**, 718 (1956).

(9) Very recently the value 3.7 has been given for the 2-phenylethyl system by J. L. Coke, F. E. McFarlane, M. C. Mourning, and M. G. Jones, *J. Amer. Chem. Soc.*, **91**, 1154 (1969).

(10) I. L. Reich, A. Diaz, and S. Winstein, *ibid.*, **91**, 5635, 5637 (1969).

(11) It seems clear that there is no one value for the −I effect of the aromatic ring. This effect will vary with the demand in the transition state for a process, and this demand varies with conditions. So to know the applicable value one must study the reactant in question and an appropriate model under the same conditions. We favor **1** as a model for neophyl systems, even though **1** is not itself probably free from *all* participation.

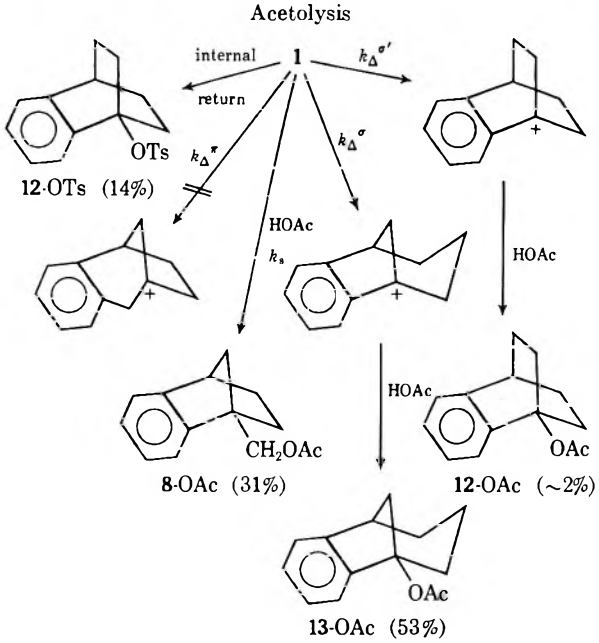
ring, and the double bond. Indeed, norbornenyl-1-carbinyl tosylate (**10**) and tosylate **1** solvolyzed at comparable rates in 80% acetone at 131°.[12] This similarity was demonstrated also by pK_a studies (see below).

In Chart II are shown the solvolysis pathways and products observed with **1**. Acetolysis of **1** showed poor first-order kinetics (negative drift). An inert, rearranged tosylate (**12**-OTs) could be separated from the reaction material. Although its structure was not proved by independent synthesis, and must therefore be open to question, **12**-OTs is probably benzobicyclo[2.2.2]octen-1-yl tosylate. It was not **1** and it is unlikely that it could be benzobicyclo[3.2.1]oct-6-en-1-yl tosylate (**13**-OTs). Attempts to make the latter from the **13** obtained in the hydrolysis study were unsuccessful. The structure **13**-OTs is considered unlikely because Bly and coworkers[13] have demonstrated that the *olefinic* analogs of **12**-OTs and **13**-OTs differ greatly in acetolytic reactivity. The former is very slow whereas the latter is much faster, faster even than the norbornenyl compound **10**. So on this basis one expects **12**-OTs to be the bicyclo[2.2.2]octenyl derivative. Such an assignment of structure is also supported by spectra (see Experimental Section).

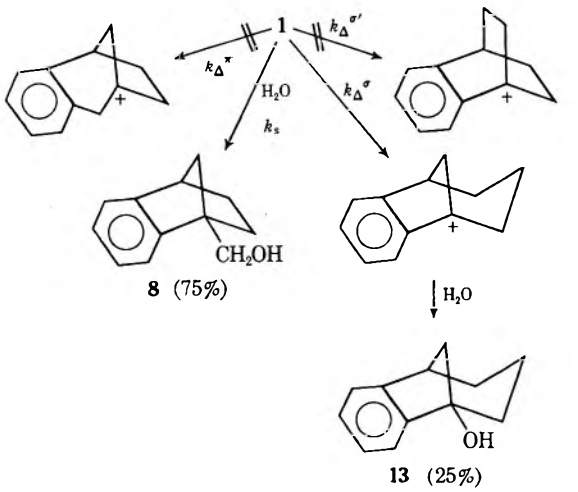
CHART II

SOLVOLYSIS PRODUCT DATA

Acetolysis

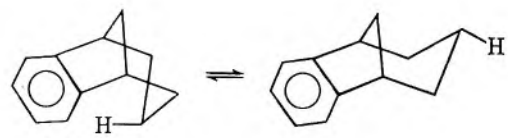


Hydrolysis



The formation of the other products can be formulated in terms of discrete σ-assisted processes ($k_\Delta{}^{\sigma}$) and unassisted processes (k_s), as indicated in Chart II. In light of the recent elucidation of σ assistance in acetolysis of neopentyl tosylate,[10] this formulation is probably preferrable to another view involving completely unassisted ionization *followed* by skeletal rearrangement.[14] It should be noted, however, that no product of aromatic migration was observed, so π assistance ($k_\Delta{}^{\pi}$), if present at all, is not detectable in this manner.

The change to aqueous acetone effectively removed ion-pair return. Besides starting material **1**, there were found only unrearranged alcohol **8** and *ethano* bridge-migrated product **13**. No evidence for **12**-OTs or its alcohol was found though trace amounts of the latter cannot be discounted. Once more, no aromatic migration was observed. The structure of **13** was assigned by analogy to the formation of bicyclo[3.2.1]-oct-6-en-1-ol in the earlier study of **10** under similar conditions,[4] and by the proton resonance at δ 2.27, ascribed to the *endo* C-3 proton. This resonance, also observed in **13**-OAc at δ 2.20, was prominent in the *bona fide* parent hydrocarbon **18** (δ 2.25) but was absent in the benzonorbornenyl-1-carbinyl and benzobicyclo[2.2.2]octenyl series of compounds prepared in this work. We attribute this downfield resonance to a deshielding effect of the aromatic ring, as shown in one conformer of this ring system.



(deshielded)

The increased preference for ethano (rather than methano) bridge migration in these systems during hydrolysis compared to acetolysis was previously observed and discussed.[4] The significant increase in unrearranged product during hydrolysis may be the result of increased unassisted solvolysis (k_s). Even though a more ionizing solvent than acetic acid (Y = −0.7 *vs.* −1.6[15]), 80% acetone is also more nucleophilic because of its aqueous content. Both features tend to increase overall solvolysis rates, but the latter feature would certainly change the partitioning of the total rate between k_s and k_Δ processes relative to acetolysis. Unassisted (k_s) processes proceed without rearrangement;[10] hence **8** predominates in the aqueous acetone.

Cationic Rearrangement of Benzonorbornenyl-1-carbinol (8).—Carbinol **8** was subjected to vigorous treatment in hydrobromic acid containing zinc bromide

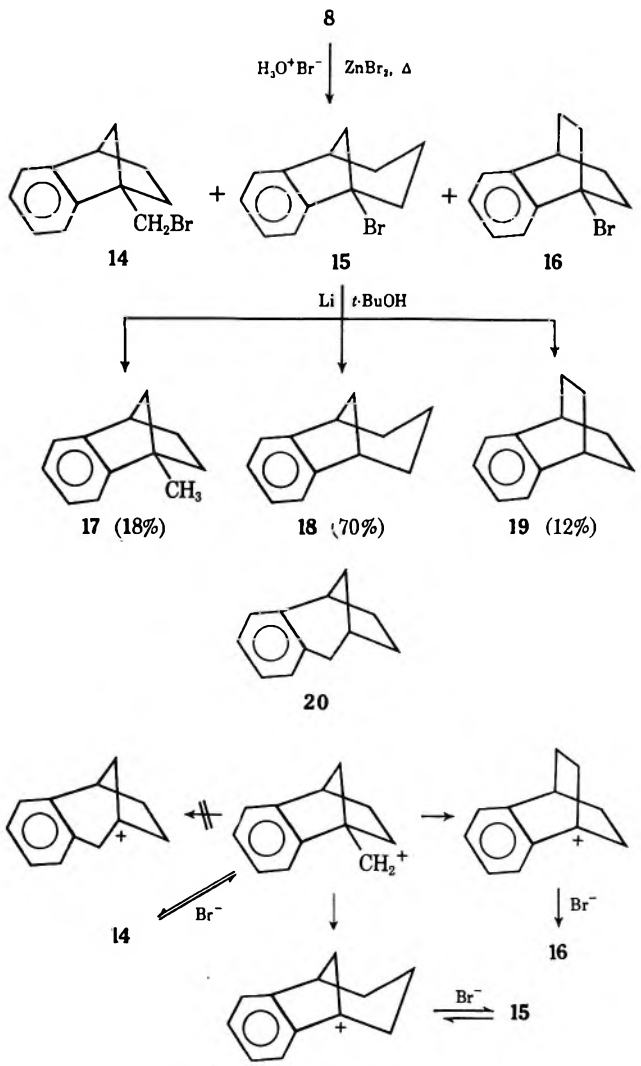
(12) J. W. Wilt and H. F. Dabek, Jr., unpublished work.

(13) R. S. Bly and E. K. Quinn, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, Abstracts, Paper 910. We appreciate the details of this work from Professor Bly.

(14) J. E. Nordlander, S. P. Jindal, P. von R. Schleyer, R. Fort, Jr., J. J. Harper, and R. D. Nicholas, *J. Amer. Chem. Soc.*, **88**, 4475 (1966).

(15) Reference 7, p 311.

CHART III

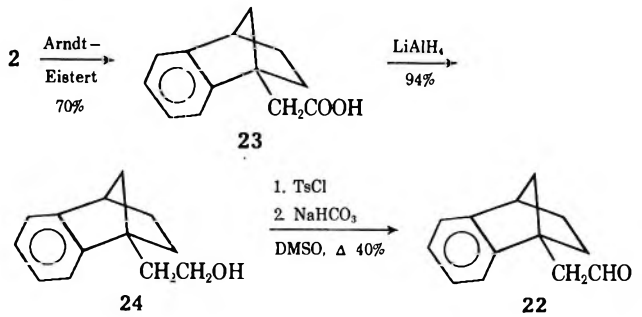


as shown in Chart III. The bromide isomers were best identified as their parent hydrocarbons formed by reduction. Again the principal rearrangement was *via* ethano bridge migration (as in solvolysis) although the exact product composition was time dependent. But now an increased percentage of methano bridge migration was observed as well. Aromatic migration was still absent (no **20** was observed). The various intermediate ions probably involved and their interconversions as suggested by the solvolysis data previously discussed are also given in Chart III. The severity of the conditions was apparently such that the barrier to either alkyl migration was now more readily surmountable but not the barrier to aromatic migration.

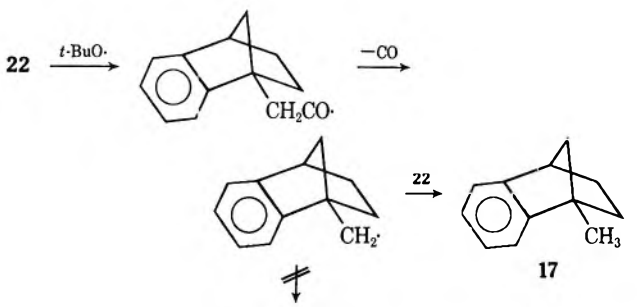
Carbinol **8** was much less easily rearranged (95% reaction at 150° for 6.5 hr) than norbornyl-1-carbinol (**21**, *ca.* 100% reaction at 80° for 4 hr[16]). Also, ethano bridge migration predominated in **8** whereas methano bridge migration did so in **21**. In the rapid reaction of **21**, the more acute methano bridge angle in the starting material presumably is of more importance. In the slow reaction of **8** the relative stabilities of the product ions determine the course of the process.[17] Similar but more detailed reasoning has been advanced for the analogous transformations of the related tosylates **9** and **10**.[4]

Decarbonylation of Benzonorbornenyl-1-acetaldehyde (22).—The decarbonylation of aldehyde **22** was investigated because past work[18] has shown that geometric restraint on the aromatic ring can decrease the extent of the neophyl radical rearrangement.

Conversion of acid **2** to its homologous acetic acid **23** *via* the Arndt–Eistert reaction followed by reduction to alcohol **24** and oxidation of its tosylate produced **22**.



Treatment of a 1 *M* solution of **22** in chlorobenzene with di-*t*-butyl peroxide gave 92% of the theoretical carbon monoxide and *only* 1-methylbenzonorbornene (**17**).



A control study showed that the other possible hydrocarbons (**18**–**20**) were totally absent. So the carbinyl radical no more allowed aromatic migration than did the cation. Moreover, as alkyl shifts in radicals are energetically improbable, the radical underwent chain transfer solely to **17**. Under similar conditions less constrained neophyl-type radicals rearrange significantly.[5]

Acidity Constants.—As a final demonstration of the inductive effect of the aromatic ring in acid **2**, its pK_a along with those of other relevant acids were determined. The results are collected in Table II, and they further illustrate the similar effects of the homoallylically positioned vinyl and aromatic functions, *ca.* 0.4–0.5 pK unit compared to the corresponding saturated model in the systems shown. Acid **7** (with its tetrachloroaryl function) is actually somewhat stronger than benzoic acid in 75% acetone.

Synthesis of Various Bridgehead-Substituted Benzonorbornenes.—To illustrate its utility as a precursor to the heretofore unknown 1-substituted benzonorbornenes, acid **2** or its acid chloride was converted into a number of these as given in Chart IV. Experimental details are available upon request, but the methods used were based on those given under the literature references.

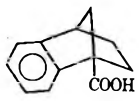
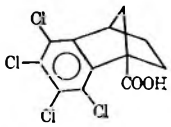
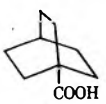
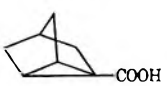
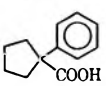
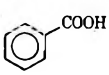
(16) W. P. Whelan, Jr., Dissertation, Columbia University, 1952, pp 61–62.

(17) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(18) J. W. Wilt and C. A. Schneider, *J. Org. Chem.*, **26**, 4196 (1961).

TABLE II

ACIDITY CONSTANTS, 25°

	pK_a 50% EtOH–H_2O (v/v)	pK_a 75% acetone–H_2O (v/v)
	5.88	7.09
		6.56
	5.98	7.61
	6.37	
	6.20	
	6.62	
	6.35	
	6.28	
$(CH_2)_3CCOOH$	6.48	7.64
	5.50	6.71

Experimental Section

Melting points (Fisher-Johns block) and boiling points are uncorrected. The following instruments were used for spectral work: nmr, Varian A-60A; ir, Perkin-Elmer Model 21 and Infracord, Beckman IR-5A; uv, Beckman DK-2 and Bausch and Lomb Spectronic 505. Nmr data are given in parts per million (δ units) relative to internal TMS, with the usual splitting abbreviations being used. The centers of multiplets are given. Area integrations were within 10% of the proper value. Only significant ir (λ) absorptions are listed, in microns (μ). Ultraviolet maxima (λ^{max}) are given in millimicrons (mμ). Gas–liquid partition chromatography (glpc) was performed on a Varian Aerograph A-90P with helium gas as carrier. Microanalyses were done by Galbraith Laboratories, Knoxville, Tenn., and by Micro-Tech Laboratories, Skokie, Ill. A number of the preparations were exploratory and the yields may not be optimum. The petroleum ether used throughout the work was a 30–60° boiling point fraction.

5,6,7,8-Tetrachloro-9,9-dimethoxy-1,4:5,8-dimethano-1,2,3,-4,5,5a,8,8a-octahydronaphthalene-1-carboxylic Acid (4).—Norbornene-1-carboxylic acid[4] (**3**, 50 g, 0.362 mol) was heated at 165° under nitrogen for 6 hr with 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene[19] (250 g, 0.9 mol). The reaction material occasionally solidified during the process, otherwise upon cooling. The solid mass was triturated with hexane to remove excess reactant, leaving a cream-colored powder (125 g, 85%, mp 218–219°). The material could be recrystallized from methanol as a white crystalline solid: mp 225–227°; δ^{CDCl_3} 10.23 br s (COOH), 3.60 s, 3.55 s (2 OCH_3), 2.77 q (5a,8a-H's, AB, J = 8 cps), 2.33 m (4-H), 1.15–1.9 m (all other H's); λ^{Nujol} 3.5–4.0, 5.83, (COOH), 6.19 (C=C).

(19) J. S. Newcomer and E. T. McBee, *J. Amer. Chem. Soc.*, **71**, 946 (1949).

Anal. Calcd for $C_{15}H_{16}O_4Cl_4$: C, 44.80; H, 4.01. Found: C, 44.62; H, 3.96.

Use of toluene or xylene as solvents in the above reaction heated for several days led to **4** in *ca.* 75% yield.

The **methyl ester** of **4** was prepared in acetone from the acid and dimethyl sulfate in the presence of sodium carbonate: pale yellow oil, 72%, bp 163–164° (0.1 mm), $n^{26}D$ 1.5379; δ^{CCl_4} essentially same as that of **4** minus the acid proton and with 3.63 s, 3.57 s, 3.47 s (3 OCH_3); λ^{neat} 5.72 (C=O), 6.21 (C=C).

Anal. Calcd for $C_{16}H_{18}O_4Cl_4$: C, 46.18; H, 4.37. Found: C, 46.24, H, 4.19.

The configurations of **4** and its methyl ester were not proved. That shown for **4** in Chart I (text) is probably correct based upon similar compounds.[20]

5,6,7,8-Tetrachloro-9-keto-1,4:5,8-dimethano-1,2,3,4,5,5a,8,-8a-octahydronaphthalene-1-carboxylic Acid (5).—The procedure given involves critical ratios of reactants. Other proportions gave poor results. Acid **4** (20 g, 0.05 mol) in concentrated sulfuric acid (80 ml) was stirred at 25° for 55 min and then poured slowly onto crushed ice (165 g). The precipitated solid was collected, triturated with water, and dried: 16.8 g, 95%, mp 140–142° dec with loss of carbon monoxide followed by resolidification and eventual melting at *ca.* 230°; δ^{CDCl_3} 10.23 br s (COOH), 2.92 q (upfield pair obscured, 5a,8a-H's, AB, $J \sim 8$ cps), 2.65 m (4-H), 1.3–2.0 m (all other H's); λ^{Nujol} 2.9–4.0, 5.82 (COOH), 5.45 (9-CO), 6.24 (C=C). As **5** decomposed upon recrystallization from ether–petroleum ether, the crude material was analyzed. The analysis is considered satisfactory allowing for the nature of the compound.

Anal. Calcd for $C_{15}H_{10}O_3Cl_4$: C, 43.85; H, 2.83. Found: C, 42.97; H, 3.10.

5,6,7,8-Tetrachloro-1,4-methano-1,2,3,4,5a,8a-hexahydronaphthalene-1-carboxylic Acid (6).—Acid **5** (150 g, 0.421 mol) was slowly heated to reflux in *o*-dichlorobenzene (1500 ml).[20a,b] Evolution of carbon monoxide[21] continued for 2 hr, after which the solvent was removed under reduced pressure with a nitrogen bleed. The residue was triturated with benzene to give **6** as a tan solid (132.5 g, 89.5%, mp 230–232°). The acid was recrystallized from methanol: microcrystalline white solid, mp 240–241°, $\delta^{pyridine}$ 3.33 q (5a,8a-H's, AB, J = 12 cps), 2.72 m (4-H), 1.4–2.5 m (all other H's); λ^{Nujol} 3.4–4.4, 5.96 (COOH), 6.23 (C=C); $\lambda^{max}_{CHCl_3}$ 282 (ϵ 3267), 293 (3367), 306 (3367), 319 (3233).[22]

Anal. Calcd for $C_{12}H_{10}O_2Cl_4$: C, 43.94; H, 3.07. Found: C, 44.12; H, 2.69.

***ar*-Tetrachlorobenzonorbornene-1-carboxylic Acid (7).**—A mixture of bromine (82 g, 0.51 mol), acid **6** (128 g, 0.39 mol), and chlorobenzene (650 ml) was heated under reflux with stirring for 7.5 hr. Hydrogen bromide was steadily evolved. The solvent was removed on a rotary evaporator and the solid residue triturated with hexane and dried to give crude **7** (~128 g, 100%, mp 200–202°). Recrystallization from aqueous methanol produced a glistening crystalline solid: mp 204–205.5°, $\delta^{pyridine}$ 3.7 m (bridgehead H), 1.0–2.9 m (other ring H's); λ^{Nujol} 3.2–4.0, 5.90 (COOH) 13.15; $\lambda^{max}_{CHCl_3}$ 247 (ϵ 3217), 284 (1283), 295 (1300).[22]

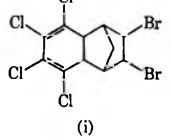
Anal. Calcd for $C_{12}H_8O_2Cl_4$: C, 44.20; H, 2.48. Found: C, 44.11; H, 2.51.

The methyl ester was prepared by reaction of **7** with diazomethane. The white crystalline product was recrystallized several times from methanol: mp 123–124.5°, δ^{CCl_4} 3.90 s

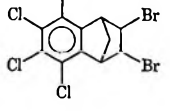
(20) (a) S. B. Soloway, Dissertation, University of Colorado, 1955; J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961); (b) C. F. H. Allen and J. Van Allan, *J. Amer. Chem. Soc.*, **64**, 1260 (1942).

(21) The decarbonylation is probably concerted and sigmasymmetric (disrotary); *cf.* J. E. Baldwin, *Can. J. Chem.*, **44**, 2051 (1966).

(22) MacKenzie[6c] employed uv spectra to differentiate hydroaromatic and aromatic compounds in a similar series. For the following tetrachlorodihydro aromatic substance (i) prepared by him the uv λ^{max} are: 279, 290, 302, and 316 mμ. The aromatized compound (ii) possessed λ^{max} at 222, 284, and 292 mμ. In each case the agreement with compounds **6** and **7** is good.



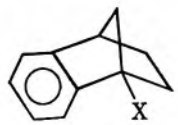
(i)



(ii)

CHART IV

1-SUBSTITUTED BENZONORBORNENES



X	Mp, bp (mm), °C	Analyses, %[a] C	H	X spectra[b]	Lit. ref
$CONH_2$	156–157 (from benzene)	*76.98*	*7.00*	*5.7–7.0 m*	*c*
		77.26	6.99	3.00, 3.15, 6.0–6.2	
CN	...[d]	*85.17*	*6.55*		*e*
		85.04	6.58	4.5	
CHO[f]	...[d]	*83.68*	*7.03*	*10.15 s*	*g*
		83.67	7.09	3.6, 3.7, 5.81	
$COOCH_3$	106–110 (0.2)	*77.20*	*6.98*	*3.67 s*	*h*
		77.00	7.18	5.81	
$COCH_3$[i,j]	90–93 (0.1)	*83.83*	*7.58*	*2.25 s*	*k*
		83.72	7.68	5.9, 7.4	
$OCOCH_3$[l]	82–84 (0.2)	*77.2*	*6.380*	*2.10 s*	*m*
		77.31	7.14	5.78, 8.08	
OH	...[d]	*82.46*	*7.55*	*6.0 s*[n]	*o*
		82.29	7.43	3.05	
Br	68–70 (0.1)	*59.21*	*4.97*	...[p]	*q*
		59.42	5.13		
$NH_3^+ Cl^-$[r,s]	240–245 dec (from ether–butanol)	Cl[t] *18.12*, 18.21		*7.0–8.5* 3.3–4.3	*m*
Cl	...[d]	*73.95*	*6.21*	...[p]	*u*
		74.10	6.30		

[a] Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill. The italicized values are the calculated figures. [b] The italicized spectra are nmr δ values indicative of the group X. Solutions in CCl_4 or $CDCl_3$ were used. The spectra were determined at 60 MHz relative to TMS. The other (λ) spectral data are infrared maxima indicative of the group X. Spectra were determined on neat liquids or on KBr disks of solids. [c] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, John Wiley & Sons, Inc., New York, N. Y., 1964, p 235. [d] Not determined. The material was collected by gas–liquid partition chromatography or by molecular distillation. [e] J. Thurman, *Chem. Ind.* (London), 752 (1964). [f] 2,4-Dinitrophenylhydrazone, mp 173.5–175° from ethyl acetate. *Anal.* Calcd for $C_{18}H_{16}O_4N_4$: N, 15.91. Found: N, 16.19. [g] H. C. Brown and R. F. McFarlin, *J. Amer. Chem. Soc.*, **80**, 5372 (1958). [h] From the acid **2** and diazomethane. [i] 2,4-Dinitrophenylhydrazone, mp 161–162° from ethyl acetate. *Anal.* Calcd for $C_{19}H_{18}O_4N_4$: N, 15.29. Found: N, 15.14. [j] Oxime, mp 120.5–129° from aqueous methanol. It is a mixture of stereoisomers. *Anal.* Calcd for $C_{13}H_{15}ON$: N, 6.96. Found: N, 7.13. [k] C. DePuy, G. Dappen, K. Eilers, and R. Klein, *J. Org. Chem.*, **29**, 2813 (1964). [l] Other methods of synthesis were also employed. The best is referenced. [m] J. W. Wilt, C. F. Parsons, C. A. Schneider, D. G. Schultenover, and W. J. Wagner, *J. Org. Chem.*, **33**, 694 (1968). [n] Varies with concentration and temperature. [o] Saponification of the acetate with alkali. [p] No characteristic spectra. [q] C. Grob, M. Ohta, R. Renk, and A. Weiss, *Helv. Chim. Acta*, **41**, 1191 (1959). [r] Acetamide, mp 156.5–157.5° from aqueous methanol. *Anal.* Calcd for $C_{13}H_{15}ON$: C, 77.58; H, 7.51. Found: C, 77.62; H, 7.55. [s] Benzamide, mp 150.5–151.5° from aqueous methanol. *Anal.* Calcd for $C_{18}H_{17}ON$: C, 82.10; H, 6.51. Found: C, 81.96; H, 6.45. [t] Volhard determination of ionic chloride. [u] J. Kochi, *J. Org. Chem.*, **30**, 3265 (1965); *J. Amer. Chem. Soc.*, **87**, 2500 (1965).

($COOCH_3$), 3.81 m (bridgehead H), 2.5–1.2 series of multiplets (other ring H's); λ^{CCl_4} 5.83, 8.0 (-$COOCH_3$).

Anal. Calcd for $C_{13}H_{10}O_2Cl_4$: C, 45.92; H, 2.96. Found: C, 46.26; H, 2.97.

Benzonorbornene-1-carboxylic Acid (2).—Acid **7** (11.7 g, 0.036 mol) and aqueous potassium hydroxide (81 g of 85% material) in 800 ml of water were stirred on a steam bath until homogeneous. Raney nickel catalyst[23] (powder, 50 g) was then added portionwise with stirring at a rate that kept the foaming under control. When all the catalyst had been added, the solution was stirred on the steam bath for 4 hr. The cooled solution was filtered from the catalyst and combined with aqueous washings of the catalyst. Acidification of this filtrate with concentrated hydrochloric acid (Congo Red endpoint) threw down acid **2**. The acid was taken up in ether, washed, dried, and recovered by evaporation as an off-white, crystalline solid negative to Beilstein's test for halogen (6.4 g, 95%, mp 88–90°). The acid could be recrystallized from heptane or hexane as colorless prisms [mp 93–94°, δ^{CCl_4} 12.9 s (COOH), 7.47 m (*peri* Ar–H, adjacent to COOH), 7.1 sharp m (other Ar–H), 3.37 m (bridgehead H), 1.0–2.7 m (other ring H's); λ^{Nujol} 3.3–4.0, 5.95 (COOH), 6.32, 13.3 (Ar–H); $\lambda_{CHCl_3}^{max}$ 264 (ϵ 1340), 271 (1320).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.56; H, 6.44. Found: C, 76.51; H, 6.54.

The deshielding of the aromatic proton noted above is characteristic of most 1-substituted benzonorbornenes and is helpful in structural assignment. There are exceptions, however (*e.g.*, carbinol **8**).

The S-benzylisothiuronium salt of **2** was made in the usual way (mp 146–147°).[24]

Anal. Calcd for $C_{20}H_{22}O_2N_2S$: C, 67.80; H, 6.21. Found: C, 67.50; H, 6.23.

The spent catalyst from the above preparation of **2** could not be used effectively again. Only partial dechlorination of **7** was observed. Application of the above procedure *at room temperature* to acid **6** produced **1,4-methanodecahydronaphthalene-1-carboxylic acid** (73%).[25] The acid was sublimed, recrystallized from heptane, and resublimed: white crystalline solid, mp 124.5–126°, neut equiv 205, calcd 205; δ^{CCl_4} 12.4 s (COOH), 1.0–2.2 m (all other H's); λ^{Nujol} 3.3–4.0, 5.92 (COOH), 13.7; blank in uv.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.23; H, 9.28. Found: C, 74.23; H, 9.59.

(23) Several other methods of reductive dechlorination were attempted with varying degrees of success. The preferred one in our hands is that described, modeled after that of N. P. Buu-Hoi, N. Dat Xuong, and N. van Bac, *Bull. Soc. Chim Fr.*, 2442 (1963).

(24) D. J. Pasto and C. R. Johnson, "Organic Structure Determination," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1969, p 404.

(25) Therefore this method[23] seems too vigorous, even under these milder conditions, for the production of unsaturated acids.

The amide of the acid above was prepared in standard fashion[26] from the acid chloride and ammonia (white solid, mp 205–206° from methanol–water).

Anal. Calcd for $C_{12}H_{19}OH$: C, 74.61; H, 9.84. Found: C, 74.37; H, 9.89.

Benzonorbornenyl-1-carbinol (8).—Reduction of acid **2** with lithium aluminum hydride in ether in standard fashion produced carbinol **8**: 99%, a difficult compound to work with but which could be recrystallized from heptane and then sublimed; mp 58–59°; δ^{CCl_4} 7.03 sharp m (Ar–H), 4.05 q (–CH_2OH, AB due to adjacent asymmetric carbon, J = 11 cps, outer lines weak), 3.27 m (bridgehead H), 2.50 s (OH, removed by D_2O), 0.83–2.17 m (other ring H's); λ^{Nujol} 3.0, 9.66, 9.75 (>C–CH_2OH), 13.3 (Ar–H). Repeated attempts did not improve the analysis and the alcohol is characterized better as its tosylate.

Anal. Calcd for $C_{12}H_{14}O$: C, 82.76; H, 8.05. Found: C, 83.20; H, 8.24.

Benzonorbornenyl-1-carbinyl Acetate (8-OAc).—Reaction of carbinol **8** with acetic anhydride in pyridine under reflux, followed by a quench in water and treatment with dilute hydrochloric acid, afforded **8**-OAc as an oil that was taken up in benzene, dried, and distilled under vacuum in a micro Hickman still for the analytical sample: 91%, δ^{CCl_4} 7.27 s (Ar–H), 4.75 q (–CH_2O–, AB due to adjacent asymmetric carbon, J = 12 cps, outer lines weak), 3.43 m (bridgehead H), 2.08 s (–$OCOCH_3$), 1.08–2 33 m (other ring H's); λ^{neat} 5.72, 8.04, 9.61 (–CH_2OCOCH_3), 13.2 (Ar–H).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.74; H, 7.46. Found: C, 77.72; H, 7.39.

Benzonorbornenyl-1-carbinyl tosylate (1) was prepared in the usual way from **8** with *p*-toluenesulfonyl chloride in pyridine:[27] 68%, mp 95.5–96.5° from benzene–pentane, δ^{CCl_4} (partial), 4.60 apparent s (–CH_2OSO–),3.35 m (bridgehead H); λ^{Nujol} 7.36, 8.4, 8.5 (–OSO_2–).

Anal. Calcd for $C_{19}H_{20}O_3S$: C, 69.51; H, 6.10. Found: C, 69.40; H, 6.13.

***ar*-Tetrachlorobenzonorbornenyl-1-carbinol and Tosylate 11.**—Acid **7** was reduced to the carbinol with lithium aluminum hydride in ether (reflux, 24 hr). Upon recrystallization from hexane it was microcrystalline: 80%, mp 116.5–117°; δ^{CCl_4} 4.35 q (–CH_2O–, AB due to adjacent asymmetric carbon, J = 11 cps), 3.65 m (bridgehead H), 2.55 m (OH), 1.0–2.5 m (other ring H's); λ^{KBr} 3.15, 9.55, 9.75 (>C–CH_2OH).

Anal. Calcd for $C_{12}H_{10}OCl_4$: C, 46.19; H, 3.23. Found: C, 46.57; H, 3.34.

Tosylate 11 was prepared in pyridine from the carbinol and *p*-toluenesulfonyl chloride: 80%, mp 153–153.5° from hexane; δ^{CDCl_3} 8.1–7.28 q (AB, Ar–H), 4.83 q (–CH_2O–, AB due to adjacent asymmetric carbon, J = 10 cps), 3.63 m (brigehead H), 2.46 s (Ar–CH_3), 2.2–1.15 m (other ring H's) λ^{KBr} 7.38, 8.41, 8.55 (–OSO_2–).

Anal. Calcd for $C_{19}H_{16}O_3Cl_4S$: C, 48.95; H, 3.46. Found: C, 49.09; H, 3.54.

Solvolysis Rate Studies.—Attempts to study tosylates **1** and **11** in 60% acetone–40% water (as was done earlier with tosylates **9** and **10**) were thwarted by lack of solubility. The tosylates were therefore studied in 80% acetone (distilled from potassium permanganate)–20% deionized water (v/v), containing *sym*-collidine (redistilled) using sealed ampoules thermostated at various temperatures (see Table I).[28] Tosylate **11** was studied only at one temperature. Ampoules were removed at certain times, cooled, and opened. Water was added (so that the end point was sharper) and the excess collidine was titrated with standard 0.02 *N* hydrochloric acid to a bromophenol blue end point. The solvolyses were first order to over 80% completion and infinity titers (10 half-lives) were >97% of theory. Additional runs made with twice as much collidine showed essentially no rate effect, so the processes are believed to be true solvolyses with no S_N2 component from the collidine.

Less satisfactory studies of **1** were done in acetic acid (distilled) containing 0.3% (v/v) acetic anhydride and sodium acetate (1.5 mmol/mmol of tosylate), again using the ampoule technique. Excess *p*-toluenesulfonic acid was added to each opened ampoule to react with the remaining sodium acetate. The excess acid was then back-titrated with standard sodium acetate in acetic acid. Serious negative deviation from first-order kinetics occurred after *ca.* 60% reaction and the rate constants for **1** in acetolysis (Table I) are initial slopes. In contrast, **9** shows first-order kinetics to over 80% reaction and the infinity titer was 99% of theory. Both first order rate constants and activation parameters were calculated in both solvents by the usual methods, employing the Eyring equation for the latter. The errors given for these parameters are average deviations from the best (visual) straight line fit of the data.

Solvolysis Product Studies.—The solvolysis products from **9** in both aqueous acetone and acetic acid have been reported[4] and they were not further investigated; nor were the products from **11**. A larger scale solvolysis of **1** in 80% acetone at 150° for 4 days produced *ca.* 50% isolated product (there remained some unchanged **1**), bp 103–105° at 0.5 mm. The material solidified on long standing. Preparative glpc on an SE-30 column (186°) separated the later eluting carbinol **8** (75%, confirmed with authentic material) from another alcohol (25%), to which was assigned the structure **6,7-benzobicyclo[3.2.1]oct-6-en-1-ol (13)**: viscous oil; δ^{CCl_4} 7.15 m (Ar–H), 3.21 m (bridgehead H), 2.27 m (*endo* C-3 proton), 2.25 s (OH), 1.32–1.87 m (other ring H's); λ^{neat} 3.0, 8.78, 8.90 (tertiary C–OH), 3.31, 3.45, 3.52, 6.9, 7.55, 7.82, 8.2, 9.4, 9.55, 9.81, 10.18, 10.7, 11.1, 11.2, 11.84, 12.3, 12.5, 13.3, 14.1, 14.8.[29]

Anal. Calcd for $C_{12}H_{14}O$: C, 82.76; H, 8.05. Found: C, 82.36; H, 7.94.

Alcohol **13** (0.9 mmol) was converted into **6,7-benzobicyclo[3.2.1]oct-6-en-1-yl acetate** in standard fashion employing acetic anhydride and pyridine (10 mmol each). The acetate was collected as a colorless oil by distillation in a micro-Hickman distillation apparatus: 85%, δ^{CDCl_3} 7.35 m (Ar–H), 3.40 m (bridgehead H), 2.50 m (C-2 methylene), 2.20 m (*endo* C-3 H), 2.10 s (–$OCOCH_3$), 1.90–1.47 m (other ring H's); λ^{neat} 5.74, 7.95, 8.19, 13.2.

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.74; H, 7.46. Found: C, 78.04; H, 7.42.

Attempts to prepare the **tosylate** of **13** were largely unsuccessful. Reaction of **13** with tosyl chloride in pyridine at 25° for 4 days led to an oily mixture of unchanged alcohol and the presumed tosylate **13**-OTs. The small amount of material precluded isolation and analysis. However, after correction for the absorptions of **13**, the ir spectrum of the presumed **13**-OTs showed λ^{neat} 7.35, 8.36, 8.48, 8.52 (–OSO_2–), 9.09, 9.78, 10.20, 10.4–10.7 (broad), 11.32, 11.54, 12.00, 12.27, 13.24, 14.3–15.2 (broad).

The preparative acetolysis of **1** (1 g, 3 mmol) in glacial acetic acid (75 ml), acetic anhydride (1 ml), and sodium acetate trihydrate (0.61 g) was carried out under reflux for 330 hr. The solvolysis mixture was poured onto solid sodium carbonate, diluted with water, and extracted, with benzene. Removal of the benzene left an oil which was treated with petroleum ether causing a solid to precipitate (100 mg, 10% yield). Recrystallization of the solid from chloroform–petroleum ether afforded **benzobicyclo[2.2.2]oct-1-enyl tosylate (12-OTs)**: mp 99–100° (no decomposition), δ^{CCl_4} 7.85 d (downfield portion of Ar–H of tosyl group, A_2B_2), 7.5–6.9 m (rest of Ar–H of tosyl group and Ar–H of bicyclic), 2.90 m (bridgehead H), 2.73–2.21 m (C-6 *exo* and C-7 *anti* H's), 2.43 s (Ar–CH_3), 2.1–1.1 (other ring H's); λ^{KBr} 7.42, 7.50, 8.43, 8.55, (–OSO_2–), 10.10, 11.12, 11.59, 12.12, 12.22, 12.68, 13.18, 13.34, 14.60, 15.13.

Anal. Calcd for $C_{19}H_{20}O_3S$: C, 69.51; H, 6.10. Found: C, 69.52; H, 6.10.

While the structure assigned to **12**-OTs must be considered provisional, three items support it. First, the bridgehead proton resonance at δ 2.90 is somewhat upfield from those found in benzonorbornene or 6,7-benzobicyclo[3.2.1]oct-6-ene derivatives (all > δ 3), but close to that of benzobicyclo[2.2.2]octene (δ 2.93). These differences possibly reflect the different percentage s character in these bridgehead C–H bonds. Second, the obvious inertness of the compound in acetolysis is in keeping with this

(26) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Interscience Publishers, Inc., New York, N. Y., 1957, p 353.

(27) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

(28) For complete details, the dissertation of H. F. D., Jr., should be consulted.

(29) A mixture of alcohol **13** (69%) together with **8** (12%) and benzobicyclo[2.2.2]octen-1-ol (19%) was also prepared from *ar*-tetrachlorobenzonorbornenyl-1-carbinol. Reaction of the carbinol with fuming sulfuric acid (30% SO_3) at 10° followed by solution in water led to the *ar*-tetrachloro derivatives of these alcohols. Dechlorination was then achieved with Raney nickel alloy in analogous fashion to the procedure described for acid **2**. The samples of alcohol **13** obtained by the solvolysis route from **1** and this route were identical (unpublished work).

bridgehead derivative.[13] Lastly, the presumed tosylate **13**-OTs had a different ir spectrum from **12**-OTs.

The petroleum ether mother liquor from which **12**-OTs precipitated was evaporated to afford a mixture of acetates (400 mg, 62%). Analysis by glpc (SE-30, 170°) indicated two closely eluting fractions. A small first portion was possibly **benzobicyclo[2.2.2]oct-2-en-1-yl acetate (12-OAc)**, although the small amount of material precluded positive identification. The major glpc fraction (97%) was an unresolved mixture of **8**-OAc and **13**-OAc, in the ratio of 37:63, respectively, as established by spectral comparison with mixtures of the authentic compounds.

Action of Carbinol 8 with Hydrobromic Acid–Zinc Bromide.—A mixture of hydrobromic acid (48%, 10 ml), zinc bromide (10 g), and carbinol **8** (0.5 g, 3 mmol) was heated at reflux with vigorous stirring for 40 hr.[15] A 6.5-hr heating period was less effective, 4% unchanged **8** being left, while a 10-hr heating period at 100° effected little change in **8**. The cooled material was diluted with water and extracted with hexane. The extracts were dried, freed of solvent, and distilled to afford a pale yellow oil (0.27 g, 47%, Hickmann microstill) and much residue. The distilled material showed no –OH in the ir spectrum, while the nmr spectrum was very complex, showing aromatic protons and a series of multiplets for the remaining protons from δ 3.4 to 1.0. The 40-hr experiment showed no δ 3.97 singlet characteristic of carbinyl bromide **14** ($-CH_2Br$), although some of this was observed in the 6.5-hr experiment.

To assist in product analysis, the bromides from the 6.5-hr experiment (0.5 g) were reduced in tetrahydrofuran (10 ml) and *t*-butyl alcohol (1.1 g) by addition of lithium shot (*ca.* 0.5 g).[6i] The exothermic reaction was selfsustaining for 2 hr, after which further refluxing was continued for 2 hr. Water was added to the cooled mixture and the hydrocarbon products were extracted with hexane. Preparative glpc (SE-30, 195°) of the dried extract produced a clear oil, shown by various analyses (see below) to be a mixture of hydrocarbons **17** (18%), **18** (70%), and **19** (12%).

Anal. Calcd for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 91.37; H, 8.88.

1-Methylbenzonorbornene (17).—Tosylate **1** (0.75 g, 2.3 mmol) was reduced in ether with lithium aluminum hydride (0.2 g) over a 4-day reflux period (a 15-hr period left 1 unchanged). The customary workup and distillation in micro-Hickman still produced **17** (45%) as a colorless oil. The residue was *ca.* 50% recovered **1**. The analytical sample of **17** was collected by glpc on Reoplex 400 (polypropylene glycol adipate) at 185°: δ^{CCl_4} 7.0 s (Ar–H), 3.27 m (bridgehead H), 1.55 s (CH_3), 1.00–2.33 m (other ring H's); λ^{neat} 7.27 ($C-CH_3$), 13.34.

Anal. Calcd for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 91.24; H, 8.92.

6,7-Benzobicyclo[3.2.1]oct-6-ene (18).—6,7-Benzobicyclo-[3.2.1]oct-6-en-3-one[30] [1.6 g, 9.3 mmol, mp 65–67°, δ^{CCl_4} 7.13 s (Ar–H), 3.35 (bridgehead H's), 1.80–2.53 m (other ring H); λ^{KBr} 5.9 (CO), 13.08–13.3] was reduced *via* the Huang-Minlon method to afford **18** as a colorless oil: 1.17 g, 80%, bp 95° at 3 mm, homogeneous on SE-30 at 190° for analytical sample; δ^{CCl_4} 7.1 s (Ar–H), 3.07 p (J = 2.5 cps, bridgehead H's), 2.25 p (*endo* C-3 H, J = 2.5 cps), 0.62–1.83 m (other ring H's); λ^{neat} 3.32, 3.36, 3.48, 3.55, 6.81, 6.90, 9.30, 10.72, 11.52, 12.81, 13.3–13.45, 14.5; lit.[30b] δ (medium not given) 3.01 (bridgehead H's).

Anal. Calcd for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 91.01; H, 8.94.

Benzobicyclo[2.2.2]octene (19) was available from an earlier study:[31] mp 61–62°, δ^{CCl_4} 7.18 s (Ar–H), 2.93 m (bridgehead H's), 1.53 symmetrical m (other ring H's, A_2B_2); λ^{KBr} 7.52, 8.41, 9.70, 10.71, 11.6, 13.42; lit.[32] mp 61–62°.

2,3-Benzobicyclo[3.2.1]oct-2-ene (20).—The literature[33] preparation of this hydrocarbon was followed (81%, bp 90–92° at 5 mm). Although the product was homogeneous on SE-30 or Reoplex 400 in glpc, nmr analysis of the product indicated that **20** was contaminated (*ca.* 30%) with the isomeric 1,2,3,3a,8,8a-hexahydrocyclopenta[*a*]indene.[34] The latter was evidenced by λ^{neat} 13.15 and by nmr resonances at δ 7.08 s (Ar–H) and 3.33–3.83 dt (poorly resolved ArCH), in good agreement with values reported for this hydrocarbon.[34] Hydrocarbon **20** was a pleasant smelling oil: δ^{CCl_4} 6.97 s (Ar–H), with multiplets centered at 2.95, 2.67, 2.47, and 1.75 (other H's); λ^{neat} 12.93, 13.5, 13.82.

Study indicated that these hydrocarbons were resolved from **17**, **18**, and **19** on GE-XE-60 (silicone gum, nitrile) at 180° and that neither was present in the reduced reaction product from carbinol **8** mentioned above. On the other hand, individual coinjection of authentic **17**, **18**, and **19** with the reaction product enhanced the appropriate glpc peak. Infrared and nmr spectra of samples of three hydrocarbons made up in the aforementioned 18:70:12 ratio matched the reaction product.

Benzonorbornenyl-1-acetic Acid (23).—Benzonorbornene-1-carboxylic acid chloride (**2A**) was prepared from the acid and thionyl chloride (85%, bp 93–96° at 0.2 mm). The acid chloride (5.15 g, 0.025 mol) was converted at 0° into the diazoketone (λ^{neat} 4.75, 6.15) by means of ethereal diazomethane (0.07 mol). Removal of the ether left a viscous oily product which was dissolved in dry methanol (200 ml), stirred, and treated portionwise with silver ion catalyst (silver benzoate in freshly distilled triethylamine) as described by Newman and Beal.[35] Gas evolution was vigorous after a short induction period and was complete in 15 min. After 3 more hr of stirring, the solvents were removed on a rotary evaporator, and the black residual oil was taken up in ether, washed successively with aqueous sodium bicarbonate (5%), dilute hydrochloric acid, water, and then brine, and dried and distilled. **Methyl benzonorbornenyl-1-acetate** was collected as a pale yellow oil (4.4 g, 81%, bp 112–117° at 0.2 mm). A sample was redistilled for analysis: bp 116° at 0.2 mm, $n^{24}D$ 1.5327, δ^{neat} 7.05 m (Ar–H), 3.51 s (OCH_3), 3.18 m (bridgehead H), 2.90 s ($-CH_2CO-$), 0.95–2.11 (other ring H's); λ^{neat} 5.78, 8.40, 8.56 ($-COOCH_3$), 13.3.

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.93; H, 7.41.

Glpc (SE-30, 180°) indicated about 1.5% contamination by methyl ester **28**.

Saponification of the ester with sodium hydroxide in aqueous alcohol and acidification produced acid **23** as an oil which slowly solidified: 86%, white solid, mp 59–60° upon recrystallization from petroleum ether and sublimation (occasionally a sample had mp 64–65° but would remelt at 59–60°); δ^{CCl_4} 12.1 broad s (COOH), 7.03 sharp m (Ar–H), 3.27 m (bridgehead H), 2.97 s ($-CH_2CO-$), 1.00–2.33 (other ring H's); λ^{Nujol} 2.9–4.0, 5.85 (COOH), 13.3.

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.23; H, 6.93. Found: C, 77.04; H, 7.05.

The **aceto-*p*-toluidide** derivative of **23** was prepared from the acid chloride (86% from **23** and thionyl chloride, bp 95–97° at 0.5 mm) and *p*-toluidine in benzene under reflux. Recrystallization from aqueous ethanol gave a microcrystalline white solid (mp 147–148°).

Anal. Calcd for $C_{20}H_{21}ON$: C, 82.44; H, 7.27. Found: C, 82.39; H, 7.27.

2-(Benzonorbornen-1-yl)ethanol (24).—Reduction of acid **23** (3.5 g, 17.3 mmol) with lithium aluminum hydride in ether in the normal fashion produced alcohol **24** as an oil that slowly solidified: 3.05 g, 94%, mp 52.5–53.5° when recrystallized from benzene and petroleum ether; δ^{CCl_4} 7.10 sharp m (Ar–H), 3.79 t ($-CH_2CH_2OH$), 3.28 m (bridgehead H), 3.22 s (OH shifted on dilution), 2.25 probable 12-line multiplet though not all observed, (AB portion of ABX_2, $-CH_2CH_2OH$, J_{AB} = 15 cps, $J_{AX(BX)} \cong 7$ cps), 0.90–2.03 m (other ring H's); λ^{neat} 3.00–3.20, 9.60 ($-CH_2OH$), 9.90, 13.3.

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.90; H, 8.69.

The **tosylate** was prepared in pyridine in the usual way:[27] 80%, mp 60–61° from benzene–petroleum ether; δ^{CCl_4} (partial) 4.33 t ($-CH_2CH_2OTs$), 3.40 m (bridgehead H), 2.53 s ($Ar-CH_3$); λ^{KBr} 7.38, 8.42, 8.50 ($-OSO_2-$).

Anal. Calcd for $C_{20}H_{22}O_3S$: C, 70.14; H, 6.48. Found: C, 70.27; H, 6.55.

Benzonorbornenyl-1-acetaldehyde (22).—Dry dimethyl sulfoxide (75 ml) was heated to 150° under nitrogen and then cooled. To this was added the tosylate of alcohol **24** (4 g, 11.7 mmol)

(30) (a) P. T. Lansbury and E. J. Nienhouse, *J. Amer. Chem. Soc.*, **88**, 4290 (1966). We thank Professor Lansbury for the details of this preparation. (b) L. Billet and G. Descotes, *C. R. Acad. Sci., Paris, Ser. C*, **268**, 69 (1969).

(31) A. R. Zigman, M.S. Thesis, Loyola University of Chicago, 1965.

(32) H. E. Simmons, *J. Amer. Chem. Soc.*, **83**, 1657 (1961).

(33) W. Baker and W. G. Leeds, *J. Chem. Soc.*, 974 (1948); S. Julia, C. Huynh, and J. Olivie, *Bull. Soc. Chim. Fr.*, 147 (1966).

(34) For a recent study of the Baker and Leeds preparation and its use to prepare this indene, *cf.* H. E. Zimmerman, R. S. Givens, and R. M. Pagni, *J. Amer. Chem. Soc.* **90**, 6096 (1968).

(35) M. S. Newman and P. F. Beal, III, *ibid.*, **72**, 5163 (1950).

and sodium bicarbonate (12 g). The heterogeneous mixture was heated at 150° with a nitrogen purge for 10 min and cooled.[36] Water was added and the material then was extracted with ether. Most of the ether was removed from the dried extracts by aspiration, and the residual oil was vigorously shaken with saturated aqueous sodium bisulfite to afford the bisulfite adduct (4.5 g). The sulfurous by-products in this adduct were removed by ether extraction in a Soxhlet apparatus for 40 hr. The purified bisulfite adduct was then mixed with aqueous sodium hydroxide (5%) and the liberated oil taken up in ether. Distillation of the neutral, dried extracts produced aldehyde **22** as a colorless oil with a slight floral odor: 0.87 g, 40%, bp 105–108° at 0.2 mm; δ^{CCl_4} 10.0 t (–CHO, J = 2 cps), 7.10 sharp m (Ar–H), 3.33 m (bridgehead H), 2.92 eight-line m (–CH_2CHO, AB portion of ABX, J_{AB} = 15 cps, J_{AX} = 2 cps, lines 1,2 and 7,8 very weak), 1.00–2.23 m (other ring H's); λ^{neat} 3.55, 3.72, 5.83 (–CHO), 13.3. The analytical sample was collected by glpc (SE-30, 190°).

Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.57. Found: C, 83.60; H, 7.67.

The **2,4-dinitrophenylhydrazone** derivative was routinely prepared (yellow needles from aqueous methanol, mp 129–131°).

Anal. Calcd for $C_{19}H_{18}O_4N_4$: N, 15.29. Found: N, 15.45.

Decarbonylation of Aldehyde 22.—A 1 *M* solution of **22** (2 mmol) in chlorobenzene (2 ml) was sparged with helium for 15 min and then treated at 140° with three successive 0.2-mmol portions of freshly distilled di-*t*-butyl peroxide equally spaced over 14 hr. Carbon monoxide (92% of theory, analyzed by glpc at 25° on a molecular sieve 5A column) was evolved steadily and the reaction half-time was *ca.* 260 min. The entire reaction contents were analyzed by glpc (SE-30) and showed only one product from **22**, 1-methylbenzonorbornene (**17**), identical in retention time and spectra with authentic material. Some 5% of the unchanged **22** was also detected. The other possible hydrocarbon products (**18–20**) were absent. On the scale employed, yield data were difficult to obtain but calibration studies indicated at least a 70% yield of **17**.

Acidity Constants.—*Ca.* 0.3-mmol portions of the acids in Table II were dissolved in 50 ml of either 50% (v/v) aqueous ethanol or 75% (v/v) acetone–25% water. The acidic solutions were then titrated at 25° with sodium hydroxide (0.05 *N*) from a microburet using a Leeds and Northrup pH meter with a Beckman glass electrode and a Coleman saturated calomel electrode. The pK_a was obtained from the pH at the half-neutralization point.

Registry No.—**1**, 15642-38-3; **2**, 13733-46-5; S-benzylisothiuronium salt of **2**, 24452-99-1; 1,4-methanodecahydronaphthalene-1-carboxylic acid, 24453-00-7; 1,4-methanodecahydronaphthalene-1-carboxamide, 24453-01-8; **4**, 16166-88-4; methyl ester of **4**, 15642-40-7; **5**, 15642-39-4; **6**, 13733-44-3; **7**, 13733-45-4; methyl ester of **7**, 24453-07-4; **8**, 13733-48-7; **8**-OAc, 24453-09-6; *ar*-tetrachlorobenzonorbornenyl-1-carbinol, 24453-10-9; **11**, 24453-11-0; **13**, 24453-12-1; **13**-OAc, 24453-13-2; **12**-OTs, 24453-14-3; **17**, 24453-15-4; **18**, 15391-62-5; methyl ester of **23**, 24453-17-6; **22**, 24453-18-7; 2,4-dinitrophenylhydrazone of **22**, 24453-19-8; **23**, 24453-20-1; aceto-*p*-toluidide derivative of **23**, 24453-21-2; **24**, 24453-22-3; tosylate of **24**, 24453-23-4.

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Notes

Studies of Benzonorbornene and Derivatives. V. Adduction of Benzyne with 5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene. A Convenient Synthesis of 1,2,3,4-Tetrachloronaphthalene[1]

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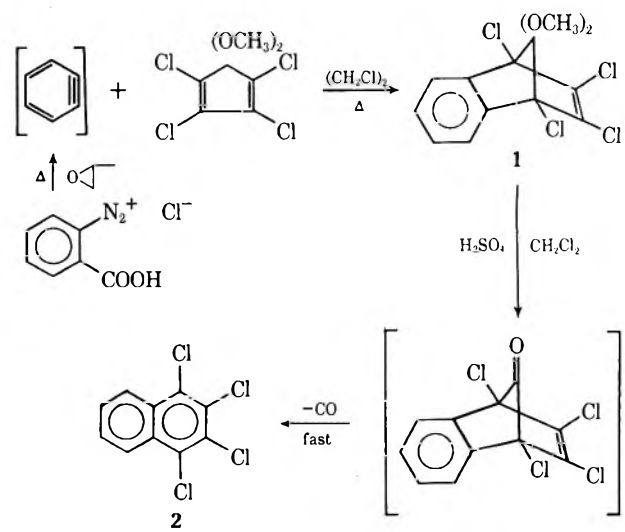
The adduction of benzyne with cyclopentadiene[3] is the method of choice for the synthesis of benzonorbornadiene. As part of a general research program in benzonorbornene chemistry, the addition of benzyne to 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene was achieved (76% based on diene). Of the numerous interesting reactions of the adduct **1**,[4] its conversion



into the rare 1,2,3,4-tetrachloronaphthalene (**2**) is particularly efficient (quantitative yield).

Syntheses of **2** are recorded.[5] None of them has,

(1) Part IV: J. W. Wilt, H. F. Dabek, Jr., J. P. Berliner, and C. A. Schneider, *J. Org. Chem.*, **35**, 2402 (1970).

(2) National Defense Education Act Fellow, 1966–1968.

(3) G. Wittig and E. Knauss, *Chem. Ber.*, **91**, 895 (1958). For a convenient recent modification, *cf.* L. Friedman and F. M. Logullo, *J. Org. Chem.*, **34**, 3089 (1969).

(4) J. W. Wilt and E. Vasiliauskas, to be published.

(5) (a) From *ar*-tetrachlorotetralin, J. von Braun, *et al.*, *Ber.*, **56B**, 2332 (1923), and modified by W. P. Wynne, *J. Chem. Soc.*, **61**, (1946); (b) from naphthalene, A. A. Danish, M. Silverman, and Y. A. Tajima, *J. Amer. Chem. Soc.*, **76**, 6144 (1954); (c) from trichloroethylene, W. L. Howard and R. E. Gilbert, *J. Org. Chem.*, **27**, 2685 (1962).

(36) N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Amer. Chem. Soc.*, **81**, 4113 (1959).

however, the convenience, ease, and yield of the present synthesis, particularly for small scale work (3–5 g).

Experimental Section

1,2,3,4-Tetrachloro-7,7-dimethoxybenzonorbornadiene (1).—Under reflux, a stirred mixture of *o*-carboxybenzenediazonium chloride[6] (25.16 g, 0.137 mol), 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene[7] (59.57 g, 0.226 mol), propylene oxide (commercial material used as is, 20.6 g, 0.355 mol), and ethylene chloride (300 ml) was heated for 3 hr. The solvent was removed by rotary evaporation and the residual dark oil was then chromatographed on alumina (400 g). Benzene (20%) in petroleum ether (bp 30–60°) eluted a milky oil (64.77 g) which upon refrigeration for 1 day deposited white crystals of 1 (16.43 g). A second crop of 1 (3.00 g) was obtained upon further standing. The filtrate was distilled to recover excess starting diene (bp 70–81° at 0.3 mm, 37.64 g, 63% recovery). The residual oil was taken up in boiling hexane and filtered. Further crystals of 1 (2.4 g) were obtained upon refrigeration of this hexane solution. The total yield of 1 was 21.83 g (47% based on diazonium salt, 76.5% based on consumed diene). Recrystallization of 1 from hexane afforded white rhombs: mp 121.5–122°; δ^{CDCl_3} (60 MHz) 7.55 (symmetrical m, A_2B_2, Ar–H), 3.77 (s), 3.47 (s, OCH_3's); λ^{KBr} 3.4 (w), 6.22 (w), 8.3 (s), 8.65 (s), 8.86 (s), 9.02 (sh), 9.8 (sh), 9.9 (m), 10.3 (m), 11.05 (m), 11.45 (w), 11.9 (w), 12.4 (w), 13.6 (s), 14.8–15.7 (broad m).

Anal.[8] Calcd for $C_{13}H_{10}O_2Cl_4$: C, 45.92; H, 2.96. Found: C, 46.16; H, 2.91.

1,2,3,4-Tetrachloronaphthalene (2).—A mixture of 1 (5.00 g, 14.7 mmol), concentrated sulfuric acid (125 ml), and methylene chloride (200 ml) was stirred at 25° as carbon monoxide evolved. A solid deposited during the course of the reaction. After 20 min the reaction appeared completed, but further stirring for a few hours was arbitrarily allowed. Evaporated solvent was replenished by addition of methylene chloride (100 ml), the phases separated, and the acid layer extracted with more solvent. The organic phase and the extracts were combined, washed well with water, dried, and evaporated. The residual solid (3.92 g, 100%) was quite pure 2 by spectra. Recrystallization once from ligroin (bp 60–90°) produced long, colorless needles: mp 200–201° (lit.[5b] mp 199–200°); δ^{CDCl_3} A_2B_2 m centered at 8.53 and 7.87; λ^{Nujol} 7.6 (s), 8.02 (m), 11.2 (m), 13.3 (s), 14.3–14.4 (m).

Registry No.—1, 24472-15-9; 2, 20020-02-4.

(6) F. M. Logullo, Dissertation, Case Institute of Technology, 1965; B. H. Klandorman and T. R. Criswell, *J. Org. Chem.*, **34**, 3426 (1969).

(7) J. S. Newcomer and E. T. McBee, *J. Amer. Chem. Soc.*, **71**, 946 (1949).

(8) Micro-Tech Laboratories, Skokie, Ill.

Self-Association in Axial β-Hydroxycyclohexanones

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Received December 1, 1969

Infrared spectra of aliphatic hydroxy ketones in the hydroxyl region (3000–3700 cm^{-1}) are sometimes difficult to interpret even at the millimolar concentration level, where intermolecular hydrogen bonding usually does not interfere. Recently, Joris and Schleyer[1] examined a number of such spectra; they note that in some cases the overtone of carbonyl vibration occurring around 3400 cm^{-1} has been mistaken for the absorption of an intramolecular hydrogen bond. The present note shows that some hydroxy ketones associate unusually strongly by intermolecular hydrogen bonding, also giving bands around 3400 cm^{-1} which have on occasion been incorrectly assigned. Such associations are sterically specific, and therefore useful for stereochemical elucidation.

Type I compounds (R = H, CH_3, C_2H_5, *n*-propyl, phenyl, and 1-furyl) show strong absorption around 3400 cm^{-1} (5×10^{-3} *M* solutions in CCl_4), which was attributed to an intramolecular hydrogen bond[2,3] and used in the elucidation of the stereochemistry of the system. Later, the discovery of the strong intermolecular association of some diols by Eglinton, *et al.*,[4,5] and our own experience with that phenomenon[6] led to reexamination of the assignment, and bands at 3400 cm^{-1} were tentatively attributed to the intermolecularly bonded species.[7,8] Nevertheless, Joris and Schleyer[1] assign these strong bands to the carbonyl overtones, contradicting their own contention that such bands should be relatively weak; they also note that the stereochemistry of I has not yet been determined.

The following experiments substantiate our previous view that the absorption at 3400 cm^{-1} is due to intermolecular hydrogen bonding. Compound I, with R = CH_3, was recrystallized from CH_3OD; the deuteration thus achieved (OH → OD) shifted the bands originally at 3604 and 3395 cm^{-1} to 2662 and 2514 cm^{-1} (5×10^{-3} *M* solutions in CCl_4). Consequently, these bands must be attributed to the stretching vibration of the hydroxyl group. The dependence of the apparent molar absorption coefficients ϵ on the concentration of I, R = CH_3, was measured (CCl_4 solutions in thermostated 30° cells, 0.2 and 1 cm; Beckman IR-12); the results are in Figure 1. The data can be explained by a monomer–dimer equilibrium; the presence of other oligomers at higher concentration cannot be excluded, however. A trial and error procedure (final mean square of the residuals is 3) gave a dimerization constant of 58 l. mol^{-1}; $\epsilon_{monomer}$ at 3604 cm^{-1} is 112; the broad band of dimer (slightly asymmetric, half-width 125 cm^{-1}) has ϵ_{dimer} 316 at 3395 cm^{-1} and ϵ_{dimer} 25 at 3604 cm^{-1}, the last value approximately corresponding to the simple overlap contribution (Cauchy curve[9] shape assumption). Following the argument of Liddel and Becker[10] the dimer must have the cyclic structure II, as proposed previously.[7,8] This dimer structure implies[8] that compound I has the stereochemistry as proposed;[2] furthermore, comparison of the band posi-

(1) L. Joris and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **90**, 4599 (1968).

(2) J. Pitha, J. Plesek, and M. Horak, *Collect. Czech. Chem. Commun.*, **26**, 1209 (1961).

(3) J. Pitha, M. N. Tilichenko, and V. G. Kharchenko, *Zh. Obshch. Khim.*, **34**, 1936 (1964).

(4) A. J. Baker, G. Eglinton, A. G. Gonzales, R. J. Hamilton, and R. A. Raphael, *J. Chem. Soc.*, 4705 (1962).

(5) W. S. Bennet, G. Eglinton, and S. Kovac, *Nature*, **214**, 5090 (1967).

(6) J. Pitha, J. Joska, and J. Fajkos, *Collect. Czech. Chem. Commun.*, **28**, 2611 (1963).

(7) J. Pitha, personal communication in M. Tichy, "Advances in Organic Chemistry: Methods and Results," Vol. 5, R. A. Raphael, E. C. Taylor, and H. Wyberg, Ed., John Wiley & Sons, Inc., New York, N. Y., 1965, p 121.

(8) F. Hanousek, *Collect. Czech. Chem. Commun.*, **29**, 1965 (1964).

(9) R. N. Jones, K. S. Seshadri, N. B. W. Jonathan, and J. W. Hopkins, *Can. J. Chem.*, **41**, 750 (1963).

(10) V. Liddel and E. D. Becker, *Spectrochim. Acta*, **10**, 70 (1957).

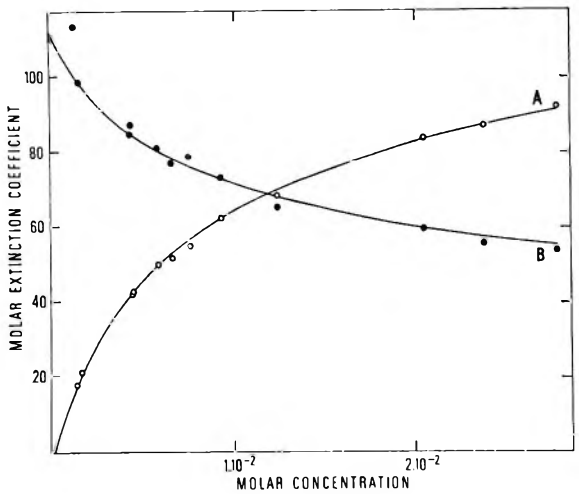
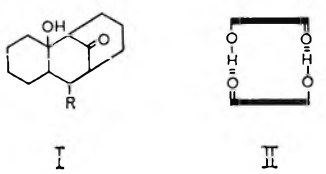


Figure 1.—Concentration dependence of the apparent molar extinction coefficients of compound I, R = CH_3. Carbon tetrachloride solutions at 30°: values observed at 3604 cm^{-1}, ●; at 3395 cm^{-1}, ○. Lines A and B represent the corresponding calculated values for monomer–dimer equilibrium [K_{dimer} = 58 l. mol^{-1} ($\epsilon_{monomer}$ 112 at 3604 cm^{-1}; ϵ_{dimer} 316 at 3395 cm^{-1} and 25 at 3604 cm^{-1})].

tion for the monomer species with data of Joris and Schleyer[1] gives additional support for the axial position of the hydroxy group. Last, but not least, the stereochemistry of the system I was studied independently by different methods with the same results (*cf.* ref 11 and references therein; also ref 7, p 189).

The dimerization constant of I (58 l. mol^{-1}) is an order of magnitude higher than that of *t*-butyl alcohol[10] (0.8 l. mol^{-1}) or the association constant of *t*-butyl alcohol–acetone[12] (1.0 l. mol^{-1}); nevertheless, it is lower



I II

than the dimerization constant of *n*-nonanoic acid[13] (1500 l. mol^{-1}, all data at 30° and in CCl_4 solutions). In the case of I no special forces can be invoked to assist dimerization, such as resonance effects in carboxylic acids or diols[14] or π–π interaction in hydroxyacetophenones.[5] The only possible factor is the steric arrangement which allows the simultaneous formation of two hydrogen bonds in the dimer II. In line with that interpretation all six known derivatives of type I give the same pattern.[2,3] It may be pointed out that in all these compounds the cyclohexane rings probably have a slightly distorted chair conformation.[15,16] Further, relatively strong and broad bands around 3400 cm^{-1} were observed for dilute solutions (around 5 × 10^{-3} *M; cf.* ref 15) of the following compounds: 4-hydroxy-2-butanone[17] (also alleged to be[1] a carbonyl overtone), and decalone and cholestane derivatives containing a cyclohexanone moiety with an axial β-hydroxy group.[18] These substances may constitute a new class of strongly self-associating compounds.[5]

Registry No.—I (R = Me), 1614-94-4.

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(11) S. Julia, D. Varech, Th. Bürer, and Hs. H. Günthard, *Helv. Chim. Acta*, **43**, 1623 (1960).
(12) E. D. Becker, *Spectrochim. Acta*, **17**, 436 (1961).
(13) G. Geiseler and I. Liebster, *Z. Phys. Chem.* (Leipzig), **222**, 330 (1963).
(14) G. E. Bass, *Proc. Nat. Acad. Sci. U. S.*, **62**, 345 (1969).
(15) G. Eglinton, J. Martin, and W. Parker, *J. Chem. Soc.*, 1243 (1965).
(16) W. A. C. Brown, G. Eglinton, J. Martin, W. Parker, and G. A. Sim, *Proc. Chem. Soc. London*, 57 (1964).
(17) G. Eglinton, in "Physical Methods in Organic Chemistry," J. C. P. Swartz, Ed., Holden-Day, Inc., San Francisco, Calif., 1964, p 67.
(18) F. Dalton, J. I. McDougall, and G. D. Meakins, *J. Chem. Soc.*, 4068 (1963).

Synthesis of Allenic Acetals from Unsaturated Carbenes[1]

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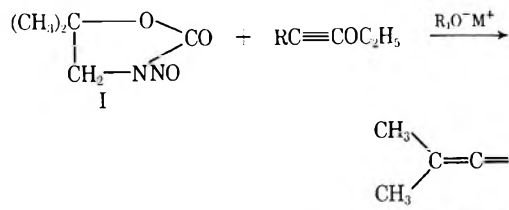
Dihalocarbenes[2] and carbethoxycarbene[3] react less easily with acetylenes than with olefins. We undertook this study to see if unsaturated carbenes[4,5] could add to acetylenes, since substituted methylenecyclopropenes might thus be synthesized.

On treatment of a solution of ethoxyacetylene and 5,5-dimethyl-N-nitrosooxazolidone (I)[5] in 1,2-dimethoxyethane (glyme) with solid lithium ethoxideethanolate,[6] the theoretical amount of nitrogen was rapidly evolved. By suitable procedures 4-methyl-2,3-pentadienal diethyl acetal (II) was isolated in 35% yield.



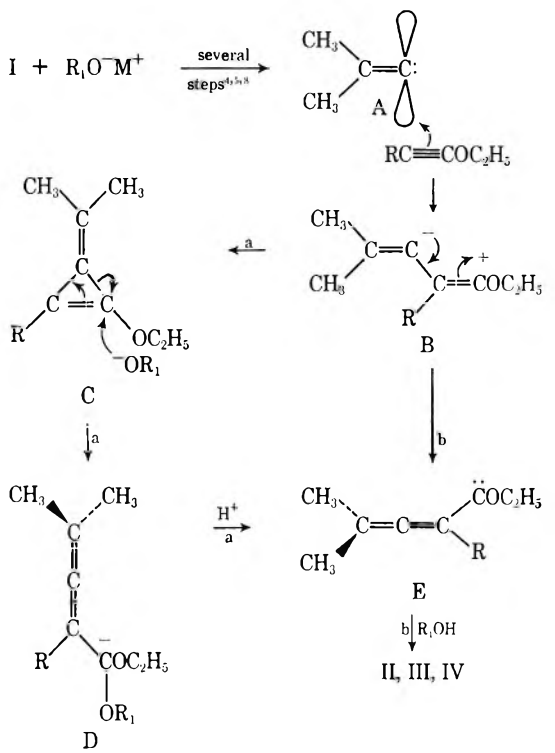
II, R = H; $R_1 = C_2H_5$
III, R = H; $R_1 = CH_3$
IV, R = CH_3; $R_1 = C_2H_5$

When sodium methoxide was used instead of lithium ethoxide, the mixed ethyl methyl acetal III was formed in 33% yield. In addition to the allenic acetals II and III, there was formed a mixture of higher boiling products which on alkaline hydrolysis yielded quantities of

(1) This research was supported by Special Fund (178107) of The Ohio State University and Grant 5552 of The National Science Foundation.
(2) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, p 177.
(3) I. A. D'yakonov, R. N. Gmyzina, and L. P. Danilkina, *J. Org. Chem. USSR*, **2**, 2038 (1966).
(4) M. S. Newman and A. O. M. Okorodudu, *J. Org. Chem.*, **34**, 1220 (1969).
(5) M. S. Newman and T. B. Patrick, *J. Amer. Chem. Soc.*, **91**, 6461 (1969).
(6) W. M. Jones, M. H. Grasley, and W. S. Brey, Jr., *ibid.*, **85**, 2754 (1963).

2-methyl-1,2-propanediol as previously described.[5] When 1-ethoxypropyne[7] was used in place of ethoxyacetylene, a 37% yield of 2,4-dimethyl-2,3-pentadienal diethyl acetal (IV) was obtained. Thus, a new route to allenic acetals is at hand.

In line with a previous suggestion[5] for the mechanism of reaction of an unsaturated carbene with olefins, the following mechanism for the reaction of unsaturated carbenes with alkoxyacetylenes is proposed.



The vacant orbital on the carbene carbon of A lies in the plane of the paper as represented. We assume that electrophilic attack[5] by A occurs on the nonoxygenated carbon of the ethoxyacetylene to yield B which then proceeds by paths a or b to the allenic product.[9] Cyclization (path a) would lead to a methylenecyclopropene C so labile that attack of alkoxide ion as shown[10] would be expected to yield D which on protonation yields the allenic acetals II, III, or IV. Alternately, rehybridization of the dipolar ion B (path b) could yield the carbene E which would react with an alcohol to give the final acetal II, III, or IV. The changes of B to C and B to E involve different geometrical paths. We cannot suggest which change is more favorable but prefer that which leads to E because this path does not require a ring closure followed by reopening.

Attempts to react I with 3-hexyne under similar conditions were unsuccessful.

(7) D. G. Farnum, M. A. T. Heybey, and B. Webster, *J. Amer. Chem. Soc.*, **86**, 673 (1964).

(8) M. S. Newman and A. O. M. Okorodudu, *ibid.*, **90**, 4189 (1968).

(9) Other mechanisms may be written but, as crucial experiments have not been conceived, only the two paths shown are discussed.

(10) Some cases where bases have been shown to add to cyclopropenes are K. B. Wiberg, R. K. Barnes, and J. Albin, *J. Amer. Chem. Soc.*, **79**, 4994 (1957); T. C. Shields and P. D. Gardner, *ibid.*, **89**, 5425 (1967); G. L. Closs in "Advances in Alicyclic Chemistry," Vol. I, H. Hart, and G. J. Karabatsos, Ed., Academic Press, New York, N. Y., 1966, p 83.

Experimental Section[11]

4-Methyl-2,3-pentadienal Diethyl Acetal (II).—To a stirred solution of 10 g (0.07 mol) of I[5] in 100 ml of glyme and 24.5 g of ethoxyacetylene[12] at room temperature was added in four portions 8 g (0.08 mol) of solid lithium ethoxide ethanolate.[6] The theoretical amount of nitrogen was evolved during 1 hr, cooling being necessary to keep the temperature near 40°. After pouring the reaction mixture onto ice a conventional work-up yielded 3.93 g (35%) of II as a pale yellow liquid, bp 72–77° at 16 mm (94% pure by glpc). The analytical sample was obtained by preparative glpc on a 12 ft × 3/8 in. aluminum column packed with 12% Carbowax 20M on 60–80 Chromosorb W at 120° using a helium flow of 100 ml/min. The infrared spectrum had a characteristic allene band at 1992 cm^{-1} (5.0 μ) and acetal bands at 1160 cm^{-1} (8.6, 9.3 μ). The nmr showed a complex multiplet at δ 4.77 (2 H, vinyl H and acetal H, AB pattern ($J \sim 8$–10 cps), the A part being further coupled with the vinyl methyl groups ($J \sim 3$ cps), a complex multiplet at δ 3.48 (4 H, OCH_2CH_3),[13] singlets at 1.83 and 1.80 (6 H, vinyl CH_3, $J \cong 3$ cps), and a triplet at 1.17 (6 H, OCH_2CH_3). The parent peak in the mass spectrum (70 eV) was at 170, mol wt 170.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.6; H, 10.6. Found: C, 70.5; H, 11.0.

A sample of II was prepared from 1-bromo-3-methyl-1,2-butadiene[14] *via* the Grignard reagent reaction with ethyl orthoformate.[15] The crude reaction product (28% yield, bp 63–80° at 17 mm) was separated into two components (4:1) by preparative glpc. The major component proved to be identical with II as shown by ir and nmr spectra, and retention time on glpc analysis.

After heating a solution of II in 3:1 water–glyme containing a small amount of sulfuric acid at 90° for 90 min, a small amount of 4-methyl-3-ketovaleraldehyde was isolated by preparative glpc. This compound proved identical with authentic ketoaldehyde prepared by acylation of methyl isopropyl ketone with ethyl formate as described.[16]

4-Methyl-2,3-pentadienal Ethyl Methyl Acetal (III).—This compound was prepared in 33% yield as described for II except that dry sodium methoxide was used in place of lithium ethoxide. The crude product, bp 65–70° (15 mm), was purified by preparative glpc to yield the analytical sample: ir band at 5.0 μ; nmr δ 4.77 (m, 2 H, =CH, $CH(OR)_2$), 3.48 (m, 2 H, OCH_2R), 3.22 (s, 3 H, OCH_3), 1.73, 1.66 (two broadened singlets, 6 H, $=C(CH_3)_2$), 1.17 (t, 3 H, OCH_2CH_3).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.2; H, 10.3. Found: C, 68.9; H, 10.6; parent peak (mass spectrum, 70 eV) *m/e* 156, mol wt 156.

2,4-Dimethyl-2,3-pentadienal Diethyl Acetal (IV).—A solution of I in glyme and excess 1-ethoxypropyne[7] was treated with lithium ethoxide ethanolate[6] as described for the synthesis of II. There was obtained in 37% yield a pale yellow oil, bp 79–84° (12 mm), which was about 95% pure by glpc. The analytical sample, obtained by preparative glpc, had an ir band at 5.0 μ and nmr bands at δ 5.73 (s, 1 H, $CH(OR)_2$), 3.42 (m, 4 H, OCH_2CH_3), 1.67 (s, 6 H, $=CCH_3$), 1.52 (s, 3 H, $=CCH_3$), 1.13 (t, 6 H, OCH_2CH_3, $J = 7$ cps).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.6; H, 10.9. Found: C, 71.5; H, 11.1; parent peak (mass spectrum, 70 eV) 184, mol wt 184.

Registry No.—II, 6136-99-8; III, 24472-13-7; IV, 24472-14-8.

(11) All temperature readings are uncorrected; microanalysis are by the Galbraith Laboratories, Knoxville, Tenn. Nmr spectra in CCl_4 relative to $(CH_3)_4Si$ were taken on a Varian A-60 instrument. Analytical glpc were performed on a 6 ft by 1/8 in. aluminum column packed with 7% Carbowax 20M on 60–80 mesh Chromosorb W.

(12) Obtained from the Farchan Research Laboratories, Willoughby, Ohio.

(13) For explanation of ABC_3 pattern see P. R. Shafer, D. R. Davis, A. Vogel, and J. D. Roberts, *Proc. Nat. Acad. Sci. U. S.*, **47**, 49 (1961).

(14) S. R. Landor, A. N. Patel, P. F. Whitier, and P. M. Greaves, *J. Chem. Soc.*, 1223 (1966).

(15) Y. Pasternak and J. C. Traynard, *Bull. Soc. Chim. Fr.*, 356 (1966).

(16) A. Richards and T. S. Stevens, *J. Chem. Soc.*, 3067 (1958).

Reaction of Ketene with Aldehydes in the Presence of Zinc Carboxylic Acid Salts

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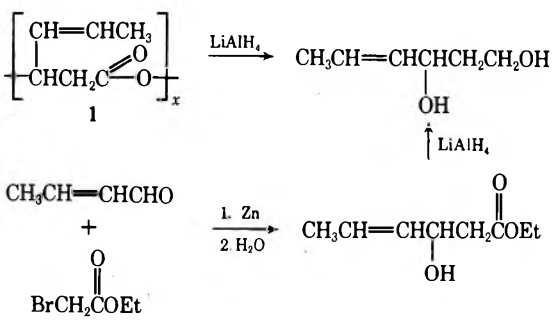
Received April 23, 1969

The first step of an industrial route to 2,4-hexadienoic acid (sorbic acid) is the production of a polymeric material by reaction of ketene with crotonaldehyde in an inert solvent containing a catalytic amount of a zinc salt of a carboxylic acid.[1] As part of our continuing study of ketene chemistry, we have investigated the identity of this polymeric reaction product and have inquired into the mode of its formation.

Analysis of the ir spectrum and, particularly, the nmr spectrum of the ketene–crotonaldehyde reaction product led to its tentative identification as poly(3-hydroxy-4-hexenoic acid) (1). In order to obtain verification of this structure, the polymer was reduced with lithium aluminum hydride to give 4-hexene-1,3-diol which was identical with an actual sample of the diol prepared by an independent route. This route involved the lithium aluminum hydride reduction of ethyl 3-hydroxy-4-hexenoate prepared by a Reformatsky reaction utilizing crotonaldehyde, ethyl bromoacetate, and zinc (Scheme I).

Scheme I

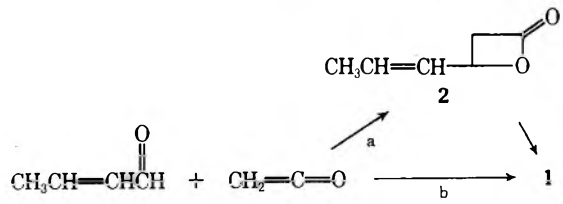


There are two general ways that polyester 1 might have been formed from ketene and crotonaldehyde. The polyester could have arisen by polymerization of 3-hydroxy-4-hexenoic acid β-lactone (2) formed initially (path a) or by the direct copolymerization of ketene and crotonaldehyde without the intermediacy of 2 (path b) (Scheme II).

Although no mechanistic work on this reaction has been published, several related pieces of work have appeared. It is generally known that ketene will react with aldehydes in the presence of a variety of catalysts to give β-lactones. In several cases, zinc salts of carboxylic acids have been shown to be effective. Hagemeyer has reported that ketene will react with aromatic aldehydes in the presence of zinc salts of fatty acids to give β-lactones.[2] Caldwell was able to isolate good yields of β-lactones by using zinc trifluoroacetate as catalyst for the reaction of ketene with aliphatic aldehydes.[3]

(1) R. N. Lacey, *Advan. Org. Chem.*, **2**, 213 (1960).
(2) H. J. Hagemeyer, U. S. Patent 2,466,420 (1949).

Scheme II



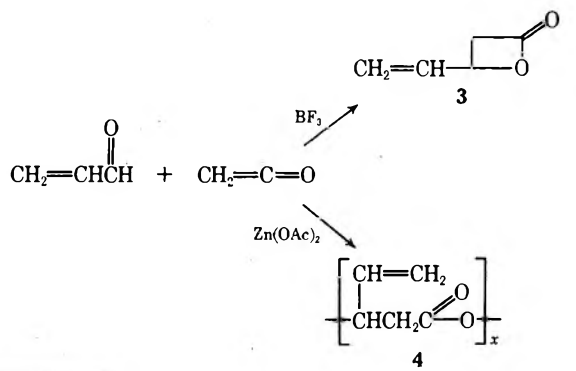
On the other hand, in some instances ketenes and aldehydes will copolymerize to polyesters directly without the intermediacy of β-lactones. Natta and coworkers have shown that dimethylketene and benzaldehyde will polymerize to poly(3-hydroxy-3-phenyl-2,2-dimethylpropionic acid) in the presence of metal alkyls or alkoxides.[4] They have shown that, at least in their particular case, the corresponding β-lactone is stable under the reaction conditions and, therefore, is not a reaction intermediate.

In order to determine whether 2 was an intermediate in the reaction of ketene with crotonaldehyde catalyzed by zinc salts of carboxylic acids, we decided to synthesize 2 and submit it to the reaction conditions. If the β-lactone were stable under these conditions, it could not have been an intermediate in the polymerization reaction.

The only synthesis of 2 is that of Hagemeyer, who presented evidence that the lactone was produced by the reaction of ketene with crotonaldehyde in the presence of boron trifluoride at −25°.[5] Hagemeyer was not able to isolate 2 but inferred its presence because of the evolution of piperylene on pyrolysis of the reaction mixture. We made several attempts to synthesize 2 by this method but none was successful. The nmr spectrum of the cold reaction mixture failed to reveal any bands characteristic of β-lactones.

Since we were unable to prepare 2, we decided to prepare the similar, yet known,[6] 3-hydroxy-4-pentenoic acid β-lactone (3). This lactone was prepared from ketene and acrolein in 70% yield by a procedure similar to that which failed for 2. As opposed to 2, lactone 3 was stable and could be distilled under vacuum at 48°.

In the presence of zinc acetate, ketene and acrolein again underwent a facile reaction, but in this case the product was poly(3-hydroxy-4-pentenoic acid) (4) (eq 1). The nmr spectrum of the crude product con-



(1)

(3) R. J. Caldwell, U. S. Patent 2,739,158 (1956).
(4) G. Natta, G. Mazzanti, G. F. Pregaglia, and G. Pozzi, *J. Polym. Sci.*, **58**, 1201 (1962).
(5) H. J. Hagemeyer, U. S. Patent 2,478,388 (1949).
(6) E. W. White in "Acrolein," C. W. Smith, Ed., John Wiley and Sons, Inc., New York, N. Y., 1962, p 142.

tained no bands characteristic of lactone **3**. In order to determine if lactone **3** could have been an intermediate in the formation of **4**, the zinc acetate catalyzed reaction was carried out with **3** initially present. During reaction the lactone was not consumed and was recovered by distillation from the reaction mixture. In this reaction, then, the polyester was not formed by polymerization of an intermediate β-lactone, but must have arisen by a process not involving the lactone.

Although the mechanism for the direct conversion of ketene and aldehydes to polyesters in the presence of zinc carboxylic acid salts is unknown at present, it is interesting to note that zinc acetate is probably not acting as a Lewis acid. In the reaction of ketene with acrolein (eq 1), boron trifluoride, a strong Lewis acid, leads to β-lactone formation, whereas zinc acetate leads to formation of the polyester. Also, *n*-butylzinc and ethyl bromozinc acetate when used as catalysts give as high a yield of polyester as does zinc acetate.

An interesting mechanistic possibility for this reaction involves the insertion of ketene into the zinc catalyst to form a zinc alkyl compound.[7] The zinc alkyl could then add to a molecule of aldehyde, as in the Reformatsky reaction, to give a zinc alkoxide. Insertion of ketene into the zinc alkoxide would re-form a zinc alkyl species which could continue the polymerization.[8]

Experimental Section

Boiling points are uncorrected. The ir spectra were obtained with a Baird-Atomic Model AB-2 spectrometer using sodium chloride cells. Nmr spectra were determined at 60 MHz with Varian Associates A-60 spectrometers. Field position values are recorded in parts per million relative to tetramethylsilane as an internal standard. Nmr peak multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), and m (multiplet). Mass spectra were recorded on an AEI Model MS 902 spectrometer. Molecular weights were determined by vapor phase osmometry by European Research Associates, Union Carbide Corp.

Poly(3-hydroxy-4-hexenoic acid) (1).—To a 5-l. four-necked reaction flask equipped with a stirrer, thermometer, condenser, and ketene diffuser were added crotonaldehyde (1260 g, 18.0 mol), toluene (2400 cc), and zinc isovalerate (13.5 g). Ketene (662 g, 15.7 mol) was added over a period of 6 hr while the temperature was maintained at 25°. During this time only 3 g of ketene came through the reaction zone unchanged. The reaction mixture was purged with nitrogen for 15 min, then stripped of solvent and excess crotonaldehyde under vacuum. The polyester, obtained as a residue from the distillation, weighed 1576 g (90% based on ketene): mol wt, 1200; ir (neat) 5.75 (C=O), 8.06 (COOC), and 10.43 μ (C=C); nmr ($CDCl_3$) 1.68 (d, 3, J = 6 Hz, $CHCH_3$), 2.61 (d, 2, J = 7 Hz, CH_2CO), and 5.6 ppm (m, 3).

Reduction of 1.—To a stirred suspension of lithium aluminum hydride (10.6 g) in ethyl ether (650 cc) was added a solution of 1 (50 g) in ethyl ether (250 cc) at a rate such that gentle reflux was maintained. After complete addition, the mixture was stirred for 2 hr, then quenched with water (25 cc). The ether solution was clarified by filtration, dried over magnesium sulfate, and distilled through a 7-in. glass helix column to give 32 g (62%) of 4-hexene-1,3-diol: bp 82–85° (1 mm); ir (neat) 2.9 (O–H) and 5.92 μ (C=C); nmr ($CDCl_3$) 1.72 (d, 3, J = 4 Hz, CH_3), 1.70 (m, 2, CH_2), 3.69 (t, 2, J = 5 Hz, CH_2OH), 4.20 (m, 1, CHOH), 4.52 (s, 2, OH), and 5.56 ppm (m, 2, HC=CH). The mass spectrum of this material possessed a parent molecular ion at m/e 116.0833 ($C_6H_{12}O_2$ required 116.0837).

Anal. Calcd for $C_6H_{12}O_2$: C, 62.07; H, 10.35. Found: C, 62.30; H, 10.38.

4-Hexene-1,3-diol.—Ethyl 3-hydroxy-4-hexenoate was prepared in 60% yield by the Reformatsky reaction of ethyl bromozinc acetate with crotonaldehyde under the conditions described by Fischer and Löwenberg.[9] The hydroxy ester (26 g, 0.16 mol) was reduced with lithium aluminum hydride (5.95 g, 0.156 mol) in ethyl ether giving 15 g (79%) of 4-hexene-1,3-diol, bp 80–85° (2 mm). The sample was identical (vpc, ir, nmr) with that obtained above. The mass spectrum of this material possessed a parent molecular ion at m/e 116.0840 ($C_6H_{12}O_2$ required 116.0837).

Attempted Preparation of 2.—A four-necked 500-cc reaction flask equipped with a stirrer, thermometer, condenser, diffusion tube, and dropping funnel was charged with dry toluene (250 cc) and boron trifluoride etherate (4 cc). To this was simultaneously added ketene (60 g, 1.4 mol) and crotonaldehyde (70 g, 1.0 mol); the temperature was maintained at −25°. After complete reaction, the catalyst was destroyed with sodium acetate (3.5 g), and the nmr spectrum of the cold solution was scanned. The nmr spectrum contained no absorption bands in the region between 3 and 4 ppm, the area in which hydrogens α to the carbonyl group of β-lactones absorb.

Preparation of 3.—The apparatus and procedure were the same as used in the attempted preparation of **2**. Acrolein (56 g, 1.0 mol) and ketene (59 g, 1.4 mol) were simultaneously added to the boron trifluoride solution at −25°. Destruction of the catalyst and distillation gave 71 g (72%) of **3**: bp 44–48° (4 mm) [lit.[6] bp 45–50° (3 mm)]; ir (neat) 5.4 (β-lactone C=O) and 8.0 μ (COOC); nmr (neat) 3.18 (dd, 1, C(=O)CH), 3.69 (dd, 1, C(=O)CH), 5.3 (m, 3), and 6.11 ppm (m, 1, O—CH).

Preparation of 4 in the Presence of 3.—A solution of acrolein (100 g), **3** (40 g), and zinc isovalerate (1 g) in benzene (150 cc) was charged into a four-necked 500-cc reaction flask equipped with a stirrer, thermometer, gas diffuser, and condenser. Ketene (70 g) was passed into the solution, but only a fraction of this (14 g) was absorbed. The reaction mixture was purged with nitrogen and distilled. Besides solvent and acrolein, there was obtained lactone **3** (27 g) and residue (22 g). Analysis of the nmr spectrum of the crude reaction mixture indicated that 36 g of **3** was present prior to distillation.

Registry No.—Ketene, 463-51-4; 4-hexene-1,3-diol, 24655-66-1; **3**, 7379-74-0.

(7) For similar reactions, see L. C. Willemsens and G. J. M. van der Kerk, *J. Organometal. Chem.*, **4**, 241 (1965); I. F. Lutsenko, V. L. Foss, and N. L. Ivanova, *Dokl. Akad. Nauk SSSR*, **141**, 1270 (Engl) (1961).

(8) M. F. Lappert and B. Prokai, *Advan. Organometal. Chem.*, **5**, 242 (1967).

(9) F. G. Fischer and K. Löwenberg, *Chem. Ber.*, **66**, 669 (1933).

Routes to 2,19-Oxido-$\Delta^{4,6}$-3-keto Steroids

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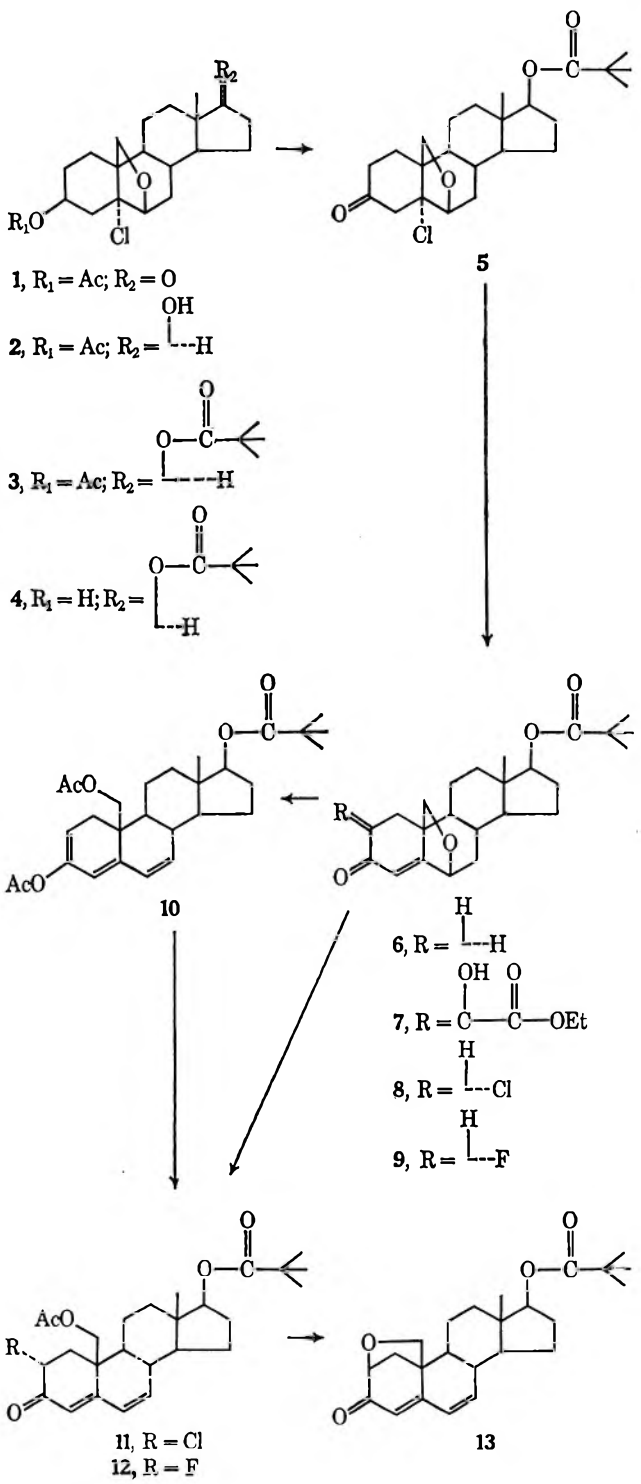
Saturated 2,19-oxido-3-keto steroids have recently been prepared from the corresponding 2β-hydroxy-3α-acetates.[1] Attempts to convert these ketones into their conjugated analogs[1b] failed, however, and the steric deformation induced by the 2,19-oxide bridge has been made responsible for this. We wish to report the preparation of 2,19-oxido-4,6-dien-3-one (**13**) from 2-halo-19-acetoxy-$\Delta^{4,6}$-3-ketones **11** and **12** by hydrolysis and concomitant substitution of the halogen atoms in position 2 by the liberated 19-hydroxy group.

The synthesis commenced with 3β-acetoxy-5α-chloro-6,19-oxidoandrostan-17-one (**1**).[2] In view of the subsequent halogenating reactions planned, it appeared desirable to protect the oxygen function in position 17 by an ester group. The pivalate was chosen, as it

(1) (a) R. Kwok and M. E. Wolff, *J. Org. Chem.*, **28**, 423 (1963); (b) M. E. Wolff, W. Ho, and R. Kwok, *Steroids*, **5**:1, 1 (1964).

(2) J. Kalvoda, K. Heusler, H. Ueberwasser, J. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 1361 (1963).

allowed for a selective hydrolysis of the 3-acetate. The 17-keto group of **1** was reduced with sodium borohydride to the 17β-alcohol **2**, which gave **3** on heating with pivaloyl chloride in pyridine. Base-catalyzed hydrolysis in methanol gave the 3β-alcohol **4**, which on oxidation with chromic acid in acetone and subsequent treatment of the reaction product **5** with pyridine gave Δ^4-3-ketone **6**. The 2-chloro derivative **8** was prepared *via* ethoxalyl derivative **7** by a modification of the method of Yasuda.[3] Treatment of the ethoxalyl derivative with perchloryl fluoride in methanolic sodium carbonate[4] gave the 2-fluoro-Δ^4-3-ketone



9. The conversion of 2-halo-6,19-oxides **8** and **9** to $\Delta^{4,6}$-3-ketones **11** and **12** was achieved by heating the two oxides in acetic anhydride in the presence of *p*-toluenesulfonic acid. Considerably more *p*-toluenesulfonic acid was required for the effective opening of the oxide ring of the 2-halo-3-ketones **8** and **9** than has been found necessary for the opening of the oxide ring of ketone **6** under comparable conditions.[5] Both the 2-chloro-$\Delta^{4,6}$-3-ketone **11** and the 2-fluoro analog **12** gave readily the 2,19-oxide **13** on treatment of their methanolic solutions with excess base at room temperature or on refluxing of the methanolic solutions with aqueous hydrochloric acid. At no time during the hydrolysis could the formation of a free 19-alcohol be observed as indicated by tlc.

In another route, 6,19-oxido-Δ^4-3-ketone **6** was converted into 3-acetoxy-2,4,6-triene **10** by treatment with isopropenyl acetate and *p*-toluenesulfonic acid.[6] Selective chlorination at position 2 with calcium hypochlorite gave **11** and hence **13** as before. Non-reductive ring opening of 6,19-oxido-Δ^4-3-keto steroids has previously been accomplished with acetic anhydride in presence of *p*-toluenesulfonic acid and the corresponding 19-acetoxy-$\Delta^{4,6}$-3-ketones were obtained.[7]

The α position has been assigned to the halogen atoms in $\Delta^{4,6}$-3-ketones **11** and **12** as then the ease of the 2,19-oxide formation could readily be explained by an intramoleular SN2 mechanism in which the β-orientated 19-hydroxy group substitutes the α-halogen atoms by rear attack on carbon atom 2. The α position of the halogen atoms of compounds **8**, **9**, **11**, and **12** has also been established by comparison of their ir,[3] uv,[3] and nmr[8] spectra with those of previously prepared analogs. The 2,19-oxide bridge in **13** is confirmed by comparison of its nmr spectrum with those of previously prepared 2,19-oxido steroids.[9]

Experimental Section[10]

6,19-Oxido-17β-pivaloxyandrost-4-en-3-one (6).—To a solution of 10 g of **1**[2] in 300 ml of methanol was added at 0° 0.80 g of sodium borohydride over 2 min with stirring. After being stirred for 30 min in an ice bath, the mixture was poured into 300 ml of 2 *N* aqueous sulfuric acid. The precipitate was filtered off, washed well with water, and dried at 80° under high vacuum for 16 hr yielding 9.0 g of **2** as indicated by tlc.

A stirred mixture of 2 g of 17 alcohol **2**, 10 ml of pyridine, and 2 ml of pivaloyl chloride was slowly heated to 100° during 1 hr and kept at this temperature for 30 min. The mixture was then poured into 50 ml of water with stirring. The precipitate of crude **3** was filtered off, washed well with water, and dried at 50° under high vacuum for 16 hr. The total crude product of **3** was then suspended in 20 ml of methanol and stirred with 0.1 g of potassium hydroxide at room temperature for 2 hr. The sus-

(3) K. Yasuda, *Chem. Pharm. Bull.*, **12**, 1217 (1964).

(4) C. Djerassi, "Steroid Reactions," Holden-Day Inc., San Francisco, Calif., 1963, pp 165–166.

(5) G. Kruger, unpublished work.

(6) D. J. Marshall, unpublished results, has prior to us used this method for the ring opening of the 17-ketone and the 17β-benzoxy analogs of **6**. We are indebted to Dr. Marshall for providing us with the experimental details of this novel and rather cleanly proceeding reaction.

(7) K. Heusler, J. Kalvoda, Ch. Meystre, H. Ueberwasser, P. Wieland, J. Anner, and A. Wettstein, *Experientia*, **18**, 464 (1962).

(8) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 46–52.

(9) Reference 8, pp 69–73.

(10) Melting points were determined with a Thomas–Hoover apparatus and are corrected. Ir spectra were determined with a Perkin-Elmer spectrophotometer, Model 21. Nmr spectra were determined in deuteriochloroform with a Varian A-60 spectrometer; chemical shifts are reported in parts per million downfield from tetramethylsilane.

pension was neutralized with 0.15 ml of glacial acetic acid and diluted with 20 ml of water. Filtration and washing with water gave 1.6 g of crude 3-alcohol **4**.

To a solution of 1.0 g of **4** in 10 ml of acetone was added 2.0 ml of 50% aqueous chromic acid over 1 hr with stirring, whereupon the mixture was poured into 100 ml of water. The precipitate of crude **5** was filtered off, washed well with water, and dried over calcium chloride overnight. It was then refluxed with 2 ml of pyridine for 15 min. Dilution with water and filtration gave 0.80 g of crude **6** which was purified by recrystallization from methanol: mp 157–158°; λ_{max}^{EtOH} 238 mμ (ε 14,320); $\nu_{max}^{CHCl_3}$ 1715 (pivalate) and 1776 cm^{-1} (Δ^4-3-ketone); the nmr spectrum showed maxima for 1 olefinic proton as a singlet at 5.80 (4 position), 2 protons as a multiplet between 4.4 and 4.8 (6 and 17 position), 2 methylenic protons as a quartet (J = 8 Hz, $\delta_A - \delta_B$ = 0.70 ppm) centered at 3.85 (19 position), 9 protons as a singlet at 1.21 (pivalate), and 3 protons as a singlet at 0.90 ppm (18 position).

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.69; H, 8.73.

2-Ethoxalyl-6,19-oxido-17β-pivaloxyandrost-4-en-3-one (**7**).—A mixture of 8 g of **6**, 8 g of 54% sodium hydride (dispersed with mineral oil), 8 ml of benzene (dried over sodium hydride), and 8 ml of diethyl oxalate was stirred under nitrogen at room temperature for 3 hr after which time a vigorous reaction set in necessitating cooling. After 4 hr the reaction mixture, which had thickened considerably, was treated with 400 ml of hexane and 200 ml of partially frozen 1 *N* aqueous hydrochloric acid. A yellow precipitate formed which was filtered off, washed with hexane and with water, and dried over calcium chloride yielding 9.5 g of crude **7**: tlc on silica gel with ethyl acetate–benzene (1:4) showed only a single extended spot and no starting material; $\nu_{max}^{CHCl_3}$ 1620 cm^{-1} (strong, -COC=COH-?) in addition to strong carbonyl bands around 1720 cm^{-1}.

2α-Chloro-6,19-oxido-17β-pivaloxyandrost-4-en-3-one (**8**) was prepared from crude **7** by the method of Yasuda[3] using pyridine and 1.2 mol of N-chlorosuccinimide. Recrystallization from methanol yielded the pure sample: mp 209–212°; λ_{max}^{EtOH} 240 mμ (ε 13,500); $\nu_{max}^{CHCl_3}$ 1720 (pivalate) and 1690 cm^{-1} (2α-chloro-Δ^4-3-ketone).

Anal. Calcd for $C_{24}H_{33}O_4Cl$: C, 68.46; H, 7.92. Found: C, 68.28; H, 7.61.

2α-Fluoro-6,19-oxido-17β-pivaloxyandrost-4-en-3-one (**9**).—A mixture of 2.0 g of **7** and 0.43 g of sodium carbonate in 20 ml of methanol was heated at 60° under nitrogen until all material had dissolved. The solution was cooled to 0° and then treated with a fine stream of perchloryl fluoride gas for 3 min, whereupon it was boiled under nitrogen for 5 min. Addition of water followed by recrystallization of the precipitate from methanol gave 0.6 g of the analytical sample: mp 218–219.5°; λ_{max}^{EtOH} 238 mμ (ε 15,300); $\nu_{max}^{CHCl_3}$ 1715 (pivalate) and 1695 cm^{-1} (2α-fluoro-Δ^4-3-ketone, overlaps with peak at 1715 cm^{-1}). The nmr spectrum showed maxima for 1 olefinic proton as a doublet (J = 4 Hz) centered at 5.85 (4 position), 0.5 proton as a pair of doublets ($J_{2\beta,1\alpha}$ = 14, $J_{2\beta,1\beta}$ = 6 Hz)[11] centered at 5.35 (2β position), 2.5 protons as a multiplet between 4.38 and 4.90 (6 and 17 positions with the remaining 0.5 2β proton, $J_{2\beta,F} \approx 45$ Hz),[11] 2 methylenic protons as a quartet (J = 8 Hz, $\delta_A - \delta_B$ = 0.65 ppm) centered at 3.89 (19 position), 9 protons as a singlet at 1.19 (pivalate), and 3 protons as a singlet at 0.89 ppm (18 position).

Anal. Calcd for $C_{24}H_{33}O_4F$: C, 71.3; H, 8.21. Found: C, 71.13; H, 8.31.

3,19-Diacetoxy-17β-pivaloxyandrosta-2,4,6-triene (**10**).—A solution of 20 g of 6,19-oxido-17β-pivaloxyandrost-4-en-3-one (**6**) in 40 ml of isopropenyl acetate was refluxed in presence of 2 g of *p*-toluenesulfonic acid for 2 hr under nitrogen, whereupon it was extracted five times with 50 ml of water, dried with sodium sulfate, and evaporated at reduced pressure. The crystalline residue was recrystallized from methanol yielding 4.1 g of the analytical sample: mp 147–148°; $\nu_{max}^{CHCl_3}$ 1725–1750 (broad, >C=O) and 1670 cm^{-1} (>C=C<); λ_{max}^{MeOH} 300 mμ (ε 14,250); the nmr spectrum showed maxima for 2 olefinic protons as an octet (ABX system; J_{AB} = 10, J_{AX} = 2, J_{BX} = 1.5 Hz) centered at 5.86 (6 and 7 position), 1 olefinic proton as a singlet at 5.55 (4 position), 1 olefinic proton as a multiplet between 5.18 and 5.48 (2 position), 1 proton as a broad triplet between 4.4 and 4.8 (17 position), 2 methylenic protons as a quartet (J = 11 Hz, $\delta_A - \delta_B$ = 0.20 ppm) centered at 4.20 (19 position), 1 proton as a pair of doublets (AMX system) centered at 2.70 (1β position, $J_{1\beta,2\beta}$ = 6 Hz), 3 protons as a singlet at 2.13 (enolic 3-acetate), 3 protons as a singlet at 2.03 (19-acetate), 9 protons as a singlet at 1.20 (pivalate), and 3 protons as a singlet at 0.85 ppm (18 position).

Anal. Calcd for $C_{28}H_{38}O_6$: C, 71.46; H, 8.14. Found: C, 71.56; H, 8.01.

2α-Chloro-17β-pivaloxy-19-acetoxyandrosta-4,6-dien-3-one (**11**). **Method A.**—A mixture of 4.60 g of **8**, 23 ml of acetic anhydride, and 4.6 g of *p*-toluenesulfonic acid was heated at 100° for 10 min under nitrogen, whereupon the mixture was cooled and poured in a fine stream into 115 ml of cold methanol saturated with ammonia. The solution was concentrated to approximately 20 ml and water was added yielding, after filtration of the precipitate formed and drying, 4.2 g of crude **11**, λ_{max} 285 mμ, which by tlc was identical with the pure product prepared by method B and which was used for the preparation of 2,19-oxide **13**.

Method B.—A solution of 13 g of **10** in 26 ml of benzene was shaken with a solution of 49 ml of acetic acid and 13 g of calcium hypochlorite in 2600 ml of water for 3 min at room temperature. Extraction of the benzene phase with water, followed by evaporation and recrystallization of the residue from methanol, gave 2.0 g of the analytically pure material: mp 95–141°; λ_{max}^{EtOH} 285 mμ (ε 25,800); $\nu_{max}^{CHCl_3}$ 1745 (acetate), 1720 (pivalate), 1680 (conjugated ketone), 1625 and 1595 cm^{-1} (>C=C<). The nmr spectrum showed maxima for 2 olefinic protons as a singlet at 6.16 (6 and 7 positions), 1 olefinic proton as a singlet at 5.92 (4 position), 1 proton as a pair of doublets (AMX system) centered at 4.93 ($J_{2\beta,1\alpha}$ = 13, $J_{2\beta,1\beta}$ = 6 Hz; 2β position), 1 proton as a broad triplet between 4.40 and 4.75 (17 position), 2 methylenic protons as a quartet (J = 12 Hz, $\delta_A - \delta_B$ = 0.22 ppm), centered at 4.31 (19 position), 1 proton as a pair of doublets centered at 2.85 ($J_{1\beta,1\alpha}$ = 12, $J_{1\beta,2\beta}$ = 6 Hz; 1β position), 3 protons as a singlet at 2.05 (acetate), 9 protons as a singlet at 1.22 (pivalate), and 3 protons as a singlet at 0.90 ppm (18 position).

Anal. Calcd for $C_{26}H_{35}O_5Cl$: C, 67.60; H, 7.63; Cl, 7.86. Found: C, 67.64; H, 7.80; Cl, 7.66.

2α-Fluoro-Δ^{4,6}-3-ketone **12** was obtained from **9** as an oil (λ_{max} 284 mμ) by the ring-opening procedure above used for the preparation of **11** from **8**. It was not further purified but used for the next reaction.

2,19-Oxido-17β-pivaloxyandrosta-4,6-dien-3-one (**13**).—A solution of 0.72 g of potassium hydroxide and 3.6 g of crude **11** in 72 ml of methanol was left to stand at room temperature for 1 hr, whereupon 1 ml of glacial acetic acid was added. The methanol was removed at reduced pressure, and the residue dissolved in a mixture of ethyl acetate and water. The organic phase was treated with charcoal, filtered, and dried with sodium sulfate yielding, after evaporation and digestion of the residue with methanol, 1.8 g of crystalline 2,19-oxide **13**. Recrystallization from methanol yielded the pure product: mp 171.5–172.5°; λ_{max}^{EtOH} 285 mμ (ε 26,880); $\nu_{max}^{CHCl_3}$ 1715 (pivalate), 1670 (Δ^{4,6}-3-ketone), 1615 and 1575 cm^{-1} (>C=C<); the nmr spectrum showed maxima for 2 olefinic protons as a singlet at 6.20 (6 and 7 positions), 1 olefinic proton as a doublet (J = 2 Hz) centered at 5.72 (4 position), 1 proton as a broad triplet between 4.50 and 4.85 (17 position), 1 proton as a pair of doublets (AMX system) centered at 4.34 ($J_{2\alpha,1\beta}$ = 6, $J_{2\alpha,1\alpha}$ = 2 Hz; 2α position), 2 methylenic protons as a quartet (J = 8 Hz, $\delta_A - \delta_B$ = 0.45 ppm) centered at 3.82 (19-position), one proton as a pair of doublets centered at 2.39 ($J_{1\beta,1\alpha}$ = 11.5, $J_{1\beta,2\alpha}$ = 6 Hz; β position), 9 protons as a singlet at 1.20 (pivalate), and 3 protons as a singlet at 0.85 ppm (18 position).

Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.95; H, 8.39. Found: C, 74.91; H, 8.11.

Crude 2-fluoro-Δ^{4,6}-3-ketone **12**, when subjected to alkaline hydrolysis as above, yielded a crystalline product which had an ir spectrum identical with that of 2,19-oxide **13**.

When a solution of 100 mg of 2-chloro-19-acetate **11** in 2 ml of 4 *N* aqueous hydrochloric acid–methanol (1:5) was refluxed for 6 hr, working up and recrystallization from methanol yielded 8 mg of a product, mp 169–171°, which by tlc was identical with the fully characterized 2,19-oxide **13** prepared above. 2-Fluoro analog **12** also yielded **13** when subjected to the same acidic hydrolysis conditions as evidenced by tlc.

Registry No.—**6**, 24099-40-9; **7**, 24099-41-0; **8**, 24099-42-1; **9**, 24099-43-2; **10**, 24099-44-3; **11**, 24099-45-4; **13**, 24099-46-5.

(11) Reference 8, p 148.

Acknowledgment.—The authors are indebted to Dr. G. Schilling, Mr. M. Boulerice, and Mrs. J. Jachner for nmr, ultraviolet, and infrared spectra and to Mr. W. Turnbull and Miss E. Wieslander for microanalyses. We would also like to thank Dr. G. S. Myers for generous supplies of starting material.

Preparation of Some $\Delta^{4,7}$- and $\Delta^{1,4,7}$-3-Keto Steroids by Deconjugation

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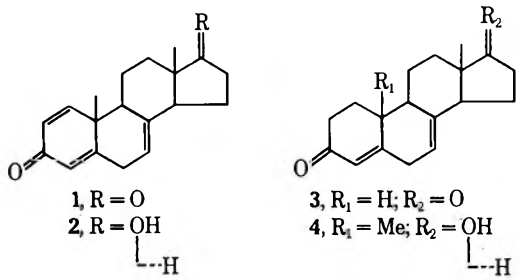
Deconjugation of unsaturated ketones can be achieved by deprotonation with strong bases followed by acid treatment of the enolate anions formed. Thus Ringold and Malhotra[1] have recently deconjugated steroidal Δ^4-3-ketones to the corresponding Δ^5-3-ketones, using potassium *t*-butoxide in *t*-butyl alcohol for the deprotonation and aqueous acetic acid for the subsequent protonation, while Shapiro, Legatt, Weber, and Olivetto[2] converted $\Delta^{1,4}$-3-ketones into the corresponding $\Delta^{1,5}$-3-ketones using basic reagents, such as potassium *t*-butoxide, sodium acetylide, sodium amide, and sodium hydride, in aprotic solvents for the deprotonation and weak acids such as acetic acid and boric acid for the subsequent protonation. In some of their experiments the authors used potassium *t*-butoxide as the base and dimethyl sulfoxide as the aprotic solvent. We wish to report the preparation of some $\Delta^{4,7}$- and $\Delta^{1,4,7}$-3-ketones by treatment of the fully conjugated ketones with sodium methoxide in dimethyl sulfoxide and subsequent reprotonation with strong aqueous acids, such as aqueous 2 *N* hydrochloric acid. When weak acids were used for the final protonation inferior yields of the desired $\Delta^{4,7}$- or $\Delta^{1,4,7}$-3-ketones were obtained and this was attributed to the intermediate formation of the isomeric $\Delta^{5,7}$- and $\Delta^{1,5,7}$-3-ketones. Thus, when in the deconjugation of 17β-hydroxyandrosta-4,6-dien-3-one the basic mixture was poured into aqueous 2 *N* acetic acid, ultraviolet analysis on the ether extract showed two sharp absorption peaks at 270 and 275 mμ which were considered to derive from 17β-hydroxyandrosta-5,7-dien-3-one and which disappeared on shaking the ether extract with 2 *N* aqueous hydrochloric acid with concomitant increase in absorption at 239 mμ, indicating additional formation of the desired $\Delta^{4,7}$-3-ketone.

Generally, the conjugated ketones were treated with two parts of sodium methoxide in ten parts of dimethyl sulfoxide at room temperature and in an atmosphere of nitrogen. The basic reaction mixture was poured into excess 2 *N* hydrochloric acid; ultraviolet analysis on a small sample of reaction mixture, acidified with 2 *N* hydrochloric acid, indicated the presence of only trace amounts of starting material. For the isolation of **4** in the pure form it was found necessary to resort to chromatography.

The preparation of **4** has previously been achieved[3] by allylic bromination of the ethylene ketal of testosterone benzoate, dehydrobromination to the corresponding 5,7-diene, alkaline hydrolysis of the benzoate in the 17 position, and acid hydrolysis of the 3-ketal with dilute sulfuric acid in alcohol, while **3** has been prepared[4] by conversion of 17β-hydroxy-4,6-estradiene-3,17-dione into the corresponding 3,17β-diacetoxy-3,5,7-triene, sodium borohydride reduction to the 3β,17-dihydroxy-5,7-diene, and subsequent Oppenauer oxidation.



1, R = O
2, R = OH
H
3, R_1 = H; R_2 = O
4, R_1 = Me; R_2 = OH
H

Experimental Section[5]

1,4,7-Androstatriene-3,17-dione (1).—To a solution of 10.0 g of 1,4,6-androstatriene-3,17-dione[6] in 100 ml of dimethyl sulfoxide, 20 g of sodium methoxide was added in one portion. The mixture was stirred for 5 min in an atmosphere of nitrogen and then poured into a stirred solution of 600 ml of ice-cold, aqueous 2 *N* hydrochloric acid. Filtration and recrystallization of the precipitate from methanol–ethyl acetate (1:1) gave 5.5 g of 1,4,7-androstatriene-3,17-dione, mp 160–170°. Two further recrystallizations gave material of mp 168–170° (softening at 161°), λ_{max}^{EtOH} 241 mμ (ϵ 15,800), $\nu_{max}^{CHCl_3}$ 1735 and 1663 cm^{-1} (17- and 3-ketones). The nmr spectrum showed maxima for 4 olefinic protons as multiplets between 6.0 and 7.3 (1, 2, and 4 positions) and 5.3 and 5.6 (7 position), 2 allylic protons (6 position) as a multiplet between 2.8 and 3.8, 3 protons (19 position) as a singlet at 1.28, and 3 protons (18 position) as a singlet at 0.82 ppm.

Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.56; H, 7.99.

17β-Hydroxy-1,4,7-androstatrien-3-one (2) was prepared as above in 60% yield from 17β-hydroxy-1,4,6-androstatrien-3-one[6] or from the 17-acetate, which was completely hydrolyzed under the reaction conditions: mp 185–186°; λ_{max}^{EtOH} 242 mμ (ϵ 17,800); $\nu_{max}^{CHCl_3}$ 3,640 (OH), 3450 (OH), and 1661 cm^{-1} (3-ketone). The nmr spectrum showed maxima for 4 olefinic protons as multiplets between 6.0 and 7.2 (1, 2, and 4 positions) and 5.15 and 5.4 (7 position), 1 proton as a broad triplet between 3.6 and 3.95 (17 position), 2 protons (6 position) as a multiplet between 2.8 and 3.5, 3 protons as a singlet at 1.25 (19 position), and 3 protons as a singlet at 0.70 ppm (18 position).

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.13; H, 8.21.

4,7-Estradiene-3,17-dione (3) was prepared as above in 46% yield from 4,6-estradiene-3,17-dione,[4] mp 147–148° (lit.[4] mp 148–149°), λ_{max}^{EtOH} 238 mμ (ϵ 15,100). The nmr spectrum showed maxima for 2 olefinic protons as a singlet at 5.9 (4 position) and as a multiplet between 5.28 and 5.48 (7 position), 2 allylic protons as a multiplet between 2.8 and 3.7 ppm (6 position), and 3 protons as a singlet at 0.80 ppm (18 position). Its infrared spectrum was identical with that of an authentic sample.

(1) H. J. Ringold and S. K. Malhotra, *Tetrahedron Lett.*, No. 15, 669 (1962).

(2) E. L. Shapiro, T. Legatt, L. Weber, and E. P. Olivetto, *Steroids*, **3**:2, 183 (1964).

(3) R. Antonucci, S. Bernstein, R. Littell, K. J. Sax, and K. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

(4) J. A. Zderic, H. Carpic, A. Bowers, and C. Djerassi, *Steroids*, **1**, 233 (1963).

(5) Melting points were determined with a Thomas–Hoover apparatus and are corrected. Ir spectra were determined with a Perkin-Elmer spectrophotometer, Model 21; nmr spectra were determined in deuteriochloroform with a Varian A-60 spectrometer; and chemical shifts are reported in parts per million downfield from tetramethylsilane.

(6) Productos Esteroides, Naucalpan, Mexico.

17β-Hydroxyandrosta-4,7-dien-3-one (4).—To 1.0 g of 17β-hydroxyandrosta-4,6-dien-3-one,[7] dissolved in 10 ml of dimethyl sulfoxide, was added 1.5 g of sodium methoxide. The mixture was stirred under nitrogen at room temperature for 1 hr and then added to 66 ml of ice-cold, aqueous 2 *N* hydrochloric acid with stirring. The precipitate was filtered, dissolved in methylene chloride, and then, after drying with sodium sulfate, chromatographed on Davidson silica gel, which had previously been deactivated by treatment with wet ether for 2 hr. Elution with methylene chloride–methanol 50:1 gave 400 mg of a yellow crystalline material which, after treatment with charcoal and recrystallization from methanol-ethyl acetate (1:1), gave 280 mg of white crystalline material: mp 162–164° (mp lit.[3] 161–163°); λ_{max}^{EtOH} 239 mμ (ε 15,400); and $\nu_{max}^{CHCl_3}$ 3638 (OH), 3465 (OH) and 1662 (3 ketone) cm^{-1}. The nmr spectrum showed maxima for 1 olefinic proton as a doublet (J = 2 Hz) centered at 5.79 (4 position), 1 olefinic proton as a multiplet between 5.1 and 5.3 (7 position), 1 proton as a broad triplet between 3.6 and 4.0 (17 position), 1 proton as a broad triplet between 3.6 and 4.0 (17 position), 2 allylic protons as a multiplet between 2.6 and 3.5 (6 position), 3 protons as a singlet at 1.19 (19 position), and 3 protons as a singlet at 0.68 ppm (18 position).

Registry No.—**1**, 14532-68-4; **2**, 24099-37-4; **3**, 13209-46-6; **4**, 13386-25-9.

Acknowledgments.—The authors are indebted to Miss J. Moffat, Mr. M. Feldman, Mr. M. Fishman, and Mr. A. Verwijs for technical assistance, to Mr. W. Kastner for the preparation of 17β-hydroxyandrosta-4,6-dien-3-one, to Mr. M. Boulerice and Mrs. J. Jachner for nmr, ir, and uv spectra, and to Mr. W. Turnbull for microanalyses.

(7) Prepared from testosterone acetate by the method of S. K. Pradhan and H. J. Ringold, *J. Org. Chem.*, **29**, 601 (1964).

Reaction of α Olefins with Aqueous Formaldehyde

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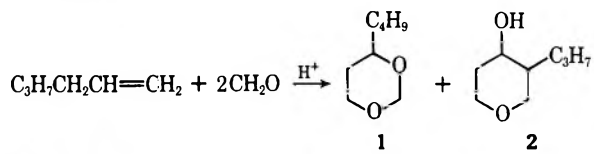
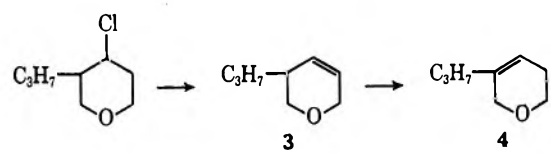
The mineral acid catalyzed condensation of formaldehyde with olefins is commonly known as the Prins reaction.[1] It is well established that straight-chain 1-olefins are much less reactive than are substituted R(R′)C=CHR″ types;[2] 1-olefins require either elevated temperatures with high catalyst concentrations[2a] or the use of acetic acid solvent[3] with substantial quantities of strong acid catalysts. This reaction generally leads to a rather complex mixture of products, mainly composed of 1,3-dioxanes, 1,3-glycols, and tetrahydropyranols,[2,3] along with minor amounts of tetrahydrofuran derivatives[2b,3,4] and the alcohol derived from hydration of the starting olefin.[3]

During the course of an investigation of modifications of the Prins reaction,[5] we have also studied the condensation of 1-olefins with aqueous formaldehyde (formalin) solutions at elevated temperatures and have developed useful synthetic procedures for the preparation of 4-alkyl-1,3-dioxanes and 3-alkyltetrahydropyran-4-ols from representative olefins from 1-pentene through 1-dodecene.

Initial studies were carried out by heating 2.0 mol of 1-hexene with 4.9 mol of 37% formalin and 8 ml of sulfuric acid at 175° in an autoclave for 5 hr. Complete conversion of the starting olefin was attained at these conditions; after distillation from a small amount of heavy residue the resulting product was analyzed by glpc and found to contain 5% of 2-hexanol, 44% of 4-butyl-1,3-dioxane (**1**), 45% of *cis,trans*-3-propyltetrahydropyran-4-ol (**2**), 6% of a mixture of dihydropyrans, and traces of other materials.



Pure **1** and **2** were obtained by fractional distillation. Structures were confirmed by elemental and spectral analysis, and in the case of **2** (a *cis–trans* mixture) by comparison with an authentic sample.[5] 2-Hexanol and other minor products were separated by preparative glpc and identified by comparison with authentic samples (ir spectra, glpc retention times). 3,6-Dihydro-3-propyl-2H-pyran (**3**) and 5,6-dihydro-3-propyl-2H-pyran (**4**) were identified in approximately 2:1 proportions by glpc comparison with a 3:2 mixture synthesized by dehydrochlorination of *cis,trans*-4-chloro-3-propyltetrahydropyran[5] with potassium hydroxide in ethylene glycol.



A study of variations in reaction parameters was carried out in an attempt to define optimum conditions for more selective production of either **1** or **2** from 1-hexene. A number of experiments were conducted in which the sulfuric acid concentration was varied between 0.24 and 0.40 *M*. In general, the higher acid concentrations provided increased reaction rates but also increased by-product formation. Replacement of the sulfuric acid by phosphoric acid decreased the reaction rate considerably; in addition, autoclave corrosion was markedly accelerated. Substitution of paraformaldehyde–water mixtures for the commercial formalin (stabilized with *ca.* 12% methanol) did not appreciably affect either the yield or product distribution nor did rather substantial variation in the olefin/formaldehyde ratio. A recycle of coproduct 4-butyl-1,3-dioxane did not affect the selectivity; the same relative distribution of products was obtained. Variation in temperature between 125 and 225° gave the expected results. At the lower end of the range reactions were slower and often incomplete while the higher temperatures gave faster reaction rates and more by-products principally dihydropyrans). Indeed, at 225° the condensation proceeded slowly in the absence of added

(1) H. J. Prins, *Chem. Weekbl.*, **16**, 1510 (1919).

(2) (a) F. Arundale and L. A. Mikeska, *Chem. Rev.*, **51**, 505 (1952); (b) M. Hellin, M. Davidson, D. Lumbroso, P. Guiliani, and F. Coussemant, *Bull. Soc. Chim. Fr.*, 2974 (1964); (c) Y. Nishimura and T. Tanaka, *Kogyo Kagaku Zasshi*, **70**, 466 (1967).

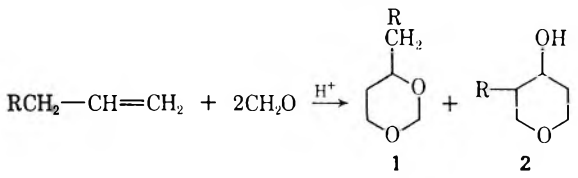
(3) L. Heslinga and M. van Gorkom, *Rec. Trav. Chim. Pays-Bas*, **85**, 293 (1966).

(4) N. A. LeBel, R. N. Kiesemer, and E. Mehmedbasich, *J. Org. Chem.*, **28**, 615 (1963).

(5) P. R. Stapp, *ibid.*, **34**, 479 (1969).

TABLE I

CONDENSATION OF 1-OLEFINS WITH FORMALIN[a]



1 2

R	Conversion, %	Yield,[b] % 1	Yield,[b] % 2
C_2H_5	100	46	42
C_3H_7	100	41	46
C_5H_{11}	85	43	45
C_7H_{15}	53	40	47
C_9H_{19}	39	42	46

[a] Reactions were carried out for 6 hr at 150° using 2 mol of olefin to 4.9 mol of 37% formalin 0.24 *M* in H_2SO_4. [b] Based on reacted olefin.

with nitrogen, and heated with stirring at 150° for 6 hr. After cooling, the product was extracted into ether and the ether extracts were washed with sodium carbonate solution and dried ($MgSO_4$); the ether was then removed. A portion of the residue was analyzed by glpc using the 5-ft column for the 1-decene and 1-dodecene reactions and the 10-ft column for the remainder. The order of elution is 2-alkanol, 4-alkyl-1,3-dioxane, dihydropyran, and 3-alkyltetrahydropyran-4-ol. The product 4-alkyl-1,3-dioxanes (Table II) and 3-alkyltetrahydropyran-4-ols (Table III) were isolated by fractionation through a 4 ft × 0.75 in. helices packed column.

Registry No.—1 (R = C_2H_5), 15601-78-2; 1 (R = C_3H_7), 2244-87-3; 1 (R = C_5H_{11}), 2244-85-1; (R = C_7H_{15}), 23433-02-5; 1 (R = C_9H_{19}), 24647-61-8; 2-*cis* (R = C_2H_5), 24647-33-4; 2-*cis* (R = C_3H_7), 24647-34-5; 2-*cis* (R = C_5H_{11}), 24647-35-6; 2-*cis* (R = C_7H_{15}), 24647-36-7; 2-*cis* (R = C_9H_{19}), 24647-37-8; 2-*trans* (R = C_2H_5), 24646-96-6; 2-*trans* (R = C_3H_7), 24646-97-7;

TABLE II

4-ALKYL-1,3-DIOXANES

R	Bp, °C	Pressure, mm	$n^{20}D$	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
C_2H_5	60–61	16.0	1.4278	$C_7H_{14}O_2$	64.6	10.8	64.7	10.9
C_3H_7	62–63	8.0	1.4355	$C_8H_{16}O_2$	66.6	11.1	66.7	11.1
C_5H_{11}	105–107	12.0	1.4397	$C_{10}H_{20}O_2$	69.8	11.6	70.0	11.8
C_7H_{15}	132–134	12.0	1.4462	$C_{12}H_{24}O_2$	72.0	12.0	72.0	12.1
C_9H_{19}	128–130	1.5	...[a]	$C_{14}H_{28}O_2$	73.6	12.3	73.7	12.4

[a] Solidified, mp 41–42° from pentane, lit.[3] mp 41.5–42.5°.

TABLE III

3-ALKYLTETRAHYDROPYRAN-4-OLS

R	Bp, °C	Pressure, mm	$n^{20}D$	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
C_2H_5	112–114	16.0	1.4598	$C_7H_{14}O_2$	64.6	10.8	64.5	10.6
C_3H_7	105–106	8.0	1.4591	$C_8H_{16}O_2$	66.6	11.1	66.4	11.0
C_5H_{11}	95–99	0.5	1.4585	$C_{10}H_{20}O_2$	69.8	11.6	69.8	11.8
C_7H_{15}	168–170	12.0	1.4588	$C_{12}H_{24}O_2$	72.0	12.0	71.9	12.0
C_9H_{19}	150–154	1.5	1.4590	$C_{14}H_{28}O_2$	73.6	12.3	73.6	12.3

acid catalyst to produce the expected spectrum of products with a rather considerable increase in dihydropyran formation.

Although attempts to improve the selectivity of the Prins reaction under these conditions to either major product were unsuccessful, this procedure does represent a most convenient and useful synthesis of 4-alkyl-1,3-dioxanes and *cis,trans*-3-alkyltetrahydropyran-4-ols. A minimum of by-products is produced and the boiling point difference between the dioxane and tetrahydropyranol is sufficiently great that separation by fractionation is easily accomplished. Table I summarizes product yields from the condensation of a number of typical 1-olefins from 1-pentene through 1-dodecene using standard conditions. It is apparent that reaction rates are slower for the higher molecular weight olefins, probably because of decreased solubility, and more nearly optimum conditions would require longer reaction times, higher temperatures, more catalyst, or some combination thereof for complete conversion.

Experimental Section[6]

Condensation of 1-Olefins with Formalin.—A 1-l. Magnedrive autoclave constructed of Hastelloy C[7] was charged with 2 mol of olefin, 400 g (4.9 mol) of 37% formalin, and 5 ml of concentrated sulfuric acid. (One-half quantities were used for the 1-decene and 1-dodecene reactions.) The autoclave was sealed, flushed

2-*trans* (R = C_5H_{11}), 24646-98-8; 2-*trans* (R = C_7H_{15}), 24646-99-9; 2-*trans* (R = C_9H_{19}), 24647-00-5; formaldehyde, 50-00-0.

(6) All melting and boiling points are uncorrected. Olefins used were Phillips Petroleum Co. Pure Grade materials. Gas chromatographic analyses were carried out on a Perkin-Elmer Model 720 gas chromatograph using 5 ft and 10 ft × 0.25 in. columns of 20% Ucon LB-550-X on Chromosorb P.

(7) Autoclave Engineers, Inc., Erie, Pa.

Chemotaxonomy of the Rutaceae. VII.[1] Alkaloids in *Evodia zanthoxyloides* F. Muell.

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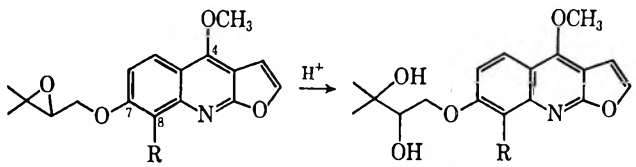
Received August 11, 1969

The alkaloids occurring in *Evodia zanthoxyloides* F. Muell. (Rutaceae) have been the subject of an extended investigation by Ritchie and coworkers.[2]

(1) Part VI: D. L. Dreyer and A. Lee, *Phytochemistry*, **8**, 1499 (1969).

(2) R. H. Prager, E. Ritchie, A. V. Robertson, and W. C. Taylor, *Aust. J. Chem.*, **15**, 301 (1962), and previous papers in this series.

During a search for limonoids in *Evodia* species[3] we have had occasion to isolate further furoquinoline alkaloids from this plant.[4] An alkaloid, $C_{18}H_{19}NO_5$, mp 141–144°, crystallized from the crude extracts in 3% yield. Its ultraviolet spectrum was similar to that of skimmianine.[6,7] The nmr spectrum showed aromatic resonances which compared well with those of skimmianine.[8] In addition, resonances were present for two methoxy groups, a two proton doublet in the methoxy region, a one proton triplet at δ 3.25, and two C-methyl groups. The chemical shifts of the aliphatic resonances suggested the presence of an epoxy group in an isopentoxy side chian. On the basis of these data and biogenetic analogy, structure **1** was tentatively suggested. Proof of structure was obtained by mild acid hydrolysis to give the known alkaloid, evoxine (**2**).

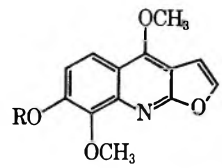


1, R = CH_3O
3, R = H

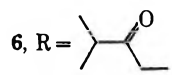
2, R = CH_3O
4, R = H

Smaller amounts of a closely related, less polar, alkaloid were recovered from the mother liquors after chromatography on alumina. The uv spectrum indicated the material was a furoquinoline alkaloid and was similar to that reported for evolitrine.[9] The nmr spectrum showed only one methoxy resonance. The downfield position of the methoxy resonance (δ 4.35) indicated the methoxy group was located at the 4 position.[8] The aliphatic resonances again indicated the presence of an epoxyisopentoxy group. Acid hydrolysis of the alkaloid gave a glycol which is formulated as **4**, analogously to evoxine (**2**).

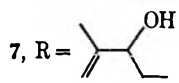
7-Isopentenyl-δ-fagarine (**5**), the isopentyl derivative corresponding to **1**, is a constituent of *Ptelea aptera* Parry (Rutaceae).[10] The furoquinoline alkaloids found in this study are reasonable biogenetic intermediates to the furoquinoline alkaloids **2**, **5**, and **6** previously found by Cannon, *et al.*,[11] in this same plant. It is not apparent if the different results found in this study are a result of geographical or seasonal differences in the plant material from that previously used[10] or if the products previously found are artifacts resulting from the acid employed in the isolation procedures.[11] The furoquinoline alkaloids, evoxine (**2**), evoxoidine (**6**), and evodine (**7**), previously reported from *E. zanthoxyloides* have not been encountered occurring naturally in this study. Eastwood, *et al.*,[7] suggested that evodine (**7**)[2] was not an artifact, since it was not formed by treatment of evoxine with acid. The direct formation of evodine from the epoxy precursor during work-up cannot be ruled out. However, in this study only evoxine (**2**) was obtained from acid-catalyzed hydrolysis of **1**.



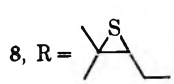
5, R =



6, R =



7, R =



8, R =

An attempt to determine the absolute configuration of the side chain of **1** was undertaken. One possible approach is to introduce an optically active chromophore into the side chain which would adsorb to longer wavelengths of the furoquinoline chromophore. Trithiocarbonates are ideal derivatives for such studies since they adsorb well into the visible region[12] and sufficient knowledge is available on the interpretation of their ORD and CD curves in terms of absolute configuration.[13]

Treatment of **1** with potassium methyl xanthate, under conditions which might be expected to give the trithiocarbonate[14] yielded instead only the episulfide (**8**).

Experimental Section[15]

Isolation.—Branch ends of *Evodia zanthoxyloides* (0.45 kg) containing seed clusters, collected June 1967, were ground and extracted with acetone. The extracts were concentrated, chloroform was added, and the solution was allowed to stand 48 hr during which time a crop of crystals was deposited. The product was collected to give 14 g of **1**: mp 141–144° (EtOAc–hexane); $[\alpha]_D$ +13° ($CHCl_3$); λ_{max}^{EtOH} 248 mμ (84,000), ~310, 320 (9000), 332 (8400), ~342; nmr δ 7.85 (d, J = 9 Hz, H-5), 7.54 (d, J = 3 Hz, H-2′), 7.20 (d, H-6), 6.95 (d, J = 3 Hz, H-3′), 4.30, 4.17 (methoxyls), 3.25 (t, J = 5 Hz, epoxy proton),[16] 1.38 (C-methyls) (in $CDCl_3$).

Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.6; H, 5.86; N, 4.17.

Tlc of the crude extracts when sprayed with Ehrlich reagent gave indication of the presence of a polar limonoid.[3,5] Solvent was removed from the mother liquors and the residue chromatographed over alumina. Elution of the column with 50% benzene in hexane eluted a nonpolar blue fluorescing spot which proved to be a monomethyl ether (**3**): mp 145–147° (EtOAc–hexane); $[\alpha]_D$ +50° ($CHCl_3$); λ_{max}^{EtOH} 247 mμ (92,000), ~297, 308 (9600), 319 (9300), 331 (7400); nmr δ 8.09 (d, J = 9 Hz, H-5), 7.49 (d,

(3) D. L. Dreyer, *Phytochemistry*, **5**, 367 (1966). For a review, see D. L. Dreyer, *Fort. Chem. Org. Naturstoffe*, **26**, 190 (1968).

(4) Tlc of the crude plant extracts (see Experimental Section) using Ehrlich's reagent as a detecting spray reagent[5] also indicated the presence of limonoids; however, the amounts present were too small to permit isolation from the plant material on hand.

(5) D. L. Dreyer, *J. Org. Chem.*, **30**, 749 (1965).

(6) L. H. Briggs and R. C. Cambie, *Tetrahedron*, **2**, 256 (1958).

(7) F. W. Eastwood, G. K. Hughes, and E. Ritchie, *Aust. J. Chem.*, **7**, 87 (1954).

(8) A. V. Robertson, *ibid.*, **16**, 451 (1963).

(9) R. G. Cooke and H. F. Haynes, *ibid.*, **7**, 273 (1954).

(10) D. L. Dreyer, *Phytochemistry*, **8**, 1013 (1969).

(11) J. R. Cannon, G. K. Hughes, K. G. Neill, and E. Ritchie, *Aust. J. Sci. Res.*, **A5**, 406 (1952); *Chem. Abstr.*, **47**, 3857 (1953).

(12) C. Djerassi, H. Wolff, D. A. Lighner, E. Bunnenberg, K. Takeda, T. Komeno, and K. Kuriyama, *Tetrahedron*, **19**, 1547 (1963).

(13) K. Kuriyama and T. Komeno, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Heyden and Son, London, 1967, p 366.

(14) *Cf.* C. G. Overberger and A. Drucker, *J. Org. Chem.*, **29**, 360 (1964); see also, A. M. Creighton and L. N. Owen, *J. Chem. Soc.*, 1024 (1960); S. M. Iqbal and L. N Owen, *ibid.*, 1030 (1960).

(15) Nmr spectra were taken at 60 MHz. The relative area of the peaks were consistent with their assignments.

(16) The ether methylene resonances were obscured by the methoxy resonances in $CDCl_3$, but were distinguishable in benzene.

J = 3 Hz, H-2'), 7.19 (q, J = 2, 9 Hz, H-6), 6.98 (d, J = 2 Hz, H-8), 6.94 (d, J = 2 Hz, H-3'), 4.35 (methoxy), 4.20 (d, J = 5 Hz, ether methylene), 3.12 (t, J = 5 Hz, epoxy), 1.38 (C-methyls) (in $CDCl_3$).

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.23; H, 5.72; N, 4.68. Found: C, 68.1; H, 5.85; N, 4.61.

Further elution of the column with increasing amounts of benzene in hexane gave a further 3 g of 1. Fractions eluted with benzene and chloroform gave, after work-up, products which corresponded to the previously reported acridones, melicopidine, 1-hydroxy-2,3-dimethoxyacridone, and xanthevoidine.[11]

Acid Hydrolysis of 1 to Evoxine (2).—Two grams of 1 was added to a boiling 10% solution of oxalic acid. The solution was refluxed for 30 min. After cooling, the solution was made basic and extracted with ethyl acetate. The ethyl acetate extracts were dried and concentrated, whereupon the product, evoxine (2), crystallized: mp 151.5–154° (lit.[11] mp 155°); 1.76-g yield; $[\alpha]D$ +13° (EtOH).[17] The evoxine was identical in all respects with an authentic sample provided by Professor E. Ritchie.

In a similar manner **3** was converted into 4: mp 145–147° (EtOAc); λ_{max}^{EtOH} 247, 277, ~296, 308, 320, 332 mμ; nmr δ 8.58 (d, J = 10 Hz, H-5), 7.93 (d, J = 2 Hz, H-2), 7.75–7.47 (m, H-6 and H-8), 7.37 (d, J = 2 Hz, H-3), 4.62 (methoxyl); (4.50–4.00 (m, $^{O}>CHCH_2O$), 1.40 and 1.35 (C-methyls) (in $CDCl_3$).

Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03. Found: C, 63.7; H, 6.02.

Episulfide of 1.—To a solution of 0.45 g of KOH and 0.7 g of CS_2 in 10 ml of methanol was added 0.8 g of 1. The mixture was warmed to effect solution. After 36 hr water was added and after standing overnight the product (8) was collected by filtration: mp 167–169° after repeated crystallization from EtOAc–hexane; nmr δ 7.97 (d, J = 9 Hz, H-5), 7.58 (d, J = 2 Hz, H-2'), 7.24 (d, J = 9 Hz, H-6), 7.03 (d, J = 2 Hz, H-3'), 4.38, 4.15 (methoxyls), 3.27 (q,[18] $^{S}>CHCH_2O$–), 1.65, 1.63 (C-methyls) (in $CDCl_3$).

Anal. Calcd for $C_{18}H_{19}NO_4S$: C, 62.5; H, 5.54; N, 4.34. Found: C, 63.0; H, 5.51; N, 3.98.

Registry No.—1, 24099-25-0; 3, 24099-26-1; 4, 24099-27-2; 8, 24099-28-3.

Acknowledgments.—Initial studies on this problem were carried out at laboratories of the U. S. Department of Agriculture in Pasadena, Calif. The author is indebted to Dr. J. A. Lamberton, CSIRO, Melbourne, Australia, for a supply of plant material, and to Professor E. Ritchie of the University of Sydney for an authentic sample of evoxine.

(17) Johns, *et al.*, reported $[\alpha]D$ +20° (EtOH) for evoxine isolated from *Choisya ternata* H. B. and K. [S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Aust. J. Chem.*, **20**, 1975 (1967)]. Evoxine previously reported from *E. zanthoxyloides* showed $[\alpha]D$ +5° (EtOH).[11]

(18) This is the X part of an ABX pattern. The AB part was overlapped by the methoxyl resonances

Interconversions of Some Diterpenic Constituents of *Podocarpus ferrugineus* D. Don.

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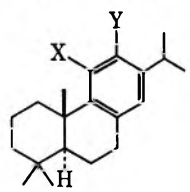
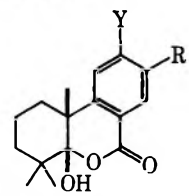
A chemical study of the diterpenic bark constituents of the New Zealand conifer *Podocarpus ferrugineus* D. Don. led for a variety of reasons to a need for their interconversion. Three such investigations are reported herewith.

Ferruginol (**1a**), a major constituent,[3] had to be converted into dehydroabietane (**1b**), a new natural product and minor constituent of the podocarp.[4] While in a related case one of the Kenner procedures had been employed,[5] it now was of interest to apply the recently discovered deoxygenation method of Musliner and Gates.[6] Treatment of ferruginol (**1a**) with 5-chloro-1-phenyltetrazole and hydrogenation of the resultant 1-phenyl-5-tetrazoyl ether over palladium–charcoal yielded dehydroabietane (**1b**).[7]

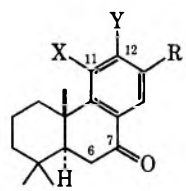


1a, X = H; Y = OH
b, X = Y = H
c, X = Y = OMe

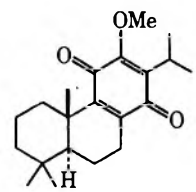


2a, R = *i*-Pr; Y = OMe
b, R = Y = H

One of the minor bark constituents[8] was the unusual B-seco-norditerpenic lactol **2a**. Its structure was determined by detailed spectral analysis and by comparison with the lactol obtained from chromic acid oxidation of 5-iso-7-ketodeoxypodocarponitrile enantiomer.[9] However, for direct structure proof a synthesis of the new product was desired. In this connection the incidental observation of the transformation of ketone **3a** into lactol **2b** on oxidation with oxygen and potassium *t*-butoxide,[10] a reaction which under controlled conditions converts 7-ketones into 6,7-diones,[11] assumed importance. A similar overoxidation converted sugiyl methyl ether (**3b**), another podocarp constituent, into lactol **2a**.



3a, X = Y = R = H
b, X = H; Y = OMe; R = *i*-Pr
c, X = OH; Y = OMe; R = *i*-Pr
d, X = Y = OMe; R = *i*-Pr
e, X = Y = OH; R = *i*-Pr



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One more minor plant component[8] proved to be cryptojaponol to which structure **3c** has been assigned.[12] The site of its O-methyl group, the only possibly questionable point of its structure, needed confirmation and a synthesis of the natural substance to be exe-

(1) National Science Foundation Cooperative Fellow, 1962–1965.
(2) Public Health Service Predoctoral Fellow, 1966–1969.

(3) *Cf.* C. W. Brandt and L. G. Neubauer, *J. Chem. Soc.*, 1031 (1939).
(4) M. Kitadani, A. Yoshikoshi, Y. Kitahara, J. de Paiva Campello, J. D. McChesney, D. J. Watts, and E. Wenkert, *Chem. Pharm. Bull.*, **18**, 402 (1970).
(5) E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.*, **80**, 217 (1958).
(6) W. J. Musliner and J. W. Gates, *ibid.*, **88**, 4271 (1966).
(7) E. Wenkert, P. Beak, R. W. J. Carney, J. W. Chamberlin, D. B. R. Johnston, C. D. Roth, and A. Tahara, *Can. J. Chem.*, **41**, 1924 (1963).
(8) D. J. Watts, Ph.D. Dissertation, Indiana University, 1969.
(9) E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.*, **80**, 211 (1958); E. Wenkert and J. W. Chamberlin, *ibid.*, **81**, 688 (1959).
(10) B. L. Mylari, unpublished result.
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(12) T. Kondo, M. Suda, and M. Tejima, *Yakugaku Zasshi*, **82**, 1252 (1962); *Chem. Abstr.*, **59**, 1685 (1963).

cuted. A clue regarding the environment of the hydroxyl and methoxyl functions of cryptojaponol came from a study of the pyridine solvent shift of its proton magnetic resonance spectrum, $\delta_{CDCl_3} - \delta_{C_5H_5N} = 0.01$ ppm for the isopropyl methyl groups. Had the compound been a 11-methoxy-12-hydroxy isomer, the proximity of the hydroxyl and isopropyl groups would have led to strong deshielding of the latter in pyridine solution.[13] Structure **3c** was confirmed when hydrogenation of cryptojaponol and subsequent oxidation with *m*-chloroperbenzoic acid yielded royleanone methyl ether (**4**).[14] The synthesis of cryptojaponol (**3c**) was accomplished in the following manner. Chromic acid oxidation[9] of 11-methoxyferruginyl methyl ether (**1c**)[15] gave 11-methoxysugiyl methyl ether (**3d**). Demethylation of the latter with boron tribromide[16,17] and remethylation of the resultant catechol **3e** with diazomethane yielded the natural product (**3c**).

Experimental Section[18]

Dehydroabietane (1b).—A mixture of 200 mg of ferruginol (**1a**), 250 mg of 1-phenyl-5-chlorotetrazole, and 1.5 g of anhydrous potassium carbonate in 50 ml of acetone was refluxed for 18 hr. The cooled mixture was filtered and the filtrate evaporated under reduced pressure. Chromatography of the residue, 436 mg, on 6 g of Woelm neutral alumina, activity I, and elution with methylene chloride yielded 227 mg of oily ferruginyl 1-phenyl-5-tetrazoyl ether. A mixture of 160 mg of the ether and 200 mg of 10% palladium–charcoal in 20 ml of 95% ethanol was hydrogenated at 35 psi pressure for 48 hr. Filtration of the mixture and evaporation of the filtrate under reduced pressure yielded 160 mg of partly crystallized oil whose exhaustive extraction with petroleum ether gave 120 mg of clear oil. Chromatography of the latter on 6 g of silica gel and elution with petroleum ether afforded 33 mg of dehydroabietane (**1b**), mp and mmp 42–43°, ir and prm spectra identical with those of an authentic specimen,[7] while elution with methylene chloride led to recovery of 81 mg of starting ether.

Lactol 2a.—A solution of 125 mg of sugiyl methyl ether (**3b**) in 3 ml of dry *t*-butyl alcohol was added to a potassium *t*-butoxide solution (27 mg of potassium in 5 ml of dry *t*-butyl alcohol). Oxygen was bubbled into the mixture for 12 hr while it was being stirred and kept slightly above freezing temperature. Thereafter, 16 ml of 10% hydrochloric acid was added and the mixture extracted exhaustively with ether. The extract was dried over anhydrous sodium sulfate and evaporated. The solid residue, 110 mg, was chromatographed on an inverted dry column of silica gel G. Elution with chloroform gave first 35 mg of starting ketone **3b** and then 13 mg of lactol **2a**, mp and mmp 168–170°, ir and pmr spectra identical with those of the natural lactol.[8]

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.43; H, 8.31.

Royleanone Methyl Ether (4).—A mixture of 15 mg of cryptojaponol and 5 mg of 10% palladium–charcoal in 8 ml of ethanol was hydrogenated at atmospheric pressure and room temperature. Filtration of the mixture and evaporation of the filtrate yielded 14 mg of 7-deoxocryptojaponol, mp 164–165° (lit.[12] mp 163–164.5°). A solution of the latter and 10 mg of *m*-chloroperbenzoic acid in 5 ml of methylene chloride was left standing for 12 hr. A solution of 100 mg of sodium sulfite in 25 ml of water was added and the mixture stirred for 1 hr. The aqueous layer was extracted with methylene chloride, and the combined organic layer and extract was dried and evaporated. Thick layer chromatography of the residue, 8 mg, on silica gel G and elution with chloroform gave 3 mg of royleanone methyl ether (**4**), mp 118–120°, ir spectrum identical with that of an authentic sample.

Cryptojaponol (3c).—A solution of 530 mg of **1c**[15] and 500 mg of chromium trioxide in 60 ml of acetic acid and 15 ml of water was stirred at room temperature for 6 hr. It was poured into 250 ml of cold saturated brine solution and extracted with methylene chloride. The extract was washed with water, saturated sodium sodium bicarbonate, and brine solutions and dried. Solvent removal yielded 495 mg of oily ketone **3d** homogeneous on thin layer chromatography, 2,4-dinitrophenylhydrazone mp 215–217°.

Anal. Calcd for $C_{28}H_{36}O_6N_4$: C, 64.11; H, 6.92; N, 10.68. Found: C, 64.36; H, 6.83; N, 10.81.

A solution of 0.5 ml of freshly distilled boron tribromide in 5 ml of dry methylene chloride was added slowly to a solution of 250 mg of **3d** in 25 ml of methylene chloride at Dry Ice–acetone bath temperature. The solution was allowed to warm to room temperature slowly and then was evaporated under vacuum. Water, 50 ml, was added to the cooled solid residue and the mixture extracted with chloroform and with ether. The combined extracts were dried and evaporated. An ether solution of the solid residue (homogeneous on tlc and devoid of methoxy pmr signals) was treated with ethereal diazomethane. Evaporation of the solution and crystallization of the solid residue, 244 mg, from methanol gave cryptojaponol, mp and mmp 204–206°, ir and pmr spectral identical with those of an authentic sample.[19]

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.39; H, 9.09. Found: C, 76.69; H, 9.26.

Registry No.—**2a**, 24099-23-8; **3c**, 16755-52-5.

Acknowledgment.—The authors are indebted to the National Science Foundation for partial support of this work.

(19) The authors are indebted to Professor T. Kondo for a gift of a specimen of the natural product.

(13) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, **90**, 5480 (1968).

(14) O. E. Edwards, G. Feniak, and M. Los, *Can. J. Chem.*, **40**, 1540 (1962).

(15) C. H. Brieskorn, A. Fuchs, J. B-s. Bredenberg, J. D. McChesney, and E. Wenkert, *J. Org. Chem.*, **29**, 2293 (1964).

(16) J. F. W. McOmie and M. L. Watts, *Chem. Ind.* (London), 1658 (1963).

(17) E. Wenkert, A. Fuchs, and J. D. McChesney, *J. Org. Chem.*, **30**, 2931 (1965).

(18) Melting points were determined on a Reichert micro hot stage and are uncorrected.

Trichloroacetylation of Dipeptides by Hexachloroacetone in Dimethyl Sulfoxide under Neutral Conditions[1a]

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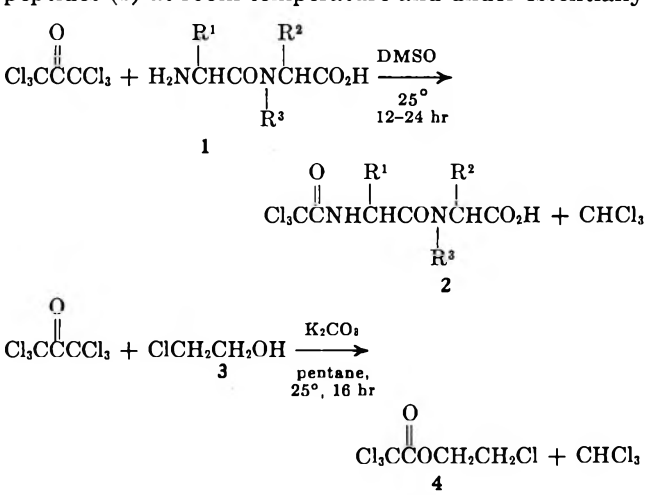
Hexachloroacetone (HCA) in dimethyl sulfoxide was found to be a convenient and inexpensive reagent for the trichloroacetylation of the amino moiety in simple peptides (**1**) at room temperature and under essentially



(1) (a) Presented at the 21st Southeastern Regional Meeting of the American Chemical Society, Richmond, Va., Nov 1969; (b) to whom inquiries should be addressed.

TABLE I

RESULTS OF NEUTRAL TRICHLOROACETYLATION EXPERIMENTS USING HEXACHLOROACETONE AND DIMETHYL SULFOXIDE[a,b]

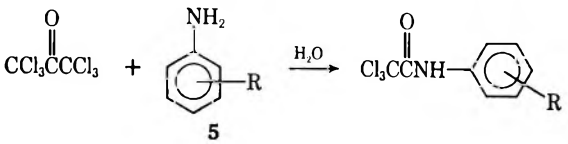
Name of dipeptide, 1	R¹	R²	R³	TCA-dipeptide, 2: Mp, °C[c]	Yield, %	Tlc R_f[d]	Ml of DMSO/ mmol of dipeptide	New carbonyl group, ν (cm⁻¹)
Glycylglycine	H	H	H	142.0–142.5	28.5	0.20	3.54	1750
L-Leucyl-L-leucine	*i*-Bu	*i*-Bu	H	177.0–178.0	89.0	0.80	1.77	1710
Glycylsarcosine	H	H	Me	173.5–174.5	51.5	0.30	1.47	1746
L-Valyl-L-leucine	*i*-Pr	*i*-Bu	H	178.0–179.0	55.5	0.80	3.47	1715
L-Phenylalanyl-L-leucine	Benzyl	*i*-Bu	H	155.5–156.0	73.2	0.80	4.16	1708

[a] Moles of HCA:mole of dipeptide, 3–4:1. [b] Reaction period is 12 hr except for glycylglycine for which it is 24 hr. [c] Melting points are corrected. [d] 50:45:5 benzene:acetone:HOAc.

neutral conditions. The carboxylate group does not interfere with this novel reaction. The foregoing transformation was uncovered during a general investigation of the interaction of certain carbonyl compounds with peptides. Glycine, an amino acid, was also easily and rapidly transformed to its trichloroacetyl derivative under similar conditions. The common by-product in these reactions was chloroform which was detected and identified by vapor phase chromatography and by isolation and characterization. It was formed in good yield.

In 1960, Simmons and Wiley[2] reported a similar reaction between HCA and ethylenechlorohydrin (**3**) which afforded an ester of trichloroacetic acid (**4**). This reaction bears a close resemblance to the type described in this paper; however, the basic conditions reported by these workers were not necessary when a mixture of HCA and DMSO was used as the acylation reagent.

More recently, two Russian workers described the trichloroacetylation of aromatic amines, **5**, with HCA in an aqueous mixture.[3] The results of this procedure



5

were variable. When R was hydrogen, methoxy, or methyl, trichloroacetylation was accomplished at room temperature. When R was *m*- or *p*-chloro, heating was required, and when R was *o*-chloro or *o*-nitro, no reaction was observed.

Table I summarizes our work on the trichloroacetylation of dipeptides, **1**, using HCA in DMSO under neutral conditions. All of the products, **2** (TCA-dipeptides), were new compounds. TCA-glycylglycine was characterized by elemental analysis. TCA-glycylsarcosine and TCA-L-leucyl-L-leucine were identified by infrared spectral data and by thin layer chromatographic comparison with the product obtained from the reaction of the dipeptide and trichloroacetyl chloride in aqueous base. TCA-L-valyl-L-leucine and TCA-L-phenylalanyl-L-leucine were characterized by infrared spectral data. The yields were generally good except in the case of TCA-glycylglycine. The water solubility of this product made a more tedious and less efficient isolation procedure necessary. No attempt was made to establish the optimum time required for the greatest yields. Thin layer chromatography indicated that the reaction was essentially complete after 12 hr in most cases and probably required much less time than that. Lastly, the possibility of racemization of the optically active dipeptides, **1**, during this reaction was not investigated.

(2) H. E. Simmons and D. W. Wiley, *J. Amer. Chem. Soc.*, **82**, 2288 (1960).

(3) V. P. Rudavskii and I. G. Khaskin, *Ukr. Khim. Zh.*, **33**, 391 (1967); *Chem. Abstr.*, **67**, 63963 (1967).

Experimental Section[4]

The thin layer chromatograms of the TCA-dipeptides, **2**, were run on microscope slides coated with 250-μ layer of Camag D-5 silica gel. Spotting was performed using 0.5–1.0 μl of a 1% solution and the solvent system was benzene–acetone–HOAc (50:45:5). The zones were detected as yellow areas on a purple background after spraying with a 0.5% aqueous $KMnO_4$ solution sometimes followed by heating. Cited R_f values are approximate.

N-Trichloroacetylglycylglycine (2, R¹, R², R³ = H).—A mixture of 0.749 g (5.67 mmol) of glycylglycine, 3.44 ml (6.0 g, 22.6 mmol) of hexachloroacetone, and 20 ml of dimethyl sulfoxide was magnetically stirred for 24 hr at room temperature in a flask equipped with a drying tube. Complete solution occurred after about 60 min. Gas–liquid chromatographic (ss column 0.25 in. × 2 m, 20% dodecyl phthalate on GC-22, 60–80 mesh, He carrier gas) analysis showed a peak with the same retention time as that of authentic chloroform. The yellow reaction solution was diluted with 60 ml of water and was then extracted with three 30-ml portions of *n*-BuOH. The butanol extract contained a fast zone (assumed to be the product) and a zone of DMSO. The product was separated from the DMSO by passing the mixture through a column of silicic acid (100 mesh) using acetone as the eluting solvent. The oily product was crystallized from methyl isobutyl ketone: yield 0.45 g (28.5%).

This product was identical in all respects (thin layer R_f values, melting point, and ir spectra) with that obtained from the reaction of glycylglycine with trichloroacetyl chloride or with trichloroacetic anhydride.

Anal. Calcd for $C_6H_7Cl_3N_2O_4$: C, 25.96; H, 2.52; N, 10.01; Cl, 38.36. Found: C, 26.17; H, 2.68; N, 10.16; Cl, 38.31.

General Procedure for the Preparation of Water-Insoluble TCA-Dipeptides, 2.—This method was employed for all of the dipeptides in Table I except glycylglycine.

N-Trichloroacetyl-L-leucyl-L-leucine (2, R¹, R² = *i*-Bu, R³ = H).—A mixture of 0.275 g (1.12 mmol) of L-leucyl-L-leucine, 0.60 ml (1.04 g, 3.94 mmol) of hexachloroacetone, and 2.0 ml of dimethyl sulfoxide was placed in a dry flask protected with a drying tube. After about 1 hr of magnetic stirring, a clear solution resulted. Glpc analysis again indicated the presence of chloroform in this solution (see previous procedure). Stirring was continued at room temperature for 11 hr, after which the reaction solution was poured into ten times its volume of crushed ice. The solid which precipitated was collected by filtration, thoroughly washed with cold water, and dried. The crystals weighed 0.39 g (89%) and were homogeneous according to thin layer chromatography. This product was then dissolved in a minimum amount of methyl isobutyl ketone and crystallization was induced by dilution with petroleum ether (bp 30–60°).

The identity of the above product was established from spectral data (see Table I), and by direct comparison of the thin layer R_f value of this product with that of the product obtained from the

(4) Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Melting points were corrected.

reaction between L-leucyl-L-leucine and trichloroacetyl chloride in aqueous NaOH.

N-Trichloroacetylglycine.—Glycine, 1.00 g (13.35 mmol), 8 ml (13.98 g, 52.25 mmol) of hexachloroacetone, and 25 ml of DMSO were magnetically stirred at room temperature for 24 hr. The reaction solution was diluted with 85 ml of water and the reaction solution was diluted with 85 ml of water and the resultant mixture was extracted with three 50-ml portions of *n*-BuOH. The butanol extract was chromatographed on a silicic acid column. A mixture of benzene, acetone, and methanol (5:4:1) was the eluting solvent. A DMSO-free oil was obtained which crystallized from methyl isobutyl ketone and petroleum ether (bp 30–60°). The yield of product was 1.88 g (63.7%); mp 130.0–130.5° (lit.[5] 131–132°). This product was identical (thin layer R_f value, melting point, and ir spectra) with that obtained from the reaction of glycine with trichloroacetic anhydride.

Larger scale preparations of N-trichloroacetylglycine showed that the reaction with hexachloroacetone in DMSO is exothermic. In one such preparation (0.134 mol of glycine) the reaction solution was poured into about 100 ml of water and the resultant solution was distilled at atmospheric pressure. At 60° (vapor temperature) a distillate was collected which was identified as chloroform by its gas chromatography retention time and by its infrared spectrum: yield, 13.32 g (0.112 mol).

Registry No.—Hexachloroacetone, 116-16-5; 2 (R^1 = R^2 = R^3 = H), 24299-47-6; 2 (R^1 = R^2 = *i*-Bu; R^3 = H), 24299-25-0; 2 (R^1 = R^2 = H; R^3 = Me), 24299-74-9; 2 (R^1 = *i*-Pr; R^2 = *i*-Bu; R^3 = H), 24299-26-1; 2 (R^1 = benzyl; R^2 = *i*-Bu; R^3 = H), 24299-27-2.

Acknowledgment.—Support of this work under a National Institutes of Health Research Grant No. I RO1 AM12761-01A1 MCHA is gratefully acknowledged.

(5) W. Lautsch and D. Heinicke, *Kolloid Zh.*, **154**, 1 (1957); **158**, 103 (1957); *Chem. Abstr.*, **52**, 5299*b* (1958).

Synthesis of Derivatives of 2-Aminoproline and 5-Aminoproline

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Synthesis of α-amino acids containing a nitrogen or oxygen atom on the carbon linked with nitrogen have been described in reports from several laboratories, and some of these compounds are constituents of Ergot alkaloids. Proline derivatives of the type previously indicated have not yet been prepared, and we present here the synthesis of derivatives of 2-amino-DL-proline and 5-amino-DL-proline.

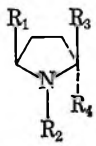
Addition of acetamide[1] to N-acetyl-Δ²-pyrroline-2-carboxylic acid[2] occurred on heating a mixture of the two substances, which produced a compound to which we attributed the structure of N,N′-diacetyl-2-amino-DL-proline (**1**). This structure is in accord with the spectral data and was confirmed through acid hydrolysis,[3] which gave α-keto-δ-acetylaminovaleric acid, recognized as the 2,4-dinitrophenylhydrazone.[2]

(1) Addition of acetamide to α-acylaminoacrylic acids has been reported: D. Shemin and R. Herbst, *J. Amer. Chem. Soc.*, **60**, 1954 (1938).

(2) K. Hasse and P. Homann, *Biochem. Z.*, **335**, 474 (1962).

(3) *trans*-N,N′-Diacetyl-3-amino-DL-proline, prepared by us [*Tetrahedron Lett.*, **35**, 3055 (1969)], was stable under the conditions employed in the hydrolytic degradation of **1**.

Starting material for synthesis of *cis*-N,N′-dicarbobenzyloxy-5-amino-DL-proline (**5**) was N-carbobenzyloxy-DL-pyrrolidine-2,5-dicarboxylic acid anhydride.[4] This compound was transformed to the corresponding monoazide **4** and gave **5** through the Curtius reaction. Catalytic hydrogenation (palladium on charcoal in acetic acid) of *cis*-N,N′-dicarbobenzyloxy-5-amino-DL-proline led to proline, which was recognized as the N-2,4-dinitrophenyl derivative.



(L forms only are shown)

Compd	R_1	R_2	R_3	R_4
1	H	$COCH_3$	COOH	$NHCOCH_3$
2	H	$COCH_3$	$COOCH_3$	$NHCOCH_3$
3	H	$COCH_3$	$CONHNH_2$	$NHCOCH_3$
4	CON_3	$COOCH_2C_6H_5$	COOH	H
5	$NHCOO-CH_2C_6H_5$	$COOCH_2C_6H_5$	COOH	H

Experimental Section[5]

N,N′-Diacetyl-2-amino-DL-proline (1).—N-Acetyl-Δ²-pyrroline-2-carboxylic acid (1 g) and 2 g of acetamide were finely powdered and heated in a vacuum sublimator at 110° for 3 hr after removal of air under high vacuum. The excess acetamide was sublimed off and the residue was crystallized from methanol to give 1.15 g (75%) of **1**, mp 175–77°.

Anal. Calcd for $C_9H_{14}N_2O_4$: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.20; H, 6.78; N, 12.95.

2,4-Dinitrophenylhydrazone of α-Keto-δ-acetylaminovaleric Acid.—A 90-mg portion of **1** was dissolved with stirring and was gently heated in 25 ml of a solution of 2,4-dinitrophenylhydrazine in 2 *N* HCl (4 mg/ml). When the reaction mixture was maintained at room temperature overnight, the hydrazone crystallized. The melting point of a sample recrystallized from acetic acid was 231° dec.

Anal. Calcd for $C_{13}H_{15}N_5O_7$: C, 44.19; H, 4.28; N, 19.83. Found: C, 43.98; H, 4.45; N, 19.61.

N,N′-Diacetyl-2-amino-DL-proline Methyl Ester (2).—Methyl ester **2** was obtained by addition of ethereal diazomethane to the parent acid in methanol at 0°. Evaporation of the solvent and crystallization from ethyl acetate gave **2**: 90% yield; mp 140–141°; nmr ($CDCl_3$) δ 1.99 and 2.04 (two s, 3, $CH_3CON<$), 2–3 range (m, 4, C-3 and C-4 H of the ring), 3.79 (s, 3, CH_3OCO), 3.6–4.2 range (m, 2, C-5 H of the ring), 7.14 (broad signal, 1, NHCO). The assignments were made on the basis of the chemical shift and ratio of intensities values.

Anal. Calcd for $C_{10}H_{16}N_2O_4$: C, 52.62; H, 7.07; N, 12.27. Found: C, 52.71; H, 7.01; N, 12.32.

N,N′-Diacetyl-2-amino-DL-prolinehydrazide (3).—Methyl ester **2** (1 g) was dissolved in 8 ml of monohydrated hydrazine which was removed 5 min later under vacuum at 30°. The residue was crystallized from ethanol–ethyl ether to give the hydrazide in 80% yield, mp 171–172°.

Anal. Calcd for $C_9H_{16}N_4O_3$: C, 47.36; H, 7.07; N, 24.55. Found: C, 47.23; H, 7.09; N, 24.68.

***cis*-N,N′-Dicarbobenzyloxy-5-amino-DL-proline (5).**—N-Carbobenzyloxy-DL-pyrrolidine-2,5-dicarboxylic acid anhydride (1.24 g) was dissolved in 75 ml of warm acetone. The solution was cooled in ice and 750 mg of sodium azide in 5 ml of water was added with stirring and cooling, immediately followed by a further amount of water to dissolve the sodium azide which separated as a solid. After the mixture stirred for 1 hr at 0°, 20 ml of water was added and the acetone was evaporated off at 30°. The cooled aqueous solution was acidified to pH 4 with 2 *N* hydrochloric acid and extracted with ethyl ether, which was

(4) G. Cignarella and G. Nathansohn, *J. Org. Chem.*, **26**, 1500 (1961).

(5) Melting points were taken on a Culatti apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 221 infrared spectrophotometer. Nmr spectra were recorded on a Varian A-60 spectrometer, at room temperature, and are given in δ units relative to TMS as internal standard.

washed with water, dried (Na_2SO_4), and evaporated at reduced pressure to give 1.40 g of the azide **4**, thick oil, ir (liquid film) 2130 cm^{-1} (azide).

The azide was warmed for 2 hr at 70° in 10 ml of anhydrous benzyl alcohol. The mixture was diluted with ethyl ether and extracted with 2 *N* sodium carbonate. The cooled alkaline solution was acidified with 2 *N* hydrochloric acid to pH 4 and reextracted with ether which was washed with water and dried (Na_2SO_4); solvent was evaporated off at reduced pressure. The oily residue was crystallized from ethanol–water to give 500 mg (28%) of *cis*-N,N′-dicarbobenzyloxy-5-amino-DL-proline, mp 141–142°.

Anal. Calcd for $C_{21}H_{22}N_2O_6$: C, 63.31; H, 5.57; N, 7.03. Found: C, 63.39; H, 5.65; N, 7.06.

Registry No.—**1**, 24377-91-1; **2**, 24377-92-2; **3**, 24377-93-3; **5**, 24377-94-4; α-keto-δ-acetylaminovaleric acid (2,4-dinitrophenylhydrazone), 24378-14-1.

A Facile Preparation of 3-Thujene from Thujone

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The bicyclic monoterpene 3-thujene (**1**) is much less readily available from natural sources than is thujone (**2**). The methods previously used[1,2] for obtaining **1** from **2** involve reduction to the thujyl alcohols, separation of isomers, and eliminations. We have found that it is possible to obtain **1** from **2** in a rather simple procedure which is applicable to large-scale work by use of the Bamford–Stevens rearrangement.[3]

Thujone (**2**) was readily converted to the *p*-toluenesulfonylhydrazone which was initially decomposed with a solution of sodium in ethylene glycol. The hydrocarbon product was analyzed by preparative vpc and shown to contain 3-thujene (**1**, 42%), 2-thujene (**3**, 16%), γ-terpinene (**4**, 13%), a fourth unidentified compound, and a trace of *p*-cymene. Using acetamide as a solvent,[4] the hydrocarbon product (97% yield) consisted of **1** (80%) and **4** (20%), **4** being slightly contaminated with an unidentified isomer. 3-Thujene was characterized by its spectral properties and by conversion to terpinene dihydrochloride.[5] This procedure therefore represents a simple process for obtaining 3-thujene from readily available thujone.

Experimental Section[6]

***p*-Toluenesulfonylhydrazide.**[7]—Hydrazine hydrate (40 g, 85%) was slowly added to a benzene solution of 60 g of *p*-toluenesulfonyl chloride (recrystallized from an ether–ligroin mixture) at 5° through the condenser into a 500-ml flask. After 2 hr the solid was filtered and recrystallized from hot water. The yield was 42.6 g (72%), mp 110–112° (lit.[7] 112°).

Thujone *p*-Toluenesulfonylhydrazone.—*p*-Toluenesulfonylhydrazide (42.6 g) and 40 g of **2**, $[\alpha]^{25}D$ +20.13°, were dissolved in 200 ml of ethanol and refluxed in a 500-ml flask for 3.5 hr until the reaction was complete as indicated by thin layer chromatography. Following reflux, the ethanol was removed under reduced pressure until a precipitate formed, and then the mixture was heated on a steam bath to effect solution. The solution was cooled to effect crystallization; the crystals were filtered, recrystallized from ethanol, and dried. The yield was 25.6 g (35%), mp 126–129°, $[\alpha]^{25}D$ +105.7°; ir ($CHCl_3$) 3310 (NH), 2980, 1610, 1170 cm^{-1}.

Anal. Calcd for $C_{17}H_{24}N_2SO_2$: C, 63.75; H, 7.50; N, 8.75. Found: C, 63.99; H, 7.74; N, 8.63.

3-Thujene (1). I. Ethylene Glycol as Solvent.—The hydrazone (5 g) and 50 ml of 1.5 *N* sodium in ethylene glycol were placed in a 100-ml flask. Most of the solid dissolved immediately and the remainder dissolved on the application of heat. Nitrogen evolution continued steadily for 15 min and the resulting organic layer was then distilled off at 141–175° yielding 1.5 ml of product. The vpc analysis indicated four products: 3-thujene (**1**, 42%), 2-thujene (**3**, 16%), contaminated slightly with another compound γ-terpinene (**4**, 13%), and 20% of an unidentified mixture.

II. Acetamide as Solvent.—The acetamide (200 g) was melted in a 500-ml three-necked flask and purged with oxygen-free nitrogen. The acetamide was cooled to 100° and 6.0 g of sodium was added in small quantities under a nitrogen atmosphere (extreme care must be taken to avoid combustion). The hydrazone (38.6 g) was added and the temperature held at 140–150°. Nitrogen evolution ceased after 25 min and the reaction mixture was cooled slightly. Water (200 ml) was added and the organic layer was extracted into petroleum ether. The ethereal solution was dried ($MgSO_4$), filtered, concentrated, and distilled giving 15.9 g (97%) of mixed hydrocarbon product. The mixture was readily separated *via* preparative vpc and **1** was characterized as follows: $n^{29}D$ 1.4471, $[\alpha]^{32}D$ −32.05°, bp 150–151°; ir (neat) 2985, 2881, 3057 cm^{-1}; nmr (neat) δ 0.02 (t, 1, J = 3 Hz), 0.90 (m, 2), 0.98 (d, 6, J = 3 Hz), 1.35 (m, 1), 1.76 (q, 3, J = 2 Hz), 2.30 (m, 2), 4.90 (m, 1); mass spectrum (70 eV) m/e 136, 93 (lit.[8]).

Terpinene Dihydrochloride.[5]—To 5 ml of glacial acetic acid was added 0.20 g of **1** and the solution was saturated with gaseous HCl. The mixture developed a red color after 9 hr of standing and was then poured over ice. The resulting solid was filtered and recrystallized from methanol: mp 47–49°; nmr ($CDCl_3$) δ 1.68 (s, 3), 1.90 (d, 6, J = 6 Hz), 1.98 (s, 9).

The absolute configurations of 3-thujene (**1**), thujone (**2**), and 2-thujene (**3**) are those verified by Norin.[9,10]

Registry No.—**1**, 3917-48-4; **2**, 546-80-5; **2** *p*-toluenesulfonylhydrazone, 18791-12-3.

Acknowledgment.—We thank the U. S. Public Health Service (A108862-01) and the Alfred P. Sloan Foundation for their support of this research.

(1) L. Tschugaev and W. Fomin, *Ber.*, **45**, 1293 (1912).
(2) D. V. Banthorpe and H. ff. S. Davies, *J. Chem. Soc. B*, 1339 (1968).
(3) W. R. Bamford and T. S. Stevens, *ibid.*, 4735 (1952).
(4) J. W. Powell and M. L. Whiting, *Tetrahedron*, **7**, 305 (1959).
(5) A. J. Birch and J. C. Earl, *J. Proc. Roy. Soc. N. S. W.*, **72**, 55 (1938).
(6) Melting points were measured on a Kofler hot stage and are uncorreeted. Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer, nuclear magnetic resonance spectra on Varian A-60 and HA-100 spectrometers with tetramethylsilane as an internal reference, and mass spectra on an AEI MS 9 mass spectrometer. Refractive indices were determined on a Bausch and Lomb ABBE-3L refractometer and optical rotations on the Perkin-Elmer P22 spectropolarimeter. Analytical and preparative vpc analyses were made on a Varian Aerograph Model 700 using a 30% Carbowax column on 45–60 Chromosorb W support at 180°. Thujone was kindly supplied by Fritzsche Bros. Inc., New York, N. Y. Elemental analysis was performed by the Midwest Microlab, Inc., Indianapolis, Ind.
(7) K. Freudenberg and F. Blümmel, *Justus Liebigs Ann. Chem.*, **440**, 51 (1924).
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(10) M. S. Bergqvist and T. Norin, *Ark. Kemi*, **22** (12), 137 (1964).

Alkaline Cleavage of Phosphetane Oxides

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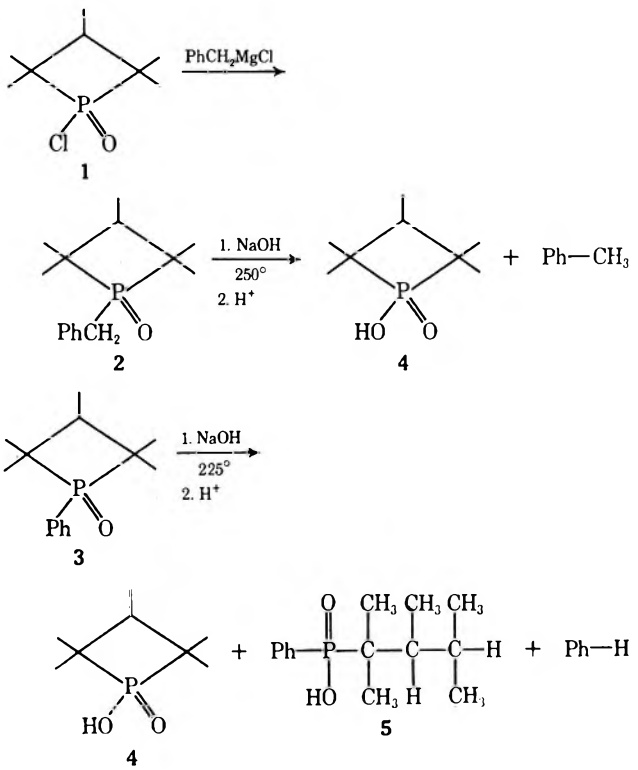
Recently, we reported the alkaline cleavage of several heterocyclic phosphine oxides.[1] In all but one

(1) (a) B. R. Ezzell and L. D. Freedman, *J. Org. Chem.*, **34**, 1777 (1969); (b) *ibid.*, **35**, 241 (1970).

case, the reactions gave the products corresponding to cleavage of the group capable of forming the more stable carbanion. We suggested[1b] that the general cleavage reaction *normally* proceeds *via* a trigonal-bipyramidal intermediate with the oxygen atoms occupying the apical positions. For heterocyclic phosphine oxides, in cases where a large amount of ring strain would be involved in placing the heterocyclic ring in diequatorial positions, some other pathway would seem necessary. We suggested, in the case of 5-benzyldibenzophosphole 5-oxide where ring cleavage predominates over cleavage of the more stable benzyl carbanion,[1a] that, owing to ring strain, the reaction proceeds by an SN2-type process. The present paper offers additional information on the cleavage of heterocycles involving ring-strain considerations.

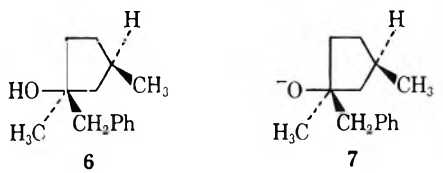
The reactions involved in this study are shown in Scheme I. The acid chloride 1 was prepared by the

SCHEME I



method of McBride and coworkers,[2] and the phosphetane oxide 3 was prepared by the method of Cremer and Chorvat.[3] The reaction of benzylmagnesium chloride with 1 to form the phosphetane oxide 2 proceeded smoothly without interference from ring-opening reactions as was observed with phenyllithium.[3,4] The preparation of 2 by the same method employed here was recently cited, without detail, in a communication.[5] Fusion of 2 with sodium hydroxide gave only 1-hydroxy-2,2,3,4,4-pentamethylphosphetane 1-oxide (4) corresponding to exclusive cleavage of the more stable benzyl carbanion. Fusion of 3 with sodium hydroxide led to both 4 and phenyl (2,3,4,4-tetramethylbutyl)-phosphinic acid (5) in approximately a 1:4 ratio. This result corresponds to preferential ring cleavage even though this means cleavage of the least stable carbanion. Clearly, the direction of cleavage for this four-membered ring is influenced by both the ring and the stability of the leaving carbanion. The fact that the ring influences the direction of cleavage is in contrast to the saturated five-membered ring,[1b] but in agreement with the unsaturated five-membered ring.[1a]

Historically, trigonal-bipyramidal intermediates have received prime attention in the field of organophosphorus chemistry. Considerable attention has recently been given to the position of the leaving group in the trigonal-bipyramidal intermediates formed during alkaline cleavage of phosphonium salts.[6] Apical departure has been shown to take precedence over cleavage of groups capable of forming more stable carbanions in certain small-ring heterocyclic phosphoniums.[7] In other cases, where exocyclic benzyl groups have cleaved in preference to small heterocyclic rings,[1a,8] it is questionable whether the benzyl group leaves from an equatorial position of the initially formed intermediate or from an apical position of a new intermediate derived from pseudorotation. Marsi,[8b] after showing that the benzyl group was cleaved from both isomers of 1-benzyl-1,3-dimethylphospholanium bromide with retention of configuration at phosphorus, suggested equatorial benzyl departure. His argument was based on the energetically unfavorable pseudorotation of intermediate 6 to an intermediate containing the electronegative hydroxyl group in an equatorial position. He further suggests that if such a pseudorotation process did occur, then intermediates that would give rise to inversion of configuration would also be reasonable. Since, as Marsi shows in his kinetic scheme, intermediate 7

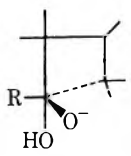


would also be expected in the reaction process, pseudorotation should have been considered for this intermediate also. Replacement of 6 by 7 in the pseudorotation scheme given by Marsi results in a reversal of the energetics. Pseudorotation of 7 to an intermediate with the oxygen atom in an equatorial position is energetically favorable since this means moving the least electronegative group (the negative oxygen) from an

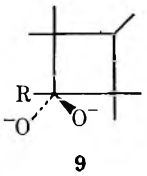
(2) J. J. McBride, E. Jungermann, J. V. Killheffer, and R. J. Clutter, *J. Org. Chem.*, **27**, 1833 (1962).
(3) S. E. Cremer and R. J. Chorvat, *ibid.*, **32**, 4066 (1967).
(4) S. E. Cremer and R. J. Chorvat, *Tetrahedron Lett.*, 413 (1968).
(5) S. E. Cremer, R. J. Chorvat, and B. C. Trivedi, *Chem. Commun.*, 769 (1969).
(6) A survey of both the phosphine oxide and phosphonium cleavage reactions is given in ref 1a and references therein.
(7) S. E. Fishwick, J. Flint, W. Hawes, and S. Trippett, *Chem. Commun.*, 113 (1967).
(8) (a) D. W. Allen and I. T. Millar, *J. Chem. Soc. C*, 252 (1969); (b) K. L. Marsi, *J. Amer. Chem. Soc.*, **91**, 4724 (1969); (c) W. Hawes and S. Trippett, *Chem. Commun.*, 295 (1968).
(9) R. Kluger, F Covitz, E. Dennis, L. D. Williams, and F. H. Westheimer, *J. Amer. Chem. Soc.*, **91**, 6066 (1969).

apical to an equatorial position. Also, pseudorotation to intermediates that would result in inversion of configuration is now unlikely in this scheme since one step requires the energetically unfavorable process of moving the negative oxygen from an equatorial to an apical position. Thus, depending on the intermediate chosen, arguments for either apical or equatorial departure can be supported by the same pseudorotation scheme.

If an intermediate is formed in the cleavage reactions of the phosphetane oxides, structure **8** seems most reasonable. The four-membered ring occupies apical-equatorial positions and the position-*vs.*-electronegativity requirements are best satisfied. It seems unreasonable that the coulombic repulsion between the oxide oxygen and the hydroxide ion would be sufficient to cause formation of an intermediate with the ring in diequatorial positions.[1,10] If **8** was formed, it is possible,



8



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considering the extreme alkaline conditions employed for the reactions, that a second equivalent of hydroxide ion would react to form the conjugate base. Pseudorotation could then lead to a more stable intermediate, **9**, if the rate of the cleavage step was slower than that of pseudorotation. As in the case with the phosphonium reactions, apical or equatorial departure for an exocyclic group would depend on the intermediate. Regardless of whether **8** or some conjugate base was the key intermediate, the influence of the ring on the direction of cleavage would have to be explained by the reaction process leading from intermediate to product. Whether this influence would be associated with a preference for apical departure as seems to be the case with phosphonium cleavage reactions[6] or a ring strain factor is not obvious. Although a comparison between the cleavage reactions of phosphetanium salts[7,8c] and the phosphetane oxides presented here suggest a strong similarity in factors determining direction of cleavage, a similar comparison for the dibenzophosphole ring system shows definite differences. The latter comparison prompted us to previously suggest an SN2-type mechanism.[1a,11]

The detailed mechanism for cleavage of phosphine oxides with sodium hydroxide is far from being established. The results, to date, are insufficient for a prediction of the direction of cleavage for small ring compounds. It is clear, however, from the results presented here and in previous papers,[1] that ring size and relative carbanion stabilities have a definite influence on the direction of cleavage. The effect of ring size is best demonstrated by a comparison of the cleavage of 1-phenyl-2,5-dicyclohexyphospholane 1-oxide[1b] and the phosphetane oxide **3**. The exocyclic phenyl group is common to both compounds and the carbanions derived from ring cleavage are of comparable stabilities. No ring cleavage is observed with the five-membered ring, whereas ring cleavage predominates with the four-membered ring. The effect of relative carbanion stability is best demonstrated by a comparison between 5-benzyldibenzophosphole 5-oxide[1a] and the phosphetane oxide **2**. The exocyclic benzyl group is common to both compounds, but the carbanion derived from cleavage of the dibenzophosphole ring is considerably more stable than the tertiary aliphatic carbanion derived from cleavage of the phosphetane ring. Even though any strain factor should be more significant for the four-membered ring, exclusive exocyclic cleavage occurs for **2** while preferential ring cleavage is observed for the dibenzophosphole ring.

Experimental Section[12]

1-Benzyl-2,2,3,4,4-pentamethylphosphetane 1-Oxide (2).—1-Chloro-2,2,3,4,4-pentamethylphosphetane 1-oxide[2] (25.2 g, 0.13 mol) in ether was added dropwise to a stirred ethereal solution of benzylmagnesium chloride prepared from magnesium (0.15 g-atom) and benzyl chloride (0.15 mol). The solution was heated and stirred 1 hr after the addition. The solution was then cooled and 300 ml of 5% hydrochloric acid was added dropwise. The organic layer was separated and washed with 5% sodium hydroxide solution and then water. The ether was evaporated and the solid residue recrystallized from benzene: yield 14.5 g (45%); mp 180–182°; nmr τ 8.5–9.2 (m, 15, $-CH_3$), 7.9–8.2 (m, 1, methine H), 6.74 (d, J_{P-H} = 11.5 Hz, P-CH_2-Ph), 2.4–2.9 (m, 5, aromatic H).

Anal. Calcd for $C_{16}H_{23}OP$: C, 71.97; H, 9.26; P, 12.37. Found: C, 72.10; H, 9.24; P, 12.19.

Cleavage of 1-Benzyl-2,2,3,4,4-pentamethylphosphetane 1-Oxide (2).—This phosphine oxide (4.7 g, 0.019 mol) was cleaved with sodium hydroxide (0.08 mol) at 250° for 1 hr. About 2 ml of toluene (identified by glpc and ir), essentially the calculated amount for exclusive benzyl cleavage, distilled during this time. The usual isolation procedure,[1] except that the acid was extracted from the acidic aqueous solution with chloroform, gave 1-hydroxy-2,2,3,4,4-pentamethylphosphetane 1-oxide (**4**): yield 2.8 g (85%); mp (after drying in a vacum desiccator over phosphorus pentoxide) 71–73° (lit.[2] mp 72–74°). The acid was identical (ir and mixture melting point) with an authentic sample prepared by hydrolysis of the acid chloride **1**.

Cleavage of 1-Phenyl-2,2,3,4,4-pentamethylphosphetane 1-Oxide (3).[3]—This compound (5.9 g, 0.025 mol) was cleaved with sodium hydroxide (0.1 mol) at 225° for 1 hr. Several drops of benzene (identified by glpc) distilled during this time. The reaction mixture was dissolved in water and then acidified with hydrochloric acid. The aqueous solution, which contained a viscous oil, was extracted with chloroform. Evaporation of the chloroform gave an oily mixture of **4** and phenyl (2,3,4,4-tetramethylbutyl)phosphinic acid (**5**) in a ratio of approximately 1:4 as determined by nmr, yield 5.6 g (94% based on the above ratio). The acid **5** could be separated from **4** by repeatedly dissolving the mixture in a dilute sodium hydroxide solution and precipitating with hydrochloric acid. The first material precipitated was taken. The solid was recrystallized from aqueous ethanol and dried in a vacuum desiccator over phosphorus pentoxide: mp 100–103°; nmr τ 8.8–9.4 (m, 15, $-CH_3$), 7.6–8.5 (m, 2, methine H), 2.1–2.7 (m, 5, aromatic H).

Anal. Calcd for $C_{14}H_{23}O_2P$: C, 66.12; H, 9.11; P, 12.17. Found: C, 65.96; H, 8.95; P, 12.10.

Registry No.—**2**, 24655-74-1; **5**, 24655-75-2.

(10) Our suggestion (ref 2b) that acyclic phosphine oxides cleaved from a trigonal-bipyramidal intermediate with the oxygen atoms in the apical positions was based on coulombic repulsion and did not consider the competing factor of having the negative oxygen in an equatorial position.

(11) It is possible that the rate of exocyclic cleavage is slow because of an increase in ring strain in going from an intermediate (**8** or **9**) to a cyclic product.

(12) Melting points were taken with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 221 spectrophotometer. Nmr spectra were taken with a Varian A-60 instrument; deuteriochloroform was used as a solvent with tetramethylsilane as an internal standard. Elemental analysis were performed by Spang Microanalytical Laboratory.

Chemistry of Cephalosporin Antibiotics. XVIII. Synthesis of 7-Acyl-3-methyl-2-cephem-4-carboxylic Acid Esters

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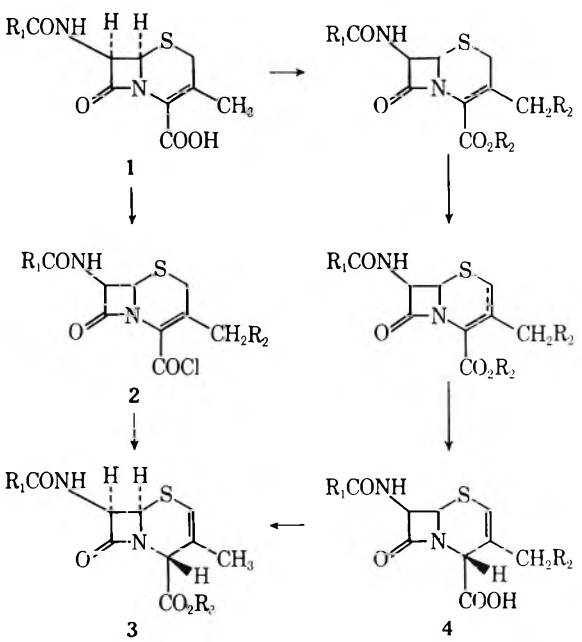
Recent publications[1,2] from these laboratories have described results which constitute the synthesis of a cephalosporin from a penicillin. In this and the following note,[3] we report additional studies of the functionalization of deacetoxymethyl cephalosporins.[2]

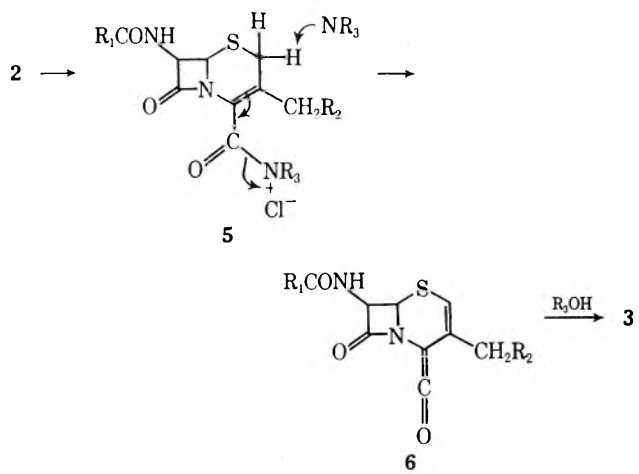
The initial part of the Webber, *et al.*,[2] sequence involves an esterification of the 3-cephem acid **1**, an isomerization, and deesterification to give the 2-cephem acid **4**, which in turn is esterified to give an easily cleavable ester in low overall yield. An alternative preparation of pure 2-cephem esters involving the acid chloride **2** and a probable ketene intermediate is described herein.



Δ^3-Cephalosporanyl chlorides are best prepared in an inert solvent with oxalyl chloride, using N,N-dimethylformamide as a catalyst. Other acid chloride forming reagents, such as thionyl chloride or phosphorus pentachloride, with or without catalysts, are less effective.

The esterification conditions are dependent upon the nature of the alcohol being employed. Tertiary alcohols may be used in excess at ice-bath temperatures; however, primary or secondary alcohols are used preferably in approximately equivalent amounts and at lower temperatures to minimize Δ^3-ester formation. The reaction conditions require that the preformed acid chloride be added slowly to a solution of the alcohol and tertiary amine base in an inert solvent. Some of the esters prepared by this method are listed in Table I. The reaction is limited only by the stability and/or acidity of the alcohol and is readily adaptable to large scale (1 mol) preparations.

The mechanism of the esterification probably involves initial acylation of the tertiary amine. Another molecule of base then removes a proton at C-2, causing a double-bond shift ($\Delta^3 \rightarrow \Delta^2$) and expulsion of the tertiary amine group to give the very reactive ketene (**5** → **6**). The ketene immediately reacts with the alcohol to give the 2-cephem ester (**6** → **3**).



The intermediacy of a ketene (**5**) can only be inferred at this time; however, acid chlorides and amine bases react to give ketenes.[4] Our attempts to isolate an adduct with phenyl isocyanate or tosyl isocyanate[5] have not succeeded. The high reactivity of the intermediate prevented its spectral identification even when generated at low temperatures (−75°).

Van Heyninger and Ahern[6] have recently shown that the 2-cephem acid formed in an equilibrative process (such as that used by Webber, *et al.*[2]) has a C-4 β hydrogen. The same stereochemistry is observed in the reaction described herein; however, the absence of Δ^3 material suggests that the stereochemistry is kinetically controlled. This may be explained by the α-face departure of the tertiary amine base preventing the attack of an alcohol molecule from that side. The alcohol, which may be held in position by a hydrogen bond to the amido hydrogen, would thus add to the β side of the ketene and give the observed stereochemical result.

Experimental Section

Melting points were determined on a Kofler melting point apparatus. Infrared spectra were determined on a Perkin-Elmer

(1) (a) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, **85**, 1896 (1963); (b) *ibid.*, **91**, 1401 (1969).

(2) J. A. Webber, E. M. Van Heyningen, and R. T. Vasileff, *ibid.*, **91**, 5674 (1969).

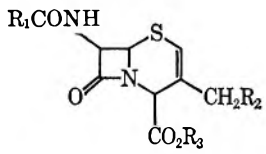
(3) G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright, and E. M. Van Heyningen, *J. Org. Chem.*, in press.

(4) (a) T. Ozeki and M. Kusaka, *Bull. Chem. Soc. Jap.*, **39**, 1995 (1966); (b) T. Ozeki and M. Kusaka, *ibid.*, **40**, 1232 (1967); (c) G. B. Payne, *J. Org. Chem.* **31**, 718 (1966); (d) W. E. Truce and P. S. Bailey, Jr., *ibid.*, **34**, 1341 (1969).

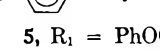
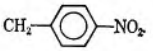
(5) E. Mundlos and R. Graf, *Justus Liebigs Ann. Chem.*, **677**, 108 (1964).

(6) E. M. Van Heyningen and L. K. Ahern, *J. Med. Chem.*, **11**, 933 (1968).

TABLE I



Compd[a]	Registry no.	Empirical formula	Mp, °C	% yield	Reaction conditions	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	24647-38-9	$C_{20}H_{24}N_2O_5S$	78–80	87	A	59.20	5.98	6.93	59.20	6.08	6.63
2	24144-88-5	$C_{24}H_{24}N_2O_6S$	112–114	90	B	61.52	5.16	5.97	61.95	5.33	6.12
3	24647-40-3	$C_{21}H_{22}N_2O_5S$	92–93	85	A	60.86	5.35	6.76	61.02	5.59	7.00
4	24647-41-4	$C_{21}H_{24}N_2O_5S$	83–85	46	A	60.56	5.81	6.73	60.34	6.01	6.91
5	24647-42-5	$C_{24}H_{22}N_2O_6S$	145–146	77	B	61.80	4.75	6.01	62.06	4.97	6.14
6	24647-43-6	$C_{23}H_{21}N_3O_7S$	130	60	B	57.25	4.18	8.70	57.10	4.47	8.45
7	24647-44-7	$C_{29}H_{26}N_2O_5S$	110	45	B	67.69	5.09	5.45	67.82	5.18	5.59
8	24647-45-8	$C_{20}H_{24}N_2O_4S$	130–131	45	B	61.84	6.23	7.21	61.59	6.23	7.04
9	24647-46-9	$C_{20}H_{24}N_2O_6S_2$	178	33	A	53.09	5.35	6.19	53.08	5.33	6.11

[a] **1**, R_1 = $PhOCH_2$; R_2 = H; R_3 = $C(CH_3)_3$. **2**, R_1 = $PhOCH_2$; R_2 = H; R_3 =  . **3**, R_1 = $PhOCH_2$; R_2 = H; R_3 = $-C(C{\equiv}CH)(CH_3)_2$. **4**, R_1 = $PhOCH_2$; R_2 = H; R_3 = $-C(CH{=}CH_2)(CH_3)_2$. **5**, R_1 = $PhOCH_2$; R_2 = H; R_3 = $CH_2C(=O)Ph$. **6**, R_1 = $PhOCH_2$; R_2 = H; R_3 =  . **7**, R_1 = $PhOCH_2$; R_2 = H; R_3 = $-CH(Ph)_2$. **8**, R_1 = $PhCH_2$; R_2 = H; R_3 = $C(CH_3)_3$. **9**, R_1 =  ; R_2 = OAc; R_3 = $C(CH_3)_3$.

Model 21 in a KBr disk. The ultraviolet spectra were measured in methanol solution. The nmr spectra were recorded with Varian Models A-60 and HA-60 spectrometers at 60 MHz in 5–10% deuteriochloroform solution with tetramethylsilane as an internal standard. Elemental analyses were determined by our microanalytical laboratory.

3-Methyl-7-phenoxyacetamido-3-cephem-4-carbonyl Chloride.—A suspension of 0.353 g (1.02 mmol) of 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylic acid in 40 ml of C_6H_6 was cooled in ice and stirred while 0.256 g (2 mmol) of oxalyl chloride and 1 drop of DMF were added. The reaction mixture was stirred at about (7–10°) for 45 min, and then the solvents were removed under reduced pressure. An nmr spectrum of the acid chloride showed the absence of any 2-cephem isomer.

The acid chloride (~200 mg) was dissolved in 10 ml of MeOH and stirred at 25° for 30 min. The solvent was removed, and the residue was redissolved in C_6H_6. The C_6H_6 solution was washed with H_2O, 3% HCl, and 10% $NaHCO_3$. The solution was dried over Na_2SO_4 and evaporated to dryness to give 0.160 g of methyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate. The ester was crystallized from EtOAc and was found to be identical with authentic material[1] by tlc, mp 135–137°, mmp 135–138°.

The acid chloride as prepared above was used in the following preparations. These preparations are presented as typical examples for the esterification of tertiary and primary alcohols, respectively. The esters listed in Table I are prepared analogously.

A. *t*-Butyl 3-Methyl-7-(phenoxyacetamido)-3-cephem-4-carboxylate.—A solution of 0.10 mol of the acid chloride (using proportions given above) in 1.0 l. of CH_2Cl_2 was added dropwise over a 3-hr period to a stirred solution of 92.5 g (1.25 mol) of *t*-butyl alcohol (freshly distilled from $KMnO_4$ and dried over molecular sieves) and 19.3 g (0.175 mol) of triethylamine (freshly distilled from phenyl isocyanate and dried over KOH pellets) in 650 ml of CH_2Cl_2 maintained under anhydrous conditions at ice bath temperature. The CH_2Cl_2 solution was washed with about 500 ml of H_2O and 100 ml of 3% HCl and evaporated to dryness. The residue was suspended in EtOAc, washed with 5% $NaHCO_3$ and H_2O, and then treated with 20 g of activated charcoal. The suspension was filtered and evaporated to dryness. The *t*-butyl ester crystallized from ether to give a total yield of 37.5 g (75%) of needles, mp 78–80°. From the neutral and basic washes was recovered 7.0 g of a mixture of Δ^2 and Δ^3 acids.

The nmr spectrum of the Δ^2 ester [δ ($CDCl_3$) C-2 H at 5.92, C-4 H at 4.66, $-OC(CH_3)_3$ at 1.50 ppm] was consistent with the proposed structure.

B. *p*-Methoxybenzyl 3-Methyl-7-(phenoxyacetamide)-2-cephem-4-carboxylate.—A solution of 2 mmol of the acid chloride in 20 ml of alcohol-free $CHCl_2$ was added dropwise over a 1-hr period to a stirred solution of 0.300 g (2.2 mmol) of *p*-methoxybenzyl alcohol and 0.300 g of triethylamine maintained at −50 to −75°. The solution was washed with H_2O and then 3% HCl and evaporated to dryness. The residue was suspended in EtOAc, washed with 5% $NaHCO_3$, dried over Na_2SO_4, and evaporated to dryness. The residue was crystallized from CCl_4 as needles, mp 108–110°. The nmr spectrum (C-2 H at 5.90, C-4 H at 4.80 ppm) was identical with that of authentic material.[2]

Chemistry of Cephalosporin Antibiotics. XIX. Transformation of Δ^2-Cephem to Δ^3-Cephem by Oxidation–Reduction at Sulfur

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Received September 17, 1969

A recent report from our laboratory details the final steps by which a penicillin can be converted into a cephalosporin.[1] A vital sequence in this synthesis is the conversion of a Δ^2-cephem ester (**1**) to a Δ^3-cephem ester (**3**) *via* the sulfoxide **2**. This process utilizes the concept that β,γ-unsaturated sulfoxides are thermodynamically more stable than the corresponding α,β-unsaturated sulfoxides.[2]

By contrast, an equilibrium mixture of cephem isomers before oxidation contains largely the unnatural

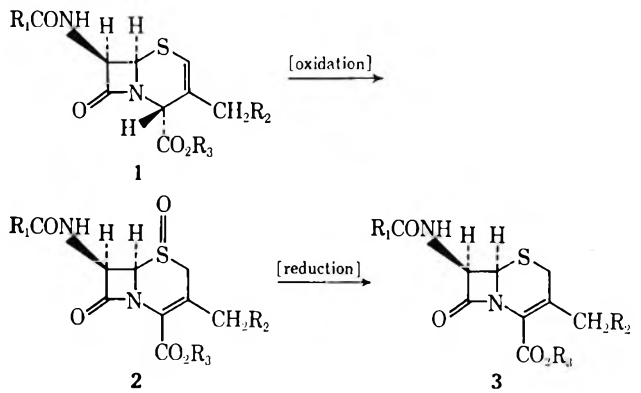
(1) J. A. Webber, E. M. Van Heyningen, and R. T. Vasileff, *J. Amer. Chem. Soc.*, **91**, 5674 (1969).

(2) D. E. O'Connor and W. I. Lyness, *ibid.*, **86**, 3840 (1964).

TABLE I
EXAMPLES OF CEPHEM SULFOXIDE FORMATION

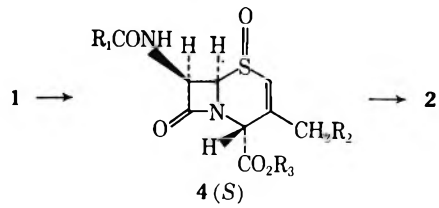
R_1	R_2	R_3	Starting sulfide isomer	Product sulfoxide isomer	Yield, %	Reaction conditions
$PhOCH_2$	H	*t*-Bu	Δ^2	Δ^2 (*R*)	0.8	A
$PhOCH_2$	H	*t*-Bu		Δ^2 (*S*)	93	A
$PhOCH_2$	H	*t*-Bu	Δ^2	Δ^3	100	A + isomerization
$PhOCH_2$	H	*t*-Bu	Δ^2	Δ^3	77	B
$PhOCH_2$	H	*t*-Bu	Δ^2	Δ^3	94	C
$C_4H_3SCH_2$ (2-thenyl)	OAc	CH_2CCl_3	Δ^3	Δ^3	62	A
$PhOCH_2$	OAc	$CH_2C_6H_4OCH_3$-*p*	$\Delta^2 + \Delta^3$	Δ^3	75	A
$PhOCH_2$	H	$-C(CH_3)_2CH{=}CH_2$	Δ^2	Δ^3	88	A
$PhOCH_2$	H	$CH_2C_6H_4NO_2$-*p*	Δ^2	Δ^3	90	A
$PhOCH_2$	H	CH_2CCl_3	Δ^3	Δ^3 (*R*)	0.5	D
				Δ^3 (*S*)	38	D
$PhOCH_2$	OH	*t*-Bu	Δ^2	Δ^3	77	A

Δ^2 isomer.[3] Woodward, *et al.*,[4] report *K* (normal/iso) = $^1/_3$ for the trichloroethyl ester of cephalothin[5] (**3**, R_1 = 2-thienylmethyl, R_2 = OAc, R_3 = H), and the desired Δ^3-cephem isomer must be isolated by elution chromatography. Since a Δ^2-cephem ester is a key intermediate in both the Woodward, *et al.*, cephalosporin synthesis, and that reported by Webber, *et al.*,[1] from our laboratory, the need for a facile, efficient method to achieve the $\Delta^2 \rightarrow \Delta^3$ transformation is clear.



Although a report indicates that Δ^2-cephem esters are resistant to mild oxidizing agents,[6] we have found that a large number of percarboxylic acids transform Δ^2-cephem esters into the corresponding Δ^3-cephem sulfoxides. Strong percarboxylic acids (*m*-chloroperbenzoic acid) gave high yields of sulfoxides (70–90%), providing temperature and solvent were maintained to minimize sulfone formation. Periodic acid gave satisfactory yields of sulfoxides in organic solutions, but weaker oxidizing agents, such as hydrogen peroxide and peracetic acid, required longer reaction times and gave lower yields. To prevent acidic decomposition of the cephalosporin nucleus, trifluoroperacetic and performic acids were used in a diluting solvent such as CH_2Cl_2. The addition of a hydroxylic solvent such as *i*-PrOH reduced the rate of sulfone formation. Some of the sulfoxides were not obtained in crystalline form, even though their nmr spectra indicated a high degree of purity. The oxidations are applicable to a variety of cephem compounds: Δ^2, Δ^3, or $\Delta^2 + \Delta^3$ mixtures. Representative examples are listed in Table I.

The initial products from the oxidation of Δ^2-cephem sulfides were the (*R*)- and (*S*)-Δ^2-sulfoxides. When these isomers were dissolved in a hydroxylic solvent, the Δ^3-cephem isomers were obtained. Oxidation in hydroxylic solvents gave the (*R*)- and (*S*)-Δ^3-cephem sulfoxides directly. The major product (**4** and **2**) in both double-bond isomers has been shown by comprehensive nmr studies to be the (*S*)-sulfoxide.[7] Difficulty in reducing Δ^3-cephem sulfoxides to Δ^3-cephem sulfides by a wide variety of conventional reducing agents[6] has prevented employment of this isomerization procedure in the past. The resistance of Δ^3-cephem sulfoxides to reduction is probably due to electronic factors since no obvious steric inhibition of the reducing agent is present. Both the β-lactam nitrogen and the α,β-unsaturated carboxyl function exert an electron-withdrawing effect which strengthens the sulfur–oxygen bond relative to that in a normal aliphatic sulfoxide.



We discovered that many common reducing agents are effective in the reduction of Δ^3-cephem sulfoxides if the sulfoxide is first activated by a reactive acid halide. For example, $Na_2S_2O_4$ did not reduce cephalosporin sulfoxides,[6] but when AcCl was added, reduction proceeded smoothly.

Several types of reducing agents were effective in the presence of a reactive acid halide: anionic reducing agents such as $S_2O_4^{2-}$ and I^- ions; cationic agents such as Sn^{2+}, Fe^{2+}, and Cu^+ ions; and trivalent phosphorus compounds, including phosphines and phosphites. These reagents reduced both cephalosporanic acid sulfoxides and their esters.

(3) Δ^2-Cephalosporanic acids are inactive as antibiotics.

(4) R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrüggen, *J. Amer. Chem. Soc.*, **88**, 852 (1966).

(5) A parenteral antibiotic having low toxicity, penicillinase resistance, and excellent activity against Gram-positive and Gram-negative bacteria marketed as KEFLIN (sodium cephalothin, Lilly) by Eli Lilly and Co.

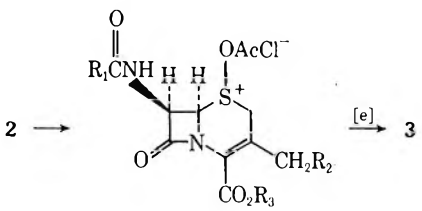
(6) J. D. Cocker, S. Eardley, G. I. Gregory, M. E. Hall, and A. G. Long, *J. Chem. Soc. C*, 1142 (1966).

(7) R. D. G. Cooper, P. V. DeMarco, C. F. Murphy, and L. A. Spangle, *ibid.*, in press.

The reductions proceeded smoothly in a wide variety of solvents such as DMF, THF, CH_2Cl_2, and CH_3CN. Even solvents in which the reactants are only partially soluble proved satisfactory.

Catalytic hydrogenation of Δ^3-cephem sulfoxides yielded only traces of reduced material even when large amounts of hydrogenation catalysts were employed. Inclusion of AcCl, however, effected the reduction in moderate yield.

We suggest that the "activating agent" reacts with the sulfoxide oxygen to form the sulfoxonium salt (**5**) which is much more reactive toward the reducing agent than the sulfoxide itself. Such activation of sulfoxides is apparent from the work of Jonsson[8] which showed that methyl *p*-tolyl sulfoxide racemizes rapidly at room temperature in Ac_2O containing 0.2 molar equiv of AcCl. Allenmark[9] has used I^-–AcCl–AcOH in a quantitative determination of dialkyl sulfoxides in AcOH, but added AcCl permits rapid determination.



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Several reagents such as PCl_3, PBr_3, $SiHCl_3$, and chloromethylene dimethyliminium chloride accomplished the reduction without external activation. These compounds all have acid halide character. The trihalophosphines reduce by donating the electron pair on phosphorous, while the success of the silanes and iminium halides probably involves hydride transfer subsequent to activation.

Experimental Section

Melting points were determined on a Mel-temp or Kofler melting point apparatus. Infrared spectra were determined with Perkin-Elmer Model 21. Thin layer chromatographic results were obtained on silica gel G, F254 plates. The nmr spectra were recorded with Varian Models A-60 and HA-60 spectrometers at 60 MHz in 5–10% deuteriochloroform solution with tetramethylsilane as an internal standard. Elemental analyses were determined by our microanalytical laboratory.

2,2,2-Trichloroethyl 3-Methyl-7-phenoxyacetamido-3-cephem-4-carboxylate.—To a stirred solution of 500 ml of CH_2Cl_2 containing 17.4 g (0.05 mol) of 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylic acid, 7.9 g (0.1 mol) of pyridine, and 14.9 g (0.1 mol) of 2,2,2-trichloroethanol was added dicyclohexylcarbodiimide (10.0 g, 0.05 mol). The reaction mixture was stirred at 25° for 90 min; then the dicyclohexylurea was removed by filtration. The organic solution was washed successively with cold 0.1 *N* HCl, saturated $NaHCO_3$, and H_2O, dried over $MgSO_4$, and evaporated *in vacuo*. The ester (9.5 g, 40%) was crystallized from ether: mp 114–116°; nmr ($CDCl_3$) δ 2.20 (3 H, s), 3.26, 3.46 (2 H, q, J = 18 Hz), 4.55 (2 H, s), 4.80, 4.95 (2 H, q, J = 12 Hz), 5.03 (1 H, d, J = 5 Hz), 5.85 (1 H, q, J = 4, 9 Hz), 6.8–7.4 (5 H, m), 7.6 (1 H, d, J = 9 Hz), showed pure Δ^3-cephem ester.

Anal. Calcd for $C_{18}H_{17}Cl_3N_2O_5S$: C, 45.06; H, 3.57; Cl, 22.17; N, 5.84. Found: C, 44.92; H, 3.86; Cl, 22.11; N, 5.89.

In a manner similar to that described above 2,2,2-trichloroethyl 3-acetoxymethyl-7-(2-thienylacetamido)-3-cephem-4-carboxylate was prepared in 62% yield. The ester crystallized from *i*-PrOH as needles: mp 120–122°;[10] uv (EtOH) 236 mμ (ϵ 11,900), 262 (7200); ir ($CHCl_3$) 1795, 1750, and 1690 cm^{-1}; nmr ($CDCl_3$) δ 2.07 (3 H, s), 3.39, 3.56 (2 H, q, J = 18 Hz), 3.83 (2 H, s), 4.75, 4.98 (2 H, q, J = 12 Hz), 4.85, 5.13, (2 H, q, J = 14 Hz), 4.99 (1 H, d, J = 5 Hz), 5.86 (1 H, q, J = 5, 9 Hz), 6.85–7.35 (4 H, m).

Anal. Calcd for $C_{18}H_{17}Cl_3N_2O_6S_2$: C, 40.95; H, 3.27; Cl, 12.14; N, 5.30; S, 20.15. Found: C, 41.19; H, 3.45; Cl, 12.23; N, 5.50; S, 19.91.

Representative Oxidation Reactions. A. *t*-Butyl 3-Methyl-7-phenoxyacetamido-2-cephem-4-carboxylate 1-Oxide.—To a stirred, cooled (in ice) solution of *t*-butyl 3-methyl-7-phenoxyacetamido-2-cephem-4-carboxylate (12.2 g, 0.03 mol) in CH_2Cl_2 (500 ml) over a 2-hr period was added a solution of 85% *m*-chloroperbenzoic acid (5.66 g, 0.028 mol) in CH_2Cl_2 (500 mol). The reaction mixture was washed successively with 10% $NaHCO_3$ and H_2O and then evaporated to give 12.0 g (93%) of a gummy product. The sulfoxide crystallized as prisms upon standing, mp 127–128°. The nmr spectrum of this compound showed it to be a Δ^2-cephem (*S*)-sulfoxide: ($CDCl_3$) δ 1.48 (9 H, d), 2.02 (3 H, s), 4.43 (2 H, s), 4.75 (1 H, d, J = 4 Hz), 4.95 (1 H, s), 6.15 (1 H, q, J = 4, 10 Hz), 6.70 (1 H, s), 6.8–7.5 (5 H, m), and 8.35 (1 H, d, J = 10 Hz).

Anal. Calcd for $C_{20}H_{24}N_2O_6S$: C, 57.13; H, 5.75; N, 6.66. Found: C, 57.16; H, 5.85; N, 6.59.

From the ether wash of the crystals above was obtained 0.110 g (0.8%) of another crystalline product, mp 160–161°. The nmr spectrum and elemental analysis of this compound also showed it to be a Δ^2 (*R*)-sulfoxide: ($CDCl_3$) δ 1.49 (9 H, s), 1.97 (3 H, s), 4.49 (2 H, s), 4.61 (1 H, s), 4.74 (1 H, d, J = 4 Hz), 5.55 (1 H, q, J = 4, 8 Hz), 6.17 (1 H, s), 6.8–7.5 (5 H, m), and 8.15 (1 H, d, J = 8 Hz).

Anal. Found: C, 57.30; H, 5.89; N, 6.71.

Both Δ^2-cephem sulfoxides, when dissolved in a hydroxylic solvent, were converted to the same Δ^3-cephem isomer produced by the performic acid oxidation cited below.

A. *p*-Methoxybenzyl 3-Acetoxymethyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-Oxide.—A mixture of Δ^2 and Δ^3 (1:3) isomers of *p*-methoxybenzyl 3-acetoxymethyl-7-phenoxyacetamidocephem-4-carboxylate (0.125 g) was dissolved in $CHCl_3$ (4 ml), cooled in ice, and stirred while 85% *m*-chloroperbenzoic acid (0.04 g) in $CHCl_3$ (2 ml) was added dropwise. After 4 hr the reaction mixture was washed with saturated $NaHCO_3$ and saturated NaCl. The organic solution was dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give 0.127 g of product. This crystallized from CH_3OH to give 0.095 g (75% yield) of isomerically pure Δ^3-cephem sulfoxide: mp 161–163°; nmr (DMSO-d_6) δ 2.0 (3 H, s), 3.75 (3 H, s), 3.60, 4.05 (2 H, q, J = 16 Hz), 4.7 (2 H, s), 4.68, 5.10 (2 H, q, J = 12 Hz), 5.25 (2 H, s), 6.0 (1 H, d, J = 4 Hz), 6.10 (1 H, q, J = 4, 10 Hz), 6.8–7.5 (5 H, m), and 8.20 (1 H, d, J = 10 Hz).

Anal. Calcd for $C_{26}H_{26}N_2O_9S$: C, 57.55; H, 4.83; N, 5.16. Found: C, 57.88; H, 5.14; N, 5.06.

B. *t*-Butyl 3-Methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-Oxide (Performic Acid as Oxidant).—A cooled (in ice) solution of 0.400 g of *t*-butyl 3-methyl-7-phenoxyacetamido-2-cephem-4-carboxylate in 20 ml of CH_2Cl_2 was stirred while 5 ml of AcOH containing 0.2 ml of 30% H_2O_2 was added dropwise. When the addition was complete, the reaction mixture was washed with H_2O and then with saturated $NaHCO_3$. The organic solution was dried over Na_2SO_4 and evaporated to dryness to give 0.32 g (77% yield) of the sulfoxide: nmr ($CDCl_3$) δ 1.51 (9 H, s), 2.10 (3 H, s), 3.23, 3.58 (2 H, q, J = 19 Hz), 4.5 (3 H, s + d, J = 4 Hz), 6.0 (1 H, q, J = 10 Hz), 6.8–7.4 (5 H, m), and 7.9 (1 H, d, J = 10 Hz).

C. *t*-Butyl 3-Methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-Oxide (Periodic Acid as Oxidant).—A solution of 0.200 g of *t*-butyl 3-methyl-7-phenoxyacetamido-2-cephem-4-carboxylate in 20 ml of Et_2O was stirred at 25° and titrated with a solution of periodic acid in Et_2O. No starting material was evident by tlc. The reaction mixture was washed successively with water and 10% $NaHCO_3$ and dried over Na_2SO_4. Evaporation of solvent gave 0.196 g of crude product which was then equilibrated ($\Delta^2 \rightarrow \Delta^3$) in CH_3OH. Nmr of the equilibrated sulfoxide was identical with that of the Δ^3-cephem sulfoxide produced above.

D. 2,2,2-Trichloroethyl 3-Methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-Oxide.—2,2,2-Trichloroethyl 3-methyl-7-phenoxyacetamido-3-cephem 4-carboxylate (1.61 g, 3.4 mmol) in glacial AcOH (10 ml) was cooled to the freezing point, and a

(8) E. Jonsson, *Tetrahedron Lett.*, 3675 (1967).

(9) S. Allenmark, *Acta Chem. Scand.*, **20**, 910 (1966).

(10) Reference 4, mp 120–123°.

solution of 30% H_2O_2 (0.76 g, 6.7 mmol) in glacial AcOH (5 ml) was added. The reaction mixture was stirred overnight, and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed twice with H_2O and once with 5% $NaHCO_3$, dried over Na_2SO_4, filtered, and evaporated to dryness to give 1.50 g of a yellow foam. Tlc showed the presence of three components, none of which was starting material. The crude product was chromatographed over silica gel (60 g) using a linear 100% benzene → 100% EtOAc gradient. The fractions were pooled according to purity as determined by tlc. The major component (0.900 g) was crystallized from acetone–ether yielding 0.620 g (38%) of (*S*)-sulfoxide: mp 176–178° dec; uv_{max} (EtOH) 216 mμ (ε 3000), 264 (sh), 268 (9350), 273 (sh); ir ($CHCl_3$) 1790, 1730, 1680, and 1040 cm^{-1}; nmr (DMSO-d_6) δ 2.13 (3 H, s), 3.74, 3.96 (2 H, t, J = 19 Hz), 4.70 (2 H, s), 5.04 (1 H, d, J = 5 Hz), 5.05, 5.17 (2 H, t, J = 12 Hz), 6.04 (1 H, q, J = 5, 10 Hz), 6.8–7.5 (5 H, m), 8.18 (1 H, d, J = 10 Hz).

Anal. Calcd for $C_{18}H_{17}Cl_3N_2O_6S$: C, 43.61; H, 3.46; Cl, 21.46; N, 5.81; S, 6.47. Found: C, 44.23; H, 4.02; Cl, 21.63; N, 5.65; S, 6.55.

A second component crystallized from acetone to give the (*R*)-sulfoxide (0.090 g, 0.5%) as prisms: mp 186–187°; uv_{max} (EtOH) quartet 217, 263 (sh), 267, and 274 (sh) mμ; ir ($CHCl_3$) 1780, 1730, 1630, and 1040 cm^{-1}; nmr (DMSO-d_3) δ 2.19 (3 H, d), 3.75, 4.19 (2 H, q, J = 16.5 Hz), 4.63 (2 H, s), 4.78 (1 H, d, J = 5 Hz), 5.08 (2 H, s), 5.65 (1 H, q, J = 5, 8 Hz), 6.8–7.5 (5 H, m), 9.32 (1 H, d, J = 8 Hz).

Anal. Found: C, 43.66; H, 3.66; Cl, 21.39; N, 5.70; S, 6.38.

Reducing Agent without External Activation. Phosphorus Trichloride.—(*S*)-2,2,2-Trichloroethyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide (2.00 g, 4.03 mmol) was dissolved in CH_2Cl_2 (100 ml) containing PCl_3 (3.2 g, 22 mmol). The solution was heated under reflux for 2.5 hr. After cooling to room temperature, the reaction was neutralized with a saturated solution of aqueous $NaHCO_3$, washed with H_2O, and dried over $MgSO_4$. Removal of solvent *in vacuo* yielded 1.65 g (85%) of reduced material, which crystallized from hot *i*-PrOH, mp 115–117°. The nmr, ir, and uv spectra and elemental analysis of the product were identical with those of an authentic sample of 2,2,2-trichloroethyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate.

Cationic Reducing Agent. Stannous Chloride.—(*S*)-2,2,2-Trichloroethyl 3-acetoxymethyl-7-(2-thienylacetamido)-3-cephem-4-carboxylate 1-oxide (2.0 g, 3.7 mmol) was dissolved in CH_3CN (15 ml) and DMF (6 ml) and stirred at 0°. Stannous chloride (624 mg, 4.04 mmol) and AcCl (1.2 g, 1.54 mmol) were added. This mixture was stirred at 0° for 1 hr and then at room temperature for an additional hour. The CH_3CN was removed *in vacuo;* the residue was poured into H_2O and extracted into EtOAc. The organic solution was washed with 3% HCl solution, 5% $NaHCO_3$ solution, and then with H_2O. After drying over Na_2SO_4, the solvent was removed to give 1.9 g (98%) of product which crystallized from hot *i*-PrOH, mp 120–122°, and was identical in all respects with authentic 2,2,2-trichloroethyl 3-acetoxymethyl-7-(2-thienylacetamido)-3-cephem-4-carboxylate.

Registry No.—2,2,2-Trichloroethyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate, 24647-47-0; 2,2,2-trichloroethyl 3-acetoxymethyl-7-(2-thienylacetamido)-3-cephem-4-carboxylate, 5317-29-3; *t*-butyl 3-methyl-7-phenoxyacetamido-2-cephem-4-carboxylate 1-oxide (*S*), 24647-49-2; *t*-butyl 3-methyl-7-phenoxyacetamido-2-cephem-4-carboxylate 1-oxide (*R*), 24647-50-5; *p*-methoxybenzyl 3-acetoxymethyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide, 24670-41-5; *t*-butyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide, 24647-51-6; 2,2,2-trichloroethyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide (*S*), 24689-52-9; 2,2,2-trichloroethyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide (*R*), 24689-53-0.

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A Novel Diaryl Ether, LL-V125α, from a Fungus of the Order Sphaeropsidales

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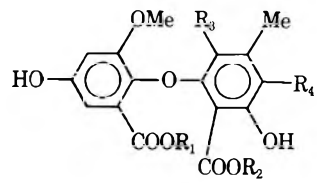
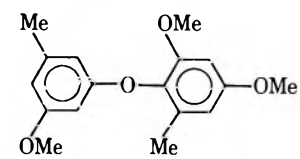
Diaryl ethers have been isolated from plants[1] and sea sponges.[2] To our knowledge the only microbial metabolite of this type isolated so far is asterric acid, I.[3] The closely related compounds, erdin hydrate, II, and geodin hydrate, III, have been obtained by chemical conversion of natural products[4] and the elaboration of III by mutants of *Aspergillus terreus* has been demonstrated.[5] Diphenyl ethers have been obtained as



I, $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$
II, $R_1 = R_2 = R_3 = R_4 = H$
III, $R_1 = CH_3$; $R_2 = H$; $R_3 = R_4 = Cl$

breakdown products from *Lichen depsidones*[6,7] and, in particular, one such compound was characterized as the trimethyl ether of alectol, IV. We have isolated



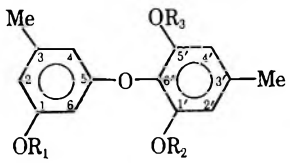
IV

the novel metabolite, 5′-methoxy-5,6′-oxydi-*m*-cresol (V), from a fungus of the order Sphaeropsidales (Lederle culture V125). By *in vitro* testing V had weak antifungal activity.

Compound V has the formula $C_{15}H_{16}O_4$ (*m/e* 260). The nmr spectrum of V in $CDCl_3$ shows sharp, three-proton singlets at δ 2.05 and 2.20 (2 CH_3, aromatic) and 3.75 (OCH_3, aromatic), two broad one-proton exchangeable singlets at 5.20 and 4.57 (2 H, phenolic),

(1) P. Bernfeld, "Biogenesis of Natural Compounds," Pergamon Press, The Macmillan Co., New York, N. Y., 1963, p 626.
(2) P. R. Burkholder, M. Guez, and G. M. Sharma, American Society of Pharmacognosy, Tenth Annual Meeting, Aug 18–22, 1969, School of Pharmacy, Oregon State University, Corvallis, Ore.
(3) R. F. Curtis, C. H. Hassall, C. W. Jones, and T. W. Williams, *J. Chem. Soc.*, 4838 (1960).
(4) C. T. Calam, A. E. Clutterbuck, A. E. Oxford, and H. Raistrick, *Biochem. J.*, **41**, 458 (1947).
(5) R. F. Curtis, P. C. Harries, C. H. Hassall, and J. D. Levi, *ibid.*, **90**, 43 (1964).
(6) Y. Asahina and F. Fugikawa, *Ber.*, **67**, 163 (1934).
(7) Y. Asahina and S. Shibata, "Chemistry of Lichen Substances," Japan Society for the Promotion of Science, Ueno, Tokyo, 1954, p 118.

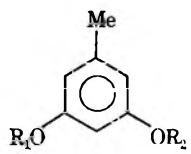
and a multiplet (5 H, aromatic) at 6.28. The dimethyl and diethyl ethers VI and VII were prepared in addition to the diacetate derivative VIII. The nmr



V, $R_1 = R_2 = H$; $R_3 = CH_3$
VI, $R_1 = R_2 = R_3 = CH_3$
VII, $R_1 = R_2 = C_2H_5$; $R_3 = CH_3$
VIII, $R_1 = R_2 = COCH_3$; $R_3 = CH_3$
IX, $R_1 = R_2 = R_3 = H$

spectrum of the dimethyl ether VI showed aromatic methoxy groups at δ 3.75 and 3.84 and, hence, one of the newly formed methoxy groups is in the same chemical environment as the one already present on the parent compound.

Reagents frequently used to cleave ethers such as sodium in liquid ammonia[8-10] or in refluxing pyridine[11] left V mostly unaltered. Procedures such as refluxing with hydriodic acid and phenol or fusion with KOH, both of which cleave IV,[5,7] merely split the methoxy groups of V to give IX. Treatment of VI with sodium in liquid ammonia gave small amounts of the mono and dimethyl ethers (X and XI) of orcinol (XII). However, similar treatment of the diethyl ether VII gave ~80% yields of the ethyl and methyl ethyl ethers XIII and XIV of orcinol. Clearly, then, V consists of or-



X, $R_1 = H$; $R_2 = CH_3$
XI, $R_1 = CH_3$; $R_2 = CH_3$
XII, $R_1 = R_2 = H$
XIII, $R_1 = C_2H_5$; $R_2 = H$
XIV, $R_1 = C_2H_5$; $R_2 = CH_3$

cinol, XII, connected through one of its oxygen atoms to its own monomethyl ether (X). A number of facts show that the bond with the second orcinol moiety is formed at the position *para* to the methyl group thus establishing V as the structure of the metabolite. This structure satisfies the condition that upon formation of the dimethyl ether the newly formed methoxy group at the 1′ position is in the same chemical environment as the original group at 5′. If the connecting bond were formed at either of the positions *ortho* to the methyl group, the dimethyl ether from both compounds would be identical with the alectol material (IV). Since VI failed to give a quinone under oxidative conditions which produce 2-methyl-6-methoxy-1,4-benzoquinone from IV and since the aryl ether linkage of VI was stable to conditions which cleaved IV, both of the latter modes of attachment are eliminated.

(8) P. A. Sartoretto and F. J. Sowa, *J. Amer. Chem. Soc.*, **59**, 603 (1937).
(9) C. D. Hurd and G. L. Oliver, *ibid.*, **81**, 2795 (1959).
(10) E. J. Strojny, *J. Org. Chem.*, **31**, 1662 (1966).
(11) V. Prey, *Ber.*, **76**, 156 (1943).

Experimental Section[12]

Fermentation and Isolation.—About 300 l. of medium consisting of 3% glucose, 0.2% NH_4OAc, 0.1% Na_2SO_4, 0.75% K_2HPO_4, 0.03% KCl, 0.01% $Mg(OAc)_2 \cdot 4H_2O$, 0.002% $FeCl_3 \cdot 6H_2O$, and 0.1% Yeastamine 95 (A. E. Staley Manufacturing Co., Decator, Ill.) with pH adjusted to 6.5 were inoculated with 12 l. of a 48-hr vegative suspension of Lederle culture V125 grown on a medium consisting of 2% Edamine (Sheffield Chemical Co., Norwich, N. Y.), 2% glucose, and 0.5% corn steep liquor (pH adjusted to 6.5). Fermentation proceeded for 140 hr at 28° using 1/2 v/v/min aeration and under mechanical stirring at 300 rpm. The pH of the harvest mash was 5.0. The broth was clarified by filtration with diatomaceous earth and the beer was extracted with equal volume of $CHCl_3$. The concentrated extract ~50 g was passed over a kilogram of acid-washed Davison 62 grade silica gel using the solvent 2% ether in CH_2Cl_2. The sixth–tenth holdback volumes yielded an oil which did not crystallize from dry solvents. The material did crystallize as the hemihydrate from $CHCl_3$–hexane to give 23 g of off-white crystals: mp 121.5–122.5°; λ_{max} (MeOH) 225 nm (ϵ 21,500) (sh), 275 (5100) and 282 (5400); λ_{max} (methanolic NaOH) 235 nm (ϵ 18,800) (sh) and 290 (5650).

Anal. Calcd for $C_{16}H_{16}O_4 \cdot 0.5H_2O$: C, 66.91; H, 6.22. Found: C, 67.14; H, 5.90 (*m/e* 260).

Derivatives of V.—The diacetate VIII was made using pyridine–acetic anhydride. The pure material was obtained by eluting with $CH_3COOC_2H_5$–hexane from silica gel: mp 75–76°; λ_{max} (MeOH) 225 nm (ϵ 19,600) (sh) and 277 (3440).

Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.92. Found: C, 66.33; H, 5.92.

Surprisingly, starting material only was isolated following treatment of V with CH_2N_2. Using $(CH_3)_2SO_4$ and 4 *N* NaOH, VI was prepared: mp 91–92°; λ_{max} (MeOH) 227 nm (ϵ 20,200) (sh), 272 (4900) and 282 (5300).

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.77; H, 6.83.

The diethyl ether VII was prepared using $(C_2H_5)_2SO_4$ and 4 *N* NaOH to get a colorless oil which could be distilled at 150° (70 μ): λ_{max} (MeOH) 225 nm (ϵ 22,400) (sh), 277 (5050) and 282 (5400).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 77.12; H, 7.65. Found: C, 77.01; H, 7.46.

Reactions of V and VI.—An attempt to cleave 1.3 g (5 mmol) of V by fusion with KOH[6] gave 0.90 g of oil following silica gel chromatography. The material was purified further by partition chromatography over diatomaceous earth using the system hexane–$CH_3COOC_2H_5$–CH_3OH–H_2O (80/20/15/6). The tenth–twelfth holdback volumes yielded 500 mg of colorless oil which spectral data showed to be IX: λ_{max} (MeOH) 220 nm (ϵ 21,900) (sh), 272 (4500) and 278 (4900); δ ($CDCl_3$) 2.02 (3 H, singlet), 2.19 (3 H, singlet), 6.27 (5 H, mulitplet), 7.73 (1 H, broad exchangeable singlet) and 8.53 (2 H, broad exchangeable singlet).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 67.67; H, 5.94.

About 1.3 g (5 mmol) of VI and 3.5 g of phenol were refluxed in 30 ml of 57% HI for 4.5 hr. Work-up of the reaction mixture gave a 65% yield of XI.

Attempted oxidation of VI in acetic acid using saturated $K_2Cr_2O_7$ solution[6] gave only starting material.

Cleavage of Aryl Ether Linkages of VI and VII.—The sodium in liquid ammonia method used to cleave thalicarpine[13] failed to split V.

When VI was subjected to the same procedure, a small yield (20%) of an oil was obtained. The oil could be distilled at 90° (70 μ) to get crystals; mp 62–63°, which proved to be X: λ_{max} (MeOH) 222 nm (ϵ 7250) (sh), 272 (1380) and 280 (1380).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.20; H, 7.17.

(12) Melting points were taken in capillary tubes and are uncorrected. Nmr spectra were recorded on a Varian A-60 instrument with trimethylsilane as internal standard. The uv spectra were made using a Cary 60 recording spectrophotometer and the mass spectrum was run on an AE-1 MS9 direct inlet mass spectrometer. Purity of compounds was determined on precoated thin layer chromatography plates of silica gel F-254 (0.25 mm) obtainable from Brinkmann Instruments, Westbury, N. Y. Systems varied from 5 to 100% $CH_3COOC_2H_5$ in hexane.

(13) S. M. Kupchan and N. Yokohama, *J. Amer. Chem. Soc.*, **86**, 2177 (1964).

This material was identical with authentic X prepared by standard methods.[14]

In a repeat of this experiment using a longer reaction time only a small yield (about 15%) of a colorless oil was recovered which could be distilled at 75° under 80 μ. Spectral data showed the oil to be XI: δ (CCl_4) 2.25 (3 H, singlet), 3.70 (6 H, singlet) and 6.19 (3 H, broad singlet).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.13; H, 7.88.

When 1.0 g (~3 mmol) of VII was treated with sodium in liquid ammonia, an ether extract yielded 470 mg of a light yellow oil which was purified over 62 grade Davison silica gel (2% $CH_3COOC_2H_5$ in hexane) to get 380 mg of a colorless oil. This oil could be distilled at 80° (100 μ). Spectral data showed the oil to be XIV: λ_{max} (MeOH) 223 nm (ε 7500) (sh), 273 (1600) and 280 (1660); δ (CCl_4) 1.35 (3 H, triplet J = 7 Hz), 2.23 (3 H, singlet), 3.70 (3 H, singlet), 3.90 (2 H, quartet, J = 7 Hz) and 6.15 (3 H, singlet).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.31; H, 8.47.

Work-up of the reaction mixture on the acid side yielded by ether extraction 370 mg of an oil which was purified by partition chromatography over 120 g of diatomaceous earth using heptane saturated with MeOH. The third and fourth holdback volumes gave 300 mg of an oil which upon distillation at 90° (100 μ) gave crystals, mp 52–53°, which proved to be XIII: λ_{max} (MeOH) 225 nm (ε 8360) (sh), 275 (1670) and 282 (1670); δ (CCl_4) 1.32 (3 H, triplet J = 7–8 Hz), 2.17 (3 H, singlet), 3.83 (2 H, quartet, J = 7–8 Hz), 5.90 (1 H, broad exchangeable singlet) and 6.08 (3 H, singlet).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.72; H, 7.83.

Hence, it may be noted that the ease of ether cleavage in V, VI, and VII is increased significantly as R_2 goes from H to CH_3 to C_2H_5.

Registry No.—V, 24741-92-2; VI, 24741-93-3; VII, 24741-94-4; VIII, 24741-95-5; IX, 24741-96-6; X, 3209-13-0; XI, 4179-19-5; XIII, 24741-99-9; XIV, 24742-00-5.

Acknowledgment.—We wish to thank Dr. P. Shu and associates for large-scale fermentation and processing, Mr. L. Brancone and staff for elemental analyses, Mr. W. Fulmor and associates for spectral data, and Dr. H. Tresner for culture isolation and classification.

(14) H. Walbaum and A. Rosenthal, *Ber.*, **67**, 770 (1924).

Photochemistry of Cycloalkenes. VII. Limonene[1]

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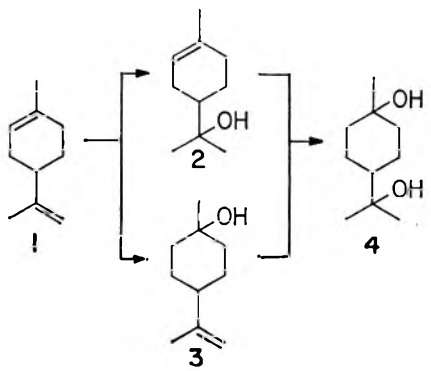
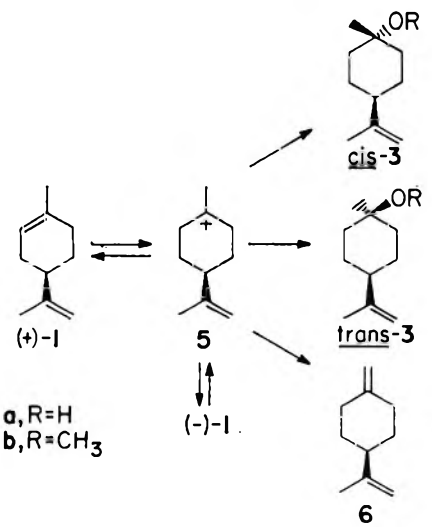
Recent studies have shown that photosensitized irradiation of cyclohexenes and -heptenes in hydroxylic solvents results in a light-initiated protonation of the olefin.[2,3] Since this behavior is specifically limited to six- and seven-membered-ring olefins, photoprotonation should afford the unique synthetic advantage of permitting the selective protonation of a cyclohexene or -heptene moiety of a complex molecule in the presence of other double bonds contained in either a larger ring or an acyclic environment.[2] This synthetic capability has now been demonstrated in the case of the diene limonene (**1**).



Acid-catalyzed hydration of limonene affords a mixture of products, including α- (**2**) and β-terpineol (**3**) and terpin (**4**), resulting from competing protonation of both double bonds.[4] In one case in which selective reaction was observed, attack occurred at the C_8–C_9 double bond to afford α-terpineol (**2**).[5] By contrast it has now been found that xylene-sensitized irradiation of (+)-limonene [(+)-**1**] in aqueous solution affords a 1.2:1 mixture of *cis*- and *trans*-β-terpineol (**3a**), respectively, as well as a small amount of the exocyclic isomer **6** with no detectable formation of the C_8–C_9 addition products α-terpineol (**2**) or terpin (**4**). Likewise, irradiation in methanolic solution affords a 1.6:1 mixture of the corresponding methyl ethers *cis*- and *trans*-**3b** as the only detectable addition products. Thus photoprotonation affords a powerful method of effecting reaction selectively at the C_1–C_2 position of limonene and, by analogy, inducing selective protonation of any cyclohexene or -heptene chromophore in the presence of an acyclic, exocyclic, or larger ring cyclic olefin.



It is of further interest to note that the recovered unreacted limonene was found to have undergone extensive racemization (84%) as would be expected for

(1) Part VI: P. J. Kropp and H. J. Krauss, *J. Amer. Chem. Soc.*, **91**, 7466 (1969).

(2) P. J. Kropp and H. J. Krauss, *ibid.*, **89**, 5199 (1967).

(3) J. A. Marshall, *Accounts Chem. Res.*, **2**, 33 (1969), and references cited therein.

(4) For a recent review of the chemistry of limonene, see J. Verghese, *Perfum. Essent. Oil Rec.*, **59**, 439 (1968).

(5) L. Kuczynski and H. Kuczynski, *Rocz. Chem.*, **25**, 432 (1951).

the reversible formation of the symmetrical carbonium ion intermediate **5**. This is further support for the previously proposed intermediacy of a free carbonium ion in the photoaddition of hydroxylic media to cyclohexenes and -heptenes.[2,3]

Experimental Section[6]

Irradiation of (+)-Limonene. A. Under Aqueous Conditions.—A solution containing 3.0 g of limonene, $[\alpha]^{22}D$ +112°, and 3.0 g of *m*-xylene in 150 ml of 50% aqueous *t*-butyl alcohol containing 1% sulfuric acid was irradiated for 2 hr. Gas chromatographic analysis revealed the continued presence of limonene (17%) and the formation of the diene **6** (2%), a 1.2:1 mixture of *cis*- and *trans*-β-terpineol (**3**, 74%), and several unidentified minor products.

The reaction mixture was neutralized with sodium hydroxide solution and the organic materials were isolated by extraction with ether in the usual fashion. Isolation by preparative gas chromatography of the first component afforded a colorless liquid, *m/e* 138, which was not further characterized but is assumed to be *p*-menth-8-ene.[7]

Isolation of the second component afforded a colorless liquid [*m/e* 136 (34), 93 (100), and 79 (57)] which exhibited an infrared spectrum identical with that of *p*-mentha-1(7),8-diene (**6**).[8] Isolation of the third component afforded recovered limonene, $[\alpha]^{30}D$ +18° (*c* 0.20, ethanol).

Isolation of the fourth component afforded *trans*-**β-terpineol** as colorless needles: mp 28–28.5° (sealed capillary); nmr spectrum τ 5.37 (s, 2, CH_2-9), 8.30 (s, CH_3-10), and 8.81 (s, CH_3-7); *m/e* 136 (52), 121 (32), 107 (32), 99 (32), 93 (60), 71 (100), 69 (41), 68 (34), and 43 (64). The infrared spectrum was identical with that reported by Mitzner, *et al.*, for "*cis*-β-terpineol"[9] and with that reported by Henbest and McElhinney for the "*trans*" isomer.[10]

Isolation of the final component afforded *cis*-**β-terpineol** as colorless needles: mp 33–34° (sealed capillary); nmr spectrum τ 5.36 (s, 2, CH_2-9), 8.31 (s, CH_3-10), and 8.79 (s, CH_3-7); *m/e* 154 (tr), 136 (84), 121 (42), 108 (28), 107 (48), 94 (19), 52 (93), 84 (20), 79 (24), 71 (100), 69 (42), 68 (29), 67 (20), 58 (20), 55 (23), and 43 (64). The infrared spectrum was identical with that reported for "*trans*-β-terpineol" by Mitzner, *et al.*,[9] and for the "*cis*" isomer by Henbest and McElhinney,[10] lit.[10] mp 36°.

B. In Methanol.—A 150-ml methanolic solution containing 3.0 g of (+)-limonene and 3.0 g of *m*-xylene was irradiated for 10 hr. Gas chromatographic analysis revealed the continued presence of limonene (6%) and the formation of *p*-mentha-1(7),8-diene (**6**) and the ethers *cis*- and *trans*-**3b** in yields of 39, 28, and 18%, respectively.

Isolation of the principal ether product afforded *cis*-*p*-**menth-8-en-1-yl methyl ether** as a colorless liquid: λ_{max} 6.02 and 11.22 μ; nmr spectrum τ 5.31 (s, 2, CH_2-9), 6.78 (s, 3, CH_3O–), 8.29 (s, CH_3-10), and 8.83 (s, 3, CH_3-7); *m/e* 168.1531 (calcd for $C_{11}H_{20}O$: 168.1514), 85 (100), 72 (36), 55 (64), 43 (34), and 39 (50).

Isolation of the minor ether component afforded *trans*-*p*-**meth-8-en-1-yl methyl ether** as a colorless liquid: λ_{max} 5.98 and 11.16 μ; nmr spectrum τ 5.33 (s, 2, CH_2-9), 6.85 (s, 3, CH_3O–), 8.29 (s, CH_3-10), and 8.91 (s, 3, CH_3-7); *m/e* 168.1524 (calcd for $C_{11}H_{20}O$: 168.1514), 136 (41), 93 (44), 72 (49), 69 (45), 55 (60), 43 (100), 42 (79), 41 (66), 40 (44), and 39 (52).

(6) Infrared spectra were obtained on neat samples with a Perkin-Elmer Infracord spectrophotometer. Nuclear magnetic resonance spectra were determined in chloroform-d_1 solution with a Varian HA-100 spectrometer, using tetramethylsilane as an internal standard. Gas chromatographic analyses were performed on an Aerograph 90-P instrument using 10 ft × 0.25 in. columns packed with 20% SE-30 or Carbowax 20M on 60–80 mesh Chromosorb W. Mass spectra were obtained using an Atlas Model CH-4 or SM-1 spectrometer. Irradiations were conducted using a Hanovia 450-W, medium-pressure mercury arc and a water-cooled Vycor immersion well. Vigorous stirring of the reaction mixture was effected by the introduction of a stream of nitrogen through a jet opening in the bottom of the outer jacket.

(7) Some reduction normally accompanies the photoprotonation of cyclohexenes; see J. A. Marshall and A. R. Hochstetler, *Chem. Commun.*, 296 (1968).

(8) B. M. Mitzner, E. T. Theimer, and S. K. Freeman, *Appl. Spectrosc.*, **19**, 169 (1965).

(9) B. M. Mitzner and S. Lemberg, *Amer. Perfum. Cosmet.*, **81** (3), 25 (1966); B. M. Mitzner, V. J. Mancini, S. Lemberg, and E. T. Theimer, *Appl. Spectrosc.*, **22**, 34 (1968).

(10) H. B. Henbest and R. S. McElhinney, *J. Chem. Soc.*, 1834 (1959).

Registry No.—(+)-**1**, 5989-27-5; *cis*-**3a**, 20288-25-9; *trans*-**3a**, 20288-26-0; *cis*-**3b**, 24655-71-8; *trans*-**3b**, 24655-72-9.

Acknowledgment.—The technical assistance of J. Alvis is gratefully acknowledged.

Studies in the Ganglioside Series. V. Synthesis of 2-Acetamido-2-deoxy-*O*-β-D-glucopyranosyl-(1→3)-*O*-β-D-galactopyranosyl-(1→4)-D-glucose[1]

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In recent communications[2-4] we described a new, highly stable and reactive hexosaminyl bromide of type III which facilitates the synthesis of aminosaccharides. We now report the synthesis of the title compound (VI, Chart I). This trisaccharide has been isolated from hydrolysates of the polysaccharides found in human milk.[5,6] It is structurally related to the so-called "ganglio-*N*-triose-II"[7] which is inherent in the molecule of the abnormal ganglioside accumulating in brain tissue with Tay–Sachs disease.[8,9]

In an earlier report[10] we have shown that selective substitution of lactose can be achieved *via* its isopropylidene derivative I and that bromo sugars react preferentially with the equatorial C-3 hydroxyl group of the benzyl lactoside II under Koenigs–Knorr conditions.

The benzyl lactoside II, previously isolated as a viscous mass, could now be obtained in pure crystalline form. It was observed that hydrolysis of I with hot aqueous acetic acid, a method commonly employed for the removal of an isopropylidene group, was invariably accompanied by partial deacetylation. Trifluoroacetic acid was found to be more suitable. The hydrolysis is carried out in chloroform containing 10% of the reagent and is complete after 20–30 min, whereby only traces of by-products are formed. While this method was being practiced in our laboratory, Goodman[11] reported the use of 90% aqueous trifluoroacetic acid for the hydrolysis of ketals in various sugar derivatives which were, however, devoid of acetoxyl groups.

The Koenigs–Knorr reaction of II with the bromide III afforded, after column chromatography, the pure substituted trisaccharide IV. Catalytic de-*O*-acylation

(1) This work was supported by U. S. National Institutes of Health, PL 480, Agreement No. 425115.

(2) D. Shapiro, A. J. Acher, and E. S. Rachaman, *J. Org. Chem.*, **32**, 3767 (1967).

(3) A. J. Acher and D. Shapiro, *ibid.*, **34**, 2652 (1969).

(4) D. Shapiro and A. J. Acher, *ibid.*, in press.

(5) R. Kuhn and H. H. Baer, *Chem. Ber.*, **89**, 504 (1956).

(6) R. Kuhn, A. Gauhe, and H. H. Baer, *ibid.*, **89**, 1027 (1956).

(7) R. Kuhn and H. Wiegandt, *ibid.*, **96**, 866 (1963).

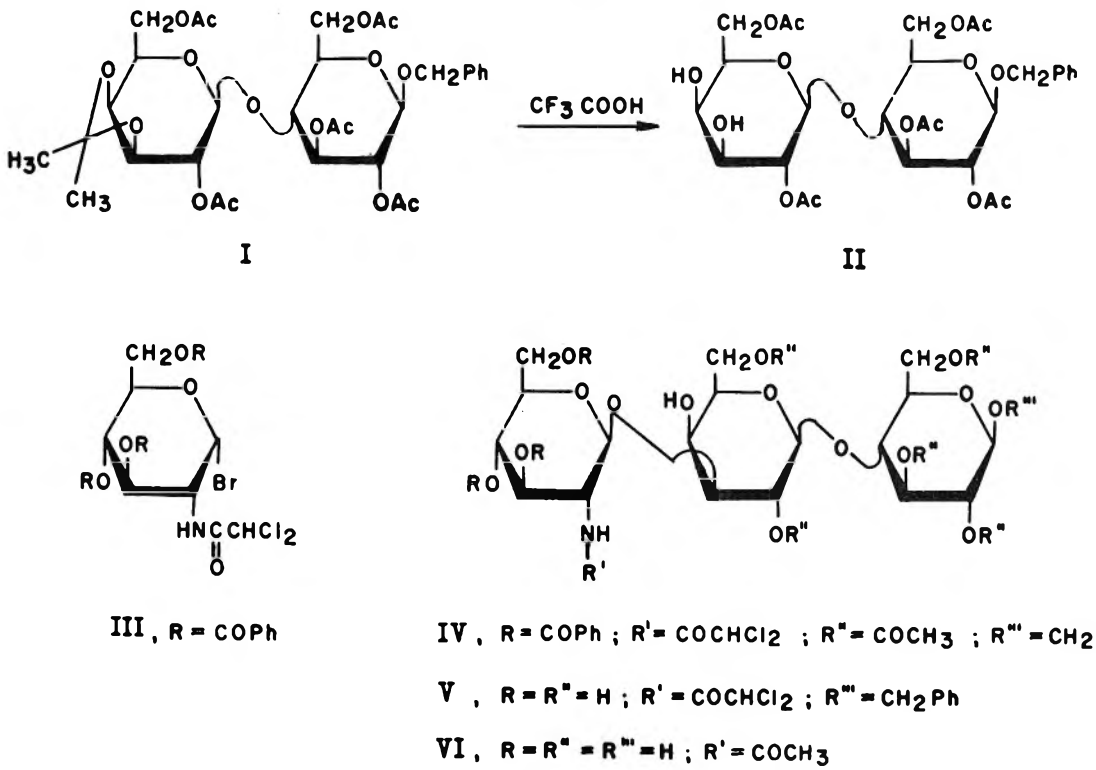
(8) L. Svennerholm, *Biochem. Biophys. Res. Commun.*, **9**, 436 (1962).

(9) L. Svennerholm, *J. Neurochem.*, **10**, 613 (1963).

(10) D. Beith-Halahmi, H. M. Flowers, and D. Shapiro, *Carbohyd. Res.*, **5**, 25 (1967).

(11) L. Goodman, *ibid.*, **7**, 510 (1968).

CHART I



under very mild conditions gave the dichloroacetyl derivative V, whose structure was confirmed by periodate oxidation. Hydrogenation of the latter compound resulted both in debenzylation and conversion of the dichloroacetyl into the acetyl group. In view of the lability of the 1→3 bond to alkali, the latter reaction is preferable to hydrolysis by dilute barium hydroxide previously reported.[2] The final trisaccharide (VI) thus obtained showed identity with the natural product in melting point and optical rotation.

Experimental Section

Benzyl 4-*O*-(2,6-Di-*O*-acetyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (I).—The compound was prepared following the procedure described previously.[10] The syrupy product eluted from the silica gel column could be crystallized from 2-propanol, $[\alpha]^{23}D$ −10.2° (c 2, chloroform), mp 85–86°.

Anal. Calcd for $C_{32}H_{42}O_{16}$: C, 56.30; H, 6.20. Found: C, 56.58; H, 6.16.

Benzyl 4-*O*-(2,6-Di-*O*-acetyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (II).—A solution of I (5.0 g) in chloroform (45 ml) was treated at room temperature for 20–30 min with trifluoroacetic acid containing 1% of water (5 ml). The optimal reaction time was determined by tlc. The solution was concentrated *in vacuo* at room temperature, and the reagent was completely removed by coevaporation with toluene. Tlc (ethyl acetate–benzene 3:1) showed one reaction product and only traces of deacetylation. Dichloromethane–ethyl acetate (4:1) eluted from a silica gel column pure starting material (1.1 g, 22%). A 1:1 mixture of the same solvents yielded II (3.18 g, 67%), which was crystallized from ether: $[\alpha]^{23}D$ −28° (c 2, chloroform), mp 158–159°; reported[10] as a syrup, $[\alpha]D$ −23.2° (chloroform).

Anal. Calcd for $C_{29}H_{38}O_{16}$: C, 54.20; H, 5.96. Found: C, 54.18; H, 5.83.

Benzyl (2-Deoxy-2-dichloroacetamido-3,4,6-tri-*O*-benzoyl-β-D-glucopyranosyl)-(1→3)-*O*-(2,6-di-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (IV).—To a solution of II (1.0 g) in dry dichloroethane (30 ml) were added mercuric cyanide (0.75 g) and 3,4,6-tri-*O*-benzoyl-2-deoxy-2-dichloroacetamido-α-D-glucopyranosyl bromide (III, 3.5 g), and the reaction was allowed to proceed with stirring at 40° for 7 days. The cooled solution was poured into a mixture of ice–water (100 ml) and chloroform (150 ml). The chloroform layer was washed several times with cold water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel Davison, grade 950, 60–200 mesh (200 g), from which IV was eluted with methylene chloride–ethyl acetate (84:16). Crystallization from alcohol and a few drops of hexane gave 0.4 g (19%) of pure IV: tlc (ethyl acetate) R_{III} 1.4; mp 125–127°; $[\alpha]^{18}D$ −50° (c 1, chloroform); ir (KBr) 5.9, 6.4 (amide), 11, 2 (β-glycoside), and 12.3 μ (CCl). The nmr spectrum showed signals at τ 2–2.8 (20 aromatic protons), 7.84–7.97 (15 acetyl protons), and 4.15 (1 dichloroacetyl proton).

Anal. Calcd for $C_{58}H_{61}Cl_2NO_{24}$: C, 56.77; H, 5.01; Cl, 5.78. Found: C, 56.82; H, 4.91; Cl, 5.55.

Benzyl (2-Deoxy-2-dichloroacetamido-*O*-β-D-glucopyranosyl)-(1→3)-*O*-(β-D-galactopyranosyl)-(1→4)-β-D-glucopyranoside (V).—For de-*O*-acylation, compound IV (350 mg) was dissolved in chloroform (3 ml) and absolute methanol (20 ml). The solution was cooled to −10° and a solution of 1 *N* barium methoxide (0.3 ml) was added. After standing at 2–5° overnight, the solution was neutralized with Dowex 50 X 8, 50–100 mesh, H^+ form. The filtrate was evaporated *in vacuo*, and the residue was crystallized from absolute alcohol and a few drops of ether: tlc (benzene–methanol, 1:1) R_{IV} 0.54, $R_{lactose}$ 2.5; yield 180 mg (90%); mp 194–195°; $[\alpha]^{18}D$ −22.6° (c 0.8, methanol). It consumed 2.08 mol of sodium metaperiodate during 72 hr at 40°.

Anal. Calcd for $C_{27}H_{39}Cl_2NO$: Cl, 10.07. Found: Cl, 10.22.

2-Acetamido-2-deoxy-*O*-β-D-glucopyranosyl-(1→3)-*O*-β-D-galactopyranosyl-(1→4)-D-glucose (VI).—The preceding compound (V, 150 mg) was hydrogenated in methanol (50 ml) with 10% palladium-on-charcoal (2 g) at 40° and 55 psi. After 48 hr, the suspension was allowed to cool and filtered through a Celite bed. The residue resulting from the evaporation of the solvent crystallized from a mixture of ethanol (4 ml), ether (1 ml), and a few drops of water: yield 75 mg (64.6%); mp 205–209°; $[\alpha]^{20}D$ +39.5° (c 0.8, water) (reported[6] mp 201–202°; $[\alpha]D$ +40.7°); tlc (1-butanol–acetone–water, 4:5:1) R_{VIII} 0.8, $R_{lactose}$ 0.7.

Anal. Calcd for $C_{20}H_{35}NO_{16}$: C, 44.03; H, 6.47. Found: C, 43.68; H, 6.63.

Registry No.—I, 18404-74-5; II, 18404-75-6; IV, 24741-58-0; V, 24741-59-1; VI, 24741-60-4.

Reaction of Malononitrile with Carbon Disulfide in an Aqueous Alkaline Medium

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A characteristic compound, 4,6-diamino-3,5-dicyano-2H-1-thiopyran-2-thione (**1**), was easily obtained in good yield from malononitrile and carbon disulfide in aqueous alkali. Compound **1** also was obtained by the reaction of the dimer (**2**) of malononitrile with carbon disulfide in an aqueous alkaline medium. The structure of **1** was proposed on the basis of ir and nmr spectra together with the course of the reaction. The ir spectrum showed two separate absorptions at 2200 cm^{-1} (conjugated CN stretching) and 2210 cm^{-1} (nonconjugated CN stretching). The nmr spectrum showed only one peak, which had a characteristic broad shape of an amino group (δ 8.50, NH_2). Thus the formation of **1** was believed to proceed through intermediate **3**, that is, to involve attack of carbon disulfide on the active methylene of **2**.

Along with **1**, a small amount of the trimer of malononitrile and di(ammoniomercapto)methylenecyanothioacetamide (**4**) were isolated from the reaction product. The structures of the latter two compounds were assigned on the basis of ir and nmr spectra and the courses of syntheses. The trimer was believed to be 4,6-diamino-3,5-dicyano-2-cyanomethylpyridine (**5**), which is different from the one obtained by Pleuger and Pape.[2]

The reaction of malononitrile and carbon disulfide in liquid ammonia gave di(ammoniomercapto)methylenemalononitrile (**6**). This type of compound is generally prepared by the action of alkoxide.[3] Compound **1** could not be synthesized by the reaction of **6** and malononitrile.

When ethyl cyanoacetate was treated with carbon disulfide in the presence of aqueous ammonia, it gave di(ammoniomercapto)methylenecyanoacetamide (**7**). In addition, a small amount of a compound ($C_9H_{17}N_5O_3S_2$), which is possibly a molecular compound of cyanoacetamide and ethyl di(ammoniomercapto)methylenecyanoacetate, was isolated. This compound, on oxidation with hydrogen peroxide, gave colorless needles, mp 223–224°. The uv spectrum resembled that of 3,5-di(methylacetylmethylene)-1,2,4-trithiole,[4] and thus the structure was tentatively designated 3,5-di(cyanocarbethoxymethylene)-1,2,4-trithiole (**8**).

Further, **7** was treated with acetic acid to give 5-amino-4-carbamoyl-1,2-dithiole-3-thione (**9**).[5] Compound **6**, unlike **7**, did not afford the corresponding dithiole on the same treatment, but **4**, which was prepared from **6** by addition of hydrogen sulfide, gave 5-amino-4-cyano-1,2-dithiole-3-thione (**10**).[5] Compound **6** on treatment with acetic acid was converted into a trimer of dimercaptomethylenemalononitrile.

Compounds **4**, **6**, and **7** were converted to the respective dimethyl derivatives for the purpose of confirmation of structure.[3]

The structures of **9** and **10** are mainly based on the characteristic uv spectra. These two compounds have been synthesized by Söderbäck from the corresponding dimercaptoethylene and sulfur[6] (Scheme I).

Experimental Section

Preparation of 4,6-Diamino-3,5-dicyano-2H-1-thiopyran-2-thione (1). Method A.—A mixture of malononitrile (bp 104–106° (7 mm), 50 g, 0.76 mol), carbon disulfide (114 g, 1.5 mol), and 280 ml of aqueous ammonia (28%) was stirred at room temperature for 6 hr. The yellow solid product was collected, washed with water and ether, recrystallized from pyridine, and dried at 130° for 6 hr to give yellow needles (**1**): yield 51 g (62%). This compound turned brownish near 300°. *Anal.* Calcd for $C_7H_4N_4S_2$: C, 40.39; H, 1.94; N, 26.92; S, 30.75; mol wt, 208.13. Found: C, 40.41; H, 2.05; N, 27.08; S, 30.32; mol wt (mass spectroscopy), 208. Uv max (99% EtOH) 253 mμ (br, log ϵ 4.10), 276 (4.09), 331 (3.93), 391 (4.16); ir (KBr) 3400 (w), 3310 (s), 3280 (sh), 3220 (s), 3140 (s, ν_{NH_2}), 2210, 2200 (s, ν_{CN}), 1650, 1630 (vs, δ_{NH_2}), 1545 cm^{-1} (*vs*. $\nu_{conj\ C=C}$); nmr (DMSO-d_6) δ 8.50 (br, 4, NH_2).

When the crude product of the above anhydrous sample was recrystallized from pyridine–water, **1** had 1 mol of water of crystallization. This compound turned brownish near 300°. *Anal.* Calcd for $C_7H_6N_4OS_2$: C, 37.17; H, 2.67; N, 24.78; S, 28.80; mol wt, 226.0. Found: C, 37.28; H, 2.93; N, 25.04; S, 28.35; mol wt, 225.4 (vapor-pressure osmometer, in acetone).

Method B.—A mixture of malononitrile (25 g, 0.38 mol), carbon disulfide (57 g, 0.75 mol), and 10 g of sodium hydroxide in 100 ml of water was shaken for 24 hr, yield 5 g (12.5%). The ir spectrum was identical with that of **1** prepared by method A.

Method C.—Malononitrile dimer (**2**) was prepared according to Carboni's tetrahydrofuran method.[7] Compound **1** was prepared, in the same way as in method A, from malononitrile dimer (20 g, 0.15 mol), carbon disulfide (15 g, 0.2 mol), and 150 ml of aqueous ammonia (28%), yield 29 g (93%). The structure determination was based on the ir spectrum.

Isolation of Malononitrile Trimer and Di(ammoniomercapto)-methylenecyanothioacetamide (4).—The reaction mixture in the case of method A, freed from **1**, was kept overnight in an icebox. About 10 g of a yellow material precipitated. Recrystallization from pyridine–water yielded 0.5 g of a light yellow powder.

Anal. Calcd for $C_9H_6N_6$: C, 54.24; H, 2.82; N, 41.98; mol wt, 198.2. Found: C, 54.24; H, 2.64; N, 41.77; mol wt (mass spectroscopy), 198. Ir (KBr) 3430, 3340 (s), 3240 (m, ν_{NH_2}), 2960 (m, ν_{CH_2}), 2218 (m, ν_{CN}), 2200 cm^{-1} (vs, $\nu_{conj\ CN}$). nmr (DMSO-d_6) δ 7.45 (s, 4, NH_2), 3.95 (s, 2, CH_2). From the above analytical results, the compound was believed to be 4,6-diamino-3,5-dicyano-2-cyanomethylpyridine (**5**).

The filtrate from which **1** and the above trimer (**5**) were removed was concentrated to about one-half volume under reduced pressure at 40–45° and kept overnight in an icebox. The yellow precipitates obtained were recrystallized from water, washed with ethanol, and dried: yellow plates (**4**), yield 6.1 g (3.9%), mp 136–137° dec (slow heating), 153–156° dec (rapid heating). *Anal.* Calcd for $C_4H_{10}N_4S_3$: C, 22.86; H, 4.86; N, 26.66; S, 45.68; mol wt, 210.15. Found: C, 23.23; H, 4.83; N, 26.56; S, 45.36; mol wt, 214.7 (vapor-pressure osmometer, in acetone). Uv max (99% EtOH) 288 mμ (sh, log ϵ 2.88), 310 (2.97), 370 (3.07); ir (KBr) 3310 (s, ν_{NH}), 3080, 2960 (s, br, $\nu_{NH_4^+}$), 2180 (s, ν_{CN}), 1590 (s, $\nu_{C=N}$), 1505 (m, $\nu_{conj\ C=C}$), 1415 cm^{-1} (s, br, $\delta_{NH_4^+}$). The compound produced a violet coloration on sodium nitroprusside test.

Methylation of 4.—To a solution of **4** (1.8 g) and sodium hydroxide (0.8 g) in 100 ml of water was added dropwise 5 g of di-

(1) (a) Chiba University; (b) The Institute of Physical and Chemical Research.

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(3) E. Söderbäck, *Acta Chem. Scand.*, **17**, 362 (1963).

(4) A. J. Kirby, *Tetrahedron*, **22**, 3001 (1966).

(5) R. Mayer, P. Rosmus, and J. Fabian, *J. Chromatogr.*, **15**, 153 (1964).

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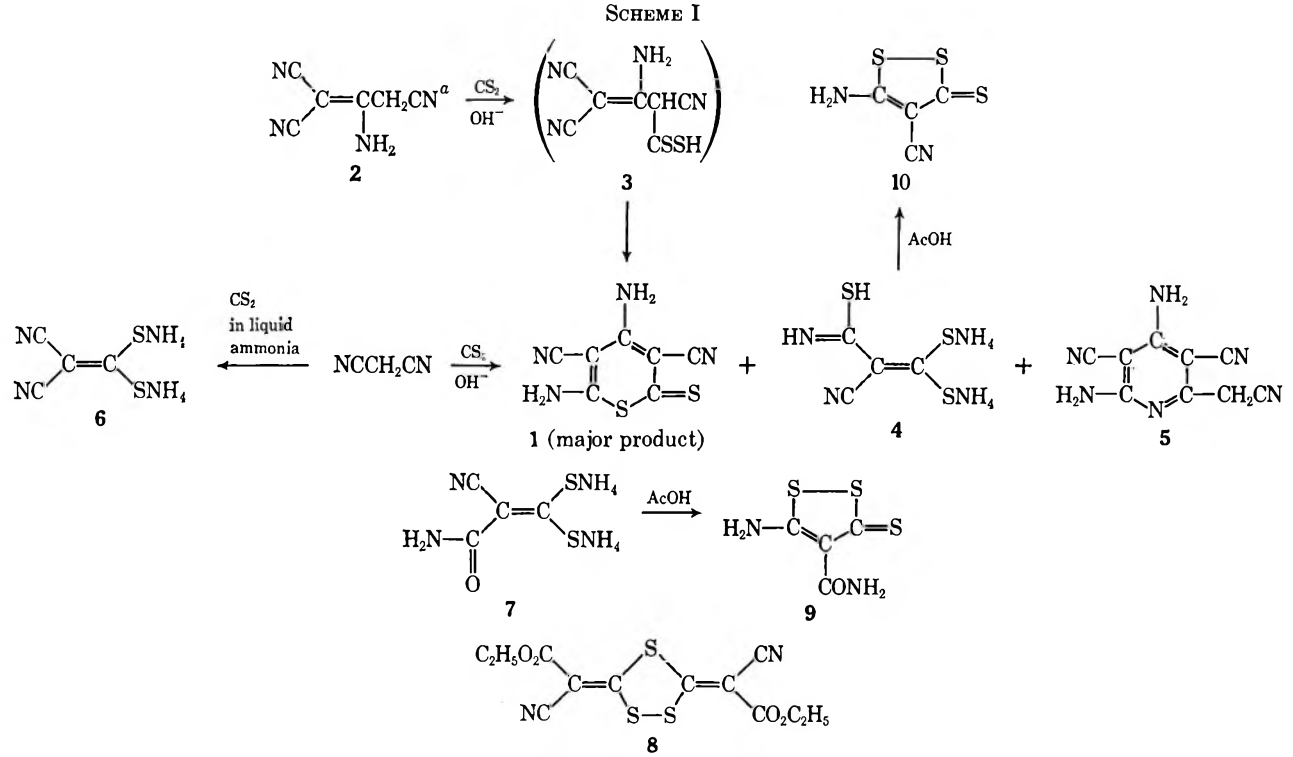
SCHEME I



[a] The structure of the dimer of malononitrile was considered to assume enamine form on the basis of the ir spectrum which showed two separate absorptions (2210 and 2200 cm^{-1}) of the two cyano groups and the nmr spectrum of NH_2 (δ 8.50 in DMSO-d_6).

methyl sulfate under stirring. The yellow material was collected and recrystallized from pyridine–water: yellow needles, yield 1.5 g (86%), mp 219–220°. *Anal.* Calcd for $C_6H_8N_2S_3$: C, 35.30; H, 3.95; N, 13.72; S, 47.03; mol wt, 204.14. Found: C, 35.52; H, 4.14; N, 14.00; S, 46.97; mol wt, 213.5 (vapor-pressure osmometer, in acetone). Uv max (99% EtOH) 245.5 mμ (log ϵ 4.05), 315 (3.94), 367.5 (4.27); ir (KBr) 3320 (s, ν_{NH}), 2990 2910 (w, ν_{CH_3}), 2192 (s, ν_{CN}), 1605 (vs, $\nu_{C=N}$), 1480 (m, $\nu_{C=C}$), 1380 cm^{-1} (vs, δ_{CH_3}); nmr (DMSO-d_6) δ 2.60 (s, 3, CH_3), 2.50 (s, 3, CH_3). The compound was di(methylthio)-methylenecyanothioacetamide. It produced a violet coloraton on sodium nitroprusside test.

Treatment of 4 with Acetic Acid.—To 4 (2 g) in 100 ml of water was added acetic acid (4.5 ml). The reaction mixture was allowed to stand for 1 hr at room temperature. The crude product was collected and recrystallized from pyridine–water to give yellow prisms, yield 1.2 g (72%). *Anal.* Calcd for $C_4H_2N_2S_3$: C, 27.60; H, 1.15; N, 16.10; S, 55.50; mol wt, 174. Found: C, 27.97; H, 0.85; N, 16.35; S, 55.25; mol wt, 180.0 (vapor-pressure osmometer, in acetone). Uv max (99% EtOH) 233.5 mμ (log ϵ 4.06), 283 (sh, 3.87), 311 (4.09), 369 (3.68); ir (KBr) 3350, 3250, 3160 (s, ν_{NH_2}), 2200 (s, $\nu_{conj\ CN}$), 1620 (vs, δ_{NH_2}), 1510 cm^{-1} (vs, ν_{ring}); nmr (DMSO-d_6) δ 9.58 (s, br, 2, NH_2). The compound was 5-amino-4-cyano-1,2-dithiol-3-thione (10). The uv spectrum agreed with that reported by Mayer, *et al.*[5] The ir spectrum also agreed with that measured by Söderbäck's method.[6]

Preparation of Di(ammoniomercapto)methylenemalononitrile (6).—A mixture of malononitrile (25 g, 0.38 mol), carbon disulfide (57 g, 0.75 mol), and *ca.* 200 ml of liquid ammonia was stirred for 30 min under cooling by Dry Ice–methanol. The reaction mixture then was allowed to stand at room temperature. A yellow solid material was recrystallized from methanol–chloroform to give light yellow plates: yield 65.5 g (98%); mp 141–142° dec (slow heating), 156–158° dec (rapid heating). *Anal.* Calcd for $C_4H_8N_4S_2$: C, 27.12; H, 4.59; N, 30.90; S, 36.41; mol wt, 176.14. Found: C, 27.00; H, 4.81; N, 30.83; S, 36.30; mol wt, 160.0 (vapor-pressure osmometer, in acetone).

The compound was methylated with dimethyl sulfate by the same method as above (see methylation of 4). Recrystallization from methanol yielded 1.5 g of colorless needles [$(CH_3S)_2C_2(CN)_2$]: yield 86%, mp 83–84° (lit.[3] mp 80–81°), undepressed by the addition of an authentic specimen.[3]

Treatment of 6 with Acetic Acid.—Compound 4 (3.3 g, 0.02 mol) and acetic acid (2.2 ml, 0.04 mol) in 100 ml of water was kept overnight at room temperature. A yellow solid material was collected and recrystallized from DMSO to give a yellow powder, yield 2 g (74%). The compound had formula $(C_4H_2N_2S_2)_3$. *Anal.* Calcd for $C_{12}H_6N_6S_6$: C, 33.81; H, 1.41; N, 19.70; S, 45.10; mol wt, 426.6. Found: C, 33.90; H, 1.41; N, 19.82; S, 45.05; mol wt, 420 (vapor-pressure osmometer, in acetone).

Conversion of 6 into 4.—Compound 6 (8 g) was dissolved in 100 ml of ethanol, and hydrogen sulfide was passed through for 30 min. The reaction mixture was shaken for an additional 3 hr; 0.5 g of 4 was obtained. The compound was identified as 4 by a mixture melting point test. Compound 4 was converted into 10 on treatment with acetic acid as mentioned above.

Preparation of Di(ammoniomercapto)methylenecyanoacetamide (7).—A mixture of ethyl cyanoacetate (120 g, 1.1 mol), carbon disulfide (161 g, 2.1 mol), and 360 ml of aqueous ammonia (28%) was stirred at room temperature for 8 hr. The crude product was collected and recrystallized from water–acetone to give light yellow prisms: yield 83 g (40%), mp 147–148° dec (slow heating), *ca.* 170° dec (rapid heating). *Anal.* Calcd for $C_4H_{10}OS_2$: C, 24.74, H, 5.19; N, 28.86; S, 32.99; mol wt, 194.15. Found: C, 25.05; H, 5.11; N, 28.65; S, 32.83; mol wt, 181.9 (vapor-pressure osmometer, in H_2O). Uv max (H_2O) 312 mμ (sh, log ϵ 3.75), 340 (3.76); ir (KBr) 3280, 3225, 3110 (m, ν_{NH_2}), 3000 (m, br, $\nu_{NH_4^+}$), 2185 (s, ν_{CN}), 1663 (m, ν_{CO}), 1625 (s, δ_{NH_2}), 1500 (s, $\nu_{conj\ C=C}$), 1415 cm^{-1} (s, br, $\delta_{NH_4^+}$); nmr (D_2O) δ 4.85 (s, 8, NH_4^+).

Compound 7 also was prepared from cyanoacetamide. A mixture of cyanoacetamide (17 g, 0.2 mol), carbon disulfide (30 g, 0.4 mol), and 140 ml of aqueous ammonia (28%) was refluxed at 70–80°) for 8 hr. Compound 7 which was obtained weighed 18 g (yield 45%).

Compound 7 was methylated using dimethyl sulfate as mentioned above. The methylated compound was recrystallized from methanol to give colorless needles, yield 77%, mp 84°. *Anal.* Calcd for $C_6H_8N_2OS_2$: C, 38.30; H, 4.29; N, 14.89; S, 34.05; mol wt, 188.14. Found: C, 38.25; H, 4.29; N, 14.70; S, 33.85; mol wt, 186.5 (vapor-pressure osmometer, in acetone). Uv max (99% EtOH) 324 mμ (log ϵ 4.13); ir (KBr) 3400, 3290, 3220, 3185 (s, ν_{NH_2}), 2930 (w, ν_{CH_3}), 2200 (s, ν_{CN}), 1650 (vs, ν_{CO}), 1610 (s, δ_{NH_2}), 1490 (s, $\nu_{conj\ C=C}$), 1385 cm^{-1} (s, δ_{CH_3}); nmr (DMSO-d_6) δ 7.05 (br, 2, NH_2), 2.70 (s, 3, CH_3), 2.55 (s, 3, CH_3).

Isolation of $C_9H_{17}N_5O_3S_2$.—The filtrate from which 7 was removed was kept overnight in an icebox. The yellow material

obtained was recrystallized from water: yellow prisms, mp 129–130° dec, yield 6 g (9%).

Anal. Calcd for $C_9H_{17}N_5O_3S_2$: C, 35.19; H, 5.54; N, 22.80; S, 20.85; mol wt, 307. Found: C, 35.13; H, 5.62; N, 22.51; S, 21.28; mol wt, 285 (vapor-pressure osmometer, in H_2O). Uv max (H_2O) 281.5 mμ (br, log ε 3.59), 343 (4.26); nmr (D_2O) δ 4.85 (s, 8, NH_4^+), 4.13 (q, 2, CH_2, J = 7 cps), 1.28 (t, 3, CH_3, J = 7 cps).

The compound was methylated with dimethyl sulfate. Colorless needles of ethyl di(methylthio)methylenecyanoacetate were obtained. Recrystallization from methanol yielded 1.3 g (92%), mp 55–56°, undepressed by the addition of an authentic specimen.[3]

When the compound was treated with hydrogen peroxide (1%), colorless needles (**8**) of mp 223–224° were obtained. The product was recrystallized from pyridine–water.

Anal. Calcd for $C_{12}H_{10}N_2O_4S_3$: C, 42.15; H, 2.93; N, 8.19; S, 28.05; mol wt, 342. Found: C, 42.22; H, 3.00; N, 8.29; S, 27.99; mol wt, 326.7 (vapor-pressure osmometer, in acetone). Uv max (99% EtOH) 230 mμ (log ε 4.37), 335 (4.35); ir (KBr) 2992, 2977 (m, ν_{CH}), 2220 (s, ν_{CN}), 1689 (sh, ν_{CO}), 1669, 1658 cm^{-1} (vs, $\nu_{C=C}$); ir ($CHCl_3$) 2985 (m, ν_{CH}), 2200 (s, ν_{CN}), 1690 (sh, ν_{CO}), 1683 cm^{-1} (s, $\nu_{C=C}$); nmr (DMSO-d_6) δ 4.30 (q, 4, CH_2, J = 7 cps), 1.27 (t, 6, CH_3, J = 7 cps). The structure was tentatively designated 3,5-di(cyanocarbethoxymethylene)-1,2,4-trithiole (**8**). This trithiole was also obtained by treating ethyl di(sodiomercapto)methylenecyanoacetate with hydrogen peroxide (5%).

Preparation of 5-Amino-4-carbamoyl-1,2-dithiole-3-thione (9).—Compound **7** (18 g, 0.09 mol) was dissolved in 100 ml of water. To this solution was added acetic acid (10 ml) and the solution was stirred at room temperature for 1 hr. The crude product was recrystallized from pyridine–water: yellow prisms, mp 247–248° dec (slow heating), *ca.* 258° dec (rapid heating), yield 8 g (45%). *Anal.* Calcd for $C_4H_4N_2OS_3$: C, 25.01; H, 2.10; N, 14.58; S, 49.95; mol wt, 192.09. Found: C, 25.31; H, 2.16; N, 14.47; S, 49.95; mol wt, 173.1 (vapor-pressure osmometer, in acetone). Uv max (99% EtOH) 240.5 mμ (log ε 3.96), 286 (sh, 3.90), 314.5 (4.54), 364.5 (3.93); ir (KBr) 3220 (s), 3140 (w), 3020 (w, ν_{NH_2}), 1650 (sh, ν_{CO}), 1640 (vs, δ_{NH_2}), 1550 cm^{-1} (vs, $\nu_{conj\ C=C}$); nmr (DMSO-d_6) δ 10.35 (br, 2, $CONH_2$), 8.70 (br, 2, NH_2). The uv spectrum of **9** agreed with that reported by Mayer, *et al.*[5]

When **9** was treated with dimethyl sulfate, methyl carbamoylcyanodithioacetate (light yellow prisms, mp 233–234°)[3] and a small amount of sulfur were obtained.

Registry No.—Malononitrile, 109-77-3; carbon disulfide, 75-15-0; **1**, 24571-55-9; **4**, 24571-56-0; **4** (methylated), 24571-57-1; **6**, 24571-58-2; **7**, 24571-59-3; **7** (methylated), 17823-69-7; **8**, 2631-93-8; **9**, 5147-79-5; **10**, 5147-74-0; **5**, 24571-64-0.

Acknowledgment.—The authors are grateful to Dr. Hiroshi Midorikawa for valuable suggestions and every facility given to them. They are also indebted to Mr. Motomu Muraoka and Mr. Katsu Sakai for their advice and assistance.

Synthesis of 2-*t*-Butylaminobenzophenones and Benzaldehydes

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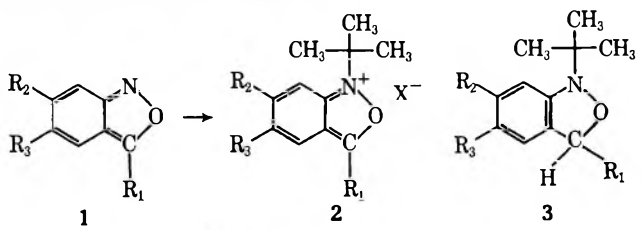
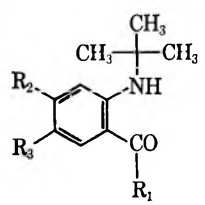
During work on a program aimed at the synthesis of various 2(1H)-quinazolinones,[1] the need arose for monoalkylated 2-aminobenzophenones as intermediates. Although many monoalkyl derivatives can be prepared by standard procedures, attempts to extend these to the introduction of the *t*-butyl group led to very limited or no success. We now wish to report a novel route to these compounds which has been realized in excellent overall yield.

Whereas 3-phenyl-2,1-benzisoxazoles (**1**) are reduced completely by lithium aluminum hydride to 2-aminobenzhydrols,[2] less powerful reagents such as metal–acid combinations[3,4] or catalytic hydrogenation[5,6] give 2-aminobenzophenones. No intermediates retaining the heterocyclic ring were detected in these cases. Possibly then, formation of the quaternary salt from the benzisoxazole and subsequent reduction might yield alkylated aminobenzophenones, but the required salts had not previously been isolated.[7] The SN1 alkylation of substituted isoxazoles had been described,[8] however, and not only was the reaction particularly efficient with *t*-butyl alcohol but the perchlorate salts were readily isolable.

Application of this procedure to several 2,1-benzisoxazoles (**1**) gave the desired salts (**2**) in good yield. Addition of sodium borohydride to a suspension of the salt (*e.g.*, **2a**) in ethanol led to rapid solution, and work-up yielded a colorless crystalline product identified from its spectral properties as the intermediate 1-*t*-butylbenzisoxazoline (**3a**). This compound proved to be surprisingly stable but it was noticed while determining the melting point that on continued heating the melt became an intense yellow which did not disappear on subsequent cooling. Spectral analysis of a sample of the yellow product isolated by chromatography showed that a thermal isomerization had occurred, the desired 2-*t*-butylaminobenzophenone (**4a**) having been cleanly formed. It was then found that this isomerization occurred in the three cases examined, heating the neat material at 160° for 4 hr being sufficient to effect better than 90% conversion.



1 **2** **3**



4

	R_1	R_2	R_3	X
a	Ph	CH_3	Cl	ClO_4
b	Ph	H	H	BF_4
c	H	H	H	BF_4
d	Ph	CH_3	H	

The use of this sequence to prepare 2-*t*-butylaminobenzaldehyde (**4c**) in good yield is particularly interesting since 2-aminobenzaldehydes in general polymerize on contact with acid,[9] the presence of which is

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often unavoidable in other tertiary butylation procedures.

Basic catalytic hydrogenolysis of the chlorine substituent in **4a** was unexceptional, leading to one further 2-*t*-butylaminobenzophenone, **4d**.

Further chemical transformations of the intermediate benzisoxazolium salts are under study.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are not corrected. Infrared spectra were measured on a Model 457 Perkin-Elmer spectrophotometer in methylene chloride; nmr spectra in deuteriochloroform solution with tetramethylsilane as an internal standard, on a Varian A-60 instrument. Microanalyses were carried out in our analytical unit.[10]

1-*t*-Butyl-5-chloro-6-methyl-3-phenyl-2,1-benzisoxazolium Perchlorate (2a).—To a solution of 9 g (0.037 mol) of **1a** in 350 ml of nitromethane were added 3.2 g (0.042 mol) of *t*-butyl alcohol and 7 g (0.042 mol) of a 60% aqueous solution of perchloric acid. The resulting solution was left at room temperature for 60 hr and then diluted with 1000 ml of anhydrous ether. The crystalline precipitate so obtained was filtered off, dissolved in 50 ml of acetone, and reprecipitated by the addition of 250 ml of ether. There resulted 13 g (88%) of **2a**, mp 183–185°. Similarly prepared were **2b**, mp 142–145°, and **2c**, mp 132–134° dec.

1-*t*-Butyl-5-chloro-6-methyl-3-phenyl-2,1-benzisoxazoline (3a).—To a stirred suspension of 13.3 g (0.033 mol) of **2a** in 100 ml of ethanol at room temperature was added in several portions 1.5 g (0.04 mol) of sodium borohydride. After the addition was complete, the stirring was continued for a further 30 min by which time only a little fine crystalline precipitate was present in the reaction mixture. Water was then added slowly to give initially a clear solution followed by precipitation of the product. Isolation by filtration and recrystallization from aqueous ethanol gave 7.5 g (75%) of **3a**: mp 115–117°; nmr δ 1.32 (9 H, s, *t*-butyl), 2.34 (3 H, s, Ar-CH_3), 6.32 (1 H, s, >CH), 6.81, 6.90 (2 H, 2 s, aromatic), 7.36 (5 H, s, phenyl). Similarly prepared were **3b** [mp 69–73°; nmr δ 1.32 (9 H, s, *t*-butyl), 6.41 (1 H, s, >CH), 6.85–7.25 (4 H, m, aromatic), 7.38 (5 H, s, phenyl)] and **3c** [oil, distilled (Kugelrohr; 0.2 mm, 90–100°); nmr δ 1.24 (9 H, s, *t*-butyl), 5.14 (2 H, s, $-CH_2-$), 6.80–7.20 (4 H, m, aromatic)].

2-*t*-Butylamino-5-chloro-4-methylbenzophenone (4a).—Under an atmosphere of nitrogen, the melt from 11 g of **3a** was maintained at a temperature of 160° for 4 hr. The resulting liquid was cooled, diluted with 50 ml of CH_2Cl_2, and filtered through a short column of aluminum oxide. Further elution with CH_2Cl_2 and evaporation of the yellow solution gave 9 g (82%) of **4a**: crystallized from pentane, mp 76–78°; ir 3.02 (NH), 6.18 μ (C=O); nmr δ 1.48 (9 H, s, *t*-butyl), 2.36 (3 H, s, Ar-CH_3), 6.90 (1 H, s, aromatic), 7.32–7.70 (6 H, aromatic), 8.89 (1 H, D_2O exchangeable, NH). Similarly prepared were **4b** [oil, distilled (Kugelrohr, 0.2 mm, 140–160°); nmr δ 1.50 (9 H, s, *t*-butyl), 6.49 (1 H, t, aromatic), 6.90–7.75 (8 H, aromatic), 8.85 (1 H, D_2O exchangeable, NH)] and **4c** [oil, distilled (Kugelrohr, 0.2 mm, 100–130°) ir 3.05 (NH), 6.07 μ (C=O); nmr δ 1.43 (9 H, s, *t*-butyl), 6.45–7.50 (4 H, aromatic), 8.70 (1 H, D_2O exchangeable, NH), 9.85 (1 H, s, -CHO)].

2-*t*-Butylamino-4-methylbenzophenone (4d).—A solution of 1.7 g of **4a** in 100 ml of methanol containing 200 mg of KOH and 200 mg of 5% palladium on carbon was shaken under an atmosphere of hydrogen until 1 equiv had been taken up (*ca.* 12 hr). After filtration, evaporation of the solvent, and isolation of the organic material, there was obtained 1.3 g (87%) of **4d**: oil, distilled (Kugelrohr, 0.2 mm, 140–160°); nmr δ 1.48 (9 H, s, *t*-butyl), 2.28 (3 H, s, Ar-CH_3), 6.26 (1 H, s, aromatic), 6.83 (1 H, s, aromatic), 7.27–7.70 (6 H, aromatic), 8.98 (1 H, D_2O exchangeable, NH).

Registry No.—**2a**, 24806-54-0; **2b**, 24766-86-7; **2c**, 24766-87-8; **3a**, 24766-64-1; **3b**, 24766-65-2; **3c**, 24766-66-3; **4a**, 24766-67-4; **4b**, 24766-68-5; **4c**, 24766-69-6; **4d**, 24766-70-9.

(10) Satisfactory elemental analyses (±0.3% for C, H, and N or Cl) were reported for all compounds.

Reaction of Electrophiles with Enolizable N-Hydrogen Ketimines

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Recent investigations[1] have shown that electrophiles such as acyl chlorides, isocyanates, and isothiocyanates can react with N-substituted imines containing an enolizable proton to form, among other products, acylenamides, enureas, and enthioureas, respectively. The amount of enamide or urea obtained was shown to depend on both the electrophile and imine employed, as well as conditions of reaction.

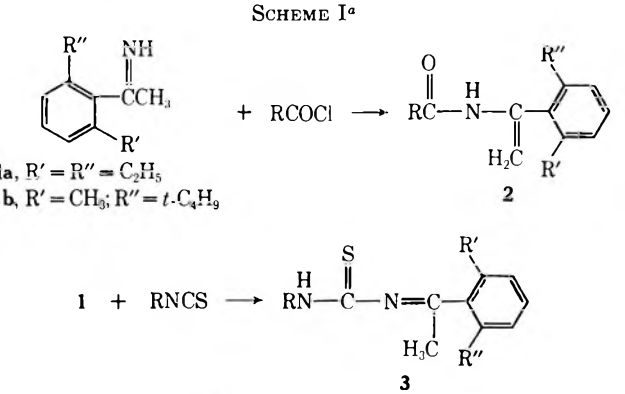
In addition to the above products, it should be possible for N-hydrogen imines to alternatively react substitutively at nitrogen to form acylimine compounds. Earlier literature references[2] disclose the acylation of enolizable ketimine derivatives (Grignard complexes from acetophenone ketimines) to give such compounds. However, the structural assignments were shown to be incorrect, as later investigations[3,4] proved the materials to be enamides.

It is therefore a principal object of the present report to demonstrate that enolizable N-hydrogen ketimines can, in fact, under certain conditions, give acylimine derivatives with electrophiles such as acyl chlorides, isocyanates, and isothiocyanates.

Several representative N-hydrogen ketimines were prepared for investigation. Material **1** is derived from reaction of 2,6-dialkylbenzonitriles with an organometallic reagent, while **4**, **8**, and **9** are available by reaction of the respective ketone with ammonia in the presence of suitable reagents[5] or through an ammonolysis of the nitramine derivative.[6]

Reaction of **1** with acid chlorides invariably gave only **2**, while **3** was the product on reaction with isothiocyanates (Scheme I). In similar manner, **4** with acid

SCHEME I[a]



[a] See Table I for specific examples of **2** and **3**.

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TABLE I

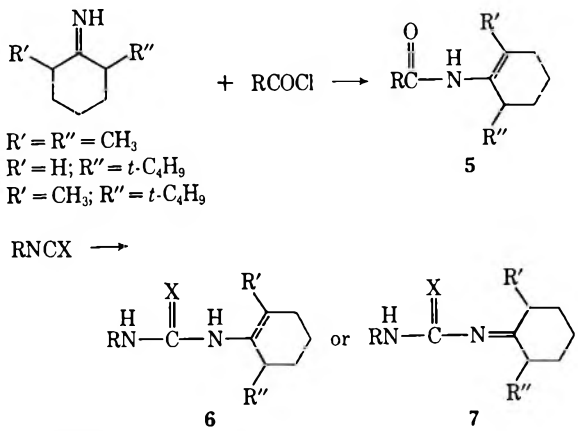
PRODUCTS FROM REACTION OF ELECTROPHILES WITH ENOLIZABLE N-HYDROGEN KETIMINES

Compd	R	R′	R″	X	Yield, %	Mp or bp (mm), °C	Calcd, % Cl	Calcd, % N	Calcd, % S	Found, % Cl	Found, % N	Found, % S	Pertinent spectra, nmr (CCl_4), δ [ir, μ]
2a	$ClCH_2$	C_2H_5	C_2H_5	O	70	149–150	14.08	5.56		14.34	5.95		4.8 (d, 1, J = 1 Hz, =CH), 6.3 (s, 1, =CH)
2b	$ClCH_2$	CH_3	$(CH_3)_3C$	O	66	103–104	13.34	5.27		13.35	5.80		4.8 (d, 1, J = 1 Hz, =CH), 6.3 (s, 1, =CH)
3	3,4-$(Cl)_2C_6H_3$	C_2H_5	C_2H_5	S	57	83–84	18.69	7.38	8.45	19.02	7.22	8.24	2.3 (s, 3, N=CCH_3) [6.1 (C=N)]
5a	$ClCH_2$	CH_3	CH_3	O	67	114–115	17.67	6.98		17.86	7.02		0.98 (d, 3, J = 7 Hz, >$CHCH_3$), 1.6 (s, 3, =CCH_3), 7.67 (broad s, 1, NH)
5b[a]	$ClCH_2$	$(CH_3)_3C$	H	O	58	103–105	15.43	6.10		15.80	6.20		6.3 (m, 0.35, =CH), 7.4 (broad s, 1, NH)
5c	$ClCH_2$	CH_3	$(CH_3)_3C$	O	50	121–123	14.54	5.75		15.10	5.87		1.6 (s, 3, =CH_3), 7.3 (broad s, 1, NH)
6a	3,4-$(Cl)_2C_6H_3$	CH_3	CH_3	S	93	150–151	21.53	8.51		21.31	8.70		1.11 (d, 3, J = 7 Hz, >$CHCH_3$), 1.7 (s, 3, =CCH_3)
6b	CH_3	H	$(CH_3)_3C$	O		137–139		13.32			13.26		(m, 1, =CH)
7a	3,4-$(Cl)_2C_6H_3$	CH_3	CH_3	O		128–131	22.79	9.00		22.60	9.07		1.3 (d, 6, J = 7 Hz, 2 >$CHCH_3$)
7b	3,4-$(Cl)_2C_6H_3$	H	$(CH_3)_3C$	O	81	124–126	21.41	8.46		21.13	7.86		
7c	3,4-$(Cl)_2C_6H_3$	H	$(CH_3)_3C$	S	58	106–108	19.84	7.84	8.97	19.57	7.87	8.80	[6.0 (C=N)]
7d	3,4-$(Cl)_2C_6H_3$	CH_3	$(CH_3)_3C$	O		130–132	20.01	7.91			7.57		1.2 (d, 3, J = 7 Hz, >$CHCH_3$)
10					74	Oil	15.57	6.15		14.81	5.89		
11					37	140–150 (1 mm)	11.82	4.67		11.94	4.87		5.8 (d, 1, J = 3 Hz, =CH)

[a] A mixture of isomers where R′ = $(CH_3)_3C$ (65%); R′ = H (35%).

chlorides gave only enamide (**5**), while, with isocyanates or isothiocyanates, **4** could give either **6** or the acylimine compound **7**. When **6** was the product, mixtures of isomers were possible, depending upon the 1 or 5 position of the double bond (Scheme II).

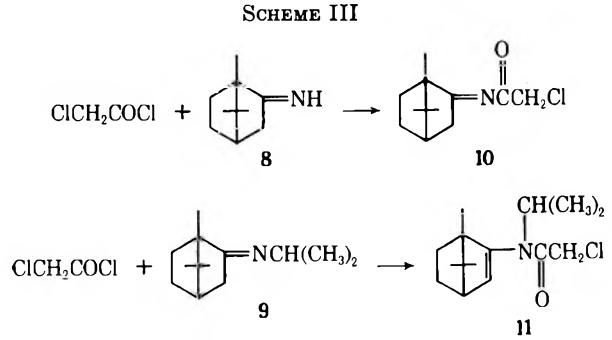
SCHEME II[a]



[a] See Table I for specific examples of **5**, **6**, and **7**.

Acyl chlorides do not invariably give enamide, however, as witnessed by the contrast in products from camphorimine (**8**) (acylimine **10**) and N-isopropylcamphorimine (**9**) (enamide **11**) (Scheme III).

SCHEME III

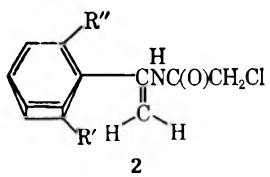


Structure proofs of the various products isolated were verified by nmr and ir spectral analyses. The enamide structure for **2a** or **2b**, is easily discerned by the presence of two different olefinic proton absorptions at δ 4.8 and 6.3.[7] The thionoacylimine **3** shows no olefinic proton absorption, but does clearly display a downfield methyl singlet, typical of methylimino or methylcarbonyl moieties.

There are several criteria for analyses of the cyclohexyl derivatives **5**, **6**, and **7**. *endo*-1,2-Cyclohexenyl rings generally show a characteristic "double hump," or two multiplets of three or four protons each centered at *ca.* δ 1.7 and 2.1–2.3. The downfield resonance is presumably due to the protons vicinal to the *endo* double bond. In contrast, cyclohexyl rings possessing an *exo* double bond display a continuous broad absorption between *ca.* δ 1.3 and 2.4. This difference is useful in assigning the enamide and enurea structure to **5** and **6**, and the imine structure to **7**. In addition, where R′ = H, the olefinic proton is quite prominent as a multiplet at *ca.* δ 5.8, while olefinic methyl (R′ = CH_3) gives a characteristic singlet at *ca.* δ 1.6. Where N**H** is not obscured by aromatic or additional amidic protons, the presence of this absorption is useful in eliminating acylimine as a possible structure.

The ir spectra are also useful in verifying structure; the presence of an acylimine (**7a**, **7b**, or **10**) shows only a broad, intense absorption between 5.9 and 6.1 μ for both C=O and C=N. However, there is a strong band at 6.1 μ for C=N in the thionoacylimine (**3**, **7c**), absent in the enthiourea (**6a**).

(7) The two olefinic protons have unexpectedly large differences in absorption. The abnormally high field resonance is assigned to the proton



cis, and nearly orthogonal, to the aromatic ring, while the more downfield absorption is assigned to the *trans* proton.

Compelling rationales for product formation must await detailed examination on whether materials arise from kinetics or thermodynamic control. Nevertheless the α-chloroacetamides would appear to arise from the latter, as they can be formed after prolonged heating. Nor would it be difficult to accept the thesis that **10** is formed because of resistance to *endo* camphene formation, whereas there is no alternative to such formation in **11**. Assuming **5** to be products of thermodynamic control, it would appear that the more substituted olefinic bond in cyclohexene is favored, unless the substituent is large (*i.e.*, *t*-butyl), where steric interactions of this group, planar to the group on nitrogen, might favor the imino or less substituted cyclohexene structure.

Experimental Section

Preparation of Enolizable Imines.—The preparation of imines **1a** and **1b**[8] is similar to the method of Heng Suen.[4]

1-(2,6-Diethylphenyl)ethylidenimine (1a).—To 100 g (0.629 mol) of 2,6-diethylbenzonitrile in 500 ml of ether was added under a nitrogen atmosphere, 0.688 mol of methyllithium. The reaction mixture was stirred 21 hr at room temperature, when 500 ml water was cautiously added. The ether layer was separated, washed with two 250-ml portions of water, dried over sodium sulfate, and then concentrated to give 108 g of an oil: ir (CCl_4) 3.05 (NH), 6.15 μ (C=N), no absorption for C≡N or C=O; pertinent nmr ($CDCl_3$) δ 2.29 (s, 3, N=CCH_3), 8.87 (broad s, 1, NH).

1-(2-*t*-Butyl-6-methylphenyl)ethylidenimine (1b).—In analogous fashion to the procedure above for **1a**, **1b** was prepared as an oil (bp 255–258°) in 98% yield from 2-*t*-butyl-6-methylbenzonitrile (mp 61–62°): ir (film) 2.9–3.15 (NH), 6.15 μ (C=N), no C≡N or C=O; pertinent nmr ($CDCl_3$) δ 2.21, 2.35 (2 s, 3 H each, $ArCH_3$ and N=CCH_3), 9.03 (broad s, 1, NH).

Imines **4a**, **4c**, and **9** have been previously described[5] as has **8**.[6] Imine **4b** was made in similar fashion to **7**, through the nitramine.

2-*t*-Butylcyclohexylidenamine. (4b).—2-*t*-Butylcyclohexanone (0.3 mol) was allowed to react with 51 g of hydroxylamine hydrochloride and 86 g of pyridine in 300 ml of absolute ethanol. After heating 3.5 hr, the material was permitted to stand 12 hr, the solvent was then evaporated, and the residue was washed with water. The oil was taken up in ether, washed with 5% HCl and once with water, and then dried over $MgSO_4$. The residue (48.4 g), upon removal of ether, showed only oxime (no C=O absorption by ir). The crude oxime (20 g) was dissolved in 200 ml of ether and mixed with 20 g of $NaNO_2$. Then 12 g of sulfuric acid diluted with water to 70 ml was added dropwise at 0–5°. After addition of acid, the material was allowed to warm to room temperature; the ether layer was separated and dried. Evaporation of solvent gave 22 g of oil: ir 6.15 (C=N), 6.4 and 7.62 μ (NO_2).

The nitramine (17.5 g) was placed in 50 ml of 28% ammonia with 100 ml of ether in a sealed pressure bottle. The material was shaken and then permitted to stand for 2 hr. The bottle was opened, the ether layer was separated and dried, and solvent was removed to give 12.5 g of an oil as **4b**, $n^{25}D$ 1.4727.

Acylenamides.—With the exception of **10**, the preparation of chloroacetamides is illustrated by the specific procedure for **2a**.

2-Chloro-N-(2,6-diethyl-α-methylenebenzyl)acetamide (2a).—The imine of 2,6-diethylacetophenone (5.8 g, 0.033 mol) was added in 50 ml of chlorobenzene to 3.8 g of chloroacetyl chloride. The mixture was refluxed for *ca.* 2 hr, during which time hydrogen chloride was evolved. The solvent was removed and the resulting crystals were recrystallized twice (charcoal) from aqueous methanol to give a 5.8-g yield.

N-(1,7,7-Trimethylnorborn-2-ylidene)-2-chloroacetamide (10).—Camphorimine (**8**, 0.053 mol, 8.0 g) was dissolved in benzene and added to a solution of 0.05 mol of chloroacetyl chloride contained in 50 ml of benzene. A white precipitate formed during this addition. After imine had been allowed to react, 0.05 mol of pyridine (5.0 g) was added at 0.5°, and the reaction was stirred further for 0.5 hr at room temperature. The pyridine hydrochloride was filtered off, and the filtrate was washed twice with water, dried over $MgSO_4$, and then stripped of solvent. The residue consisted of an oil and some crystals (the latter was shown to be α-chloroacetamide). The oil was taken up in pentane, the solution was filtered, and oily **9** was obtained afters olvent evaporation and filtration through clay.

The en- and iminoureas and thio analogs were all prepared from the respective isocyanate or isothiocyanate and imine at room temperature, contained in an inert solvent such as benzene. A specific example is as follows.

1-(2-*t*-Butylcyclohexylidene)-3-(3,4-dichlorophenyl)-2-thiourea (7c).—3,4-Dichlorophenyl isothiocyanate (0.027 mol, 5.5 g) was mixed in benzene with 4.0 g (0.026 mol) of 2-*t*-butylcyclohexylidenamine. After standing 12 hr the solution was vacuum treated to remove solvent. The residue was a semisolid (ketone and some unreacted isothiocyanate present). The material was triturated with pentane and then filtered to give 5.4 g of **6c**, mp 103–106°. This material was recrystallized from methylcyclohexane.

Registry No.—**1a**, 24766-71-0; **1b**, 24766-72-1; **2a**, 24766-73-2; **2b**, 24766-74-3; **3**, 24766-75-4; **4b**, 24766-76-5; **5a**, 24766-77-6; **5b**, 24766-78-7; **5c**, 24766-79-8; **6a**, 24766-80-1; **6b**, 24766-81-2; **7a**, 24766-82-3; **7b**, 24766-83-4; **7c**, 24766-84-5; **7d**, 24766-85-6; **10**, 24744-55-6; **11**, 24744-56-7.

(8) Kindly supplied by Dr. R. K. Howe.

Chlorosulfonyl Isocyanate Addition to Bicyclo[2.1.0]pentane[1]

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The reactions of mercuric,[3a] lead,[3b] and thallium acetate,[3b,c] *p*-toluenesulfonic acid in acetic acid,[3d] hydrobromic acid,[3b] and halogens[3e] with the title compound have all proceeded *via* exclusive cleavage of the internal cyclopropane σ bond. The dominant influence in these bicyclopentane ring scissions is the relief of strain which accompanies cleavage or partial cleavage of the bent bridgehead bond in the transition state. This relief of strain energy overrides any electronic, steric, and/or statistical factors which determine the course of cleavage in less strained bicyclo[*n*.1.0]alkanes.

The general response of **1** to these electrophiles has been formation of *trans*-1,3-disubstitution products,[3a-d] although bromination and chlorination of **1** in the dark afforded *trans*-1,2-dihalocyclopentanes predominantly.[3e] With electron-deficient acetylenes[3f] and olefins,[3g] **1** underwent competitive reactions leading to both *cis*-fused 1,3 cycloadducts and ene-type products. On the basis of very careful kinetic, product ratio, and solvent polarity studies, Gassman, Mansfield, and Mur-

(1) This research is supported by Public Health Service Grants identified as R01-AI08063-01-03 from the National Institute of Allergy and Infectious Diseases.

(2) Postdoctoral Research Assistant (1968–1969) on a grant[1] supported by the NIH.

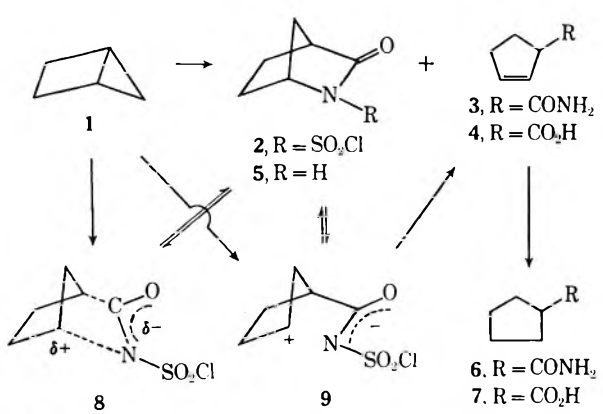
(3) (a) R. Ya. Levine, B. N. Kostin, and T. K. Ustynuk, *J. Gen. Chem., USSR*, **30**, 383 (1960); (b) R. Criegee and A. Rimmelin, *Chem. Ber.*, **90**, 414 (1957); (c) R. J. Ouellette, A. South, Jr., and D. L. Shaw, *J. Amer. Chem. Soc.*, **87**, 2602 (1965); (d) R. T. LaLonde and L. S. Forney, *ibid.*, **88**, 3767 (1963); (e) R. T. LaLonde and L. S. Forney, *ibid.*, **87**, 4217 (1965); (f) P. G. Gassman and K. T. Mansfield, *ibid.*, **90**, 1524 (1968), and preceding papers; (g) P. G. Gassman, K. T. Mansfield, and T. J. Murphy, *ibid.*, **91**, 1684 (1969); (h) P. G. Gassman and K. T. Mansfield, *ibid.*, **90**, 1517 (1968).

phy[3f,g] have suggested that this competitive process is mechanistically most consistent with the formation of diradical rather than zwitterionic intermediates. The presence of such intermediates precludes the possibility of a concerted process, as do the Woodward–Hoffman selection rules.[4] It should be noted that in all these reactions of electron-deficient carbon–carbon multiple bonds with strained carbon–carbon single bonds, experimental procedures included sealed ampoules, reaction times of 2–14 days, and reaction temperatures from 100 to 165°.[5]

In this note we wish to report on the addition of chlorosulfonyl isocyanate (CSI) to **1** under much less vigorous conditions, also leading to both cycloaddition and ene-type products. Relevant here is the report that such cumulative double-bond systems as CSI (and ketenes) play an antarafacial role in cycloaddition reactions in which molecular orbital symmetry considerations permit a near concerted thermal addition between an olefin and two orthogonal p orbitals on the N=C bond of CSI *via* an asymmetrical transition state.[6]

Thus treatment of **1** (slight excess) with CSI in methylene chloride solution for 12 hr at 0° afforded 1-chlorosulfonyl-2-aza-3-ketobicyclo[2.2.1]heptane (**2**, 35%) and, from the aqueous extract, a mixture of 3-cyclopentenecarboxamide (**3**) and its hydrolysis product, cyclopentene-3-carboxylic acid (**4**). Cycloadduct **2** was obtained as an oil which could not be induced to crystallize even after prolonged standing at −20 to −30°, although it was quite stable at that temperature. This oil was moderately stable at room temperature but unstable to distillation; column chromatography using silica gel as adsorbent and methylene chloride as eluent led to the separation of **2** as a single component on vpc. In the infrared, **2** displayed the expected absorptions at 5.52 (C=O) and 7.12 and 8.45 μ (SO_2), while, in the nmr, the bridgehead protons appeared as triplets at δ 4.98–4.78 and 4.02–3.66 coupled with the six-proton multiplet at 2.68–1.48.

Chromatographic separation of the olefinic mixture afforded pure **3** (38%) as a colorless solid and **4** (9%) as a colorless oil. Catalytic reduction of **3** and **4** gave the saturated amide (**6**) and acid (**7**), respectively. Carboxylic acids **4** and **7** were converted to their respective carboxamides **3** and **6** in conventional fashion *via* their acid chlorides and ammonia.



Reduction of **2** with benzenethiol–pyridine (75%), $LiAlH_4$ (45%) and pH-controlled hydrolysis (55%) afforded the more stable, crystalline lactam, 2-aza-3-ketobicyclo[2.1.0]heptane (**5**), in which the infrared carbonyl absorption had undergone the precedented red shift to 5.72 μ and the exchangeable NH proton made its appearance in the nmr at δ 7.28–6.72.

The reaction of **1** in solvents of increasing polarity, ether (0°) and methylene chloride (−80 to 75°), and a dark reaction (20°) all gave the same cycloadduct (**2**)/ene (**3** + **4**) product ratio (Table I). With a solvent of intermediate polarity (chloroform) a decrease in ene-type products increased the product ratio. The effect of free-radical inhibitors (*p*-benzoquinone and aniline) were inconclusive since CSI reacts with such reagents.

TABLE I

PRODUCT RATIOS FROM THE REACTION OF 1 WITH CSI UNDER VARIOUS CONDITIONS

Temp, °C	Reaction time, hr	Solvent	Product ratio of 2/(3 + 4)
−80	12	CH_2Cl_2	0.71
0	24	CH_2Cl_2	0.71
20	12	CH_2Cl_2	0.72
75	24	CH_2Cl_2[a]	0.66
0	12	Et_2O	0.69
0	12	$CHCl_3$	1.13

[a] Sealed tube reaction.

Mechanistically, the low reaction temperatures, the success of the dark reaction and the state of the art in CSI chemistry[7] make the diradical pathway least attractive. What remains of the two-step process is initial formation of Graf's 1,4-dipolar cation (**9**) followed by concomitant cyclization to **2** and proton loss to **3**. An alternative possibility is the kinetically controlled, electrophilic, near-synchronous cyclization (*via* polar transition state **8**[8]) to adduct **2**, followed by partial ionization to the charge-separated intermediate **9** which stabilizes itself by proton loss to **3**. Kinetic experiments hopefully leading to a resolution of this recurring dichotomy in almost all CSI cycloaddition reactions are under way.

Experimental Section

Bicyclo[2.1.0]pentane (**1**) was prepared by a modified[3b,g,9] version of Criegee's procedure.[3b]

Reaction of Bicyclo[2.1.0]pentane (1) with CSI.—A solution of CSI (12.6 g, 0.89 mol) in 10 ml of CH_2Cl_2 was added dropwise to an ice-cold stirred solution of **1** (6.8 g, 0.10 mol) in 50 ml of the same solvent. After the addition was complete, the mixture was stirred at room temperature for an additional 12 hr, after which it was slowly added to 20 g of ice. The methylene chloride layer was separated, washed with six 10-ml portions of H_2O, and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* afforded **1-chlorosulfonyl-2-aza-3-ketobicyclo[2.2.1]heptane** (**2**, 7.3 g, 35%) as an oil which was unstable to distillation and could not be induced to crystallize. Vpc indicated the presence of only a single component: ir (neat) 5.52 (C=O), 7.15 and 8.50 μ (SO_2); nmr ($CDCl_3$) δ 4.98–4.78 (t, 1, CH), 4.02–3.66 (t, 1, CH), and 2.62–1.48 (m, 6, CH_2).

(4) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 2046 (1965).

(5) Only the reaction of **1** with dicyanoethylene (5 days) was carried out at room temperature.[3h]

(6) R. B. Woodward and R. Hoffmann, *Angew. Chem. Int. Ed.* Engl., **8**, 781 (1969).

(7) R. Graf, *Angew. Chem. Int. Ed. Engl.*, **7**, 172 (1968); E. J. Moriconi, "Mechanisms of Reactions of Sulfur Compounds," Vol. 3, Intra-Science Research Foundation, Santa Monica, Calif., 1968, p 131.

(8) R. Gompper, *Angew. Chem. Int. Ed. Engl.*, **8**, 312 (1969).

(9) P. G. Gassman and K. T. Mansfield, *Org. Syn.*, **49**, 1 (1969). We are grateful to Professor P. G. Gassman for providing us with a preprint of his synthesis prior to publication.

The combined aqueous washes were extracted for 3 days with CH_2Cl_2 in a Raab extractor. Evaporation of the solvent *in vacuo* left a semisolid residue (10.3 g) which was shown by vpc to consist of two major products. This mixture was dissolved in 25 ml of CH_2Cl_2 and chromatographed over silica gel using successively, pentane, pentane–CH_2Cl_2, CH_2Cl_2, and CH_2Cl_2–CH_3OH (9:1) as eluents. The eluates were collected in fractions of 50 ml each. The CH_2Cl_2 fraction afforded **cyclopentene-3-carboxylic acid** (**4**, 1.9 g, 9%) as a colorless oil: bp 68–70° (0.5 mm), lit.[10a] bp 65° (15 mm); ir (neat) 5.95 μ (C=O); nmr ($CDCl_3$) δ 12.25 (s, 1, CO_2H), 6.05–5.65 (m, 2, olefinic H), 3.80–3.40 (m, 1, $CHCO_2H$), and 2.30–1.90 (m, 4, CH_2). Both the amide **3** (mp 135–137°) and the anilide (mp 120–122°, lit.[10a] mp 120°) were prepared.

Anal. Calcd for $C_6H_8O_2$: C, 64.28; H, 7.14. Found: C, 64.42; H, 7.15.

The CH_2Cl_2–CH_3OH fractions led to **cyclopentene-3-carboxamide** (**3**, 7.85 g, 38%): mp 135–137° (from CH_2Cl_2); nmr ($CDCl_3$) δ 7.50–6.45 (two broad peaks which disappeared in DMSO-d_6, 2, $CONH_2$), 5.90–5.62 (m, 2, olefinic H), 3.57–3.20 (m, 1, CH), and 2.61–1.73 (m, 4, CH_2).

Catalytic reduction (5% Pd–C) of **4** in absolute EtOH at atmospheric pressure gave cyclopentanecarboxylic acid (**7**, 80%), bp 116–118° (60 mm), lit.[10b] bp 104° (11 mm). Similar reduction of **3** afforded **cyclopentanecarboxamide** (**6**, 82%), mp 178–180° (from CH_3Cl_2) (lit.[10b] mp 179°). Successive treatment of **7** with thionyl chloride and ammonia converted it to the amide **6** which was identical in all respects with **6** obtained from reduction of **3**.

Table I summarizes the results of studies of the reaction of **1** with CSI under various conditions.

Reduction of 2 with Benzenethiol–Pyridine.—A solution of pyridine (5.6 g, 0.70 mol) in 15 ml of acetone was added dropwise to a Dry Ice cooled and stirred solution of 10.5 g (0.05 mol) of **2** and 10.4 g (0.10 mol) of benzenethiol in 25 ml of acetone. After continued stirring for 1 hr, 60 ml of water was slowly added to precipitate the phenyl disulfide which was removed by filtration. The filtrate was extracted with five 25-ml portions of ether; the combined ether extracts were dried (Na_2SO_4) and filtered; and the solvent was removed *in vacuo* to give 4.5 g (75%) of **2-aza-3-ketobicyclo[2.2.1]heptane** (**5**) as an oil slightly contaminated with phenyl disulfide. Distillation at 80–82° (0.5 mm) gave **5** as a colorless viscous oil which solidified on cooling: mp 32–34°; ir (neat) 3.10 (NH) and 5.72 μ (C=O); nmr ($CDCl_3$) δ 7.28–6.72 (broad singlet which disappeared in D_2O, 1, NH), 4.20–3.98 (t, 1, NCH), 3.66–3.36 (m, 1, CH), and 2.20–1.10 (m, 6, CH_2).

Anal. Calcd for C_6H_9NO: C, 64.82; H, 8.15; N, 10.00. Found: C, 64.52; H, 8.03; N, 9.97.

Registry No.—Chlorosulfonyl isocyanate, 1189-71-5; **1**, 185-94-4; **2**, 24689-57-4; **3**, 24647-27-6; **4**, 2348-89-2; **5**, 24647-29-8.

(10) (a) Heilbron, I, "Dictionary of Organic Compounds," Vol. 1, Oxford University Press, London, 1965, p 647; (b) p 645.

Salicylamide–Acetylenedicarboxylate Reactions as a Route to Benzoxazinones[1]

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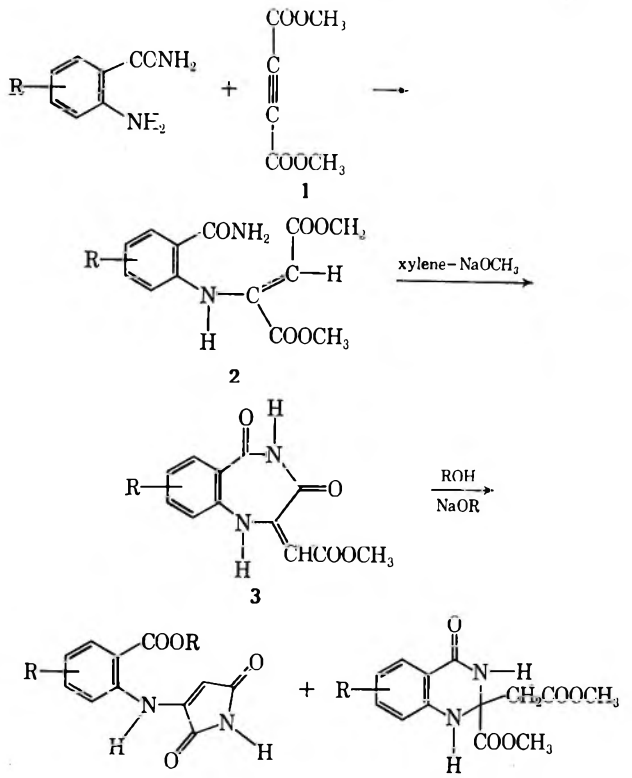
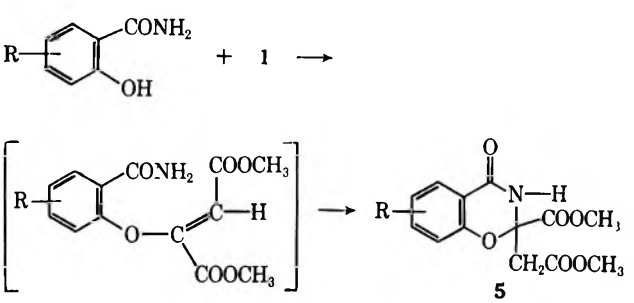
Previous reports from these laboratories have pointed to the considerable utility of acetylene esters in hetero ring-forming reactions.[2] We have noted that anthranilamides reacted with dimethyl acetylenedicarboxylate (**1**) to yield the corresponding anilinofumarates (**2**). These intermediate enamines underwent facile ring closure to 1,4-benzodiazepin-3,5-diones (**3**) which could be isolated in nonhydroxylic solvents but which



underwent ring-contraction rearrangement in alcoholic media to mixtures of maleimides and quinazolinones.[3]

Our studies on salicylamides and salicylanilides show that these systems more closely parallel the reactions of thiosalicylamide and **1**[4] rather than anthranilamides and **1**.[3] The amine and thiol additions were exothermic, required no base catalysis, and provided excellent yields of adducts which could be cyclized to seven-membered heterocyclics in the anthranilamide series and to six-membered benzothiazinones in the thiosalicylamide situation. The *o*-hydroxyamides yield exclusively six-membered benzoxazinones but they require base catalysis for both the OH-to-alkyne addition and for the cyclization step. With the exception of salicylamide and **1**, catalyzed by N-methylmorpholine, it is not possible to isolate the presumed intermediate phenol adducts (**4**).

Bases sufficiently strong to bring about hydroxyl addition to acetylenedicarboxylate are also capable of promoting cyclization to the benzoxazinones. This



(1) (a) Taken in part from the M.S. Thesis of L. A. S., Lehigh University, 1969. (b) Supported by Grant No. 1R01MH-13562 from the National Institute of Mental Health.

(2) See N. D. Heindel, P. D. Kennewell, and C. J. Ohnmacht, *J. Org. Chem.*, **34**, 1168 (1969), and references cited therein.

(3) N. D. Heindel, V. B. Fish, and T. F. Lemke, *ibid.*, **33**, 3997 (1968).

(4) N. D. Heindel, V. B. Fish, M. F. Ryan, and A. R. Lepley, *ibid.*, **32**, 2678 (1967).

method, therefore, does constitute a convenient one-step synthesis of a hitherto unknown type of substituted 1,3-benzoxazin-4-ones (**5**). Nmr and mass spectral studies (see Experimental Section) eliminate the alternative isomeric 1,4-benzoxazepin-4-ones as the possible reaction products. These six-membered heterocyclic compounds are prepared in 45–93% yields, with one exception, by the sodium methoxide catalyzed reaction of the corresponding salicylamide or salicylanilide with **1**. The condensation of 1-hydroxy-2-naphthamide with dimethyl acetylenedicarboxylate was exceedingly sluggish and presumably reflects a *peri* steric effect at the hydroxyl.

The intermediate adduct, **4**, isolated from the N-methylmorpholine-catalyzed addition of salicylamide and **1** was of fumarate geometry reflecting a transoid addition. Amines[5,6] and thiols[4,7] have been observed to add with similar *trans* stereospecificity. Previous workers in amine–acetylene ester adducts have noted that both geometric isomers are necessary to make an accurate structure assignment by nmr.[8,9] Reliable stereoelectronic criteria permit fumarate assignment to the more deshielded vinyl resonance.[9]

Although we obtained only one isomer of **4** (single vinyl resonance in nmr) we were able to prepare suitable maleate–fumarate models for spectral comparison by thermal equilibration of the adducts of **1** with methyl salicylate and methyl 5-chlorosalicylate. The fumarate vinyl proton in these substances was detected at δ 6.68 and the maleate vinyl at 5.00–5.03 ppm. In **4** the vinyl singlet was observed at δ 6.75 ppm thus permitting its assignment as a fumarate isomer.

Molecular models show that this intermediate adduct, **4**, is sterically capable of undergoing cyclization to a seven- or eight-membered system by amide displacement upon the corresponding side-chain ester, or of undergoing Michael-type internal NH addition to the six-membered system (benzoxazinones) or the seven-membered system (benzoxazepinones).

Even under experimental conditions (xylene/sodium methoxide) which effected excellent conversions of **2** to the benzodiazepine, **3**, none of the benzoxazepine counterpart was detected from **4**. Invariably, elemental analysis and nmr and infrared spectroscopy supported the benzoxazinone structure, **5**. The ring closure of **4** was indeed base catalyzed since prolonged reflux in methanol returned starting material. Amine bases can bring about cyclization but best results were obtained with sodium methoxide in methanol.

Experimental Section[10]

2-Carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-4H-1,3-benzoxazin-4-one (**6**).—A solution of 2.74 g (20 mmol) of salicylamide, 2.84 g (20 mmol) of **1**, and 0.11 g (2 mmol) of sodium methoxide in 64 ml of methanol was refluxed for 24 hr and concentrated *in vacuo*. Cooling precipitated white crystals of **6**: 2.55 g (46%); from methanol, mp 128.0–129.5°; nmr spectrum ($CDCl_3$) δ 3.31 (AB q, 2, J = 18 Hz, $-CH_2-$), 3.76 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), and 6.9–8.1 ppm (m, 5, Ar **H** and NH); ir spectrum (KBr) 3183 (NH) and 1754, 1742, 1675 cm^{-1} (C=O); mass spectrum (72 eV) m/e (rel intensity) 279 (<1), 220 (100), 206 (29), and 121 (35).[11]

Anal. Calcd for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.66; N, 5.02. Found: 55.77; H, 4.53; N, 5.10.

2-Carbomethoxy-2-carbomethoxymethyl-6-bromo-2,3-dihydro-4H-1,3-benzoxazin-4-one (**7**).—The reaction of 5-bromosalicylamide and **1** as described above gave a 56% yield of the bromobenzoxazinone, **7**: from benzene, mp 156.5–158.0°; nmr spectrum ($CDCl_3$) δ 3.31 (AB q, 2, J = 18 Hz, $-CH_2-$), 3.79 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 6.78–7.18 (m, 3, Ar **H**) and 7.80 ppm (broad s, 1, NH); ir spectrum (KBr) 3180 (NH) and 1757, 1730, 1687 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{12}BrNO_6$: C, 43.58; H, 3.35; N, 3.91. Found: C, 43.79; H, 3.42; N, 3.93.

2-Carbomethoxy-2-carbomethoxymethyl-6-chloro-2,3-dihydro-4H-1,3-benzoxazin-4-one (**8**).—When equimolar quantities (30 mmol) of 5-chlorosalicylamide and **1** were treated as above a 45% yield, mp 158.5–160.0°, from benzene, of **8** was obtained: nmr spectrum ($CDCl_3$) δ 3.30 (AB q, 2, J = 18 Hz, $-CH_2-$), 3.77 and 3.78 each (s, 3, OCH_3), 6.90–7.95 (m, 3, Ar **H**), and 7.68 ppm (broad s, 1, NH); ir spectrum (KBr) 3185 (NH) and 1759, 1735, 1685 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{12}ClNO_6$: C, 49.76; H, 3.83; N, 4.47. Found: C, 49.88; H, 3.84; N, 4.44.

2-Carbomethoxy-2-carbomethoxymethyl-6,8-diiodo-3-(4-iodophenyl)-2,3-dihydro-4H-1,3-benzoxazin-4-one (**9**).—A suspension of 5.91 g (10 mmol) of 3,4′,5-triiodosalicylanilide,[12] 1.70 g (12 mmol) of **1**, and 1 mmol of sodium methoxide in 50 ml of methanol was refluxed with stirring for 24 hr. Concentration and cooling precipitated a greenish-white solid which was recrystallized from 1:1 benzene: petroleum ether (60–110°) to yield 5.34 g (73%) of the white benzoxazinone, **9**: from benzene, mp 187–188°; nmr spectrum (trifluoroacetic acid) δ 3.42 (d, 2, $-CH_2-$), 3.72 (s, 3, OCH_3), 3.90 (s, 3, OCH_3), 7.1–8.5 ppm (m, 6, Ar **H**); ir spectrum (KBr) 1755, 1735 and 1685 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{14}I_3NO_6$: C, 31.11; H, 1.91; I, 51.98. Found: C, 30.90; H, 1.85; I, 51.89.

2-Carbomethoxy-2-carbomethoxymethyl-3-phenyl-2,3-dihydro-4H-1,3-benzoxazin-4-one (**10**) was prepared by dropwise addition of 30 mmol of **1** to a solution of 30 mmol of salicylanilide and 3 mmol of sodium methoxide in 50 ml of methanol. The addition required 30 min and the mixture was then stirred at room temperature for 24 hr during which time the benzoxazinone, **10**, precipitated. Concentration of the mother liquors produced additional material for a total of 9.89 g (93%) of white microneedles: from methanol, mp 170–172°; nmr spectrum (trifluoroacetic acid) δ 3.42 (s, 2, $-CH_2-$), 3.55 (s, 3, OCH_3), 3.83 (s, 3, OCH_3), and 7.0–8.1 ppm (m, 9, Ar **H**); ir spectrum (KBr) 1762, 1748 and 1690 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{17}NO_6$: C, 64.23; H, 4.79; N, 3.94. Found: C, 64.44; H, 5.01; N, 3.92.

2-Carbomethoxy-2-carbomethoxymethyl-3,4-dihydro-2H-naphth[2,1-*e*]1,3-oxazin-4-one (**11**) was prepared by reaction of 5.61 g (30 mmol) of 1-hydroxy-2-naphthamide, 4.26 g (30 mmol) of **1**, and 0.16 g (3 mmol) of sodium methoxide in 32 ml of methanol. After 4-hr reflux the reaction mixture was cooled and filtered to remove 2.15 g of 1-hydroxy-2-naphthamide. The oily residue was diluted with cold ether and filtered to isolate 1.0 g (10%) of the naphthoxazinone, **11**: from methanol, mp 150.5–152.0°; nmr spectrum ($CDCl_3$) δ 3.45 (s, 2, $-CH_2-$), 3.70 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), and 7.3–8.4 ppm (m, 7, Ar **H** and NH); ir spectrum (KBr) 3190 (NH) and 1755, 1742 and 1675 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{15}NO_6$: C, 62.01; H, 4.56; N, 4.26. Found: C, 62.16; H, 4.73; N, 4.29.

Comparison of the infrared spectrum of the oily mother liquors with that of an authentic sample[13] revealed that the material was mainly dimethyl methoxyfumarate, the product of the addition of methanol to **1**.

(5) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966).

(6) E. C. Taylor and N. D. Heindel, *J. Org. Chem.*, **32**, 3339 (1967).

(7) W. E. Truce in "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, Inc., New York, N. Y., 1961, pp 112–120.

(8) A. N. Kurtz, W. E. Billups, R. B. Greenlee, H. F. Hamil, and W. T. Pace, *J. Org. Chem.*, **30**, 3141 (1965).

(9) J. E. Dolfini, *ibid.*, **30**, 1298 (1965).

(10) Proton nmr spectra were obtained on a Varian A-60 spectrometer and are reported in δ (parts per million) units from TMS. Mass spectra were obtained on a Perkin-Elmer Hitachi RMU-6E spectrometer and infrared spectra on a Perkin-Elmer 257 spectrometer, calibrated against polystyrene. Combustion analyses were provided by Dr. George I. Robertson, Jr., Florham Park, N. J.

(11) Fragment ions corresponding to the loss of CH_2COOCH_3 (m/e 206) and to the loss of $COOCH_3$ (m/e 220) have been observed in a related quinazolinone diester (ref 3), and support the benzoxazinone assignment in this case.

(12) U. S. Patent 2,906,711 (1960); *Chem. Abstr.*, **54**, 3873 (1960).

(13) E. Winterfeldt and H. Preuss, *Chem. Ber.*, **99**, 450 (1966).

Dimethyl *o*-carboxamidophenoxyfumarate (4) was prepared by stirring together at room temperature for 24 hr a solution of 20 mmol each of salicylamide, 1, and N-methylmorpholine in 27 ml of diethyl ether. Addition of water and agitation precipitated 0.76 g (14%) of the phenol adduct, 4, which was recrystallized from methanol: mp 124.5–126.5°; nmr spectrum ($CDCl_3$) δ 3.75 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 6.75 (s, 1, vinyl H), 7.6 (broad s, 2, NH_2), and 6.6–8.2 ppm (m, 4, Ar H); ir (KBr) 3440, 3344, 3300, and 3240 (NH) and 1725 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.66; N, 5.02. Found: 55.63; H, 4.69; N, 5.07.

Cyclization of 4 in Xylene–Sodium Methoxide.—A solution of 0.40 g (1.4 mmol) of dimethyl *o*-carboxamidophenoxyfumarate, 4, and a catalytic quantity of sodium methoxide (0.4 mmol) in 50 ml of xylene was refluxed for 17 hr, filtered, and concentrated. The crude crystals were washed with cold ether and filtered to yield 0.18 g (45%) of the benzoxazinone, 6, identified by melting point and ir comparison with authentic sample.

Dimethyl *o*-carbomethoxyphenoxy-2-butene-1,4-dioate (12) was synthesized by allowing an ethereal solution of 0.20 mol each of methyl salicylate, triethylamine, and 1 to stand at room temperature for 2 days. The ether was removed, the residue dissolved in benzene, washed well with water, dried ($MgSO_4$), and distilled to yield 37.6 g (64%) of a pale yellow oil: bp 175–180° (1 Torr); nmr spectrum ($CDCl_3$) δ 3.70, 3.78, 3.92, 3.94, 3.98 and 4.03 for the respective methoxy singlets, 5.00 (s, 1, maleate vinyl H, 50%), 6.68 (s, 1, fumarate vinyl H, 50%) and 6.8–8.2 ppm (m, 4, Ar H).

Anal. Calcd for $C_{14}H_{14}O_7$: C, 57.14; H, 4.73. Found: C, 57.20; H, 4.71.

Dimethyl *o*-carbomethoxy-*p*-chlorophenoxy-2-butene-1,4-dioate (13) was prepared from methyl 5-chlorosalicylate as described above: bp 181–184° (1 Torr); 63%; nmr spectrum ($CDCl_3$) δ 3.62, 3.68, 3.71, 3.78, 3.93 and 3.95 for the methoxy singlets, 5.03 (s, 1, maleate vinyl H, 42%), 6.68 (s, 1, fumarate vinyl H, 58%) and 6.8–8.1 ppm (m, 3, Ar H).

Anal. Calcd for $C_{14}H_{13}ClO_7$: C, 51.14; H, 3.96. Found: C, 51.19; H, 4.08.

Registry No.—1, 762-42-5; 4 (R = H), 24704-24-3; 6, 24716-40-3; 7, 24716-41-4; 8, 24716-42-5; 9, 24716-43-6; 10, 24716-44-7; 11, 24716-45-8; 12 maleate, 24704-25-4; 13 maleate, 24710-88-1; 12 fumarate, 24710-82-5; 13 fumarate, 24710-83-6.

Fragmentation of a Sydnone *via* Elimination[1a,b]

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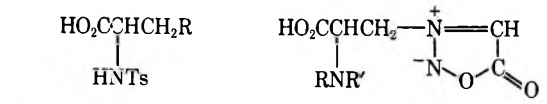
Although a number of characteristic reactions of sydnones have been thoroughly documented,[2] a novel type of fragmentation reaction has now been encountered during the course of an attempted preparation of 3-sydnonealanine (2a). It was hoped that 2a would possess carcinolytic activity because certain sydnones have tumor-inhibiting properties (*cf.* ref 2), the alanine moiety is biologically compatible, and there is a striking structural and electronic (zwitterionic) similarity between 2a and the isomeric azaserine (4), the latter being a well-known antileukemic agent.

The projected synthesis of 2a involved a standard sequence of reactions proceeding from the selectively protected 3-amino-2-(tosylamino)propionic acid (1b),[3] which was readily available by Hofmann degradation of N^2-tosylasparagine (1a).[3–5] Condensation of 1b with glycolonitrile[6] followed by acid hydrolysis of the resulting glycinonitrile 1c and nitrosation of the corresponding glycine 1d were all carried out in good yield.

The cyclodehydration of 1e with acetic anhydride under a variety of conditions gave two products (A and B) or mixtures thereof. Optimum yields (*ca.* 65%) of one of these compounds (A), mp 176–178° dec, were realized after 24 hr at room temperature, whereas heating for 30 min or allowing the reactants to stand at room temperature for 2 weeks produced a second compound (B), mp 143–145° dec, in 30–50% yield along with dark-colored, noncrystalline products.

The presence of both the sydnone ring and the *p*-toluenesulfonamido groups in A was indicated by ultraviolet maxima at 300 and 232 mμ, respectively. Identification of A as the N-acetyl derivative 2c of the expected sydnone 2b was supported also by its infrared spectrum, which showed the sydnone ring CH absorption[2] as well as three closely spaced bands in the 1700–1730-cm^{-1} region (C=O). No sulfonamide NH stretching absorption was observed.



1a, R = $CONH_2$
b, R = NH_2
c, R = $NHCH_2CN$
d, R = $NHCH_2CO_2H$
e, R = $N(NO)CH_2CO_2H$

2a, R = R′ = H
b, R = H; R′ = Ts
c, R = CH_3CO; R′ = Ts

3

4

Ts = *p*-$CH_3C_6H_4SO_2$

N-Acetyl-N-tosylalanine (5b) was prepared from N-tosylalanine (5a)[4] and acetic anhydride as a model to assist in the assignment of the carbonyl bands of 2c. Infrared comparison (Nujol) of the two compounds suggests that the high-frequency band (1728 cm^{-1}) of 2c is the sydnone carbonyl. Differentiation of the carbonyl bands of 2c was effected further by examining the spectra of 2c and 5b in dioxane. Assignments (see Experimental Section) were determined by comparison with N-acetyl-N-tosylglycine in which the positions (in dioxane) of the acetamido (1712 cm^{-1}) and carboxyl (1754 cm^{-1}) functions have been established.[7]

The formation of B from the N-nitrosoglycine 1e *via* the intermediate sydnone 2c appeared likely since B

(1) (a) Sydnones. V. Part IV: C. J. Thoman, S. J., D. J. Voaden, and I. M. Hunsberger, *J. Org. Chem.*, **29**, 2044 (1964). (b) This investigation was supported, in part, by a research grant (CA-05478) from the National Cancer Institute of the U. S. Public Health Service. (c) To whom all inquiries should be sent. This paper is taken, in part, from the Ph.D. dissertation of L. J. F., University of Massachusetts, 1965.

(2) F. H. C. Stewart, *Chem. Rev.*, **64**, 129 (1964).

(3) The terms tosylamino and tosyl refer to the *p*-toluenesulfonamido and *p*-tolylsulfonyl functions, respectively.

(4) Since the starting materials for the syntheses described herein were DL-asparagine and DL-alanine, all compounds with an asymmetric center have the DL configuration.

(5) J. Rudinger, K. Poduska, and M. Zaoral, *Collect. Czech. Chem. Commun.*, **25**, 2022 (1960).

(6) J. M. Tien and I. M. Hunsberger, *J. Amer. Chem. Soc.*, **83**, 178 (1961).

(7) M. Zaoral and J. Rudinger, *Collect. Czech. Chem. Commun.*, **26**, 2316 (1961).

also was obtained by heating **2c** with acetic anhydride. The single ultraviolet maximum at 232 mμ precluded the presence of a sydnone ring. Furthermore, the empirical formula indicated that two of the original three nitrogen atoms of **2c** had been lost. The acrylic acid structure **3** is in complete accord with the infrared spectrum of B. Finally, catalytic hydrogenation of **3** provided **5b** which was identical (mixture melting point and infrared spectrum) with the material obtained by treatment of **5a** with acetic anhydride.

This unexpected fragmentation of an otherwise stable sydnone[8] under the usual conditions of its synthesis, *i.e.*, dehydrative cyclization with acetic anhydride, may well prove to be a general reaction for such suitably constructed compounds. While the mechanism of the reaction has not been studied, acetate ion (in equilibrium with the acetic acid formed in the reaction) possibly acts as a mild acceptor for the methine proton activated by the carboxyl and sulfonamido groups. In addition, the cyclic azomethineimine structure[9] for sydnones or structures contributing to the aromatic resonance hybrid have a formal positive charge at ^{3}N.[2] This should lend additional driving force for the E2 elimination. The related problem concerning the fate of the presumed eliminated fragment (*i.e.*, the sydnonyl anion or formally the unknown parent heterocycle, sydnone) must await full elucidation of the reaction stoichiometry.

The sydnone **2c** and the intermediates **1a–e** were submitted to the Cancer Chemotherapy National Service Center for testing in their antitumor screen. All compounds were inactive.

Experimental Section

Melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were determined with a Beckman IR-5, a Perkin-Elmer Model 21, or a Perkin-Elmer Model 337 spectrophotometer fitted with a grating. Ultraviolet spectra were determined with a Cary Model 14 recording spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

N^2-Tosylasparagine (1a).—This compound was prepared from DL-asparagine monohydrate by the procedure used for the corresponding D isomer.[10] The crude product (85%, a white microcrystalline powder, mp 169–172°) was used for the next step without further purification. Recrystallization from 1:4 ethanol–water gave the analytical sample as colorless plates, mp 171–173° (lit.[11] mp 174.5–175.5°).

Anal. Calcd for $C_{11}H_{14}N_2O_5S$: C, 46.15; H, 4.93; N, 9.79; S, 11.18. Found: C, 46.48; H, 5.04; N, 9.70; S, 11.24.

3-Amino-2-(tosylamino)propionic Acid (1b).—Hofmann degradation of **1a** according to the method for the corresponding L isomer[5] gave crude **1b** (79%), sufficiently pure (mp 223–224° dec) for use in the next step. An analytical sample (colorless lathes) was prepared by recrystallization from 1:3 glacial acetic acid–water and drying for 24 hr at 78° (3 mm) over P_2O_5, mp 225–226° dec.

Anal. Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.51; H, 5.47; N, 10.85; S, 12.39. Found: C, 46.39; H, 5.45; N, 11.02; S, 12.55.

3-[(Cyanomethyl)amino]-2-(tosylamino)propionic Acid (1c).—To a cold solution of 9.60 g (0.240 mol) of NaOH in 162 ml of water, 61.9 g (0.240 mol) of **1b** was added in portions. If all the amino acid did not dissolve, small additional amounts of 5% aqueous NaOH were added until complete solution occurred or until no more solid dissolved. The stirred solution was warmed to room temperature and treated with 23.5 g (0.29 mol) of 70% aqueous glycolonitrile. The white precipitate that formed within 15 min redissolved after *ca.* 30 min. After 12 hr, the orange solution was clarified by filtration and cooled. Slow addition of concentrated HCl to pH 2–3 (pH paper) precipitated a very finely divided solid that was washed with cold water and dried *in vacuo* over P_2O_5: yield 60.4 g (85%) of a peach-colored powder; mp 163–166° dec. This product was suitable for use in the next step.

Crude **1c** crystallized with difficulty from the common organic solvents and partially reverted to the starting material **1b** on attempted recrystallization from water or aqueous ethanol. A sample was purified by dissolving in the minimum amount of 5% aqueous $NaHCO_3$, diluting with a fourfold volume of water, and reprecipitating with 10% aqueous HCl. Thorough washing with water and drying yielded a light pink, microcrystalline solid. This process, repeated three times, gave a sample: mp 172–174° dec, followed by partial resolidification and gradual remelting at 180–193°; ir (Nujol) 3260 (sulfonamide NH), 1630 (ionized carboxyl), 1320 and 1165 cm^{-1} (SO_2).

Anal. Calcd for $C_{12}H_{15}N_3O_4S$: C, 48.48; H, 5.09; N, 14.14; S, 10.76. Found: C, 48.35; H, 5.13; N, 14.10; S, 10.56.

3-[(Carboxymethyl)amino]-2-(tosylamino)propionic Acid (1d).—A solution of 59.4 g (0.200 mol) of crude **1c** in 630 ml of concentrated HCl was diluted with 315 ml of water and refluxed for 3.5 hr. After evaporating to dryness *in vacuo*, the residue was taken up in ice-cold water, filtered from insolubles, and again evaporated *in vacuo* to dryness. Careful treatment (ice bath) of the red-brown, semisolid residue with 342 ml (*ca.* 10% over theory) of 5% aqueous $NaHCO_3$ gave a suspension (pH 2, pH paper) which was chilled thoroughly and filtered. The solid which was washed with cold water, sucked dry, washed with ether, and dried gave 48.3 g (76%) of a pink, microcrystalline powder, mp 172–174° dec. Recrystallization from 1:1 ethanol–water (charcoal) yielded colorless flat needles (60%): mp 177–179° dec, unchanged by further recrystallization; ir (Nujol) 3260 (sulfonamide NH), 1715 (carboxyl), 1620 (ionized carboxyl), 1330 and 1160 cm^{-1} (SO_2).

Anal. Calcd for $C_{12}H_{16}N_2O_6S$: C, 45.57; H, 5.10; N, 8.86; S, 10.12. Found: C, 45.46; H, 5.02; N, 8.76; S, 10.11.

3-[(Carboxymethyl)nitrosamino]-2-(tosylamino)propionic Acid (1e).—A stirred suspension of 28.0 g (0.886 mol) of once-recrystallized **1d**, 8 ml of concentrated HCl, and 105 ml of water was treated with small portions of concentrated HCl (*ca.* 11 ml) until complete solution occurred. With cooling (−5°), a solution of 6.73 g of sodium nitrite in 50 ml of water was added during 30 min. Stirring was continued for 1 hr at −5°, 1 hr at 0°, and overnight at room temperature. Sufficient ether was added to dissolve the precipitate and the two clear layers separated. The aqueous layer was saturated with NaCl and extracted with three additional portions of ether, and the combined extracts were dried ($MgSO_4$). Evaporation *in vacuo* gave a frothy oil which was triturated with dry chloroform and air-dried: yield, 29.4 g (96%) of a pale yellow powder (positive Liebermann test); mp 146–149° dec with partial melting from 94°. The melting point of this product, which appeared to be a solvate (probably hydrate), varied widely from run to run. On occasion, melting at 70–77° followed by partial solidification (95–140°) and decomposition (147–149°) was observed. This material could be used for preparation of the sydnone **2c** without further purification; however, superior yields were realized when it was recrystallized from ethyl acetate–hexane, 77–90% recovery of a pale yellow solid (positive Liebermann test), mp 151–153° dec. Additional recrystallization from ethyl acetate–hexane provided an analytical sample: mp 152–153° dec; ir (Nujol) 3145 (sulfonamide NH), 1750 (carboxyl), 1690 (carboxyl), 1335 and 1155 cm^{-1} (SO_2).

Anal. Calcd for $C_{12}H_{15}N_3O_7S$: C, 41.73; H, 4.38; N, 12.17; S, 9.29. Found: C, 41.82; H, 4.81; N, 11.76; S, 9.06.

N-Acetyl-N-tosyl-3-sydnonealanine (2c).—A stoppered suspension of 6.00 g (0.0174 mol) of once-recrystallized **1e** and 18 ml of acetic anhydride was stirred at room temperature. Within about 12 hr complete solution occurred. After 24 hr, the mixture of crystalline precipitate and yellow supernatant liquid was cooled (ice bath) and 120 ml of ice-cold water added. The ice bath was removed after several hours but stirring continued for several more hours. An additional 90 ml of water was added and the suspension stirred vigorously until all the oily semisolid had solidified. After cooling (ice bath), the product which was washed with cold water and dried gave 4.30 g (67%) of cream-colored powder, mp 172–175° dec. Recrystallization from

(8) Samples of **2c** have been stored for at least a year without appreciable deterioration.

(9) F. H. C. Stewart and N. Danieli, *Chem. Ind.* (London), 1926 (1963).

(10) A. Kjaer and E. Vesterager, *Acta Chem. Scand.*, **14**, 961 (1960).

(11) M. R. Bovarnick, *J. Biol. Chem.*, **148**, 151 (1943).

ethanol–hexane (charcoal) yielded clusters of colorless prisms (negative Liebermann test), mp 175–177° dec. An additional recrystallization yielded pure **2c**: mp 176–178° dec; uv max (dioxane) 232 and 300 mμ (ε 15,000 and 6300); ir (Nujol) 3155 (sydnone CH), 1728 (sydnone C=O), 1714 (carboxyl or acetamido C=O), 1703 (carboxyl or acetamido C=O), 1355 and 1165 cm^{-1} (SO_2); ir (dioxane) 1765 (sydnone C=O), 1750 (carboxyl C=O), and 1715 cm^{-1} (acetamido C=O).

Anal. Calcd for $C_{14}H_{15}N_3O_7S$: C, 45.53; H, 4.09; N, 11.38; S, 8.66. Found: C, 45.06; H, 4.06; N, 11.27; S, 8.65.

2-[N-Acetyl(tosylamino)]acrylic Acid (3). A. From 2c and Acetic Anhydride.—A suspension of 500 mg (1.4 mmol) of **2c** and 2.5 ml of acetic anhydride was heated on the steam bath with protection from moisture. The solid gradually dissolved with moderate evolution of gas; after 30 min the orange solution was cooled (ice bath) and 8.5 ml of ice-cold water was added. Stirring was continued for several hours during which the initially formed oil became a semisolid. On being warmed to room temperature the solid dissolved, and the solution was evaporated to dryness *in vacuo*. Drying *in vacuo* over KOH produced a semisolid which on trituration and washing with several portions of anhydrous ether left 110 mg (29%) of **3** as a light tan powder, mp 140–144° dec. Two recrystallizations from ethyl acetate–hexane (charcoal) yielded clusters of small colorless needles: mp 143–145° dec; ir (Nujol) 1720 (acetamido C=O), 1690 (conjugated carboxyl C=O), 1635 (conjugated olefin C=C), 1350 and 1165 (SO_2), and 915 cm^{-1} (olefin CH deformation).[12]

Anal. Calcd for $C_{12}H_{13}NO_5S$: C, 50.88; H, 4.63; N, 4.95; S, 11.30. Found: C, 50.81, 50.69; H, 4.64, 4.53; N, 4.80; S, 11.34.

B. From 1e and Acetic Anhydride.—A stoppered suspension of 1.00 g (2.9 mmol) of once-recrystallized **1e** and 5 ml of acetic anhydride was allowed to stand in the dark at room temperature with occasional swirling. Within 12 hr complete solution occurred; after 2 weeks the clear, orange solution was added with stirring to 20 ml of cold water (ice bath). The ice bath was removed after several hours, but vigorous stirring was continued overnight until the amorphous semisolid was converted into a uniform suspension of flocculent solid. After cooling, the product which was filtered, washed thoroughly with ice water, and dried gave 0.44 g (54%) of cream-colored powder, mp 141–143° dec. Its ir was identical with that obtained for the product in part A above.

N-Acetyl-N-tosylalanine (5b). A. From 5a and Acetic Anhydride.—A stoppered suspension of 7.29 g (0.0300 mol) of powdered N-tosyl-DL-alanine (**5a**)[13] and 30 ml of acetic anhydride was stirred at room temperature. Within 12 hr solution occurred, and after 26 hr this was cooled (ice bath) and 100 ml of ice-cold water added with stirring. The ice bath was removed after 3 hr but stirring was continued for 1 hr during which the initially formed colorless oil dissolved. A small sample of this solution was removed, diluted with excess water, and scratched to initiate crystallization. The reaction mixture then was seeded, and after standing 2 hr (ice bath) the solid was filtered, washed with cold water, and air-dried: yield, 6.30 g (74%) of a snow-white solid; mp 122–123°. Recrystallization from 2:1 carbon tetrachloride–benzene gave colorless prisms: mp 122.5–123.5°; uv max (dioxane) 232 mμ (ε 14,500); ir (Nujol) 1713 (carboxyl or acetamido C=O), 1700 (carboxyl or acetamido C=O), 1350 and 1170 cm^{-1} (SO_2); ir (dioxane) 1755 (carboxyl C=O) and 1707 cm^{-1} (acetamido C=O).

Anal. Calcd for $C_{12}H_{15}NO_5S$: C, 50.52; H, 5.30; N, 4.91; S, 11.22. Found: C, 50.57; H, 5.19; N, 4.80; S, 11.48.

The acetyl group of **5b** was readily cleaved to regenerate **5a**.[14] Thus, when a solution of 2.00 g (7 mmol) of **5b** and 5 ml concentrated NH_4OH, which had been allowed to stand at room temperature for 1 hr, was diluted with water (5 ml) and acidified (pH 1–2) with concentrated HCl, a colorless oil separated which readily solidified. Filtration, washing, and drying gave a 92% yield of **5a**: mp 140–142°, no melting point depression with authentic[13] **5a** and identical ir.

B. By Catalytic Reduction of 3.—PtO_2 (40 mg), 280 mg (0.99 mmol) of **3**, and 20 ml of glacial HOAc was hydrogenated (Parr apparatus) for 12 hr at 40 psig. The catalyst was washed with a little glacial HOAc the combined filtrates were evaporated *in vacuo* almost to dryness. Addition of 15 ml of water to the residual oil and scratching initiated solidification. After cooling (ice bath), the solid was filtered, washed with cold water, and dried: yield 210 mg (75%) of cream powder; mp 122–124°, mmp 122–124° with sample prepared as in A. The ir was identical with that obtained for the product in A.

Registry No. —**1b**, 24571-53-7; **1c**, 24627-11-0; **1d**, 24599-14-2; **1e**, 24627-12-1; **2c**, 24627-13-2; **3**, 24571-54-8; **5b**, 24627-13-4.

(12) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen and Co., London, 1960, p 34.

(13) A. F. Beecham, *J. Amer. Chem. Soc.*, **79**, 3257 (1957).

(14) J. M. Swan and V. du Vigneaud, *ibid.*, **76**, 3110 (1954).

Dehydration of Amidoximes with and without Rearrangement[1]

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Carbodiimides **4** and amidines **5** have been obtained for the first time from the reaction between an N-aryl or N-alkyl amidoxime **1** and benzenesulfonyl chloride in pyridine.[2,3] As expected, a 2-substituted benzimidazole is the major product from an N-aryl amidoxime,[3] but similar dehydration of an N-alkyl amidoxime, previously unexplored, does not give an intramolecular cyclization.

Dehydration of an amidoxime without rearrangement leaves an azomethine nitrene **6**. Presumably as a triplet, the nitrene abstracts hydrogen from solvent to bring about the formation of an amidine **5**. Ring closure by intramolecular insertion into an appropriate aromatic CH bond may proceed from a nitrene such as **6a** and **6d**.[4] However, the formation of benzimidazoles in the dehydration of N-aryl amidoximes **1a** and **1d** does not depend on nitrene intermediacy insofar as ring closure from a corresponding nitrenium cation may occur.[5] The formation of a carbodiimide has been found to be concerted with the elimination of carbon dioxide from an oxadiazolone rather than by rearrangement of an azomethine nitrene which is also produced.[4] We now suggest that carbodiimide formation proceeds from an O-benzenesulfonyl ester **2** of an amidoxime simultaneously with α or 1,3 elimination.

(1) Financial assistance was received from NASA Grant No. NGR 14-012-004.

(2) M. W. Partridge and H. A. Turner, *J. Pharm. Pharmacol.*, **5**, 103 (1959), established the initial product as a carbodiimide (RN=C=NH) which rearranged into a cyanamide (RNHCN) in the similar dehydration of a primary amidoxime.

(3) M. W. Partridge and H. A. Turner, *J. Chem. Soc.*, 2086 (1958), produced 2-substituted benzimidazoles from similar treatment of N-aryl amidoximes. When carried out in aqueous sodium hydroxide, carbodiimides, but not benzimidazoles, were obtained from $C_6H_5NHC(R)=NOH$ and benzenesulfonyl chloride.

(4) J. H. Boyer and P. J. A. Frints, in press.

(5) Cyclization into a 2-substituted benzimidazole from azomethine nitrenium cations, produced by dissociation of the ester,[2] has been proposed. A discrepancy between product yields for **3a**,[6] **4a**, and **3d**[7] and the corresponding yields previously obtained[3] (Table I) has not been accounted for.

(6) F. C. Cooper and M. W. Partridge, *J. Chem. Soc.*, 225 (1953). An authentic sample was prepared by mixing equivalent amounts of 2-benzylbenzimidazole and benzenesulfonic acid in chloroform.

(7) K. Hoffmann in "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., John Wiley & Sons, Inc., New York, N. Y., 1953, p 380: **3d** hydrochloride mp 90–92°; **3d** picrate mp 212–213°.

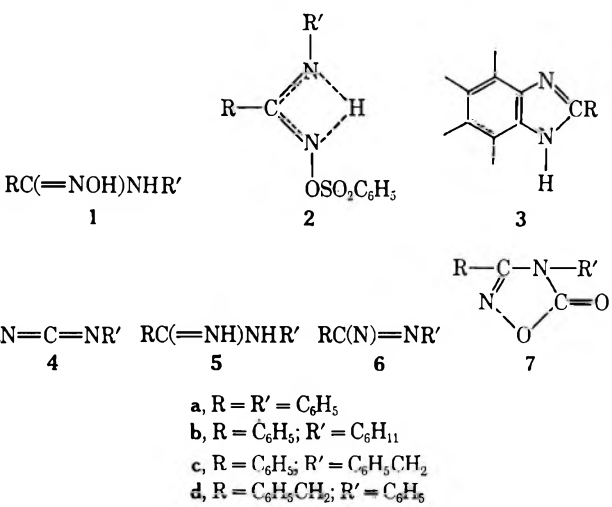
TABLE I

PRODUCTS FROM AMIDOXIMES 1 AND BENZENESULFONYL CHLORIDE IN ANHYDROUS PYRIDINE[a]

		Products[b]							
		3[c]		4			5		
1	Solvent[a]	Mp, °C	Yield, %	Bp, °C (mm)	Yield, %	Derivative,[d] mp, °C	Mp, °C	Yield, %	Derivative,[e] mp, °C
a	Benzene	290–291[h]	72[f]		18[g]	236–237[h]		0	
b	Benzene			116–118[h] (0.7)	64	180–182[h]	114–115[h]	Trace	278–280[i]
	Dioxane				83[i]			1.5	
c	Benzene			138–140[h] (0.25)	88[i]	168–169[h]		Trace	222–225[k]
d	Dioxane	187–188[h]	72[l]		0		137–139[h]	10	

[a] Benzene was dried over sodium wire. Dioxane was refluxed over lithium aluminum hydride for 3 hr and distilled from the hydride immediately before use. Pyridine was stored over potassium hydroxide pellets for at least 1 week before use. [b] Each product identification consisted of identical comparison of ir and/or nmr spectra with authentic spectra and mixture melting point. [c] **3a** picrate mp 270–272°;[6] **3d** benzenesulfonate mp 183–184°,[6] **3d** hydrochloride mp 90–92°,[7] **3d** picrate mp 212–213°.[7] [d] Each carbodiimide **4a–c** was converted into the corresponding urea by stirring with 6 *N* hydrochloric acid for a few minutes. The melting point of each urea is recorded. [e] **5b** hydrochloride and **5c** hydrochloride precipitated from aqueous acid solution. The melting point of each hydrochloride is recorded. [f] A 98% yield was reported.[3] [g] A 69% yield was reported for the reaction in aqueous sodium hydroxide.[3] [h] J. H. Boyer and P. J. A. Frints, submitted for publication. [i] Yield based on assumed quantitative conversion into the corresponding urea. [j] P. Oxley and W. F. Short, *J. Chem. Soc.*, 499 (1949). [k] P. Oxley and W. F. Short, *ibid.*, 1114 (1947). [l] A 63% yield was previously reported.[3]

In agreement with earlier observations on the azomethine nitrenes **6a–d**[4] cyclization accompanying dehydration of amidoximes has not been observed when an



N–C bond formation required (1) attack at an aliphatic carbon atom, (2) indole rather than benzimidazole ring closure, and (3) ring closure to a six-membered ring. In contrast to results from oxadiazolones **8**[4] fragmentation of an amidoxime into a nitrile (RCN) and a nitrene (R′N) was not detected.

Experimental Section

Each amidoxime **1a–d** was previously prepared as an intermediate for conversion into an oxadiazolone **7a–d**.[4]

Except for product isolation the general procedure described by Partridge and Turner[2,3] was followed for treating each amidoxime with benzenesulfonyl chloride in pyridine. A solution of 0.01 mol of the amidoxime dissolved in 10 ml of benzene and 5 ml of pyridine, protected from moisture, was cooled to 0–5° in an ice bath. A solution of 1.76 g (0.01 mol) of benzenesulfonyl chloride in 5 ml of benzene was added dropwise with stirring. The addition was completed in 30 min during which time a colorless solid separated and a light yellow color developed. The mixture was kept overnight at 0–5°.

Products from N-Cyclohexylbenzamidoxime.—Removal of the solvent from the reaction mixture obtained from N-cyclohexylbenzamidoxime left a light brown oil and a solid residue. Extraction with 25 ml of hexane left 3.3 g of an insoluble colorless solid, mp 107–115°. Its aqueous solution was made basic by adding solid potassium hydroxide and was then extracted with chloroform in which 8 mg of light brown solid, mp 105–110°, did not dissolve and gave an ir spectrum which resembled that of N-cyclohexylbenzamidine. Removal of hexane from the first extraction left 1.85 g of an oil from which N-cyclohexyl-N′-phenylcarbodiimide distilled at 116–118° (0.7 mm),[4] 1.27 g (64%), and left a dark black residue. Both ir and nmr spectra of the distillate were identical with the respective spectra for an authentic sample of N-cyclohexyl-N′-phenylcarbodiimide.[4] Quantitative hydrolysis with 2 *N* hydrochloric acid gave N-cyclohexyl-N′-phenylurea, mp and mmp 180–182°, with both ir and nmr spectra identical with the respective spectra for an authentic sample of the urea.[4]

When anhydrous dioxane was substituted for benzene, the reaction mixture was stirred with 10 ml of 6 *N* hydrochloric acid. Amost immediately, a precipitate of colorless N-cyclohexy-N′-phenylurea appeared. After 30 min it was isolated, 1.65 g (7.5 mmol), 75%, mp 181–182.5°. A chloroform extract of the filtrate was dried over magnesium sulfate, filtered, and concentrated to give a light brown solid, mp 150–160°, which recrystallized from acetone as 170 mg (0.7 mmol), 7.8%, mp and mmp 180–181.5° of N-cyclohexyl-N′-phenylurea, ir and nmr spectra identical with those of authentic material. The acid solution was treated with potassium hydroxide pellets while cooling in an ice bath and was extracted with chloroform. After drying, filtering, and evaporating, the chloroform extracts a brown solid, which became colorless N-cyclohexylbenzamidine hydrochloride after washing with ether, mp 278–280°,[4] 42 mg (0.17 mmol), 1.7%, identical with those of an authentic sample. After treating the hydrochloride with potassium hydroxide pellets with stirring for 15 min, the solution was extracted with ether. Evaporation of the dried ether extracts gave 30 mg (0.15 mmol), 1.5%, of colorless N-cyclohexylbenzamidine, mp and mmp 112–114°, ir and nmr spectra identical with those for an authentic sample.[4]

Isolation of 2-Phenylbenzimidazole.—In working up the reaction mixture from N-phenylbenzamidoxime, hexane extraction left an insoluble solid. After washing with 10% potassium hydroxide, the solid recrystallized from ethanol as colorless 2-phenylbenzimidazole, mp 290–291°,[4] 1.39 g (72%).

Other products are isolated by similar procedures and are described in Table I.

Registry No.—**1a**, 3488-57-1; **1b**, 24706-91-0; **1c**, 3488-55-9; **1d**, 24711-18-0; benzenesulfonyl chloride, 98-09-9.

The Preparation and Cleavage of Some 3,3-Dimethyl-3-silatetrahydrocarbazoles

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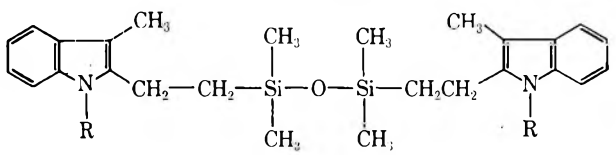
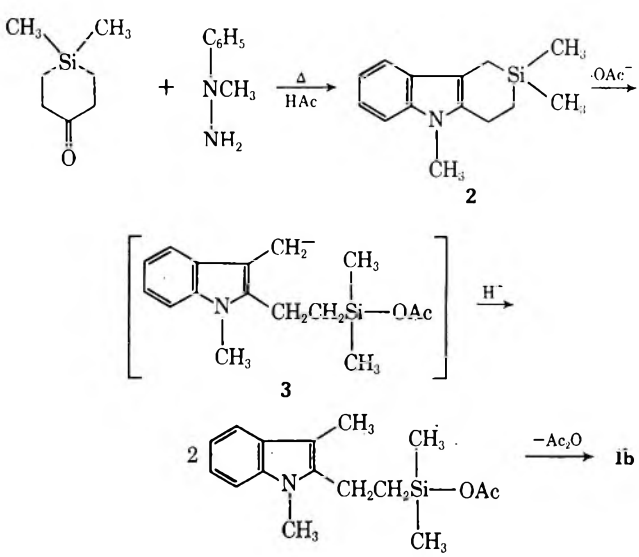
In a continuing study of polymethyleneindoles,[1] the preparation of sila analogs of tetrahydrocarbazole was undertaken. A modified Fischer indole synthesis[2] with 4,4-dimethyl-4-silacyclohexanone[3] and phenylhydrazine in refluxing glacial acetic acid (3 hr) led to an unstable, colorless product (1a), which underwent air oxidation to orange and then brown solids. With 1-methyl-1-phenylhydrazine, the more stable **1b** was obtained. Alkylation of **1a** with methyl iodide and dimethylaminopropyl chloride gave **1b** and **1c**, respectively. Analyses of these products established the presence of oxygen (0.5 g-atom) and led to assignment of the disiloxane structures **1a–c**; nmr spectra were consistent with the CH_2CH_2Si–O moiety.



1a, R = H
b, R = CH_3
c, R = $(CH_3)_2N(CH_2)_3$

The formation of **1** suggested that the desired dimethylsilatetrahydrocarbazole is formed early in the reaction period and is cleaved during further refluxing. When 4,4-dimethyl-4-silacyclohexanone was refluxed with 1-methyl-1-phenylhydrazine in glacial acetic acid for 5 min, a 72% yield of **2** was obtained. By refluxing **2** in acetic acid containing 15% water for 3 hr, **1b** was obtained in 65% yield. In the absence water, or when 1% water was added to the reaction mixture, no products could be isolated. The formation of **1b** from **2** is presumably initiated by nucleophilic attack of acetate ion on silicon, a reaction well known for benzylic silanes.[4] Protonation of the resonance-stabilized anion **3** and elimination of acetic anhydride then led to **1**.



Experimental Section

Melting points are uncorrected. Nmr spectra were obtained on a Varian 60-Mc spectrometer using tetramethylsilane as internal reference. The ir spectra were obtained in CCl_4, using a Perkin-Elmer Model 21 double-beam spectrophotometer. Uv spectra were obtained with a Perkin-Elmer Model 202 spectrophotometer.

Microanalysis were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

N-Methyl-3,3-dimethyl-3-silatetrahydrocarbazole (2).—To a solution of 2.1 g of 4,4-dimethyl-4-silacyclohexanone (0.015 mol) in 12 ml of glacial acetic acid (under nitrogen) was added, all in one portion, 2 g of 1-methyl-1-phenylhydrazine (0.015 mol + 10% excess). The mixture was refluxed exactly 5 min and allowed to cool to room temperature. The crystalline product was slurried with 20 ml of methanol and refrigerated for 3 hr. Filtering and washing twice with 5 ml of cold methanol gave crystals (3 g, 72.6%), mp 75–76°. Recrystallization from methanol gave white flakes, mp 77°.

Anal. Calcd for $C_{14}H_{19}NSi$: C, 73.30; H, 8.35; N, 6.10; Si, 12.25. Found: C, 73.42; H, 8.41; N, 6.06; Si, 12.18.

Nmr ($CDCl_3$) δ 7.45 (m, 1 H, Ar), 7.15 (m, 3 H, Ar), 3.53 (s, 3 H, N-CH_3), 2.95 (t, 2 H, J = 7 cps, CH_2–CH_2–Si), 1.85 (s, 2 H, $CH_2Si<$), 0.95 (t, 2 H, J = 7 cps, $CH_2CH_2Si<$), 0.17 [s, 6 H, $Si(CH_3)_2$]; uv max (95% EtOH) 232 mμ (ε 22,200); ir 8 μ [$Si(CH_3)_2$].

1,3-Bis[2-(1,3-dimethylindol-2-yl)ethyl]-1,1,3,3-tetramethyldisiloxane (1b).—A solution of 5.68 g of 4,4-dimethyl-4-silacyclohexanone (0.04 mol) dissolved in 30 ml of glacial acetic acid was protected by a stream of nitrogen and treated dropwise with 5.3 g of 1-methyl-1-phenylhydrazine (0.02 mol + 10%). The mixture was refluxed for 3 hr and allowed to cool until crystallization started (30 min). It was then diluted with 30 ml of acetic acid and allowed to stand for 24 hr. Filtering and washing with acetic acid gave crystals (6 g), mp 106–108°. An additional 1.6 g (mp 106–107°) was obtained from the filtrate by dilution with an equal volume of water, making a total yield of 80%. Recrystallization once from methanol gave beige crystals, mp 109–110°.

Anal. Calcd for $C_{28}H_{40}N_2OSi_2$: C, 70.53; H, 8.45; N, 5.87; Si, 11.78; mol wt, 476. Found: C, 70.26; H, 8.19; N, 6.06; Si, 11.71; mol wt, 454 (mass spectra showed M^+ at 476).

Nmr ($CDCl_3$) δ 7.3 (m, 4 H, Ar), 3.65 (s, 3 H, NCH), 2.8 (t, 2 H, J = 8 cps, -CH_2CH_2Si=), 2.28 (s, 3 H, -C-CH_3), 0.82 (t, 2 H, J = 8 cps, CH_2CH_2Si=), 0.2 [s, 6 H, $Si(CH_3)_2$]; uv max (95% EtOH) 230 mμ (ε 65,500); ir (CCl_4) 8 μ [$Si(CH_3)_2$], 9.5 (Si–O–Si).

1,1,3,3-Tetramethyl-1,3-bis[2-(3-methylindol-2-yl)ethyl]disiloxane (1a).—In a 200-ml flask equipped with a dropping funnel, nitrogen intake, and reflux condenser was placed 5.68 g of 4,4-dimethyl-4-silacyclohexanone (0.04 mol) and 30 ml of glacial acetic acid. After the mixture started to reflux, 4.8 g of phenylhydrazine (0.04 mol + 10%) was introduced dropwise. The mixture was boiled for 3 hr, allowed to cool to 60°, and 5 ml of water was added slowly, followed by 50 ml of 70% acetic acid. Refrigeration and filtration yielded a product which was recrystallized from 150 ml of methanol, weighed 4.6 g (51.3%), and melted at 117–119°. One additional recrystallization from methanol gave a product with mp 119–120°.

Anal. Calcd for $C_{26}H_{36}N_2OSi_2$: C, 69.59; H, 8.09; N, 6.24; Si, 12.52. Found: C, 69.65; H, 8.23; N, 6.09; Si, 12.77.

Nmr (CDCl) δ 7.1 (m, 5 H, Ar, NH), 2.6 (t, 2 H, J = 8 cps, CH_2CH_2Si), 2.05 (s, 3 H, =CCH_3), 0.75 (t, 2 H, J = cps, CH_2CH_2Si), 0.1 [s, 6 H, $Si(CH_3)_2$]; uv max (95% EtOH) 228 mμ (ε 66,500); ir (CCl_4) 8 μ [$Si(CH_3)_2$], 9.5 (Si–O–Si).

(1) (a) L. M. Rice, E. Hertz, and M. E. Freed, *J. Med. Chem.*, **7**, 313 (1964); (b) M. E. Freed, E. Hertz, and L. M. Rice, *ibid.*, **7**, 628 (1964).
(2) C. U. Rogers and B. B. Corson, *J. Amer. Chem. Soc.* **69**, 2910 (1947).
(3) R. A. Benkeser and E. W. Bennett, *ibid.*, **80**, 5414 (1958).
(4) C. Eaborn, "Organosilicon Compounds," Academic Press Inc., New York, N. Y., 1960, p 143.

1,3-Bis[2-(1-[3-dimethylaminopropyl]-3-methylindol-2-yl)-ethyl]-1,1,3,3-tetramethyldisiloxane (1c).—A freshly prepared solution of 15.07 g of IVa (0.07 mol) in 100 ml of dimethylformamide was stirred under nitrogen and treated with 3.7 g of sodium hydride in mineral oil (51.5%). Stirring was continued for 1 hr. γ-Dimethylaminopropyl chloride (8.9 g) was added dropwise, and the suspension was heated at 60° and stirred for 24 hr. The reaction mixture was poured into 2 l. of water and extracted with ether. The ethereal solution was extracted with 5% hydrochloric acid and the acid extract was made basic, extracted again with ether, and dried over sodium sulfate. The ether was removed and the residue was distilled giving 13.2 g of the product, bp 240–250° (0.04 mm).

Anal. Calcd for $C_{36}H_{58}ON_4Si_2$: C, 69.85; H, 9.44; N, 9.05; Si, 9.07; mol wt, 619. Found: C, 69.96; H, 9.40; N, 9.32; Si, 9.35; mol wt, 582.

The dihydrochloride was prepared with alcoholic hydrogen chloride in acetonitrile; ether was added until the solution clouded. Drying *in vacuo* at 110° gave a product that melted at 170–171°.

Anal. Calcd for $C_{36}H_{60}OCl_2N_4Si_2$: C, 62.48; H, 8.74; Cl, 10.25; N, 8.10; Si, 8.12. Found: C, 62.24; H, 8.95; Cl, 9.91; N, 8.18; Si, 7.82.

The dimethiodide, prepared in refluxing ethanol (MeOH–EtAc), had mp 145–147°.

Anal. Calcd for $C_{38}H_{64}ON_4I_2Si_2$: C, 50.55; H, 7.11; I, 28.11. Found: C, 50.43; H, 7.11; I, 27.97.

Conversion of 2 to 1b.—N-Methyl-3,3-dimethyl-3-silatetrahydrocarbazole (2) (0.5 g, 0.00218 mol) was refluxed with 6 ml of glacial acetic acid and 1 ml of water for 3 hr. When cooled to room temperature and starting to crystallize, the mixture was diluted with 2 ml of methanol and refrigerated. Later it was filtered, washed with 5 ml of methanol containing 1 ml of water, and dried giving 0.34 g (65%) of **1b**, mp 108°. One recrystallization from methanol gave material having mp 109–110°. A mixture melting point with a sample described above showed no depression, and the two materials had identical spectra.

When the same experiment was performed employing glacial acetic acid or glacial acetic acid containing only 1% water, the resulting products appeared to be mixtures, since they were of indefinite melting point (125–135°) and more highly colored.

Registry No.—**1a**, 24571-87-7; **1b**, 24571-88-8; **1c**, 24571-89-9; **1c**·2HCl, 24571-90-2; **1c**·2MeI, 24571-51-5; **2**, 24571-52-6.

Reactions of Acenaphthenequinone and Ammonium Acetate in the Presence of Aryl Aldehydes

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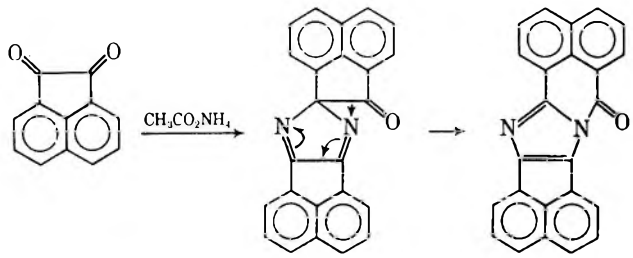
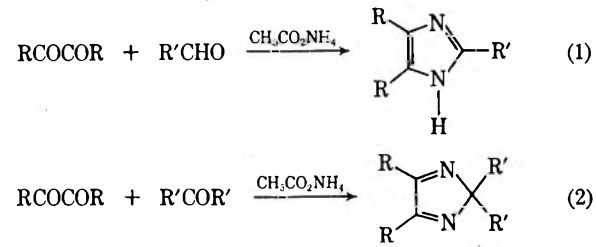
1,2 diketones and ammonium acetate in acetic acid react with arylaldehydes to form 2,4,5-trisubstituted imidazoles[1] (reaction 1) and with ketones to form 2,2,4,5-tetrasubstituted 2H-isoimidazoles[2] (reaction 2). However, with acenaphthenequinone, **1**, and salicylaldehyde, under the conditions of reaction 1, the major product is a red solid to which the imidazole structure **3** has been assigned. Product **3** is not derived from the aldehyde (*i.e.*, by reaction 1), but instead is the result of a reaction in which **1** acts both as a diketone and as a monoketone. For reasons described below, the product does not appear to be the 2H-isoimidazole **2** which would normally be the product of reaction 2 but is **3**, a rearrangement product of **2**.



1 **2** **3**



(1) (2)

The infrared spectrum of **3** is identical with the spectrum of a compound which was isolated from the reaction of **1** with ammonia previously[3–7] and had been assigned structure **2**.[6,7] Structure **2**, however, seems less likely than **3** for several reasons. First, the ability of the reaction product to withstand temperatures as high as 400° without decomposition or rearrangement is not characteristic of isoimidazoles,[8] but is typical of imidazoles.[9] Second, the infrared spectrum of the product displays a sharp absorption band at 1500 cm^{-1} which has been found to be characteristic of arylimidazoles[10] and is also present in fused-ring imidazoles such as benzimidazole.[11] The characteristic absorption of simple 2H-isoimidazoles at 1550 cm^{-1} [10] is not present in the product. These spectral data are consistent with the structure containing the imidazole ring. Third, the deep red color of the product (λ_{max} in ethanol mμ 480) requires extensive conjugation which is present in structure **3** but not in **2** where the conjugation is interrupted by the sp^3 center in the 2 position of the isoimidazole ring. Objection to structure **2** on the basis of the color has been made by Schönberg and Singer.[5]

The composition of **3** is consistent with the elemental analysis and the high resolution mass spectrum (the most abundant peak is the parent ion at *m/e* 344.0943; calcd for $C_{24}H_{12}ON_2$, 344.0950). In addition to the

(1) (a) D. Davidson, M. Weiss, and M. Jelling, *J. Org. Chem.*, **2**, 319 (1937); (b) for a review see K. Hofmann, "Imidazole and Its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1953, p 33.

(2) M. Weiss, *J. Amer. Chem. Soc.*, **74**, 5193 (1952).

(3) C. Graebe and E. Gfeller, *Justus Liebigs Ann. Chem.*, **276**, 1 (1893).

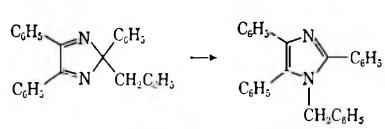
(4) A. Schönberg and F. Nedzati, *Ber.*, **54**, 238 (1921).

(5) A. Schönberg and E. Singer, *Chem. Ber.*, **98**, 3436 (1965).

(6) O. Tsuge and M. Tashiro, *Bull. Chem. Soc. Jap.*, **36**, 970 (1963).

(7) O. Tsuge and M. Tashiro, *ibid.*, **39**, 2477 (1966).

(8) 2-Benzyl-2,4,5-triphenyl-2H-isoimidazole rearranges to N-benzyl-



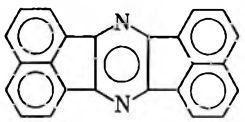
lophine at 250° in the melt and at *ca.* 118° in acetic acid.[2] Furthermore, 2-benzoyl-2,4,5-triphenyl-2H-isoimidazole appears to rearrange to N-benzoyllophine during an intermediate step in the formation of lophine from benzil and ammonium acetate in acetic acid at *ca.* 118°.[2]

(9) See ref 1b, pp 45–46.

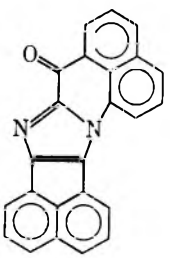
(10) D. M. White and J. Sonnenberg, *J. Org. Chem.*, **29**, 1926 (1964).

(11) K. J. Morgan, *J. Chem. Soc.*, 2343 (1961).

parent ion prominent peaks were noted for ions with compositions of $C_{23}H_{11}N_2$, $C_{22}H_{12}N$, and $C_{22}H_{10}N$. The peaks correspond to loss of CO and H, CO and CN, and CO and HCN, respectively, and are consistent with structure **3**. The mass spectrum of an impure sample of **3** also contains peaks at 328.0985 and at 164 which are probably the parent ion and a doubly charged ion of small amounts of an impurity, acenaphthazine, **4**.[12]

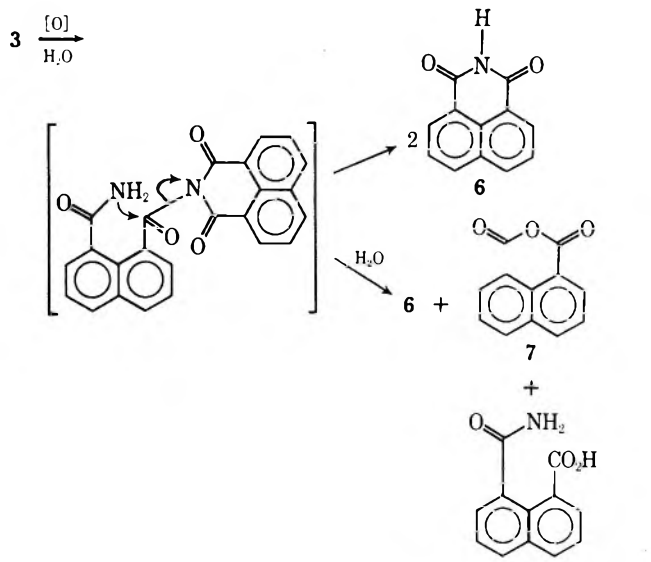


4



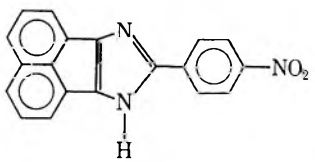
5

An isomer of **3**, structure **5**, is also consistent with the mass spectrum but seems unlikely since its formation would involve aryl migration instead of aroyl migration during rearrangement of the intermediate isoimidazole.[13] Further support for structure **3** was obtained by oxidative hydrolysis with sodium dichromate. Naphthalimide (**6**) was isolated in 65% yield along with a smaller amount of naphthalic anhydride, **7** (24%), and a trace of material which appears to be the monoamide of naphthalic acid. The formation of these products can be rationalized from structure **3** by the oxidation of the double bond common to the imidazole and acenaphthene rings and by hydrolysis of the imino group.[14]



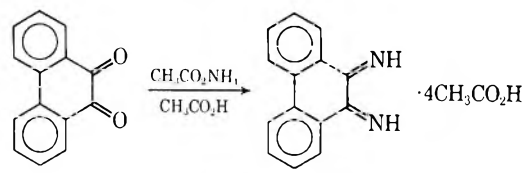
An intramolecular displacement reaction in the intermediate would produce two molecules of naphthalimide while hydrolysis would produce the other degradation products also.

The competition between **1** and the aldehyde to function as the monocarbonyl component of the reaction is indicated by the yield of **3** in the absence of aldehyde and when several aldehydes with various substituents were present. With salicylaldehyde, a relatively unreactive aldehyde **3** was formed in 70% yield which is only slightly lower than when the aldehyde was absent (87%). With benzaldehyde, the yield was 33% and with the reactive aldehyde *p*-nitrobenzaldehyde only a trace of **3** was detected. The other products which were formed when the aldehydes were present were brown solids which were not isolated in pure form with the exception of the product from *p*-nitrobenzaldehyde. In this case, 2-(*p*-nitrophenyl)-acenaphthimidazole (**8**) was isolated.



8

Phenanthraquinone (**9**) does not undergo a reaction analogous to the formation of **3**. When heated with ammonium acetate in acetic acid, the diimine **10** was produced. When aryl aldehyde was present, the



9 10

2-arylphenanthrimidazoles were formed in high yield even with compounds such as salicylaldehyde.[15]

Experimental Section[16]

7H-Acenaphth[1′,2′:4,5]imidazo[1,2-*b*]benz[*d*,*e*]isoquinolinone, 3.—Acenaphthenequinone (1, 1.9 g, 0.05 mol), 40 g of ammonium acetate, and 100 ml of acetic acid were heated at reflux for 2.5 hr. The mixture was cooled to 25° and a dark solid was removed by filtration. The solid was washed with acetic acid and then with ethanol and dried at 120° and 10 mm for 20 hr. The deep red-violet product weighed 7.5 g, 87% yield, mp 360–365°. Sublimation at 290° and 0.01 mm produced two zones of sublimate, a trace of a more volatile yellow solid **5**, and deep red crystals of **3**, mp 388–390°. The infrared spectrum showed characteristic bands at 3040 w (CH stretch), 1695 s (carbonyl), 1535 m, 1500 w (imidazole), 1470 ms, 1335 ms, 1280 s, 910 m, 818 ms, 764 s cm^{-1} (3 adjacent aryl H's). The mass spectrum showed peaks at *m/e* 344.0943 (relative abundance 100), 315.0930 (7), 290.0969 (4), 289 (2), 288.0800 (4), 172 (12), 166 (2), 158 (2), 138 (8). Impure samples of **3** also displayed peaks at 328.0985 and 164. Compound **3** was readily soluble in trifluoroacetic acid and hot dipolar aprotic solvents such as hexamthyltriphosphoramide, but was only slightly soluble in less polar solvents such as chloroform and ethanol.

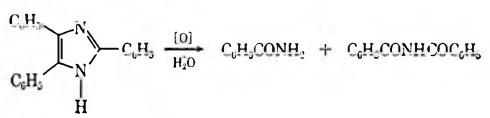
Anal. Calcd for $C_{24}H_{12}ON_2$: C, 83.7; H, 3.51; N, 8.1. Found: C, 83.7; H, 3.7; N, 8.0.

The procedure above was followed except that salicylaldehyde (5.3 g, 0.05 m) was also added at the start of the reaction. Compound **3** was isolated as red crystals, mp 388–390° (after sublimation and recrystallization from chloroform–ethanol),

(12) Acenaphthazine has been identified as a side product from **1** and ammonia.[7]

(13) The greater tendency for aroyl migration rather than aryl migration is indicated by the lower stability of 2-benzoyl-2,4,5-triphenyl-2H-isoimidazole (where the benzoyl group appears to migrate preferentially)[2,8] compared with 2,2,4,5-tetraphenyl-2H-isoimidazole which melts without decomposition near 200° and survives synthesis conditions in acetic acid at reflux.[2]

(14) Chromium oxide oxidation of lophine produces analogous products:



E. Fischer and H. Truschke, *Ber.*, **18**, 1706 (1880).

(15) E. A. Steck and A. R. Day, *J. Amer. Chem. Soc.*, **65**, 452 (1943).

(16) Infrared spectra were obtained with potassium bromide pellets. Melting points are uncorrected.

yield 6.0 g (70%). Similarly, with benzaldehyde (5.3 g, 0.05 mol) instead of salicylaldehyde: **3** was formed: mp 365–370°; after sublimation, mp 388–390°, yield 2.8 g (33%).

2-(*p*-Nitrophenyl)acenaphthimidazole, 8.—Acenaphthenequinone (**1**, 9.1 g, 0.05 mol), *p*-nitrobenzaldehyde (7.56 g, 0.05 mol), 40 g of ammonium acetate, and 100 ml of acetic acid were heated at reflux 2 hr. The mixture was cooled to 25° and filtered to remove a solid which was washed with acetic acid, dried at 120° and 10 mm, and weighed 11.4 g. Extraction of the solid with 1000 ml of boiling ethanol dissolved 6.0 g. A second ethanol extraction dissolved in additional 2.5 g. The residue, 2.9 g, contained <1 g of **3** by thin layer chromatography, infrared analysis, and sublimation. The combined ethanol extracts were cooled to 5° and crystals formed. Filtration, washing with ethanol, and drying afforded **8**, 6.2 g, mp 300–305° (between 215 and 295° phase changes occur which have the appearance of partial melting and then resolidification). Recrystallization from ethanol and sublimation at 240° and 0.01 mm produced pure yellow-orange crystals of **8**, mp 310–312°. The infrared spectrum showed bands at 3000–2600 m (broad NH), 1587 ms, 1500 s (nitro, imidazole), 1470 s, 1330 s (nitro), 1310 s, 850 m (2 adjacent Ar H's), 812 m, 760 (acenaphthene H's) cm^{-1}.

Anal. Calcd for $C_{19}H_{11}N_3O_2$: C, 72.8; H, 3.54; N, 13.4. Found: C, 72.9; H, 3.45; N, 13.3.

A second crop of impure **8**, 1.0 g, was isolated from concentration of the ethanol extracts.

Oxidation of 3.—The procedure was similar to the one of Tsuge and Tashiro.[6] To a suspension of **3** (0.50 g, 1.45 mmol) in 15 ml of acetic acid was added 1.5 g of sodium dichromate. The mixture was heated at reflux (116°) for 1 hr. The dark red solution was poured into 50 ml of water, and the precipitate was filtered off and washed with water. The solid was triturated with 70 ml of 10% sodium carbonate solution for 1 hr. The solid that remained was collected on a filter, washed with water, and dried; wt 0.43 g; analysis indicated a mixture of 70% naphthalimide and 30% naphthalic anhydride. Acidification of the sodium carbonate solution afforded 0.04 g of crystals after drying, mp 294–302°. Anaysis indicated these to be 85% naphthalimide and 15% naphthalic anhydride. Ether extraction of the filtrate removed 0.07 g of a material which had an infrared and mass spectrum consistent with approximately one-third naphthalimide and two-thirds of the monoamide of naphthalic acid. Analyses of the three fractions were carried out by infrared and nmr. The spectra were compared with spectra of mixtures of naphthalimide and naphthalic anhydride of known composition. In addition, each fraction was sublimed to separate the more volatile anhydride from the imide. No melting point depressions were noted when each zone of the sublimate was mixed with the appropriate known compound. Mass spectra of the fractions were identical with mass spectra of the known compounds. The overall yields of the two major components were naphthalimide, 0.35 g (65%), and naphthalic anhydride, 0.13 g (24%).

Registry No.—Acenaphthenequinone, 82-86-0; ammonium acetate, 631-61-8; **3**, 24744-77-2; **8**, 17988-08-8.

A Novel Catalytic Salt Effect in Base-Initiated Aryne Reactions Conducted in Dimethylamine Solvent[1a]

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Received April 11, 1969

We have routinely carried out aryne reactions in dimethylamine[2] using bromo aromatic compounds with either sodamide or potassium amide as the base and a reaction time of 3 hr to prepare the corresponding N,N-dimethyl aromatic amines in high yields (90–93%). In addition, high yields of aromatic amines can be obtained using chloro aromatic compounds and potassium amide in dimethylamine. Recently, we have observed that the reaction of chlorobenzene and *o*- or *p*-chlorotoluene produces the corresponding aromatic amine in low yields (5–7%) if sodamide is used as the base. However, if these reactions are carried out in the presence of the sodium salts of certain nitriles (0.5 equiv per equiv of sodamide), high yields (67–78%) of the appropriate aromatic amines are obtained. In addition, a small amount (8–17%) of the corresponding

$$\mathrm{ArCl} + \mathrm{NaNH_2} + \mathrm{NaCHRCN} \xrightarrow{\mathrm{HN(CH_3)_2}} \mathrm{ArN(CH_3)_2} + \mathrm{ArCHRCN}$$

arylated nitriles is produced. Table I summarizes the aforementioned results.

In addition the yields of N,N-dimethylaniline obtained from the action of sodamide on chlorobenzene are increased from 5 (no salt present) to 28, 56, and 56% by the addition of 0.8 equiv/equiv of sodamide of the inorganic salts, sodium nitrite, sodium thiocyanate, and potassium thiocyanate, respectively. Similarly, the yields of N,N-dimethyl-*o*- and -*m*-toluidines obtained from the action of sodamide on *o*-chlorotoluene are increased from 5 to 50, 80, and 80% by the addition of 0.8 equiv of sodium nitrite, sodium thiocyanate, and potassium thiocyanate, respectively. The isomer ratios of the N,N-dimethyltoluidines are in all cases 53:47, *ortho*:*meta*, respectively. In contrast, no increase in yields is observed by the addition of the salts KCl, KBr, NaCl, NaBr, Na_2SO_4, $NaNO_3$, KNO_3, or KI.

The specific action of only certain salts in increasing the conversion of chloro aromatics argues against a general salt effect. In addition, it appears that the anion portion of the salt is responsible for the catalytic behavior. Interestingly, only those salts which are linear and in which the negative charge is resonance stabilized appear to be effective catalysts. See, for example

$$^{-}\mathrm{CH_2{-}C{\equiv}N} \longleftrightarrow \mathrm{CH_2{=}C{=}N^{-}}$$

$$^{-}\mathrm{S{-}C{\equiv}N} \longleftrightarrow \mathrm{S{=}C{=}N^{-}}$$

Since the rate-determining step of the aryne reaction[3] is the abstraction of a hydrogen atom by a strong base, it appears that the salts are increasing the base strengths of sodamide in liquid dimethylamine. This action could either be the result of the salts (1) increasing the concentration of sodamide in dimethylamine, or (2) effecting a change in the aggregate populations which most likely exist in dimethylamine. Unfortunately, little is known concerning (1) the solubility of sodamide in dimethylamine, (2) the effect of salts on the solubility of sodamide in dimethylamine, and, most importantly, (3) the form in which sodamide exists in dimethylamine. We currently are investigating the mechanistic aspects of these unusual catalytic effects.

(1) (a) Supported in part by R. A. Welch Grant N-118, Houston, Texas; (b) Robert A. Welch Predoctoral Fellows.

(2) Reactions of this general type were first developed for synthetic purposes by J. F. Bunnett and T. K. Brotherton, *J. Org. Chem.*, **22**, 832 (1957).

(3) J. D. Roberts, D. A. Semenow, H. E. Semenow, and L. A. Carlsmith, *J. Amer. Chem. Soc.*, **78**, 601 (1956).

TABLE I
REACTION OF HALO AROMATIC COMPOUNDS WITH ALKALI AMIDES IN DIMETHYLAMINE

Halo aromatic, GC_6H_4X			Salt, NaCHR.CN	N,N-Dimethylarylamines			Arylated salt		
					Isomer ratio[a]			Isomer ratio[a]	
G	X	Base	R	Yield, %	o:m	m:p	Yield, %	o:m	m:p
H	Br	$NaNH_2$		91					
H	Br	KNH_2		93					
H	Cl	KNH_2		87					
H	Cl	$NaNH_2$		5					
H	Cl	$NaNH_2$	H	78			11		
H	Cl	$NaNH_2$	C_6H_5	68			8		
o-CH_3	Cl	KNH_2		90	53:47				
o-CH_3	Cl	$NaNH_2$		5	53:47				
o-CH_3	Cl	$NaNH_2$	H	62	53:47		17	50:50	
o-CH_3	Cl	$NaNH_2$	C_6H_5	67	53:47		14	50:50	
p-CH_3	Cl	KNH_2		90		50:50			
p-CH_3	Cl	$NaNH_2$	H	64		50:50	18		50:50

[a] Isomer ratios were determined by vpc analysis.

Experimental Section[4]

Chemicals.—All starting halo aromatic compounds and potassium were obtained from J. T. Baker Chemical Co. and were of the highest purity grade available. Sodamide was obtained from Fisher Chemical Co. and was used as received. Anhydrous dimethylamine was obtained from Matheson Co. and was distilled directly into the reaction flask through an anhydrous potassium hydroxide filled drying tube. All inorganic salts were thoroughly dried under vacuum at 110° for 24 hr and then stored in a drybox until use. All weighing procedures of the salts were also carried out in the drybox.

General Procedure for the Aryne Reaction.—In a typical experiment, the organic salt was prepared by adding 0.2 mol of the approximate nitrile to a stirred suspension of 0.4 mol of sodamide or potassium amide (prepared by the action of 0.4 g-atom of potassium in 200 ml of ammonia in the presence of 0.01 g of ferric nitrate, followed by removal of ammonia) in 500 ml of anhydrous dimethylamine. The inorganic salt (0.05 mol) was added directly to a stirred suspension of the base in 500 ml of anhydrous dimethylamine. After 30 min, the appropriate halo aromatic compound was added over a period of 5 min and the resulting mixture was allowed to stand for an additional 3 hr. At this time, the mixture was quenched by the addition of 0.45 mol of ammonium chloride and the solvent was removed by heating with a steam bath. The residue was washed out of the flask first with 150 ml of water and then with 100 ml of ether. The combined mixture was filtered, acidified with 50 ml of 6 *N* hydrochloric acid and was extracted with several portions of ether to remove the arylated acetonitrile and starting halo-aromatic compound. The acidic aqueous layer was made basic by the addition of sodium hydroxide (pH 14) and then was extracted with several portions of ether in order to remove the arylated amines. The combined acidic and basic ether extracts were dried (sodium sulfate), concentrated, and distilled in order to determine the percentage yields of each product.

Authentic Compounds.—N,N-Dimethylaniline was purchased from Aldrich Chemical Co. N,N-Dimethyl-*o*-toluidine, bp 98–99° (17 mm) [lit.[5] bp 98.5–99° (17 mm)], and N,N-dimethyl-*m*-toluidine, bp 207–208° (atm) [lit.[5] bp 206–207° (atm)], were prepared by the method of Hünig.[5] Phenylacetonitrile was purchased from Eastman Kodak Co. Diphenylacetonitrile, mp 73–74° (lit.[6] mp 73.5–74.5), was prepared by the method of Leake,[7] whereas o-methylphenylacetonitrile, bp 244° (atm) [lit.[8] bp 244° (atm)], *m*-methylphenylacetonitrile, bp 116° (8.5 mm) [lit.[8] bp 133° (15 mm)], and *p*-methylphenylacetonitrile, bp 122° (13 mm) [lit.[9] bp 122 (13 mm)], were prepared by the method of Titley.[8]

Registry No.—Bromobenzene, 108-86-1; chlorobenzene, 108-90-7; *o*-chlorotoluene, 95-49-8; *p*-chlorotoluene, 106-43-4; $NaNH_2$, 24781-98-4; KNH_2, 24781-99-5; acetonitrile (sodium salt), 14904-37-1; phenylacetonitrile (sodium salt), 14904-38-2.

(4) All melting points are uncorrected. The quantitative determinations were performed on a MicroTek Instrument Model GC 1600 using helium as the carrier gas at a flow rate of 45 ml/min and inlet and detector temperatures at 300°. A 5 ft × 1/8 in. i.d. column packed with 3% SE-30 (silicone rubber) on Chromosorb W, acid washed, mesh 80–100, was used to analyze the nitriles whereas the amines were analyzed using a 10 ft × 1/8 in. i.d. column packed with 5% Carbowax 20M (polyethylene oxide) on Chromosorb W, acid washed, 60–80 mesh. The peak areas were measured by a Ball-Disc integrator, an integral part of the Sargent recorder Model SR. The chromatographic bands were identified by comparing their retention times with those of authentic samples. Percentages of each compound were calculated from the areas of the bands. These areas were assumed to be equal to the peak height times the width at one-half peak height. Molar response ratios were determined and the observed areas were corrected as necessary.

(5) S. Hünig, *Chem. Ber.*, **85**, 1056 (1952).

(6) F. W. Bergstrom and R. Agostinho, *J. Amer. Chem. Soc.*, **67**, 2152 (1945).

(7) W. W. Leake, Ph.D. Thesis, University of Pittsburgh, 1958, p 130.

(8) A. F. Titley, *J. Chem. Soc.*, 515 (1926).

(9) H. Pupe and F. V. Wiederkehr, *Helv. Chim. Acta*, **7**, 654 (1924).

Quinazolines and 1,4-Benzodiazepines. XLV.[1a] 1,4-Benzodiazepines from 4-Isoquinolones

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In connection with our interest in examining new possibilities for the synthesis of 1,4-benzodiazepine derivatives,[1b] we have examined the ring expansion of some substituted 2,3-dihydro-4(1H)-isoquinolones.

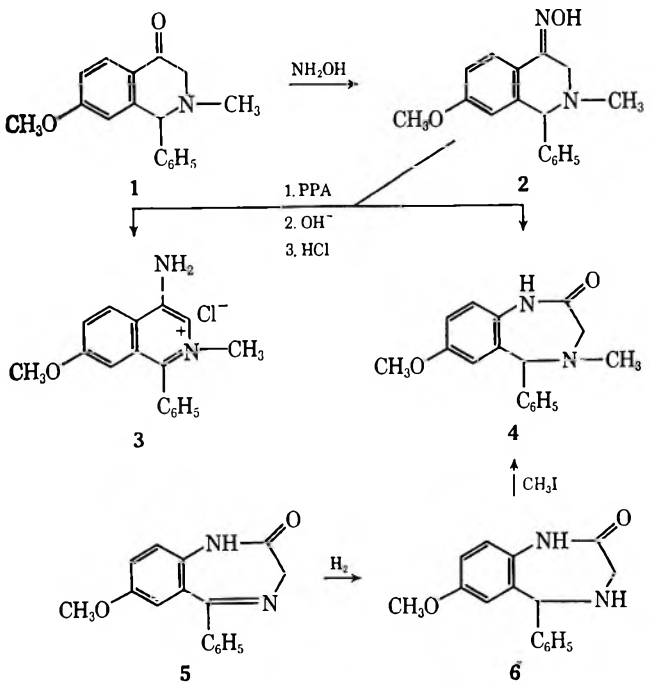
In our initial experiments (Scheme I) we prepared the oxime **2** from the known isoquinolone **1**[2] and examined the products obtained by treating this with polyphosphoric acid. In addition to the expected Beckmann rearrangement product, the benzodiazepinone **4**, we also obtained the isoquinolinium salt **3**. In fact, **3** was the major product found in the reaction mixture and was obviously the result of a Schroeter type of dehydration reaction.[3] A possible mechanism for the

(1) (a) Paper XLIV: R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.*, **34**, 649 (1969). (b) See G. A. Archer and L. H. Sternbach, *Chem. Rev.*, **68**, 747 (1968), and references cited therein.

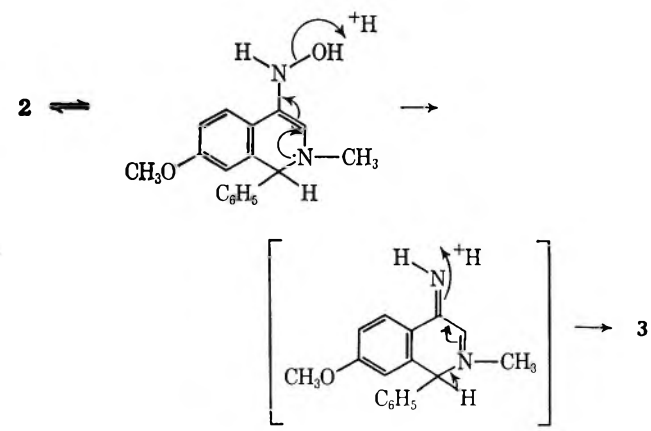
(2) G. Grethe, H. Lee, M. Uskokovic, and A. Brossi, *J. Org. Chem.*, **33**, 491 (1968).

(3) G. Schroeter, *Ber.*, **63**, 1308 (1930).

SCHEME I



dehydration of **2** which involves the tautomeric hydroxylamine is shown below.



The structure of **4** was confirmed by reducing the known 2,3-dihydrobenzodiazepinone,[4] **5**, to the corresponding tetrahydro derivative **6** and then selectively alkylating this product[5] to give an authentic sample of **4**.

Treatment of either of the quaternary salts **7** or **8** with phenyllithium[6] or with phenylmagnesium bromide led to the new isoquinolone **9a**[7] (Scheme II). Oximation of **9a** and the known **9b**[2] led to the oximes **10a** and **10b**, respectively. Polyphosphoric acid treatment of these oximes under the conditions used for compound **2** again afforded as the major products, the dehydration compounds **12a** and **12b**. The quaternary compound **7** was prepared by Grethe and coworkers by mercuric acetate oxidation of the corresponding dihydroquinolone.[8] We found that the yield in this reaction could be increased from the 37% reported, to approximately 90% by using chloranil as the oxidant.

The best yields of 1,4-benzodiazepin-2-ones were obtained by using Schmidt rearrangement conditions. Thus the ketones **9a**, **9b**, and **15** (prepared by catalytic debenzylation of **9a**) gave excellent yields of the corresponding benzodiazepines **11a**, **11b**, and **14**, respectively. The structures were ascertained for **11a** and **14** by a direct comparison with authentic samples. The known **14**[5] was treated with benzyl chloride to afford the 4-benzyl derivative **11a**. The structure of **11b** was ascertained by a comparison of its spectral properties with other tetrahydrobenzodiazepin-2-ones.[5]

The structures of the Schroeter rearranged products **3**, **12a**, and **12b**, was shown for **12b**, which on catalytic hydrogenation gave compound **13**. This compound was also obtained by hydrogenation of the oxime **10b**. When palladium was used as the catalyst, this reduction could be stopped after debenzylation when the intermediate reduction product **16** was isolated. This could also be prepared directly from the ketone **15** by oximation with hydroxylamine. As with the other oximes, dehydration was preferred over rearrangement, and with polyphosphoric acid the 4-aminoisoquinoline **18** was formed.

As expected the ketone **15** was unstable as the free base, and on exposure to air was slowly oxidized to the 4-hydroxyisoquinoline, compound **17**. This conversion was more rapidly effected by refluxing in solution with chloranil.

An additional example of a Beckmann rearrangement under reducing conditions[9] was observed when the oxime **10b** was treated with $LiAlH_4$ in refluxing tetrahydrofuran. The major product isolated was the tetrahydro-1,4-benzodiazepine, compound **19**. The structure of this compound was confirmed by an alternate preparation from **11b** by $LiAlH_4$ reduction.

Experimental Section[10]

1,2,3,4-Tetrahydro-7-methoxy-2-methyl-1-phenyl-4-isoquinolone Oxime (2).—A mixture of 1.0 g of 1,2,3,4-tetrahydro-7-methoxy-2-methyl-1-phenyl-4-isoquinolone,[2] 1.0 g of hydroxylamine hydrochloride, 2.0 g of hydrated sodium acetate, 10 ml of water, and 20 ml of ethanol was heated under reflux for 0.5 hr. The mixture was cooled and filtered. The precipitate was recrystallized from a mixture of dioxane and water to give 797 mg (86%) of the pure oxime, mp 211–214°.

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.59; H, 6.58; N, 9.38.

4-Amino-7-methoxy-2-methyl-1-phenylisoquinolinium Chloride (3).—A mixture of 0.9 g of **2** and 10 g of polyphosphoric acid was heated to 125–130° for 10 min and then poured into ice. The mixture was made basic with ammonium hydroxide and extracted with dichloromethane.[11] The aqueous solution was next acidified with concentrated hydrochloric acid and the resulting precipitate was obtained by filtration. The salt was recrystallized from a

(4) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).

(5) R. I. Fryer, B. Brust, J. Earley, and L. H. Sternbach, *J. Med. Chem.*, **7**, 386 (1964).

(6) See W. J. Gensler, "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1960, p 475.

(7) First prepared in these laboratories by Dr. G. Grethe.

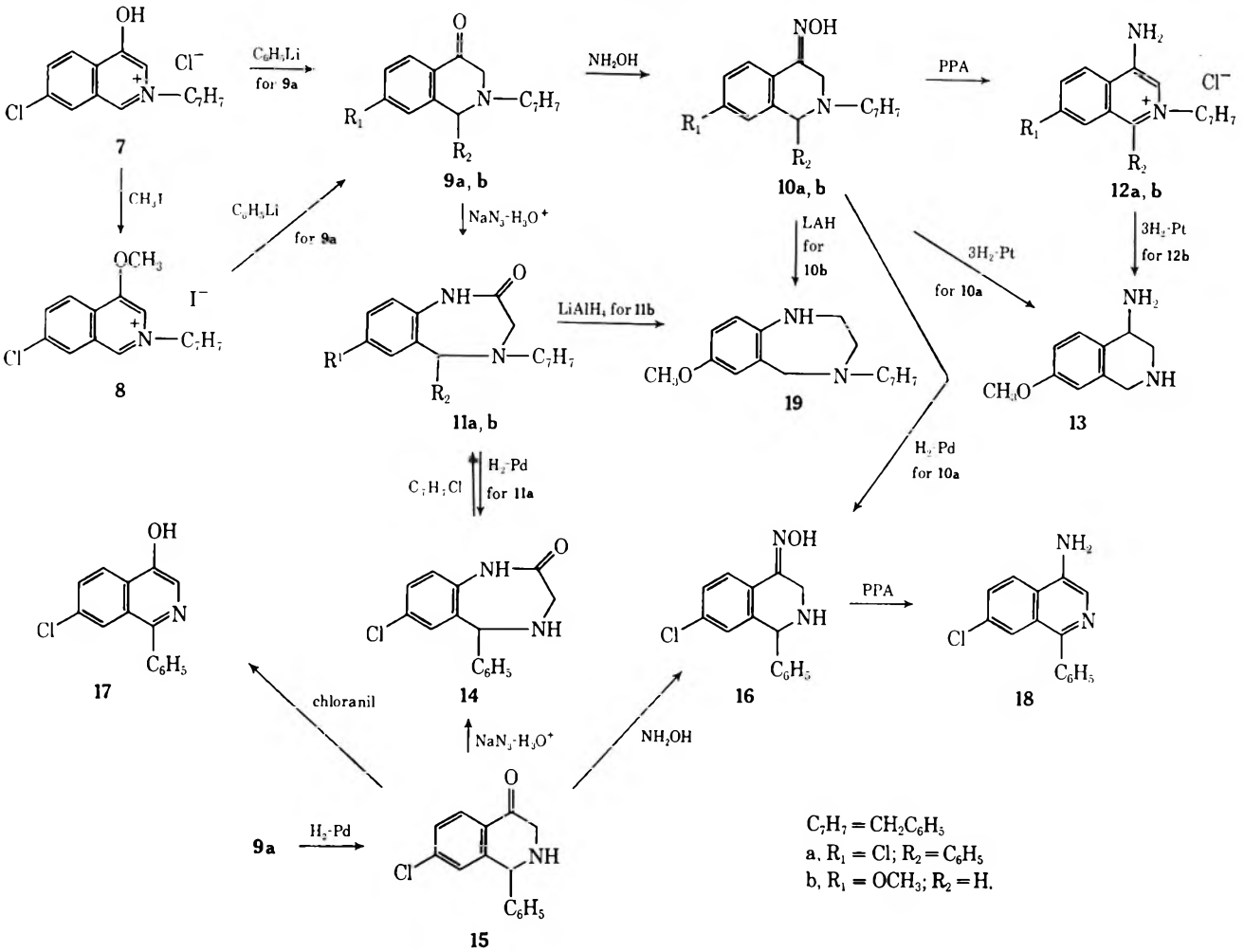
(8) G. Grethe, H. L. Lee, M. Uskokovic, and A. Brossi, *J. Org. Chem.*, **33**, 494 (1968).

(9) Acetophenone oximes have been rearranged and reduced under similar conditions. See E. Larson, *Svensk. Kem. Tidskr.*, **61**, 242 (1949), and *Chem. Abstr.*, **44**, 1898 (1950); and R. E. Lyle and H. J. Troscianiec, *J. Org. Chem.*, **20**, 1757 (1955).

(10) All melting points were determined microscopically on a hot stage and are corrected. The uv spectra were determined in 2-propanol on a Cary Model 14 spectrophotometer, nmr spectra with a Varian A-60 instrument, and ir spectra on a Beckman IR-9 spectrophotometer. All spectra were compared in order to confirm or exclude the expected changes.

(11) The dichloromethane layers contain all of the benzodiazepinone **4**.

SCHEME II



methanol–ether mixture to give 0.4 g of **3** as yellow rods, mp 211–213°.

Anal. Calcd for $C_{17}H_{17}ClN_2O$: C, 67.88; H, 5.70; N, 9.31. Found: C, 68.01; H, 5.93; N, 9.41.

7-Methoxy-4-methyl-5-phenyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (4). A. From 2.—A mixture of 500 mg of the oxime **2** and 10 g of polyphosphoric acid was slowly heated to 130° and maintained at this temperature ±5° for 10 min. The reaction mixture was then treated with 300 g of ice, made basic with ammonium hydroxide, and filtered. The precipitate was dissolved in a small amount of dioxane and filtered through 5 g of neutral activated alumina. Solvent was removed under reduced pressure. The residual oil (300 mg) was next dissolved in 50 ml of dichloromethane which was then extracted with 3 *N* hydrochloric acid (three 25-ml portions). The acid extracts were combined, made basic (ammonium hydroxide), and extracted with dichloromethane (three 20-ml portions). The dichloromethane layers were combined, washed with water (two 10-ml portions), dried (anhydrous sodium sulfate), filtered, and evaporated to give 200 mg of crystalline product. Recrystallization from dichloromethane gave 100 mg of the pure benzodiazepinone, mp and mmp (with an authentic sample prepared as in B) 214–215°.

B. From 6.—A solution of 3 g of **6** in 25 ml of N,N-dimethylformamide was treated with 5 g of methyl iodide. The solution was stirred at 45° for 6 hr and allowed to stand at room temperature for 12 hr when 400 ml of water was added. The aqueous mixture was extracted with three 100-ml portions of dichloromethane, which were then combined, washed with water, dried over anhydrous sodium sulfate, and evaporated. The mixture was recrystallized from dichloromethane to give 1.3 g (39%) of **4** as white prisms, mp 214–215°.

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.33; H, 6.43. Found: C, 72.53; H, 6.49.

7-Methoxy-5-phenyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (6).—A mixture of 6.4 g (0.0242 mol) of 7-methoxy-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one (**5**),[4] 2 g of platinum oxide, 100 ml of acetic acid, and 100 ml of water was hydrogenated at room temperature and under atmospheric pressure until hydrogen uptake ceased. The mixture was filtered and the filtrate was adjusted to pH 8 with sodium hydroxide solution. This was then extracted with three 100-ml portions of methylene chloride. The organic layers were combined, washed with water, dried over sodium sulfate, and evaporated. The residue was recrystallized from a mixture of acetone and hexane to give 5.65 g (87.5%) of **6** as white prisms, mp 150–153°.

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01. Found: C, 71.71; H, 6.06.

2-Benzyl-7-chloro-4-hydroxyisoquinolinium Chloride (7).[8]—A solution of 79.5 g (0.258 mol) of 2-benzyl-7-chloro-2,3-dihydro-4-(1H)-isoquinolone hydrochloride[8] and 128 g (0.523 mol) of chloranil in 2.4 l. of glacial acetic acid was refluxed and stirred for 4 hr. The solvent was evaporated and the residue was washed several times with hot benzene. The crystalline solid was suspended in 500 ml of warm ethanol, 150 ml of saturated methanolic hydrogen chloride was added, and the mixture was stirred for 10 min. Cooling and filtration afforded 71.8 g (91%) of **7** as white prisms, mp 284–286° dec.

2-Benzyl-4-methoxy-7-chloroisoquinolinium Iodide (8).—A mixture of 6.12 g (20 mmol) of **7**, 18 ml of methyl iodide, 5.68 g of potassium carbonate, and 80 ml of dry acetone was refluxed and stirred for 3.5 hr. A bright yellow precipitate formed within 30 min. The solid material was collected and the filtrate was evaporated to a yellow-orange solid, which after washing with hot benzene was recrystallized from a mixture of chloroform and ether to give 2 g of **8** as yellow prisms: mp 182–184°; nmr ($CDCl_3$) δ 4.34 (s, 3, OCH_3), 6.42 (s, 2, CH_2), 8.95, 10.48 (AB, 2, J = 1 Hz, H-1, H-3).

Anal. Calcd for $C_{17}H_{16}ClNO$: C, 49.60; H, 3.67; N, 3.40. Found: C, 49.56; H, 3.75; N, 3.42.

The original precipitate was extracted with hot methanol which was then evaporated. The residue was recrystallized from

a mixture of chloroform and ether to give 6.4 g of **8** as a tan solid. This material was used without further purification for the preparation of **9a**.

2-Benzyl-7-chloro-1,2-dihydro-1-phenyl-4(3H)-1-isoquinolone (9a). A. From 7.—Compound **7** (15.2 g, 49.7 mmol) was added in small portions to 75 ml of an ice-cold 2 *N* solution of phenyllithium in benzene–ether which was kept under nitrogen. The reaction mixture was allowed to warm to room temperature and after stirring for 1 hr 10 ml of methanol was added cautiously. The thick slurry was poured into 500 ml of ether and the mixture was stirred for several minutes. The insoluble material was filtered. To the filtrate was added 10 ml of 10 *N* hydrochloric acid in methanol. The precipitated salt was collected, washed with ether, dissolved in methylene chloride, and extracted twice with sodium bicarbonate solution. The organic phase was dried over anhydrous sodium sulfate and evaporated. The residue was crystallized from a mixture of methanol and ether to give 5 g of **9a** as white prisms, mp 115–123°. Recrystallization from methanol and ether yielded 3.9 g (22.5%) of pure material: mp 119.5–121°; ir ($CHCl_3$) 1685 cm^{-1} (C=O); uv max (2-propanol) 255–256 mμ (ε 16,400), sh 290 (2400); nmr ($CDCl_3$) δ 3.25, 3.58 (AB, 2, J_{gem} = 17.5 Hz, CH_2CO), 3.52, 3.73 (AB, 2, J_{gem} = 13.5 Hz, $NCH_2C_6H_5$) 4.92 (s, 1, CH).

B. From Compound 8.—Compound **8** (6 g, 14.6 mmol) was added in small portions to 20 ml of an ice-cold 2.28 *N* solution of phenyllithium in benzene–ether which was kept under nitrogen. The reaction mixture was allowed to warm to room temperature and after 7 hr of stirring 6 ml of methanol was added cautiously to destroy excess reagent. The thick brown slurry was poured into 300 ml of ether and the insoluble material was filtered off. The filtrate was evaporated and the residue was refluxed for 2 hr in 75 ml of 28% HBr in glacial acetic acid. The solvent was removed under reduced pressure and the oily residue was washed several times with ether and benzene. The product was then dissolved in methylene chloride and extracted with dilute sodium hydroxide solution. The organic phase was dried over anhydrous sodium sulfate and evaporated. Crystallization from methanol–ether gave 1.05 g (20.7%) of **9a**, mp 119–121°.

2-Benzyl-1,2-dihydro-7-chloro-1-phenyl-4(3H)-isoquinolone Oxime (10a).—A solution of 0.5 g of **9a** in 2 ml of ethanol was treated with 0.5 g of hydroxylamine hydrochloride, 1 g of sodium acetate, and 10 ml of water. The solution was heated under reflux for 0.5 hr and then cooled in an ice bath. The precipitated product was removed by filtration and recrystallized from a mixture of ether and petroleum ether, bp 30–60°, to give 350 mg (67%) of **10a** as pale yellow rods, mp 152–155°.

Anal. Calcd for $C_{22}H_{19}ClN_2O$: C, 72.82; H, 5.28. Found: C, 72.94; H, 5.50.

2-Benzyl-1,2-dihydro-7-methoxy-4(3H)-isoquinolone Oxime (10b).—A mixture of 10.0 g of 2-benzyl-1,2-dihydro-7-methoxy-4(3H)-isoquinolone,[2] 10.0 g of hydroxylamine hydrochloride, 20.0 g of sodium acetate hydrate, 100 ml of water, and 200 ml of ethanol was heated under reflux for 0.5 hr. The mixture was cooled and filtered to give 8.9 g (83.5%) of the oxime, mp 189–192°. Recrystallization from an aqueous dioxane solution gave the pure oxime, mp 192–194°.

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43. Found: C, 72.53; H, 6.37.

4-Benzyl-7-chloro-1,3,4,5-tetrahydro-5-phenyl-2H-1,4-benzodiazepin-2-one (11a). A. From 9a.—A solution of 0.3 g (0.864 mmol) of **9a** in 20 ml of chloroform was treated at 0° with 1.2 ml of concentrated sulfuric acid. The reaction mixture (<10°) was next treated portionwise (30 min) with 0.141 g (2.17 mmol) of sodium azide and was then heated to 50° for 90 min. The mixture was cooled in an ice bath, 3 g of potassium carbonate was added, and the mixture was then made basic with a 50% aqueous solution of potassium hydroxide. The precipitate was removed by filtration and the filtrates were separated and extracted with two 10-ml portions of chloroform. The combined chloroform layers were washed with 20 ml of saturated brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was recrystallized twice from a mixture of dichloromethane, ether, and petroleum ether to give 0.17 g (55%) of **11a** as white rods, mp 197–204°.

Anal. Calcd for $C_{22}H_{19}ClN_2O$: C, 72.82; H, 5.28. Found: C, 72.83; H, 5.53.

B. From 14.—A mixture of 50 g of **14**[5] and 21 ml of benzyl chloride in 250 ml of N,N-dimethylformamide was heated overnight at 60°. The precipitate was filtered and partitioned between dichloromethane and dilute ammonium hydroxide. The organic layer was separated, washed, dried, and evaporated. The residue was recrystallized from a mixture of ethanol and chloroform to give 10.5 g of **14** as white rods, mp and mmp (with a sample prepared as in A) 197–204°. The original filtrates were treated with ether when the hydrochloride of the starting material (**14**) precipitated. The solution was filtered, poured into 1 l. of water, made basic with ammonium hydroxide, and again filtered. The precipitate was dissolved in dichloromethane which was washed, dried, and evaporated. The residue was recrystallized from a mixture of ethanol and chloroform to give an additional 22.6 g of product, mp 197–204°.

4-Benzyl-7-methoxy-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (11b).—A solution of 2.0 g (7.35 mmol) of 2-benzyl-2,3-dihydro-7-methoxy-4(1H)-isoquinolinone (**9b**)[2] in 40 ml of chloroform was cooled to 0° and 8 ml of concentrated sulfuric acid was added dropwise with stirring. The reaction mixture was treated with 1.2 g (18.4 mmol) of sodium azide over a 1-hr period, keeping the temperature below 10°, and was then stirred at 50° for 90 min. The mixture was cooled in an ice bath (<30°) while 5 g of potassium carbonate was added, followed by 20 ml of a 50% aqueous solution of potassium hydroxide. The solution was filtered, and the filtrates were extracted with two 10-ml portions of chloroform. The combined organic layers were washed with 30 ml of saturated brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was crystallized from methanol and then recrystallized from a mixture of dichloromethane and petroleum ether, bp 30–60°, to give 1.7 g (81%) of **11b** as white rods, mp 145–148°.

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.40; H, 6.46; N, 9.88.

4-Amino-2-benzyl-7-chloro-1-phenylisoquinolinium Chloride (12a).—A mixture of 0.9 g of **10a** and 10 g of polyphosphoric acid was heated to 125–135° for 15 min. The mixture was cooled, made basic with ammonium hydroxide, and extracted with chloroform. The chloroform layer was washed with brine, dried over sodium sulfate, and evaporated to dryness. The residual oil was treated with 3 *N* HCl and was allowed to stand until the product crystallized. The quaternary salt obtained by filtration was dissolved in dichloromethane, which was dried over sodium sulfate, filtered, and evaporated. Recrystallization of the residue from a mixture of methanol and ether gave 0.7 g (74%) of **12a** as pale yellow rods, mp 213–215°.

Anal. Calcd for $C_{22}H_{18}Cl_2N_2$: C, 69.30; H, 4.76; N, 7.35. Found: C, 69.12; H, 4.88; N, 7.29.

4-Amino-2-benzyl-7-methoxyisoquinolinium Chloride (12b).—A mixture of 10 g of **10b** and 45 ml of polyphosphoric acid was heated at 130° for 15 min with stirring. The mixture was cooled, poured into ice, and made basic with ammonium hydroxide. The basic solution was filtered and the filtrate was first extracted with dichloromethane and then acidified with concentrated hydrochloric acid. The quaternary was salted out with sodium chloride. Filtration gave 9 g of **12b** as yellow rods. Recrystallization from water gave the analytical sample, mp 128–130°.

Anal. Calcd for $C_{17}H_{17}ClN_2O$: C, 67.88; H, 5.70; N, 9.31; Cl, 11.79. Found: C, 67.86; H, 5.94; N, 8.94; Cl, 11.76.

4-Amino-1,2,3,4-tetrahydro-7-methoxyisoquinoline Dihydrochloride (13). A. From 10b.—A mixture of 2 g of **10b**, 25 ml of glacial acetic acid, 5 ml of water, and 0.2 g of platinum oxide was hydrogenated at room temperature and atmospheric pressure until hydrogen uptake ceased. The catalyst was removed by filtration and the filtrates were made basic with sodium hydroxide. The basic solution was extracted with three 100-ml portions of dichloromethane which were then combined, washed with saturated brine, dried over sodium sulfate, and evaporated to dryness. The residue was dissolved in ether and treated with an excess of ethanolic hydrogen chloride solution. The precipitate was recrystallized from a mixture of methanol and ether to give **13** as white prisms, mp 248–255°.

Anal. Calcd for $C_{10}H_{14}N_2O \cdot 2HCl$: C, 47.82; H, 6.42; N, 11.15. Found: C, 47.71; H, 6.51; N, 11.42.

B. From 12b.—A mixture of 1.5 g of **12b**, 25 ml of acetic acid, 5 ml of water, and 0.25 g of platinium oxide was hydrogenated at room temperature and atmospheric pressure until hydrogen uptake ceased. The product was obtained as described in A to give the dihydrochloride as white prisms, mp and mmp 248–255°.

7-Chloro-1,3,4,5-tetrahydro-5-phenyl-2H-1,4-benzodiazepin-2-one (14). A. From 11a.—A solution of 1 g (2.75 mmol) of **11a** in 40 ml of glacial acetic acid, 10 ml of concentrated hydrochloric acid, and 40 ml of water was treated with 0.2 g of

a 10% palladium-on-charcoal catalyst. Hydrogenation at atmospheric pressure was stopped when 80 ml of hydrogen had been adsorbed, and the reaction mixture was filtered through Celite and made basic with ammonium hydroxide. The solution was extracted with 100 ml of dichloromethane which was washed with 50 ml of saturated brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was recrystallized from a mixture of dichloromethane and hexane to give 0.5 g (67%) of **14** as white prisms, mp and mmp (with an authentic sample[5]) 183–185°.

B. From 15.—A suspension of 200 mg (0.68 mmol) of **15** in 30 ml of chloroform was cooled in an ice bath to 0–3°. While stirring, 4 ml of concentrated sulfuric acid was added, followed by the portionwise addition of 1.0 g of sodium azide (addition time 1 hr, temperature 10°). The reaction mixture was then heated to 50° for 1.5 hr, cooled, poured over ice, and neutralized with solid potassium carbonate. After adding 2 ml of 50% KOH, the solids were removed by filtration and washed with dichloromethane. The organic layer of the filtrates was separated and the aqueous phase was twice extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and evaporated to a crystalline solid, which after washing with a mixture of ether and petroleum ether yielded 0.90 g (48.4%) of product as white prisms, mp 174–178°. Recrystallization from a mixture of dichloromethane, ether, and petroleum ether gave the pure product, mp and mmp (with an authentic sample[5]) 180–183°.

7-Chloro-2,3-dihydro-1-phenyl-4(1H)-isoquinolone Hydrochloride (15).—A solution of 1 g (2.88 mmol) of **9a** in 75 ml of glacial acetic acid was treated with 0.1 ml of concentrated hydrochloric acid, 5 ml of water, and 200 mg of a 10% palladium-on-carbon catalyst. The reaction mixture was hydrogenated at atmospheric pressure and room temperature until the uptake of hydrogen slowed down considerably (total uptake 160 ml). Solids were removed by filtration over Celite. The Celite was washed with dichloromethane and the filtrates were combined. After removal of the solvent, the residue was treated with 2 ml of 10 *N* hydrogen chloride in methanol which was then evaporated to a solid residue. The crude product was washed with acetonitrile to give 450 mg (53.2%) of **15**·HCl as a white crystalline material, mp 233–235°. Recrystallization from a mixture of acetonitrile and ether afforded an analytical sample: mp 235° dec; ir (KBr) 1715 cm^{-1} (C=O); uv max (2-propanol) 210 mμ (ε 24,200), 256–257 (12,720), sh 285 (2100), sh 297 (1650).

Anal. Calcd for $C_{15}H_{12}ClNO \cdot HCl$: C, 61.24; H, 4.45; N, 4.76. Found: C, 61.15; H, 4.53; N, 4.74.

1-Phenyl-7-chloro-2,3-dihydro-4(1H)-isoquinolone Oxime (16).

A. From 15.—A mixture of 1.16 g (3.33 mmol) of **9a**, 40 ml of glacial acetic acid, 1 ml of concentrated hydrochloric acid, 10 ml of water, and 0.3 g of 10% palladium on carbon was hydrogenated and worked up in the same way as described for the preparation of **15**. The crude product was partially dissolved in 50 ml of ethanol and refluxed under nitrogen for 2 hr together with a mixture of 3.5 g of hydroxylamine hydrochloride, 4.5 g of sodium acetate, and 4.5 g of sodium bicarbonate. The solid precipitate which formed was filtered after cooling, washed well with water, dissolved in ether, and dried over anhydrous sodium sulfate. The solvent was removed and the remaining residue was triturated with ether–hexane. Filtration afforded 500 mg (55%) of crude **16** as white prisms, mp 162–172°. Recrystallization of a sample from ether–hexane gave analytically pure **16**: mp 168–171°; ir (KBr) 3270 (N–OH), 2800 cm^{-1} (broad, OH); uv max (2-propanol) 263 mμ (ε 16,000), infl 293 (2800), sh 304 (1600); nmr (DMSO) δ 3.76 (s, 2, CH_2), 5.00 (s, 1, CH), 11.08 (br, 1, NOH).

Anal. Calcd for $C_{15}H_{13}ClN_2O$: C, 66.06; H, 4.80; N, 10.27. Found: C, 66.01; H, 4.81; N, 10.22.

B. From 10a.—A mixture of 363 mg (1 mmol) of **10a**, 50 ml of acetic acid, 0.1 ml of concentrated hydrochloric acid, and 0.2 g of 10% palladium on carbon was hydrogenated and worked up in the same manner already described. The crude residue obtained after removal of the reaction solvents and the washings was taken up in methylene chloride and extracted with a solution of saturated sodium bicarbonate in water. The organic phase was dried over anhydrous sodium sulfate and evaporated to a crystalline solid which, after treatment with ether–petroleum ether, yielded 150 mg (55%) of **16**, mp and mmp (with a sample prepared as in A) 168–171°.

1-Phenyl-4-hydroxy-7-chloroisoquinoline (17).—A mixture of 8.7 g (25 mmol) of **9a**, 250 ml of glacial acetic acid, 10 ml of concentrated hydrochloric acid, 5 ml of water, and 750 mg of 10% palladium on carbon was hydrogenated as previously described to give **15**, and the mixture was then filtered over Celite. The filtrate (225 ml) corresponding to 21.2 mmol of starting material was refluxed and stirred for 1.5 hr with 6.1 g (25 mmol) of chloranil. After removal of the solvent, the residue was washed several times with warm benzene, suspended in dilute ammonium hydroxide, and stirred for several minutes. The solid was then filtered, washed with water, ether, and hot benzene and finally recrystallized from a mixture of methanol and methylene chloride to give 2.4 g (44%) of pure **17** as white prisms: mp 270–274°; ir (KBr) broad OH centered at 2500 cm^{-1}; uv max (2-propanol); 215 mμ (ε 44,600), 259 (26,100), 309 (7200), 342–345 (7250); nmr (DMSO) δ 7.40–8.40 (9 aromatic H).

Anal. Calcd for $C_{15}H_{10}ClNO$: C, 70.46; H, 3.94; N, 5.48. Found: C, 70.62; H, 4.03; N, 5.41.

1-Phenyl-7-chloro-4-aminoisoquinoline (18).—A mixture of 100 mg (0.37 mmol) of **16** and 4.5 g of polyphosphoric acid was heated for 12 min at 120–130° with occasional stirring. The reaction mixture was cooled and poured onto ice. The solution was basified with ammonium hydroxide. The precipitated solid was collected and washed repeatedly with water to give 100 mg of crude **18**, mp 142–146°. This was recrystallized from ether and petroleum ether to give 55 mg (58%) of analytically pure **18** as white prisms: mp 143–145.5°; ir (KBr) 3450, 3320 (NH_2) broad 3140, 1650 cm^{-1}; uv max (2-propanol) 213–214 mμ (ε 43,250), 263–266 (16,600), infl 330 (6600), 362–364 (8000); nmr ($CDCl_3$) δ 4.17 (s, 2, NH_2), 7.30–8.20 (9 aromatic H).

Anal. Calcd for $C_{15}H_{11}ClN_2$: C, 70.73; H, 4.35; N, 11.00. Found: C, 70.76; H, 4.29; N, 10.96.

4-Amino-2-benzyl-1,2,3,4-tetrahydro-7-methoxyisoquinoline (19). **A. From 10b.**—A mixture of 3 g (0.01 mol) of **10b**, 0.8 g (0.21 mol) of lithium aluminum hydride, and 75 ml of dry tetrahydrofuran was stirred and heated under reflux for 6 hr. The mixture was cooled and 1 ml of water was added, followed by the addition of enough saturated potassium bicarbonate solution required to coagulate the solids. The solution was filtered and the filtrates were extracted with dichloromethane which were then washed with water, dried over sodium sulfate, and evaporated. The residual oil was dissolved in benzene and chromatographed over Florisil using benzene and ether as eluents. The benzene fractions were discarded. The ether fractions gave, on evaporation, 1 g (35%) of a colorless oil which was crystallized from a mixture of ether and petroleum ether, bp 30–60°, to give pure **19** as white prisms, mp 43–49°.

Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44. Found: C, 76.21; H, 7.17; N, 10.19.

B. From Compound 11b.—A mixture of 0.5 g of **11b**, 0.176 g of lithium aluminum hydride, and 50 ml of dry tetrahydrofuran was heated under reflux for 10 hr. The mixture was cooled and excess reagent was decomposed with water. Saturated potassium bicarbonate solution was added as in A and the solution was filtered and evaporated. The residue was dissolved in ether and the product was extracted into 0.5 *N* hydrochloric acid. The acid layer was made basic and was extracted with dichloromethane. The organic layers were dried and evaporated, and the residual oil was chromatographed over Florisil as above to give 50 mg of **19** as white prisms, mp and mmp 43–49°.

Registry No.—**2**, 24781-76-8; **3**, 24781-77-9; **4**, 24781-78-0; **6**, 24781-79-1; **7**, 15365-49-8; **8**, 24781-81-5; **9a**, 24781-82-6; **10a**, 24781-83-7; **10b**, 24781-84-8; **11a**, 24781-85-9; **11b**, 24781-86-0; **12a**, 24781-87-1; **12b**, 24781-88-2; **13**, 24781-89-3; **14**, 1824-69-7; **15**, 24781-91-7; **16**, 24781-92-8; **17**, 24781-93-9; **18**, 24781-94-0; **19**, 24781-95-1.

Acknowledgment.—We thank Dr. A. Brossi for valuable discussions and also the following members of the Physical Chemistry Department under the direction of Dr. P. Bommer: Dr. T. Williams for nmr spectra, Dr. W. Benz for mass spectra, Dr. V. Toome for uv spectra, Mr. S. Traiman for ir spectra, and Dr. F. Scheidl for the microanalyses.

The Kinetics of the Acid-Catalyzed Hydrolysis of α-Acetoxystilbene[1]

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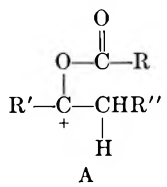
Received September 28, 1969

We have recently shown that enol esters are hydrolyzed in mineral acid by two alternative mechanisms.[3,4] One of these mechanisms is the normal ester hydrolysis process; the other mechanism is a process initiated by olefin protonation to give rise to a carbonium ion of type A as the first intermediate. In the



A

absence of substantial carbonium ion stabilization by R′, the normal ester mechanism predominates in dilute mineral acid. This is the situation which is observed for vinyl acetate[4] and for *p*-nitro-α-acetoxystyrene.[3] Structures providing better carbonium ion stabilization allow olefin protonation to predominate even at low acidities, *e.g.*, *p*-methoxy-α-acetoxystyrene.

In the present study we wish to examine briefly other factors which may influence the balance between these two mechanisms. It is well known that the rate of acid-catalyzed hydrolysis of esters is relatively insensitive to wide variation of the alcoholic moiety in terms of both steric and electronic effects. For example, Euranto[5] has reported that the rates for the hydrolysis of a diverse group of formate esters are within a factor of 3, for structural variation including methyl formate, chloromethyl formate, and *t*-butyl formate. Extremes of steric hindrance might be expected to result in some diminution of the rate of hydrolysis. In the present situation, it is to be noted that *trans*-α-acetoxystilbene (1) has the acetate group in a position which is severely crowded. Nevertheless, the depression of rate is relatively modest. In 50% mineral acid, 1 hydrolyzes 60 times more slowly than vinyl acetate; *cis*-α-acetoxystilbene (2) hydrolyzes only 10 times more slowly than vinyl acetate. This situation should be contrasted with the very sharp differences observed when structural changes are made in the carboxylate moiety (R).

On the other hand, rates of olefin protonation are relatively sensitive to structural variation at the carbon β to the potential carbonium ion center. For example, the hydration of styrene occurs 500 times more rapidly than proton attack upon *cis*-stilbene initiates isomerization.[6,7]

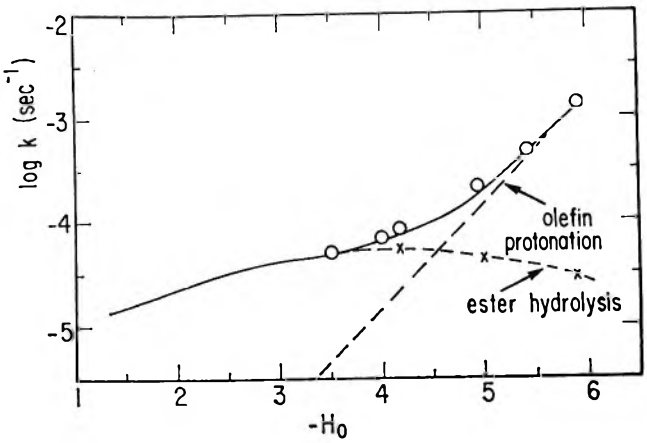


Figure 1.— Rate of hydrolysis of *trans*-α-acetoxystilbene: ×---×, calculated rate of normal ester hydrolysis; - - -, calculated rate of hydrolysis by olefin protonation; ——, calculated total rate of hydrolysis; ○ ○, observed rate of hydrolysis.

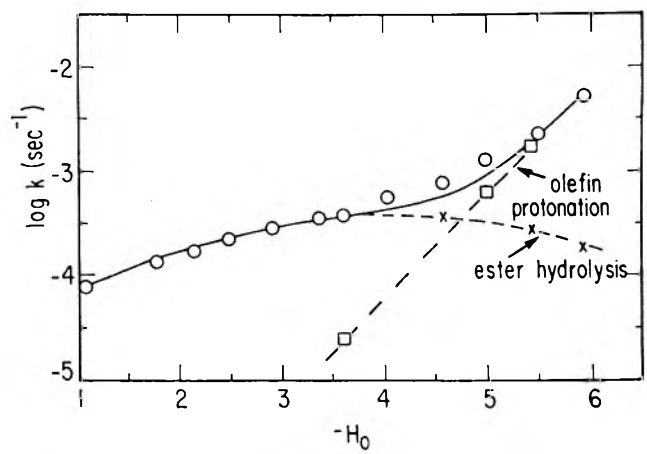


Figure 2.—Rate of hydrolysis of *cis*-α-acetoxystilbene: ×---×, calculated rate of normal ester hydrolysis; □---□, calculated rate of hydrolysis by olefin protonation; ——, calculated total rate of hydrolysis; ○ ○, observed rate of hydrolysis.

It should thus be expected that α-acetoxystilbene should show a rate of hydrolysis by the normal ester mechanism similar to that observed for *p*-nitro-α-acetoxystyrene, and an olefin protonation rate substantially suppressed from that observed for α-acetoxystyrene. We have therefore measured the rates of acid-catalyzed hydrolysis for both stereoisomers of α-acetoxystilbene.

The two stereoisomers were prepared by the procedure of House and Trost.[8] The higher melting isomer mp 100–101.5° has been previously obtained by Nesmeyanov, *et al.*[9] That this is the *trans* stereoisomer 1 is supported by its spectral characteristics, with the vinyl proton signal in the nmr occurring at lower fields than in 2.[10]

The results of the kinetic measurements are graphically displayed in Figures 1 and 2.

It is to be noted that, as the acidity of the medium is increased, the rate of hydrolysis effectively reaches a

(1) Supported in part by a grant from the National Science Foundation, GP-6133X.

(2) National Institutes of Health Postdoctoral Fellow, 1965–1968 (GM-20266).

(3) D. S. Noyce and R. M. Pollack, *J. Amer. Chem. Soc.*, **91**, 119 (1969).

(4) D. S. Noyce and R. M. Pollack, *ibid.*, **91**, 7158 (1969).

(5) E. Euranto, *Ann. Univ. Turku, Ser. A*, **42**, 20 (1960); *Chem. Abstr.*, **54**, 18042 (1960).

(6) W. M. Schubert, B. Lamm, and J. R. Keeffe, *J. Amer. Chem. Soc.*, **86**, 4727 (1964); W. M. Schubert and B. Lamm, *ibid.*, **88**, 120 (1966).

(7) D. S. Noyce, D. R. Hartter, and F. B. Miles, *ibid.*, **90**, 4633 (1968).

(8) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965).

(9) A. N. Nesmeyanov, A. E. Borisov, I. S. Savel'eva, and M. A. Osipova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1249 (1961); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1161 (1961); *Chem. Abstr.*, **56**, 1469 (1962).

(10) R. C. Fahey and D. J. Lee, *J. Amer. Chem. Soc.*, **88**, 5555 (1966).

plateau between 40 and 50% perchloric acid, and finally near 60% acid abruptly begins to increase again. We ascribe this complex profile to the interplay of the two mechanistic pathways available for hydrolysis of enol acetates. For the *cis* isomer 2, below 59% perchloric acid, the predominant mode of hydrolysis is the normal ester pathway; above this acidity, the majority of the hydrolysis proceeds by way of olefin protonation.

For calculation of the predicted rate for hydrolysis by the normal ester mechanism, the following procedure was used. Yates and McClelland[11] have observed that many esters show a very similar rate–acidity profile in the middle range of sulfuric acid concentration, with eq 1 describing the behavior of the ester, with $m \cong 0.62$ and $r \cong 2$. Lane, Cheung, and Dorsey,[12]

$$\log k + mH_0 = r \log a_{H_2O} + \text{constant} \quad (1)$$

in a particularly careful study of the behavior of ethyl acetate, show that $m = 0.645$ and $r = 2$. To calculate the expected rate for normal ester hydrolysis for *cis*-α-acetoxystilbene (2) we have used eq 2, with data for the activity of water from Robinson and Baker[13] with

$$\log (\text{rate}_{\text{ester}})_{cis} = -0.62H_0 + 2 \log a_{H_2O} - 4.65 \quad (2)$$

the constant term (−4.65) chosen to give a predicted rate in agreement with experiment at the lower acidities ($H_0 \cong -1.5$). In the most concentrated acid solution a very small correction for protonation of the ester has been made assuming pK_{BH^+} of −7.00. For the predicted rate of reaction by way of olefin protonation, eq 3 was used[14] with the constant term (−8.22) chosen to match the observed rates in 63% sulfuric acid ($H_0 = -5.9$).

$$\log (\text{rate}_{\text{olef}})_{cis} = -H_0 - 8.22 \quad (3)$$

Calculated rates for the *trans* isomer are obtained in a similar fashion, using eq 4 and 5, with the constant terms chosen as above.

$$\log (\text{rate}_{\text{ester}})_{trans} = -0.62H_0 + 2 \log a_{H_2O} - 5.51 \quad (4)$$

$$\log (\text{rate}_{\text{olef}})_{trans} = -H_0 - 8.82 \quad (5)$$

Finally it should be noted that the rates of olefin protonation for *cis*-stilbene[7] and for *cis*-α-acetoxystilbene are very similar.

Experimental Section[15]

α-Acetoxystilbenes.—The procedure of House and Trost[8] was followed. Ten grams of desoxybenzoin was dissolved in 150 ml of carbon tetrachloride and 51 g of acetic anhydride was added with stirring. After the dropwise addition of 0.5 ml of 70% perchloric acid, stirring was continued for 2.5 hr. The reaction mixture was washed thoroughly with aqueous sodium bicarbonate solution, the carbon tetrachloride layer was dried over anhydrous sodium sulfate, and the solvent was removed on a rotary evaporator. The crude residue contained approximately 60% *trans*-α-acetoxystilbene, 10% *cis*-α-acetoxystilbene, and 30% deoxybenzoin as determined from the nmr spectrum.

The crude reaction mixture was dissolved in a minimum amount of diethyl ether and pentane was added to 500 ml. Upon cooling, 4.7 g of *trans*-α-acetoxystilbene was collected as pale yellow crystals.[16] Recrystallization from pentane gave colorless needles: mp 100.0–101.5° (lit. 100.5–101.0°); uv max 287 mμ (ε 27,400, ethanol); ir (CCl_4) 1764 cm^{-1}; nmr (CCl_4) δ 7.14–7.50 (m, 10 H), 6.55 (s, 1 H), 2.26 (s, 3 H).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.65; H, 5.98.

The mother liquors from the crystallization of the *trans* isomer were concentrated, and the *cis* isomer was separated from desoxybenzoin and remaining *trans* isomer by glpc on a 5 ft × 0.25 in. 20% SE-30 column. ***cis*-α-Acetoxystilbene** was obtained as a viscous oil: uv max 262 mμ (ε 12,000); ir (CCl_4) 1764 cm^{-1}; nmr (CCl_4) δ 7.03–7.95 (broad multiplet, 10 H), 6.33 (s, 1 H), 2.14 (s, 3 H).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.68; H, 6.04.

Kinetic Runs.—An aliquot (10–50 μl) of a stock solution of the substrate in ethanol was mixed with 3 ml of the appropriate acid solution in a stoppered cuvette. The kinetics were followed on a Gilford Model 2000 spectrophotometer with a thermostated cell compartment (25°). The rate constant obtained showed no dependence on the concentration of ethanol (0.3–1.6 vol %). For *cis*-α-acetoxystilbene reactions were followed at 280 mμ and showed good first-order behavior to greater than 85% reaction. For *trans*-α-acetoxystilbene the kinetics were followed at 288 mμ. All reactions of the *trans* compound showed excellent first-order behavior to greater than 95% reaction. Infinity spectra were recorded on a Cary Model 14 spectrophotometer, and were identical with those obtained for an authentic sample of desoxybenzoin in the same acid media. The rate constants were obtained from the slopes of the plots of log $(A_\infty - A_t)$ *vs.* time.

Registry No.—*trans*-α-Acetoxystilbene, 13892-81-4; *cis*-α-acetoxystilbene, 24647-07-2.

(16) No attempt was made to maximize the yield.

Preparation of Maleoyl Fluoride. Nuclear Magnetic Resonance Spectra of Maleoyl Fluoride, Fumaryl Fluoride, and Fumaryl Chloride Fluoride

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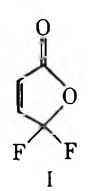
Received December 5, 1969

The preparation of maleoyl fluoride from maleic anhydride and sulfur tetrafluoride has been reported by Hasek, *et al.*[1] We have repeated their reaction conditions (13 hr at 150°) and observe that the products are fumaryl fluoride, unreacted anhydride, and a compound we believe to be 4,4-difluoroisocrotonolactone (I). Under the above conditions it is likely that maleoyl fluoride will be isomerized to fumaryl fluoride.



I

We have used lower reaction temperatures and find that if the mixture is heated to about 75° for 5 hr maleoyl fluoride is one of the products. The amount produced varies from run to run but usually is in the range

(11) K. Yates and R. A. McClelland, *J. Amer. Chem. Soc.*, **89**, 2686 (1967).
(12) C. A. Lane, M. F. Cheung, and G. F. Dorsey, *ibid.*, **90**, 6492 (1968).
(13) R. A. Robinson and O. J. Baker, *Trans. Proc. Roy. Soc. N. Z.*, **76**, 250 (1946).
(14) In the previous study, ref 3, it was observed that the slope of the plot for log *k vs.* $-H_0$ was close to unity for the carbonium ion pathway.
(15) Analyses are by the Microanalytical Laboratory of the Department of Chemistry, University of California.

(1) W. R. Hasek W. C. Smith, and V. A. Engelhardt, *J. Amer. Chem. Soc.*, **82**, 543 (1960).

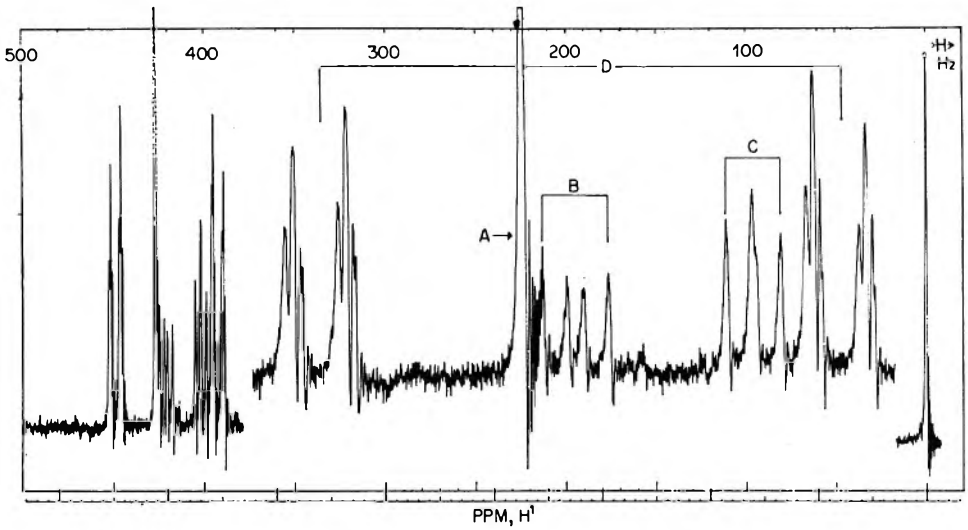


Figure 1.—Nmr spectrum of the products obtained from the action of SF_4 on maleic anhydride: A (maleic anhydride), B (fumaryl fluoride), C (maleoyl fluoride), and D (4,4-difluoroisocrotonolactone).

of 20 to 50% as determined from the nmr spectrum (see Figure 1) after removal of the SF_4 and HF. In several instances all of the reaction mixture was not removed from the cylinder after it had been heated. This remaining portion, after standing for several days at room temperature in the cylinder, invariably gave a greater amount of maleoyl fluoride relative to that of I. Higher reaction temperatures result in a larger percentage of I and fumaryl fluoride.

It should be pointed out that the commercial grade SF_4 (Matheson) used in our work contained HF. It is possible that the discrepancy between our work and that of ref 1 is due to this fact, since HF might catalyze the isomerization of maleoyl fluoride to fumaryl fluoride at 150°. However, it is known that maleic acid isomerizes to fumaric acid on heating. There is a reason to suspect a similar isomerization will occur in the case of maleoyl fluoride. Furthermore, maleoyl fluoride was identified by infrared spectroscopy in the earlier work. Both it and fumaryl fluoride will give similar infrared spectra.[2] Finally the boiling point reported for maleoyl fluoride (100–105°)[1] is near that of fumaryl fluoride (106°).

A complete separation of maleoyl fluoride from I was not achieved in our work even though numerous vacuum trap-to-trap distillations were tried. Maleoyl fluoride is the less volatile component but there is evidence that concentrated samples of it slowly equilibrate to a mixture of maleoyl fluoride, fumaryl fluoride, anhydride and I. The normal boiling point of maleoyl fluoride was not determined but it is expected to be in excess of 106°. The mass spectrum of a sample containing about 90% maleoyl fluoride (by nmr) showed a *m/e* peak at 120. This was the highest *m/e* peak of any significance. Except for the relative intensities of the fragment peaks the spectrum was very similar to the one obtained from a pure sample of fumaryl fluoride.

A comparison of the nmr parameters of maleoyl fluoride with those of fumaryl fluoride gives additional evidence of its preparation. Both give rise to AA′-XX′-type spectra and eight of the ten lines theoretically possible are observed in the A and X parts of the spectra. The outer four lines, symmetrically displaced about the center, are weak, particularly in the spectrum of the latter compound, and are not visible in Figure 1. A complete analysis of the spectra, including the ^{13}C satellites and using the computer program LAOCN3,[3] gives the parameters listed in Table I. The ^{13}CF couplings and isotopic shifts are in good agreement with those of the related compounds.[4]

TABLE I
NMR PARAMETERS OF MALEOYL FLUORIDE AND FUMARYL FLUORIDE

OFC—CH=CH—CFO[a]
(3) (1) (2) (4)

	Maleoyl fluoride	Fumaryl fluoride
$\delta(1) = \delta(2)$,[b] ppm	6.73	6.94
$\delta(3) = \delta(4)$,[c] ppm	41.18	30.40
J_{12}	±12.13	±15.77
$J_{13} = J_{24}$	±4.17	±7.51
$J_{14} = J_{23}$	±1.83	∓0.21
J_{34}	4.78	±0.22
$J_{^{13}CH}$	178	
$J_{^{13}CF}$	346	345
$J_{^{13}CCF}$		72
$\delta_{^{13}CF} - \delta_{^{12}CF}$, ppm	0.15	0.12

[a] Approximately 15% in $CFCl_3$. [b] From TMS. [c] From $CFCl_3$ (downfield).

The parameters listed in Table I are actually conformationally averaged ones. J_{13} in particular has been found to be temperature and solvent dependent and this information, along with a study of the vibrational spectra,[5] has been used to determine the relative stabilities of the isomers in these compounds and in fumaryl chloride. There is probably a large concentration of the unsymmetrical isomer of maleoyl fluoride

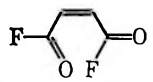
(2) This would not necessarily be true if fumaryl fluoride existed only as the more symmetric C_{2h} isomer. We find that several rotational isomers are present.

(3) S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, **41**, 3863 (1964).

(4) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. II, Pergamon Press, London, 1965.

(5) T. P. Vasileff and D. F. Koster, unpublished work.

(II) which would account for the differences in $\delta(3)$, J_{13} and J_{14}, when compared with the same parameters of fumaryl fluoride.



II

The small negative coupling constant, J_{14}, in fumaryl fluoride appears to be real. In the calculations it was originally assigned a value of zero. Allowing it to vary to the value listed results in an improved calculated spectrum. To further substantiate this, fumaryl chloride fluoride was prepared and its nmr spectrum analyzed. It is possible to determine the relative signs of the coupling constants from the analysis of this ABX spectrum and indeed J_{AX} is opposite to J_{BX}. The parameters are as follows: δ_A 6.923 ppm, δ_B 7.143 ppm (from TMS), δ_X 31.414 ppm (downfield from $CFCl_3$) ($J_{AB} = \pm 15.60$, $J_{AX} = \pm 7.11$, and $J_{BX} = \mp 0.28$ cps). Since the magnitude of the coupling constants here are very nearly the same as those of fumaryl fluoride it is reasonable to assume that the sign J_{14} is opposite to J_{13} in fumaryl fluoride.

Compound I has been identified solely from its nmr spectrum. This product should not be unexpected since SF_4 is reported[1] to react with carbonyl groups to give *gem*-difluoro compounds. The proton and fluorine spectra are consistent with the ABX_2 type expected. The parameters are as follows: δ_A 6.501 ppm, δ_B 7.411 ppm (from TMS), δ_X −83.5 ppm (upfield from $CFCl_3$) ($J_{AB} = 5.7$, $J_{AX} = 0.8$ and $J_{BX} = 0.9$ cps). The *cis* HH coupling (J_{AB}) is identical with the *cis* HH coupling in maleic anhydride.[6]

An unambiguous assignment of the protons A and B is not possible. It is more likely that the low field proton is the one β with respect to the carbonyl group and this assignment is chosen here. The small three-bond HF coupling is not unreasonable[7] since the dihedral angle is about 60 degrees.

Experimental Section

Fumaryl Fluoride.—A 2:1 molar ratio of antimony trifluoride and fumaryl chloride was stirred and heated at 100° for about 1 hr. The more volatile fumary fluoride (bp 106°) was then distilled from the mixture and subsequently identified by nmr and mass spectroscopy.

Fumary Chloride Fluoride.—A 2:1 molar ratio of fumaryl chloride and antimony trifluoride was heated for about 1 hr at 100°. Fumaryl chloride fluoride was not completely separated from fumaryl chloride but an enriched sample (approximately 80%) was prepared by vacuum trap-to-trap distillation. The compound was identified by its ABX nmr pattern.

Reaction of Maleic Anhydride with Sulfur Tetrafluoride.—A 11.3-g (0.12 mol) sample of maleic anhydride was weighed into a 125-ml monel cylinder fitted with a needle valve. The cylinder and its contents were vacuum degassed. Sulfur tetrafluoride (0.23 mol) was vacuum transferred and condensed into the cylinder. Following a heating period of about 5 hr at 75–80° the cylinder was allowed to cool to room temperature and the volatile components were vented. Small amounts of dissolved SF_4 and HF were removed by vacuum degassing. Partial separation of maleoyl fluoride was achieved by vacuum trap-to-trap transfer. The product was identified by its nmr and mass spectra. Compound I, a product of the reaction was identified by its proton and fluorine nmr spectrum.

(6) D. F. Koster, unpublished results.

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

Spectra.—The nmr spectra were recorded with A-56/60 and HA-100 nmr spectrometers. A CEC 21-104 mass spectrometer was used in recording the mass spectral data.

Registry No.—I, 24647-21-0; II, 692-71-7; fumaryl fluoride, 24647-23-2; fumaryl chloride fluoride, 24647-24-3.

Acknowledgment.—We wish to thank Miss Verneda Wright for technical assistance and Mr. Walter Boyd for help in obtaining the fluorine nmr spectra. The spectra were recorded on an HA-100 nmr spectrometer purchased with the aid of a grant from the National Science Foundation.

Geometrical Isomers of Bisimines of Tetramethyl-1,3-cyclobutanedione

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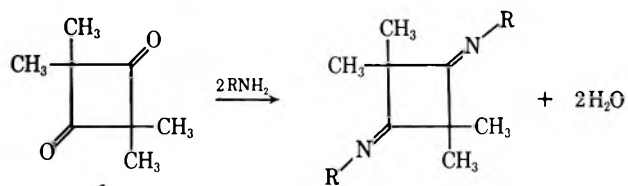
Geometric isomerism of aliphatic and aromatic azomethines has been studied extensively by nmr.[1-3] The configuration about the carbon–nitrogen double bond was established by the use of long-range coupling constants and by variable-temperature studies. More recently a report on the nmr conformational analysis of conjugated diimines has appeared.[4] The factors influencing isomerization about the azomethine grouping are still only vaguely understood.[5]

We wish to report the first example of geometrical isomerization of bisimines of alicyclic β diketones. Steric crowding as well as transannular participation are two factors which may influence the position of equilibrium about the carbon–nitrogen double bond making these systems unique.

The bisimines **2–5** were prepared by the reaction of tetramethyl-1,3-cyclobutanedione (**1**) with 2 mol of the



1

2–5 (*cis* and *trans*)

2, R = phenyl
3, R = cyclohexyl
4, R = *o*-methoxyphenyl
5, R = *o*-chlorophenyl

appropriate amine according to previously described procedures.[6] All spectral properties and elemental analyses were consistent with the structures.

(1) D. A. Nelson and R. L. Atkins, *Tetrahedron Lett.*, 5187 (1967).

(2) G. J. Karabatsos and S. S. Lande, *Tetrahedron*, **24**, 3907 (1968), and references therein.

(3) D. Y. Curtin, E. J. Grubbs, and C. G. McCarty, *J. Amer. Chem. Soc.*, **88**, 2775 (1966), and ref 4, 32, and 36 therein.

(4) J. M. Kliegman and R. K. Barnes, *Tetrahedron Lett.*, 1953 (1969).

(5) N. P. Marullo and E. H. Wagener, *ibid.*, 2555 (1969).

(6) R. H. Hasek, E. U. Elam, and J. C. Martin, *J. Org. Chem.*, **26**, 4340 (1961).

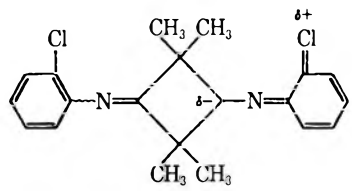
At the probe temperature of 35° in CCl_4 the protons of the methyl groups of tetramethyl-1,3-cyclobutanedione (1) exhibit a single sharp resonance at δ 1.29. Under the same conditions the methyl groups of the bisimine derivatives show proton resonance at three distinct field positions (Table I).

TABLE I
METHYL RESONANCES OF BISIMINES OF TETRAMETHYL-1,3-CYCLOBUTANEDIONE

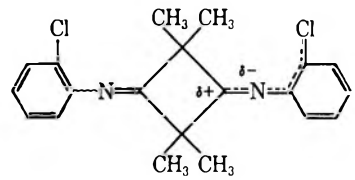
	δ, ppm[a]	
Compd	*trans*	*cis*
2	1.26	1.01, 1.52
3	1.32	1.20, 1.47
4	1.22	0.89, 1.55
5	δ 1.33 (broad singlet)	

[a] δ values are reported in CCl_4 at a probe temperature of 35° using TMS as the internal standard.

The observed resonances are attributed to mixtures of *cis* and *trans* isomers. There are nonequivalent methyl groups for the *cis* isomers to which the combined high- and low-field singlets have been attributed. The proton resonance of the equivalent methyl groups of the *trans* isomers is assigned to the intermediate field singlet which is the most intense. The high- and low-field singlets of the *cis* isomer are of equal area and represent approximately 33% of the product mixture. To verify the isomerization the nmr spectra of **2**, **3**, and **5** were observed at different temperatures. When the temperature was raised, the three separate singlets of compound **2** coalesced to one broad singlet at a temperature of 100°. A similar phenomenon was observed for compound **3**. In the latter case, however, the coalescence temperature was 165° which may be due to the more bulky cyclohexyl rings. On cooling the samples to room temperature the proton resonance of the methyl groups gradually returned to that of the original spectrum taken at 35° and possessed the same *cis* to *trans* ratio. That isomerization was being observed and that it was not simply restricted rotation about the R group attached to the nitrogen is demonstrated. Compound **5** at 35° shows a broad singlet for the proton resonance of the methyl groups, whereas three distinct singlets are observed at 10°. If simple rotation barriers were being observed, **3** would be expected to require a lower coalescence temperature than **5**, and this is not observed. On the other hand, if *cis–trans* isomerization is being observed, **5** would be expected to have a lower coalescence temperature than **2** or **3** because of the contribution of resonance structures, of which **5a** is a single contributing form, and inductive effects (**5b**) which impart partial single-bond character to the azomethine linkage. Similar resonance structures are less predominant in **2** and absent in **3**.



5a



5b

It is impossible on the 60-MHz instrument to detect two separate *o*-methyl resonances for the *cis* and *trans* isomers of **4**. The 100-MHz spectrum shows two distinct singlets with a separation of 2 Hz. The more intense low-field singlet represents the *o*-methyl resonance of the *trans* isomer.

Experimental Section

Nuclear magnetic resonance spectra were observed at 60 and 100 MHz. High-temperature studies were run in DMSO-d_6 and low temperature studies in CCl_4. The temperature was controlled to ±2° using the Varian V-6040 temperature controller.

The bisimines were prepared according to a procedure described by Hasek.[6] All spectral properties were consistent with the structures. Compounds **2** and **3** were previously analyzed.[6]

Anal. Calcd for **4**: C, 75.40; H, 7.48. Found: C, 74.44; H, 7.49. Calcd for **5**: C, 66.86; H, 5.61. Found: C, 66.39; H, 5.89.

Registry No.—*cis*-**2**, 24627-15-4; *trans*-**2**, 24627-16-5; *cis*-**3**, 24627-17-6; *trans*-**3**, 24627-18-7; *cis*-**4**, 24627-19-8; *trans*-**4**, 24627-20-1; *cis*-**5**, 24627-21-2; *trans*-**5**, 24627-22-3.

Acknowledgment.—The authors wish to thank Dr. William S. Wadsworth, Jr., for his helpful discussions and Dr. David A. Nelson of the University of Wyoming for his helpful discussions and for performing the 100-MHz nmr experiment.

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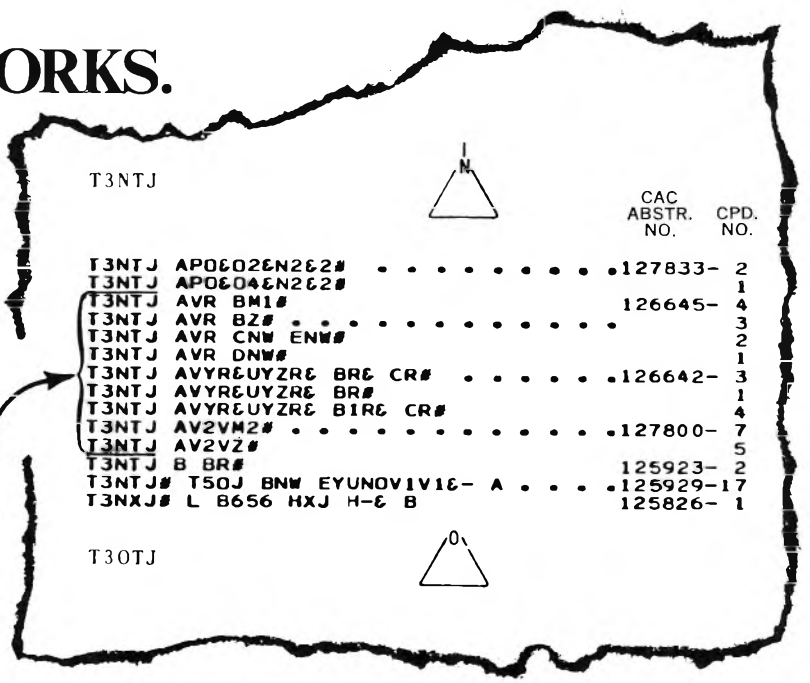

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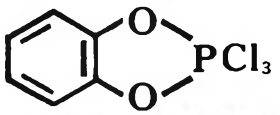
Catechylphosphotrichloride



This reagent converts carboxylic acids into acid chlorides and carbonyl compounds into *gem*-dichlorides. Amides are dehydrated by the reagent to nitriles, and esters are cleaved to the acid chloride and the alkyl chloride.[1] Catechylphosphotrichloride is used in the conversion of amines into isothiocyanates[2] and is superior to phosphorus pentachloride for the conversion of cyclic ketones (8-12 membered rings) into 1-chlorocycloalkenes.[3]

[1]H. Gross and J. Gloede, *Chem. Ber.*, 96, 1387 (1963).
[2]D. Martin, E. Beyer, and H. Gross, *Chem. Ber.*, 98, 2425 (1965).
[3]K. Schank, B. Eistert, and J. H. Pelzmann, *Chem. Ber.*, 99, 1414 (1966).

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[1]H. Normant, *Angew. Chem. Int. Ed. Engl.*, 6, 1046 (1967).
[2]H. O. House, R. W. Giese, K. Kronberger, J. P. Kaplan and J. F. Simeone, *J. Amer. Chem. Soc.*, 92, 2800 (1970).

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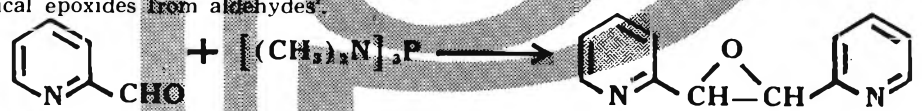

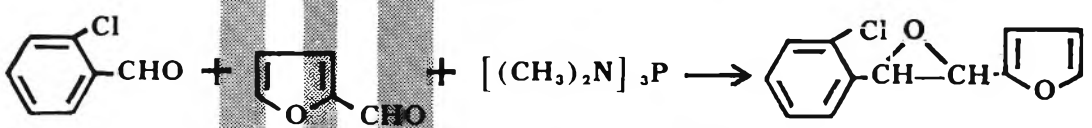

[1]V. Mark, *J. Amer. Chem. Soc.*, 85, 1884 (1963).

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[1]M. Bodanszky and M. A. Ondetti, "Peptide Synthesis," Interscience Publishers, New York, N.Y., 1966, pp. 90, 151 and references therein.
[2]G. W. Anderson, J. Blodinger, and A. D. Welcher, *J. Amer. Chem. Soc.*, 74, 5309 (1952).
[3]C. Ressler and V. Du Vigneaud, *J. Amer. Chem. Soc.*, 79, 4513 (1957); P. G. Katsoyannis, D. T. Gish, and V. Du Vigneaud, *ibid.*, 79, 4516 (1957) and references therein.
[4]D. Samuel and B. L. Silver, *Chem. Ind. (London)*, 556 (1961).

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